

# Pancreatic neuroendocrine neoplasms: Clinicopathological features and pathological staging

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**Summary.** The nomenclature and classification of pancreatic neuroendocrine neoplasms has evolved in the last 15 years based on the advances in knowledge of the genomics, clinical behaviour and response to therapies. The current 2019 World Health Organization classification of pancreatic neuroendocrine neoplasms categorises them into three groups; pancreatic neuroendocrine tumours (PanNETs) (grade 1 grade 2, grade 3), pancreatic neuroendocrine carcinomas and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) based on the mitotic rate, Ki-67 index, morphological differentiation and/or co-existing tissue subtype. PanNETs are also classified into non-functional NET, insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma, ACTH-producing NET and serotonin producing NET based on hormone production and clinical manifestations. A portion of the cases were associated with genetic syndromes such as multiple neuroendocrine neoplasia 1 (MEN 1), neurofibromatosis and Von Hippel-Lindau syndrome. In view of the distinctive pathology and clinical behaviour of PanNETs, the current 8<sup>th</sup> AJCC/UICC staging system has separated prognostic staging grouping for PanNETs from the pancreatic neuroendocrine carcinomas or MiNENs. Pancreatic neuroendocrine carcinomas and MiNENs are staged according to the prognostic stage grouping for exocrine pancreatic carcinoma. The new stage grouping of PanNETs was validated to have survival curves separated between different prognostic groups. This refined histological and staging would lead to appropriate selections of treatment strategies for the patients with pancreatic neuroendocrine neoplasms.

**Key words:** WHO, Staging, Pancreatic neuroendocrine neoplasm, NET

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## Introduction

In recent years, based on genetic, pathological and clinical studies, there is a trend to unify the classification of pancreatic neuroendocrine neoplasms (PanNENs) and neuroendocrine neoplasms (NENs) in other parts of the body (Gill et al., 2019). In addition, there are many advances in the treatment of patients with pancreatic neuroendocrine neoplasms (PanNENs) and clinical outcome is improving (Ishida and Lam. 2020). For further improvement in the management of these patients, improvements are needed in the understanding of pathogenesis and proper classification for triage of patients for therapies. Most recently, World Health Organization has updated the 2017's classification of the PanNENs in 2019 (Gill et al., 2019). In addition, American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) published new staging manuals for pancreatic neuroendocrine tumours (PanNETs) in 2017 and 2018 (Bergsland et al., 2017; Brierly et al. 2018a). These revised approaches to classification of PanNENs coupled with the whole genomic sequencing data from the International Cancer Genome Consortium (Mafficini and Scarpa, 2018) have revolutionized our understanding and management of patients with PanNENs.

In view of these recent advances, the current review updates the current classification, clinicopathological features and pathological staging of PanNENs in a holistic approach which contributes to understand the biology of PanNENs, resulting in accurate diagnosis and appropriate decision of management strategies.

## Evolution of concepts and classification

### *Classification of pancreatic neuroendocrine neoplasms*

The nomenclature and classification of pancreatic neuroendocrine neoplasms has changed very much in the last 15 years based on the advances in knowledge of the genomics, clinical behaviour and responses to therapies



(Table 1). In the past, this group of tumours has been labelled “islet cell tumour (adenoma/carcinoma)”, “poorly differentiated endocrine carcinoma”, “apudoma” and “carcinoid”. These terms are now obsolete.

It is worth pointing out that the third Edition of World Health Organisation (WHO) Classification of tumours of the Digestive system which was published in 2000 did not include the classification of pancreatic neuroendocrine neoplasms. It is not until 2004, in the third Edition of WHO’s Classification of tumours of endocrine organs published in 2004, that the term “pancreatic endocrine tumour” is used to unify the name of this group of tumours (Heitz et al., 2004). At the time, pancreatic endocrine tumours were classified as well-differentiated endocrine tumour, well-differentiated endocrine carcinoma, poorly differentiated endocrine carcinoma (small cell carcinoma) and mixed exocrine-endocrine carcinoma. The differentiation between different groups of pancreatic endocrine tumours are based on mitotic counts, Ki-67 index, size of the tumour as well as angioinvasion and perineural invasion. At the time, pathological stage grouping was not applicable for this group of tumours.

Six years later, in the fourth Edition of WHO’s tumours of digestive system published in 2010, pancreatic endocrine tumours are classified as neuroendocrine tumour (NET) grade 1, NET grade 2, neuroendocrine carcinoma (large cell or small cell) and mixed adenoneuroendocrine carcinoma (Klimstra et al., 2010). This classification relies strongly on the proliferative activities in terms of mitotic count and Ki-67 index. Grade 1 NET is with mitotic count <2 per 10 high power field (HPF) and/or  $\leq 2\%$  Ki-67 index and grade 2 NET is with mitotic count, 2-20 per 10 HPF

and/or 3-20% Ki-67 index. In this classification, grade 3 tumours with mitotic count, >20 per HPF and/or >20% Ki-67 index are classified as neuroendocrine carcinoma (NEC). This classification was thought to reflect patients’ clinical prognosis and biological characteristics of the neoplasms. At the time, the pathological stage grouping for this tumour is based on the exocrine pancreatic carcinoma.

The 2010 WHO classification with this group of tumours did not consider tumour differentiation. In a large European multicentre study involving 305 gastrointestinal neuroendocrine carcinomas (PanNECs) (as defined in the 2010 classification), those with Ki-67 index <55% had a better prognosis, but a lower response rate to platinum-based chemotherapy than those with Ki-67 index >55% (Albarwani et al., 2012). Similar results were obtained from an American study focusing on 62 pancreatic neuroendocrine tumours with high Ki-67 index (grade 3) showing that pancreatic neuroendocrine neoplasms with poor differentiation had higher lymph node metastases and higher Ki-67 index (Basturk et al., 2015). The findings indicated that all PanNECs, in the 2010 classification, should not be considered one single disease as they have different biological and genetic components with distinct response to treatment. Thus, there was a need for modification of the classification (Basturk et al., 2015).

In the 2017’s fourth Edition of WHO’s Classification of tumours of endocrine, the whole group of tumours are labelled as “neuroendocrine neoplasms” instead of “neuroendocrine tumours” (Kl6ppel et al., 2017). The classification divides the neoplasms into NET grade 1, NET grade 2, NET grade 3, NEC (or poorly differentiated neuroendocrine neoplasm) and mixed

**Table 1.** Changes in terminology for pancreatic neuroendocrine neoplasms.

WHO 2004 (Endocrine)	WHO 2010 (Digestive)	WHO 2017 (Endocrine)	WHO 2019 (Digestive)
Well-differentiated endocrine tumour# Well-differentiated endocrine carcinoma	NET grade 1## NET grade 2##	NET grade 1@ NET grade 2@ NET grade 3@	NET grade 1* NET grade 2* NET grade 3*
Poorly differentiated endocrine carcinoma - Small cell carcinoma	Neuroendocrine carcinoma (NEC) (large cell or small cell)/[grade 3] ##	Neuroendocrine carcinoma (NEC) (small cell or large cell)/Poorly differentiated neuroendocrine neoplasm	Neuroendocrine carcinoma (NEC)(small cell or large cell)
Mixed exocrine- endocrine carcinoma (MEEC)	Mixed adenoneuroendocrine carcinoma (MANEC)	Mixed neuroendocrine-non- neuroendocrine neoplasm +Mixed ductal-NEC +Mixed acinar-NEC +Mixed acinar-ductal-NEC	Mixed neuroendocrine-non- neuroendocrine neoplasm (MiNEN) +Mixed ductal carcinoma- NEC +Mixed ductal carcinoma-NET +Mixed acinar cell carcinoma-NEC +Mixed acinar cell carcinoma-ductal carcinoma-NEC

