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SYSTEMATIC REVIEWS AND META-ANALYSES

Clinicopathological features and surgical outcomes of intraductal tubulopapillary neoplasm of the pancreas: a systematic review

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Abstract
Background and aims Intraductal tubulopapillary neoplasms (ITPNs) of the pancreas are rare. The purpose of this study was to collate and analyze published data on ITPNs of the pancreas to determine the clinicopathological features of the tumors and the surgical outcomes of patients.
Patients and methods We searched MEDLINE and Igakuchuo-Zasshi for the period of 1980 to 2015 for case reports on surgical resection for ITPN of the pancreas. We evaluated the clinicopathological data associated with pancreatic ITPNs, the prognosis for each patient, and surgical outcomes described in the case reports.
Results We obtained clinicopathological data for 58 patients (33 men and 25 women) with a mean age of 61 years (range, 35–84 years) who had undergone surgical resection for ITPN of the pancreas, including one patient from our clinic. Although ITPNs of the pancreas have different clinicopathological features to intraductal papillary mucinous neoplasms, the treatment strategy for patients with ITPNs is the same as for patients with other cystic neoplasms of the pancreas. The immunohistochemical features of ITPNs included testing positive for cytokeratin 7 and/or cytokeratin 19 and negative for trypsin, MUC2, MUC5AC, and fascin. The overall 1-, 3-, and 5-year survival rates after surgery for the 37 cases with available data were 97.3, 80.7, and 80.7 %, respectively.
Conclusion Surgical treatment is the only curative management option for patients with ITPN of the pancreas. To determine the best management strategy for this tumor and improve accuracy of prognosis for patients, we will continue to collect and analyze epidemiological and pathological data.

Keywords Pancreas · Intraductal tubulopapillary neoplasm · Intraductal papillary mucinous neoplasm · Computed tomography · Magnetic resonance imaging

Introduction

Intraductal tubulopapillary neoplasms (ITPNs) of the pancreas are very rare tumors that are characterized by intraductal tubulopapillary growth, ductal differentiation, scant intracellular mucin production, and cellular dysplasia. ITPNs are estimated to account for <1 % of all pancreatic exocrine tumors and 3 % of all pancreatic intraductal neoplasms [1, 2]. ITPN was first described in 2009 [2], and according to 2010 World Health Organization classification, there are two subtypes of intraductal neoplasms of the pancreas: intraductal papillary mucinous neoplasms (IPMNs) and ITPNs [1]. ITPNs include intraductal tubular carcinomas and are defined as grossly visible and tubule-forming epithelial neoplasms with high-grade dysplasia and ductal differentiation without overt production of mucin [1]. If a lesion has a component of invasive carcinoma, it is referred to as an "ITPN with an associated invasive carcinoma" [1].

We conducted a retrospective analysis of published cases of ITPN of the pancreas to determine the clinicopathological features of the tumors and the surgical outcomes, including survival rates, for patients with these tumors.

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Method

Eligibility criteria

The reporting of this systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [3]. Observational studies written in English or written in Japanese with an English abstract were eligible for inclusion. There were no limitations regarding the date of publication of the included studies. Only articles for which full-text versions could be retrieved were included. For a study to be suitable for the qualitative synthesis, it had to contain information on patients being surgically treated for ITPN of the pancreas. In addition, the study had to describe a defined follow-up period exceeding the primary hospital stay, in which there had to be assessment of the patients' prognosis after surgical management. Any study not meeting the above-mentioned requirements was not eligible for inclusion.

Literature search

A literature search was performed using the following terms: "intraductal tubulopapillary neoplasms," "pancreas," and "intraductal neoplasm without mucin." The latter are now defined as ITPNs. The following databases were searched from 2009 to 2015 for case reports on surgical resection for ITPN of the pancreas: MEDLINE and Igakuchuo-Zasshi (a database of Japanese articles with English abstracts). Studies were included regardless of publication status. Studies in the reference lists of the retrieved articles, including relevant systematic reviews, were also searched.

After carefully reading articles in detail, cases of intraductal neoplasm without mucus that were published before 2009, when the term "intraductal tubulopapillary neoplasm" was introduced, were considered ITPNs. This enabled us to collect and analyze more clinical data, although retrospective rediagnosis of patients is not ideal.

