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Evaluation of efficacy of pancreatic juice cytology for risk classification according to international consensus guidelines in patients with intraductal papillary mucinous neoplasm; a retrospective study

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ABSTRACT

Objectives: Pancreatic juice cytology (PJC) for intraductal papillary mucinous neoplasm (IPMN) is a possible tool to enhance preoperative diagnostic ability by improving risk classification for malignant IPMN, but its efficacy is controversial. This study evaluated the efficacy of PJC for risk classification according to international guidelines.

Methods: We retrospectively analyzed 127 IPMN patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) preoperatively. PJC was performed in 125 of the 127 cases. High-risk stigmata (HRS, n = 57), worrisome features (WF, n = 64), and other characteristics (n = 6) were classified according to the 2017 international guidelines.

Results: Among the 127 IPMN patients, 71 (55.9%) had malignant IPMN (invasive and non-invasive intraductal papillary mucinous carcinoma). The accuracy of WF for classifying malignant IPMN was increased by the addition of PJC, but the accuracy of HRS was not (WF to WF + PJC: 33.1% [42/127] to 48.8% [61/125], HRS to HRS + PJC: 65.4% [83/127] to 52.8% [66/125]). Post-ERCP pancreatitis (PEP) occurred in 32 (25.2%) of 127 IPMN patients. Severe PEP was not detected. Significant risk factors for PEP were female sex, obesity, and endoscopic naso-pancreatic drainage (ENPD) (P = .03, P = .0006, and P = .02, respectively). In patients with ENPD tube placement, a main pancreatic duct size of <5 mm was a significant risk factor for PEP (P = .02).

Conclusion: PJC could increase the accuracy of WF for classifying malignant IPMN. The additive effect of PJC for risk classification may be limited, however, and it is not recommended for all IPMN cases due to the high frequency of PEP.

Abbreviations: (BD-IPMN), Branch duct-intraductal papillary mucinous neoplasm; (BMI), Body mass index; (CA19-9), Carbohydrate antigen 19-9; (ENPD), Endoscopic naso-pancreatic drainage; (ERCP), Endoscopic retrograde cholangiopancreatography; (HRS), High-risk stigmata; (ICG), International consensus guideline; (IPMA), Intraductal papillary mucinous adenoma; (IPMC), Intraductal papillary mucinous carcinoma; (IPMN), Intraductal papillary mucinous neoplasm; (MD-IPMN), Main duct-intraductal papillary mucinous neoplasm; (MPD), Main pancreatic duct; (MX-IPMN), Mixed type IPMN; (NPV), Negative predictive value; (PEP), Post-ERCP pancreatitis; (PJC), Pancreatic juice cytology; (PPV), Positive predictive value; (SPACE), Serial pancreatic-juice aspiration cytologic examination; (WF), Worrisome feature.

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Introduction

Intraductal papillary mucinous neoplasm (IPMN) is a disease entity that includes intraductal papillary mucinous adenoma (IPMA) and intraductal papillary mucinous carcinoma (IPMC). Most IPMNs are benign and have a good prognosis, but some can progress into pancreatic ductal adenocarcinoma derived from IPMN [1]. Diagnosing malignant IPMN in its early phase and determining the appropriate indications for surgery is problematic, however, because of the difficulty obtaining preoperative pathologic evidence and the limited diagnostic ability of imaging studies.

International consensus guidelines for the management of IPMN of the pancreas (ICG) were established in 2006 [2], and revised in 2012 [3] and 2017 [4]. ICG 2017 classifies the risk factors of IPMN as high-risk stigmata (HRS), worrisome features (WF), or other characteristics assessed mainly with imaging studies, and determines surgical indications based on the classification. As the rate of malignancy in patients with just HRS (48.8%–56.5%) is unsatisfactory [5,6], the diagnostic ability of the presently available imaging studies for malignant IPMN is limited. Therefore, a non-imaging diagnostic tool for predicting malignant IPMN, such as cytodiagnosis, may be necessary to improve the diagnostic ability.

