学位論文　博士（医学）甲

Carcinoembryonic antigen level in the pancreatic juice is effective in malignancy diagnosis and prediction of future malignant transformation of intraductal papillary mucinous neoplasm of the pancreas
(膵 IPMN の悪性診断と将来的な悪性化予測における膵液中 CEA 値の有用性)

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Carcinoembryonic antigen level in the pancreatic juice is effective in malignancy diagnosis and prediction of future malignant transformation of intraductal papillary mucinous neoplasm of the pancreas

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Abstract

Background

The present study aimed to determine the ability of diagnosing malignancy and predicting malignant transformation in patients with IPMN using carcinoembryonic antigen (CEA) level in the pancreatic juice.

Methods

We enrolled patients with IPMN who underwent endoscopic retrograde pancreatography (ERP) between 2002 and 2018. We examined the ability of diagnosing malignancy in 63 patients who underwent surgery (surgical group). Furthermore, we examined the value of predicting malignant transformation in 52 patients who underwent follow-up for over 1 year after ERP (follow-up group).

Results

In the surgical group, the overall sensitivity and specificity of CEA level (≥97 ng/ml) in the pancreatic juice for diagnosing malignancy were 45% and 100%, respectively. The specificity was excellent for all IPMN types; however, the sensitivity was highest in main duct type, followed by mixed type and branch duct type.

In the follow-up group, malignant transformation was observed in four patients (7.7%) during the follow-up, and the median time until malignant transformation was 58 months.

High CEA level in the pancreatic juice demonstrated a statistically significant difference in multivariate analysis and was found to be an independent predictor of malignant transformation (hazard ratio 17; $P = 0.02$). The cumulative malignant transformation rate was significantly higher in the high CEA group than that in the low CEA group (5-year cumulative malignant transformation rates, 69% vs. 0%, $P < 0.001$).

Conclusions

CEA level in the pancreatic juice is useful not only in diagnosing malignancy but also in predicting future malignant transformations in IPMN patients receiving follow-up.

Keywords: Intraductal papillary mucinous neoplasm, Endoscopic retrograde pancreatography, Carcinoembryonic antigen, Pancreatic juice, Malignant transformation

Introduction

Intraductal papillary mucinous neoplasm (IPMN) presents a wide spectrum of atypia ranging from low-grade dysplasia (LGD) to invasive carcinoma. The international consensus guidelines were proposed in 2006 [1] and 2012 [2] and were subsequently followed by the most recent revisions of international consensus Fukuoka guidelines in 2017 [3]. In the current guidelines, “worrisome features” (WF) and “high-risk stigmata” (HRS) are classified based on imaging findings for stratifying the risk of malignancy. In the presence of WF, endoscopic ultrasonography (EUS) is recommended. However, EUS-FNA of IPMN concerned with peritoneal dissemination due to the leakage of cyst fluid and recurrence to the puncture rout [4, 5]. On the other hand, pancreatic juice cytology under endoscopic retrograde pancreatography (ERP) has low sensitivity, and the role of malignant IPMN in preoperative diagnosis is limited [6].

Studies concerning CEA level in the pancreatic juice in IPMN have reported that a CEA level in the pancreatic juice of >110 ng/ml suggests malignancy [7]. Subsequent reports indicate the usefulness of CEA level in the pancreatic juice for diagnosing malignancy of the branch duct type (BD) [8] and invasive intraductal papillary mucinous carcinoma (IPMC) in the mixed type and main duct type (MD) [9]. However, only few such reports exist, and further examination is warranted. Moreover, currently, there are

no reports regarding the usefulness of CEA level in the pancreatic juice in predicting future malignant transformation of IPMN.

In the present study, we examined the usefulness of CEA level in the pancreatic juice collected under ERP for diagnosing malignancy and predicting malignant transformation of IPMN in patients receiving follow-up examination.

Methods

Patients

This retrospective observational study enrolled patients with IPMN who underwent ERP for collecting pancreatic juice between March 2002 and March 2018. A flow chart of the study is presented in Figure 1. The present study was conducted with the approval of the ethical review board of University of Yamanashi.

