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Clinical Review

Systematic review of current prognostication systems for pancreatic neuroendocrine neoplasms

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ABSTRACT

Background: Pancreatic neuroendocrine neoplasms are a heterogenous group of rare tumors whose natural history remains poorly defined. Accurate prognostication of pancreatic neuroendocrine neoplasms is essential for guiding clinical decisions. This paper aims to summarize all the commonly utilized and recently proposed prognostication systems for pancreatic neuroendocrine neoplasms published in the literature to date.

Methods: A systematic review of Pubmed, Scopus, and Embase databases, of the period from January 1, 2000–November 29, 2016, was conducted to identify all published articles reporting on prognostication systems of pancreatic neuroendocrine neoplasms.

Results: A total of 23 articles were included in our review, and a total of 25 classification systems were identified. There were 2 modifications of the World Health Organization 2004 criteria, 4 modifications of the World Health Organization 2010 criteria, 2 modifications of the American Joint Committee on Cancer 2010 staging system, 3 modifications of the European Neuroendocrine Tumor Society 2006 tumor, node, metastasis staging system, 7 novel categorial classification systems, and 2 novel proposed continuous classifications. The most commonly included variables included age, size of tumor, presence of distant and lymph node metastases, Ki-67 index, and mitotic count.

Conclusion: Numerous prognostication systems have been proposed for pancreatic neuroendocrine neoplasms, of which the most commonly used systems presently include the World Health Organization 2010 criteria and the two tumor, node, metastasis staging systems by the European Neuroendocrine Tumor Society and the American Joint Commission on Cancer. However, prognostication systems for pancreatic neuroendocrine neoplasms continue to evolve with time as more prognostication factors are identified. More validation and comparative studies are needed to identify the most effective prognostication system.

Introduction

Pancreatic neuroendocrine neoplasms (PNENs) are a rare entity and comprise less than 2% of all pancreatic neoplasms.[1,2] The clinical incidence for PNENs is reported to be less than 0.25 to 1 in 100,000 in the United States,[2] although the incidence of PNENs has been increasing in recent years with the increasing widespread use of cross-sectional imaging, resulting in the increased detection of incidentalomas.[3,4] PNENs are widely heterogenous tumors and may vary in their presentation and prognosis. Although most are likely to be benign and indolent tumors, some PNENs follow a more aggressive course. Despite efforts to elucidate prognostic factors, the natural history and prognosis of PNENs have remained poorly defined and difficult to predict.

The clinical presentation of PNENs may be largely classified into functional and nonfunctional tumors. Functional tumors include insulinomas, gastrinomas, somatostatinomas, glucagonomas, and VIP-omas. Insulinomas follow the most benign course: 10% of insulinomas have metastatic potential in comparison with 50% of

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somatostatinomas.[5] Furthermore, 5-year survival rates for insulinomas have been reported to be as high as 97% in comparison with 30% for nonfunctioning tumors.[6]

At present, surgery remains the only curative mode of treatment for PNENs and is the treatment of choice for most tumors in surgically fit patients, with good life expectancy.[7–9] However, despite advances in surgical techniques, pancreatic surgeries remain associated with high morbidity rates.[10] This presents a clinical dilemma because PNENs may follow a long and indolent course. Hence, accurate prognostication of PNENs is crucial to guide clinical decisions regarding treatment plans and for clinicians to counsel patients appropriately.

Numerous studies have been conducted to identify prognostic factors for PNENs, and commonly recognized factors include tumor size, presence of metastases, lymph node status, tumor margins, and tumor characteristics.[11] Many prognostication systems have been suggested for prognosticating PNENs based on various combinations of prognostic factors, although there remains a lack of consensus with regard to the most effective prognostication system for classifying PNENs. In the face of numerous prognostication systems, there is potential for confusion and communication difficulties when various systems are utilized. This systematic review aims to summarize all the commonly utilized and recently proposed prognostication systems for PNENs published in the literature to date.

Methods

A literature review was performed using the Pubmed, Scopus, and Embase databases, of the period from January 1, 2000–November 29, 2016, to identify all published articles reporting on prognostication systems of PNENs. The key words used in the search include ("pancreatic neuroendocrine" or "pancreatic endocrine") AND ("staging" OR "grading" OR "classification" OR "prognos*"). Key references of shortlisted articles were also searched manually to identify additional relevant articles. The search results were obtained (by R.T. and T. Teo), and final inclusion was discussed with senior author (B.K.G.). This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Inclusion and exclusion criteria

The inclusion criteria for this study included the following: (1) English language articles, (2) full-text articles, (3) articles validating or proposing new prognostication systems for PNENs, and (4) multivariate analysis of prognostic indicators of mortality. The exclusion criteria included the following: (1) abstracts, letters, editorials, expert opinions, reviews, and case reports; (2) articles written in languages other than English; (3) articles only looking at recurrence-free survival; (4) articles evaluating gastroenteropancreatic neuroendocrine tumors as a whole; (5) animal studies; and (6) overlapping studies. Only the most recent study for a single center was included for overlapping studies.

Data extraction and statistical analysis

Data from full-text articles were extracted and included prognostication method, score calculation, study cohort, validation cohort, variables used, results of comparison with other prognostication systems, and year published. No statistical analysis was required for this study

Results

The Pubmed search yielded 427 results, the Embase search yielded 1,527 results, and the Scopus search returned 1,105 results (Fig. 1). A total of 12 additional studies were identified from the reference list of studies (1,438 duplicate articles were excluded, and 1,633 articles underwent abstract review). A total of 1,546 articles were excluded via study types (including case reports, review articles, and conference abstracts). Finally, 87 articles were selected for full-text review and 23 articles were eventually included in our study, which are summarized in Table 1.

Summary of clinical prognostication systems

A total of 25 classification systems were described, of which 22 were categorical and 3 were continuous systems. These included the following:

- The original World Health Organization (WHO) criteria in 2000,[12] the revised WHO classification in 2004,[13] and its revisions by Schmitt et al.[14] in 2007 and by La Rosa et al.[15] in 2009[15]
- The WHO 2010 classification system,[16] which was modified from the European Neuroendocrine Tumor Society (ENETS) grading system,[17,18] and its subsequent revisions by Scarpa et al.,[19] Hamilton et al.,[20] Ricci et al.,[21] and Kaltenborn et al.[22]
- The American Joint Commission on Cancer (AJCC) 6th edition[1] and the 7th edition of the tumor, tumor, node, and metastasis (TNM) staging system[23] and its subsequent revisions by Martin et al.[24] and by Qadan et al.[25]
- The ENETS TNM staging system[17,18] and its revisions by Scarpa et al.,[19] Luo et al.,[26] and Ye et al.[27]

In addition, various studies have proposed novel classification systems in a bid to improve prognostication for PNENs, most of which have not undergone external validation and are not widely utilized—the Bilimoria score in 2008,[28] the Memorial Sloan-Kettering Cancer Center (MSKCC) grading and staging criteria,[29] the Zhang immunohistochemistry grading system proposed in 2009,[30] the Botsis criteria in 2010,[31] the Zhang histopathologic grading system in 2011,[32] the Kaltenborn 3-year survival score,[22] and the Ye grading system in 2016.[27] Ellison et al.[33] and Ye et al.[27] each proposed a continuous system with nomograms in 2014 and 2016, respectively. The most commonly included variables included age, size of tumor, presence of distant and lymph node metastases, and proliferation index in the form of mitotic count or Ki67 index. Table 2 summarizes the current available prognostication systems for assessing prognosis of PNENs.

Historical development of the prognostication systems

In 1995, Capella et al.[34] recommended the first prognostication system for lung, pancreatic, and intestinal neuroendocrine tumors based on consensus expert opinion. Tumors were evaluated based on predominant cell type; degree of differentiation; presence of clinical syndrome; tumor size; and presence of local, vascular, and distant metastases; and divided into four groups: benign, unknown potential, low malignancy, and high malignancy. Numerous studies have since validated this classification system and demonstrated its usefulness in prognostication.[35–37] This system formed the basis of the WHO classification in 2000 (that included all Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs)) and 2004 (that included only PNENs). Importantly, in addition to size of tumors, the WHO 2004 revised classification included proliferation activity (as determined by mitotic count or Ki67 index) as a criterion to distinguish between benign and uncertain behavior PNENs.

In 2002, MSKCC[38] developed a nomogram to predict the disease-specific survival of patients and modified it again in 2007.[29] The group defined staging based on tumor size (>2 cm) and the presence of metastases and defined grading based on mitotic rate and presence of necrosis. Subsequently, in 2006, ENETS

Table 1
Shortlisted articles and their proposed prognostication system.

