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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Macroscopic morphology for estimation of malignant potential in pancreatic neuroendocrine neoplasm

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Abstract
Purpose Pancreatic neuroendocrine neoplasm (Pan-NEN) representing approximately 1.3 % of pancreatic malignancy cases in incidence has been a so rare disease that it remains major problem to analyze the malignant potential. The aim of this study was to verify whether the macroscopic morphology of Pan-NEN, a novel pathological classification, contributes to malignant potential.
Methods From a total of 86 patients with Pan-NEN, 41 surgical sections obtained from the primary site were classified by their morphology into a simple nodular (SN) group and a non-SN group. The non-SN group was further divided into three subtypes: simple nodular with extranodular growth (SNEG), confluent multinodular (CM), and infiltrative (IF). The clinicopathological features of the SN and the non-SN groups were retrospectively compared.
Results Overall 5-year survival rates with and without surgical resection were 94 and 48 %, respectively. SN and non-SN types were identified in 21 and 20 patients, respectively. The non-SN group comprised 14 SNEG type, 2 CM type, and 4 IF type. Synchronous lymph node metastases ($p = 0.009$), synchronous liver metastases ($p = 0.048$), microinvasion to an adjacent organ ($p < 0.001$), vascular invasion ($p = 0.023$), and neural invasion ($p = 0.019$) were more significant in the non-SN group than in the SN group. As judged by WHO 2004 classification and TNM stages (AJCC and ENETS), non-SN type showed malignant trend ($p < 0.05$). Moreover, overall 5-year survival rates of SN and non-SN groups were 100 and 84.4 %, respectively ($p = 0.048$).
Conclusions Non-SN tumors may have higher malignant potential than SN tumors.

Keywords Pancreatic neuroendocrine tumor · Morphology · Clinicopathological features · Postoperative outcome

Introduction

The incidence and prevalence of pancreatic neuroendocrine neoplasm (Pan-NEN) are increasing; Pan-NEN represents approximately 1.3 % of pancreatic malignancy cases in incidence and 10 % of cases in prevalence (Yao et al. 2007, 2008). It has recently been reported that incidentally diagnosed Pan-NEN has increased in overall incidence because of advances in imaging modalities (Yao et al. 2008). The pathological Pan-NEN classification changed substantially in the last decade (Falconi et al. 2012; Kloppel 2011). In 2010, the World Health Organization (WHO) classified Pan-NEN into neuroendocrine tumor (NET) G1, NET G2, and neuroendocrine carcinoma (NEC) based on the mitotic count and/or Ki-67 index (Klimstra et al. 2009). Although the classification referred to the proliferative capability of Pan-NEN, it remains unclear whether histological grade

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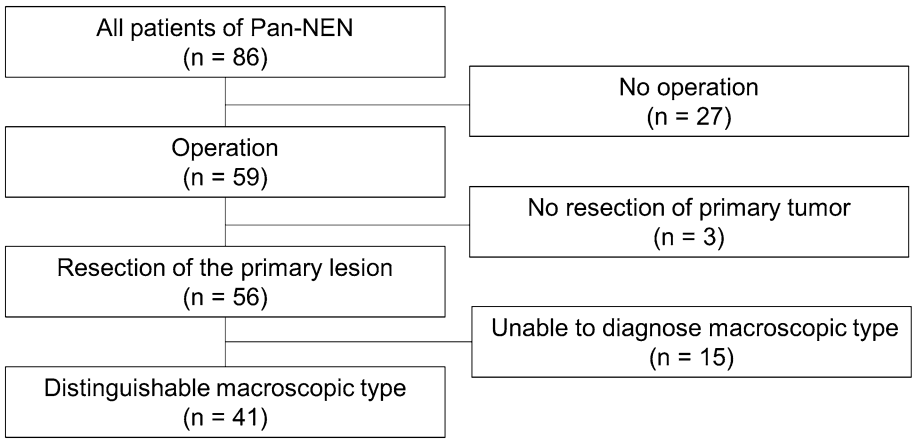

