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Should we regard all main duct type intraductal papillary mucinous neoplasms of the pancreas (MD-IPMN) as an indication of surgery? -A retrospective study in 29 patients with MD-IPMN showing mural nodules-

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ABSTRACT

Purpose: To elucidate predictive factors for malignant main duct type IPMN (MD-IPMN).
Methods: All 29 subjects had mural nodules (MNs) in the main pancreatic duct (MPD) on preoperative endoscopic ultrasonography and underwent surgery (19, malignant; 10, benign). Possible predictive factors for malignancy such as background, imaging, and histological factors including histological subtype (HS), were evaluated.
Results: Multivariate analysis revealed an MPD diameter of ≥12 mm ($p = 0.042$) and non-gastric type ($p = 0.001$) to be the statistically significant predictive factors for malignancy. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy to detect malignancy by using "an MPD diameter of ≥12 mm and/or non-gastric type" were 95%, 70%, 86%, 88%, and 86%, respectively. In 7 subjects in whom HS was preoperatively evaluated using pancreatic specimens obtained before surgery, the agreement rate of the preoperative HS with definitive HS evaluated using resected specimens was 86%.
Conclusions: For MD-IPMNs with MNs, "an MPD diameter of ≥12 mm and/or non-gastric type" are indicated for surgery. On the other hand, careful surveillance without immediate pancreatic surgery may be an option for MD-IPMNs showing both an MPD diameter of <12 mm and gastric type.
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Introduction

Intraductal papillary mucinous neoplasms of the pancreas (IPMNs) are mucin-producing intraductal epithelial neoplasms showing dilation of main and/or branch pancreatic ducts. According to the international consensus guidelines revised in 2012 and 2017 [1,2], IPMNs can be classified into three morphological types, i.e., main duct type IPMN (MD-IPMN), branch duct type IPMN (BD-IPMN), and mixed type IPMN, based on imaging and/or histological studies. Surgical treatment is highly recommended for patients with MD-IPMNs because of its high frequency of malignancy, perhaps resulting in a paucity of reports on the investigation of the predictive factors for malignancy in those patients [3–6]. However, the majority of patients with IPMNs are elderly for whom pancreatic surgery can cause severe complications and a decline of activities of daily living [7]. Therefore, investigations of the predictive factors for malignancy are needed even in patients with MD-IPMNs in order to clarify candidates with MD-IPMNs in whom surgery can be avoided.

Recently, it has been proposed that IPMNs can be histologically classified into 4 histological subtypes (HSs), and this histological classification is reported to reflect clinical features including a prognosis [8,9]. In addition, we recently reported a preoperative estimation of HS by evaluating pancreatic juice collected under endoscopic retrograde cholangiopancreatography (ERCP) in patients with BD-IPMNs [10], which indicates the possibility of applying this estimation of HS to the decision of surgery [10,11].

Based on the situations mentioned above, the aim of this study

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was to elucidate the predictive factors for malignant MD-IPMNs by investigating the clinicopathological findings in patients clinically diagnosed with MD-IPMNs in our medical center who had undergone surgical treatment and who could be histologically reevaluated, including HS, by using their resected specimens.

Patients and methods

Patients

The Sendai City Medical Center institutional review board approved this study (registration number: 2017 - 0011). Of the 151 patients with IPMN who had undergone surgical treatment in our medical center between January 1985 and April 2016, 36 were diagnosed as having MD-IPMNs by using preoperative imaging studies. Of those patients, 29 patients who could be histologically re-evaluated regarding HS and histological grade were recruited to this study. In this study, MD-IPMNs were diagnosed if the following criteria were met: (1) patients with mural nodules (MNs) located mainly in the main pancreatic duct (MPD) by using endoscopic ultrasound (EUS), and/or (2) patients without branch duct IPMN and with an MPD dilation of $\geq$5 mm having findings of mucin production and lacking other etiology of MPD dilation such as chronic pancreatitis.

Methods

Candidates of the predictive factors for malignancy

We retrospectively evaluated possible predictive factors for malignancy, such as background factors, imaging factors, and histological factors. For background factors, age, sex, symptoms, such as abdominal pain and icterus, the presence of diabetes mellitus, laboratory data including serum amylase (AMY) levels, serum carbohydrate antigen 19-9 (CA19-9) levels, and serum carcinoembryonic antigen (CEA) levels were evaluated. For imaging factors, the diameter of the MPD, the height of MNs, and the size of cysts were evaluated, and HS was evaluated for histological factors.

Preoperative imaging studies

For imaging studies, EUS was performed in addition to magnetic resonance cholangiopancreatography (MRCP) and/or contrast enhanced computed tomography (CECT) in all subjects. MPD diameter and cystic size were measured using MRCP or CECT. Cyst size and MPD diameter could be retrospectively evaluated by using CT films before March 2000 or a digital image database of CT/MRI images after April 2000. Although the presence of MNs and MN heights for all subjects were measured by using EUS with a B-mode display, they were measured by using printed films from EUS for subjects before 2002 and digital image data from EUS for subjects after 2003, both of which were good enough for retrospective evaluations. The height of MNs was defined as the vertical distance from the top of MNs to the septum from which MNs arose [12]. MPD diameter was defined as the one in the most dilated MPD.