We excluded 69 patients who had not assessed CEA level in the pancreatic juice, five patients with concomitant pancreatic carcinoma in IPMN and one patient with concurrent gallbladder carcinoma. We examined the diagnostic value of CEA level in the pancreatic juice in 63 patients who underwent surgery after the initial examination (surgical group). Furthermore, among the 67 patients who underwent a follow-up examination, we excluded seven patients with HRS at the initial examination and eight patients with a follow-up period of <1 year. Thus, the follow-up group comprised 52 patients who were

examined for predicting malignant transformation of IPMN.

ERP was performed using a duodenoscope (JF260V; Olympus Medical Systems, Tokyo, Japan), a cannula (MTW ERCP catheter; MTW Endoscopy, Wesel, Germany), and a 0.025-inch guidewire (RevoWave-SJ; Piolax Medical Devices Inc, Kanagawa, Japan). The cannula was guided into the main pancreatic duct. Over the guide-wire, 5Fr endoscopic naso-pancreatic drainage (ENPD) tube (GF Drainage Catheter Set; Gadelius Medical K. K., Tokyo, Japan) was inserted into the main pancreatic duct. The guidewire was then withdrawn, and pancreatic juice was collected using a syringe. Cases with high risk of PEP for abundant mucin or high possibility of self removal of ENPD tube were collected pancreatic juice with the cannula. Pancreatic juice was centrifuged at 3500 rpm for 5 minutes, the supernatant (10μL) was used for measuring the CEA concentration. CEA levels were determined with an electrochemiluminescence immunoassay (ECLIA). The severity of post-ERCP pancreatitis (PEP) was defined by Cotton's criteria [10].

The international consensus guidelines 2017 define HRS as obstructive jaundice caused by a cystic lesion, contrast-enhanced nodule diameter of ≥5 mm, and main pancreatic duct diameter of ≥10 mm. Pathological diagnosis was performed in accordance with the 2010 WHO classification and the Baltimore consensus meeting, which defined LGD as benign and high-grade dysplasia (HGD) and invasive IPMN as malignant [11, 12]. Malignant

transformation was defined as that presenting the pathological findings of HGD or invasive IPMN in patients who underwent surgery, biopsy, or cytology during follow-up[13]. Pancreatic juice cytology was classified as class I–V according to the degree of structural and cytological dysplasia, in which class IV and V were defined as positive [14]. Information pertaining to patient background, imaging findings, and pathological findings were collected from the electronic medical record system. The size of branch cyst and main pancreatic duct diameter were measured using CT or MRI, whereas mural nodules were assessed using EUS. Surgery is indicated for the following criteria according to the international guideline: obstructive jaundice, diameter of the main pancreatic duct ≥ 10mm, presence of contrast-enhanced nodules (CT), mural nodules measuring ≥5 mm (EUS), progression within the main pancreatic duct, positive pancreatic juice cytology, and recurrent mucinous pancreatitis.

IPMN was classified into BD type, MD type, and mixed type based on the form observed on imaging in accordance with the guidelines[3]. The BD type was defined as branch duct dilatation (≥5 mm) communicating with the main pancreatic duct without main pancreatic dilatation (<5 mm); the MD type as the main pancreatic duct dilatation (≥5 mm) without branch duct dilatation (<5 mm); and the mixed type as the main pancreatic duct dilatation (≥5 mm) with branch duct dilatation (≥5 mm) communicating with the main pancreatic

duct.

Diagnosis of malignancy using CEA level in the pancreatic juice

We examined the ability of diagnosing malignancy using CEA level in the pancreatic juice in 63 patients with IPMN who underwent surgery after diagnosis and for whom a pathological diagnosis was obtained. The cut-off value for CEA level in the pancreatic juice was determined using a receiver operating characteristic (ROC) curve (Youden index).