NET: neuroendocrine tumour. #2004: well-differentiated endocrine tumour of 2 types: (1) Confined to the pancreas, non-angioinvasive, no perineural invasion, Less than 2cm, 2 mitoses/10HPF and  $\leq 2\%$  Ki-67 positive cells; (2) Confined to pancreas and one or more of the features:  $\geq 2$ cm, 2-10 mitoses/10 HPF, >2% K-67 positive cells, angioinvasion, perineural invasion. ## 2010: G1- mitotic count, < 2 per 10 HPF and/or  $\leq 2$  Ki-67 index; G2 - mitotic count, 2-20 per 10 HPF and/or 3-20% Ki-67 index; G3 - mitotic count, > 20 per HPF and/or >20 Ki-67 index. @ 2017: G1 - mitotic count, < 2 per 10 HPF and/or < 3 Ki-67 index; G2 - mitotic count, 2-20 per 10 HPF and/or 3-20 Ki-67 index; G3 - mitotic count, > 20 per HPF and/or >20 Ki-67 index. \*2019: G1 - mitotic count, < 2 per mm<sup>2</sup> and < 3 Ki-67 index; G2 - mitotic count, 2-20 per mm<sup>2</sup> and 3-20 Ki-67 index; G3 - mitotic count, > 20 per mm<sup>2</sup> and 20 Ki-67index.

neuroendocrine-non-neuroendocrine neoplasm. The pathological stage grouping for this tumour is based on the exocrine pancreatic tumour in the seventh edition of American Joint Cancer Committee/Union for International Cancer Control (AJCC/UICC) cancer staging Manuel (Edge et al., 2010).

The 2017 WHO classification allows the separation of NET grade 3 from NEC based on tumour differentiation. In addition, in this version, the cut-off value of Ki-67 was changed to 3% instead of 2%. Thus, grade 1 NET is with mitotic count <2 per 10 HPF and/or <3% Ki-67 index, grade 2 NET is with mitotic count, 2-20 per 10 HPF and/or 3-20% Ki-67 index and grade 3 NET is with mitotic count, >20 per HPF and/or >20% Ki-67 index. As the Ki-67 index is the main criterion in the classification, WHO group did not recommend causal visual estimation (eyeballing) and advised manual counting using printed images. In addition, WHO endorsed to count the index in hotspots of proliferation, counting more than 500 cells and in 50 high power fields. Causal visual estimation (eyeballing) is not recommended.

In 2019, in the most recent edition of WHO classification, the Fifth Edition of WHO classification of tumours of digestive system, pancreatic neuroendocrine neoplasms (PanNENs) are divided into NET grade 1, NET grade 2, NET grade 3, NEC and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) (Gill et al., 2019). For standardisation of mitotic rates to be used in all body systems, counting by area (per 2 mm<sup>2</sup>) is used instead of magnification (per 10 HPF). Grade 1 NET is with mitotic count <2 per/2 mm<sup>2</sup> and <3% Ki-67 index, grade 2 is mitotic count with 2-20/2 mm<sup>2</sup> and 3-20% Ki-67 index whereas grade 3 NET is with mitotic count, >20/2 mm<sup>2</sup> and >20% Ki-67 index. It is worth noting that both mitotic count and Ki-67 index are required for classification and counting Ki-67 index alone is insufficient.

Digital imaging analysis is another means to assess Ki-67 index (Tang et al., 2012). Coupled with the increased popularity of whole slide imaging (Lam and Leung, 2020), digital analysis of Ki-67 may be an acceptable method for Ki-67 assessment. Careful exclusion of the interference of proliferating non-tumour nuclei, such as lymphocytes, endothelial cells and other stromal cells, might be required for an accurate Ki-67 proliferative index (Tang et al., 2012).

Starting from eighth Edition of AJCC/UICC cancer staging Manuel, PanNETs are described as a group in a separate chapter (Bergsland et al., 2017; Brierly et al., 2018a). PanNEC should be staged using the prognostic grouping for exocrine carcinoma of the pancreas (Kahar et al., 2017; Brierly et al. 2018b).

#### *Classification of mixed tumours in pancreas -Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)*

A subgroup of neuroendocrine neoplasm, which is rare and occurs with other neoplasms (Table 1). In 2004

third edition on WHO classification of tumours of endocrine organs, this group of mixed tumours was named “mixed exocrine-endocrine carcinoma (MEEC) (Heitz et al., 2004). In the 2010 fourth edition on WHO classification on tumours of digestive system, the term “mixed adenoneuroendocrine carcinoma (MANEC) is employed for the group of mixed tumours (Klimstra et al., 2010). In addition, there is an arbitrary requirement for each component to be ≥30% for the diagnosis of this group of tumours.

However, MANECs are rare and diagnosis is controversial; one or both components may be low-grade malignant, and/or the non-neuroendocrine component may not be adenocarcinoma (e.g. squamous or sarcomatoid phenotypes). Therefore, in the 2017 fourth edition of WHO classification of tumours of endocrine system, the more general term “neoplasm” is substituted for the term “carcinoma”, and the term “non-neuroendocrine” is used instead of “adeno-” to reflect these findings (Klöppel et al., 2017). This group of mixed tumours are termed “neuroendocrine-non-neuroendocrine neoplasm”. The tumours are classified as mixed ductal-neuroendocrine carcinoma, mixed acinar-neuroendocrine carcinoma and mixed acinar-ductal-neuroendocrine carcinoma.

In 2019’s fifth edition on WHO classification tumours of Digestive system, the abbreviation, MiNEN, is first used for neuroendocrine-non-neuroendocrine neoplasm (Gill et al., 2019). The use of MiNEN is further elaborated as a preferred term for the group of tumours (as compared to MANEC used in the past) as the tumours may arise from neoplasms other than carcinoma and better reflect the heterogeneous variety of morphologies. In this classification scheme, different from the 2017 classification, MiNEN were further sub-classified as mixed ductal carcinoma-NET, mixed ductal carcinoma-NEC, mixed acinar cell carcinoma-NEC and mixed acinar cell carcinoma-ductal carcinoma-NEC. If the non-endocrine neoplastic component of MiNENs is carcinoma, the neoplasm should be staged using the AJCC/UICC stage grouping for pancreatic exocrine carcinoma (Kakar et al., 2017; Brierly et al., 2018b).

Although the aetiology of MiNENs still remains unclear, three potential hypotheses have been proposed (Frizziero et al., 2020). The first is a concept of pluripotent stem cell, in which these two components might originate from a common pluripotent stem cell progenitor that is capable of divergent differentiation. The second postulates a monoclonal origin from a single ancestor cell; the neuroendocrine components may be derived from initially non-neuroendocrine cell phenotype. The third theory is a collision concept, in which each component may originate from two individual stem cells independently, in a synchronous or metachronous manner (collision tumours).

In the fifth edition of WHO classification of tumours of Digestive system, neoplasms in which the non-neuroendocrine component is composed solely of the precursor neoplasm, are not considered MiNENs (Gill et

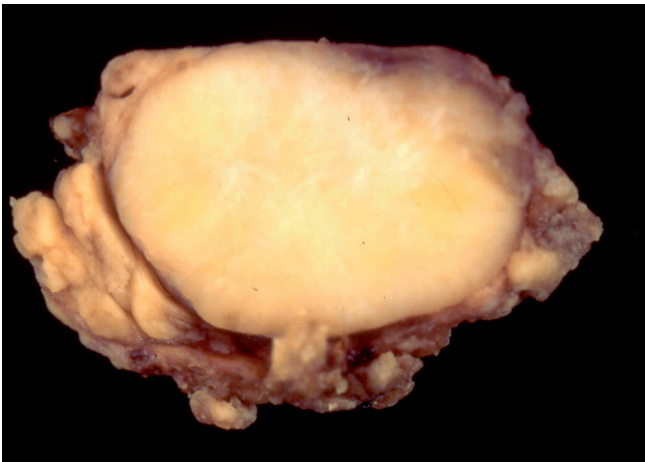


al., 2019). In addition, independent neuroendocrine and non-neuroendocrine neoplasms arising in the same organ should not be classified as MiNEN, even if they demonstrate the morphology of true collision tumours. Thus, the MiNEN category applies only to neoplasms in which the two components are assumed to be clonally related. The presence of neuroendocrine differentiation in the neuroendocrine component should be confirmed by immunolabelling for neuroendocrine markers such as synaptophysin and/or chromogranin A.