Histological evaluations

All the resected specimens of subjects were histologically evaluated, including HS, by pathologists with specific expertise in pancreatic pathology (Y.N., T.S., M.U., and F.F.). Before this study, immunostaining was performed for the resected specimens of subjects who had undergone surgical treatment between 1985 and 2004 when immunostaining was not performed. Two pathologists (Y.N. and T.S.) reevaluated the grade of MD-IPMNs in consideration of the immunostaining findings and also evaluated the HS of the resected specimens in the same manner. Resected specimens were prepared as follows: After fixation in formaldehyde solution, resected specimens were cut into 5- to 6-mm-thick slices. The slices were embedded in paraffin and were cut into 3-μm serial sections for hematoxylin and eosin (H&E) staining, periodic acid-Schiff and Alcian blue (PAS-AB) staining, and several immunostaining.

According to the WHO classification [13], we classified resected specimens as follows: invasive carcinoma derived from IPMN (IC) and high-grade dysplasia (HGD) were defined as being malignant, and low-grade dysplasia (LGD) was defined as being benign.

As for the pathologic diagnosis of malignancy in resected specimens, the presence of cells positive for p53 staining and/or MUC1 staining along with a high Ki-67 labeling index of 10% or more was considered indicative of malignancy in addition to findings of cytologic and structural atypia with H&E staining [10,14–16], the pathological diagnosis of malignancy being determined by the consensus of two or more pathologists. The antibodies used for immunostaining were the following: p53 protein (DO-7; DAKO, Glostrup, Denmark), Ki-67 (MIB-1; Immunotech, Marseilles, France), MUC1 glycoprotein (Ma695; Novocastra, Newcastle, UK), MUC2 glycoprotein (Ccp58; Novocastra), MUC5AC glycoprotein (CLH2; Novocastra), and MUC6 glycoprotein (CLH5; Novocastra). HSs were classified into 4 types, namely, gastric, intestinal, pancreatobiliary and oncocytic type, according to the consensus classification by Furukawa et al. [8,9] In case of the coexistence of two or more kinds of HS in resected specimens, the HS with the highest histologic grade was used.

Preoperative pathological evaluations using pancreatic juice obtained under ERCP

Preoperative pathological evaluations including HS was performed in some patients of this study, and we conducted an additional preliminary study. The methods of sampling pancreatic juice were as follows: after pancreatography was carried out using a cannula 1.7 mm in diameter (PR-104Q-1 or PR-109Q-1; Olympus, Tokyo, Japan), a 0.025-inch guidewire was advanced deep into the MPD and the cannula was changed to a sampling catheter with a side-hole (PR-130Q; Olympus, Tokyo, Japan) over the guidewire. A sampling of pancreatic juice with negative pressure was carried out for about 5 min while the catheter was gradually pulled back toward the major papilla.

Pancreatic juice obtained by the above-mentioned methods was evaluated using the cell-block method [10,14,15], and the cell-block sections were prepared using the sodium alginate method and subjected to H & E staining, PAS-AB staining, and immunostaining including MUC staining. The method of the evaluation of HS by using the specimens preoperatively obtained was the same with the one by using the resected specimens. All of the preoperative evaluations on HS were carried out before pancreatic surgery.

Statistical analysis

The Pearson χ [2] test or the Fisher exact test was used for the categorical variables, whereas Student's *t*-test or the Mann-Whitney *U* test was used for continuous data. Continuous variables which showed significant differences in the univariate analysis were converted into categorical variables by calculating the cut-off value for the diagnosis of malignancy using a receiver operating characteristic (ROC) curve. Multivariate analysis was performed for the factors which showed $p < 0.05$ by univariate analysis. Multiple logistic regression analysis was used in the multivariate analysis. All statistical analyses were performed with SPSS software version 11.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Characteristics of the 29 patients

Details of the 29 patients are shown in Table 1 and Table 2. The mean age of subjects was 70 ± 7 years, and 18 of the 29 were male. Eight patients (28%) had symptoms, such as abdominal pain and icterus. Regarding the histological findings of the resected specimens, of the 29 subjects, 6 (21%) were diagnosed with IC, 13 (45%) were HGD, and 10 (34%) were LGD. For each HS, 10 (34%) were diagnosed with gastric type, 14 (49%) were intestinal type, and 5 (17%) were pancreatobiliary type. In all subjects, papillary nodules in the MPD were histologically detected. On imaging studies, the mean diameter of the MPD was 15 ± 9 mm (6–40). All subjects had MNs mainly located in the MPD, and the mean height of MNs was 11 ± 6 mm (5–30). Of 29 subjects, 15 (52%) had dilated branch ducts, the mean size of those being 37 ± 18 mm (15–70 mm).