Pancreatic juice cytology (PJC) under endoscopic retrograde cholangiopancreatography (ERCP) is widely accepted and recognized as a useful non-imaging tool for assessing patients with pancreatic cancer because of its high sensitivity and specificity (80% and 100%, respectively) [7,8]. On the other hand, ICG 2017 does not currently recommend routine ERCP including PJC in IPMN patients because of the low sensitivity (33%–66%) of PJC for malignant IPMN and the high frequency of post-ERCP pancreatitis (PEP) [4,5,9–11]. The diagnostic value of PJC for malignant IPMN, however, is controversial: PJC has high specificity (91%–100%) [5,9,12]; most previous studies included only a small number (<100) of surgically resected IPMN cases who underwent preoperative PJC [5,10,11]; few studies have focused on the diagnostic ability of a combination of PJC and imaging studies; and optimum PJC procedures is unknown in IPMN patients.

Therefore, the aim of this study was to evaluate the efficacy of PJC for risk classification according to ICG 2017, utilizing a database of only 127 IPMN patients who underwent preoperative ERCP, subsequent pancreatectomy. The risk factors for PEP in IPMN patients were also investigated.

Methods

Patients

A total of 127 consecutive IPMN patients who underwent preoperative ERCP, subsequent pancreatectomy, from April 2000 to September 2017 at our hospital were retrospectively analyzed. IPMN was preoperatively assessed by computed tomography, magnetic resonance imaging, and endoscopic ultrasonography in all cases. Of those, PJC under ERCP was performed in 125 cases. PJC was not performed in two cases because adenocarcinoma was demonstrated by biopsy from the main pancreatic duct (MPD) or gastric invasion of IPMC. Patients with pancreatic ductal adenocarcinoma apart from IPMNs were excluded. This study was approved by the Institutional Review Board for Clinical Research at Kobe University Hospital (approval number: 180022) and performed in accordance with the principles of the Declaration of Helsinki.

Classification of IPMN

In all 127 cases, IPMNs were diagnosed and classified into low-grade dysplasia (so-called “IPMA”), high-grade dysplasia (so-called “carcinoma *in situ*” or “non-invasive IPMC”), and invasive carcinoma (so-called “invasive IPMC”) based on histologic findings in resected specimens. High-grade dysplasia and invasive carcinoma were defined as malignant IPMN because cytology could not distinguish them. The type of IPMN was classified according to ICG 2017 [4]. Main duct IPMN (MD-IPMN) was defined as segmental or diffuse dilation of MPD of >5 mm without other causes of obstruction, branch duct IPMN (BD-IPMN) as pancreatic cysts >5 mm in diameter that communicate with the MPD, and mixed type IPMN (MX-IPMN) as meeting the criteria for both MD-IPMN and BD-IPMN. Risk factors of IPMNs were classified into HRS, WF, and other characteristics. HRS included the following features: MPD size ≥10 mm, enhanced mural nodules ≥5 mm, and obstructive jaundice in a patient with cystic lesions of the pancreatic head. WF included the following features: cysts ≥3 cm, enhanced mural nodules <5 mm, thickened enhanced cyst walls, MPD size 5–9 mm, abrupt change in the MPD caliber with distal pancreatic atrophy, lymphadenopathy, an elevated serum level of carbohydrate antigen 19-9 (CA19-9), a rapid rate of cyst growth >5 mm over 2 years, and pancreatitis.

Procedure of ERCP and PJC

ERCP was performed using conventional lateral-viewing scopes (JF-240, TJF-240, JF- 260V, and TJF-260V; Olympus, Japan). After pancreatography, the catheter was carefully advanced deep and pancreatic juice was collected through the catheter. Brush cytology has been performed using RX Cytology Brushes™ (Boston Scientific, Marlborough, MA) since 2008. Brush cytology targeted the stricture in patients with MPD caliber changes, and the internal parts of IPMN or the connection between the MPD and IPMN in patients without MPD caliber changes. Serial pancreatic-juice aspiration cytologic examination (SPACE) has been performed using a shape-memory reverse alpha type 5-French endoscopic naso-pancreatic drainage (ENPD) tube (GADELIUS MEDICAL K.K., Sweden) since 2010. In patients with ENPD placement, PJC via an ENPD tube was performed repeatedly. Pancreatic juice collected as mentioned above was immediately submitted for cytology to avoid degeneration of the cells. The specimens were categorized as “insufficient material”, “normal”, “atypical”, “suspicious”, or “malignant”. “Atypical” was atypical cytology but no evidence of malignancy. “Suspicious” was strongly suggestive of malignancy. In this study, “suspicious” and “malignant” were defined as positive.