Predicting malignant transformation using CEA level in the pancreatic juice

We examined the predictive value of malignant transformation of IPMN using CEA level in the pancreatic juice in 52 patients who underwent a follow-up for >1 year after ERP. We excluded patients for whom the follow-up period was <1 year and who presented HRS at the initial examination. The cut-off value for the high or low CEA group in the pancreatic juice was the value set in the analysis of diagnosing malignancy.

Statistical analysis

ROC curve analysis was used to determine the cut-off value for CEA level in the pancreatic juice. Univariate analysis of factors associated with malignant transformation

was performed using a chi squared test. For multivariate analysis and hazard ratio, the Cox proportional hazards model was used. The cumulative malignant transformation rate for the high CEA level group and low CEA level group was examined using the Kaplan–Meier method, and a comparison between the two groups was performed using the log rank test. All statistical analyses were performed with BellCurve for Excel software (version 2.20; Social Survey Research Information Co., Ltd., Tokyo, Japan). Statistical significance was set at $P < 0.05$.

Result

Between March 2002 and March 2018, there were a total of 1,066 patients with IPMN. Of these, 121 underwent surgery, and the remaining 945 patients received follow-up observation. One hundred ninety-one patients with IPMN underwent ERP for collecting pancreatic juice. Of these patients, pancreatic cannulation failed in 7 patients (3.7%). Twenty-two patients (11.5%) developed PEP. Severity was mild in 21 patients and moderate in 1 patient. There was no severe patient. All cases were improved with conservative treatment.

Diagnosing malignancy using CEA level in the pancreatic juice in patients

undergoing resection

Characteristics of patients in the surgical group are presented in Table 1. Patients in the surgical group had a median age (range) of 69 (37–83) years and included 43 men and 20 women. The distribution of IPMN type was as follows: BD type in 18 patients, MD type in 10 patients, and mixed type in 35 patients. The median size (range) of branch cyst was 27 (0–139) mm, median main pancreatic duct diameter (range) was 6 (1.2–33) mm, median nodule size (range) was 5.5 (0–25) mm, and median CEA level in the pancreatic juice (range) was 22.6 (1.2–25991) ng/ml. Pancreatic juice cytology was positive in nine patients (15%). The pathological diagnosis was LGD in 32 patients (51%), HGD in 16 patients (25%), and invasive IPMC in 15 patients (24%).

The ROC curve of patients in the surgical group are presented in Supplementary figure 1. CEA level in the pancreatic juice for diagnosing malignancy was set at 97 ng/ml. The AUC level was 0.69. The information about the ability of diagnosing malignancy using CEA level in the pancreatic juice in the surgical group is presented in Table 2. The sensitivity, specificity, and accuracy of CEA level in the pancreatic juice for diagnosing malignancy were 45% (14/31), 100%, and 73% (46/63) for all patients (n = 63); 29% (2/7), 100%, and 72% (13/18) for BD type (n = 18); 44% (7/16), 100%, and 74% (26/35) for mixed type (n = 36); and 63% (5/8), 100%, and 70% (7/10) for the MD type (n = 10),

respectively. The specificity was 100% for all types, whereas the sensitivity was high in the MD type, followed by the mixed type and BD type. Univariate and multivariate analysis of predictors of malignancy in the surgical group showed that mural nodule size of ≥5mm (OR, 4.99; 95% CI, 1.34–18.6; P = 0.017) and high CEA levels in the pancreatic juice (≥97 ng/ml) (OR, 1.02; 95% CI, 1.00–1.04; P = 0.046) were independent predictors of malignancy (Supplementary Table 1).

Predicting malignant transformation using CEA level in the pancreatic juice

Characteristics of the patients in the follow-up group are presented in Table 1. Patients in the follow-up group had a median age (range) of 69 (53–85) years and included 28 men and 24 women. The distribution of IPMN type was as follows: the BD type in 33 patients (63%), MD type in 3 patients (6%), and mixed type in 16 patients (31%). The median (range) size of the branch cyst was 30 (0–62) mm, median main pancreatic duct diameter (range) was 3.3 (0–9) mm, median nodule diameter (range) was 0 (0–4) mm, and the median CEA level (range) in the pancreatic juice was 14.5 (0.5–3521) ng/ml. Results of pancreatic juice cytology were negative in all patients. The median follow-up period (range) was 59 (13–117) months, and malignant transformation during the follow-up was observed in four patients (7.7%). The median period (range) until malignant

transformation was 58 (23–90) months.