Number	Author/year	Prognostication system	Variables included	Remarks
Classification systems				
1	Solcia et al. 2000[12]	WHO 2000	Predominant cell type, degree of differentiation, presence of clinical syndrome, tumor size, presence of local and angioinvasion, presence of distant metastases	Formulated based on consensus opinion, modified from the Capella classification proposed in 1995
2	Heitz et al. 2004[13]	WHO 2004	Tumor invasion, size, mitotic count, Ki-67 index, presence of angioinvasion or perineural invasion, presence of distant metastases	Formulated based on consensus opinion, modified from the WHO 2000 and the Capella classification proposed in 1995
3	Rindi et al. 2006[17,18]	ENETS TNM	Tumor size and invasion, lymph nodes, metastases	Formulated based on consensus opinion, modified from the WHO 2000 and the Capella classification proposed in 1995
4	Rindi et al. 2006[17,18]/ Bosman et al. 2010[16]	ENETS Grading/ WHO 2010	Ki-67 index, mitotic count	Adapted from the ENETS grading system proposed in 2006, formulated based on consensus opinion of 62 experts
5	Bilimoria et al. 2007[1]	AJCC 6th edition	Tumor size and invasion, lymph nodes, metastases	Validated use of AJCC 6th edition classification for exocrine pancreatic tumors on PNENs; based on 4,793 patients from the National Cancer Database
6	Schmitt et al. 2007[14]	Schmitt modified WHO 2004 criteria	Tumor size, number of mitosis, Ki-67 index, presence of angioinvasion, presence of gross local invasion, presence of metastases and CK-19 index	Adapted from the WHO 2004 criteria based on a single institution of 216 patients; no external validation
7	Bilimoria et al. 2008[28]	Bilimoria score	Age, grade, and presence of distant metastases	Formulated based on 3,851 patients from the National Cancer Database; externally validated by Goh et al.[2]
8	Ferrone et al. 2007[29]	MSKCC criteria	Grading: tumor mitotic count (mitoses/50hpf) and necrosis Staging: size and presence of metastases/ nodal metastases	Formulated based on a prospective database of 183 patients; externally validated by Goh et al.[2] and Botsis et al.[31]
9	La Rosa et al. 2009[15]	La Rosa grading criteria	WHO 2000 criteria, tumor differentiation and mitotic count	Formulated based on a single institution database of 155 patients
10	Zhang et al. 2009[30]	Zhang immunohistochemistry grading system	KIT and CK expression	Formulated based on a single institution database of 97 patients; no external validation
11	Edge et al. 2010[23]	AJCC 7th edition	Tumor size and invasion, lymph nodes, metastases	Adapted from AJCC 6th edition TNM classification for exocrine pancreatic tumors
12	Botsis et al. 2010[31]	Botsis criteria	Presence of distant metastases, elevated AST, age at diagnosis > 60 years, presence of perineural/lymphovascular invasion	Formulated based on a single institution database of 98 patients; no external validation

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Table 1 (*continued*)

Number	Author/year	Prognostication system	Variables included	Remarks
13	Scarpa et al. 2010[19]	Scarpa modified TNM staging	Tumor size and invasion, presence of distant metastases, lymph nodes	Formulated based on a single institution database of 274 patients; modified TNM criteria not externally validated
		Scarpa modified Ki-67 grading criteria	Ki-67 index	Externally validated by Martin-Perez et al.,[42] Khan et al.,[39] Bettini et al., Panzuto et al.,[40] and Rindi et al.
14	Martin et al. 2011[24]	Martin staging criteria	Tumor size and invasion, grade, presence of distant metastases or lymph node metastases	Formulated based on 6,447 patients from the SEER series and 300 patients from a prospective database; no external validation
15	Zhang et al. 2011[32]	Zhang histopathologic grading	Mitotic count, presence of necrosis and infiltrating borders	Formulated based on a single institution database of 97 patients; no external validation
16	Hamilton et al. 2012[20]	Hamilton (modified Ki-67) criteria	Ki-67 index	Formulated based on asingle institution database of 140 patients; no external validation
17	Ricci et al. 2014 (21)	Ricci modified WHO 2010	Ki-67 index	Formulated based on a single institution database of 64 patients
18	Qadan et al. 2014[25]	Qadan modified TNM staging	Size, presence of distant metastases, lymph nodes	Formulated based on 1,202 patients from the SEER database; no external validation
19	Kaltenborn et al. 2016[22]	Kaltenborn mortality after surgery score	Ki-67 index, pr-operative platelet count	Formulated based on a single institution database of 41 patients; no external validation
		Kaltenborn observed 3-year survival score	Preoperative platelet count, minimal distance of resection margin from tumor in millimeters, number of positive lymph nodes, histologic tumor infiltration	
20	Ye et al. 2016[27]	Ye grading system	Functional status and mitotic count	Formulated based on a single institution database of 78 patients; no external validation
21	Luo et al. 2016[26]	Luo (modified TNM) criteria	Tumor size and invasion, lymph nodes, metastases	Formulated based on 2,529 patients from the SEER series and 1,143 patients from a multicentric series; no external validation
Nomograms				
1	Ellison et al. 2014[33]	Ellison nomogram	Ki-67 index, age at surgery ($>$ 63 versus $<$ 63 years), sex	Formulated based on a single institution database of 326 patients; no external validation
2	Ye et al. 2016[27]	Ye grading nomogram	Functional status and mitotic count	Formulated based on a single institution database of 78 patients; no external validation
		Ye modified ENETS nomogram	Tumor size and invasion, nodal status, mitotic count, functional status, and mitotic count	

Table 2
List of proposed prognostication systems for PNENs.

Capella	Group 1- Well differentiated endocrine tumour; benign behaviour: confined to pancreas; non angioinvasive; <20mm in size; functioning or nonfunctioning Group 2- well differentiated endocrine tumour; uncertain behaviour: confined to pancreas; angioinvasive or >20mm in size; functioning or non functioning Group 3- well differentiated endocrine carcinoma; low group malignant carcinoma, with group local involvement or metastases; functioning or nonfunctioning Group 3- poorly differentiated endocrine carcinoma; high group malignant carcinoma (small to intermediate cells)		
WHO 2004	Well differentiated endocrine tumour with benign behaviour - Confined to pancreas, <2cm in diameter, ≤2 mitoses/ 10hpf, ≤2 Ki-67 positive cells, no angioinvasion or perineural invasion Well differentiated endocrine tumour with uncertain behaviour - Confined to pancreas and ≥1 of the following features: 2cm in diameter, >2 mitoses/ 10hpf, >2 Ki-67 positive cells, angioinvasion, perineural invasion Well differentiated endocrine carcinoma, low grade malignancy - Macroscopic local invasion or metastases Poorly differentiated endocrine carcinoma, high grade malignancy - >10 mitoses/ 10 hpf		
WHO 2010/ ENETS grading	ENETS grading system: G1: <2 mitoses/10 hpf and <2% Ki67 index G2: 2-20 mitoses/10 hpf or 2- 20 Ki67 index G3- >20 mitoses/10 hpf or >20% Ki67	WHO 2010 classification: Well differentiated pancreatic neuroendocrine tumours • G1: <2 mitoses/10 hpf and <2% Ki67 index • G2: 2-20 mitoses/10 hpf or 2- 20 Ki67 index Poorly differentiated pancreatic neuroendocrine carcinomas • G3: >20 mitoses/10 hpf or >20% Ki67 Mixed adenoneuroendocrine carcinomas • G3 tumours containing non-neuroendocrine components	
AJCC TNM 7th Edition	T1- T<2cm, confined to pancreas T2- T> 2cm, confined to pancreas T3- Tumour extends beyond pancreas, but does not involve superior mesenteric artery or coeliac axis T4- Tumour involves superior mesenteric artery or coeliac axis	N0- Regional nodes not involved N1- Regional nodes involved NX-Regional nodes not assessed	M0- Distant metastases absent M1- Distant metastases present
	Stage IA- T1 N0 M0 Stage IB- T2 N0 M0 Stage IIA- T3 N0 M0 Stage IIB- T1/2/3 N1 M0 Stage III- T4 any N M0 Stage IV- any T any N M1		
ENETS TNM	T1- T<2cm, limited to pancreas T2- T as 2-4 cm, limited to pancreas T3- T>4cm, but limited to pancreas or invading duodenum or bile duct T4- Tumour invading adjacent organs (stomach, spleen, colon, adrenal gland) or walls of large vessels (superior mesenteric artery or coeliac axis)	N0- Regional nodes not involved N1- Regional nodes involved NX-Regional nodes not assessed	M0- Distant metastases absent M1- Distant metastases present
	Stage I- T1 N0 M0 Stage IIA- T2 N0 M0 Stage IIB- T3 N0 M0 Stage IIIA- T4 N0 M0 Stage IIIB- any T N1 M0 Stage IV- any T any N M1		
Bilimoria score	Age 0: <55 1: 55- 75 2: >75	Grade 0: well/ moderately differentiated 1: poorly differentiated	Distant metastases 0: none 1: liver 3: other distant metastases
	Score 1: 04 Score 2: 1-2 Score 3: ≥3		
Luo modified TNM criteria	T1- T<2cm, limited to pancreas T2- T as 2-4 cm, limited to pancreas T3- T>4cm, but limited to pancreas or invading duodenum or bile duct T4- Tumour invading adjacent organs (stomach, spleen, colon, adrenal gland) or walls of large vessels (superior mesenteric artery or coeliac axis)	N0- Regional nodes not involved N1- Regional nodes involved NX-Regional nodes not assessed	M0- Distant metastases absent M1- Distant metastases present
	Stage IA- T1 N0 M0 Stage IB- T2 N0 M0 Stage IIA- T3 N0 M0 Stage IIB- T1/2/3 N1 M0 Stage III- T4 any N M0 Stage IV- any T any N M1		
MSKCC criteria	Staging I: Tumour size <2 cm II: Tumour size ≥2cm III: Presence of distant metastases or regional nodal disease Grade Low grade: no evidence of necrosis, <2 mitoses/ 50 hpf Intermediate grade: necrosis or ≥2 mitoses/ 50 hpf		
Schmitt modified WHO 2004 criteria	I (no relapse/ no death of disease): WHO 2004 well-differentiated tumour with benign behaviour and CK 19 +/- II (relapse/ no death of disease): WHO 2004 well-differentiated tumour with uncertain behaviour and CK 19 - III (relapse/ death of disease): WHO 2004 well-differentiated tumour with uncertain behaviour and CK 19 + or well differentiated endocrine carcinoma and CK 19 +/- IV (rapid progress/ death of disease): WHO 2004 poorly differentiated endocrine carcinoma and CK 19 +/-		
Botsis criteria	Presence of distant metastases- 1 point Elevated AST- 1.25 points Age at diagnosis over 60- 1.5 points Presence of perineural/ lymphovascular invasion- 2 points		
	Low risk: 0-1.5 Intermediate risk: 2-3.5 High risk: >3.5		
Martin staging criteria	T1- T<3cm, localised to pancreas T2- T >3cm, localised to pancreas T3- T extending to adjacent organs and vessels	G1- GI (low grade)/ GII (medium grade) G2- GIII (high-grade)/ GIV (dedifferentiated)	M0- No distant/ lymph node metastases M1- presence of distant metastasis/ lymph node metastases