Univariate analysis for the possible predictive factors for malignancy in 29 subjects

In order to identify the predictive factors for malignant MD-IPMNs, the possible predictive factors mentioned above were investigated by univariate analysis (Table 3). With regard to background factors, there were no statistical differences in age, sex, symptoms, and diabetes mellitus ($p = 0.987$, 0.411, 0.066, and 0.581, respectively). Laboratory data (serum AMY, CA19-9 and CEA levels) also showed no statistical differences ($p = 0.458$, 0.944, and 0.934, respectively). Of the 22 cases for whom we could obtain data about serum CA19-9 levels, 5 (23%) had elevated CA19-9 levels (>37 U/ml) and all of the cases involved malignancies. However, there were no significant differences between those with and without elevated serum CA19-9 levels ($p = 0.114$). Regarding image findings, both the diameter of the MPD (malignant, 18 ± 9 mm; benign, 10 ± 5 mm) and the height of MNs (malignant, 13 ± 6 mm; benign, 8 ± 2 mm) showed statistically significant differences between malignant and benign subjects ($p = 0.007$ and 0.012, respectively). Dilated branch ducts existed in 11 out of the 19 malignant subjects (58%) and in 4 out of the 10 benign subjects (40%), which showed no significant difference ($p = 0.359$). In 15 subjects who had dilated branch ducts, the size of dilated branch ducts (41 ± 18 mm, malignant; 24 ± 6 mm, benign) also showed no statistically significant difference between malignant and benign subjects ($p = 0.076$).

Regarding histopathological findings, HS was evaluated. There was a statistically significant difference in the rate of malignancy among HSs ($p < 0.001$). The subjects having a malignancy mainly consisted of non-gastric type MD-IPMNs (89%, 17/19), whereas the subjects having a benignancy mainly consisted of gastric type MD-IPMNs (80%, 8/10).

Table 1
Baseline characteristics of 29 patients.

Age *	70 ± 7 [53–78]
Sex(male:female)	18:11
Symptoms	8 (28%)
Diabetes mellitus	8 (28%)
Laboratory data	
AMY (IU/l, n = 20) *	129.9 ± 115.9 [33.0–430.0]
CA19-9 (U/ml, n = 22) *	28.5 ± 62.4 [2.0–298.0]
CEA (ng/ml, n = 20) *	2.5 ± 1.9 [0.7–9.6]
Image findings	
Location (Ph: Pb: Pt)	12: 13: 4
Diameter of MPD (mm)*	15.2 ± 8.6 [6.0–40.0]
Height of MN (mm)*	11.3 ± 5.5 [5.0–30.0]
Existence of the dilated branch ducts	15 (52%)
Size of the dilated branch ducts (mm)	37 ± 18 [15–70]
Surgical procedure	
PD:DP:TP:Seg	10: 15: 3: 1
Pathological findings	
1.Grade	
IC	6 (21%)
HGD	13 (45%)
LGD	10 (34%)
2.Histological subtypes	
gastric type	10 (34%)
intestinal type	14 (49%)
pancreatobiliary type	5 (17%)
oncocytic type	0 (0%)

Abbreviation: AMY, serum amylase levels; CA19-9, serum carbohydrate antigen 19-9 levels; CEA, carcinoembryonic antigen; MPD, main pancreatic duct; MN, mural nodule; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; Seg, segmental pancreatectomy; IC, invasive cancer; HGD, high grade dysplasia; LGD, low grade dysplasia; Ph, pancreatic head; Pb, pancreatic body; Pt, pancreatic tail. *: mean ± SD [range].

Multivariate analysis for the possible predictive factors for malignancy in 29 patients

The possible predictive factors for malignancy which showed $p < 0.05$ by the univariate analysis were the diameter of the MPD, the height of MNs and HS, which were investigated by multivariate analysis. For the 2 continuous variables of MPD diameter and MN height, appropriate cut-off values were determined using ROC curve analysis for the diagnostic ability to detect malignant MD-IPMNs in order to convert those into categorial variables, and then the 3 possible predictive factors for malignancy for multivariate analysis were determined as follows: an MPD diameter of ≥12 mm (sensitivity, 74%; specificity, 90%), an MN height of ≥10 mm (sensitivity, 74%; specificity, 80%), and non-gastric type. Multivariate analysis revealed an MPD diameter of ≥12 mm ($p = 0.042$; OR, 18.2; 95%CI, 1.1–33.3) and non-gastric type ($p = 0.001$; OR, 34.0; 95%CI, 4.0–286.8) to be statistically significant predictive factors for malignancy (Table 3). Relationship between those predictive factors and malignancy is shown in Fig. 1. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy to detect malignancy using "an MPD diameter of ≥12 mm and/or non-gastric type" were 95% (18/19), 70% (7/10), 86% (18/21), 88% (7/8), and 86% (25/29), respectively. In other words, most of subjects showing an MPD diameter of ≥12 mm and/or non-gastric type were malignant (86%, 18/21), and most of those showing both an MPD diameter of <12 mm and gastric type were benign (88%, 7/8).

