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REVIEW ARTICLE

Systematic review of resectable intraductal tubulopapillary neoplasm with special reference to recurrence patterns

Takaomi Seki[1] · Akira Watanabe[1] · Norifumi Harimoto[1] · Ken Shirabe[1]

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Abstract

Purpose Intraductal tubulopapillary neoplasm is a rare pancreatic tumor. The purpose of this study was to clarify the recurrence type and prognosis in recurrent cases after intraductal tubulopapillary neoplasm resection.

Methods PubMed was searched for previous reports on surgical resection of intraductal tubulopapillary neoplasm of the pancreas that were published from 2009 to July 2020. The clinical features obtained from these reports were summarized and analyzed.

Results The clinicopathological data of 35 intraductal tubulopapillary neoplasm cases were obtained. Of these, 21 were males, and 14 were females, with an average age of 57.9 years old. Invasive findings were observed in 21 of 35 patients (60%). Recurrence was observed in 11 of the 35 cases (31.4%), including remnant pancreatic recurrence in 6 cases (17.1%) and liver metastasis in 5 cases (14.3%). The tumor size was significantly larger in the liver metastasis group than in the remnant pancreas recurrence group ($P = 0.04$), and patients with liver metastases tended to have a poorer prognosis than those with remnant pancreas recurrence.

Conclusions The recurrence type of intraductal tubulopapillary neoplasm resection was mainly remnant pancreatic recurrence and liver metastasis recurrence. Total pancreatectomy for remnant pancreatic recurrence may be suitable because of its good prognosis.

Keywords Intraductal tubulopapillary neoplasm · Intraductal tubulopapillary carcinoma · Pancreatic cancer · Intraductal papillary mucinous neoplasm

Introduction

Intraductal tubulopapillary neoplasm (ITPN) was proposed as a new disease concept by Yamaguchi et al. [1] in 2009 and was categorized as a new entity in the pancreatic intraductal neoplasm family in the 2010 World Health Organization (WHO) classification of tumors of the digestive system [2]. ITPN is rare, with an incidence rate of 0.9% among exocrine pancreatic tumors and 3% among pancreatic tumors. ITPN is a solid tumor that fills the pancreatic duct and is non-mucus-producing. It grows as a tubulopapillary neoplasm in the pancreatic duct, with scattered small necrotic foci that have a tendency to differentiate into gland ducts (positive expression of pancreatic duct epithelial markers cytokeratin [CK]-7 and CK-19) but not into acinar cells (negative expression of trypsin, a marker for acinar differentiation). An immunohistochemical assessment of the mucin core protein expression in tumors shows negative findings for MUC2, MUC5AC, and fascin (differentiation from intraductal papillary mucinous neoplasm [IPMN]) and no KRAS or BRAF mutations.

Several systematic reviews of ITPN have been reported thus far. Basturk et al. [3] reported that ITPN had a better prognosis than normal pancreatic cancer, even with invasive findings. Furthermore, they compared the overall survival rates with and without invasive findings and found no significant difference. Date et al. [3] also analyzed 58 cases of ITPN resection and reported their clinicopathological features and surgical outcomes. The overall survival rates was 81.5% in patients with an invasive component and 77.8% in those with a non-invasive component. Kuan et al. [4] reported the latest clinical and pathological findings in both

✉ Norifumi Harimoto
nharimotoh1@gunma-u.ac.jp; fttfyf@gmail.com

[1] Division of Hepatobiliary and Pancreatic Surgery, Department of General Surgical Science, Graduate School of Medicine, Gunma University, 3-39-22, Showamachi, Maebashi 371-8511, Japan

ITPN of the pancreas and the rarer ITPN of the bile duct. There have been no reports concerning recurrence of ITPN, although ITPN is a relatively newly identified and rare disease that is gradually being elucidated as a result of the accumulation of cases and seems to have a favorable prognosis.

We herein report our analysis of the recurrence types and prognosis of recurrent ITPN resection cases based on a systematic review.