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Table 2 (*continued*)

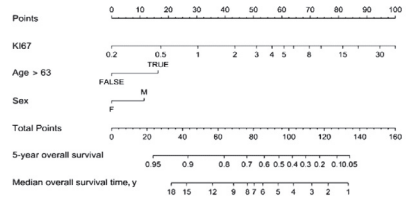
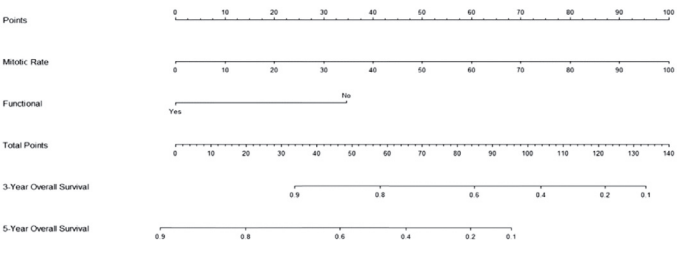
	Stage I: T1-2, G1, M0 Stage II: T1-2, G2, M0 Stage III: T3G2M0 or Tany, G1, M1 Stage IV: Tany, G2, M1		
Hamilton criteria	G1: Ki 67 index <5% G2: Ki 67 index 5- 9% G3: Ki 67 index >9%		
Zhang histopathological grading	Absence of necrosis= 0 Presence of necrosis= 1	Absence of infiltrating border= 0 Presence of infiltrating border= 1	Mitotic count 0/50 hpf= 0 Mitotic count 1-3/50 hpf=1 Mitotic count ≥4/ 50 hpf= 2
	Grade 1: score 0 or 1 Grade 2: score 2 Grade 3: score 3 or 4		
Zhang immunohistochemistry grading system	Low risk: (KIT-/ CK-) Intermediate risk: (KIT-/ CK+) High risk: (KIT+/ CK+)		
Scarpa criteria	Modified TNM T1- T<2cm, limited to pancreas T2- T as 2-4 cm, limited to pancreas T3- T>4cm, excluding the infiltration of duodenum or bile duct T4- Tumour invasion of any adjacent structure, including duodenum and bile duct Tumour invasion into duodenum or bile duct may be clinical (jaundice or duodenal bleeding due to infiltration) or radiological (dilation of pancreatic or bile duct)	N0- Regional nodes not involved N1- Regional nodes involved NX-Regional nodes not assessed	M0- Distant metastases absent M1- Distant metastases present
	Stage I- T1 N0 M0 Stage IIA- T2 N0 M0 Stage IIB- T3 N0 M0 Stage IIIA- T4 N0 M0 Stage IIIB- any T N1 M0 Stage IV- any T any N M1		
	Modified Ki-67 grading G1: Ki 67 index <5% G2: Ki 67 index 5- 20% G3: Ki 67 index >20%		
Kaltenborn Observed 3-year survival score **Kaltenborn Mortality after surgery score** **Kaltenborn Tumour recurrence risk score**	Ki-67/platelet-mortality score= 1.125 x Ki-67 - 0.140 x preoperative platelet count Survival probability over 3 years in %= Exp(Y)/(1+Exp(Y)), with Y=-12.492+(0.054 x preoperative platelet count in thousand/ml) + (0.112 x minimal distance of the resection margin from the tumor in mm) + (-1.574 x number of positive lymph nodes) + (2.292 x histological tumor infiltration, if yes= 1; if no= 0) Risk in %=Exp(Y)/(1+Exp(Y)), with Y=-4.360 + (0.015 x tumor diameter in cm) + (0.010 x preoperative platelet count in thousand/ µl) + (1.077 x distant metastases, if yes=1; if no= 0)+(-0.026 x Ki-67 positive cells in %) + (-1.086 x upper abdominal pain, if yes=1; if no=0)		
Ricci modified WHO 2010 criteria	G1: <2% Ki67 index G2a: 2-5% Ki-67 index G2b: 5- 20% Ki-67 index G3: >20% Ki-67 index		
Qadan TNM staging	T1= 0-1 cm T2= 1.1-2 cm T3= 2.1- 4 cm T4= >4 cm	N0- Regional nodes not involved N1- Regional nodes involved NX-Regional nodes not assessed	M0- Distant metastases absent M1- Distant metastases present
	Stage I- T1N1 T1N0 Stage II- T2N0 T2N1 T3N0 Stage III- T3N1 T4N0 T4N1 Stage IV- any tumour with distant mets (M1)		
Ye grading system	Low grade: Functioning and ≤20 mitoses/10HPF High grade: Non-functioning +/- > 20 mitoses/10HPF		
Ellison nomogram			
Ye grading nomogram			

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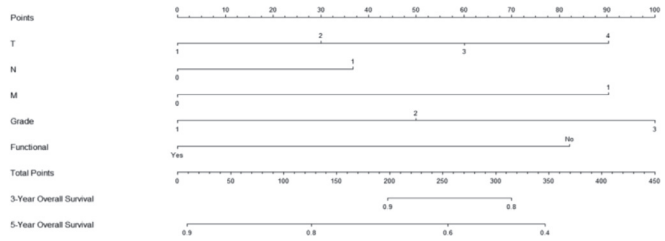
Table 2 (*continued*)

Ye modified ENETS nomogram	

developed and published a separate grading and staging system, which was based on the consensus statement of 62 experts. The ENETS grading and staging system has become one of the most popular and commonly utilized systems today. This was the first classification system that considered the distinctive growth pattern of these tumors from other GEP-NENs, and the grading system was based solely on mitotic count and Ki67 index.

In 2007, Bilimoria et al.[1] first validated the use of the AJCC TNM staging system for pancreatic adenocarcinomas on PNENs and further derived a simplified postresection prognostic score based on 836 patients in 2008,[28] which utilized age, grade, and presence of distant metastases to stratify PNENs. The points were summed into a raw score that was divided into 3 groups. The 5-year survival rates were observed to be significantly different between the 3 prognostic score categories, and the concordance index for the prognostic score (0.63) was found to be comparable with that for the AJCC 6th edition pancreatic adenocarcinoma staging system. In 2009, La Rosa et al.[15] proposed an alternative model based on the WHO 2000 classification, suggesting that high-grade cancers may be separated from intermediate-grade cancers by the presence of a high-proliferative rate (>10 mitoses/10 HPF) or a poorly differentiated histologic feature, which was essentially similar to the WHO 2004 classification. Also in 2009, Zhang et al.[30] proposed a novel immunohistochemistry classification system based on KIT and CK

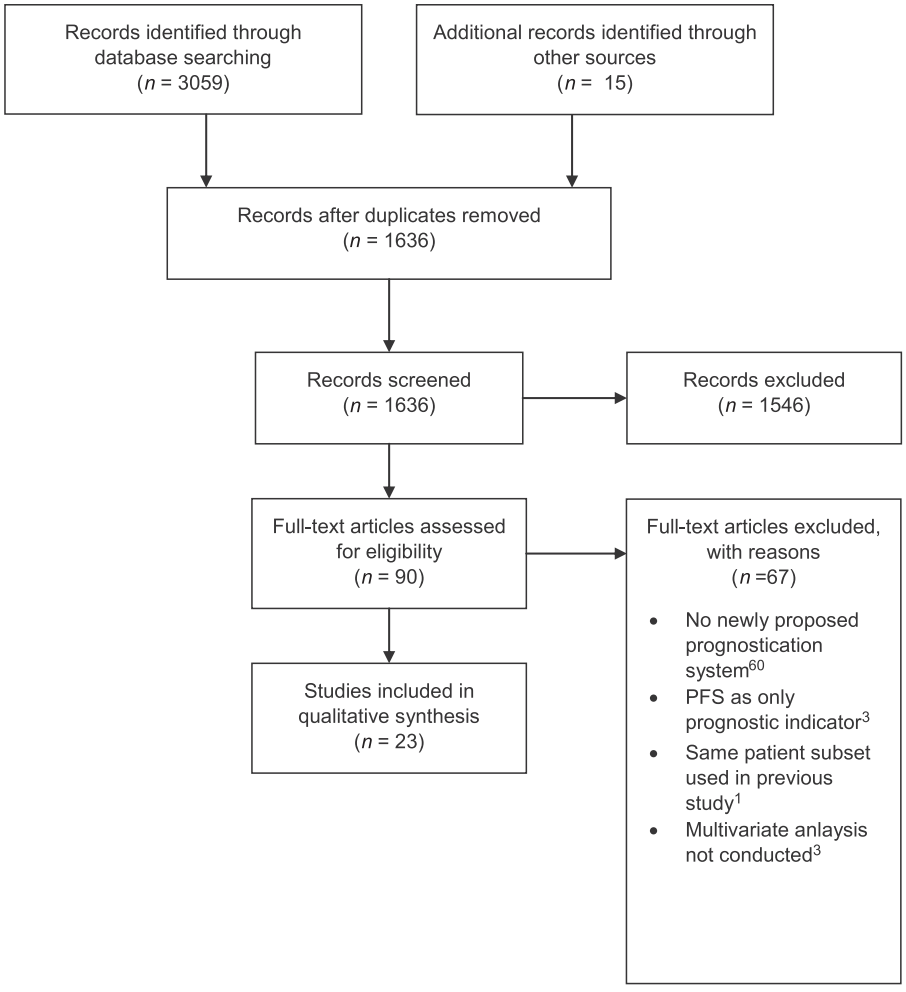


Fig. 1. PRISMA flow diagram of results of the literature search.

expression: low risk (KIT–/CK–), intermediate risk (KIT–/CK+), and high risk (KIT+/CK+). It was reported that survival, metastasis, and recurrence rates were significantly different among the three groups.