Preoperative estimation of HS by using pancreatic juice or biopsy specimens obtained transpapillary

Considering the results of this study that found HS to be one of the predictive factors for malignant MD-IPMNs, 7 out of the 29 subjects in whom preoperative HS was evaluated using pancreatic juice or pancreatic biopsy specimens was additionally investigated (Figs. 2 and 3). In all the 7 subjects, the pancreatic specimens preoperatively collected were adequate for the preoperative diagnosis of malignancy and the determination of HS. Accuracy to detect malignancy was 71%, whereas the agreement rate of the HS determined preoperatively with that of resected specimens was 86% (Table 4). Although the preoperative diagnosis of HS was discordant with that of resected specimens in only 1 out of those 7 subjects, this may be due to an insufficient amount of the specimens derived from the papillary epithelium of IPMN because of an MPD obstruction caused by an infiltration of invasive cancer. No post-ERCP adverse events developed in those 7 patients.

Table 2
Clinicopathological characteristics of individual patients.

Case	Age	Sex	Location	Height of MN (mm)	Diameter of MPD (mm)	Size of DBD (mm)	Histological grade	Histological subtype
1	69	M	Pb	30	33	–	IC	intestinal
2	64	M	Pb	8	10	–	IC	PB
3	78	F	Ph	14	14	25	IC	PB
4	73	M	Pb	12	30	–	IC	intestinal
5	66	M	Pt	20	25	–	IC	intestinal
6	71	F	Ph	15	15	–	IC	intestinal
7	70	M	Ph	13	15	35	HGD	intestinal
8	60	M	Ph	5	7	30	HGD	intestinal
9	75	M	Pb	18	40	70	HGD	intestinal
10	72	F	Pb	10	20	50	HGD	intestinal
11	72	F	Pb	12	20	50	HGD	intestinal
12	75	M	Pb	11	13	55	HGD	intestinal
13	53	M	Pb	7	7	24	HGD	gastric
14	65	M	Pt	5	10	15	HGD	intestinal
15	78	F	Ph	10	18	30	HGD	intestinal
16	65	M	Pb	12	12	–	HGD	gastric
17	71	F	Pb	8	9	–	HGD	PB
18	77	F	Ph	20	22	–	HGD	intestinal
19	75	F	Pb	18	20	70	HGD	PB
20	75	F	Ph	8	8	22	LGD	gastric
21	77	M	Pb	7	10	30	LGD	gastric
22	63	M	Ph	9	10	–	LGD	intestinal
23	73	M	Pb	6	6	15	LGD	gastric
24	73	M	Pt	11	11	27	LGD	gastric
25	60	M	Ph	9	9	–	LGD	gastric
26	77	F	Ph	7	7	–	LGD	gastric
27	73	M	Pt	10	25	–	LGD	gastric
28	55	F	Ph	6	6	–	LGD	gastric
29	73	M	Ph	8	8	–	LGD	PB

Abbreviation: MN, mural nodule; MPD, main pancreatic duct; DBD, dilated branch duct; Ph, pancreatic head; Pb, pancreatic body; Pt, pancreatic tail; IC, invasive cancer; HGD, high grade dysplasia; LGD, low grade dysplasia; PB.

Table 3
Univariate and multivariate analysis for possible predictive factors for malignant MD-IPMN.

Factors	Univariate			Factors	Multivariate		
	Malignant (n = 19)	Benign (n = 10)	p-value		p-value	Odds ratio	95%CI
Age *	70 ± 6	70 ± 7	0.987				
Sex (Male: Female)	11: 8	7: 3	0.411				
Symptoms	3 (16%)	5 (50%)	0.066				
Diabetes mellitus	5 (26%)	3 (30%)	0.581				
AMY (IU/l, n = 20) *	147 ± 128	90 ± 64	0.458				
CA19-9 (U/ml, n = 22) *	38 ± 74	8 ± 4	0.944				
CEA (ng/ml, n = 20)*	2.6 ± 2.2	2.1 ± 1.0	0.934				
Location (Ph: Pbt)	6: 13	6: 4	0.140				
Diameter of MPD *	18 ± 9	10 ± 5	0.007	MPD diameter ≥ 12 mm	0.042	18.2	1.1–33.3
Height of MN *	13 ± 6	8 ± 2	0.012	MN height ≥ 10 mm	0.740		
Existence of DBD	11 (58%)	4 (40%)	0.359				
Size of DBD (n = 15) *	41 ± 18	24 ± 6	0.076				
Histological subtypes (Gastric: Non-gastric)	2: 17	8: 2	<0.001	Non-gastric type	0.001	34.0	4.0–286.8

Abbreviation: AMY, serum amylase levels; CA19-9, serum carbohydrate antigen 19-9 levels; CEA, carcinoembryonic antigen; Ph, pancreatic head; Pbt, pancreatic body and tail; MPD, main pancreatic duct; MN, mural nodule; DBD, dilated branch duct. *: mean ± SD.