### Clinicopathological features updates

#### *PanNETs*

Macroscopically, PanNETs are usually well demarcated, grey-white to yellow in colour (Fig. 1).



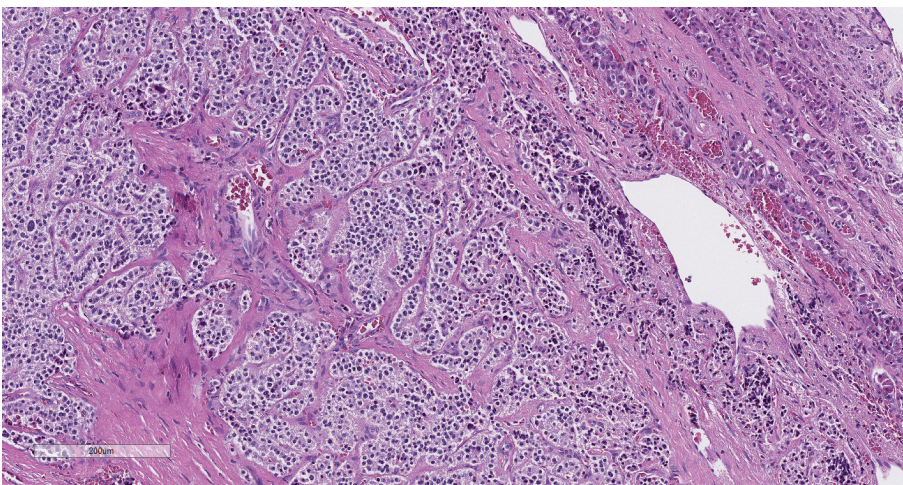
**Fig. 1.** Macroscopic appearance of a pancreatic neuroendocrine tumour showing a well demarcated tumour with homogenous yellow-white surface.

They often have a homogeneous solid appearance. Occasionally they are vascular, congested with patches of haemorrhages. Rarely, they could be cystic and radiologically could be confused with other non-neoplastic, benign and neoplastic cystic lesions in the pancreas (Abdelkader et al., 2020). Multiple tumours could be seen in genetic syndromes such as multiple endocrine neoplasia 1 (MEN1) (Lo et al., 1998).

Microscopically, PanNET is characterised by a well differentiated tumour with small to medium-sized solid nests of cuboidal cells with granular cytoplasm in vascular stroma. Dense fibrosis or hyalinisation may be present (Fig. 2). The tumour cells are often arranged in trabeculae, glandular or rosette patterns. There is minimal nuclear pleomorphism and a lack of necrosis. The nuclei often contain coarsely clumped chromatin, described as having a stippled salt-and-pepper appearance. Typically, the cytoplasm of the tumour cells stain for neuroendocrine markers such as chromogranin, synaptophysin and CD56 (Lam and Lo, 1997). These markers identify the neurosecretory granules which can be seen by electron microscopic examination (Fig. 3). Nevertheless, with the use of neuroendocrine markers for diagnosis, electron microscopy is not in use in the diagnosis of PanNET nowadays.

Functioning PanNETs are defined as PanNETs associated with hormonal hypersecretion syndromes. Non-functioning PanNETs cause nonspecific symptoms (e.g. vague abdominal pain) or incidental space occupying lesion on radiological examinations. However, non-functioning PanNETs may be positive for hormones on immunohistochemical examination. The distinction between functioning and non-functioning PanNETs is based on clinical presentation, and there is no absolute difference in hormone markers' expression between the two categories.

PanNET is characterized by increased serum chromogranin A (Al-Risi et al., 2017) and positive somatostatin receptor scintigraphy (SRS) (Al-Risi et al.,



**Fig. 2.** Microscopic appearance of a pancreatic neuroendocrine tumour showing trabeculae of tumour cells with granular cytoplasm in stroma which is hyalinised and vascular (hematoxylin and eosin). x 10.

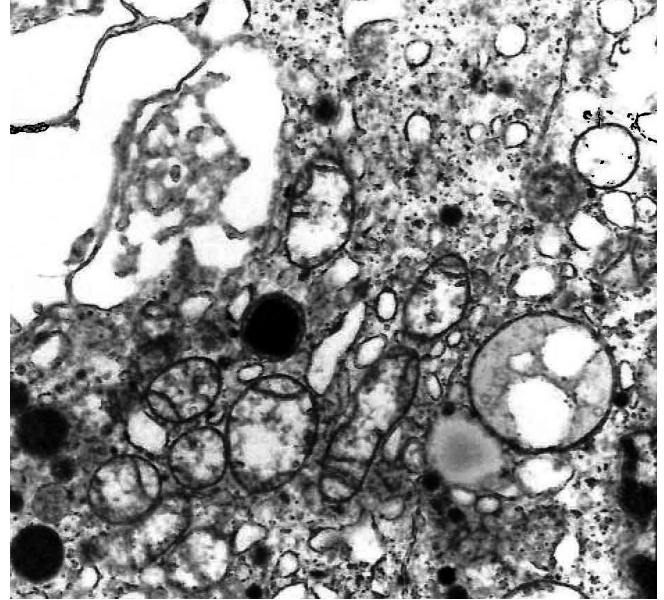


2017). In rare instances, PanNETs could secrete alpha-fetoprotein (AFP) (Lam et al., 2001; Zhu et al., 2015). These AFP-secreting PanNETs could be functioning (insulinoma or glucagonoma) or non-functioning.

Table 2 summarises the epidemiological data, location and size of different groups of PanNETs. In general, non-functioning PanNETs and common functioning NETs occur with a mean age in the sixth decades. The two least common functional PanNETs, ACTH-producing and serotonin-producing PanNETs are noted in younger adult with a mean age in the fifth decade. There is no gender predilection for gastrinoma and VIPoma. All the other PanNETs are more common in females.

### Non-functioning tumour

Non-functioning PanNET is the most common type of PanNET. Tumours less than 5 mm are called microadenomas and they are benign. Approximately 55% to 75% of non-functional PanNETs are malignant (Kent et al., 1981; Venkatesh et al., 1990; Rindi et al., 2012). Metastases occur both to regional lymph nodes and to the liver. Distant metastases usually occur late during the disease and are mainly found in lung and bone (Venkatesh et al., 1990; Kulke et al., 2010). Rarely, oncocytic (Carstens and Cressman, 1989; Volante et al., 2006; Sugihara et al., 2006), pleomorphic (Zee et al.,



**Fig. 3.** Electron microscopy of a pancreatic neuroendocrine tumour showing numerous membrane-bound electron dense secretory granules in the cytoplasm. x 40,000.