Data collection and assessment

To collect data, a standard data extraction form was developed. Information from included studies was systematically extracted and added to a customized Microsoft Excel spreadsheet. We extracted data on the following: patient demographics, including age and sex; tumor location and size; type of operation; and survival times. We also extracted data on the published prognosis for each patient.

Statistical analysis

Survival rates were generated using the Kaplan–Meier method and compared using the log-rank test. All analyses were performed using SPSS® (SPSS Inc, Chicago, IL). Values are expressed as mean ± standard deviation. P values <0.05 were considered statistically significant.

Results

Patient treated in our clinic

A 54-year-old woman with upper abdominal pain and anorexia was admitted to our hospital for examination and treatment of a developing abdominal cyst. Levels of tumor markers, including carcinoembryonic antigen and carbohydrate 19-9, were within normal ranges. Abdominal plain computed tomography (CT) revealed a cystic lesion in the head of the pancreas (Fig. 1a). Contrast-enhanced abdominal CT showed a cystic mass with a maximum diameter of 43 mm in the head of the pancreas, which seemed to contain mural nodule components (Fig. 1b). On magnetic resonance imaging (MRI), the

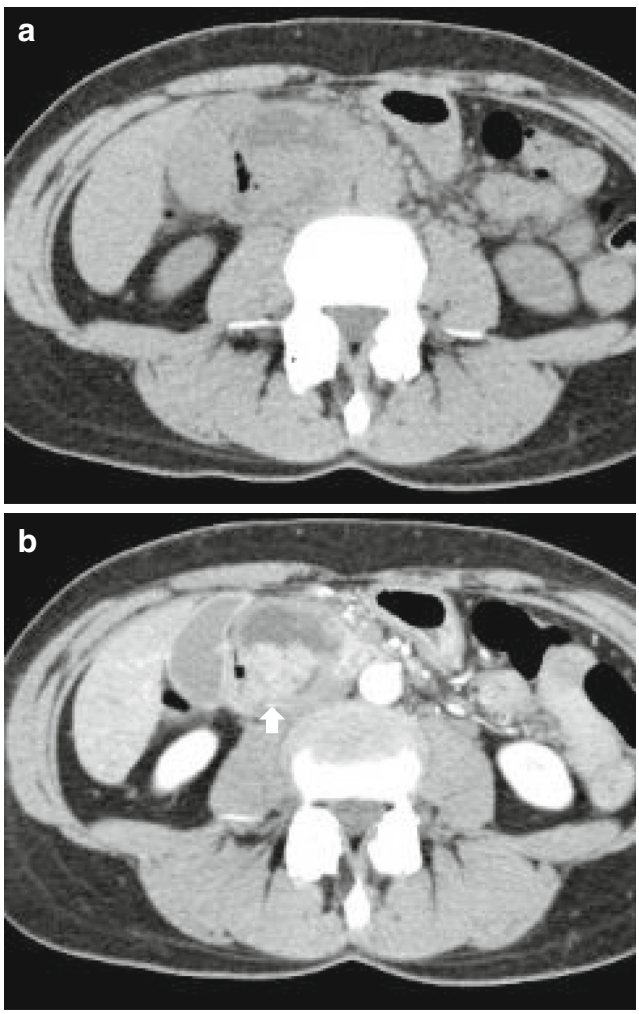

Fig. 1 **a** Contrast-enhanced computed tomography (CT) image showing cystic lesion in the head of the pancreas. **b** Contrast-enhanced CT image showing tumor-containing mural nodule components (*white arrowhead*)