Discussion

Of the 29 patients with MD-IPMNs recruited to this study, 19 (66%) showed malignancy, and multivariate analysis revealed an MPD diameter of ≥12 mm and non-gastric type to be significant predictive factors for malignancy. The high prevalence of malignancy in patients with MD-IPMNs of this study was similar to that of previous reports, whereas most of MD-IPMNs showing both an MPD diameter of <12 mm and gastric type were benign, suggesting that conservative management for selected patients with MD-IPMNs may be possible.

Regarding the predictive factors for malignant MD-IPMNs, Roch et al. [3] reported that an MPD diameter was not indicative of malignant MD-IPMN and that the patients with both a benignancy determined by preoperative cytology and normal serum CA19-9 levels had a low risk of malignancy. However, it should need to be taken into consideration that the study herein reported defined IPMNs with an MPD diameter of ≥5 mm on the preoperative image as MD-IPMNs. Ogura et al. [4] reported that patients with MD-IPMNs showing an MPD diameter <15 mm, a benignancy determined by cytology, and no MNs, can undergo conservative follow-up. Takuma et al. [5] reported that conservative follow-up may be an option for patients with MD-IPMNs showing an MPD diameter of <10 mm, no MNs, and a benignancy determined by cytology. Although surgical resection was recommended for all patients with MD-IPMNs having MNs according to the international consensus guidelines [1,2] and the reports mentioned above, all the 29 subjects in this study had MNs with the maximum height of >5 mm

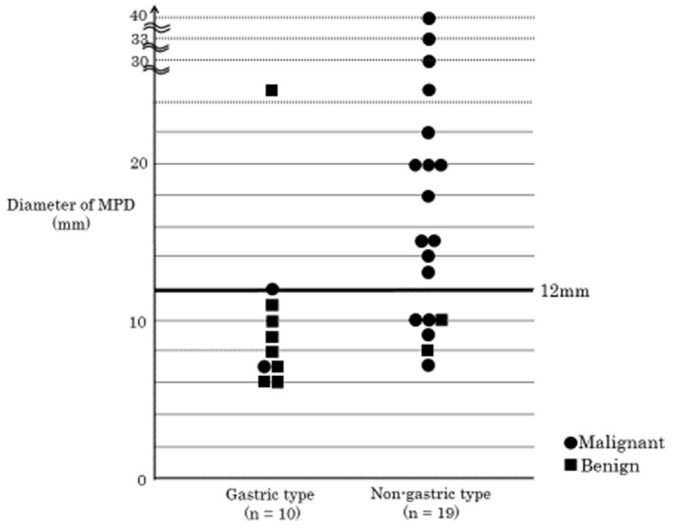

Fig. 1. The relationship between the two predictive factors for malignant MD-IPMN and histological grade.

which mainly located in the MPD, and 34% of the 29 subjects underwent unnecessary surgery because their MD-IPMNs were diagnosed as being benign by using the resected specimens. It is debatable whether those 34% of patients should be considered to be high proportion or not. In any case, careful attention should be paid to whether surgery for IPMNs is performed or not because many IPMNs are detected in the elderly who often have comorbidities or show low daily activities. Therefore, the results of this study are considered to be meaningful when "tailor-made medicine" is applied to those elderly patients with MD-IPMNs. In other words, a clinical plan of "wait-and-see" for those patients having MD-IPMNs showing benign features is reasonable. On the other hand, long-term prognosis for patients with IPMN having MNs located in the MPD is unclear, and so they should undergo careful surveillance by using imaging studies including EUS which can be used to evaluate the details of MNs at 3–6 months interval.

Regarding image findings, the only predictive factor for malignant MD-IPMNs was revealed to be the diameter of the MPD in this study. On the other hand, MNs are reported to be useful for the determination of surgery in patients with BD-IPMNs. Between MD-IPMNs and BD-IPMNs, there are some differences in biological features, such as the rate of malignancy and the differences in the rate of each HS, which is the reason why the morphological classification of IPMN is still considered to be important. The results of this study may indicate that MD-IPMNs have a biological background that the diameter of the MPD rather than the height of MNs reflect malignancy.

In this study, HS was also revealed to be a predictive factor for malignant MD-IPMNs. Furukawa et al. [8] reported that HS was related to the rate of malignancy in patients with IPMNs. More specifically, most gastric type IPMNs are benign and most non-gastric type IPMNs are malignant. In addition, they reported that most BD-IPMNs are gastric type, and that the rate of intestinal type in the BD-IPMNs is about half of that in the MD-IPMNs, which is the reason why the rate of malignancy was different depending on the morphological classification of IPMN. In this study, intestinal type BD-IPMNs accounted for almost half of the subjects (49%), whereas not a few gastric type MD-IPMNs also existed (34%). However, 13 out of the 19 malignant MD-IPMNs (68%) were intestinal type, whereas 8 out of the 10 benign MD-IPMNs (80%) were gastric type, suggesting that HS can be a useful tool for the diagnosis of malignancy in patients with MD-IPMNs. However, HSs in this study were determined by using the resected specimens. Therefore, a preoperative evaluation of HS is needed in order to use that as a predictive factor for malignancy.