Fig. 1 Study design

defined by a single proliferative feature is sufficient to evaluate malignant potential. There are few reports discussing whether the new WHO 2010 grading predicts Pan-NEN recurrence after curative resection. Two different TNM staging systems have been introduced by the American Joint Committee on Cancer (AJCC) (Kloppel 2011; Kloppel et al. 2010) and the European Neuroendocrine Tumor Society (ENETS) (Falconi et al. 2012; Salazar et al. 2012). The definition of tumor factor (T factor) is different in the two staging systems, although they partly adopt the same definition of T factor using tumor size. The other T factors of the two classifications include invasion of major arteries and surrounding structures. Thus, the malignant character of Pan-NEN is generally classified using three parameters: proliferation status, tumor size, and invasiveness. However, according to recent reports, WHO G1 tumors or those less than 2 cm develop metastatic disease or recurrence (Haynes et al. 2011; Sharpe et al. 2015). Moreover, some studies reported that tumor size is not correlated with prognosis (Birnbaum et al. 2014; Cherenfant et al. 2013; Fischer et al. 2008). It is desirable to explore new strategies to predict malignant potential based on lymph node, liver, and distant metastases, as well as long-term prognosis.

Tumor morphology has been found to be associated with malignant properties and the survival rate (Michelassi et al. 1988; Stahel 1992). Analysis of preoperative morphology might be predictive of the invasive, metastatic, or even recurrence potential after cancer treatment (Michelassi et al. 1988; Montironi et al. 2009; Park et al. 2009; Stahel 1992; Yang et al. 2009). There have been many reports of gross morphology in hepatocellular carcinoma, and its morphology is a well-known prognostic factor (Choi et al. 2009; Inayoshi et al. 2003; Nagano et al. 2008; Shimada et al. 2001). Furthermore, differences in gene expression were correlated with their morphologies (Murakata et al. 2011). However, the clinical significance of morphological appearance remains unknown in Pan-NEN. In the present study, we established a novel macroscopic morphological classification. We classified patients who underwent pancreatectomy for Pan-NEN into groups and compared the clinicopathological features between the groups. Our study identified important correlations between macroscopic morphology and malignant potential.

Methods

Patients and methods

Between April 2001 and March 2014, a total of 86 patients with Pan-NEN received treatment at the Tokyo Medical and Dental University. Of these patients, 59 underwent initial resection for Pan-NEN. Among them, 56 were resected for a pancreatic primary lesion. Among them, tissue was available from 41 patients whose surgical specimens were sufficient to estimate the macroscopic type, and they were enrolled in the study (Fig. 1). Written informed consent was obtained from each subject, and study procedures were approved by an institutional review board. For morphological investigation, hematoxylin and eosin staining and Elastica-van Gieson staining were performed. We established a novel pathological classification of Pan-NEN according to macroscopic morphology as follows: simple nodular type (SN), SN type with extranodular growth (SNEG), confluent multinodular type (CM), and infiltrative type (IF). The largest area of the lesion was evaluated to determine the gross type in the low-power field (Fig. 2a). SN type is defined as a well-demarcated tumor nodule, with or without a fibrous capsule. As shown in the left panel of Fig. 2b, a fibrous capsule distinguishes tumor from pancreas in the high-power and low-power fields. No capsule was identified in the right panel of Fig. 2b. Extranodular tumor growth, capsule, or surrounding pancreatic tissue invasion is not observed (Fig. 2a, b). The non-SN type comprises an SNEG, a CM, and an IF, as further described below. When an SN-type tumor shows varying degrees of extranodular

