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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

A novel classification of portal venous tumor invasion to predict residual tumor status after surgery in patients with pancreatic neuroendocrine neoplasms

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Abstract

Purpose To elucidate whether portal venous tumor invasion (PVTI) is a prognostic factor for patients with pancreatic neuroendocrine neoplasms (Pan-NENs).

Methods From 2002 to 2019, 240 patients with Pan-NEN were included to examine prognostic factors. PVTI based on computed tomography (CT) images are classified into four types: no PVTI (Vp0/1), PVTI not invading the superior mesenteric vein (Vp2), PVTI invading the superior mesenteric vein or portal vein (Vp3), and PVTI invading the portal bifurcation (Vp4).

Results Simultaneous liver metastases (SLM) determined the overall survival (OS) in 240 patients. The 5-year OS rates with and without SLM were 46% and 92%, respectively ($P < 0.001$). PVTIs were observed in 56 of the 240 patients (23%). Among such patients, 39, 11, and 6 had Vp2, Vp3, and Vp4, respectively. The 5-year OS rates with and without PVTI were 62% and 82%, respectively ($P < 0.001$). Severity of PVTI did not decide PFS and OS after R0/1 resection. There was significant difference in the prognoses between Vp0/1 and Vp2–4. In 161 patients without SLM, 21 had PVTI (13%). According to a multivariate analysis, PVTI and Ki-67 index were independent prognostic factors for progression-free survival (PFS) in patients without SLM. The 5-year PFS rates with and without PVTI were 18% and 77%, respectively ($P < 0.001$). The 5-year OS rates with and without PVTI were 76% and 95%, respectively ($P = 0.02$). PVTI was associated with tumor functionality, high serum NSE, and high Ki-67 index.

Conclusions PVTI may be a predictor for postoperative recurrence.

Keywords Pan-NENs · Classification · Tumor thrombus · Portal venous tumor invasion

Introduction

Pancreatic neuroendocrine neoplasms (Pan-NENs) have specific imaging features and clinical characteristics distinct from those of pancreatic adenocarcinoma (Modlin et al. 2008). Pan-NENs account for 1–2% of all pancreatic tumors (Franko et al. 2010), and their incidence rate has been increasing due to advancements in diagnostic modalities (Yao et al. 2008; Ito et al. 2015). Surgical resection has been considered as the primary treatment based on the European Neuroendocrine Tumor Society and National Comprehensive Cancer Network guidelines (Falconi et al. 2016). The North American Neuroendocrine Tumor Society guidelines suggest that primary tumor resection and aggressive surgical approach had improved the survival of patients with Pan-NENs (Kunz et al. 2013). In these guidelines, treatment strategy mainly depends on the presence

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or absence of distant metastasis and local resectability. To achieve R0 resection, preoperative imaging plays an important role (Kim et al. 2013).

Liver metastasis is one of the most important prognostic factors of Pan-NEN (Milione et al. 2019; Birnbaum et al. 2014). In nonmetastatic patients, R0 resection is the first-line treatment, and it generally leads to longer survival (National Comprehensive Cancer Network. NCCN guidelines: neuroendocrine and adrenal tumors. Version 3.2018 2018; Falconi et al. 2016). However, whether patients have high risk of recurrence even after curative surgery remains unclear.

Advanced Pan-NEN has a tendency to invade the portal vein and sometimes occludes the vein and forms a thrombus. Portal venous tumor invasion (PVTI) including the portal venous occlusion and the portal venous thrombus may cause liver metastases and be a direct determinant for local resectability as important as main artery invasion. Venous invasion developing to the superior mesenteric vein (SMV) made complete resection more difficult, and its extension into the portal bifurcation made it infeasible without good response to neoadjuvant chemotherapy. Portal venous tumor thrombosis was observed in 3.9–33% of patients with nonfunctional Pan-NENs (Balachandran et al. 2012; Prakash et al. 2015; Bok et al. 1984; Stafford-Johnson et al. 1998). However, previous reports involved significantly small cohorts that discussed clinical impacts of PVTI on prognosis. Moreover, several current clinical staging classifications of Pan-NENs have never included information about PVTI, while information on the staging classifications of hepatocellular carcinoma has been included. The presence of preoperative PVTI may increase occult liver metastasis, but whether PVTI would be a risk factor for postoperative recurrence remains unclear. Therefore, this study aimed to elucidate whether PVTI is a prognostic factor for patients with Pan-NENs.

Methods

Study design

Between April 2002 and April 2019, 275 patients were pathologically diagnosed with Pan-NENs at Tokyo Medical and Dental University Hospital (Tokyo, Japan). Among them, 240 patients who were evaluated by enhanced computed tomography (CT) before treatment were enrolled with approval of the ethics committees of the faculty of our university (permission no. M2000-1080, G2017-018). Moreover, all patients provided written informed consent for inclusion in the study (Fig. 1).