**Table 2.** Demographic and clinical features of pancreatic neuroendocrine tumours.

Type	non-functioning	insulinoma	gastrinoma	VIPoma	glucagonoma	somatostatinoma	ACTH-producing NET	serotonin-producing NET
Localization	2/3 of surgically resected in head	evenly distribute or slight predominance in head and tail	no site predilection	most common in tail	predominately in tail	predominately in head (2/3)	no site predilection	no site predilection
Genetic syndromes	MEN1, MEN4, VHL, NF1, TS, Cowden	MEN1, NF1, TS	MEN1, MEN4, NF1, TS	MEN1 (in 10%)	MEN1, GCHN	MEN1, VHL	MEN1	no association
Age	mean age= 50 to 55 years	peak incidence- sixth decade	fifth and sixth decade	mean age =51 years (15-82 years)	mean age= 52 years	mean age = 55 years (30-74)	mean age = 42 years 2/3 less than 50 years	mean age = 41 years
Gender	No sex predilection	slightly more in females	no sex predilection	no sex predilection	male to female = 1 to 1.25	more common in females	male to female = 1 to 2	more common in females
Order of frequency	1	2	3	4	5	6	7	8
Proportion in PanNENs/ PanNETs	>60% (70=80%) of PanNENs	4 to 20% of resected PanNENs	4 to 8% of all PanNETs	0.6 to 1.5% of PanNENs; 2 to 6% of functioning-PanNETs	1 to 2% of all PanNETs	<1% of functioning PanNETs	NA	NA
Incidence	NA	4 per million person-years	NA	0.05 to 0.2 per million person-years	NA	0.025 per million person-years	rare - approximately 140 cases	rare - approximately 50 cases
Size (mm)	Median - 35; range: 20 to 50	Mean - 16; 80% - 10 to 20	Mean - 38	Mean - 45 to 53	Mean - 50 range: 30 to 70	Mean - 50 to 60	Mean - 48; range 25 to 150	Mean - 52; range 10 to 60

PanNENs: pancreatic neuroendocrine neoplasms; PanNETs: pancreatic neuroendocrine tumours; MEN1: multiple endocrine neoplasia type 1; MEN4: multiple endocrine neoplasia type 4; VHL: von Hippel-Lindau disease; NF1: neurofibromatosis type 1; TS: tuberous sclerosis; GCHN: glucagon cell hyperplasia and neoplasia; VIPoma: vasoactive intestinal polypeptide-secreting tumours; ACTH: adrenocorticotrophic hormone. NA: not available.

2005) and clear cell (often occur in patients with VHL) (Hoang et al., 2001; Singh et al., 2006) variants are noted.

Although non-functioning, multiple hormones can be demonstrated on immunohistochemical examination in non-functioning PanNETs. As this subtype of PanNET is clinically non-functioning, differential diagnoses include acinar cell carcinoma, pancreatoblastoma and ductal adenocarcinoma. Histologically, the most important differential diagnosis of non-functioning PanNETs is solid pseudopapillary neoplasm (SPN) of the pancreas (Lam et al., 1999; Klöppel et al., 2019). Solid pseudopapillary neoplasm of the pancreas is often composed of monomorphic tumour cells with hyalinised or myxoid fibrovascular cord. These tumour cells are focally positive for synaptophysin. Like non-functioning PanNET, the tumour is often located in the tail of pancreas. Different from PanNET, solid pseudopapillary neoplasm occurs often in young females (mean age in third decade) and is larger in size (mean size = 84 mm) (Lam et al., 1999). In addition, solid pseudopapillary neoplasm shows pseudopapillae, foamy histiocytes, calcification (occasional ossification) and cholesterol crystals surround by foreign body giant cells. PAS positive globules are noted in the tumour cells. Furthermore, solid pseudopapillary neoplasm of the pancreas is negative for chromogranin and shows nuclear expression of beta catenin and often E-cadherin, CD10, progesterone receptor and CD117 (Lam et al., 1999; Cao et al., 2006; Patnayak et al., 2013). The immunohistochemical profiles help in the differential diagnosis of solid pseudopapillary neoplasm of the pancreas and PanNET especially on endoscopic ultrasound-guided fine needle aspiration (Raddaoui et al., 2016).

The clear cell variant of PanNET should be distinguished from metastatic renal cell carcinoma and the oncocytic variant of PanNET should be differentiated from hepatocellular carcinoma and adrenocortical

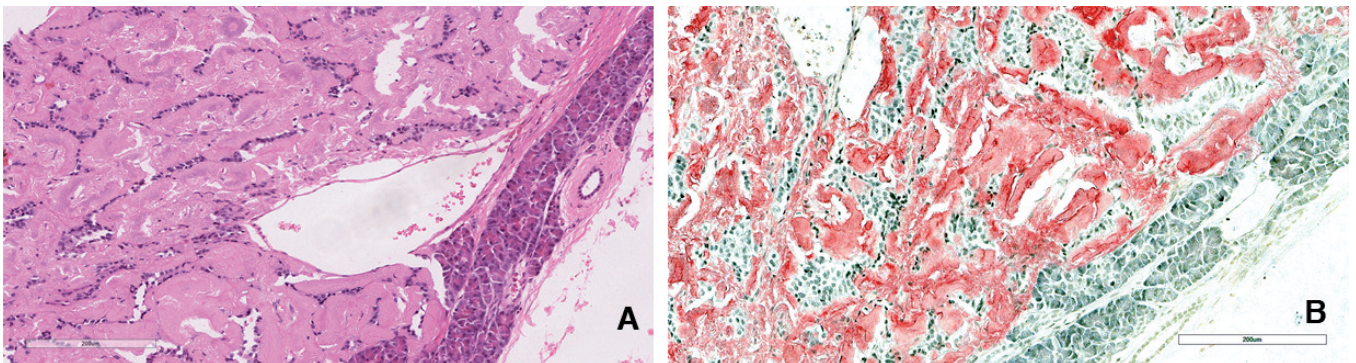
carcinoma.

#### Insulinoma

Insulinoma is a functioning neuroendocrine tumour which secretes insulin. It is the most common functioning PanNET (Lam and Lo, 1997; Lo et al., 1997). Multiple endocrine neoplasia type 1 (MEN1) occurs in 4 to 10% of patients with insulinomas (Lo et al., 1998). Approximately 90% of patients with MEN1 have multiple insulinomas. Different from other functioning PanNETs, insulinoma is mostly benign. The incidence of metastasizing insulinoma is 0.17 per million person years. Thus, metastasizing insulinomas accounted for approximately 4% of insulinomas. Insulinomas present with localised disease with regional lymph node metastasise present in one-third of cases (Sada et al., 2020). Insulinoma is usually small in size (equal or less than 20 mm). Patients with larger tumour are prone to metastasis. The growth pattern of insulinomas is mainly trabecular or solid. Some cases have calcification and psammoma bodies. The stroma may be hyalinized and with amyloid deposits which can be highlighted by use of Congo red stain (Fig. 4). The type of amyloid is called amylin or islet amyloid polypeptide (IAPP). The amyloid is specific for insulinomas (Lam and Lo, 1997). The tumour shows strong staining for insulin. Approximately half of insulinomas had scattered cells of other hormones. This is particularly true for metastasizing insulinoma.

#### Gastrinoma

Gastrinoma are composed of cells producing gastrin and with uncontrolled gastrin secretion causing Zollinger-Ellison syndrome (Shao et al., 2019). The syndrome is characterized by duodenal ulcer and/or gastro-oesophageal reflux disease. MEN1 occurs in approximately 20 to 25% of pancreatic gastrinoma (Shao et al., 2019; Cho and Kasi, 2020). Gastrinoma occur in



**Fig. 4.** A. Pancreatic neuroendocrine tumour with a large amount of amorphous pink amyloid deposits (hematoxylin and eosin). B. Amyloid in the stroma highlighted by Congo red stain (hematoxylin and eosin). x 10.

duodenum three times more than in pancreas (Krampitz and Norton, 2013). Despite this, gastrinoma is the second most common functioning NET of pancreas. Approximately 60% of pancreatic gastrinoma show lymph node metastases (Delcore et al., 1988; Bartsch et al., 2012). Gastrinomas in the pancreas have a higher malignant potential than those in the duodenum (Shao et al., 2019). In patients with liver metastasis, the 5-year survival rates are approximately 60%-80% on curative resection. Calcification is common in the stroma of the tumour (Lam and Lo, 1997). In addition to focal expression of gastrin, gastrinoma also express somatostatin receptor 2A (STR2A) and other hormones.