We previously reported that HS can be preoperatively estimated by using pancreatic specimens collected by using ERCP in patients with BD-IPMNs [10]. In 28 subjects with resected BD-IPMNs in our previous report, the concordance rate of the preoperative HS with HS of resected specimens was very high (93%). Considering the anatomy of the pancreatic duct, the equivalent efficacy mentioned above can also be expected in patients with MD-IPMNs. In fact, preoperative diagnosis of HS was performed in 7 patients with MD-IPMNs in this study after 2005 when a preoperative evaluation of HS was first performed in our medical center, and the concordance rate was high (86%) despite the small number of patients. Therefore, preoperative evaluation of HS in addition to the evaluation of malignancy by using pancreatic specimens preoperatively obtained may lead to more accurate diagnosis of malignant MD-IPMNs.

This study has some limitations. First, this was a retrospective study for patients with MD-IPMNs who had undergone surgical treatment. The patients who did not undergo surgical treatment because of advanced age or poor general condition could be excluded in this study, which may have led to a selection bias. As far as we searched, there were 6 patients with MD-IPMNs who underwent surveillance without surgery during this study period. All 6 patients met the criteria for MD-IPMNs in this study, and only 2 of the 6 patients had MD-IPMNs without MNs. Unlike BD-IPMNs or mixed type IPMNs, we think that most of "pure" MD-IPMNs have MNs and that MD-IPMNs without MNs are relatively rare. Thus, the selection bias for including subjects in this study may be not relatively important. Second, this was single center study with a small number of patients. Third, regarding an additional preliminary study using pancreatic specimens obtained preoperatively, in general, cytology for IPMNs is performed by using specimens obtained through EUS-FNA, and transpapillary sampling is not done routinely worldwide. Although it is unclear which method is better to obtain cytology specimens, we have recently reported that pancreatic juice cytology using the cell-block method can be used to detect malignancy in patients with branch duct-type IPMNs [10]. In particular, to obtain pancreatic specimens for the diagnosis of malignancy in the patients of this study having MNs located in the MPD, we think that it is better to use the transpapillary approach than it is to perform EUS-FNA. Although post-ERCP pancreatitis (PEP) is a matter of concern when transpapillary tissue acquisition is performed, the rates of PEP in this study and our previous study were not so high (0–8%). In addition, administration of nonsteroidal anti-inflammatory drugs may reduce the risk of PEP in patients who undergo transpapillary tissue acquisition. Although these limitations exist, the results of this study are notable, especially regarding two points, namely, that all subjects in this study had MNs mainly in the MPD which were indicated for surgical treatment according to the previous reports and that the usefulness of HS as a predictive factor for malignancy in patients with MD-IPMNs was revealed, indicating the future possibility for preoperative diagnosis of malignant MD-IPMNs.

In conclusion, "an MPD diameter of $\geq$12 mm and/or non-gastric type" are indicated for surgery in patients with MD-IPMNs having MNs. On the other hand, careful surveillance without immediate pancreatic surgery may be an option in selected patients with MD-IPMNs showing both an MPD diameter of <12 mm and gastric type. Histological evaluations using pancreatic specimens preoperatively