Clinical data

Patients' characteristics, such as age, sex, serum neuron-specific enolase (NSE) value, functionality, and genetic syndromes, such as multiple endocrine neoplasia type 1 and von Hippel–Lindau disease, were collected. Primary tumor factors, such as location, size, World Health Organization (WHO) 2017 grade, lymph node, and liver metastasis, were examined. Histological venous invasion, neural invasion, lymphatic invasion, Ki-67 index, mitotic rate, and tumor differentiation were examined, if possible (Table 1). Lymphatic and vascular invasion were evaluated immunohistochemically using D2-40 and CD31, respectively. Tumor grade was classified according to the WHO 2017 Classification. If the discrepancy between the Ki-67 index and mitotic count was identified, the higher grade was assigned according to the WHO recommendation. We quantified the Ki-67 index and mitotic count by counting at least 500 cells in hot spots. All pathological findings were made by at least two pathologists and all findings for the present study were reviewed by one pathologist (YK). Progression-free survival (PFS) was measured from the time of the first treatment until the day of progression or relapse or death due to any cause. Disease progression was determined by radiographic findings every 3 months according to the Response Evaluation Criteria in Solid Tumors version 1.1. Overall survival (OS) was measured from the start of treatment until death. We conducted a prognostic survey of all patients in October 2019.

Computed tomography analysis and protocol

CT was performed using a 64-row CT system (Aquilion 64; Toshiba Medical Systems, Tokyo, Japan). The acquisition parameters for using the multi-detector row CT for hepatobiliary–pancreatic setting in our institution were as follows: tube voltage, 120 kVp; helical pitch, 27.0; and reconstruction thickness, 1.0–2.0 mm. Nonionic iodinated contrast material (Omnipaque 350; Daiichi Pharmaceutical, Tokyo, Japan) was infused at 2 mL/kg of body weight. Contrast medium was administered at a flow rate of 3.0 mL/s. The bolus tracking technique (Real Prep; Toshiba Medical Systems) was used to acquire arterial phase scanning data as described elsewhere (Kato et al. 2020). The region of interest was placed in the abdominal aorta, below the diaphragmatic dome, and the trigger threshold level was set to a CT value of 150 Hounsfield units with a 15-s delay. Portal phase scanning and equilibrium phase were started 80 s and 150 s, respectively, after the contrast media injection. CT images were assessed using SYNAPSE VINCENT® version 5.0 (FUJIFILM Medical, Tokyo, Japan).

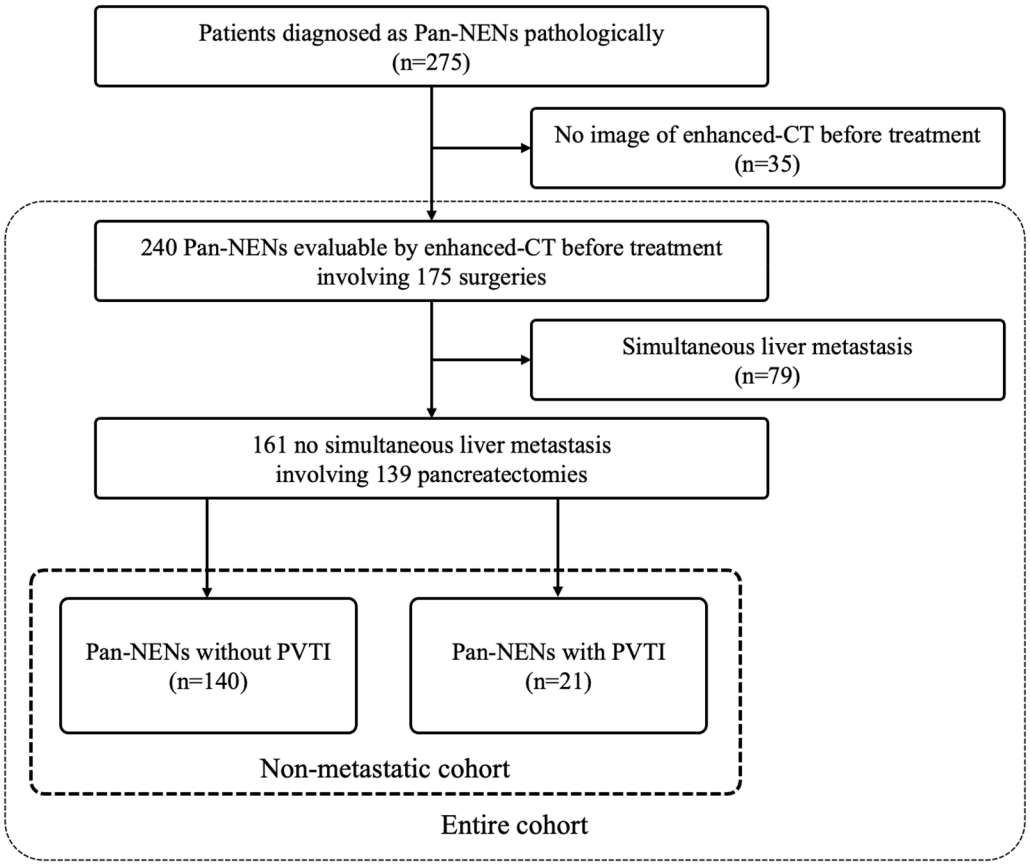

Fig. 1 Study design. *CT* computed tomography; *Pan-NENs* pancreatic neuroendocrine neoplasms; *PVTI* portal venous tumor invasion

We defined PVTI as tumor extension into an adjacent vein with enhancement of the thrombus or tumor invasion with complete occlusion of the splenic vein. PVTIs were classified into four types (Fig. 2). As shown in the upper CT image of Fig. 2, the head of the tumor invasion developing from the pancreatic tumor into the liver parenchyma beyond the portal bifurcation was defined as Vp4. When the head of the PVTI invaded into the SMV, it was defined as Vp3 (middle CT image of Fig. 2). Vp2 was defined as no tumor invasion into the SMV (lower CT image of Fig. 2). No radiologic PVTI cases were defined as Vp0/1 that include no venous invasion (vp0) and histologic venous invasion (vp1). All venous thrombi were observed from the vein near the primary tumor. All CT images were reviewed by two radiologists and one investigator (TK).