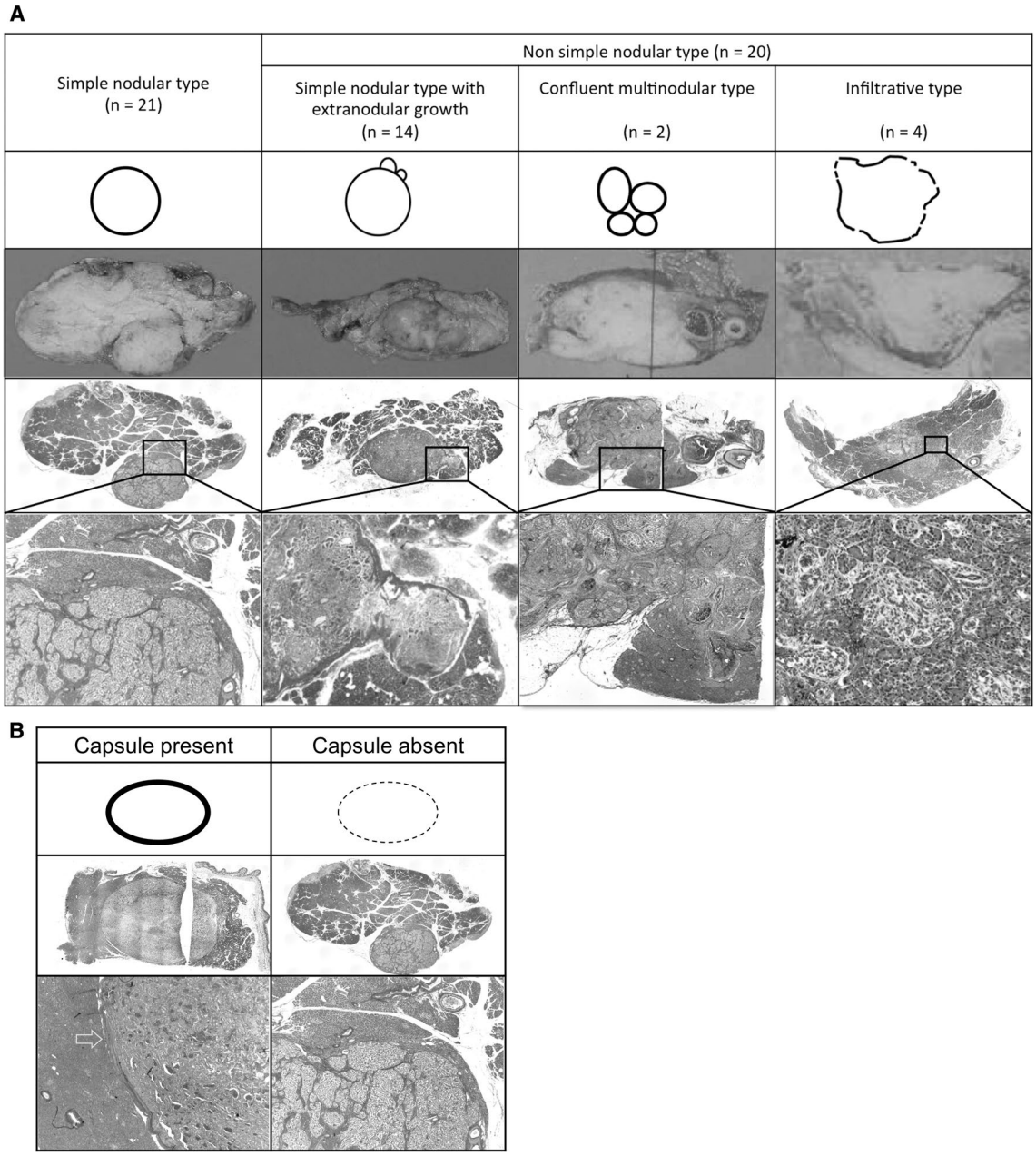

Fig. 2 Macroscopic morphology of Pan-NEN. **a** Tumors were divided into 4 groups according to their morphology. **b** Tumor with or without capsule

growth beyond the tumor border, with or without a fibrous capsule, including intracapsular or extracapsular invasion and invasion of surrounding pancreatic tissue, the tumor is categorized as SNEG (Fig. 2a, b). The CM type consists of agglomerated small tumor nodules and is sharply marginated. No fibrous capsule is seen covering the entire tumor in the CM type, as shown. In the IF type, the tumor/non-tumor boundary is irregular or indistinct. Tumor cells sometimes surround normal acinar cells (Fig. 2a). The diagnosis was evaluated by 3 independent investigators. When the diagnosis of the pathologists differed, we used the diagnosis of 2 pathologists. There was no case with 3 different pathologic diagnoses. This system classifies Pan-NEN into 2 major types: SN and non-SN.