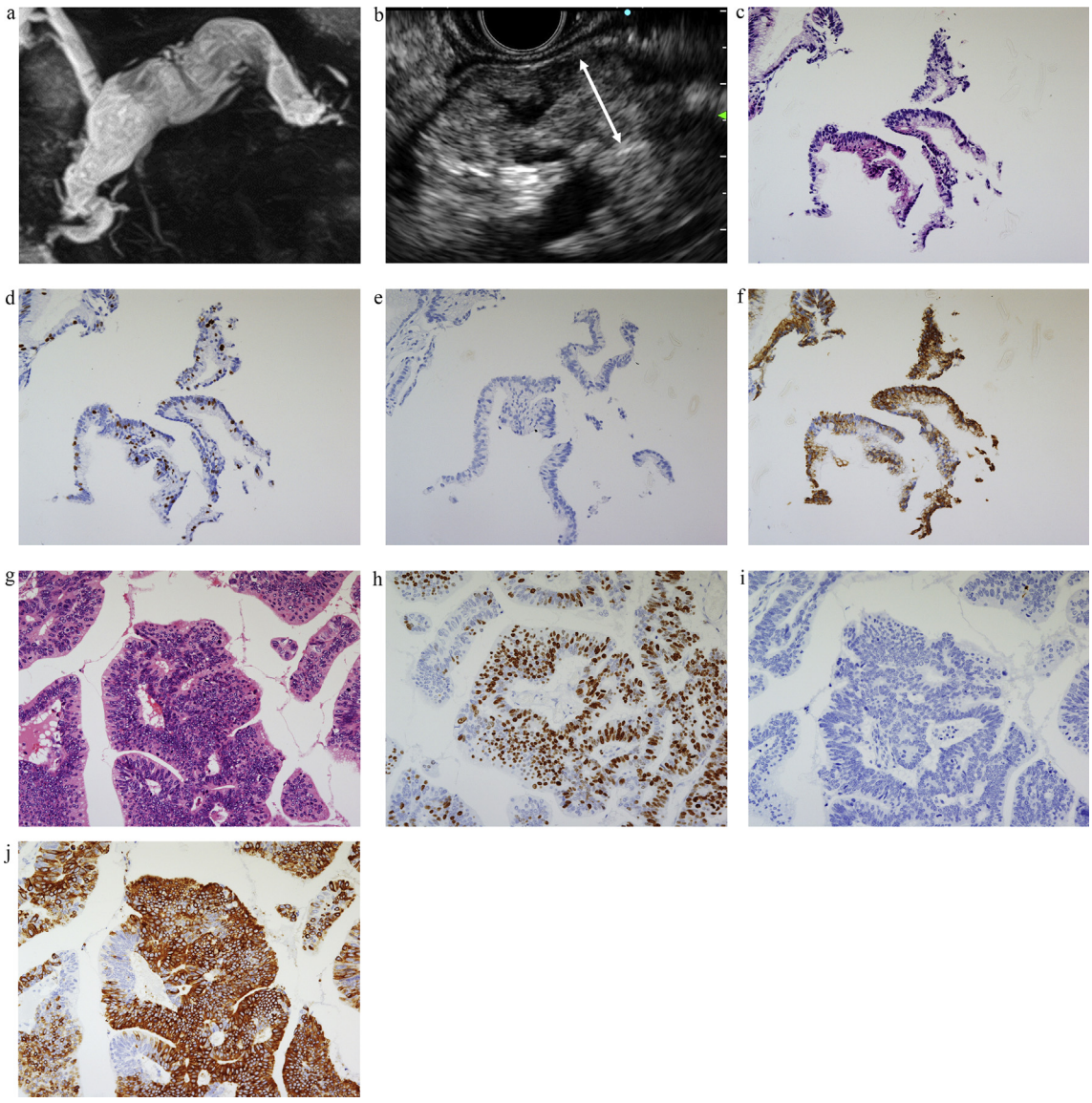

Fig. 2. This patient (**case 4 in** Tables 2 and 4) was histologically diagnosed with malignant MD-IPMN. MRCP showed MPD dilatation especially in the pancreatic body and tail, its maximum diameter being 30 mm (A). Mural nodules with a height of 12 mm (the two-direction arrow shows the height of mural nodules) were detected in the MPD of pancreatic body by using EUS (B). Histological findings of biopsy specimens preoperatively obtained by using ERCP (C–F): hematoxylin and eosin (H&E) staining (C, orig. mag. × 50) showed clusters of mucin-producing atypical cells. Ki67 labeling index (D, orig. mag. × 50) was 20%, suggesting malignant MD-IPMN. MUC1 staining was negative (E, orig. mag. × 50) and MUC2 staining was diffusely positive (F, orig. mag. × 50), indicating intestinal type. Histological findings of resected specimen (G–J): H&E staining (G, orig. mag. × 50) showed that the MPD was filled with high papillary protrusions composed of mucin-producing atypical cells. Ki67 labeling index (H, orig. mag. × 50) was 20%, p53 staining was negative, MUC1 staining was negative (I, orig. mag. × 50), and MUC2 staining (J, orig. mag. × 50) was positive, resulting in the pathologic diagnosis of malignant MD-IPMN with intestinal type.