Definition of PEP

PEP was defined as progressive pain accompanied by an increase in the serum pancreatic amylase level to three times higher than the upper normal limit within 24 h after ERCP. The severity of PEP was defined by Cotton's criteria [13].

Statistical analysis

Statistical analyses were performed using JMP software (ver.12.2.0, SAS Institute Inc., Cary, NC). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of HRS, WF, PJC and their combination for identifying malignant IPMN were calculated and histopathologic diagnosis was used as the reference standard. The clinical characteristics associated with PEP were analyzed using Student's t-test for continuous data and the chi square test (or Fisher's exact probability test where appropriate) for categorical data. A *P*-value of less than 0.05 was considered statistically significant.

Results

Clinical background of all IPMN patients

The clinical background is shown in Tables 1 and 2. Among the 127 IPMN patients analyzed in this study, 77 were men and 50 were women with a median age of 68 years (range 43–84 years). On imaging studies, 18 patients had MD-IPMN, 60 had BD-IPMN, and 49 had MX-IPMN. A total of 57, 64, and 6 patients were classified as those having HRS, WF, and the other characteristics, respectively. Based on the histologic findings, low-grade dysplasia was diagnosed in 56 (44.1%) patients, high-grade dysplasia in 35 (27.6%), and invasive carcinoma in 36 (28.3%).

Diagnostic abilities of HRS, WF, PJC, and their combination for classifying malignant IPMN.

The diagnostic abilities of HRS, WF, and PJC, and their combination are provided in Table 3. The findings indicate that adding PJC increased the specificity of HRS and WF, and that adding PJC improved the accuracy of WF but did not improve the accuracy of HRS due to a remarkable decrease in the sensitivity of HRS.

Diagnostic abilities of PJC procedures

The cytology procedure performed and the results in 125 IPMN patients who underwent PJC are listed in Table 4. PJC under ERCP was performed in 125 of 127 cases, and positive cytology was obtained in 44 patients (35.2%) (14 and 30 patients had “malignant” and “suspicious”, respectively). Of those, 30 cases were true positive (total true-positive rate 68.2%) (true-positive rates for “malignant” and “suspicious” were 100% (14/14) and 53.3% (16/30), respectively).

Diagnostic abilities of PJC and the frequency of PEP stratified based on the cytology procedure are shown in Table 5. The findings indicate that adding brush cytology and SPACE to the one-time sampling of the pancreatic juice increased the sensitivity and accuracy of positive PJC, and that adding SPACE increased the frequency of PEP.

Risk factors for PEP

PEP occurred in 32 (25.2%) of 127 IPMN patients. Of those patients, PEP severity was mild in 23 patients, moderate in 9 patients, and severe in 0 patients. Differences in the patient characteristics were analyzed between the PEP and non-PEP groups.

Significant risk factors for PEP are listed in Table 6. In the univariate analysis, significant risk factors for PEP were female sex, obesity, and ENPD placement ($p = .03$, $p = .0006$, and $p = .02$, respectively). On the other hand, the incidence of PEP was low in patients with pancreas atrophy ($p = .02$). In addition, the incidence of PEP was 33.3%, 25.0%, and 15.4% in patients with MPD size <5 mm, 5–9 mm, and ≥10 mm, respectively. The incidence of PEP tended to be low in patients with a larger diameter MPD, although the difference was not significant.

Furthermore, the PEP risk factors in 44 patients with ENPD placement were analyzed and are listed in Table 7. Significant risk factors for PEP were obesity, past history of acute pancreatitis, and MPD size <5 mm ($p = .008$, $p = .001$, and $p = .02$, respectively).