Four patients with malignant transformation are presented in Table 3. At the initial examination, MD dilatation (≥5 mm) was observed in three patients (75%) and mural nodules were observed in two patients (50%). CEA level in the pancreatic juice was elevated (≥97 ng/ml) in three of the four patients (75%) with malignant transformation. Among the three patients who underwent surgery, HGD was observed in two patients and invasive IPMC in one. Surgical resection was not performed in one patient owing to advanced age. However, the observation of an invasive mass with the main pancreatic duct dilatation on CT and adenocarcinoma in pancreatic juice cytology led to the diagnosis of invasive IPMN.

Univariate and multivariate analyses of predictors of malignant transformation are presented in Table 4. High CEA level in the pancreatic juice (≥97 ng/ml) showed a statistically significant difference in both univariate ($P < 0.01$) and multivariate analyses (HR 17.0; 95% CI, 1.5–192; $P = 0.02$). This parameter was found to be an independent predictor of malignant transformation.

The cumulative HRS and malignant transformation rates for the high CEA level (≥97 ng/ml) and low CEA level (<97 ng/ml) groups are presented in Figure 2A and 2B. The cumulative HRS and malignant transformation rates were significantly higher for the high

CEA group than those for the low CEA group (5-year cumulative HRS and malignant transformation rates, 75% vs. 6%, $P < 0.001$; 69% vs. 0%, $P < 0.001$), respectively.

The 69-year-old male patient with high CEA level (3521 ng/ml) in the pancreatic juice at initial examination showed malignant transformation in the follow-up period. At the initial examination, the duct of Santorini was dilated with a diameter of 6 mm (Figure 3a). This patient had no HRS finding on imaging and negative pancreatic juice cytology. Fifty-five months later, the duct of Santorini diameter increased to 11 mm (Figure 3b). Surgery was performed and pathological examination revealed HGD.

The 62-year-old male patient with low CEA level (23 ng/ml) in the pancreatic juice at the initial examination have not shown malignant transformation in the follow-up period. At the initial examination, the size of the branch cyst was 33 mm and the diameter of the main pancreatic duct was 5 mm (Figure 3c). This patient had no HRS finding on imaging and negative pancreatic juice cytology. Sixty-six months later, no changes were observed on imaging findings compared with those at the initial examination (Figure 3d). The patient continues to receive follow-up.

Discussion

In the present study, we examined the value of CEA level in the pancreatic juice for

diagnosing malignancy in the surgical group and for predicting future malignant transformation in the follow-up group. In the surgical group, when the cut-off value for CEA level in the pancreatic juice was set to 97 ng/ml, specificities were high for all IPMN types. In the follow-up group, malignant transformation was observed in 4 out of 52 patients (7.7%) during the follow-up (median 59 months), and high CEA level in the pancreatic juice was an independent predictor of malignant transformation. The cumulative malignant transformation rate was significantly higher for the high CEA level group than that for the low CEA level group.

Reportedly, CEA is secreted from the mucosal epithelium of IPMN, which is probably the mechanism underlying the elevation of CEA levels in the pancreatic juice [15]. In invasive IPMN, CEA immunostaining is positive at a high frequency [16]; therefore malignant transformation of IPMN is likely to cause increased CEA secretion in the pancreatic juice.