cyst content was of low intensity on T1-weighted images (Fig. 2a) and high intensity on T2-weighted images (Fig. 2b). The mural nodule showed a high signal on diffusion-weighted imaging (DWI) (Fig. 2c). A magnetic resonance cholangiopancreatographic image showed interruption of the main pancreatic duct and mild dilation of the main pancreatic duct at the body and tail of the pancreas, indicating possible communication between the cystic lesion of the head of the pancreas and the main pancreatic duct (Fig. 2d). Considering the malignant potential of the cystic lesion based on preoperative radiological findings, especially the positive signal on DWI, a pancreaticoduodenectomy with regional lymphadenectomy was planned. Gross observation of the resected specimen revealed a cyst with a maximum diameter of 55 mm and a clear margin (Fig. 3a). Histopathological examination of the specimen revealed that the tumor was thickly composed of solid proliferating tumor cells with tubular, cribriform, or papillary formation and that the positive signal areas on DWI generally corresponded to the histological sites of malignancy (Fig. 3b, c). There was no lymph node metastasis, and mucin was not detectable. Immunohistochemical investigation showed that the tumor cells expressed cytokeratin (CK) 7, CK19, cancer antigen (CA) 19-9, MUC1, and MUC6. They tested negative for CK20, CA125, carcinoembryonic antigen, chromogranin A, synaptophysin, CD56, trypsin, p53, MUC2, MUC5AC, and CDX2 (Fig. 3d–f). More than 80 % of the neoplastic cells displayed Ki-67 immunoreactivity. The final diagnosis was ITPN with an associated invasive carcinoma in pathological stage T2N0M0 (p-stage 1B) according to the classification of the Union for International Cancer Control [4]. The patient's postoperative course was uneventful, and she was discharged 13 days after the surgery. During the 24-month follow-up period, there was no evidence of recurrence or metastasis.

Literature review

We identified 23 articles available in electronic databases by searching PubMed and 16 articles from other sources (Fig. 4). We included 33 of these in our narrative synthesis and systematic review [2, 5–36]. We extracted comprehensive data on 58 cases of curative surgical resection for ITPN of the pancreas, which included a patient who we had treated in our clinic (Table 1). The published diagnoses for all of the patients were true indications for surgical resection.

Clinicopathological features of ITPNs

Of the 58 cases of ITPN of the pancreas for which we found comprehensive data, 33 occurred in men and 25 occurred in women. The mean patient age was 62 years (range, 35–84 years). The IPTNs were not associated with any specific clinical syndrome. The clinical characteristics of these cases of ITPN of the pancreas are shown in Table 1.

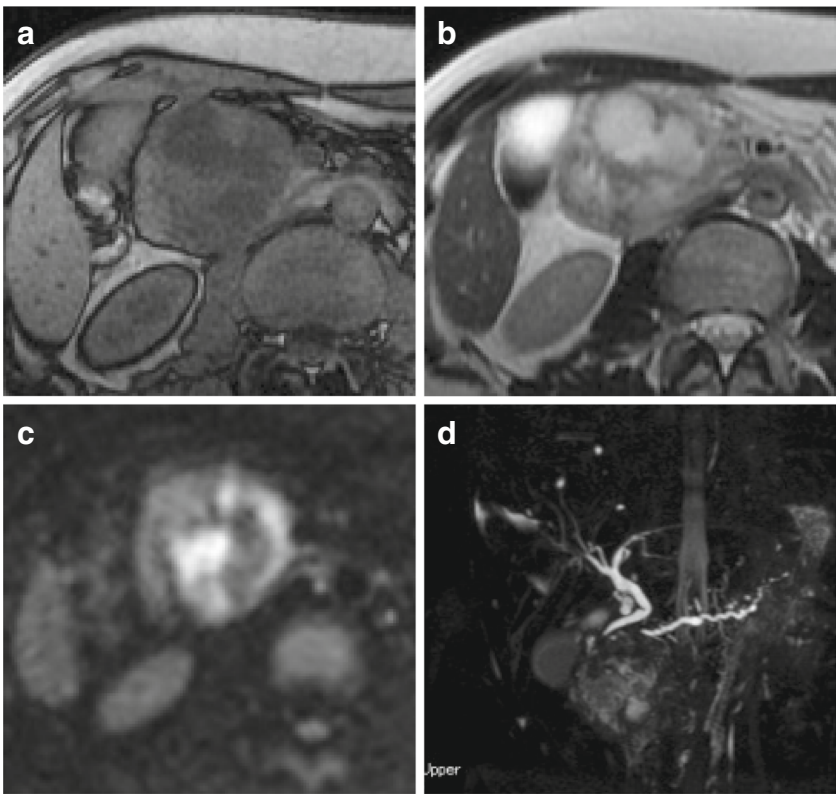

Fig. 2 **a** Magnetic resonance (MR) image showing cyst content to be of low intensity on T1-weighted images. **b** MR image showing cyst content to be of high intensity on T2-weighted images. **c** MR image showing that the mural nodule had a high signal on diffusion-weighted imaging. **d** MR cholangiopancreatographic image showing the interruption of the main pancreatic duct and a mild dilation of the main pancreatic duct at the body and tail of the pancreas

