Izumo *et al.*
World Journal of Surgical Oncology (2025) 23:79
https://doi.org/10.1186/s12957-025-03734-0

World Journal of Surgical Oncology

RESEARCH

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Evaluation of the details and importance of lymphatic, microvascular, and perineural invasion in patients with non-functioning pancreatic neuroendocrine neoplasms based on tumor size and the 2022 World Health Organization classification: a 23-year retrospective analysis

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Abstract

Background Although, recently observation methods has been proposed as one of the treatment options for non-functioning pancreatic neuroendocrine neoplasms (NF-PanNENs), determining treatment strategies may be difficult for small and low-malignant NF-PanNENs; thus, clarifying the significance of lymphatic, microvascular, and perineural invasion in these patients is of great clinical importance. This study aimed to assess the incidence and role of lymphatic, microvascular, and perineural invasion in patients with NF-PanNENs based on tumor size and the 2022 World Health Organization classification.

Methods From 2000 to 2023, we retrospectively investigated the incidence of lymphatic, microvascular, and perineural invasion and their impact on recurrence in 80 patients who underwent curative resection and were diagnosed with NF-PanNENs.

Results Of the 80 patients, 14 (18%), 20 (25%), and six (9%) patients had lymphatic, microvascular, and perineural invasion. Patients with neuroendocrine tumor (NET) G1 had significantly fewer occurrences of lymphatic, microvascular, and perineural invasion than those with NET G2 (10%, 15%, and 7% vs. 40%, 55%, and 35%; all $P < 0.05$.). Patients with a tumor size < 20 mm had significantly lower rates of lymphatic and microvascular invasions than those with a tumor size ≥ 20 mm (12% and 17% vs 33% and 48%; $P = 0.034$ and 0.0073, respectively). In all patients, NET G2, tumor size ≥ 20 mm, local invasion T2–3, presence of lymph node metastasis, and presence of microvascular invasion were significant risk factors for shorter recurrence-free survival (RFS) (all $P < 0.05$). In patients with NET G1 and tumor

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size < 20 mm, five (10%), eight (16%), and four (8%) patients had lymphatic, microvascular, and perineural invasion. The presence of microvascular invasion was also an independent risk factor for RFS ($P < 0.05$).

Conclusions Information on the frequency and role of lymphatic, microvascular, and perineural invasion based on tumor size and malignancy on recurrence may be useful when considering treatment strategies for small- and low-grade NF-PanNENs.

Keywords Microvascular invasion, Lymphatic invasion, Perineural invasion, Recurrence, Non-functioning pancreatic neuroendocrine neoplasm

Background

Neuroendocrine neoplasms (NENs) are a general term for tumors arising from neuroendocrine cells. They are classified as Neuroendocrine tumor (NET) G1, NET G2, NET G3, neuroendocrine carcinoma (NEC), and mixed neuroendocrine and non-neuroendocrine neoplasm (MiNEN) based on the Ki-67 proliferation index, mitotic index, and histological differentiation grade; each has a different oncological malignancy and prognosis [1]. In addition, pancreatic NENs (PanNENs) include those accompanied by hormone production symptoms and those with genetic backgrounds, each of which is thought to have different malignancies and therapeutic indications [2–5].

In recent years, the number of patients with PanNENs has been increasing owing to advances in diagnostic imaging technologies and the widespread recognition of PanNEN [6–10]. The incidence of small, well-differentiated, localized, and non-functioning (NF)-type PanNENs (NF-PanNENs) has gradually increased. Radical surgical resection is the only curative and survival-prolonging treatment for localized NF-PanNENs [10, 11]. However, observation has recently been proposed as one of the treatment strategy or small and low-grade NF-PanNENs [2–4, 12]. This is thought to be due to the high rate of morbidity associated with surgical resection for NF-PanNENs [13], in addition to the possibility that these NF-PanNENs are not highly malignant [12]. However, it is still not clear whether this watchful waiting is acceptable.

Previous studies have reported that indicators, such as the World Health Organization (WHO) grading, local tumor invasion, synchronous lymph node metastasis (LNM), and liver metastasis, are associated with prognosis in patients with NF-PanNENs [14–18]; however, the relationship between lymphatic, microvascular, and perineural invasion and patient outcomes remains unclear.

In various gastroenterological cancers and NENs, if histopathological factors, including lymphatic and/or microvascular invasion, are detected after endoscopic treatment, radical surgery with lymph node dissection is an additional treatment option to improve outcomes [5, 19–21]. Conversely, if pathological examination after endoscopic local resection shows no lymphatic or microvascular invasion, the possibility of metastasis is low and additional treatment may not be necessary [5, 19–21]. This recommendation is based on the oncological role of lymphatic and/or microvascular invasion in these cancers and neoplasms, which has been investigated and discovered to be suggestive of potential LNM and poor prognosis. Lymphatic and microvascular invasion are essential for tumor metastasis from local areas to other sites [5, 19–21]. To become a selective option for some NF-PanNENs, which are considered low-grade malignancies, it is important to clarify the role and frequency of lymphatic, microvascular, and perineural invasions, which are potential indicators of distant metastasis.

Moreover, although a few previous studies have reported the frequency of these invasions in patients with PanNENs, these studies included a mixture of various PanNENs, some of which contained functionality, hereditary disease, and different WHO grades [22–26]. Owing to the diversity of the patient backgrounds, it is difficult to draw clear conclusions from these previous studies regarding the role of lymphatic, microvascular, and perineural invasion in patients with NF-PanNET G1 and G2 without genetic backgrounds. Because NF-PanNET G1 and G2 are the most common type of PanNEN and determining treatment strategies may be difficult, clarifying the significance of lymphatic, microvascular, and perineural invasion in these patients is of great clinical importance.