In the previous reports on preoperative diagnosis of IPMN, Hirono et al. noted that the measurement of CEA level in the pancreatic juice is a useful diagnostic method to distinguish malignant from benign IPMNs. When the cut-off value was set to 110 ng/ml, they diagnosed malignancy with a sensitivity of 67% and specificity of 96% [7]. In the current study, the cut-off value and high specificity were consistent with those reported

by a previous study [7]. The sensitivity for diagnosing malignancy was the highest for the MD type and lowest for the BD type. This result is possibly because CEA secreted from the tumor of the main pancreatic duct is directly collected in MD-IPMN, whereas a part of CEA produced from a tumor in the branch duct flows into the main pancreatic duct and is collected in BD-IPMN.

To the best of our knowledge, there are no reports on the association between CEA level in the pancreatic juice and of future malignant transformation of IPMN. In reports examining the natural history of BD-IPMN, the malignant transformation rate during the follow-up observation ranged from 1%–6.3% [13, 17-19]. Moreover, mural nodules and tumor extension within MD at the initial examination are associated with malignant transformation of the lesion. Furthermore, in mixed type and MD type, the malignant transformation rate during follow-up is 13%–46%. Additionally, the size of MD dilatation and diffuse MD dilatation are associated with malignant transformation [20-22]. In the present study, we examined predictors of malignant transformation in all IPMN types. High CEA level in the pancreatic juice was the only independent predictor of malignant transformation; however, mural nodules and the main pancreatic duct diameter are not associated with malignant transformation. This result suggests that CEA level in the pancreatic juice is a better predictor of malignant transformation than imaging findings.

In the current guidelines, the risk of malignant transformation is stratified according to imaging findings, whereby examination modality and intervals are defined. However, the results of the present study indicate that CEA level in the pancreatic juice can detect the risk of malignant transformation that cannot be perceived in imaging findings, thus enabling the identification of groups at high risk of future malignant transformation.

In previous reports examining CEA levels in the pancreatic juice, the cut-off value was set using ROC analysis; however, no reports examined the validity of the cut-off values in independent subjects (validation group), and the reproducibility remains unclear. In the present study, the cut-off value was set at 97 ng/ml based on the ROC analysis in the surgical group, and the same value was used for the follow-up group for predicting malignant transformation. As a result, the rate of malignant transformation was significantly higher in the high CEA group, demonstrating a high potential for malignancy. These findings served to validate the cut-off value of CEA level in the pancreatic juice for the prediction of malignant potential of IPMNs and proved to be reproducible. However, because there is a risk of PEP, patients who undergo pancreatic juice sampling should be selected carefully. Based on the results of this study, we believe that mixed and MD types are good indications for CEA measurement in pancreatic juice. In contrast, the BD type is not a good indication because CEA secreted from a tumor is unlikely to flow

into the main pancreatic duct.

The present study has several limitations. First, this was a single-center, retrospective observational study with a small sample size. Second, a selection bias may have occurred concerning patient background and the indication of examination and surgery. Third, small number of patients with malignant transformation was limitation of this study. However, the multivariate analysis showed that CEA in the pancreatic juice was statistically significant predictor of future malignant transformation in the follow-up group, and there was a clear difference in the five-year cumulative malignant transformation rate “69% vs. 0%”. Therefore, we believe that these are reliable results. Further large studies are warranted to confirm these results.

In conclusion, measuring CEA level in the pancreatic juice is useful for diagnosing malignancy in IPMN and for predicting the risk of malignant transformation during follow-up.

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Figure legends

Figure 1

Flowchart of case selection in this study

Figure 2

a. Progress rate to HRS in patients from the high CEA group (n = 6) and low CEA group (n = 46)

b. Malignant transformation rate in patients from the high CEA group (n = 6) and low CEA group (n = 46)

Figure 3

Clinical course of patients with high and low CEA levels in the pancreatic juice

The patients with high CEA level (3521 ng/ml) in the pancreatic juice: at the initial examination (3a), the duct of Santorini was dilated with a diameter of 6 mm. The patients demonstrated negative results for HRS and pancreatic juice cytology. Fifty-five months later (3b), the main pancreatic duct diameter increased to 11 mm (HRS transformation); subsequently, surgery was performed. Pathological diagnosis revealed HGD.