Materials and methods

Literature search

PubMed (URL: https://www.ncbi.nlm.nih.gov) was searched for reports on surgical resection of ITPN of the pancreas. The search was performed using the term "intraductal tubulopapillary neoplasm". The final search was completed in July 2020. All English-language articles related to reports on surgical resection of ITPN of the pancreas were analyzed. Cases were extracted from the selected articles. The extracted cases were further sorted by postoperative course and recurrence type. The entire process of this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [5].

Results

From the 86 articles identified, 1 that was not written in English ($n=1$), those of obvious irrelevance ($n=45$), and 1 for which detailed information was not available ($n=1$) were excluded, leaving 39 articles [1], 4, 6, 39. Seventy-nine cases were extracted from these 39 articles, and from these 79, we excluded 44 cases for which the postoperative course was not reported ($n=19$), cases with no recurrence that were not followed for more than 12 months after surgery ($n=8$), cases with the recurrence type not reported ($n=16$), and there were cases in which pre-recurrence and post-recurrence were reported, and such cases were counted as one case. These findings are summarized in Fig. 1. We, therefore, finally analyzed 35 ITPN cases extracted by the algorithm (Fig. 1); Table 1 shows the clinicopathological summary of these cases. Table 2 shows characteristic of patients according to the recurrence patterns of ITPN.

Of the 35 analyzed cases, 21 were males, and 14 were females, with an average age of 57.9 years. Invasive findings were observed in 21 of the 35 patients (60%). Recurrence was observed in 11 of the 35 cases (31.4%), including remnant pancreatic recurrence in 6 cases (17.1%) and liver metastasis in 5 cases (14.3%) (Fig. 2). Regarding the tumor diameter, the median size was 3.5 (range 0.5–12.0) cm in the no-recurrence group, 1.7 (range 1.0–2.2) cm in the remnant pancreas recurrence group, and 8.0 (range 3.3–15.0) cm in the liver metastasis group. The tumor size was significantly larger in the liver metastasis group than in the remnant pancreas recurrence group. One case each in the remnant pancreatic recurrence and liver metastasis groups with an unknown tumor diameter was excluded ($P=0.04$). Invasive findings were observed in four of the five cases of recurrence of liver metastasis. Three cases showed lymph node metastasis, and all had recurrence of liver metastasis. [6, 20, 35] There was one case in which the surgical margin was considered positive, and that case had recurrence of liver metastasis. [35] No surgical treatment was performed for recurrence of liver metastasis, while chemotherapy was performed in two cases [6, 20]. One case had recurrence of the remnant pancreas 192 months after surgery. After recurrence, total pancreatectomy (TP) was performed in five of the six cases with remnant pancreatic recurrence, and no further recurrence has since been reported in any of these cases at the time of publication.

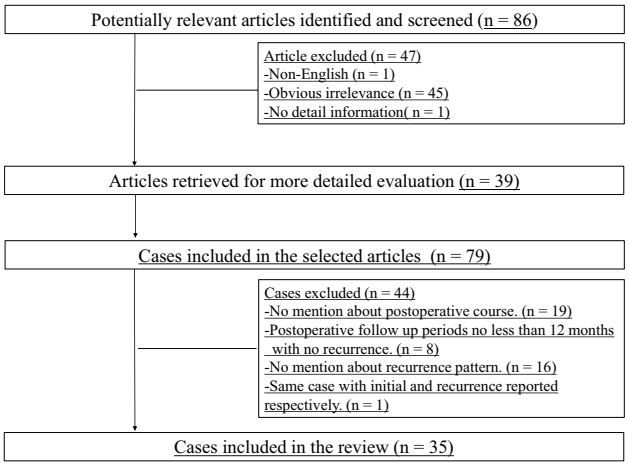

Fig. 1 Extraction algorithm for the selection of articles and cases concerning intraductal tubulopapillary neoplasm