We compared background characteristics and pathological findings of the SN and non-SN groups. Background characteristics included age, gender, genetic disorders such as multiple endocrine neoplasia (MEN) type 1, tumor functionality, early enhancement obtained from contrast-enhanced computed tomography (CT), and synchronous

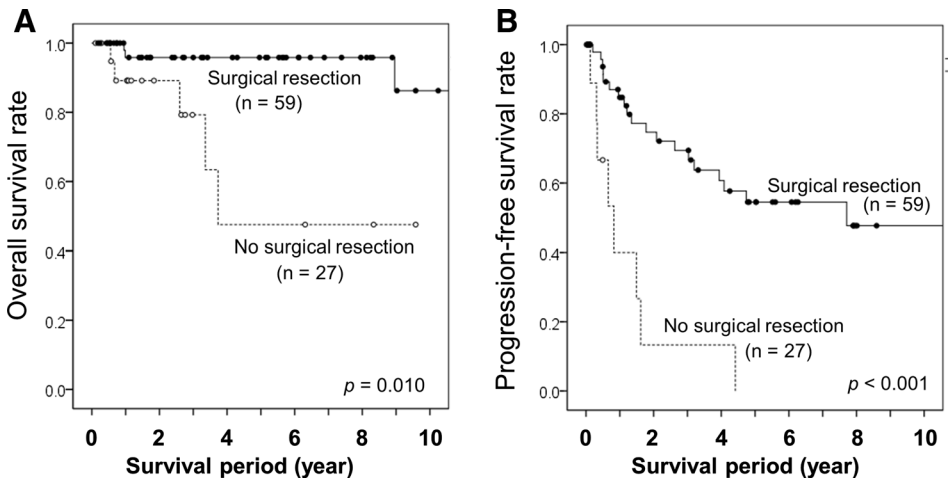

Fig. 3 Survival curve of Pan-NEN patients with or without surgery. **a** Overall survival and **b** progression-free survival

lymph node and liver metastases. Pathological data included tumor size, tumor number, macroinvasion and microinvasion of adjacent organs, mitotic count, fibrous capsule, microvascular invasion, microlymphatic invasion, neural invasion, and invasion of the main pancreatic duct. Immunohistochemical findings included the Ki-67 index, hormone production, and somatostatin-sensitive receptor (SSTR) 2A expression.

According to the WHO 2010 Classification of Tumors of the Digestive System, Pan-NEN is classified into 3 grades on the basis of mitotic count and the Ki-67 proliferative index. G1: mitotic count of <2 per 10 high-power fields (hpf) and <3 % Ki-67 index; G2: mitotic count of 2–20/10 hpf or 3–20 % Ki-67 index; and G3: mitotic count of >20/10 hpf or >20 % Ki-67 index. When there is a discrepancy between Ki-67 index and mitotic count, higher grade was assigned as WHO recommended (Klimstra et al. 2009). We quantified the Ki-67 proliferative index and mitotic count by counting at least total 500 cells in "hot spots." We diagnosed microvascular invasion, microlymphatic invasion, neural invasion, and invasion of the main pancreatic duct according to general rules for the study of pancreatic cancer (Nakao 2010). We scored SSTR2A by both subcellular localization and the extent of staining, as follows: score 0, absence of immunoreactivity; score 1, pure cytoplasmic immunoreactivity, either focal or diffuse; score 2, membranous reactivity in less than 50 % of tumor cells, irrespective of the presence of cytoplasmic staining; and score 3, circumferential membranous reactivity in more than 50 % of tumor cells, irrespective of the presence of cytoplasmic staining (Volante, et al. 2007).