The patients with low CEA level (23 ng/ml) in the pancreatic juice: at the initial

examination (3c), the size of the branch cyst was 33 mm and the diameter of the main pancreatic duct was 5 mm. The patients demonstrated negative results for HRS and pancreatic juice cytology. Sixty-six months later (3d), no changes were noted in imaging findings compared with those at the initial examination. The patient continues to receive follow-up.

Supplementary figure 1

The receiver operating characteristic curve used to determine the CEA cut off levels in the pancreatic juice of patients in the surgical group. The cut-off value was determined using Youden index. The area under the curve level was 0.69. The cut-off level for diagnosing malignancy was set at 97 ng/ml.

Table 1. Patient Characteristics

Characteristics	Surgical group No. (%) (n=63)	Follow-up group No. (%) (n=52)
Age (years) ,median (range)	69 (37-83)	69 (53-85)
Sex,male	43 (68)	28 (54)
Symptom,presence	10 (16)	3 (6)
Abdominal pain	6 (10)	3 (6)
Jaundice	2 (3)	0 (0)
Body weight loss	2 (3)	0 (0)
Diabetes	16 (26)	16 (31)
Pancreatitis	4 (6)	1(2)
Smoking	28 (54)[a]	25 (53)[b]
Family History of pancreatic cancer	2 (4)[c]	4 (9)[d]
Serum tumor marker		
Eleveted CEA	12 (19)	7 (13)
Eleveted CA19-9	8 (13)	4 (8)
Location of tumor		
Head	26 (41)	33 (63)
Body/tail	33 (49)	15 (29)
Diffuse	6 (10)	4 (8)
Morphological type		
Branch duct	18 (29)	33 (63)
Main duct	10 (15)	3 (6)
Mixed	35 (56)	16 (31)
Pathological diagnosis		
Low grade dysplasia	32 (51)	2 (4)
High grade dysplasia	16 (25)	2 (4)
Invasive IPMN	15 (24)	1 (2)
NA	0 (0)	47 (90)
Size of branch cyst, median (range) , mm	27 (0-139)	30 (0-62)
Diameter of main pancreatic duct, median (range) , mm	6 (1.2-33)	3.3 (0-9)
Size of mural nodule, median (range) , mm	5.5 (0-25)	0 (0-4)
CEA levels in the pancreatic juice, median (range) , ng/ml	22.6 (1.2-25991)	14.5 (0.5-3521)
Pancreatic juice cytology, ClassⅣ/Ⅴ	9 (15)[e]	0 (0)
Follow-up Period, median (range) , month	NA	59 (13-117)

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; NA, not applicable.

[a] Of 52 patients. [b] Of 47 patients. [c] Of 48 patients. [d] Of 43 patients. [e] Of 61 patients.

Table 2. The ability of diagnosing malignancy with CEA level in the pancreatic juice in the surgical group*

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Overall (n=63)	45	100	100	65	73
Branch duct type (n=18)	29	100	100	69	72
Mixed type (n=35)	44	100	100	68	74
Main duct type (n=10)	63	100	100	40	70

PPV, positive predictive value; NPV, negative predictive value; HGD, high grade dysplasia

CEA, carcinoembryonic antigen

*CEA cut off value, 97 ng/ml

Table 3. Patients with malignant transformation

Case	1	2	3	4
Age, year	62	68	80	70
Sex	Male	Female	Male	Male
Morphological type	Branch duct	Mixed	Main duct	Mixed
Location of tumor	Head	Head	Diffuse	Head
Size of branch cyst, mm	35	13	4	26
Diameter of main pancreatic duct, mm	4	9	9	8
Size of mural nodule, mm	4	0	4	0
CEA levels in the pancreatic juice, ng/ml	80	154	161	3521
Time to malignant transformation, month	90	45	23	58
Pathological diagnosis	Invasive IPMN	HGD	Adenocarcinoma in cytology*	HGD

* Surgical resection was not performed owing to advanced aged.