Therefore, we aimed to reveal the detailed features and prognostic significance of lymphatic, microvascular, and perineural invasion in patients with NF-PanNET G1 and G2 without genetic diseases, especially based on tumor size and the WHO 2022 classification. Large-scale observational studies are required to clarify the oncological significance of these findings. Therefore, a preliminary pilot study was conducted.

Methods

Study design

This study was approved by the institutional review board of Yamanashi University (approval number: H30897). The requirement for informed consent was waived due to the retrospective nature of this study. In

this retrospective study, we analyzed the medical records of 94 patients who underwent curative surgical resection for PanNEN at the Department of Digestive Surgery, University of Yamanashi Hospital between 2000 and 2022. We excluded patients who underwent residual tumor resection; had hormone-producing symptoms; had genetic diseases, such as multiple endocrine neoplasia type 1 (MEN type 1) and von Hipple Lindau (VHL); a pathological grade NET G3, NEC, and MiNEN; or had an unknown examination status. Finally, 80 patients who underwent curative surgical resection of G1 and G2 NF-PanNETs were retrospectively analyzed. We analyzed the frequency of lymphatic, microvascular, and perineural invasion and evaluated the association between clinicopathological factors and recurrence-free survival (RFS) based on tumor size and malignant grade, as defined by the 2022 WHO classification [1].

The clinicopathological data were collected and examined. The preoperative parameters included age, sex, diagnostic opportunity, and tumor location. Intraoperative parameters included the type of surgical procedure and number of dissected lymph nodes. Postoperative parameters included postoperative complication grade defined by the Clavien–Dindo classification [27]; Ki-67 index of pathological tumor specimens; 2022 WHO classification [1]; pathological tumor size; grade of local invasion; the existence of LNM; the presence of lymphatic, microvascular, and perineural invasion; recurrence; recurrence period; and prognosis.

Definition of NF-PanNEN

PanNEN was defined as exhibiting cord-like, rosette-like, and alveolar-like structures detected using hematoxylin and eosin staining; immunohistochemical staining for chromogranin A and synaptophysin protein markers was positive; and other pancreatic tumors were excluded by histopathological examination. We defined PanNEN without clinical symptoms of hormone production as NF-PanNEN. Based on the 2022 WHO classification [1], well-differentiated NF-PanNENs with Ki-67 proliferation indices < 3%, 3–20%, and > 20% were defined as NET G1, NET G2, and NET G3, respectively. In addition, poorly differentiated NF-PanNEN with a Ki-67 proliferation index > 20% was defined as NEC G3. PanNENs containing 30% or more of each neuroendocrine and non-neuroendocrine component were classified as MiNENs.

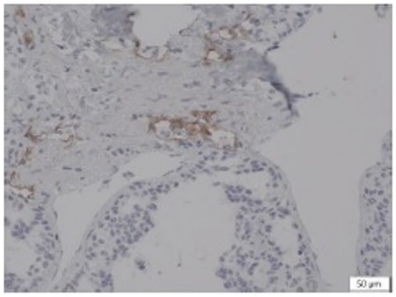
Assessment of lymphatic, microvascular, and perineural invasion

Lymphatic invasion was indicated by the presence of cancer cells and nests in the interstitial space. A space filled with lymph and lymphocytes is likely to be a lymphatic vessel, and this space was concluded to represent a lymphatic vessel when the endothelial cells were identified around the space. The presence or absence of lymphatic invasion was evaluated using D2-40 immunohistochemical staining. Microvascular invasion is likely when a circular, semicircular, or oblong tumor cell nest with regular margins is located in the vicinity of the vessels and distant from the main lesion. When a tumor cell nest is surrounded by venous wall structures, such as an internal elastic membrane or perivascular smooth muscle, it is considered to represent microvascular invasion. Victoria blue and/or Elastica Van Gieson staining was used to elucidate the elastic fibers in the vessel walls. Perineural invasion was detected based on the presence of tumor cells in the perineural space and nerve fiber bundles. S-100 protein staining was used to assist in the diagnosis of perineural invasion. Perineural invasion was defined as an invasion distinct from the extrapancreatic plexus nerve invasion. Immunohistochemical staining, which aids in the diagnosis of lymphatic, microvascular, and perineural invasion, was routinely performed as necessary to aid in the interpretation of hematoxylin and eosin staining and evaluated by staining representative cut sections of the tumor. Representative immunohistochemical images of lymphatic, microvascular, and perineural invasions are show in Fig. 1.