### Glucagonoma

Glucagonoma are composed of cells producing glucagon and pre-proglucagon-derived peptide, with uncontrolled glucagon production causing glucagonoma syndrome. Glucagonoma syndrome is a triad of weight loss, diabetes mellitus and characteristic skin rash - necrolytic migratory erythema (Cui et al., 2020). Neurological manifestations have also been reported (Wat et al., 1995). The tumour is more common in the tail of the pancreas. Approximately 500 cases were reported in the literature (Song et al., 2018). Metastases were detected in approximately half of the patients with glucagonomas (Song et al., 2018). The most common site of metastases is to the liver (80%), followed by lymph nodes, mesentery/omentum/peritoneum. Bone metastases have been reported (Wat et al., 1995; Song et al., 2018). Nevertheless, metastasis occurs late (John and Schwartz, 2016) and approximately 70% of patients with glucagonomas survives for 5 years. Thus, early diagnosis is important, and the presence of liver metastases may still allow curative resection (Al-Faouri et al., 2016). The tumour is immunohistochemically positive for glucagon and pancreatic polypeptide (PP).

### VIPoma

VIPoma is comprised of PanNET with secretion of vasoactive intestinal peptide (VIP) with WDHA (Verner-Morrison) syndrome - watery diarrhoea, hypokalaemia and achlorhydria. More than half of the cases present with distant metastases at diagnosis (Schizas et al., 2019). Approximately 200 pancreatic VIPoma were noted in the literature. The tumour is most often located in the tail of the pancreas. Lymphovascular invasion and perineural invasion is common. Immunoreactive VIP positive cells are scattered. Pancreatic polypeptide (PP) is frequently expressed.

### Somatostatinoma

Somatostatinoma presents with somatostatinoma syndrome which comprise diabetes/glucose intolerance, cholelithiasis and diarrhoea/steatorrhoea. High fasting somatostatin level can be demonstrated. Somatosta-

tinoma can occur in the duodenum (approximately 20%) though it is less common than in the pancreas (approximately 70%) (Elangovan and Zulfiqar, 2020). Less common sites are in ampulla of Vater and small intestine. Approximately 75% of the tumours are metastatic at presentation, with liver involvement early in the course and bone metastasis found later. The 5-year overall survival rate ranges from 60% to 100%. On pathological examination, the tumour may have tubular and glandular architecture and with intraglandular psammomatous calcifications. Vascular and perineural invasion are frequent and the tumour is often grade 2. Apart from somatostatin, tissue expression of other hormones can be seen in one-fourth of the cases.

### Adrenocorticotrophic hormone (ACTH)-producing neuroendocrine tumour

ACTH-producing PanNET can result in Cushing syndrome and be responsible for approximately 15% of ectopic Cushing syndrome (Maragliano et al., 2015). Around 140 cases have been reported in the literature (Byun et al., 2017). Multiple hormones production is common. Approximately 40% of these tumours have Zollinger-Ellison syndrome and 5% have insulinoma syndrome. Growth hormone-releasing hormone (GHRH) production has been reported (Tadokoro et al., 2016). Rarely, Cushing' syndrome may be due to corticotropin-releasing hormone (CRH) (Sauer et al., 2014). Lymphovascular and perineural invasion are common in this tumour. Most ACTH-producing PanNETs are aggressive and with liver metastases (Kondo et al., 2010; do Amor Divino et al., 2017). A significant number of cases are associated with lymph node metastasis (Byun et al., 2017). Immunohistochemical expression of ACTH and other peptide hormones are common. The 5-year survival rate of patients with ACTH-producing PanNET is 35% (Tikkanen, 1989).

### Serotonin-producing neuroendocrine tumour

This tumour is the least common member of the group of functioning PanNETs. Approximate 50 cases have been reported in the literature (McCall et al., 2012; Milanetto et al., 2020). It has been termed "carcinoid", but the term is not recommended in the current WHO classification. Diagnosis was based on urinary 5-hydroxyindole-acetic acid (5-HIAA) levels or serum serotonin (5-HT). Carcinoid syndrome presents only when there are liver metastases. Liver metastases nearly always present in functioning tumours (Milanetto et al., 2020). The serotonin producing PanNETs were less likely to have lymph node metastasis and more likely to involve large pancreatic ducts (McCall et al., 2012). The pancreatic functioning tumours associated with the carcinoid syndrome arise in younger patients and are larger, more frequently malignant, and more aggressive neoplasms than non-functional PanNETs with serotonin production (La Rosa et al., 2011). The tumour often has



trabecular architecture and stromal fibrosis. The fibrosis can lead to narrowing of pancreatic duct and pancreatic duct obstruction (Kawamoto et al., 2011). Perineural invasion, vascular invasion as well as invasion of adjacent organ by the tumour is frequent. In addition to expression of serotonin, serotonin-producing tumours also express somatostatin receptor 2A (STR2A) (La Rosa et al., 2011).

#### *Pancreatic neuroendocrine carcinoma (PanNEC)*

Like PanNETs, NECs occur in older adults in sixth to seventh decade of life (Lepage et al., 2007; Basturk et al., 2014; Heetfeld et al., 2015). PanNECs are rare. They are more common in men which is different from majority of PanNETs which is more common in women (Basturk et al., 2014).

The clinical presentations of PanNECs include back pain, and jaundice or non-specific abdominal symptoms which are like pancreatic ductal adenocarcinoma. PanNECs are mostly non-functioning. Nevertheless, small cell neuroendocrine carcinoma of pancreas with Cushing's syndrome/ectopic ACTH secretion have been reported (Corrin et al., 1973; Sandler et al., 1992). There are functioning high-grade neuroendocrine neoplasms reported in the literature which include two cases with secretion of ACTH and one with VIP (Basturk et al., 2015; Bleicher et al., 2019; Graham et al., 2019). However, according to the revised WHO classification, they should be labelled as "grade 3 PanNET" rather than "PanNECs". Different from PanNETs, serum chromogranin and somatostatin receptor scintigraphy are negative in PanNEC. Serum calcitonin and CA19-9 may be elevated (Uccella et al., 2017). There is no association with genetic syndromes such as MEN1 or von Hippel-Lindau syndrome. More than 90% of the patients had metastases at presentation. The median survival of the patients with PanNEC is usually less than a year.

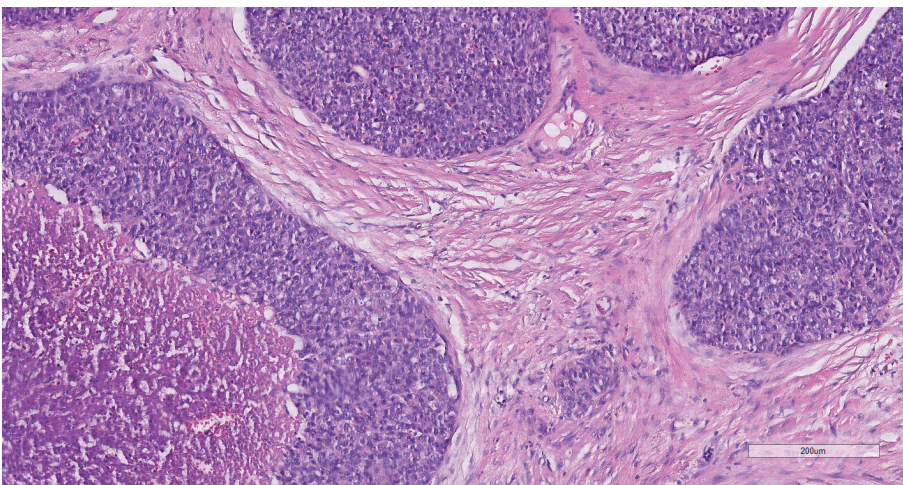
PanNECs occur more commonly in the head of the

pancreas (Basturk et al., 2014). The size of PanNECs is like PanNETs (mean 40 mm). Macroscopically, the tumour often shows vague nodularity and with haemorrhagic necrosis (Basturk et al., 2014).