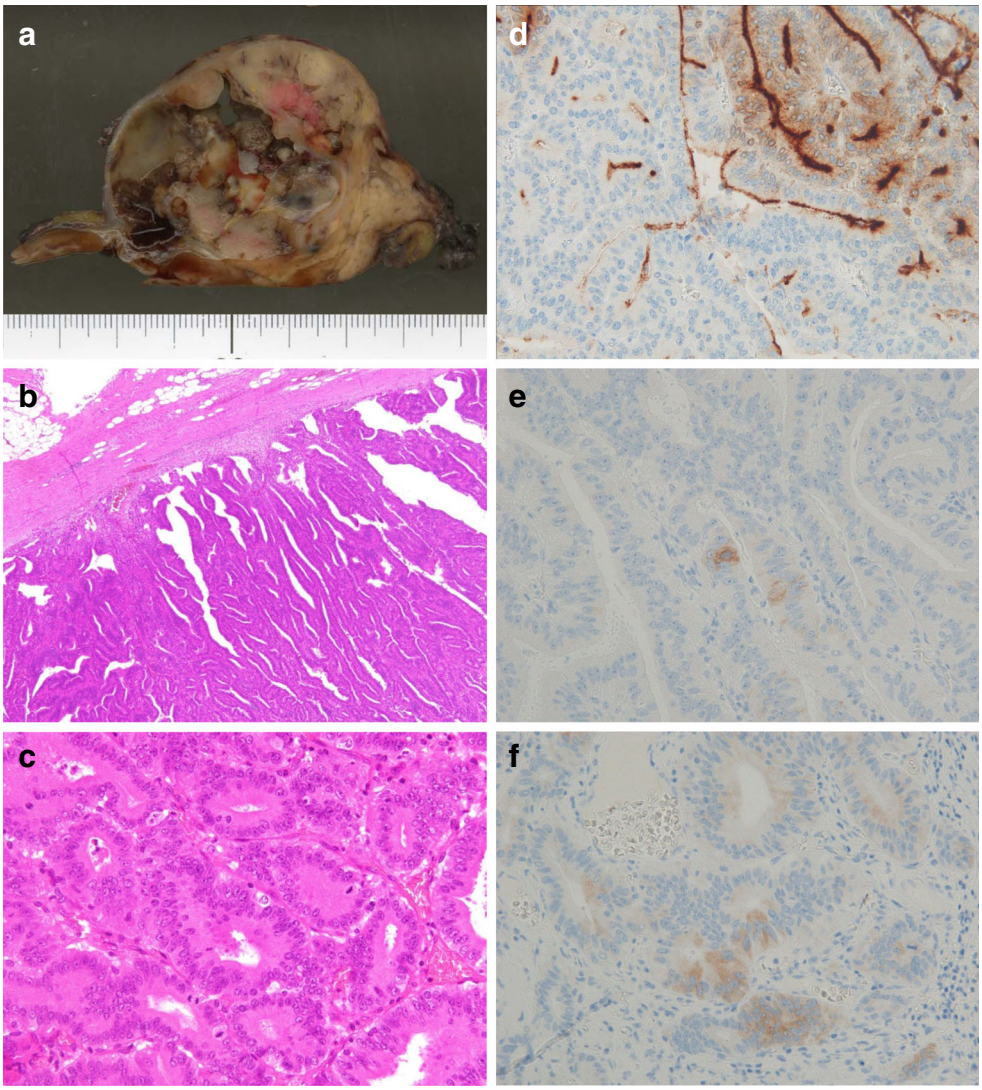

Fig. 3 **a** The resected specimen, revealing a cyst with a maximum diameter of 55 mm and a clear margin. **b**, **c** Histopathological images revealing that the tumor was thickly composed of solid proliferating tumor cells with tubular, cribriform, or papillary formation; there was no lymph node metastasis, and mucin was not detectable (**b** hematoxylin and eosin stain, low-magnification image; **c** hematoxylin and eosin stain, high-magnification image). **d**–**f** Histopathological images showing that neoplastic cells tested positive for MUC1 and MUC6 and negative for MUC5AC (**d** MUC1; **e** MUC5AC; **f** MUC6)

In 20 cases, the patients did not have symptoms; in the remaining 30 cases, the patients were diagnosed while they had clinical symptoms. The symptoms were abdominal pain or sense of fullness with either jaundice or diarrhea in 24 patients, jaundice in three, exacerbation of diabetes mellitus in one, excessive thirst in one, appetite loss in one, fever in one, and weight loss in one.