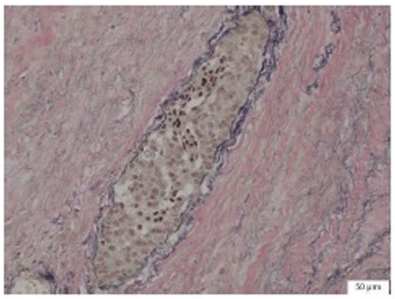
Surgical procedure

In this study, pancreaticoduodenectomy (PD), distal pancreatectomy (DP), and total pancreatectomy (TP) were the major resection procedures. Spleen-preserving DP, central pancreatectomy, enucleation, and partial pancreatectomy were defined as limited resection procedures. Regional LND was performed with major resection. In patients who underwent PD, the LND region included the area around the subpyloric, infrapyloric, common hepatic artery (CHA), hepatoduodenal ligament, anterior and posterior surfaces of the pancreatic head, and the superior mesenteric artery (SMA). In patients who underwent DP, the LND regions included the areas along the left gastric artery, CHA, celiac artery, splenic hilum, splenic artery, SMA, and the inferior margin of the pancreas. In the patients who underwent TP, the LND regions included the PD and DP. In limited resections, LND was only partially performed around the NF-PanNEN, such as LN sampling resection; regional LND was not performed. This was because the Japanese guidelines allow for limited resection with partially LND for small NF-PanNEN [5]. We performed major resection with regional LND for large tumors and/or NET G2, which were preoperatively diagnosed using endoscopic ultrasonography-guided fine-needle aspiration. Conversely, limited resection was performed in patients with small tumors and NET G1 in whom LNM was not suspected in

(a) Presence of lymphatic invasion using D2-40 immunohistochemical staining.



(b) Presence of microvascular invasion using Elastica Van Gieson staining.



(c) Presence of perineural invasion using S-100 protein staining.

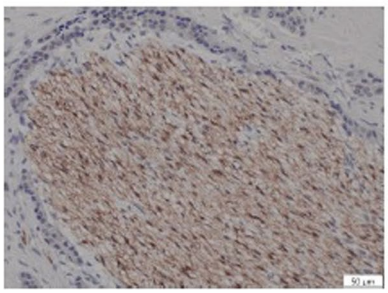


Fig. 1 Representative histologic and immunohistochemical images of lymphatic, microvascular, and perineural invasions. **a** Presence of lymphatic invasion using D2-40 immunohistochemical staining. **b** Presence of microvascular invasion using Elastica Van Gieson staining. **c** Presence of perineural invasion using S-100 protein staining

preoperative imaging studies. In addition, limited resection is sometimes performed, depending on the patient's background and tumor location. Particularly, in cases of tumor lesions in the pancreatic head, limited resection is sometimes performed instead of major resection.

Follow-up

After surgery, the patients underwent laboratory examinations and imaging studies every 3–6 months as a standard follow-up strategy for the first 5 years. In principle, imaging studies, including ultrasonography (US), contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), somatostatin receptor scintigraphy, and positron emission tomography, were performed when indicated. The choice of imaging modality ultimately depended on the discretion of the attending physician and the patient's general condition. The follow-up strategy continued beyond 5 years after surgery, as long as the patients were able to attend a hospital, and the patients who were followed up at other hospitals were referred back to our hospital when necessary. Five years postoperatively, patients underwent the same examinations every 6–12 months. A tumor initially identified in postoperative imaging studies

was considered a recurrence. Elevations in tumor markers alone, such as neuron-specific enolase and pro-gastrin-releasing peptide, were not considered to indicate recurrence. All sites were counted when two or more recurrence sites were simultaneously observed. After NF-PanNEN recurrence, drug therapy, surgical resection, and/or peptide receptor radionuclide therapy (PRRT) were planned and performed according to the patient's background and tumor status. RFS time was calculated from the day of surgery until the diagnosis of recurrence or the last follow-up day if there was no recurrence.

Statistical analyses

We selected factors that seemed to be clinically and pathologically relevant to the prognosis as the factors to be examined. Univariate analysis was performed to determine independent predictors of RFS in patients with NF-PanNENs. RFS rates were compared based on the presence or absence of risk factors identified in the univariate analysis. Because only a small number of recurrences were caused by NF-PanNENs, only the univariate analysis was performed for RFS. Survival analyses were performed using the Kaplan–Meier method, log-rank test, and Cox proportional hazards model. The Chi-square test was used to analyze the frequency between the two groups. Statistical significance was set at $P < 0.05$. All analyses were performed using JMP 17.0.0 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics are shown in Table 1. Based on the 2022 WHO classification, 60 (75%) and 20 (25%) patients had NET G1 and NET G2. The median tumor size was 12 (2–80) mm and the number of patients with tumor size < 20 mm and ≥ 20 mm was 59 (74%) and 21 (26%), respectively. Fourteen (18%), 20 (25%), and 6 (9%) patients had lymphatic, microvascular, and perineural invasion. The correlation between microvascular, lymphatic, and perineural invasion is shown in Supplemental Table 1. Regarding the local invasion, 58 (73%), 13 (16%), and nine (11%) had T1, T2, and T3, respectively. Four patients (5%) had synchronous LNM. Six patients

Table 1 Patient characteristics

		n **= 80**
Age (years, range)		**64(30–81)**
Sex	Male / Female	44 (55%) / 36 (45%)
Diagnostic opportunity	Medical check-up / Follow-up for another disease / Detected by resected specimens / Abdominal pain	55 (68%) / 20 (25%) / 3 (4%) / 2 (3%)
Tumor location	Head / Body / Tail	31 (39%) / 24 (30%) / 25 (31%)
Surgical procedures	Major resection	40 (50%)
	DP / PD / TP	21 / 18 / 1
	Limited resection	40 (50%)
	SPDP / PP / EN / CP	20 / 15 / 3 / 2
Number of dissected lymph node		4 (0–27)
Postoperative complications	≥ III	26 (33%)
Ki-67 index (%, range)		2 (1–10)
WHO 2022 classification	NET G1 / NET G2	60 (75%) / 20 (25%)
Pathological tumor size (mm, range)		12 (2–80)
Local invasion	T1 / T2 / T3	58 (73%) / 13 (16%) / 9 (11%)
Synchronous lymph node metastasis	With	4 (5%)
Lymphatic invasion	With	14 (18%)
Microvascular invasion	With	20 (25%)
Perineural invasion	With	11 (14%)
Recurrence	With (duplication)	6 (9%)
	Liver / Paraaortic lymph node	6 / 1
Recurrent period after surgery (years, range)		2.0 (0.6–11.3)
Dead form NF-PanNEN		2 (3%)
Dead from another disease		9 (11%)
Postoperative observation period (years, range)		6.8 (0.3–23.3)