The AJCC subsequently introduced a staging system for PNENs in 2010 based on the TNM staging system for its exocrine counterpart. The criteria used in the definition of T stages was different from that used in the ENETS staging criteria, which led to the existence of two parallel TNM staging systems that used identical terminology and referred to different extents of disease. WHO incorporated the ENETS grading system into its 2010 classification system, and this incorporation led to a unified grading approach to all GEP-NENs. According to the WHO 2010 classification, there were three classes of PNENs—the well-differentiated PNENs known as pancreatic neuroendocrine tumors, the poorly differentiated PNENs known as pancreatic neuroendocrine carcinoma, and the mixed adenoneuroendocrine tumors. The well-differentiated pancreatic neuroendocrine tumors were further classified into G1 and G2 tumors based on their Ki-67 index and mitotic activity. In the same year, Scarpa et al.[19] proposed several modifications to the ENETS staging and grading system based on a study of 274 surgically treated PNENs. Cutoff points of 5% and 20% were used for Ki-67 grading because they were found to have provided the most efficient prognostication on multivariate and Cox model of survival analysis. The following modifications were applied to the T staging criteria: (1) T3 was defined only by tumor dimensions; (2) T4 was defined as the presence of tumor invasion of any adjacent structure, including duodenum and bile duct; and (3) duodenal and bile duct involvement was assessed via clinical means (presence of jaundice/duodenal bleeding) and radiologic means (dilatation of pancreatic or bile duct size), in addition to the usual histopathologic means.

Also in 2010, Botsis et al.[31] developed yet another prognostic model based on a cohort of 98 patients. The risk score looked at age, presence of perineural or lymphovascular invasion, elevated aspartate transaminase (AST), and distant metastases, and classified PNENs into low, intermediate, and high-risk groups. In 2011, Zhang et al.[32] suggested a new 3-tier grading system based on a histopathologic score calculated from number of mitoses, presence of tumor necrosis, and infiltrating tumor border, and found that it was able to discriminate recurrence, survival, functional status, and tumor metastasis rates among the 3 groups. Martin et al.[24] proposed a new 4-tier staging system based on age, size, grade, and tumor metastases in 2011. T1 tumors were defined as $\leq$3cm and localized to the pancreas, T2 tumors $>$ 3cm and localized to the pancreas, and T3 tumors included all that extended to adjacent organs and vessels. G1 tumors were defined as well differentiated or moderately differentiated tumors, and G2 tumors as poor or undifferentiated tumors. The stages were then regrouped as follows: stage I (T1–2, G1, M0), stage II (T1–2, G2, M0), stage III (T3G2M0, Tany G1, M1), and stage IV (Tany, G2, M1).

In 2012, Hamilton et al.[20] conducted a study on 140 patients who were surgically treated for PNENs and suggested cutoff points of 5% and 9% for Ki-67 index. The study reported that this proposed stratification was able to prognosticate the tumors into 3 risk groups with statistical significance and optimized determination of risk of recurrence. Similarly in 2014, Ricci et al.[21] proposed dividing G2 tumors into 2 subcategories: tumors with Ki-67 index 2%–5% and tumors with Ki-67 index 5%–20%. This was based on a study of 64 surgically resected tumors and was found to improve prognostication. In 2014, Qadan et al.[25] conducted a study on 1,202 patients from the Surveillance, Epidemiology, and End Results (SEER) database, evaluating the efficacy of the AJCC system, and proposed a novel TNM system that reportedly had superior prognostication ability. T stage in the novel TNM system was based on size alone: tumors ranging between 0.1 and 1.0 cm were T1, between 1.1 and 2.0 cm were T2, between 2.0 and 4.0 cm were T3, and greater than 4.0 cm were T4. TNM combinations were regrouped as well, such that T1N1 and T1N0 tumors were classified as stage I tumors; T2N0, T2N1, and T3N0 were classified as stage II tumors; and T3N1, T3N0, and T4N1 were classified as stage III tumors. Any tumors with distant metastases were stage IV tumors. The team found that their proposed staging system improved discriminatory ability between stages and homogeneity within stages. In the same year, Ellison et al.[33] published another nomogram based on a single-center cohort of 326 nonfunctional, surgically resected PNENs. The nomogram utilized a cutoff age of 63 years, sex, and a continuous Ki67 index to provide a 5-year overall survival rate for PNENs.

More recently, Luo et al.[26] conducted a study using the SEER registry ($n = 2,529$) and a multicentric series ($n = 1,143$) and proposed a modified staging system in 2016. The parameters used to define T, N, M were upheld, while the AJCC definition for each individual stage was adopted (ie, stage I, II, III, I; Table 2). The study found that the survival curves were well separated by stage with the modified staging system and provided a better prognostication compared with the AJCC 2010 system. In the same year, a study was conducted by Ye et al.[27] on 78 patients. They found that mitotic grade and functional status were predictive of survival rates on multivariate analysis. A prognostic nomogram was proposed based on these two factors and was reported to correlate strongly with survival. In addition, the study incorporated the AJCC, ENETS, and WHO classification system with nonfunctional status and mitotic grades, and found that the regrouped nomograms had a better predictive value than the premise systems based on the concordance index.

With recent studies reporting on the importance of thrombocytes in tumor recurrence and survival, Kaltenborn et al.[22] conducted a study on 41 patients with malignant PNENs with the intention of investigating the clinical relevance of preoperative platelet count in PNENs. Three preoperative scores were proposed, with the endpoints of tumor recurrence risk, 3-year survival rate, and mortality rate after surgery. Notably, the prognostic model developed to predict the 3-year survival rate was the most statistically robust model and was based on preoperative platelet count, minimal resection distance, number of positive lymph nodes, and presence of tumor infiltration. This prognostic model has yet to be externally validated.

Comparison between prognostication systems

A total of 9 studies attempted to compare their proposed prognostication systems with other available models, which are summarized in Table 3. Ferrone et al.,[29] who proposed the MSKCC staging and grading system in 2007, found that their prognostication system was superior to WHO 2004 in predicting outcome. Despite only including 2 prognostic factors in their staging system, it was found that their staging system alone was comparable with WHO 2004, with the additional benefits of being simpler and more reproducible (CI, 0.71 versus 0.72). The prognostic accuracy of the system was improved when combined with the grading criteria (CI 0.76).

La Rosa et al.[15] found that their proposed alternative WHO classification system (which was essentially similar to WHO 2004) was superior to the WHO 2000 classification system according to the Harrell's C index (0.83 versus 0.82), which was further improved when combined with ENETS TNM staging system to further stratify the intermediate grade cancers (Harrell's $C = 0.87$). The study however, failed to prove the superiority of its classification system over the ENETS TNM staging system (Harrell's $C = 0.87$), and no definitive conclusion could be reached on the best combination of parameters to determine prognosis.

Scarpa et al.[19] found that their modified ENETS staging system improved the system's prognostication ability by assigning a pro-

Table 3
Comparison of prognostication systems.