The tumor locations and operative methods are shown in Table 1. In 34 patients (59 %), the tumor was located in either the head of the pancreas alone (32 patients) or the head and body (two patients); in 19 patients (33 %), the tumor was in the body and/or tail of the pancreas; and in three patients, the tumor affected the whole pancreas. All patients underwent attempted curative resection. The surgical methods used included the following: pancreaticoduodenectomy (PD), including pylorus-preserving PD (PpPD) (20 patients [34 %]), distal pancreatectomy (10 [17 %]), and total pancreatectomy (five [9 %]).

Accurate preoperative diagnosis of ITPN of the pancreas is very difficult because no characteristics on imaging studies can be used to differentiate it from cystic neoplasm of the pancreas. In terms of size, ITPNs of the pancreas generally seem to be larger than ordinary pancreatic adenocarcinomas. The mean size of the ITPNs of the pancreas for 49 patients with available data was 4.5 ± 3.3 cm (range, 1–15 cm) (Table 1). To date, the most difficult discrimination lies between ITPN and IPMN pancreatobiliary types [2, 14, 37]. Tumor cells form tubulopapillae and contain little cytoplasmic mucin. Furthermore, ITPNs have some particular immunohistochemical features; they test positive for CK 7 and/or CK 19 and negative for trypsin, MUC2, MUC5AC, and fascin [2, 14, 37]. However, in two cases, the surgically resected specimen from patients with ITPN tested positive for MUC5AC [13, 18]. Of the 47 cases that we analyzed, 31 IPTNs had an invasive component, although involvement of an invasive component was not significantly associated with age, sex, or tumor size.

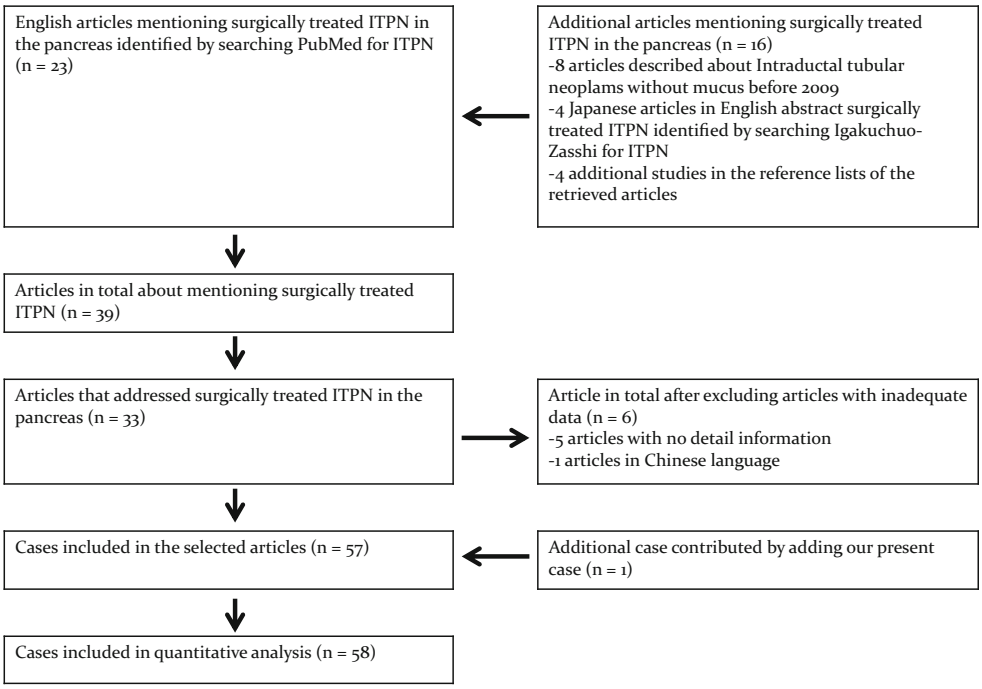

Fig. 4 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) design showing selection of articles and cases for review

Survival outcomes of patients with ITPNs

Survival outcome data was only available for 37 cases of ITPNs of the pancreas, including the patient from our clinic (Table 1). The overall 1-, 3-, and 5-year survival rates after surgery were 97.3, 80.7, and 80.7 %, respectively (Fig. 5a). The overall 5-year survival rate was 81.5 % in patients with an invasive component (after pathologically complete resection of the ITPN of the pancreas) and 77.8 % in patients with a noninvasive tumor ($p = 0.900$) (Fig. 5b).