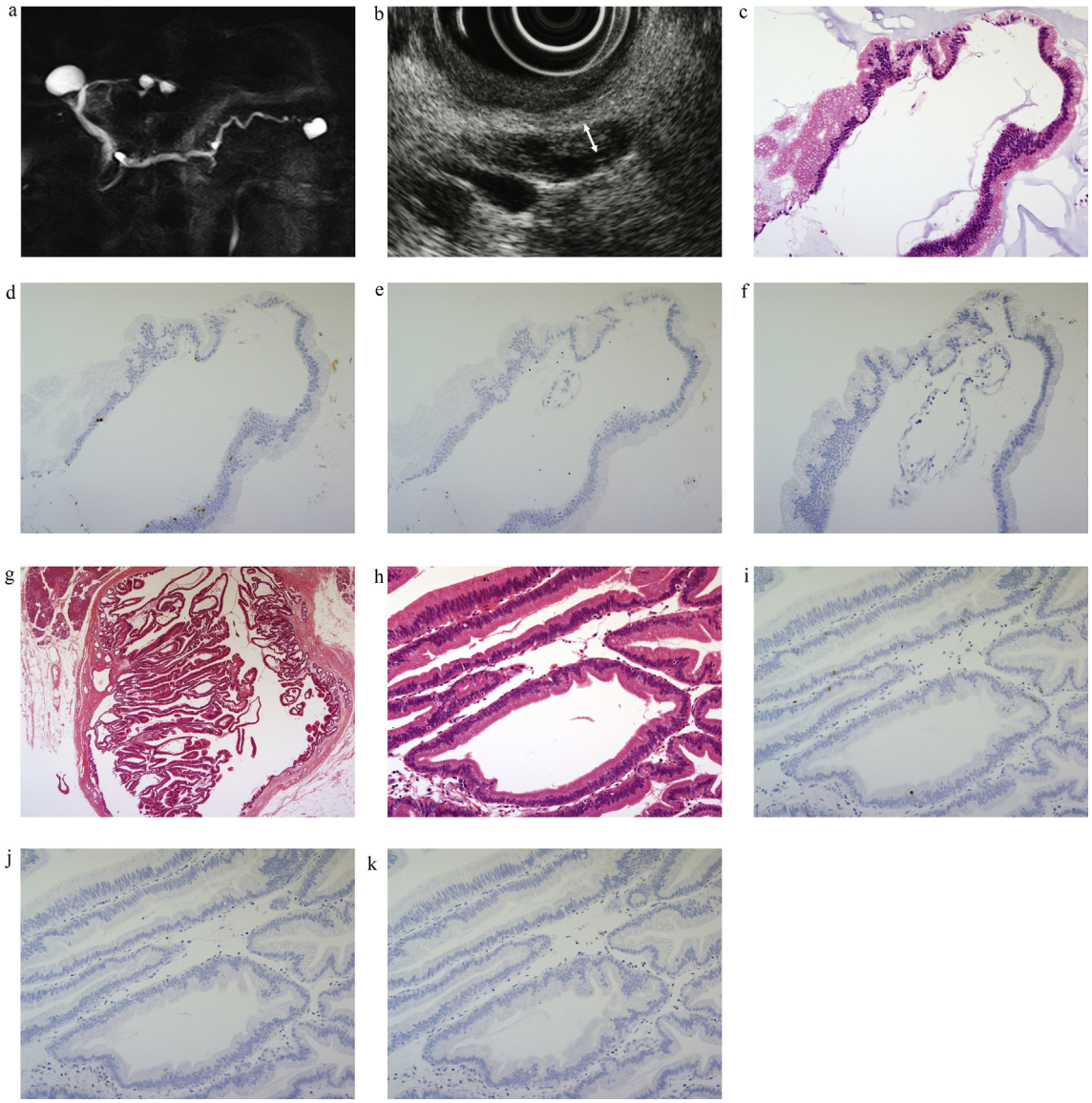

Fig. 3. This patient (**case 28 in** Tables 2 and 4) was histologically diagnosed with benign MD-IPMN. MRCP showed MPD dilatation up to 6 mm in diameter (A). EUS demonstrated mural nodules detected in the MPD of pancreatic neck were 6 mm in height (B, the two-direction arrow shows the height of mural nodules). Histological findings of the specimens preoperatively obtained from pancreatic juice (C–F): hematoxylin and eosin (H&E) staining (C, orig. mag. × 50) showed clusters of mucin-producing atypical cells. Ki67 labeling index (D, orig. mag. × 50) was less than 5%, suggesting benign MD-IPMN. Both MUC1 and MUC2 staining (E, orig. mag. × 50; F, orig. mag. × 50) were negative, suggesting gastric type. Pathological findings of resected specimen (G–K): hematoxylin and eosin (H&E) staining (G, orig. mag. × 5; H, orig. mag. × 50) showed that the MPD was filled with papillary protrusions composed of atypical cells. Ki67 labeling index (Ki67LI) (I, orig. mag. × 50) was 2%, p53 staining was negative, MUC1 staining (J, orig. mag. × 50) was negative, and MUC2 staining (K, orig. mag. × 50) was negative, resulting in a pathologic diagnosis of low-grade MD-IPMN with gastric type.

Table 4
Comparison of the preoperative histological subtype (HS) evaluated using pancreatic juice (PJ) or biopsy specimens (BS) with postoperative HS evaluated using resected specimens.

Case	Age (y.o)	Sex	Pancreatic specimens evaluated preoperatively	Preoperative HS determined by using PJ or BS	Preoperative grade determined by using PJ(Class) or BS	HS determined by using resected specimens	Histological grade determined by using resected specimens	Concordance of HS
2	64	M	PJ	PB	IIIb	PB	IC	Yes
3	78	F	PJ	gastric	II	PB	IC	No
4	73	M	BS	Intestinal	malignant	intestinal	IC	Yes
18	77	F	PJ	Intestinal	II	intestinal	HGD	Yes
19	75	F	PJ	PB	IV	PB	HGD	Yes
27	73	M	PJ	gastric	II	gastric	LGD	Yes
28	55	F	PJ	gastric	I	gastric	LGD	Yes

obtained may contribute to more accurate diagnosis of malignant MD-IPMNs.

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