Microscopically, PanNECs are recognized by the presence of neuroendocrine markers and poorly differentiated morphological features. The expression of neuroendocrine markers in PanNECs are usually weaker than in PanNETs. PanNECs are divided into small cell type (SCNECs) or large cell type (LCNECs). The relative proportion of the two subtypes are different in different studies (Basturk et al., 2014; Bukhari et al., 2020).

SCNECs are composed of relatively small tumour cells with a high nucleus to cytoplasm ratio, hyperchromatic nuclei, and nuclear moulding. The appearance of this type is like small cell carcinoma of the lung. LCNECs is characterized with cells that are often round to polygonal, and the nuclei have either vesicular chromatin or prominent nucleoli. Both types of NECs have prominent mitotic figures and foci of necrosis (Fig. 5). Sometimes, these may create a peritheliomatous or pseudopapillary-like pattern (Basturk et al., 2014).

Ki-67 proliferative index of >20% and mitotic count of >20 mitoses/2 mm<sup>2</sup> criteria are required for the diagnosis of PanNECs. The proliferative index of PanNECs overlaps with grade 3 PanNETs. Thus, it is important to differentiate LCNECs of pancreas from grade 3 PanNET. It is worth noting that different from PanNET, PanNECs have poorly differentiated morphological features having high mitotic count and sometimes with necrosis. In addition, a majority of the PanNECs have Ki-67 index of >50% (Fig. 6A). Moreover, NECs often show p53 overexpression (strong nuclear expression) (Fig. 6B) and loss of RB expression (Tang et al., 2016). In contrast, PanNETs are negative for p53 overexpression (Lam and Lo, 1998) and with loss of DAXX/ATRX expression (Tang et al., 2016).



**Fig. 5.** Pancreatic neuroendocrine carcinoma characterised by solid islands of tumour cells with granular cytoplasm as well as having nuclear atypia and tumour necrosis (hematoxylin and eosin). x 10.

The other differential diagnosis of pancreatic LCNEC includes acinar cell carcinoma. Acinar cell carcinoma has abundant eosinophilic granular apical cytoplasm due to zymogen granules with basal nuclei and prominent nucleoli. It may have solid or trabecular pattern and often show focal positivity to synaptophysin and chromogranin. Nevertheless, pancreatic acinar cell tumour has a lower Ki-67 proliferative index, and stains for trypsin and BCL 10 (La Rosa et al., 2015).

#### *Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)*

MiNEN is rare. In one of the largest reviews reporting on European patients with MiNENs of the gastroenteropancreatic tract, Frizziero et al. analysed 69 cases of MiNENs. Of these, 9% (n=6) were pancreatic MiNENs (Frizziero et al., 2019).

The clinical presentations of MiNENs are like those of pancreatic ductal adenocarcinoma. In the literature, a case of pancreatic MiNEN composed of ductal carcinoma and gastrinoma showing Zollinger-Ellison syndrome have been documented in the head of pancreas of a 62-year-old man (Terada et al., 1999) and a case of pancreatic ductal carcinoma with neuroendocrine component producing Verner-Morrison syndrome being noted in the pancreatic head of a 62-year-old woman (Ordóñez et al., 1988). Other than these, MiNENs of pancreas are non-functioning.

The gross appearance of the MiNENs depends more on the non-endocrine component which is often carcinomas. Thus, the tumour often has the features of carcinoma such as large size and necrosis on macroscopic examination.

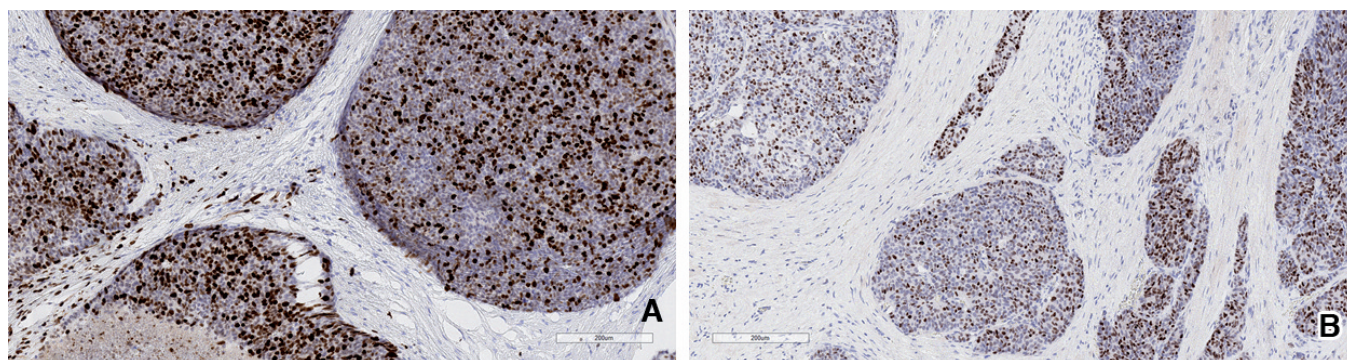
In pancreatic MiNEN, acinar cell carcinoma as one component is more common than ductal adenocarcinoma (Varshney et al., 2020). The neuroendocrine component can be NET or NEC. In 2018, Strait and colleagues noted 44 pancreatic MiNEN with acinar carcinomas in the literature (Strait et al., 2018). In 2020, Niiya and colleagues reviewed 29 cases in a search of the literature

from 2000 to 2018 (Niiya et al., 2020). Thus, less than 50 cases were reported. The reviews noted that the tumours were two to three times more common in men. The median age at presentation is in the seventh decade (median age at 65, range=33 to 89). The median tumour diameter is 39mm (range, 6 to 220 mm). The tumour occurs in any portion of the pancreas and slightly more than half (56%) of the tumours are in the pancreatic head. Approximately one third of the patients had distant metastases at presentation with the liver as the most common sites of metastases. The median survival of the patients was 17 months.

Pancreatic MiNENs composed of ductal carcinoma are less common. High grade pancreatic intraepithelial neoplasia may be observed together with the carcinoma. In 2011, Araki and colleagues reviewed 18 reports of MiNEN with the carcinoma component being ductal carcinoma (Araki et al., 2011). The tumours are two times more common in men (12 males and 6 females). The median age is in the seventh decade (62-year-old, range=29 to 76). The median survival of the patients was 13 months. The tumour occurs in any portion of the pancreas and slightly more than half (56%) of the tumours are in the pancreatic head. The mean diameter of the tumours is 45 mm (range, 5 to 190 mm).

Pancreatic mixed acinar cell carcinoma-ductal carcinoma - NEC is a pancreatic MiNEN with tri-lineage differentiation of acinar, ductal and neuroendocrine. It is very rare and has been reported by Newman and colleagues in a pancreatic tail of a 35-year-old man (Newman et al., 2009).

On microscopic examination, both neuroendocrine and non-neuroendocrine components should account for  $\geq 30\%$  of the tumour cell population according to the current WHO classification. Due to the quantitative threshold, it might be difficult for pathologists to accurately discriminate between MiNENs and neuroendocrine neoplasms with a minor non-neuroendocrine differentiation ( $<30\%$ ), or vice versa via biopsy specimens. As the component having  $<30\%$  of tumour cell population does not fulfil the criterion of



**Fig. 6.** Pancreatic neuroendocrine carcinoma. **A.** High proliferative index evidence with over 50% of nuclei of cancer stained by Ki-67. **B.** High number of tumour cells stained with mutated p53 protein.