Discussion

We conducted a retrospective analysis of 58 cases with ITPN of the pancreas, with a focus on the clinicopathological features and surgical outcomes [2, 5–36]. Clinically, it is difficult to accurately diagnose ITPNs, although modern imaging modalities provide informative findings. IPMN, pancreatic intraepithelial neoplasia, MCN, acinar cell carcinoma, solid and pseudopapillary neoplasm (SPN), and tumor metastasis of renal cell carcinoma were part of the differential diagnosis for the treating physicians. The most difficult diagnoses to distinguish are ITPN and IPMN pancreatobiliary type [2, 14, 37]. Contrast-enhanced CT and MRI show ITPN as a cystic lesion with a dilated and irregular main pancreatic duct, but without an abundance of low attenuation mucin [18]. These findings are diagnostically significant for ITPNs. However, since IPMN, pancreatic intraepithelial neoplasia, MCN, acinar cell carcinoma, SPN, and tumor metastasis of renal cell carcinoma have similar radiological features, ITPNs of the pancreas are indistinguishable from other cystic tumors of the pancreas based on these CT findings. Moreover, because the cyst wall is sometimes thin, as was the case in our patient, enhancement of the inner cyst wall is not always seen. The preoperative CT scan for our patient did not provide information on the type of cystic lesion. MRI generally provides more information about cyst content than CT. However, in the cases that we analyzed, the nature of the fluid in the ITPN varied according to factors such as bleeding, chronic inflammation, and infection. Therefore, MRI seems to be of less use than expected for assessing lesions of the pancreas, especially mural nodules of cystic tumors, but is still useful for eliminating the possibility of malignant potential [38].

Guidelines on the management of pancreatic cystic neoplasms [39] will be updated this year. However, our systematic review shows that the biological behavior of ITPNs might be different from that of MCNs and/or IPMNs. Although it is difficult to obtain a radiological preoperative diagnosis of tumor type, it is important to detect “worrisome features” and “high-risk stigmata” that suggest surgical resection for ITPNs rather than obtain a diagnosis of tumor type in the preoperative setting. Diffusion-weighted MRI exploits the random motion of water molecules in biological tissues; the signal intensity reflects the impeded diffusion of water molecules. Pancreatic adenocarcinoma is usually associated with low apparent diffusion coefficient (ADC) in comparison to healthy pancreatic parenchyma because of the presence of fibrosis and increased cell density in these malignant lesions, which are associated with impeded free water diffusion. In contrast, lesions with increased fluid content may show increased ADCs due to increased random motion of water molecules. Diffusion-

Table 1 Reported surgically resected cases of intraductal tubulopapillary neoplasm of the pancreas