Abbreviations: *DP* Distal pancreatectomy, *PD* Pancreaticoduodenectomy, *TP* Total pancreatectomy, *SPDP* Splenic preserving distal pancreatectomy, *PP* Partial pancreatectomy, *EN* Enucleation, *CP* Central pancreatectomy, *WHO* World Health Organization, *NET* Neuroendocrine tumor, *NF-PanNEN* Non-functioning pancreatic neuroendocrine neoplasm

(9%) experienced recurrence, and the median recurrent period after surgery was 2.0 years (range: 0.6–11.6). The 1-, 3-, and 5-year RFS rates were 98.7, 93.2, and 93.2%, respectively. Recurrence (with duplication) predominantly occurred in the liver (six patients), followed by the para-aortic LN (one patient). Only two patients (3%) died from NF-PanNENs, whereas nine patients (11%) died from another disease.

Frequency of lymphatic, microvascular, and perineural invasion based on the tumor size and WHO grading

Based on the 2022 WHO classification, patients with NET G1 had significantly fewer occurrences of lymphatic, microvascular, and perineural invasion than those with NET G2 (NET G1: 10, 15, and 7%. NET G2: 40, 55, and 35%; $P=0.004, <0.001$, and 0.0031, respectively) (Table 2a). From the viewpoint of tumor size, patients with tumor size < 20 mm had significantly lower rates of lymphatic and microvascular invasion than those with tumor size ≥ 20 mm (< 20 mm: 12 and 17%; ≥ 20 mm: 33 and 48%; $P=0.034$ and 0.0073, respectively) (Table 2b). Moreover, the incidence rates of these invasions in patients with tumor size < 10 mm were 14%, 14%, and 5%, respectively, and microvascular invasion was significantly less prevalent in smaller tumor sizes (Supplemental Table 2). The frequency of these invasions in patients with a combination of the 2022 WHO classification and tumor size is shown in Table 2c. Even among patients with NET G1 and tumor size < 20 mm, lymphatic, microvascular, and perineural invasion was observed in 10, 16, and 8% of cases, respectively.

Risk factors and scoring system for RFS

In the univariate analysis, NET G2 (vs. NET G1, $P<0.001$), tumor size ≥ 20 mm (vs. < 20 mm, $P=0.03$), local invasion T2–3 (vs. T1, $P=0.038$), LNM (vs. absence, $P=0.0012$), and presence of microvascular invasion (vs. absence, $P=0.0079$) were significant risk factors for shorter RFS (Table 3). When each assigned risk score was one point, the 5-year RFS rates of patients with risk scores of 0 ($n=42$), 1 ($n=14$), 2 ($n=11$), 3 ($n=4$), 4 ($n=6$), and 5 ($n=3$) were 100%, 91.7%, 90.0%, 80.0%, 66.7%, and 66.7, respectively ($P=0.014$). Moreover, the 5-year RFS rates of patients with risk scores of 0–1 ($n=56$) and 2–5 ($n=24$) were 98.1% and 81.7% ($P=0.0046$) (Fig. 2). The hazard ratio (HR) of the risk score groups 2–5 was 2.8 times higher than that of risk score groups 0–1 ($P=0.040$). Similarly, in patients with NET G1 and a tumor size < 20 mm, LNM (vs. absence, $P<0.001$) and microvascular invasion (vs. absence, $P=0.020$) were independent risk factors for RFS (Supplemental Table 3). When each assigned risk score was one point, the 5-year RFS rates of patients with risk scores of 0 ($n=43$) and 1–2 ($n=8$) were 100% and 87.5% ($P=0.020$).

Discussion

This study is the first to clarify the detailed frequency of lymphatic, microvascular, and perineural invasion according to tumor size and latest WHO grading in patients with NF-PanNENs based on a uniform pathological diagnostic method. We revealed that even in patients with NET G1 and tumor size < 20 mm, microvascular invasion was a risk factor for recurrence, with an incidence of 16%. Moreover, a risk-scoring system that

Table 2 Frequency of lymphatic, microvascular, and perineural invasion based on the 2022 World Health Organization classification and tumor size

(a)

	NET G1 ($n=60$)	NET G2 ($n=20$)	*P* value
Presence of lymphatic invasion	6 (10%)	8 (40%)	0.004
Presence of microvascular invasion	9 (15%)	11 (55%)	< 0.001
Presence of perineural invasion	4 (7%)	7 (35%)	0.0031

(b)

	Tumor size < 20 mm ($n=59$)	Tumor size ≥ 20 mm ($n=21$)	*P* value
Presence of lymphatic invasion	7 (12%)	7 (33%)	0.034
Presence of microvascular invasion	10 (17%)	10 (48%)	0.0073
Presence of perineural invasion	6 (10%)	5 (24%)	0.14