HGD, high grade dyaplasia; CEA, carcinoembryonic antigen

Table 4. Factors associated with malignant transformation in the follow-up group

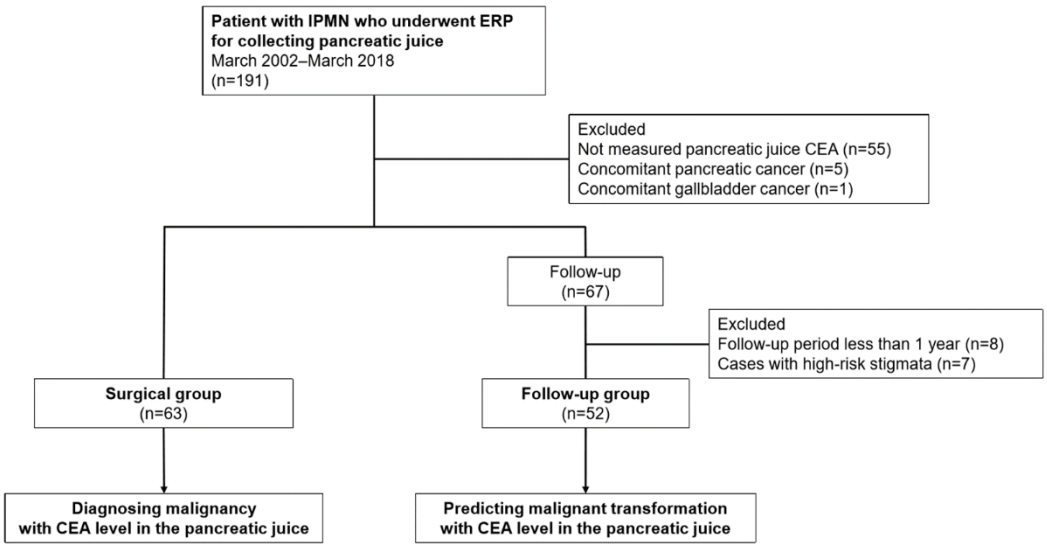
Characteristic		Malignant transformation Yes (n=4)	No (n=48)	Univariate Analysis P Value	Multivariate Analysis P Value	Hazard Ratio (95%CI)
Age, year	≥75	1	15	0.94	NA	NA
	< 75	3	33			
Sex	Male	3	25	0.33	NA	NA
	Female	1	23			
Location of tumor				0.42	NA	NA
	Head	3	30			
	Body/tail	0	15			
	Diffuse	1	3			
Size of branch cyst, mm	≥30	1	30	0.14	0.35	0.23 (0.01–5.1)
	< 30	3	18			
Diameter of main pancreatic duct size, mm	≥5	3	16	0.17	0.39	4 (0.17–96)
	< 5	1	32			
Presence of mural nodule (< 5mm)	Yes	2	13	0.6	NA	NA
	No	2	35			
CEA levels in the pancreatic juice, ng/ml	≥97	3	3	< 0.01	0.02	17 (1.5–192)
	< 97	1	45			

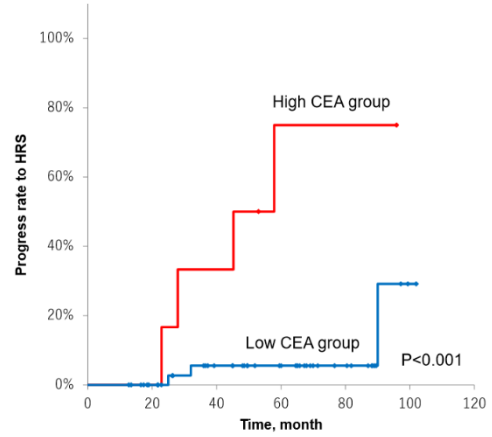
CEA, carcinoembryonic antigen; HGD, high grade dysplasia; NA, not applicable

Supplementary Table 1. Factors associated with the malignancy of surgical group at initial diagnosis