Treatment

Pancreatic tumors with or without distant metastasis in the presence or absence of prior chemotherapy were basically resected completely, if possible. The resectability of primary tumor was determined according to the criteria of pancreatic ducal adenocarcinoma. Segmental resection and reconstruction of the portal vein were performed to achieve negative margin, if necessary. R0 and R1 surgery was defined as histologically and macroscopically complete excision of tumor in the transection plane, respectively. Patients with distant metastases or unresectable tumors, such as Vp3 and Vp4, received chemotherapy. When the number of tumors would not increase for 3–6 months or if Vp3–Vp4 tumors would shrink to Vp0/1–Vp2 tumors, complete resection was recommended. Some unresectable metastatic tumors were reduced to palliate the endocrine symptoms of functional tumors.

Statistical analyses

Clinicopathological factors were compared using the Mann–Whitney *U* test and Chi-squared test, and categorical variables were analyzed using Student's *t* test. The cumulative survival rate was calculated using the Kaplan–Meier method, and a statistically significant difference was investigated using the log-rank test. Significant variables with P value < 0.05 were subjected to a multivariate analysis. The multivariate analysis used a logistic regression model to examine factors associated with poor prognosis. Data

Table 1 Patient characteristics in all patients (entire cohort)

Characteristic	Entire cohort $n=240$
Clinical features	
Age, years, median (range)	56 (18–83)
Sex, male, *n* (%)	114 (48%)
NSE, median, ng/mL (range)	12.3 (2.9–1870)
Functionality, *n* (%)	40 (17%)
Genetic syndrome	
MEN type 1, *n* (%)	15 (6%)
VHL disease, *n* (%)	5 (2%)
Tumor	
Location, tail, *n* (%)	93 (39%)
Size, mm, median (range)	20 (0.1–150)
Tumor grade, G1/G2/NET-G3/NEC-G3, *n* (%)	111/86/26/17 (46/36/11/7%)
Macroscopic PVTI, Vp01/2/3/4, n (%)	184/39/11/6 (77/16/5/2%)
Lymph node metastasis, *n* (%)	91 (38%)
Simultaneous liver metastasis, *n* (%)	79 (33%)
Pathology	
Venous invasion, *n* (%)[a]	75 (44%)
Neural invasion, *n* (%)[a]	45 (27%)
Lymphatic invasion, n (%)a	31 (18%)
Ki-67 index, %, median (range)[b]	3.5 (0–90)
Mitotic rate, /10 HPF (range)[b]	1 (0–60)
Treatment	
Surgery, *n* (%)	175 (73%)
Primary resection, *n* (%)	166 (69%)
R0/1 surgery, *n* (%)	150 (63%)
Prior systemic chemotherapy, *n* (%)	29 (12%)

HPF high-power fields; *MEN* multiple endocrine neoplasia; *NEC* neuroendocrine carcinoma; *NET* neuroendocrine tumor; *NSE* neuron-specific enolase; *PVTI* portal venous tumor invasion; *VHL* von Hippel–Lindau

[a]Analyzed from primary resected patients with or without SLM ($n=166$)

[b]Evaluated using specimens obtained by surgery or biopsies in 240 cases

are expressed as median values ± standard deviation. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The median observation period was 894 days. Patients' baseline characteristics are shown in Table 1. The median age of patients was 56 years. Among the 240 patients included, 48% were male. The median NSE value was 12.3 ng/mL (normal range < 16.3 ng/mL). Non-functionality was associated with 200 patients (83%). The numbers of insulinoma, gastrinoma, glucagonoma, VIPoma, and ACTHoma were 21, 12, 5, 1, and 1, respectively. Genetic diseases, such as multiple endocrine neoplasia type 1 (MEN-1) and von Hippel–Lindau disease, were observed in 20 patients (8%).

Tumors were observed in the pancreatic head, body, and tail in 36%, 25%, and 39% of patients, respectively. The median tumor size was 20 mm. The median Ki-67 index was 3.5%, and the median mitotic rate was 1/10 high-power field. A total of 17 patients (7%) had poor differentiated tumors. Based on the 2017 WHO classification, 46%, 36%, 11%, and 7% of patients were graded as NET-G1, NET-G2, NET-G3, and NEC-G3, respectively. Radiologic PVTI was observed in 56 of the 240 patients (23%) based on CT images at the first visit. Moreover, 184 (77%), 39 (16%), 11 (5%), and 6 (2%) patients were classified as Vp0/1, Vp2, Vp3, and Vp4, respectively. In 39 Vp2 patients as judged by CT images, 11 patients had the portal venous tumor thrombus and 28 patients had complete occlusion due to tumor invasion. All patients with Vp3 and Vp4 had the portal venous