Authors/year	Country	Sample size	Comparison	Systems compared	Best	Results	Remarks
Ferrone et al. 2007[29]	United States	183	2 systems	MSKCC criteria versus WHO 2004	MSKCC criteria	MKSCC combined staging and grading criteria is superior to MSCC staging alone, which is superior to WHO 2004 (CI 0.76 vs 0.72 vs 0.71)	Patients with primary well-differentiated PNEN that had undergone resection
La Rosa et al. 2009[15]	Italy	155	3 systems	Alternative La Rosa (WHO 2004), WHO 2000, ENETS TNM	No best criteria determined	Proposed alternative WHO classification (essentially WHO 2004) was superior to WHO 2000, which is further improved when combined with ENETS TNM staging; did not prove superiority of its classification system over ENETS TNM staging system however	Based on 155 patients with all histologic subtypes of PNENs, operated with the intention to cure
Botsis et al. 2010[31]	United States	98	4 systems	Botsis criteria, MSKCC criteria, ENETS TNM, WHO 2004	Botsis criteria	Botsis criteria is superior to WHO 2004, which is superior to MSKCC grading, which is superior to ENETS TNM staging (CI 0.93 vs 0.72 vs 0.60 vs 0.59)	All patients diagnosed with PNENs
Scarpa et al. 2010[19]	Italy	274	5 systems	Modified ENETS TNM, modified Ki-67 grading, WHO 2010, AJCC TNM, ENETS TNM	No best criteria determined	Modified ENETS with Ki-67 grading to stratify same stage disease was superior to both ENETS and AJCC TNM Modified Ki-67 cutoff rates to 5% and 20% were superior to the original cutoff rates of 2% and 20%	Based on 274 patients with histologically diagnosed pancreatic endocrine tumors who were operated on
Rindi et al. 2012[7]	8 European centres in Germany, Switzerland, Italy, United Kingdom, Netherlands	1,072	2 systems	ENETS TNM versus AJCC TNM	ENETS TNM	Both criteria were independent predictors of survival rates • AJCC staging showed large 95% CI for each stage, indicating inaccurate predictive ability; most patients in stage I and the rest equally distributed in stage II, III and IV • ENETS TNM was able to distribute patients into 4 statistically significant and equally populated risk groups	Based on 1,072 patients who had undergone previous surgery for their cancer and for which at least 2 years of follow-up was available
Ellison et al. 2014[33]	United States	326	3 systems	ENETS TNM, AJCC TNM, Ellison prognostic nomogram	Ellison prognostic nomogram	No significant difference in prognostic strength among the three, but Ellison prognostic nomogram has the additional benefit of including only Ki-67 as a measured variable and is more parsimonious • AJCC: predictive ability of 68% and mean absolute errors in calibration of 0.0142	326 sporadic, nonfunctional, surgically resected PanNET patients

(*continued on next page*)

Table 3 (*continued*)

Authors/year	Country	Sample size	Comparison	Systems compared	Best	Results	Remarks
						• ENETS: predictive ability of 68%, and mean absolute error of 0.0172, respectively • Ellison nomogram: predictive ability of 74%, mean absolute error of 0.0277	
Qadan et al. 2014[25]	United States (SEER database)	1,202	2 systems	AJCC TNM versus Qadan TNM	Qadan TNM	Qadan TNM reported statistically significant difference between different disease stages ($P < .0001$ between stage II and III, $P = .008$ between stage III and IV), and no significant difference between individual cases within each disease stage	Based on patients who were identified to undergo surgical resection with curative intent
Ricci et al. 2014[21]	Italy	64	4 systems	WHO 2000, WHO 2010, ENETS TNM, modified WHO 2010	No best criteria determined	Modified WHO 2010 is superior to ENETS TNM staging, which is superior to WHO 2010 WHO 2000 is superior to WHO 2010 criteria	Based on 64 patients with R0 resection
Yang et al. 2015[84]	China	120	2 systems	ENETS TNM versus AJCC TNM	ENETS TNM	No notable difference between stage I and stage II in both systems; difference only observed between stage I and III and IV ENETS had advantage of statistically significant advantage between stage III and IV that AJCC did not demonstrate	Based on 145 surgically treated and histologically diagnosed patients
Luo et al. 2016[26]	China and United States	1,143 (multicentric China series); 2529 (SEER registry)	3 systems	AJCC TNM, ENETS TNM, Luo TNM	Luo TNM	Luo TNM prognosticates PNENs best into distinct groups with different survival rates; ENETS had better distribution across different stages, and AJCC had better prognostication	Based on SEER database and 8 Chinese centers; included all patients with pathologically confirmed PNENs
Ye et al. 2016[27]	China and United States	78	6 systems	Modified WHO, AJCC and ENETS against their respective counterparts	Modified ENETS TNM	Modified WHO 2010, AJCC, and ENETS staging was superior to their original counterpart, but modified ENETS was the best among the three (CI 0.73 vs 0.605 vs 0.576)	Included all PNENs that underwent surgery

portional risk of death according to stage of disease, and the introduction of clinicoradiologic parameters allowed the system to be used without the need for surgical exploration. Furthermore, the addition of Ki-67 grading to stratify same-stage disease increased the power of predicting disease-related mortality by 10%. Comparison was made against the AJCC staging criteria as well and found to be more effective in prognosticating 5-year survival rates. The study further reported that modifying Ki67 cutoff levels to 5% and 20% allowed better differentiation between G1 and G2 tumors. Several other studies similarly demonstrated the superiority of this cutoff level.[39–42]

Botsis et al.[31] found that their proposed prognostic score based on age, presence of perineural or lymphovascular invasion, distant metastases, and AST was superior to the WHO 2004, ENETS staging, and MSKCC grading system in stratifying patients according to concordance index (0.93 vs 0.72 vs 0.59 vs 0.60, respectively). Ricci et al.[21] also found that categorizing G2 tumors into 2 subcategories based on their proposed modified WHO 2010 system was superior to the ENETS TNM staging system in predicting tumor recurrence. Comparison between the original ENETS TNM staging and WHO 2010 criteria had initially found ENETS TNM to be superior (HR of 5.2; 95% CI 1.8–14.8; $P = .002$; Harrell's C = 0.82). In addition, the study reported that WHO 2000 was superior to WHO 2010 in stratifying patients with an HR of 7.1 (95% CI 0.8–55; $P = .064$; Harrell's C = 0.85). The group subsequently conducted another study on 120 patients,[43] comparing among 4 models: (1) original Ki-67 cutoffs; (2) increasing Ki-67 cutoff to 5% and 20%; (3) modified Ki-67 categories in which G2 consists of 2 subgroups (2%–5% versus 5%–20%); and (4) continuous Ki-67 index. It was found that model 3 had the best predictive power among the 4 proposed models (c index = 0.799; c index = 0.814, $P = .012$; c index = 0.865, $P = .015$; c index = 0.848, $P = .013$, respectively).

Ellison et al.[33] made a comparison between their proposed nomogram and the AJCC and ENETS staging system and found that there was no significant difference among the AJCC, ENETS, and their proposed nomogram in both discrimination and calibration ability. Their proposed nomogram had the additional benefit of including only Ki67 as the measured variable and was found to be more parsimonious than the other two.

Qadan et al.[25] found that the AJCC classification system was unable to differentiate the 5-year survival rates for PNENs among various stages and suggested that their proposed prognostication system was superior in terms of homogeneity and discriminatory effect. Unlike the AJCC system, there was reported statistically significant differences among disease stages ($P < .0001$ between stage II and III, $P = .008$ between stage III and IV), and no significant difference between individual cases within each disease stage.

Luo et al.[26] found that the ENETS staging classification had a better distribution of PNENs across various stages compared with AJCC, although the ENETS staging system did not provide a good stratification in prognostication. The study reported that ENETS stage I and IIA had similar prognoses, and stage IIIB paradoxically had a better prognosis than stage IIIA patients. The proposed classification that maintained the ENETS TNM definition but adopted AJCC staging definition was reported to prognosticate PNENs better into distinct groups with various survival rates. Ye et al.[27] reported that their three proposed modified WHO, AJCC, and ENETS classification systems were superior to their original counterpart, of which the modified ENETS staging system had the highest concordance index (0.73 vs 0.605 vs 0.576), suggesting that it had the highest predictive value.

Hence, not surprisingly with these discordant and varied findings, there remains a lack of consensus regarding the best prognostication system for PNENs despite the multitude of studies published pertaining to this issue. At present, the WHO 2010, AJCC, and ENETS criteria are the most commonly used systems and have the most substantial evidence supporting their use.

Advantages and limitations of the commonly used prognostication systems

The WHO 2000/2004 criteria was one of the most widely utilized and generally accepted system in the prognosticating of PNENs.[2,7,10,14,15,19,29–31,35–38,40,41,44–56] Although it had been heavily criticized to be based on expert opinion rather than on published data,[57] its utility was subsequently extensively validated by numerous studies.[19–31] Nonetheless, it was associated with several limitations.[11] First, the system utilized a mixture of staging and grading criteria and depended heavily on detailed and laborious pathologic examination, which made its application cumbersome. The multiple grading parameters, although presumed to be made more accurate because of its inclusion of well-accepted prognostic factors, made it difficult to reproduce among various pathologists and institutions. Second, it was limited in its ability to distinguish between benign and malignant PNENs because deaths occurred in tumors belonging in the benign category as well.[35] Third, some groups found that the criteria failed to demonstrate any difference among well-differentiated tumors with benign and undefined behavior and suggested that there was limited utility of the undefined group.[2,29.37,41] Fourth, well-differentiated endocrine carcinomas with metastases varied greatly in their progression rate and needed more clearly defined criteria to assess their prognosis.[10]

These limitations were addressed in the ENETS grading system proposed in 2006, which was subsequently adapted as the WHO 2010 classification system. This prognostication system introduced several nomenclature changes and was subsequently validated in various studies to be a strong predictor of survival.[7,10,19,20,27,33,39,42,47,48,55,58–75] Despite this, there were several problems pertinent to this prognostication system as well. First, grading was determined based either on mitotic count or Ki-67 index. Although the grading system recommends that both proliferative measures should be determined and the higher grade assigned, most institutions utilized only Ki-67 index because determination of mitotic count is often less consistently reproducible and more technically difficult.[39] Khan et al.[39] demonstrated that, despite the correlation between Ki-67 index and mitotic count, there was a 44% discordance in PNENs when using these indices to assign grade. This lack of concordance may result in different grades being assigned depending on the indices used. The study further demonstrated that Ki-67 was more clinically useful in prognosticating patients when subjected to multivariate analysis. McCall et al.[61] similarly demonstrated this and concluded that grade discordant tumors (where Ki-67 indicates a higher grade) often have more aggressive histopathologic features and worse prognostic outcomes. Second, several studies have shown that, although G3 is an independent factor for prognosis, the WHO 2010 classification system often fails to demonstrate a significant difference between G1 and G2 tumors.[7,9,19,39] The distinction between G1 and G2 tumors is based on a subtle distinction in the Ki-67 index, which may be unable to accurately prognosticate patients. Scarpa et al.[19] and Khan et al.[39] have suggested raising the cutoff point to 5% for G1 and G2 tumors and have demonstrated that this cutoff point prognosticates PNEN tumors more effectively.[19,39,42] Ricci et al.[21] similarly found that the prognostication power of WHO 2010 was improved when G2 tumors were split into two subgroups (Ki-67 2%–5% and 5%–20%).