(c)

	NET G1 and tumor size < 20 mm ($n=51$)	NET G1 and tumor size ≥ 20 mm ($n=9$)	NET G2 and tumor size < 20 mm ($n=28$)	NET G2 and tumor size ≥ 20 mm ($n=12$)	*P* value
Presence of lymphatic invasion	5 (10%)	1 (11%)	2 (25%)	6 (50%)	0.023
Presence of microvascular invasion	8 (16%)	1 (11%)	2 (25%)	9 (75%)	0.0007
Presence of perineural invasion	4 (8%)	0 (0%)	2 (25%)	5 (42%)	0.0031

Abbreviations: *RFS* Recurrence-free survival, *WHO* World Health Organization, *NET* Neuroendocrine tumor

Table 3 Univariate analysis of risk factors for recurrence-free survival in all patients

			Univariate	
Prognostic factors	**Definition**	**n**	**5-year RFS**	***P* value**
Symptom	Without	78	92.9	0.97
	With	2	100	
Tumor location	Head	31	96.7	0.47
	Body or Tail	49	90.6	
Surgical procedure	Limited	40	100	0.076
	Major	40	85.6	
Postoperative complications	≤ II	54	92.0	0.30
	≥ III	26	95.5	
WHO 2022 classification	NET G1	60	98.3	< 0.001
	NET G2	20	76.7	
Tumor size (mm)	< 20	59	96.4	0.030
	≥ 20	21	82.9	
Local invasion	T1	58	96.4	0.038
	T2-3	22	83.8	
Lymph node metastasis	Absence	76	95.5	0.0012
	Presence	4	50.0	
Lymphatic invasion	Absence	66	95.0	0.21
	Presence	14	83.3	
Microvascular invasion	Absence	60	98.1	0.0079
	Presence	20	79.2	
Perineural invasion	Absence	69	93.7	0.74
	Presence	11	88.9	

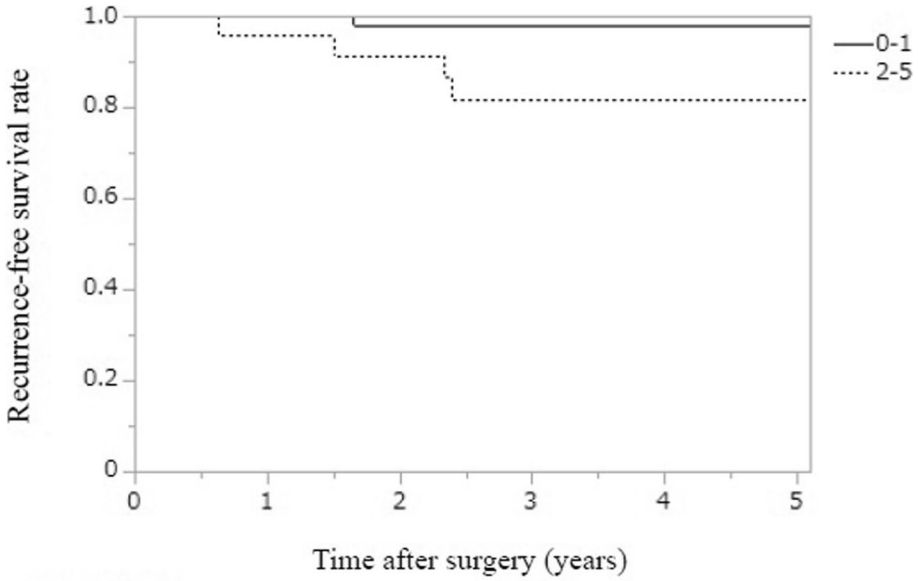
Abbreviations: *RFS* Recurrence-free survival, *WHO* World Health Organization, *NET* Neuroendocrine tumor

includes the presence of microvascular invasion may be useful for predicting recurrence. These findings are novel and may be informative when considering treatment strategies for patients with NF-PanNENs, especially for those with small- and low-grade malignancies.

NENs were previously called carcinoids [28]; however, they are now classified according to the 2022 WHO definition based on the Ki-67 proliferation index, mitotic index, and histological degree of differentiation. According to the latest 2022 WHO classification [1], PanNEN is classified into NET G1, NET G2, NET G3, NEC, and MiNEN, which have different oncological malignancies and prognoses. NET has a histologically well-differentiated type and initially has low-grade nuclear features; however, as it progresses from NET G1 to NET G2 and NET G3, the prognosis becomes poor. In contrast, NEC is a high-grade malignancy at an early stage and clinically exhibits aggressive behavior and poor survival [29]. NECs containing certain amounts of adenocarcinoma, squamous cell carcinoma, acinar cell carcinoma, or other components are known as MiNENs. Recently, genetic analysis demonstrated that the genetic mutations and onset mechanisms of NET and NEC are different [30]. In addition, there are two types of PanNENs: functioning-PanNENs, which have hormone-producing symptoms, such as insulinoma and gastrinoma, and NF-PanNENs, which do not have different oncological malignancies, prognoses, or treatment strategies [2–5]. It is also known that NF-PanNENs coexist with hereditary diseases, such as MEN Type 1 and VHL, and the malignancies and treatment strategies differ depending on the presence or absence of these genetic backgrounds [2–5]. Thus, PanNEN should be considered a comprehensive collective term for tumors with diverse oncological and clinical characteristics derived from neuroendocrine cells. Individual treatment strategies are needed for each PanNEN.