Statistical analysis

Statistical comparisons of the clinicopathological characteristics for significance were made by the Chi-square test or Fisher's exact test with a single degree of freedom, and Student's *t* test was used to analyze the differences between continuous values. *p* values less than 0.05 were considered to have statistical significance. All statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL, USA).

Results

In all, 86 patients received treatment for Pan-NEN at our hospital. Of them, 59 patients underwent operation, and remaining 27 patients with unresectable tumor received treatment other than operation. Overall 5-year survival rates with and without surgical resection were 94 and 48 %, respectively. Progression-free 5-year survival rates with and without surgical resection were 53 and 13 %, respectively (Fig. 3). The surgically resected group showed significantly increased overall 5-year survival ($p = 0.010$) and progression-free survival ($p < 0.001$). The mean observation time was 1579 days.

In surgically resected cases, the tumors were classified into the aforementioned macroscopic types, although the tumors of unresected patients could not be classified. SN, SNEG, CM, and IF were determined in 21, 14, 2, and 4 patients, respectively (Fig. 2a). The non-SN type was observed in 24 tumors of Pan-NEN patients. These results led us to determine whether the malignant potential of the non-SN type is greater than that of the SN type.

As shown in Table 1, synchronous lymph node metastases (30 %: $p = 0.009$) and synchronous liver metastases (20 %: $p = 0.048$) are associated with the non-SN group, while they are not observed in the SN group. Moreover, microinvasion to an adjacent organ was observed in 55 % of the non-SN group, but was not observed in the SN group ($p < 0.001$). These features are consistent with the definition of endocrine carcinoma in the WHO 2004 classification. The non-SN group has symbolic malignant features

Table 1 Baseline characteristics of simple nodular type and non-simple nodular type

		SN ($n = 21$)	Non-SN ($n = 20$)	p value
Background				
Age		57.6 ± 13.3 years	53.7 ± 10.5 years.	0.335
Male		10 (48 %)	11 (55 %)	0.758
MEN type 1	(+)	1 (5 %)	2 (10 %)	0.606
Functional tumor	(+)	5 (24 %)	6 (30 %)	0.734
CT early enhancement	(+)	15 (71 %)	16 (80 %)	0.727
Synchronous LNs metastasis	(+)	0 (0 %)	6 (30 %)	0.009*
Synchronous Liver metastasis	(+)	0 (0 %)	4 (20 %)	0.048*
Pathological findings				
Tumor size		2.3 ± 2.8 cm	3.4 ± 4.0 cm	0.293
Solitary tumor	(+)	17 (81 %)	16 (80 %)	0.939
Macroinvasion of adjacent organ	(+)	0 (0 %)	2 (10 %)	0.232
Microinvasion of adjacent organ	(+)	0 (0 %)	11 (55 %)	<0.001*
v	(+)	4 (20 %)	11 (58 %)	0.023*
ly	(+)	1 (7 %)	4 (29 %)	0.157
ne	(+)	1 (10 %)	6 (60 %)	0.019*
Invasion of main pancreatic duct	(+)	0 (0 %)	3 (19 %)	0.226
Mitotic count (/10 HPF)		1.2 ± 1.2	3.9 ± 10.8	0.317
Ki-67 index		1.6 ± 1.1	5.2 ± 11.6	0.162
Hormone production	(+)	16 (76 %)	19 (95 %)	0.410
SSTR2A Score 2 or 3		14 (70 %)	13 (72 %)	0.880
Capsule	(+)	12 (57 %)	13 (65 %)	0.751