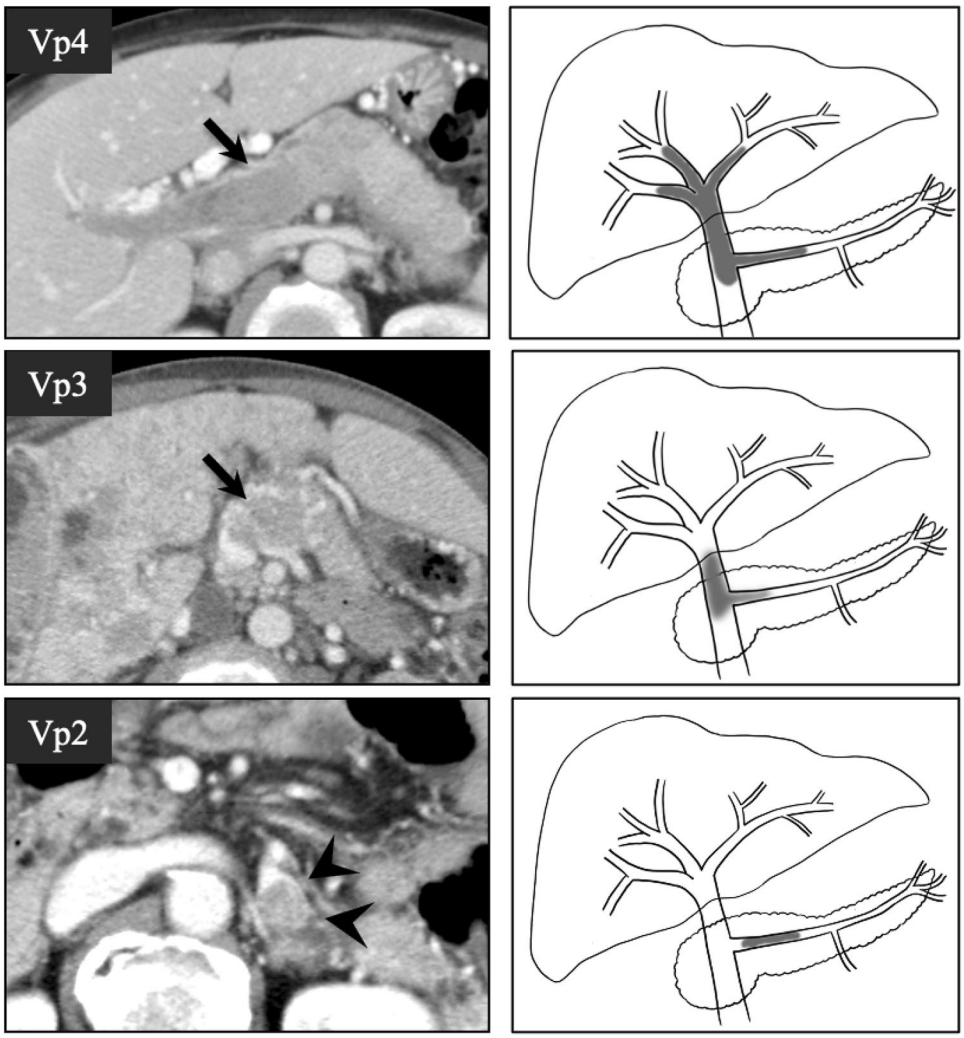

Fig. 2 Radiologic definition of PVTI based on contrast enhanced CT in Pan-NENs. Note the edge of PVTI extending from pancreatic tumor. Vp0/1, Vp2, Vp3, and Vp4 are defined as no PVTI, not invading the superior mesenteric vein (Vp2), PVTI invading the superior mesenteric vein or portal vein (Vp3), and PVTI invading the portal bifurcation (Vp4), respectively. *CT* computed tomography; *Pan-NENs* pancreatic neuroendocrine neoplasms; *PVTI* portal venous tumor invasion

tumor thrombus. Pathological lymph node metastases were observed in 38% of patients. Simultaneous liver metastasis (SLM) was observed in 79 patients (33%). Surgery was performed in 175 patients (73%). Primary tumors were resected in 166 patients with or without SLM (69%). At the first visit, 150 patients underwent R0/1 surgery (63%). Chemotherapy before surgery was performed in 29 patients (12%) with or without hormonal symptoms.

Prognostic factor predicting the prognosis of patients without simultaneous liver metastasis

As shown in Fig. 3, the 5-year OS rate of patients with and without SLM were 46% and 92%, respectively ($P < 0.001$). With SLM, OS can be certainly determined. Moreover, even in patients without SLM, the 5-year OS rates of patients with and without metachronous liver metastases were 76% and 100%, respectively ($P < 0.001$).

These results led us to determine risk factors that are the most responsible for metachronous liver metastases in 161 patients without SLM (Table 2). According to a univariate analysis for PFS, high NSE value ($P = 0.006$), large tumor size ($P < 0.001$), high Ki-67 index ($P < 0.001$), high mitotic rate ($P < 0.001$), pathological lymph node metastasis ($P < 0.001$), venous invasion ($P = 0.02$), neural invasion ($P = 0.04$), lymphatic invasion ($P = 0.01$), non-R0/1 surgery ($P < 0.001$), and radiologic PVTI ($P < 0.001$) were identified as risk factors for PFS. According to a multivariate analysis, Ki-67 index (hazard ratio, 7.3; $P = 0.002$) and radiologic PVTI (hazard ratio, 6.4; $P = 0.01$) were independent risk factors for PFS. As shown in Fig. 4, the 5-year PFS rates of patients with and without PVTI were 18% and 77%, respectively ($P < 0.001$). Moreover, the 5-year OS rates of patients with and without PVTI were 76% and 95%, respectively ($P = 0.02$). These results suggest that preoperatively diagnosed PVTI is an important determinant of prognoses in patients without SLM, indicating that PVTI based on CT images is possibly a prognostic factor for patients with Pan-NEN.