Table 1
Patient background of all IPMN patients in the study.

	$n = 127$
median age (range), years	68 (43–84)
male/female sex, *n*	77/50
median BMI (range), kg/m^2	22.3 (13.9–30.5)
alcohol drinking[a], *n* (%)	13 (10.2%)
smoking[b], *n* (%)	81 (63.8%)
past history of DM, *n* (%)	35 (27.6%)
past history of acute pancreatitis, *n* (%)	12 (9.4%)
family history of pancreatic cancer, *n* (%)	7 (5.5%)
CA19-9 ≥37 U/ml, *n* (%)	30 (23.6%)

BMI, body mass index; DM, diabetes mellitus; CA19-9, carbohydrate antigen 19-9.
[a] Alcohol intake ≥50 g/day.
[b] Smoking regularly in present or in the past.

Table 2
Morphologic and histologic characteristics of IPMN in this study.

	$n = 127$
Macroscopic type	
MD-IPMN, *n* (%)	18 (14.2%)
BD-IPMN, *n* (%)	60 (47.2%)
MX-IPMN, *n* (%)	49 (38.6%)
Imaging Findings	
main tumor (cyst) located in head, *n* (%)	83 (65.4%)
cyst size ≥3 cm, *n* (%)	72 (56.7%)
multifocal lesions, *n* (%)	56 (44.1%)
MPD size ≥10 mm, *n* (%)	39 (30.7%)
5–9 mm, *n* (%)	40 (31.5%)
<5 mm, *n* (%)	48 (37.8%)
pancreas atrophy, *n* (%)	36 (28.3%)
Risk Classification according to ICG 2017	
HRS, *n* (%)	57 (44.9%)
WF, *n* (%)	64 (50.4%)
others, *n* (%)	6 (4.7%)
Histologic Findings (Final Diagnosis)	
low-grade dysplasia, *n* (%)	56 (44.1%)
high-grade dysplasia, *n* (%)	35 (27.6%)
invasive carcinoma, *n* (%)	36 (28.3%)

MD-IPMN, main duct intraductal papillary mucinous neoplasm; BD-IPMN, branch duct IPMN; MX-IPMN, mixed type IPMN; MPD, main pancreatic duct; HRS, high-risk stigmata; WF, worrisome feature.

Discussion

The major findings of this study are as follows. First, PJC could increase the accuracy of WF. Second, the sensitivity and accuracy of PJC could be increased by obtaining additional samples of pancreatic juice under ERCP, as well brush cytology and repeated PJC via the ENPD tube. Third, ENPD placement in IPMN patients with a non-dilated MPD was a significant risk factor for PEP. The present study is the first to evaluate the efficacy of PJC with a very large number of surgically resected patients who underwent preoperative PJC. We assessed the efficacy of PJC for risk classification of IPMN according to ICG 2017, and the advantages and disadvantages of the PJC procedure in detail, utilizing only surgical cases.

Our results showed that the sensitivity and specificity of HRS/WF for classifying malignant IPMN were 59.2%/35.2% and 73.2%/30.4%, respectively. Many previous studies reported similar results [5,6]. Preoperative diagnosis based on HRS or WF might mislead the diagnosis of malignant IPMN in IPMN patients. HRS or WF alone has limited diagnostic ability for determining the appropriate surgical indication. On the other hand, the sensitivity and specificity of PJC alone for classifying malignant IPMN was 43.5% and 75.0%, respectively, and was thus also insufficient for determining the surgical indication. The specificity of HRS and WF was markedly increased by adding PJC (HRS to HRS + positive PJC: 73.2%–96.4%, WF to WF + PJC positive: 30.4%–80.4%). The accuracy of WF was also increased (WF to WF + positive PJC: 33.1%–48.8%). The accuracy of HRS was not increased (HRS to HRS + positive PJC: 65.4%–52.8%), however, because of a remarkable decrease in its sensitivity. These results suggest that PJC would add less value to HRS, although IPMN patients with both HRS and positive PJC should be strongly encouraged to undergo pancreatic surgery. The additional

Table 3
Effect of PJC on the diagnostic ability of risk classification for malignant IPMN.