Case	Author	Year	Age	Gender	Symptom	Location	Surgery	Size (cm)	Invasion	Survival (months)	Outcome
1	Suda K	1995	78	F	None	H	–	3.0	+	–	–
2	Suda K	1995	55	M	None	H	–	7.0	+	84	AF
3	Suda K	1995	47	M	None	H	–	3.0	+	60	DD
4	Suda K	1995	75	F	None	H	–	4.0	+	48	AF
5	Tajiri T	2004	65	M	Jaundice	H	–	5.5	+	18	DD
6	Tajiri T	2004	36	F	Back pain	B	–	2.0	+	48	AF
7	Tajiri T	2004	40	F	Epigastric pain	H	–	3.0	+	72	AF
8	Tajiri T	2004	67	M	Back pain	T	–	3.0	+	24	DO
9	Ito K	2005	51	M	None	H	PPPD	5.5	+	17	AF
10	Itatu K	2006	50	F	Abdominal pain, diarrhea	H	PPPD	–	+	23	AF
11	Thirot-Bidault A	2006	67	M	Weight loss	T	DP	3.0	+	–	–
12	Hisa T	2007	84	M	None	B	–	2.8	−	15	DO
13	Oh DK	2008	63	F	Abdominal pain, diarrhea	T	TP	2.5	+	–	–
14	Terada T	2009	67	M	Abdominal pain	–	PD	–	−	–	
15	Yamaguchi H	2011	60	F	None	H	PPPD	6.0	−	19	DO
16	Yamaguchi H	2011	35	F	Abdominal pain	B	SPDP	1.0	−	72	AF
17	Yamaguchi H	2011	68	F	None	H	PD	2.5	−	29	AF
18	Yamaguchi H	2011	53	M	Abdominal pain	B	DP	2.0	−	36	AF
19	Yamaguchi H	2011	60	F	Abdominal pain	H	PPPD	4.5	−	24	AF
20	Yamaguchi H	2011	73	F	None	H	PD	5.2	−	33	AF
21	Yamaguchi H	2011	72	M	None	B	DP	1.0	+	33	AF
22	Yamaguchi H	2011	44	M	Abdominal pain	H	PPPD	6.0	+	72	AF
23	Yamaguchi H	2011	48	M	Jaundice	HBT	TP	15.0	+	7	DD
24	Yamaguchi H	2011	62	F	None	–	–	–	+	7	AF
25	Yamaguchi H	2011	68	M	None	–	–	–	−	2	AF
26	Yamaguchi H	2011	70	M	Exacerbation of diabetes mellitus	HB	PD	4.0	−	24	AF
27	Shimizu S	2011	63	M	Abdominal pain	T	DP	1.0	+	72	AF
28	Bhuva N	2011	50	M	Epigastric pain	H	PPPD	–	+	28	AD
29	Jokoji R	2012	68	M	Epigastric pain	B	DP	1.8	+	15	AF
30	Urata T	2012	78	F	None	B	DP	–	+	43	AD
31	Tajiri T	2012	66	M	Appetite loss	H	PD	–	−	12	AF
32	Shibasaki Y	2012	61	M	Abdominal pain	HBT	TP	11.5	+	14	AF
33	Guan H	2012	41	F	None	H	PD	2.3	−	–	–
34–38	Motosugi U	2012	67	3M/2F	ND	2H/2B/1HB	–	0.6–8.1	ND	–	–
39	Kasugai H	2013	69	F	Excessive thirst	H	TP	12.0	−	24	AF
40	Furuhata A	2013	74	M	Fever	H	–	7.0	+	–	
41	Matushita K	2013	47	F	None	H	PD	–	+	30	AF
42–47	Chang X	2014	64	2M/4F	Four abdominal pain/one jaundice/one none	4H/1B/1T	–	1.5–4.5	ND	–	–
48	Someya Y	2014	74	M	Fever	H	PD	7.0	+	24	AF
49	Matsuda M	2014	71	M	None	B	DP	9.0	+	21.5	DD
50	Del Chiaro M	2014	78	M	Abdominal pain	H	TP	1.1	−	–	–
51	Ahls MG	2014	43	F	Epigastric pain	H	PPPD	2.6	−	–	–
52	Ito H	2014	75	M	None	B	DP	–	+	–	–
53	Takayama S	2015	54	F	Diarrhea	H	PD	5.0	+	10	AF
54	Yoshida Y	2015	75	M	None	H	PD	1.2	−	–	–
55	Kitaguchi K	2015	61	M	None	H	PD	1.2	+	22	AF

Table 1 (continued)

Case	Author	Year	Age	Gender	Symptom	Location	Surgery	Size (cm)	Invasion	Survival (months)	Outcome
56	Matthews Y	2015	55	M	Abdominal pain	T	DP	10.0	+	36	AD
57	Kölby D	2015	42	M	Abdominal pain	HBT	PD	3.5	+	19	AF
58	Our case	2015	54	F	Abdominal pain	H	PD	5.5	+	24	AF

H head of the pancreas, *B* body of the pancreas, *T* tail of the pancreas. *PpPD* pylorus-preserving pancreaticoduodenectomy, *DP* distal pancreatectomy, *TP* total pancreatectomy, *PD* pancreaticoduodenectomy, *SPDP* spleen preserved distal pancreatectomy, *ND* not described, *AF* alive without recurrent free, *DD* death caused by primary disease, *DO* death caused by other diseases, *AD* alive with recurrent diseases

weighted MRI is recommended for detecting pancreatic cancer and characterizing pancreatic masses [40]. Our results suggest that, compared with conventional MRI alone, adding DWI to conventional MRI improves diagnostic accuracy by improving detection of malignant lesions and differentiation of malignant lesions from benign neoplasms of the pancreas.