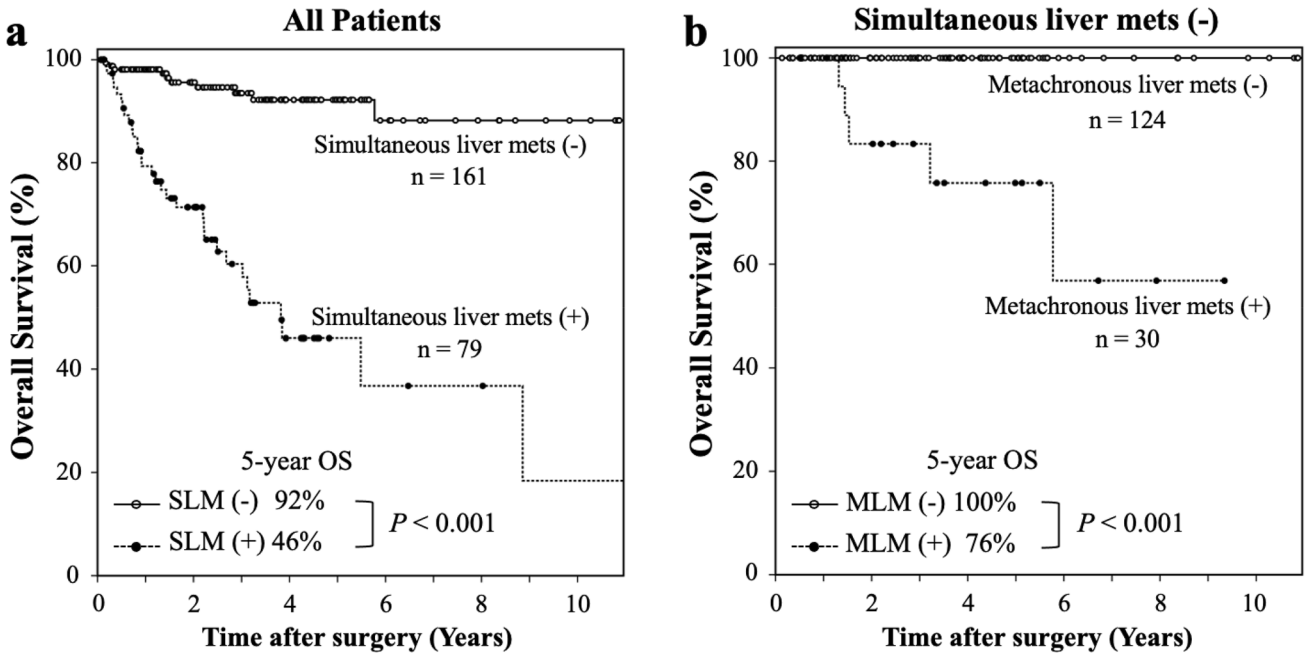

Fig. 3 OS of Pan-NEN patients with and without liver metastasis. **a** OS of 240 patients with or without SLM. **b** OS of 161 patients without SLM in the presence or absence of MLM. *MLM* metachronous liver metastasis; *OS* overall survival; *Pan-NENs* pancreatic neuroendocrine neoplasms; *SLM* simultaneous liver metastasis

Table 2 Multivariate analysis of progression-free survival in 161 patients with pancreatic neuroendocrine tumors without SLM (non-metastatic cohort)

Characteristics in non-metastatic cohort	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age, > 60 years	0.9 (0.5–0.9)	0.8		
Sex, male	1.0 (0.5–1.9)	0.9		
NSE, > 12.3 ng/mL	2.6 (1.3–5.1)	0.006	1.2 (0.5–3.1)	0.7
Location, tail	0.5 (0.2–1.2)	0.1		
Functionality, positive	0.7 (0.3–1.6)	0.4		
Genetic syndrome, positive	0.6 (0.2–2.1)	0.5		
Tumor size, > 20 mm	6.2 (3.0–12)	< 0.001	0.5 (0.1–2.2)	0.4
Ki-67 index, > 3.5%	11 (5.2–22)	< 0.001	7.3 (2.0–26)	0.002
Mitotic rate, ≥ 2/10 HPF	5.1 (2.6–9.8)	< 0.001	1.7 (0.4–7.3)	0.7
Lymph node metastasis, positive	5.1 (2.7–9.6)	< 0.001	0.8 (0.2–2.6)	0.7
Venous invasion, positive	3.1 (1.5–6.4)	0.02	1.0 (0.3–3.8)	1.0
Neural invasion, positive	2.2 (1.0–4.6)	0.04	1.1 (0.4–2.8)	0.9
Lymphatic invasion, positive	3.3 (1.6–6.9)	0.01	2.5 (0.9–6.8)	0.8
Non-R0/1 surgery, positive	4.3 (2.2–8.4)	< 0.001	0.5 (0.1–2.2)	0.4
Radiologic PVTI, positive	5.5 (2.9–10)	< 0.001	6.4 (1.5–27)	0.01