MiNENs, the presence of the component (<30%) can be described but does not affect the diagnostic categorization. Minor presence of SCNECs (<30%) with a non-neuroendocrine component should be mentioned in the diagnosis due to the more aggressive nature of SCNECs.

### Pathological staging

The current 8<sup>th</sup> AJCC/UICC staging system has separated prognostic staging grouping for NENs arising in the pancreas, i.e., for PanNETs and for PanNECs/MiNENs. The staging system applying to well-differentiated PanNETs was developed (Bergsland et al., 2017; Brierly et al., 2018a). In the previous 7<sup>th</sup> AJCC/UICC TNM staging system, PanNETs were staged using the same system for exocrine pancreatic carcinomas (Edge et al., 2010). However, there was a significant overlap of survival between Stage II and III disease, i.e., clinical outcome of PanNETs patients with Stage III was statistically the same or occasionally better than those with Stage II (Rindi et al., 2012). The staging system developed by European Neuroendocrine Tumor Society (ENETS) was claimed to be superior to the 7<sup>th</sup> AJCC/UICC TNM system in terms of a predictor of patient survival (Rindi et al., 2006, 2012). Therefore, the current 8<sup>th</sup> AJCC/UICC TNM classification system for PanNETs was modified in line with the ENETS system (Bergsland et al., 2017; Brierly et al., 2018a).

In the current AJCC/UICC TNM staging, a narrower T definition is incorporated. T3 was defined in the 7<sup>th</sup>

AJCC/UICC system as a peripancreatic tumour spread without involvement of the celiac axis or the superior mesenteric artery (Edge et al., 2010). However, assessing peripancreatic tumour spread pathologically is occasionally very complicated because the pancreas has irregular lobules and fatty degeneration/replacement (Choe et al., 2019). In addition, the majority of PanNETs show an expansile growth pattern. These findings may lead to false classification and overestimation of T staging. Therefore, the AJCC system was modified according to the ENETS system, i.e., T3 is defined as a tumour limited to the pancreas, greater than 4 cm in size, or invading the duodenum or common bile duct, and T4 is defined as a tumour invading adjacent organs (stomach, spleen, colon and adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery) (Table 3). Since the criterion of peripancreatic soft tissue invasion was removed and PanNETs are staged mainly based on size, the problem in assessing peripancreatic tumour spread as mentioned above has been solved. In a large-scale validation of the 8<sup>th</sup> AJCC/UICC staging system for close to 1,000 patients with PanNETs, significant difference in disease-free survival was shown among all individual T categories (You et al., 2019).

In the current AJCC/UICC system for PanNETs, as in the 7<sup>th</sup> staging system, N0 is defined as no regional lymph node involvement, and N1 is defined as regional lymph node involvement (Bergsland et al., 2017; Brierly et al., 2018a). Regional lymph nodes for tumours located

**Table 3.** The 7<sup>th</sup>, 8<sup>th</sup> AJCC/UICC and ENETS staging system definitions for well-differentiated pancreatic neuroendocrine tumours.

7 <sup>th</sup> AJCC/UICC Staging System				8 <sup>th</sup> AJCC/UICC and ENETS Staging System			
T1	Tumour limited to the pancreas, ≤2 cm in greatest dimension			T1	Tumour limited to the pancreas <sup>a</sup> , <2 cm		
T2	Tumour limited to the pancreas, >2 cm in greatest dimension			T2	Tumour limited to the pancreas <sup>a</sup> , 2-4 cm		
T3	Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery			T3	Tumour limited to the pancreas <sup>a</sup> , >4 cm; or tumour invading the duodenum or common bile duct		
T4	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)			T4	Tumour invading adjacent organs <sup>b</sup> or the wall of large vessels (celiac axis or the superior mesenteric artery)		
N0	No regional lymph node metastasis			N0	No regional lymph node involvement		
N1	Regional lymph node metastasis			N1	Regional lymph node involvement		
M0	No distant metastasis			M0	No distant metastasis		
M1	Distant metastasis			M1	Distant metastasis		
Stage	T	N	M	Stage	T	N	M
IA	T1	N0	M0	I	T1	N0	M0
IB	T2	N0	M0	II (A*)	T2	N0	M0
IIA	T3	N0	M0	II (B*)	T3	N0	M0
IIB	T1-3	N1	M0	III (A*)	T4	N0	M0
III	T4	Any N	M0	III (B*)	Any T	N1	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

<sup>a</sup>: Limited to the pancreas means there is no invasion of adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery). Extension of tumour into peripancreatic adipose tissue is NOT a basis for staging. <sup>b</sup>: Adjacent organs mean stomach, spleen, colon and adrenal gland. \*Stage IIA/IIB and IIIA/IIIB are only used in ENETS system. AJCC: American Joint Cancer Committee; UICC: Union for International Cancer Control; ENETS: European Neuroendocrine Tumour Society. T: Definition of primary tumour; N: Definition of regional lymph node; M: Definition of distant metastasis.



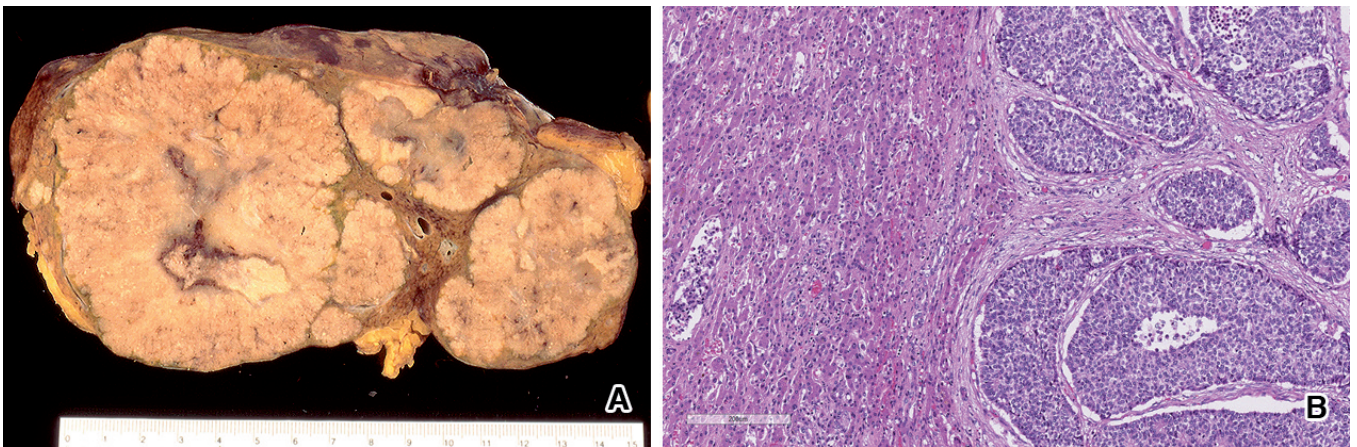
in the head and neck of the pancreas include lymph nodes along the common bile duct, common hepatic artery, portal vein, posterior and anterior pancreaticoduodenal arcades, and the superior mesenteric vein and right lateral wall of the superior mesenteric artery. Regional lymph nodes for tumours located in the body and tail of the pancreas include lymph nodes along the common hepatic artery, celiac axis, splenic artery and splenic hilum. Peripancreatic lymph nodes' involvement is also considered a regional disease and is classified as N1. As the procedure and range of lymph node dissection has not been fully established in treatment strategies for patients with PanNETs at this juncture, the surgical techniques and lymph node dissection/sampling methods may vary slightly among different institutions (Rindi et al., 2012; You et al., 2019). The rate of having "no lymph node sampling" was higher in patients who underwent enucleation or spleen-preserving distal pancreatectomy compared to patients treated with other surgical procedures (Parekh et al., 2012). If accurate assessment of the N category is not feasible, accurate TNM staging to predict prognosis becomes difficult (Rindi et al., 2012; You et al., 2019). In fact, the lymph node status could not be assessed in 737 out of 1,072 patients with PanNETs in a previous study to validate ENETS staging system (Rindi et al., 2012). Therefore, the lymph node status must be assessed very carefully, considering the differences in the surgical techniques and lymph node dissection/sampling methods among the institutions. A significant difference in disease-free survival was shown between N0 and N1 categories (Harimoto et al., 2019).