The current overall 5-year survival rate of 81.5 % in patients with an invasive component is comparable to or better than the survival rates for invasive malignant IPMNs in other reports, although some of the cases that we examined in this study included patients who met criteria for surgical treatment with intent to cure IPMNs [37, 41, 42]. Furthermore, even if ITPNs had an invasive component, excellent curative treatment was achieved for patients compared to patients with IPMNs.

In terms of immunohistochemical features, ITPNs tested positive for CK 7 and/or CK 19 and negative for trypsin, MUC2, MUC5AC, and fascin [2, 14, 37]. Neither acinar differentiation nor aberrant expression of beta-catenin was observed. After attempted curative resection, a good prognosis in patients with ITPNs might be more likely when the lesion tests negative for MUC5AC in immunohistochemical studies. It has been reported that MUC5AC is aberrantly expressed in premalignant and malignant lesions, and several pancreatic cancer cell lines, and that MUC5AC is frequently expressed in malignant IPMNs, whereas no intense MUC5AC expression is detected in normal or hyperplastic lesions [43]. It has been suggested that expression of MUC5AC plays a role in the invasiveness of cancers by direct involvement in immune suppression that enables tumor cells to avoid the host immune system [44]. Several authors have suggested that overexpression of MAC5AC may reduce survival time in patients with pancreatic cancer [43–46].

This study had some limitations associated with errors and biases inherent in a small retrospective study. A major limitation of this study is that the results cannot simply be extrapolated because it included case reports published before diagnostic guidelines for ITPN were defined. ITPN of the pancreas is a rare disease, and because we included cases published before 2009 and cases of "intraductal tubular neoplasm without mucus," our selection criteria might have contributed to heterogeneous outcomes. Another limitation is the lack of re-evaluation of the specimens by a dedicated pathologist. A definite diagnosis of ITPN is a pathological diagnosis that requires high specialization in pancreatic disease. Owing to the relatively recent description of ITPNs and the fact that they are extremely rare, accurate diagnosis is challenging, even for high-volume pancreatic pathologists. Therefore, determining the best management strategy for this tumor and improving the accuracy of prognosis for patients will require collection and analysis of further epidemiological and pathological data.

In conclusion, we treated a patient with ITPN of the pancreas with an associated invasive carcinoma. In this and other cases, it would have been difficult to diagnose ITPN

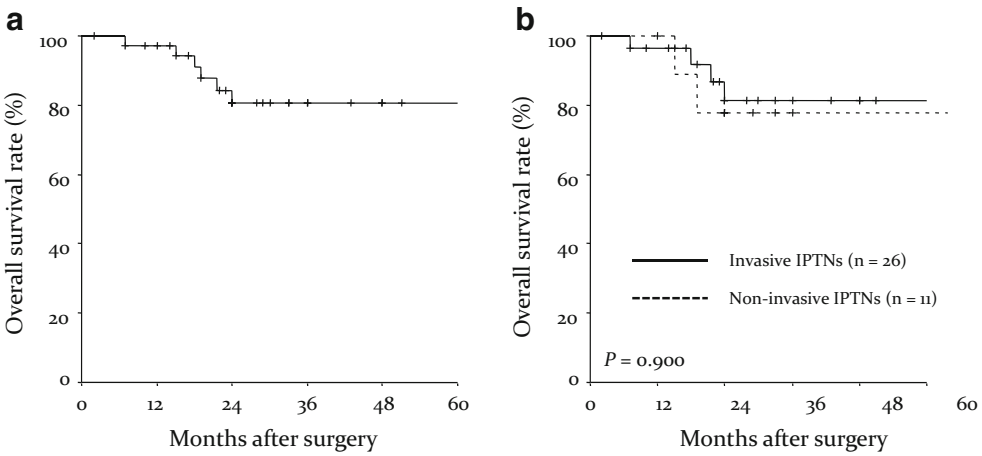

Fig. 5 **a** Overall survival for all patients with ITPN for whom data were available. **b** Overall survival for patients with intraductal papillary mucinous neoplasms who had a tumor with an invasive component and those who had a noninvasive tumor

preoperatively, even with the various imaging modalities that are available. Currently, surgical treatment is the only curative management option for ITPNs of the pancreas. In patients with a cystic lesion of the pancreas, ITPN should be considered part of the differential diagnosis.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethics committee of the Kochi Health Sciences Center and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A patient provided written informed consent.

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