SN simple nodular type, *MEN* multiple endocrine neoplasia, *CT* computed tomography, *v* vascular invasion, *ly* lymphatic invasion, *ne* neural invasion, *SSTR* somatostatin-sensitive receptor

compared with the SN group. In the WHO 2004 classification, well-differentiated endocrine carcinoma had a significantly worse prognosis than well-differentiated endocrine tumors. In particular, benign behavior in well-differentiated endocrine tumors is associated with an extremely good prognosis, and uncertain behavior in a well-differentiated endocrine tumor has a slightly worse prognosis than a tumor with benign behavior (Scarpa, et al. 2010). The difference between these two categories is due to factors such as vascular invasion, neural invasion, tumor size, mitotic count, and Ki-67 index. In this context, we examined whether these factors are observed more in non-SN-type than in SN-type tumors. Vascular invasion (58 vs. 20 %; $p = 0.023$) and neural invasion (60 vs. 10 %; $p = 0.019$) were significantly more advanced in the non-SN than in the SN group (Table 1). However, there was no significant difference between SN and non-SN groups in macroinvasion into adjacent organs, lymphatic invasion, and tumor size. These factors determined the malignant grade in the WHO 2004 classification. Moreover, the mitotic count and Ki-67 index, which mainly determined the WHO 2010 classification, did not differ between the two morphological types. There was no significant difference in age, gender, functionality, tumor number, pathological hormone production, and score of SSTR2A, or in genetic disorders such as MEN type 1, CT early enhancement, pathological invasion into the main pancreatic duct, or the presence of a capsule.

The relationships between our morphological classification and the WHO classifications of 2004 and 2010, the AJCC TNM classification, and the ENETS classification are shown in Table 2. The higher rate of malignant potential in WHO 2010 grade 1 of non-SN group ($N = 10$) is especially noteworthy: 6 cases (60 %) had vascular invasion, 3 (30 %) had lymph node metastasis, and 1 (10 %) had liver metastasis. The proportion of G1 patients in the SN group tended to be higher than that in the non-SN group ($p = 0.0516$).

In well- or poorly differentiated endocrine carcinoma in the WHO 2004 classification, the SN type was observed less often than the non-SN type ($p = 0.041$), though there is no difference between G1 and G2 and NEC of WHO 2010 classification ($p = 0.948$). AJCC stages III and IV were not observed in the SN group and were dominant in the non-SN group significantly. AJCC stage of non-SN group had more malignant potential than that of SN group significantly ($p = 0.02$). Moreover, no SN tumors were observed in ENETS stages III and IV. ENETS stage of non-SN group had more malignant potential significantly ($p = 0.024$).

Table 2 Relationship between morphology and WHO classification

	SN type	Non-SN type			*p*
	SN	SNEG	CM	IF	
WHO 2004 classification					0.041*
Tumor					
WDET	13	4	0	2	
Carcinoma					
WDEC	8	10	1	2	
PDEC	0	0	1	0	
WHO 2010 classification					0.948
G1					
G1	17	7	0	3	
G2 and NEC					
G2	4	7	1	1	
NEC	0	0	1	0	
AJCC					0.02*
Stage I	20	9	0	3	
Stage II	1	3	0	1	
Stage III	0	0	0	0	
Stage IV	0	2	2	0	
ENETS					0.024*
Stage I	16	6	0	2	
Stage II	5	5	0	1	
Stage III	0	1	0	1	
Stage IV	0	2	2	0	
Total	21	14	2	4	

SN simple nodular type, *SNEG* simple nodular type with extranodular growth, *CM* confluent multinodular type, *IF* infiltrative type, *NEC* neuroendocrine carcinoma

As shown in supplemental Fig. 1, overall 5-year survival rate of SN and non-SN was 100 and 84.4 %, respectively ($p = 0.048$), when observed the 41 patients between April 2001 and March 2015 (mean observation time is 2051 days).