	Diagnostic ability for malignant IPMN				
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
HRS	59.2 (42/71)	73.2 (41/56)	73.7 (42/57)	58.6 (41/70)	65.4 (83/127)
WF	35.2 (25/71)	30.4 (17/56)	39.1 (25/64)	27.0 (17/63)	33.1 (42/127)
positive PJC	43.5 (30/69)	75.0 (42/56)	68.2 (30/44)	51.9 (42/81)	57.6 (72/125)
Combination of risk classification and PJC					
HRS and positive PJC	17.4 (12/69)	96.4 (54/56)	85.7 (12/14)	48.6 (54/111)	52.8 (66/125)
HRS and/or positive PJC	84.1 (58/69)	51.6 (29/56)	68.2 (58/85)	72.5 (29/40)	69.6 (87/125)
WF and positive PJC	23.2 (16/69)	80.4 (45/56)	59.3 (16/27)	45.9 (45/98)	48.8 (61/125)

IPMN, intraductal papillary mucinous neoplasm; HRS, high-risk stigmata; WF, worrisome feature; PJC, pancreatic juice cytology; PPV, positive predictive value; NPV, negative predictive value.

Table 4
Details of cytology procedure in 125 IPMN patients who underwent PJC.

	$n = 125$
Cytology Procedure	
only one-time sampling, *n* (%)	35 (28.0%)
brush cytology, *n* (%)	83 (66.4%)
SPACE, *n* (%)	44 (35.2%)
Histologic Findings	
positive PJC, *n* (%)	44 (35.2%)
true-positive PJC, *n* (%)	30 (24.0%)

PJC, pancreatic juice cytology; SPACE, serial pancreatic-juice aspiration cytologic examination.

Table 6
Risk factors for PEP in IPMN patients.

	PEP (n = 32)	**Non-PEP (n = 95)**	***P*-value**
female sex	18/32 (56.3%)	32/95 (33.7%)	0.03
median BMI (range), kg/m^2	23.5 (16.8–30.5)	22.1 (13.9–30.0)	0.0006
pancreas atrophy	4/32 (13.3%)	32/95 (34.8%)	0.02
MPD size of <5 mm	16/32 (50.0%)	32/95 (33.7%)	0.10
ENPD placement	17/32 (53.1%)	27/95 (29.0%)	0.02

PEP, post-ERCP pancreatitis; BMI, body mass index; MPD, main pancreatic duct; ENPD, endoscopic naso-pancreatic drainage.

value of PJC to WF is also limited because it cannot rule out malignant IPMN due to the low sensitivity of WF + PJC (23.2%). On the other hand, this study showed that the sensitivity of HRS and/or positive PJC for classifying malignant IPMN was high (84.1%). Considering the low sensitivity of HRS alone for classifying malignant IPMN (59.2%), negative PJC might increase the validity of a follow-up strategy without surgery for IPMN patients with non-HRS.

The present study showed that the sensitivity and accuracy of positive PJC for classifying malignant IPMN was increased by performing one-time sampling of the pancreatic juice under ERCP as well as brush cytology and SPACE in IPMN patients. Brush cytology and SPACE are effective in patients with pancreatic cancer.[7] Our results indicate that those procedures might also be effective in IPMN patients. However, adding SPACE might increase the frequency of PEP.

PEP is the most serious complication of ERCP, and IPMN is reported to be a risk factor for PEP [14,15]. This study demonstrated that the PEP frequency was high (25.2%) and that female sex, obesity, and ENPD placement are significant risk factors for PEP. Female sex and obesity are already known as general risk factors for PEP [16,17]. Our study suggests that these general PEP risk factors might be risk factors for PEP in IPMN patients. In addition, ENPD placement was confirmed to be a significant risk factor for PEP in our study. In all PEP patients with ENPD placement, removal of the ENPD tube immediately improved symptoms and reduced the serum pancreatic enzyme levels. These findings indicate that mucus produced by IPMN might impede the flow of pancreatic juice via the ampulla and ENPD tube. An examination of 44 patients with ENPD placement revealed that an MPD size <5 mm was a significant risk factor, in addition to obesity and past history of acute pancreatitis. According to these results, IPMN patients with a non-dilated MPD and the general risk factors for PEP may be ineligible for ENPD placement.