Third, there have been suggestions that G3 consists of two distinct groups of tumors with different prognoses; it is found that prognosis for well-differentiated tumor with Ki- 67 index >20% is significantly different from that of tumors with a similar Ki-67 index but morphologically poorly differentiated.[42,71,76] Despite current recommendations by WHO that grading should be based solely on proliferation activity, there has been emerging evidence that morphological differentiation is relevant as well. In 2015, Hijioka et al.[76] evaluated the survival outcomes of 11 pancreatic

neuroendocrine carcinomas (NEC), according to the WHO 2010 classification, and proposed that this group of PNENs could be subclassified into well-differentiated and poorly differentiated NECs The latter was further subdivided into large and small cell types. The study found that well-differentiated and poorly differentiated NECs contained tumors that were clinically and molecularly different in several aspects and suggested that subcategorizing NECs would facilitate more personalized treatment for these tumors. This finding was echoed by Basturk et al. as well.[77]

Despite the various classification systems proposed, there was a lack of the TNM staging system for PNEN that is more closely analogous with the staging of other solid organ tumors. Rindi et al.[17,18] proposed the first TNM staging criteria for PNENs in 2006 which was based on the consensus opinion of 62 experts. This was subsequently adopted by ENETS. In 2007, Bilimoria et al.[1] applied the AJCC 6th edition staging criteria for pancreatic adenocarcinomas to PNENs and demonstrated its utility in stratifying PNENs as well. Subsequently in 2010, AJCC included PNENs in the 7th edition of its classification system for the first time. AJCC's proposal of the use of a common staging system for two different pathologic disease processes raised questions of whether this would be oversimplifying the issue,[25] because PNENs are known to be indolent tumors in comparison with the aggressive nature of pancreatic adenocarcinomas.

The TNM staging systems provided a major leap toward a uniform nomenclature for PNENs because it was intuitive and commonly recognized as the universal staging system for all cancers. However, there is substantial discrepancy between the ENETS and AJCC staging system, in particular in the T staging definitions between the two.[78] The North American Neuroendocrine Tumor society published guidelines in the diagnosis and management of PNENs and stated that PNENs may be diagnosed with both ENETS and AJCC staging systems, although the system that is being used should be clearly indicated.[78] The WHO classification system stated that the AJCC system should be utilized to stage PNENs, although the ENETS TNM system was also mentioned.[78]

Both the AJCC and ENETS TNM staging systems have been extensively validated[2,7,9,10,15,19,25–27,30,31,33,40,44,46–48,51,62,65–70,72,75,79–83] and shown to be effective in prognosticating PNENs, albeit with certain limitations. Although found to be prognostic of overall survival, studies validating the AJCC staging system were unable to differentiate between stage I and II tumors, and between III and IV tumors.[25,33,81] Furthermore, AJCC defines stage III tumors as tumors with involvement of the celiac vessels or superior mesenteric arteries without distant metastasis, which is of limited utility in PNENs because these often do not invade major vessels, unlike pancreatic adenocarcinomas.[26] Hence, most studies only report a small number of patients in stage III. In the study by Rindi et al.,[7] only 5.3% of the study population had stage III disease. Similarly, in the studies by Strosberg et al.[77] and Luo et al.[18] only 4% and 2.2% of patients respectively were classified as stage 3. Similarly, the ENETS staging system has been found to be able to only differentiate between high-stage and low-stage tumors, with little utility in distinguishing between intermediate stage tumors.[10,15,19,26,31,51]

Despite this, several studies have suggested that the ENETS staging system is superior to the AJCC system in prognosticating PNENs. Rindi et al.[7] showed in their study that ENETS could perfectly allocate PNENs into four risk groups, although this finding was not replicated in other studies. Yang et al.[84] suggested that ENETS was advantageous over AJCC because their study showed a statistical difference between stage III and IV tumors, using the ENETS staging system, which was not seen with AJCC. Luo et al.[26] demonstrated that ENETS distributed PNENs more evenly into various risk groups. Of note, despite the multiple discrepancies between the ENETS and AJCC staging systems,[83] it has yet to translate into significant differences in therapeutic options in clinical practice.[78] Five other studies have attempted to modify the TNM staging system for PNENs, but none of these modified staging systems have been successfully validated externally. Casadei et al.[53] attempted to validated Scarpa et al.'s modified TNM staging system[19] in 2012 but found that it was not prognostic of survival rates on univariate analysis.

Hochwald et al.[38] proposed a two-tiered classification system in 2002 and found that it had similar prognostic strength to WHO 2004. This was subsequently modified into the MSKCC prognostication system,[29] which was externally validated by Goh et al.[2] and Botsis et al.[31] Criticisms of this prognostication system include oversimplification of classification altogether and lack of external data, proving superiority to other prognostication system,[31] In 2008, Bilimoria et al.[28] reported excellent survival discrimination with their postresection score based on age, grading, and distant metastases. To date, the study by Goh et al.[2] was the only external study that attempted to validate this score, but found that it was only useful in predicting survival rates and not recurrence rates.

In addition to the prognostication systems discussed earlier in this report, multiple studies have attempted to suggest prognostication systems that have yielded variable results.[22,27,30–33] This is largely attributed to a small study population because of the rarity of PNENs, methodology differences, and a lack of robust multivariate analysis substantiating the development of these prognostication systems.[31] A paucity of external data have validated these prognostication systems as well, limiting their application in clinical practice.

Currently, the prognostication systems are constantly evolving as more evidence emerges regarding its use in the classification of PNENs. Of note, the WHO has recently revised its classification system after 7 years. Some of these changes include raising the cutoff levels of Ki-67 for G2 tumors to 3% and recognizing that G3 tumors comprise 2 subsets of well-differentiated and poorly differentiated tumors.[11] The AJCC has also recently made changes to its classification system in its 8th edition and largely adopted the ENETS classification criteria, ameliorating the discrepancy between the 2 staging systems. It is inevitable that these prognostication systems will continue to evolve with the identification of newer and novel prognostic markers.

Based on current findings in the literature, in our opinion, the most important and significant prognostication factors for PNEN today would be tumor differentiation (well-differentiated versus poorly differentiated), Ki-67 or mitotic count, localized primary tumor, presence of nodal involvement, and presence of distant metastases. Hence, we believe that a system based on these factors would likely be the most accurate for the prognostication of PNENs. This system could be a combined staging/grading categorical system like the current ENETS criteria or an individualized continuous prognostic nomogram that would be more accurate but less user friendly. Ideally, a large international multi-institution study involving thousands of patients with long-term follow-up would need to be performed to determine the optimal prognostication system for these rare tumors. However, even so, with the numerous confounding factors, such as the differing treatment regimens adopted today in various countries and institutions for these tumors, it may be difficult—if not impossible—to interpret the results of such a study.

In conclusion, numerous prognostication systems have been proposed for PNEN, of which the most commonly used systems currently include the WHO 2010 criteria and the two TNM staging systems by ENETS and AJCC. However, prognostication systems for PNENs will continue to evolve with time as novel prognostication factors are identified. More validation and comparative studies are needed to identify the most effective prognostication system today.

References

1. Bilimoria KY, Bentrem DJ, Merkow RP, Tomlinson JS, Stewart AK, Ko CY, et al. Application of the pancreatic adenocarcinoma staging system to pancreatic neuroendocrine tumors. *J Am Coll Surg*. 2007;205:558–563.