No cases of neoadjuvant therapy were reported. Adjuvant therapy was performed in seven patients. [6, 9, 21, 28, 29, 31, 33] Four cases received tegafur-gimeracil-oteracil potassium (S-1) (one case was after TP for remnant pancreatic recurrence). [10, 28, 29, 31] One case was treated with gemcitabine (GEM) and had liver and lymph node metastases [6]. Two cases were treated with GEM and capecitabine [21, 33]. One of these two cases had recurrence of liver metastasis [33]. Remnant pancreatic recurrence was observed in two patients who received S-1 as adjuvant treatment [29, 31]. Only one patient developed multiple liver metastases 4-months after surgery and died 3-months later [1]. Figure 3 shows the recurrence-free and overall survival rates of ITPN according to the recurrence type. In Figs. 3 and 4, one case of liver metastasis recurrence in the non-invasive

Table 1 Clinical features of reported cases of ITPN

Case	Author	Reference number	Age (years) Gender	Location	Tumor size(cm)	Neoadjuvant therapy	Surgical procedure	Adjuvant therapy	Pathological cut end of pancreas	Vascular invasion	Lymph node metastasis	Invasion site	Invasion type	Recurrence site	Chemotherapy	Outcome
1	Yamaguchi	1	35, F	Body	1	–	DP	–	NR	–	–	–	–	No recurrence	–	Alive
2	Yamaguchi	1	68, F	Head	2.5	–	PD	–	NR	–	–	–	–	No recurrence	–	Alive
3	Yamaguchi	1	53, M	Body	2	–	DP → TP	–	–	–	–	–	–	Remnant pancreas	–	Alive
4	Yamaguchi	1	72, M	Body	1	–	DP	–	NR	+	–	Stroma, vein, bile duct, duodenum	+	No recurrence	–	Alive
5	Yamaguchi	1	44, M	Head	6	–	PPPD	–	NR	+	–	Stroma, vein, bile duct, duodenum	+	No recurrence	–	Alive
6	Yamaguchi	1	48, M	Whole	15	–	TP	–	NR	+	–	Stroma, vein, bile duct, duodenum	+	Liver metastasis	–	Died (7 months)
7	Yamaguchi	1	70, M	Body	4	–	Sub-TP	–	NR	–	–	–	–	No recurrence	–	Alive
8	Bhuva	7	50, M	Head	NR	–	PPPD	GEM	NR	+	+	Vessels	+	Liver and nodal metastases	GEM → FOLFOX	Alive
9	Tajiri	8	66, M	Head	NR	–	PD	–	NR	–	–	–	–	No recurrence	–	Alive

Table 1 (continued)

Case	Author	Reference number	Age (years) Gender	Location	Tumor size(cm)	Neoadjuvant therapy	Surgical procedure	Adjuvant therapy	Pathological cut end of pancreas	Vascular invasion	Lymph node metastasis	Invasion site	Invasion type	Recurrence site	Chemotherapy	Outcome
10	Jokoji	9	66, M	Body/Tail	1.8	–	DP	–	NR	–	–	Pancreatic parenchyma	+	No recurrence	–	Alive
11	Urata	10	78, F	Body	2.2	–	DP	S-1	–	–	–	Pancreatic parenchyma	+	Remnant pancreas	–	Alive
12	Kasugai	12	69, F	Body/Tail	12	–	TP	–	–	–	–	–	–	No recurrence	–	Alive
13	Someya	13	74, M	Head	7	–	PD	–	NR	NR	NR	NR	+	No recurrence	–	Alive
14	Ahls	15	43, F	Head	2.6	–	PPPD	–	NR	–	–	–	–	No recurrence	–	Alive
15	Tajima	17	80, M	Body/Tail	0.5	–	NR	–	-	–	–	–	–	No recurrence	–	Alive
16	Kitaguchi	20	61, M	Head	1.2	–	SSPPD	–	-	–	–	Intestine	+	No recurrence	–	Alive
17	Matthews	21	55, M	Tail	10	–	DP, partial gastrectomy	–	NR	–	+	Gastric muscularis propria, pancreatic and splenic parenchyma	+	Liver metastasis and peritoneal dissemination	+	Alive
18	Kölby	22	42, M	Whole	3.5	–	PD	GEM, capecitabine	-	+	–	Vessels, nerves	+	No recurrence	–	Alive

Table 1 (continued)