Strengths of our study include the very small number of missing data-points because the preoperative information was collected prospectively; therefore, the rate of missing items was less than 5% for all variables. In addition, this study included only patients who underwent surgery and a relatively large number of PJC cases. Our study also has several limitations. First, because this study was retrospective, the PJC procedures, including only one-time sampling of pancreatic juice under ERCP, brush cytology, and SPACE, differ depending on the era. Second, the details of the ERCP procedure in relation to PEP, such as operator, cannulation time, and trainee involvement, could not be investigated, although ERCP was performed based on a fixed rule in our hospital. Third, the specificity of PJC for malignant IPMN (75.0%) was low because our study defined not only “malignant” but also “suspicious” as positive. In the clinical setting, it is difficult to distinguish malignant IPMN from IPMA and diagnose “malignant” clearly by cytodiagnosis, which leads to an increase in the diagnosis of “suspicious”. Therefore, in most cases of “suspicious”, surgery would be recommended.

Table 5
Diagnostic abilities of PJC and PEP frequency stratified based on cytology procedure for malignant IPMN.

	Diagnostic ability for malignant IPMN						PEP frequency
	n (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	*n* (%)
one-time sampling only	35 (28.0%)	5.9 (1/17)	94.4 (17/18)	50.0 (1/2)	51.5 (17/33)	51.4 (18/35)	7 (20.0%)
one-time sampling + brush cytology	46 (36.8%)	52.0 (13/25)	61.9 (13/21)	61.9 (13/21)	52.0 (13/25)	56.5 (26/46)	8 (17.4%)
one-time sampling + SPACE	7 (5.6%)	33.3 (2/6)	100.0 (1/1)	100.0 (2/2)	20.0 (1/5)	42.9 (3/7)	2 (28.6%)
one-time sampling + brush cytology + SPACE	37 (29.6%)	66.7 (14/21)	68.8 (11/16)	73.7 (14/19)	61.1 (11/16)	67.6 (25/37)	15 (40.5%)

IPMN, intraductal papillary mucinous neoplasm; PJC, pancreatic juice cytology; PEP, post-ERCP pancreatitis; PPV, positive predictive value; NPV, negative predictive value; SPACE, serial pancreatic-juice aspiration cytologic examination.

Table 7
Risk factors for PEP in 44 IPMN patients with ENPD placement.

	PEP (n = 17)	Non-PEP (n = 27)	*P*-value
median BMI (range), kg/m^2	25.3 (16.8–29.2)	22.0 (17.9–27.8)	0.008
past history of acute pancreatitis	5/17 (29.4%)	0/27 (0%)	0.001
MPD size of <5 mm	8/17 (47.1%)	4/27 (14.8%)	0.02

PEP, post-ERCP pancreatitis; ENPD, endoscopic naso-pancreatic drainage; BMI, body mass index; MPD, main pancreatic duct.

Considering the clinical situation, our data which defined "suspicious" as positive cytology would be suitable for practical application.

In conclusion, PJC could increase the accuracy of WF for classifying malignant IPMN. The additive effect of PJC for risk classification, however, may be limited. PJC, especially ENPD, is not recommended for all IPMN cases due to the high frequency of PEP.

Conflicts of interest

All authors declare no conflicts of interest for this article.

Author contributions

K.Y collected and analyzed data and wrote the manuscript. A.M designed the study concept, analyzed data, and wrote the manuscript. T.N, H.S, H.T, M.T, A.S, T.K, M.T, S.A, Y.Y, T.T, S.T, R.N, Y.S, T.I, M.K, and S.F collected and analyzed data. H.K, T.I, T.F, and Y.K were involved in study supervision and revised the manuscript.

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