PanNEN was previously considered a rare malignant neoplasm; however, recently, its incidence has gradually increased [6–10]. As the frequency of PanNENs increases, several clinicopathological factors associated with the prognosis of PanNENs, such as WHO grading, tumor size, LNM, liver metastasis, and some immune nutritional indices, have been reported [14–18]. However, these studies examined a variety of PanNENs together, and careful consideration is required for interpretation because of the diversity of PanNENs.

The standard treatment for NF-PanNENs is radical surgical resection [10, 11]. In recent years, some guidelines have proposed observation as an optional treatment strategy for small, low-grade NF-PanNENs [2–4]. The National Comprehensive Cancer Network guidelines mention that in patients with NF-PanNENs with tumor size < 2 cm and incidental detection, observation is considered a treatment option based on estimated surgical risk, tumor location, and patient comorbidities [2]. The European Neuroendocrine Tumor Society guideline stated that non-operative management was tolerable in patients with NF-PanNENs with a tumor size ≤ 20 mm, NET G1, low malignant NET G2, asymptomatic, and located in the pancreatic head [3]. The North American Neuroendocrine Tumor Society guidelines described that initial observation is an acceptable treatment strategy for NF-PanNENs that are asymptomatic and with a tumor size < 1 cm, and recommended that the decision to observe or resect an asymptomatic NF-PanNET 1–2 cm in size be individualized [4]. A large multicenter study from Japan proposed observational treatment in patients with NF-PanNET G1 and tumor size < 20 mm or NF-PanNET G2 and tumor size < 10 mm, based on the outcome after curative surgery [12]. A past report from Brazil showed that both observation and surgical resection were same outcome in patients with NF-PanNET and tumor size < 20 mm [31]. From Chinese literature, a monogram predicting prognosis has been reported, with the cut-off value for tumor size set at 26 mm [32].



Numbers at risk

Year	0	3 years	5 years
Risk scores 0–1	56	49	43
Risk scores 2–5	24	17	16

Fig. 2 Kaplan–Meier analyses of recurrence-free survival (RFS) rates in patients with non-functioning pancreatic neuroendocrine neoplasms (NF-PanNENs) depending on the risk score. The 5-year RFS rates of patients with risk scores of 0–1 and 2–5 were 98.1% and 81.7% ($P = 0.0046$). The hazard ratio (HR) of risk score groups 2–5 was 1.8 times higher than that of risk score groups 0–1 ($P = 0.040$)

Furthermore, a nationwide survey in Korea reported that tumor size was not a significant risk factor for recurrence [33]. However, all these suggestions are based on retrospective studies, and their reliability is unclear. Currently, a nationwide prospective cohort study of watchful waiting for small NF-PanNENs in the Netherlands [34], and a comparative prospective multicenter cohort study of resection versus observation for small, asymptomatic, and sporadic NF-PanNENs in Europe [35], are being conducted, the results of which should be closely monitored.

Metastasis of malignant neoplasms from the primary site to other organs can occur via hematogenous and/or lymphatic routes, while local recurrence can occur via infiltration of surrounding nerve plexuses; however, microvascular, lymphatic, and perineural invasion are prerequisites for these events. In some gastrointestinal cancers and NETs, the presence of lymphatic and/or microvascular invasion is used to determine whether additional radical resection with regional LND is indicated after endoscopic local treatment [5, 19–21]. The impact of these factors on prognosis has been clarified; however, there has been insufficient research on the frequency and role of these factors in NF-PanNENs. In particular, if an observation strategy is to be accepted as an option for small, low-grade NF-PanNENs, the incidence and prognostic impact of lymphatic, microvascular, and perineural invasion must be clarified. Furthermore, in NF-PanNENs, there is still no evidence that additional radical resection with regional LND based on pathological factors after local resection improves the prognosis, and it is not realistic to perform it in clinical practice. Therefore, the presence of lymphatic, microvascular, and perineural invasion should be used as predictors of recurrence rather than as indications for additional resection after minimally invasive local treatment. In this study, considering the oncological diversity of PanNENs, we clarified the frequency of these invasions, and the importance of recurrence based on tumor size and malignant grade. The fact that microvascular invasion is a risk factor for recurrence and has an incidence of 16%, even in patients with NF-PanNENs with NET G1 and tumor size < 20 mm, should be taken into consideration when selecting treatment strategies for small, low-grade NF-PanNENs. Postoperative adjuvant therapy improves recurrence rates and prognosis for many cancers [19–21], and is therefore implemented; however,

no adjuvant therapy has been proven to be effective for NF-PanNENs. Future clinical trials are required to demonstrate the significance of adjuvant therapy in NF-PanNENs and to identify cases with a high risk of recurrence and poor prognosis. Our proposed risk-scoring system, which includes microvascular invasion, may help identify patients who are candidates for adjuvant therapy.

In clinical practice, CT, MRI, and US are often used as routine postoperative imaging modalities and are performed every 3–12 months based on the WHO grading. Recently, somatostatin receptor scintigraphy has been recommended every 2 years for NET G1 and every year for NET G2 and G3 [3]. Furthermore, in patients undergoing non-operative management, these examinations should be performed periodically during the follow-up period. However, these imaging techniques are expensive and physically invasive. Therefore, indiscriminately using these imaging modalities is undesirable. The recurrence risk scoring system and the incidence of microvascular invasion identified in this study may also be useful when considering the frequency of these examinations.