Discussion

Despite substantial progress over the past few years, predicting outcome in Pan-NEN remains a challenge. Part of the difficulty relates to the low prevalence. The current series includes 41 patients who underwent pancreatic resection for primary tumors over 14 years. This is the first report analyzing malignant potential using macroscopic findings in Pan-NEN. Non-SN primary tumors had more malignant properties than SN tumors. The non-SN type had synchronous lymph node and liver metastases, microinvasion into adjacent organ, microvascular invasion, and neural invasion, compared with the SN type. Moreover, all SN-type tumors are classified in stages I–II by both the AJCC and ENETS TNM systems. Thus, it is important to distinguish the non-SN from the SN type. Moreover, overall 5-year survival rate decreased in non-SN group more than in SN group.

No prior studies on Pan-NEN morphology have been reported. We established a novel morphological classification, although this is a single-center retrospective study and is limited by the small number of subjects due to the rarity of the disease. Tumor morphology has been found to be associated with malignant properties and prognosis in various types of malignancies (Michelassi et al. 1988; Stahel 1992). In hepatocellular carcinoma (HCC), Eggel established a gross morphological classification on the basis of autopsy data in 1901, and there have been many other reports on the relationship between morphology and malignant potential (Kudo et al. 2015). There are many studies indicating that the SN type showed better prognosis and less malignant potential than other types (Choi et al. 2009; Inayoshi et al. 2003; Nagano et al. 2008; Shimada et al. 2001). Moreover, HCC morphology is related to gene expression (Murakata et al. 2011). The novel morphological classification of Pan-NEN clearly defined tumor malignancy. The SN type had better properties than the non-SN type. In the near future, gene expression in non-SN-type Pan-NEN responsible for a poor prognosis may be revealed.

In the present study, the non-SN type is strongly associated with synchronous lymph node and liver metastases. Hashim et al. (2014) reported that the presence of synchronous lymph node metastasis was associated with a significantly poor prognosis for both disease-free and overall survival. Synchronous liver metastases are also well-known predictive factors of poor prognosis in Pan-NEN (Fischer et al. 2008, 2014). Lymph node metastasis is an N factor, and liver metastasis is an M factor in the TNM classification in both AJCC and ENETS systems, and these staging systems are correlated with prognosis (Scarpa et al. 2010). Thus, synchronous lymph node and liver metastases are obviously correlated with poor prognosis, and the non-SN type should be a prognostic factor. The non-SN group is also associated with vascular invasion and neural invasion. There have been some reports that vascular invasion and neural invasion are predictive factors (Fischer et al. 2014; Han et al. 2014; Hashim et al. 2014; Kazanjian et al. 2006; La Rosa et al. 2009; Tsutsumi et al. 2014). Han et al. reported that neural invasion and vascular invasion correlated with shorter overall survival in an analysis of 104 cases (Han et al. 2014). These reports indicate that the non-SN type is associated with malignant potential.

We also analyzed the relationship between our morphological classification and the WHO 2004 and 2010, AJCC, and ENETS TNM classification systems. We found a higher rate of malignant potential in G1 patients classified

by the WHO 2010 system in the non-SN group. This suggests that our classification might extract poor prognosis patients from the G1 group.

Unfortunately, we could not analyze the prognosis of Pan-NEN using this novel morphological classification because of limitations. The first limitation of this study is that we could not classify the tumors of unresected patients, whose prognoses were worse than those of resected patients. The second limitation was the small number of participants. In patients who underwent surgical resection, only 2 died of their disease, leaving enough to be able to analyze prognosis, although the postoperative survival rate was consistent with that of previous reports (Cherenfant et al. 2013; Haynes et al. 2011; Sharpe et al. 2015). A third limitation of this classification is based on pathological diagnosis; prediction of prognoses before treatment was not possible. Development of modalities that can assess morphology in Pan-NEN might be useful in determining treatment protocols in inoperable disease.

In conclusion, we established a novel classification system based on morphology in Pan-NEN and demonstrated that the non-SN type is associated with malignant potential. These results suggest that non-SN type may have higher malignant potential than SN type and the morphological classification deserves further investigation.

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Compliance with ethical standards

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

Ethical approval For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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