M0 is defined as no distant metastasis, and M1 is defined as distant metastasis in the current AJCC/UICC staging system (Bergsland et al., 2017; Brierly et al., 2018a). A wide range of frequencies of occurrence (21 to 80%) of metastatic lesions were noted in patients with

PanNENs. The most frequent site of metastasis was the liver (40 to 93%) (Fig. 7), followed by the bone (12 to 20%) and the lung (8 to 10%) (Ito et al., 2010; Nigri et al., 2018; Ishida et al., 2019). Involvement of the para-aortic or other distant lymph nodes, i.e., retroperitoneal, retrocrural and mesenteric lymph nodes, is considered M1 disease. Peritoneal dissemination is also defined as M1 disease (Bergsland et al., 2017; Brierly et al., 2018a).

Overall, the survival curves in the current 8<sup>th</sup> AJCC/UICC system were well separated between all stages (You et al., 2019). Although the current system was modified according to ENETS staging system, the ENETS one is imperfect, i.e., outcome of patients with Stage IIIB (any T, N1, M0) was better than those with Stage IIIA (T4, N0, M0) (Ekeblad et al., 2008; Scarpa et al., 2010; Rindi et al., 2012; You et al., 2019). There was also no significant difference in survival outcome between Stage IIB (T3, N0, M0) and Stage IIIA (You et al., 2019). The inaccurate discrimination was caused by poorer prognosis of the unresectable T4 compared to N1 cases, different surgical techniques and lymph node dissection/sampling methods, or small sample size of T4 (Rindi et al., 2012; You et al., 2019). The current 8<sup>th</sup> AJCC/UICC system combined Stage IIA and IIB/Stage IIIA and IIIB of ENETS system into one group (Stage II/Stage III), respectively, which is considered acceptable (Rindi et al., 2012; You et al., 2019) and superior to the ENETS staging system, as well as the previous 7<sup>th</sup> edition system. Therefore, the current system helps stratify the patients' prognosis and provide accurate clinical information.

In the past, there was no prognostic stage group for PanNECs and MiNENs. In the current AJCC/UICC staging system and the 5<sup>th</sup> WHO classification, it is recommended that PanNECs and MiNENs are staged according to the prognostic stage grouping for exocrine pancreatic carcinoma (Kakar et al., 2017; Brierly et al.,



**Fig. 7.** Pancreatic neuroendocrine tumour with liver metastases. **A.** The whole segment of liver is extensively replaced by multiple metastatic nodules of pancreatic neuroendocrine tumour. **B.** Microscopic examination reveals the multiple islands of pancreatic neuroendocrine tumour (right) in the liver (left).

2018b; Gill et al., 2019) (Table 4). In comparison to AJCC/UICC staging system for well-differentiated PanNETs, T1 group is subdivided into T1a to T1c depending on the size of the tumour. Also, the classification of T3 simply involves tumour dimensions of more than 4cm and disregards the invasion of the duodenum or common bile duct. For lymph nodes metastases (N grouping), there is a subdivision of N into N1 and N2 based on the number of lymph nodes involved. The prognostic stage grouping for PanNECs and MiNENs are different from PanNETs (Table 4).

In a relatively large-scale validation of the 8<sup>th</sup> AJCC/UICC staging system for PanNECs (n=568), overlap existed between Stage I and Stage II disease (Wang et al., 2020). The median overall survival in Stage I, II, III and IV were 62, 138, 15 and 7 months, respectively, and no statistical significance was observed for hazard ratio between Stage I and Stage II disease by multivariable analyses (Wang et al., 2020). The inaccurate discrimination might be caused by poor prognosis of PanNECs, unestablished treatment strategies for patients with PanNECs, or relatively small sample size of Stage I-III (n=154 in Stage I-III, n=414 in Stage IV) (Wang et al., 2020). As the two neoplasms are very rare (PanNECs, 2 to 3%; MiNENs, <1% of all PanNENs, respectively) (Halfdanarson et al., 2008;

Niederle et al., 2010; Basturk et al., 2014, 2015), further validation and additional modification of the 8<sup>th</sup> AJCC/UICC staging system for PanNECs and MiNENs might be required for accurate discrimination.

## Conclusions

The current WHO classifications categorise PanNENs simply, correctly and practically, i.e., the classification has greatly contributed to the standardisation of diagnosis of PanNENs. PanNETs are also classified into non-functional NET, insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma, ACTH-producing NET and serotonin producing NET based on hormone production and clinical manifestations. These, along with refined pathological staging of 8<sup>th</sup> AJCC/UICC staging system allows better prognostic stage grouping and selection of proper treatment strategies for patients with PanNENs.

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**Table 4.** The 8<sup>th</sup> AJCC/UICC staging system definitions for pancreatic neuroendocrine carcinomas and mixed neuroendocrine-non-neuroendocrine neoplasms and comparison to pancreatic neuroendocrine tumours.

8 <sup>th</sup> AJCC/UICC Staging System for PanNECs and MiNENs				
Tis	Carcinoma in situ <sup>a</sup>	N0	No regional lymph node metastases	
T1 <sup>b</sup>	Tumour ≤2 cm in greatest dimension	N1	Metastasis in one to three regional lymph nodes	
T2	Tumour >2 cm and ≤4 cm in greatest dimension	N2	Metastasis in four or more regional lymph nodes	
T3	Tumour >4 cm in greatest dimension			
T4	Tumour involves celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size	M0	No distant metastasis	
		M1	Distant metastasis	
Prognostic Stage Groups				
T	N	M	PanNECs and MiNENs	PanNETs
Tis	N0	M0	0	NA <sup>c</sup>
T1	N0	M0	IA	I
T2	N0	M0	IB	II
T3	N0	M0	IIA	III
T1	N1	M0	IIB	III
T2	N1	M0	IIB	III
T3	N1	M0	IIB	III
T1	N2	M0	III	NA <sup>c</sup>
T2	N2	M0	III	NA <sup>c</sup>
T3	N2	M0	III	NA <sup>c</sup>
T4	Any N	M0	III	III
Any T	Any N	M1	IV	IV

<sup>a</sup>: Carcinoma in situ includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia. <sup>b</sup>: T1a, Tumour ≤0.5 cm in greatest dimension; T1b, Tumour >0.5 cm and <1 cm in greatest dimension; T1c, Tumour 1-2 cm in greatest dimension. <sup>c</sup>: Tis and N2 is not defined in the 8<sup>th</sup> AJCC/UICC Staging System for PanNETs. AJCC: American Joint Cancer Committee; UICC: Union for International Cancer Control; T: Definition of primary tumour; N: Definition of regional lymph node; M: Definition of distant metastasis; NA: not available; PanNECs: pancreatic neuroendocrine carcinomas; MiNENs: mixed neuroendocrine-non-neuroendocrine neoplasms; PanNETs: pancreatic neuroendocrine tumours.

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