2. Goh BKP, Chow PKH, Tan YM, Cheow PC, Chung YFA, Soo KC, et al. Validation of five contemporary prognostication systems for primary pancreatic endocrine neoplasms: Results from a single institution experience with 61 surgically treated cases. *ANZ J Surg*. 2011;81:79–85.
3. Cloyd JM, Poultsides GA. Non-functional neuroendocrine tumors of the pancreas: Advances in diagnosis and management. *World J Gasteroenterol*. 2015;21:9512–9525.
4. Vinik AI. Advances in diagnosis and treatment of pancreatic neuroendocrine tumors. *Endocr Pract*. 2014;20:1222–1230.
5. Ehehalt F, Saeger HD, Schmidt CM, Grutzmann R. Neuroendocrine tumors of the pancreas. *Oncologist*. 2009;14:456–467.
6. Saif MW. Pancreatic neoplasm in 2011: An update. *JOP*. 2011;12:316–321.
7. Rindi G, Falconi M, Klersy C, Albarello L, Boninsegna L, Buchler MW, et al. TNM staging of neoplasms of the endocrine pancreas: Results from a large international cohort study. *J Natl Cancer Inst*. 2012;104:764–777.
8. Bettini R, Partelli S, Boninsegna L, Capelli P, Crippa S, Pederzoli P, et al. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. *Surgery*. 2011;150:75–82.
9. Fischer L, Bergmann F, Schimmack S, Hinz U, Priess S, Muller-Stich BP, et al. Outcome of surgery for pancreatic neuroendocrine neoplasms. *Br J Surg*. 2014;101:1405–1412.
10. Fischer L, Kleeff J, Esposito I, Hinz U, Zimmermann A, Friess H, et al. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. *Br J Surg*. 2008;95:627–635.
11. Klöppel G, Klimstra DS, Hruban RH, Adsay V, Capella C, Couvelard A, et al. Pancreatic neuroendocrine tumors: Update on the new World Health Organization classification. *AJSP Rev Rep*. 2017;22:233–239.
12. Solcia EKG, Sobin L. *Histological typing of endocrine tumours*. Berlin, Heidelberg: Springer; 2000.
13. Heitz PU KP. *Perren A pathology and genetics of tumours of endocrine organs*. 3rd ed. Lyon, France: IARC Press; 2004.
14. Schmitt AM, Anlauf M, Rousson V, Schmid S, Kofler A, Riniker F, et al. WHO 2004 criteria and CK19 are reliable prognostic markers in pancreatic endocrine tumors. *Am J Surg Pathol*. 2007;31:1677–1682.
15. La Rosa S, Klersy C, Uccella S, Dainese L, Albarello L, Sonzogni A, et al. Improved histologic and clinicopathologic criteria for prognostic evaluation of pancreatic endocrine tumors. *Hum Pathol*. 2009;40:30–40.
16. Bosman FT, Carneiro F, Hruban RH, Theise ND. *WHO Classification of tumours of the digestive system*. 4th ed. Geneva: World Health Organization; 2010.
17. Rindi G, Kloppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, et al. TNM staging of foregut (neuro)endocrine tumors: A consensus proposal including a grading system. *Virchows Arch*. 2006;449:395–401.
18. Rindi G, Kloppel G, Couvelard A, Komminoth P, Korner M, Lopes JM, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: A consensus proposal including a grading system. *Virchows Arch*. 2007;451:757–762.
19. Scarpa A, Mantovani W, Capelli P, Beghelli S, Boninsegna L, Bettini R, et al. Pancreatic endocrine tumors: Improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. *Mod Pathol*. 2010;23:824–833.
20. Hamilton NA, Liu TC, Cavatiao A, Mawad K, Chen L, Strasberg SS, et al. Ki-67 predicts disease recurrence and poor prognosis in pancreatic neuroendocrine neoplasms. *Surgery*. 2012;152:107–113.
21. Ricci C, Casadei R, Taffurelli G, D'Ambra M, Monari F, Campana D, et al. WHO 2010 classification of pancreatic endocrine tumors. Is the new always better than the old? *Pancreatology*. 2014;14:539–541.
22. Kaltenborn A, Matzke S, Kleine M, Krech T, Ramackers W, Vondran FWR, et al. Prediction of survival and tumor recurrence in patients undergoing surgery for pancreatic neuroendocrine neoplasms. *J Surg Oncol*. 2016;113:194–202.
23. Edge SB BD, Compton CC, Fritz AG, Greene FL, Trotti A. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010.
24. Martin RC, Kooby DA, Weber SM, Merchant NB, Parikh AA, Cho CS, et al. Analysis of 6,747 pancreatic neuroendocrine tumors for a proposed staging system. *J Gastrointest Surg*. 2011;15:175–183.
25. Qadan M, Ma Y, Visser BC, Kunz PL, Fisher GA, Norton JA, et al. Reassessment of the current American Joint Committee on Cancer staging system for pancreatic neuroendocrine tumors. *J Am Coll Surg*. 2014;218:188–195.
26. Luo G, Javed A, Strosberg JR, Jin K, Zhang Y, Liu C, et al. Modified Staging classification for pancreatic neuroendocrine tumors on the basis of the American Joint Committee on Cancer and European Neuroendocrine Tumor Society Systems. *J Clin Oncol*. 2017;20(35):274–280.
27. Ye L, Ye H, Zhou Q, Li Z, Lin Q, Tan L, et al. A retrospective cohort study of pancreatic neuroendocrine tumors at single institution over 15 years: New proposal for low- and high-grade groups, validation of a nomogram for prognosis, and novel follow-up strategy for liver metastases. *Int J Surg*. 2016;29:108–117.
28. Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors analysis of 3851 patients. *Ann Surg*. 2008;247:490–500.
29. Ferrone CR, Tang LH, Tomlinson J, Gonen M, Hochwald SN, Brennan MF, et al. Determining prognosis in patients with pancreatic endocrine neoplasms: Can the WHO classification system be simplified? *J Clin Oncol*. 2007;25:5609–5615.
30. Zhang L, Smyrk TC, Oliveira AM, Lohse CM, Zhang S, Johnson MR, et al. KIT is an independent prognostic marker for pancreatic endocrine tumors: A finding derived from analysis of islet cell differentiation markers. *Am J Surg Pathol*. 2009;33:1562–1569.
31. Botsis T, Anagnostou VK, Hartvigsen G, Hripcsak G, Weng C. Developing a multivariable prognostic model for pancreatic endocrine tumors using the clinical data warehouse resources of a single institution. *Appl Clin Inform*. 2010;1:38–49.
32. Zhang L, Lohse CM, Dao LN, Smyrk TC. Proposed histopathologic grading system derived from a study of KIT and CK19 expression in pancreatic endocrine neoplasm. *Hum Pathol*. 2011;42:324–331.
33. Ellison TA, Wolfgang CL, Shi C, Cameron JL, Murakami P, Mun LJ, et al. A single institution's 26-year experience with nonfunctional pancreatic neuroendocrine tumors: A validation of current staging systems and a new prognostic nomogram. *Ann Surg*. 2014;259:204–212.
34. Capella C, Heitz PU, Hofler H, Solcia E, Kloppel G. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. *Virchows Arch*. 1995;425:547–560.
35. Deshpande V, Fernandez-del Castillo C, Muzikansky A, Deshpande A, Zukerberg L, Warshaw AL, et al. Cytokeratin 19 is a powerful predictor of survival in pancreatic endocrine tumors. *Am J Surg Pathol*. 2004;28:1145–1153.
36. Heymann MF, Joubert M, Nemeth J, Franc B, Visset J, Hamy A, et al. Prognostic and immunohistochemical validation of the Capella classification of pancreatic neuroendocrine tumours: An analysis of 82 sporadic cases. *Histopathology*. 2000;36:421–432.
37. Schindl M, Kaczirek K, Kaserer K, Niederle B. Is the new classification of neuroendocrine pancreatic tumors of clinical help? *World J Surg*. 2000;24:1312–1318.
38. Hochwald SN, Zee S, Conlon KC, Colleoni R, Louie O, Brennan MF, et al. Prognostic factors in pancreatic endocrine neoplasms: An analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *J Clin Oncol*. 2002;20:2633–2642.
39. Khan MS, Luong TV, Watkins J, Toumpanakis C, Caplin ME, Meyer T. A comparison of Ki-67 and mitotic count as prognostic markers for metastatic pancreatic and midgut neuroendocrine neoplasms. *Br J Cancer*. 2013;108:1838–1845.
40. Panzuto F, Boninsegna L, Fazio N, Campana D, Brizzi MP, Capurso G, et al. Metastatic and locally advanced pancreatic endocrine carcinomas: Analysis of factors associated with disease progression. *J Clin Oncol*. 2011;29:2372–2377.
41. Bettini R, Boninsegna L, Mantovani W, Capelli P, Bassi C, Pederzoli P, et al. Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. *Ann Oncol*. 2008;19:903–908.
42. Martin-Perez E, Capdevila J, Castellano D, Jimenez-Fonseca P, Salazar R, Beguiristain-Gomez A, et al. Prognostic factors and long-term outcome of pancreatic neuroendocrine neoplasms: Ki-67 Index shows a greater impact on survival than disease stage. The large experience of the Spanish national tumor registry (RGETNE). *Neuroendocrinology*. 2013;98:156–168.
43. Ricci C, Casadei R, Taffurelli G, Campana D, Ambrosini V, Pagano N, et al. Validation of the 2010 WHO classification and a new prognostic proposal: A single centre retrospective study of well-differentiated pancreatic neuroendocrine tumours. *Pancreatology*. 2016;16:403–410.
44. Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clin Cancer Res*. 2008;14 7798-1803.
45. Tsuchiya A, Koizumi M, Ohtani H. World Health Organization classification (2004)-based re-evaluation of 95 nonfunctioning "malignant" pancreatic endocrine tumors reported in Japan. *Surg Today*. 2009;39:500–509.
46. Pomianowska E, Gladhaug IP, Grzyb K, Rosok BI, Edwin B, Bergestuen DS, et al. Survival following resection of pancreatic endocrine tumors: Importance of R-status and the WHO and TNM classification systems. *Scand J Gastroenterol*. 2010;45:971–979.
47. Song KB, Kim SC, Kim JH, Hong SM, Park KM, Hwang DW, et al. Prognostic factors in 151 patients with surgically resected non-functioning pancreatic neuroendocrine tumours. *ANZ J Surg*. 2016;86:563–567.
48. Sellner F, Thalhammer S, Stattner S, Karner J, Klimpfinger M. TNM stage and grade in predicting the prognosis of operated, non-functioning neuroendocrine carcinoma of the pancreas–a single-institution experience. *J Surg Oncol*. 2011;104:17–21.
49. Ito H, Abramson M, Ito K, Swanson E, Cho N, Ruan DT, et al. Surgery and staging of pancreatic neuroendocrine tumors: A 14-year experience. *J Gastrointest Surg*. 2010;14:891–898.
50. Schurr PG, Strate T, Rese K, Kaifi JT, Reichelt U, Petri S, et al. Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: An Institutional experience. *Ann Surg*. 2007;245:273–281.
51. Casadei R, Ricci C, Pezzilli R, Campana D, Tomassetti P, Calculli L, et al. Value of both WHO and TNM classification systems for patients with pancreatic endocrine tumors: Results of a single-center series. *World J Surg*. 2009;33:2458–2463.
52. Gao C, Fu X, Pan Y, Li Q. Surgical treatment of pancreatic neuroendocrine tumors: Report of 112 cases. *Dig Surg*. 2010;27:197–204.
53. Casadei R, Ricci C, Tomassetti P, Campana D, Minni F. Factors related to long-term survival in patients affected by well-differentiated endocrine tumors of the pancreas. *ISRN Surg*. 2012;2012.
54. Chung JC, Choi DW, Jo SH, Heo JS, Choi SH, Kim YI. Malignant nonfunctioning endocrine tumors of the pancreas: Predictive factors for survival after surgical treatment. *World J Surg*. 2007;31:579–585.
55. Uguz A, Unalp OV, Yeniay L, Farajov R, Yoldas T, Sezer TO, et al. Factors CD10, cytokeratin 19 and staging-grading systems in predicting the prognosis of pancreatic neuroendocrine tumors (PNET). *Acta Endocrinol Buch*. 2012;8:653–666.
56. You DD, Lee HG, Paik KY, Heo JS, Choi SH, Choi DW. The outcomes after surgical resection in pancreatic endocrine tumors: An institutional experience. *Eur J Surg Oncol*. 2009;35:728–733.
57. Ballian N, Loeffler AG, Rajamanickam V, Norstedt PA, Weber SM, Cho CS. A simplified prognostic system for resected pancreatic neuroendocrine neoplasms. *HPB (Oxford)*. 2009;11:422–428.