Case	Author	Reference number	Age (years) Gender	Location	Tumor size(cm)	Neoadjuvant therapy	Surgical procedure	Adjuvant therapy	Pathological cut end of pancreas	Vascular invasion	Lymph node metastasis	Invasion site	Invasion type	Recurrence site	Chemotherapy	Outcome
19	Date	4	54, F	Head	5.5	–	PD	–	–	–	–	NR	+	No recurrence	–	Alive
20	Savant	23	82, F	Body	3.3	–	DP	–	–	–	–	–	–	Liver metastasis	–	Alive
21	Maghrebi	27	62, M	Whole	NR	–	TP	–	NR	–	–	–	–	No recurrence	–	Alive
22	Basturk	3	25, F	Tail	10	–	NR	–	NR	NR	NR	NR	+	No recurrence	–	Alive
23	Basturk	3	53, M	Tail	2	–	NR	–	NR	NR	NR	NR	+	No recurrence	–	Alive
24	Basturk	3	50, M	NR	NR	–	NR	–	NR	NR	NR	NR	+	No recurrence	–	Alive
25	Basturk	3	73, F	Tail	3.7	–	NR	–	NR	NR	NR	NR	+	No recurrence	–	Alive
26	Basturk	3	64, M	Head	3	–	NR	–	NR	NR	NR	NR	+	No recurrence	–	Alive
27	Basturk	3	67, M	Head	3.5	–	NR	–	NR	NR	NR	NR	+	No recurrence	–	Alive
28	Inomata	29	55, F	Head	5	–	PPPD	–	NR	–	–	–	–	No recurrence	–	Alive
29	Sakamoto	30	72, M	Head	NR	–	SSPPD	S-1	NR	–	–	–	–	No recurrence	–	Alive
30	Saeki	31	54, M	Body	2	–	PD→TP	S-1	–	–	–	–	–	Remnant pancreas	–	Alive

Table 1 (continued)

Case	Author	Reference number	Age (years) Gender	Location	Tumor size(cm)	Neoadjuvant therapy	Surgical procedure	Adjuvant therapy	Pathological cut end of pancreas	Vascular invasion	Lymph node metastasis	Invasion site	Invasion type	Recurrence site	Chemotherapy	Outcome
31	Umemura	33	50, F	Body	1.5	–	DP→TP	–	–	–	–	–	–	Remnant pancreas	–	Alive
32	Ko	34	61, M	Body	1	–	SSPPD →TP	S-1	–	+	–	Stroma, vessels	+	Remnant pancreas	–	Alive
33	Zhang	36	36, F	Head	4	–	PD	GEM, capecitabine	+	+	+	Vessels	+	Liver metastasis	–	Alive
34	Zhou	37	23, F	Tail	9	–	DP	–	NR	–	–	Stroma	+	No recurrence	–	Alive
35	Ohno	40	72, F	Head	NR	–	PD→TP	–	NR	NR	NR	NR	+	Remnant pancreas	–	Alive

Size is represented by the maximum width of the tumor

PD pancreaticoduodenectomy, *PPPD* pylorus-preserving pancreaticoduodenectomy, *DP* distal pancreatectomy, *TP* total pancreatectomy, *SSPPD* subtotal stomach-preserving pancreaticoduodenectomy, *GEM* gemcitabine, *CDDP* cisplatin, *S-1* tegafur-gimeracil-oteracil potassium, *FOLFOX* 5-Fluorouracil, Leucovorin and Oxaliplatin, *NR* not reported

Table 2 Characteristic of patients according to the recurrence patterns of ITPN

	No recurrence ($n=24$)	Recurrence to remnant pancreas ($n=6$)	Recurrence to liver ($n=5$)	P value
Age Median, range (years)	63 (23–80)	57.5 (50–78)	50 (36–82)	N.s
Male / Female	15/9	3/3	3/2	N.s
Tumor size Median, range (cm)	3.5 (0.5–12.0) NR ($n=4$)	1.7 (1.0–2.2) NR ($n=1$)	8.0 (3.3–15.0) NR ($n=1$)	$P=0.04$*
Tumor location: Head/Body/Tail/Body, Tail/whole/NR	11/10/2/1	1/5/0/0	2/2/1/0	N.s
Surgical procedure: PD/DP/TP/NR	10/4/3/7	3/3/0/0	2/2/1/0	N.s
Invasive type ± (%)	14/10 (58.3)	3/3 (50.0)	4/1 (80.0)	N.s