Genetic syndrome includes multiple endocrine neoplasia type 1 and von Hippel–Lindau disease

CI confidence interval; *HPF* high-power fields; *NSE* neuron-specific enolase; *PVTI* portal venous tumor invasion

$P < 0.05$ is considered significant

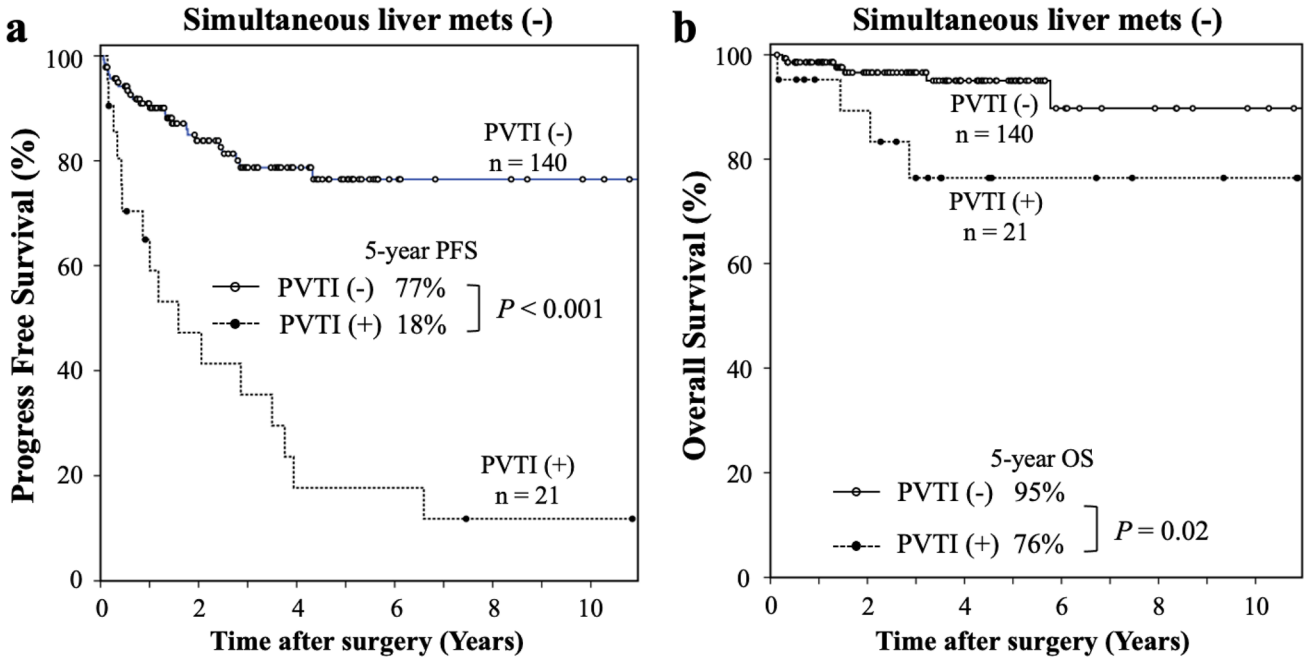

Fig. 4 Prognoses of no SLM Pan-NEN patients in the presence or absence of radiologic PVTI. **a** Progression-free survival. **b** Overall survival. *Pan-NENs* pancreatic neuroendocrine neoplasms; *PVTI* portal venous tumor invasion; *SLM* simultaneous liver metastasis

Characteristics of patients with radiologic portal venous tumor invasion

In this context, these results led us to examine the characteristics of cases with PVTI in 161 patients without SLM (Table 3). PVTI was associated with another malignant risk factors, such as high NSE value ($P = 0.01$), tumor functionality ($P = 0.02$), large tumor size ($P < 0.001$), WHO 2017 tumor grade ($P < 0.001$), pathological lymph node metastasis ($P < 0.001$), venous invasion ($P = 0.004$), neural invasion ($P = 0.04$), high Ki-67 index ($P < 0.001$), and high mitotic rate ($P < 0.001$). As a result, R0/1 surgery may be performed for patients without PVTI rather than those with PVTI ($P < 0.001$), and prior systemic chemotherapy may be provided to patients with PVTI rather than those without PVTI ($P = 0.004$).

In 240 patients, the 5-year PFS rates with and without PVTI were 9% and 60%, respectively, as shown in Supplemental Fig. 1 ($P < 0.001$). The 5-year OS rates of patients with and without PVTI were 62% and 82%, respectively ($P < 0.001$). These results illustrate that PVTI is a prognostic factor for patients with or without SLM. The severity of PVTI depends on tumor size even in 240 patients (shown in Supplemental Fig. 2b). Only 1 of the 124 patients with Pan-NEN with tumors < 20 mm developed PVTI (Vp2), and all patients with tumors > 50 mm developed any kinds of PVTI, such as Vp2, Vp3, and Vp4. The incidence rate of PVTI was also correlated with tumor grade; 6% of NET-G1 patients, 35% of NET G-2 patients, and 50% of NET-G3 patients had any kinds of PVTI (shown in Supplemental Fig. 2c). However, the severity of PVTI did not always depend on tumor differentiation. For example, Vp4 was not observed in both NET-G1 and NEC-G3, but was observed in both NET-G2 and NET-G3.