58. Yang M, Tian B, Zhang Y, Su AP, Yue PJ, Xu S, et al. Evaluation of the World Health Organization 2010 grading system in surgical outcome and prognosis of pancreatic neuroendocrine tumors. *Pancreas*. 2014;43:1003–1008.
59. Sallinen V, Haglund C, Seppanen H. Outcomes of resected nonfunctional pancreatic neuroendocrine tumors: Do size and symptoms matter? *Surgery*. 2015;158:1556–1563.
60. Sanchez-Bueno F, Rodriguez Gonzalez JM, Torres Salmeron G, Bernabe Penalver A, Balsalobre Salmeron M, de la Pena Moral J, et al. Prognostic factors in resected pancreatic neuroendocrine tumours: Experience in 95 patients. *Cir Esp*. 2016;94:473–480.
61. McCall CM, Shi C, Cornish TC, Klimstra DS, Tang LH, Basturk O, et al. Grading of well-differentiated pancreatic neuroendocrine tumors is improved by the inclusion of both ki67 proliferative index and mitotic rate. *Am J Surg Pathol*. 2013;37:1671–1677.
62. Birnbaum DJ, Turrini O, Vigano L, Russolillo N, Autret A, Moutardier V, et al. Surgical management of advanced pancreatic neuroendocrine tumors: Short-term and long-term results from an international multi-institutional study. *Ann Surg Oncol*. 2015;22:1000–1007.
63. Tsuchikawa T, Hirano S, Tanaka E, Kato K, Matsumoto J, Sichinohe T. Multidisciplinary treatment strategy for advanced pancreatic neuroendocrine tumors—A single center experience. *Hepatogastroenterology*. 2012;59:2623–2626.
64. Cienfuegos JA, Rotellar F, Salguero J, Ruiz-Canela M, Nunez Cordoba JM, Sola I, et al. A single institution's 21-year experience with surgically resected pancreatic neuroendocrine tumors: An analysis of survival and prognostic factors. *Rev Esp Enferm Dig*. 2016;108:689–696.
65. Wang DS, Zhang DS, Qiu MZ, Wang ZQ, Luo HY, Wang FH, et al. Prognostic factors and survival in patients with neuroendocrine tumors of the pancreas. *Tumour Biol*. 2011;32:697–705.
66. Brunner SM, Weber F, Werner JM, Agha A, Farkas SA, Schlitt HJ, et al. Neuroendocrine tumors of the pancreas: A retrospective single-center analysis using the ENETS TNM-classification and immunohistochemical markers for risk stratification. *BMC Surg*. 2015;15:49.
67. Shiba S, Morizane C, Hiraoka N, Sasaki M, Koga F, Sakamoto Y, et al. Pancreatic neuroendocrine tumors: A single-center 20-year experience with 100 patients. *Pancreatology*. 2016;16:99–105.
68. Morin E, Cheng S, Mete O, Serra S, Araujo PB, Temple S, et al. Hormone profiling, WHO 2010 grading, and AJCC/UICC staging in pancreatic neuroendocrine tumor behavior. *Cancer Med*. 2013;2:701–711.
69. Zhu LM, Tang L, Qiao XW, Wolin E, Nissen NN, Dhall D, et al. Differences and similarities in the clinicopathological features of pancreatic neuroendocrine tumors in China and the United States: A multicenter study. *Medicine (Baltimore)*. 2016;95:e2836.
70. Clewemar Antonodimitrakis P, Sundin A, Wassberg C, Granberg D, Skogseid B, Eriksson B. Streptozocin and 5-fluorouracil for the treatment of pancreatic neuroendocrine tumors: Efficacy, prognostic factors and toxicity. *Neuroendocrinology*. 2016;103:345–353.
71. Crippa S, Partelli S, Bassi C, Berardi R, Capelli P, Scarpa A, et al. Long-term outcomes and prognostic factors in neuroendocrine carcinomas of the pancreas: Morphology matters. *Surgery*. 2016;159:862–871.
72. Han X, Xu X, Jin D, Wang D, Ji Y, Lou W. Clinicopathological characteristics and prognosis-related factors of resectable pancreatic neuroendocrine tumors: A retrospective study of 104 cases in a single chinese center. *Pancreas*. 2014;43:526–531.
73. Partelli S, Inama M, Rinke A, Begum N, Valente R, Fendrich V, et al. Long-term outcomes of surgical management of pancreatic neuroendocrine tumors with synchronous liver metastases. *Neuroendocrinology*. 2015;102:68–76.
74. Yang M, Tian B, Zhang Y, Su A, Yue P, Xu S, et al. Epidemiology, diagnosis, surgical treatment and prognosis of the pancreatic neuroendocrine tumors: Report of 125 patients from one single center. *Indian J Cancer*. 2015;52:343–349.
75. Keutgen XM, Nilubol N, Glanville J, Sadowski SM, Liewehr DJ, Venzon DJ, et al. Resection of primary tumor site is associated with prolonged survival in metastatic nonfunctioning pancreatic neuroendocrine tumors. *Surgery*. 2016;159:311–318.
76. Hijioka S, Hosoda W, Mizuno N, Hara K, Imaoka H, Bhatia V, et al. Does the WHO 2010 classification of pancreatic neuroendocrine neoplasms accurately characterize pancreatic neuroendocrine carcinomas? *J Gastroenterol*. 2015;50:564–572.
77. Basturk O, Yang Z, Tang LH, Hruban RH, Adsay V, McCall CM, et al. The high–grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. *Am J Surg Pathol*. 2015;39:683–690.
78. Liszka T, Pajaogonekk J, Mrowiec S, Zielinska-Pajaogonekk E, Golka D, Lampe P. Discrepancies between two alternative staging systems (European Neuroendocrine Tumor Society 2006 and American Joint Committee on Cancer/Union for International Cancer Control 2010) of neuroendocrine neoplasms of the pancreas. A study of 50 cases. *Pathol Res Pract*. 2011;207:220–224.
79. Yang M, Zeng L, Zhang Y, Su AP, Yue PJ, Tian BL. Surgical treatment and clinical outcome of nonfunctional pancreatic neuroendocrine tumors: A 14-year experience from one single center. *Medicine (Baltimore)*. 2014;93:e94.
80. Yang M, Zeng L, Zhang Y, Wang WG, Wang L, Ke NW, et al. TNM staging of pancreatic neuroendocrine tumors an observational analysis and comparison by both AJCC and ENETS systems from 1 single institution. *Medicine (Baltimore)*. 2015;94:e660.
81. Figueiredo FAF, Giovannini M, Monges G, Charfi S, Bories E, Pesenti C, et al. Pancreatic endocrine tumors: A large single-center experience. *Pancreas*. 2009;38:936–940.
82. Oh TG, Chung MJ, Park JY, Bang SM, Park SW, Chung JB, et al. Prognostic factors and characteristics of pancreatic neuroendocrine tumors: Single center experience. *Yonsei Med J*. 2012;53:944–951.
83. Strosberg JR, Cheema A, Weber J, Han G, Coppola D, Kvols LK. Prognostic validity of a Novel American Joint Committee on Cancer staging classification for pancreatic neuroendocrine tumors. *J Clin Oncol*. 2011;29:3044–3049.
84. Yang M, Ke NW, Zeng L, Zhang Y, Tan CL, Zhang H, et al. Survival analyses for patients with surgically resected pancreatic neuroendocrine tumors by world health organization 2010 grading classifications and American Joint Committee On Cancer 2010 staging systems. *Medicine (Baltimore)*. 2015;94:e2156.