Data are expressed as the median and range (minimum, maximum) or number of patients (percentage) as appropriate

PD pancreaticoduodenectomy (includes pylorus-preserving pancreaticoduodenectomy and subtotal stomach-preserving pancreaticoduodenectomy), *DP* distal pancreatectomy, *TP* total pancreatectomy (includes sub-total pancreatectomy)

N.s. not significant

*P values reflect the comparison between the liver metastasis group and remnant pancreas recurrence group

group was excluded because the survival recurrence period was unknown. Figure 3a shows the recurrence-free survival rate of ITPN according to the recurrence pattern. Patients with liver metastases tended to have a poorer prognosis than those with remnant pancreas recurrence, but this was not statistically significant ($P=0.07$). Figure 3b shows the overall survival rate of ITPN according to the recurrence pattern. No significant difference was found here either ($P=0.15$).

Figure 4 shows the recurrence-free and overall survival rates of ITPN according to the invasion type. There was no significant difference in the recurrence-free survival rate ($P=0.25$) or overall survival rate ($P=0.40$) between the two groups.

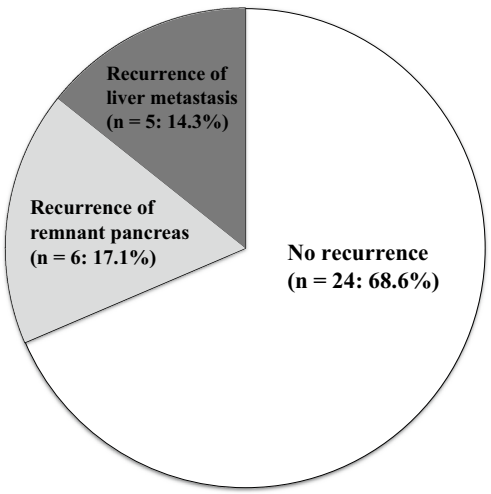

Fig. 2 Recurrence type among ITPN resection cases

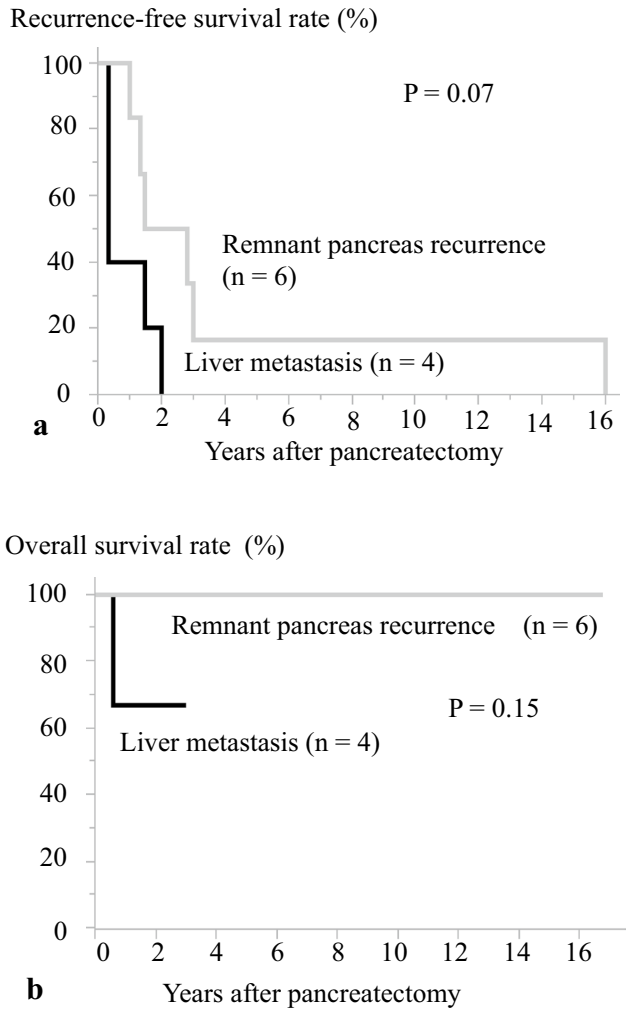