In cases with PVTI in 161 patients without SLM, a total of 11, 6, and 4 patients had Vp2, Vp3, and Vp4, respectively. Seven Vp2 patients received up-front surgery, and three received surgery after chemotherapy. Eight of the 10 patients who received surgery were achieved R0/1 resection, and six had metachronous liver metastases. One patient with Vp2 could not receive resection because of complicated pancreatitis as a result of chemotherapy. Among the six patients with Vp3, three without severe stenosis of SMV received R0/1 resection and the remaining three with severe stenosis received chemotherapy but could not receive surgery after chemotherapy. In all patients with Vp4 treated with chemotherapy, none had received surgery after chemotherapy. The rate of R0/1 resection in Vp0/1, Vp2, Vp3, and Vp4 patients without SLM were 99, 73, 50, and 0%, respectively (data not shown).

Discussion

Liver metastasis has been considered as the most important determinant for prognosis of patients with Pan-NEN. Properly determining risk factors for metachronous liver metastasis after surgery is considered important. PVTI was

Table 3 Characteristics of 161 patients with pancreatic neuroendocrine tumors without SLM (non-metastatic cohort) according to the presence of portal venous tumor invasion

Characteristic	Non-metastatic cohort $n=161$		*P* value
	PVTI (−) $n=140$	PVTI (+) $n=21$	
Clinical features			
Age, years, median (range)	56 (20–80)	61 (18–83)	0.3
Sex, male, *n* (%)	65 (46%)	10 (48%)	0.9
NSE, median, ng/mL (range)	11.3 (2.9–367)	15.6 (7.5–72)	0.01
Functionality, *n* (%)	19 (14%)	7 (33%)	0.02
Genetic syndrome, *n* (%)	14 (10%)	1 (5%)	0.59
Tumor			
Location, tail, *n* (%)	45 (32%)	5 (24%)	0.7
Size, mm, median (range)	13 (0.1–85)	60 (16–130)	< 0.001
Tumor grade, G1/G2/NET-G3/NEC-G3, *n* (%)	97/35/3/5 (69/25/2/4%)	4/12/3/2 (19/57/14/10%)	< 0.001
Lymph node metastasis, *n* (%)	20 (14%)	13 (62%)	< 0.001
Pathology			
Venous invasion, *n* (%)[a]	39 (31%)	10 (83%)	0.004
Neural invasion, *n* (%)[a]	24 (19%)	5 (42%)	0.004
Lymphatic invasion, *n* (%)[a]	24 (19%)	2 (17%)	0.9
Ki-67 index, %, median (range)[b]	1.6 (0.2–80)	8.0 (1.1–90)	<0.001
Mitotic rate, /10 HPF (range)[b]	1 (0–34)	3.5 (0–60)	<0.001
Treatment			
Surgery, *n* (%)	127 (91%)	12 (57%)	<0.001
Primary resection, *n* (%)	127 (91%)	12 (57%)	<0.001
R0/1 surgery, *n* (%)	126 (90%)	10 (48%)	<0.001
Prior systemic chemotherapy, *n* (%)	5 (4%)	3 (14%)	0.004

CI confidence interval; *HPF* high-power fields; *MEN* multiple endocrine neoplasia; *NEC* neuroendocrine carcinoma; *NET* neuroendocrine tumor; *NSE* neuron-specific enolase; *PVTI* portal venous tumor invasion; *VHL* von Hippel–Lindau disease

$P<0.05$ is considered significant

[a]Analyzed by specimens of primary resections from 139 patients without SLM (PVTI [-], $n=127$; PVTI [+], $n=12$)

[b]Evaluated using specimens obtained by surgery or biopsies in 161 patients without SLM

reported as a risk factor for recurrence in various cancers, such as hepatocellular carcinoma (HCC) and renal cell carcinoma (Ikai et al. 2004; Chan et al. 2016; Kim et al. 2004). However, a study elucidating the malignant potential of PVTI in Pan-NENs has not been conducted yet. The present study confirmed the prognostic importance of SLM and metachronous liver metastases, while it provided evidence that PVTI based on CT images and Ki-67 index determined the PFS rate of patients without SLM. Moreover, the present study initially showed that Pan-NENs with PVTI had high malignant potential, such as high TNM stage and high grade, which may have contributed to the poorer prognosis of patients with PVTI than of those without PVTI. This is the first study to elucidate the malignant evidence of PVTI derived from Pan-NENs. These results suggested that patients with Pan-NEN with PVTI in preoperative CT images should be closely followed up even after complete resection.

The incidence rate of PVTI with Pan-NENs was 3.9–33% (Balachandran et al. 2012; Bok et al. 1984; Stafford-Johnson et al. 1998). The discrepancy may attribute to the difference in both patient characteristics and diagnostic criteria of PVTI using CT. Some studies evaluating PVTI by conventional angiography illustrated that three of 76 patients (3.9%) had PVTI (Bok et al. 1984). The previous largest retrospective study comprising 88 patients reported a high incidence rate of venous tumor thrombus at 33% (Balachandran et al. 2012). It involved nonfunctional Pan-NENs only. The median size of tumors was 46 mm, which was significantly larger than that in a present study (20 mm). Moreover, the previous study did not illustrate the stage of disease and tumor grade. In the present study, the incidence rates

of PVTI in the entire cohort and nonmetastatic cohort were 23% and 13%, respectively. Moreover, tumor grade was strongly correlated with the PVTI status (shown in Supplemental Fig. 2c).