This study had some limitations. First, this observational study spanned over a long period of 23 years. The patients received different diagnoses and treatments at various times. In particular, changes in imaging modalities and surgical procedures were significant and may have affected patient outcomes. Second, because the number of recurrences and deaths from NF-PanNENs was low and the number of deaths due to other diseases was higher, RFS was analyzed only in the univariate analysis, and disease-specific survival and overall survival rates were not analyzed, rendering these evaluations insufficient. Finally, given that our investigation was retrospective and conducted at a single institution, the inherent biases in such settings cannot be excluded. These results are satisfactory as a pilot study to clarify the details and oncological importance of lymphatic, microvascular, and perineural invasion based on tumor size and malignancy; however, large-scale research is required to confirm these results.

Conclusions

In conclusion, we revealed the details and importance of lymphatic, microvascular, and perineural invasion based on tumor size and the 2022 WHO classification, and subsequently developed a recurrence predictive score. These results may be useful when considering treatment strategies, particularly for small and low-grade NF-PanNENs.

Abbreviations

NET	Neuroendocrine tumor
NEC	Neuroendocrine carcinoma
MiNEN	Mixed neuroendocrine neoplasm
PanNEN	Pancreatic neuroendocrine neoplasm
NF-PanNEN	Non-functioning-type pancreatic neuroendocrine neoplasm
WHO	World Health Organization
LNM	Lymph node metastasis
MEN type 1	Multiple endocrine neoplasia type 1
VHL	Von Hipple Lindau
RFS	Recurrence-free survival
PD	Pancreaticoduodenectomy
DP	Distal pancreatectomy
TP	Total pancreatectomy
CHA	Common hepatic artery
SMA	Superior mesenteric artery
US	Ultrasonography
CT	Computed tomography
MRI	Magnetic resonance imaging
PRRT	Peptide receptor radionuclide therapy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03734-0.

Supplementary Material 1.

Acknowledgements
The authors thank Editage (www.editage.jp) for the English language editing.

Authors' contributions
WI, HK, and DI contributed to conception and design. WI, HK, RS, YN, HA, and DI contributed to development of methodology. WI, KM, and TK contributed to pathological considerations. WI, HK, RS, YN, HA, SM, KT, KS, KS, SF, YK, and DI contributed to development of data acquisition and analysis. WI, HK, KM and DI contributed to, writing, reviewing, and/or revising of the manuscript. All authors have read, reviewed, and approved the final manuscript.

Funding
This study did not receive any specific grants from funding agencies in the public, commercial, or non-profit sectors.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board of Yamanashi University (approval number: H30897). The requirement for informed consent was waived due to the retrospective nature of this study.

Consent for publication
We agreed the consent for publication.

Competing interests
The authors declare no competing interests.

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Received: 16 December 2024 Accepted: 26 February 2025
Published online: 08 March 2025

References

1. WHO Classification of Tumours Editorial Board. WHO classification of endocrine and neuroendocrine tumours. Lyon: IARC; 2022.
2. National Comprehensive Cancer Network clinical practice guidelines in oncology. Neuroendocrine Tumors Version 1. 2023. https://www.nccn.