Fig. 3 **a** The recurrence-free survival rate according to the recurrence pattern. **b** The overall survival rate according to the recurrence pattern. Patients with liver metastases tended to have a poorer prognosis than those with remnant pancreas recurrence

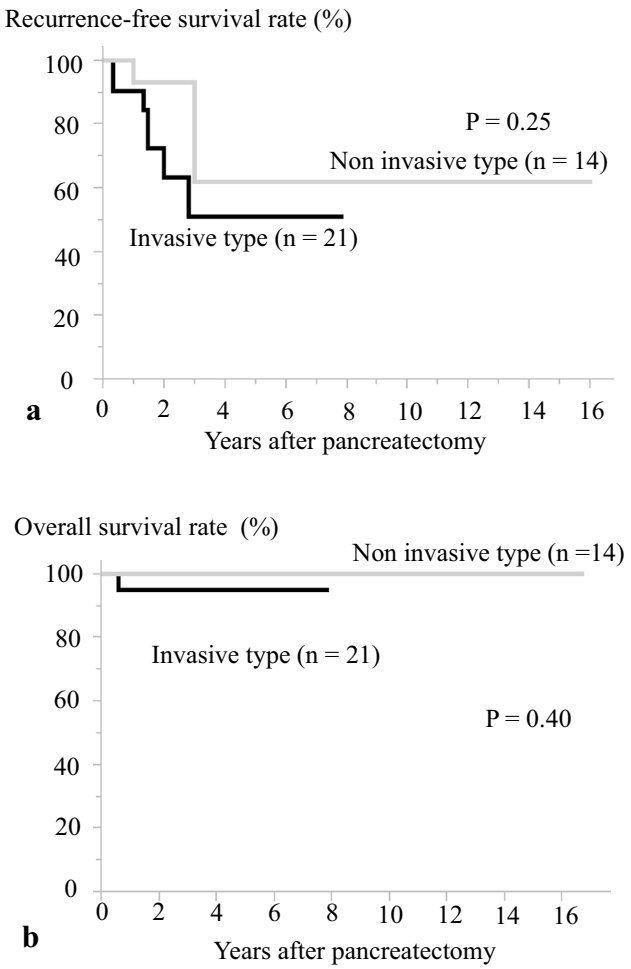

Fig. 4 **a** The recurrence-free survival rate of ITPN according to the invasive type. **b** The overall survival rate of ITPN according to the invasive type

Discussion

ITPN is a relatively newly identified rare disease whose concept was first established in 2009, and details of its treatment and prognosis remain unclear, even after 10 years. Although characteristic image findings and pathological findings have been reported, the preoperative diagnosis is relatively difficult at present, and most cases are diagnosed after resection. The 5-year survival rates of ITPN were reported to be 71%–80.7%, [3, 3] showing a better prognosis than pancreatic cancer, but there are no reports concerning the recurrence of ITPN, making ours the first to examine ITPN recurrence. The recurrence type was found to be mainly remnant pancreatic recurrence and liver metastasis recurrence, which may be accompanied by lymph node metastasis. The tumor size was significantly larger in the liver metastasis group than in the remnant pancreas recurrence group ($P = 0.04$). The recurrence-free survival rates tended to be poorer in patients with liver metastases than in those with remnant pancreas recurrence.