As shown in Table 1, the median age, sex, and rate of nonfunctioning tumor in the present study were consistent with those in the previous large study of 9,821 Pan-NENs using the National Cancer Data Base (Bilimoria et al. 2007). In our nonmetastatic cohort, tumor factors, such as tumor location, tumor size, tumor grade, and pathological lymph node metastasis were similar to those of a previous study about Pan-NENs with nonmetastatic patients (Zaidi et al. 2019) (data not shown). Both 5-year OS and 5-year PFS of the nonmetastatic cohort in the present study were 76% and 92%, respectively. These survival rates were also consistent with those of a previous study (Zaidi et al. 2019).

Several previous retrospective studies have been attempted to identify prognostic factors of Pan-NENs, and several risk factors, such as tumor size, lymph node metastasis, distant metastasis, and Ki-67 index, have been reported as determinant factors (Milione et al. 2019; Partelli et al. 2013; Murphy et al. 2017; Sho et al. 2019). A recent meta-analysis comprising 2822 patients proposed that positive surgical resection margin, lymph node, advanced tumor grade and TNM stage, distant metastasis, vascular invasion, and necrosis of specimens had decreased OS. In Table 2, independent risk factors identified using the multivariate analysis of PFS were Ki-67 index and radiologic PVTI. Tumor size, mitotic rate, lymph node metastasis, and lymphovascular invasion were not considered as prognostic factors, although some tumor size and lymph node metastasis have been key determinants for the WHO classification and International Union Against Cancer staging.

Several biomarkers have been proposed to predict the tumor's malignant potential. According to a previous study, downregulated pancreatic beta cell genes involving PAX6 predicted metachronous liver metastasis (Kudo et al. 2018). Triple positive neuroendocrine markers, such as chromogranin A, synaptophysin, and neural cell adhesion molecule, have been reported as practical indicators of prognoses (Liu et al. 2019). B-cell lymphoma 2 has also been evaluated as a biomarker in Pan-NENs (Yachida et al. 2012). However, these indicators are not determined before surgery. Radiologic PVTI is a prognostic indicator that can be evaluated before surgery, different from the abovementioned biomarkers. PVTI may predict poor prognosis more efficiently before surgery than other biomarkers and may determine patients who require more careful postoperative follow-up.

As shown in Table 3, tumors with PVTI had correlation with many factors related to malignancy, such as high tumor grade or lymphovascular invasion. The severity of PVTI based on CT images did not contribute to the prognoses of all patients, as shown in Supplemental Fig. 3. However, it is difficult to conclude that the severity of PVTI may not decide the prognoses of patients, because all patients with radiologic PVTI did not always receive R0/1 surgery. For example, three out of 6 patients with Vp3 could not receive R0/1 resection due to the presence of the severe SMV stenosis with tumor thrombus. In this context, it is possible that 8 out of 11 Vp2 patients and 127 out of 140 Vp0/1 patients actually received R0/1 surgery. Moreover, the number of patients with Vp3 and Vp4 was too small to discuss the prognosis. So, PVTI grading may be useful for evaluating the residual tumor status in the nonmetastatic cohort. Supporting our results, the previous report suggested that the presence of PVTI could be a determinant of the operation plan (Balachandran et al. 2012).

The portal vein obstruction revealed by preoperative imaging correlated with a poor prognosis regardless of its PVTI degree. The obstruction with tumor thrombosis may easily cause liver metastasis, and tumor invasion that causes portal vein obstruction may also increase the opportunity of distant metastasis. Portal vein obstruction may cause superior mesenteric venous hypertension and many side collateral circulation routes, spreading microtumors to distant organs involving liver. Although the CT findings of PVTI determined the prognosis, the severity of PVTI levels cannot always predict the prognosis due to the above-mentioned complicated pathological conditions.

Multidisciplinary treatment against patients with severe PVTI was an important issue to improve patients' clinical outcomes. In the treatment of HCC, radiotherapy has recently emerged as a valid treatment option (Dawson 2011; Zhang et al. 2009), and several retrospective studies reported a favorable toxicity of radiotherapy for PVTI (Huang et al. 2009; Lee et al. 2014). Additional treatment with chemotherapy, such as radiotherapy, may be required for unresectable local progression with PVTI even in the treatment of Pan-NENs.

This study has some limitations. This study had selection bias, because it was a retrospective study conducted at a single institution. The relatively small sample size possibly limited our analysis to determine other important prognostic factors. A long enrollment period of patients from 2002 to 2019 was also observed. All treatments were predominately performed to Asian patients. Despite these limitations, the present study could determine the novel aspect regarding the treatment of Pan-NENs. We hope that this novel biomarker could be beneficial in the treatment of all Pan-NENs.

In conclusion, this study showed that PVTI plays a pivotal role in the treatment of Pan-NENs as an important prognostic factor. Patients with PVTI had a high risk of postoperative recurrences even after complete resection, and these patients should be closely followed up after surgery.

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Availability of data and material The data sets analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest There are no conflicts of interests for any of the authors.

Ethical approval This study was approved by the ethics committees of the faculty of Tokyo Medical and Dental University (permission no. M2000-1080, G2017-018).

Informed consent All patients provided written informed consent for inclusion in the study.

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