Characteristic		Malignancy		Univariate Analysis P Value	Multivariate Analysis P Value	Odds Ratio (95%CI)
		Yes (n=31)	No (n=32)			
Age, year	≥75	13	8	0.19	0.85	NA
	< 75	18	24			
Sex	Male	20	23	0.6	NA	NA
	Female	11	9			
Location	Ph	15	14	0.8	NA	NA
	Pb/Pt	16	18			
Diameter of main pancreatic duct size, mm	≥5	25	19	0.1	0.16	NA
	< 5	6	13			
Size of mural nodule, mm	≥5	22	12	0.011	0.017	4.99 (1.34-18.6)
	< 5	9	20			
CEA levels in the pancreatic juice, median (range), ng/ml		63 (1.2-25991)	16.1 (1.8-87)	0.01	0.046	1.02 (1.00-1.04)

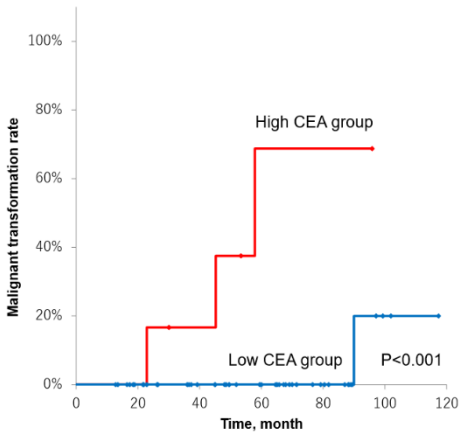
CEA, carcinoembryonic antigen; NA, not applicable


Patient with IPMN who underwent ERP for collecting pancreatic juice
March 2002–March 2018
(n=191)
Excluded
Not measured pancreatic juice CEA (n=55)
Concomitant pancreatic cancer (n=5)
Concomitant gallbladder cancer (n=1)
Follow-up
(n=67)
Excluded
Follow-up period less than 1 year (n=8)
Cases with high-risk stigmata (n=7)
Surgical group
(n=63)
Follow-up group
(n=52)
Diagnosing malignancy with CEA level in the pancreatic juice
Predicting malignant transformation with CEA level in the pancreatic juice



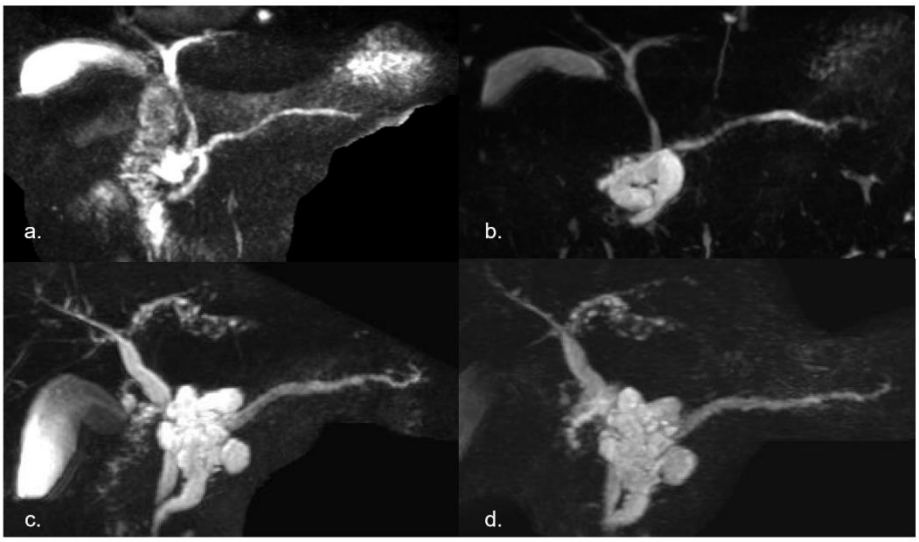
No at risk

High CEA	6	6	4	1	1	0	0
Low CEA	46	40	29	21	12	2	0



No at risk

High CEA	6	5	4	1	1	0	0
Low CEA	46	40	31	23	13	3	0


a.
b.
c.
d.