Many cases of remnant pancreatic recurrence have been reported in recent years. For remnant pancreatic recurrence, several factors, such as tumor cell-positive excision sections, multifocal lesions, and intrapancreatic micrometastasis, are considered. The resection margins were reported to be negative in all six cases of remnant pancreatic recurrence, and tumor remnants are unlikely to be the cause of recurrence. The pathological findings of recurrent tumors indicate that the tumor is basically located in the main pancreatic duct but may also be located in the pancreatic parenchyma. There were multiple recurrences in two cases [30, 33]. One non-invasive case experienced recurrence with new invasive findings, [30] but the histological findings, immunostaining, and molecular characteristics were similar to those of the primary tumor. In one case of recurrent tumor, the Ki-67 labeling index increased, and the risk of malignancy may also increase with recurrence. However, there was a case in which invasive findings were observed in primary tumors but not in recurrent tumors.

Saeki et al. [30] noted that if the remnant pancreatic tumor is metachronous and multicentric, it develops mainly in the main pancreatic duct. Similarities should be confirmed by comparing the pathological findings of the original and recurrent tumors, which may help predict recurrence mechanisms. Regarding the mechanism underlying remnant pancreatic recurrence, the clinicopathological findings were similar to those of the original tumor in previous reports, and micrometastases were predominant in the original tumor in contrast to cases of metachronous or multicentric recurrence [30, 32]. As a new possibility, Ko et al. [33] pointed out the possibility of the implantation of tumor cells, as a recurrent tumor was found in the pancreatic duct in a resected specimen of total pancreatectomy, but no clear malignant tumor was found in the pancreatic duct epithelium, and tumor cells were floating in the pancreatic duct. The true mechanism of remnant pancreatic recurrence is unknown and requires further study. One case of recurrence developed 192 months after surgery, so long-term follow-up is required. After remnant pancreas recurrence, TP was performed in five of six cases, and a good prognosis was established. TP may be suitable, depending on the patient's status, as there were no cases of remnant pancreas recurrence after TP. However, since one case of liver metastasis recurrence was reported in a patient who underwent TP as the initial surgery, [1] it is necessary to conduct careful follow-up after TP.

Recurrence of liver metastases tends to occur in large tumors and is often associated with invasive findings. In our review, recurrence of liver metastasis was observed in all three cases with lymph node metastasis in the resected specimen, and lymph node metastasis may be a risk factor for recurrence of liver metastasis. Cases of recurrence of liver metastasis often have invasive findings, but one case did not show

invasive findings. The cause of liver metastasis recurrence may be due to either preoperative or intraoperative iatrogenic factors. A strict pathological examination with fine slices may be required to search for invasive findings. This case showed high-grade dysplasia and had a high Ki-67 labeling index of 70% and high malignancy, so it would not have been strange for liver metastasis recurrence to occur.

The basic treatment of ITPN is resection. In addition, neoadjuvant therapy and adjuvant therapy may be considered. However, there were no cases of neoadjuvant treatment. Adjuvant treatment was performed in seven cases [6, 9, 21, 28, 29, 31, 33]. However, five of them experienced a relapse. It is hoped that viable neoadjuvant and adjuvant therapy strategies will be established with the accumulation of more cases. Chemotherapy is often selected as a treatment for recurrence of liver metastases, and GEM, S-1, and 5-Fluorouracil, Leucovorin and Oxaliplatin (FOLFOX) are routinely administered for pancreatic cancer; however, their effects are unclear. Chemotherapy was administered in two cases [6, 20]. Bhuva et al. [6] reported that the combination of FOLFOX and integrated Yttrium-90 radioembolization was partially successful for managing recurrence of liver metastasis. Regarding the treatment strategy for recurrence of liver metastases, there is no consensus chemotherapy regimen, and marked efficacy cannot be expected, so resection should be considered when possible. However, liver metastases are often unresectable, in which case chemotherapy or radiation therapy, similar to the approach with normal pancreatic cancer, may be a suitable option. Palliative care is selected if treatment is not possible or desired. The prognosis is poor if recurrence of liver metastasis occurs. It is, therefore, important to prevent such recurrence.

In conclusion, this is the first report to examine ITPN recurrence. The recurrence type of ITPN resection is mainly remnant pancreatic recurrence and liver metastasis recurrence, but the type may be affected by the tumor size. TP for remnant pancreatic recurrence may be a suitable treatment approach because of its good prognosis.

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Declarations

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

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