org/login?, ReturnURL=, https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf.
3. Kos-Kudła B, Castaño JP, Denecke T, et al. European Neuroendocrine Tumour Society (ENETS) 2023 guidance paper for nonfunctioning pancreatic neuroendocrine tumours. J Neuroendocrinol. 2023;35:e13343. https://doi.org/10.1111/jne.13343.
4. Howe JR, Merchant NB, Conrad C, et al. The North American neuroendocrine tumor society consensus paper on the surgical management of pancreatic neuroendocrine tumors. Pancreas. 2020;49(1):1–33.
5. Japan Neuroendocrine Tumor Society; Committee for guidelines for the diagnosis of pancreatic and gastrointestinal neuroendocrine tumors. Clinical Practice Guidelines for Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NEN). Tokyo: Kanehara Publishing Co. Ltd; 2019.
6. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3:1335–42. https://doi.org/10.1001/jamaoncol.2017.0589.
7. Ito T, Igarashi H, Nakamura K, et al. Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. J Gastroenterol. 2015;50:58–64. https://doi.org/10.1007/s00535-014-0934-2.
8. Masui T, Ito T, Komoto I, et al. Nationwide registry for patients with neuroendocrine neoplasm of pancreas, gastrointestinal tract, lungs, bronchi, or thymus in Japan. Int J Clin Oncol. 2022;27:840–9. https://doi.org/10.1007/s10147-022-02130-y.
9. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063–72. https://doi.org/10.1200/JCO.2007.15.4377.
10. Hill JS, McPhee JT, McDade TP, et al. Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. Cancer. 2009;115:741–51. https://doi.org/10.1002/cncr.24065.
11. Doi R. Determinants of surgical resection for pancreatic neuroendocrine tumors. J Hepatobiliary Pancreat Sci. 2015;22:610–7. https://doi.org/10.1002/jhbp.224.
12. Hijioka S, Yamashige D, Esaki M, Japan Pancreas Society Clinical Research Promotion Committee Group (Corporate Authorship), et al. Factors affecting nonfunctioning small pancreatic neuroendocrine neoplasms and proposed new treatment strategies. Clin Gastroenterol Hepatol. 2024;22(7):1416–26.
13. Izumo W, Higuchi R, Yazawa T, et al. Evaluation of preoperative risk factors for postpancreatectomy hemorrhage. Langenbecks Arch Surg. 2019;404(8):967–74.
14. Rindi G, Falconi M, Klersy C, et al. TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. J Natl Cancer Inst. 2012;104:764–77. https://doi.org/10.1093/jnci/djs208.
15. Fischer L, Bergmann F, Schimmack S, et al. Outcome of surgery for pancreatic neuroendocrine neoplasms. Br J Surg. 2014;101:1405–12. https://doi.org/10.1002/bjs.9603.
16. Song KB, Kim SC, Kim JH, et al. Prognostic factors in 151 patients with surgically resected non-functioning pancreatic neuroendocrine tumours. ANZ J Surg. 2016;86(7–8):563–7. https://doi.org/10.1111/ans.12738.
17. Izumo W, Higuchi R, Furukawa T, et al. Evaluation of the site and frequency of lymph node metastasis with non-functioning pancreatic neuroendocrine tumor. Eur Surg Res. 2019;60(5–6):219–28. https://doi.org/10.1159/000504410.
18. Miura T, Ohtsuka H, Aoki T, et al. Increased neutrophil-lymphocyte ratio predicts recurrence in patients with well-differentiated pancreatic neuroendocrine neoplasm based on the 2017 World Health Organization classification. BMC Surg. 2021;21:176. https://doi.org/10.1186/s12893-021-01178-3.
19. The Japan Esophageal Society. Guidelines for diagnosis and treatment of carcinoma of the esophagus 2022. Kanehara Publishing Co. Ltd: Tokyo; 2022
20. Japanese Society for Cancer of the Colon and Rectum. JSCCR Guidelines for the Treatment of Colorectal Cancer. Tokyo: Kanehara Publishing Co. Ltd; 2022. p. 2022.
21. Japanese Gastric Cancer Association. Gastric cancer treatment guidelines. 6th ed. Tokyo: Kanehara Publishing Co. Ltd; 2021.
22. Zhou X, Xie H, Xie L, et al. Factors associated with lymph node metastasis in radically resected rectal carcinoids: a systematic review and meta-analysis. J Gastrointest Surg. 2013;17:1689–97. https://doi.org/10.1007/s11605-013-2249-7.
23. Genç CG, Jilesen AP, Partelli S, et al. A new scoring system to predict recurrent disease in grade 1 and 2 nonfunctional pancreatic neuroendocrine tumors. Ann Surg. 2018;267:1148–54. https://doi.org/10.1097/SLA.0000000000002123.
24. Kim JY, Lee SH, An S, et al. Carbonic anhydrase 9 expression in well-differentiated pancreatic neuroendocrine neoplasms might be associated with aggressive behavior and poor survival. Virchows Arch. 2018;472:739–48. https://doi.org/10.1007/s00428-018-2353-x.
25. Masui T, Sato A, Nakano K, et al. Comparison of recurrence between pancreatic and duodenal neuroendocrine neoplasms after curative resection: a single-institution analysis. Ann Surg Oncol. 2018;25:528–34. https://doi.org/10.1245/s10434-017-6260-1.
26. Izumo W, Higuchi R, Furukawa T, et al. Evaluation of the significance of lymphatic, microvascular and perineural invasion in patients with pancreatic neuroendocrine neoplasms. Cancer Diagn Progn. 2022;2(2):150–9.
27. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–13.
28. Oberndorfer S. Karzinoide tumoren des dunndarms. Frankf Zschr Path. 1907;1:426.
29. Strosberg JR, Coppola D, Klimstra DS, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. Pancreas. 2010;39:799–800.
30. Yachida S, Totoki Y, Noë M, et al. Comprehensive genomic profiling of neuroendocrine carcinomas of the gastrointestinal system. Cancer Discov. 2022;12(3):692–711.
31. Arra DASM, Ribeiro HSC, Henklain G, Barbosa A, Torres SM, Diniz AL, Godoy AL, Farias IC, Costa WL Jr, Coimbra FJF. Surgery or active surveillance for pNETs < 2 cm: Preliminary results from a single center Brazilian cohort. J Surg Oncol. 2022;126:168–74. https://doi.org/10.1002/jso.26931.
32. Li J, Huang L, Liao C, Liu G, Tian Y, Chen S. Two machine learning-based nomogram to predict risk and prognostic factors for liver metastasis from pancreatic neuroendocrine tumors: a multicenter study. BMC Cancer. 2023;23:529. https://doi.org/10.1186/s12885-023-10893-4.
33. Kwon W, Jang JY, Song KB, Hwang DW, Kim SC, Heo JS, Choi DW, Hwang HK, Kang CM, Yoon YS, Han HS, Park JS, Hong TH, Cho CK, Ahn KS, Lee H, Lee SE, Jeong CY, Roh YH, Kim HJ, Korean Pancreas Surgery Club. Risk factors for recurrence in pancreatic neuroendocrine tumor and size as a surrogate in determining the treatment strategy: a Korean Nationwide Study. Neuroendocrinology. 2021;111:794–804. https://doi.org/10.1159/000511875.
34. Heidsma CM, Engelsman AF, van Dieren S, et al. Watchful waiting for small non-functional pancreatic neuroendocrine tumours: nationwide prospective cohort study (PANDORA). Br J Surg. 2021;108(8):888–91.
35. Partelli S, Massironi S, Zerbi A, et al. Management of asymptomatic sporadic non-functioning pancreatic neuroendocrine neoplasms no larger than 2 cm: interim analysis of prospective ASPEN trial. Br J Surg. 2022;109(12):1186–90.

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