European Journal of Surgical Oncology 45 (2019) 1054–1060

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Survivals of patients with surgically treated and High-grade pancreatic neuroendocrine carcinomas: A comparative study between two American Joint Committee on Cancer 8th tumor-node-metastasis staging systems

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ARTICLE INFO

Article history:
Received 25 October 2018
Received in revised form
19 December 2018
Accepted 7 January 2019
Available online 11 January 2019

Keywords:
Pancreatic neuroendocrine carcinomas
AJCC
8th edition
TNM staging
Grading

ABSTRACT

Background and objective: We aimed to compare the two new defined tumor-node-metastasis (TNM) systems in the American Joint Committee on Cancer (AJCC) 8th staging manual for overall survival (OS) analysis of G3 pancreatic neuroendocrine carcinomas (p-NECs) that are currently proposed for pancreatic exocrine adenocarcinomas (p-EACs) and G1/G2 pancreatic neuroendocrine tumors (p-NETs), respectively.

Methods: The data of patients who were surgically treated and histopathologically diagnosed with G3 p-NECs at West China Hospital of Sichuan University from January 2002 to June 2017 were retrospectively analyzed and compared using the two new AJCC staging systems.

Results: Applying the p-EAC AJCC 8th TNM staging system to G3 p-NECs, the estimated 3-year OSs for each stage were 86.7%, 76.0%, 44.5% and 20.7%, respectively ($P < 0.001$). According to the G1/G2 p-NETs staging system, the estimated OSs at 3 years for each new AJCC stage were 100.0%, 83.6%, 47.1% and 20.7%, respectively ($P < 0.001$). The system for p-EACs significantly discriminated the survival difference of G3 p-NECs between Stage I and Stage II ($P = 0.019$), while the other one for G1/G2 p-NETs could not ($P = 0.108$). The consistent results of Akaike information criteria with Harrell's concordance index indicated that the AJCC 8th staging system for p-EACs was superior when applied to G3 p-NECs for its better prognostic stratification and more accurate prediction ability for OS.

Conclusions: Our analysis demonstrated that both TNM systems in the AJCC 8th staging manual were prognostic for patients with G3 p-NECs; however, the classification originally applied to p-EACs was superior and supported its use in clinical practice.

Introduction

Pancreatic neuroendocrine neoplasms (p-NENs) are a group of heterogeneous neoplasms that differ in terms of their clinical presentation, behavior and prognosis based on both histological features and cancer stage at the time of diagnosis [1–4]. P-NENs are uncommon, accounting for approximately 2%–3% of primary pancreatic malignancies [5,6]. The estimated annual incidence of p-NENs ranged from 2.5 to 5.2 in 1,000,000 individuals [5–7], substantially increasing over the last 3 decades due to widespread awareness on the part of pathologists and physicians as well as advances in diagnostic imaging techniques [2,8,9].

Histologic grades and various classifications have evolved to attempt to stratify p-NENs into prognostic groups. In 2006, the European Neuroendocrine Tumor Society (ENETS) was the first to propose a tumor-node-metastasis (TNM) staging system and a

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https://doi.org/10.1016/j.ejso.2019.01.010
0748-7983/

grading system for p-NENs [10]. The grading system of ENETS has since been modified and is now incorporated into the World Health Organization (WHO) 2010 classification that divides p-NENs into three groups [11]: morphologically well-differentiated p-NEN, according to the WHO, consists of grade 1 (G1) pancreatic neuroendocrine tumors (p-NETs) that are immunohistochemically defined as having a mitotic rate of <2 mitotic figures per 10 high power fields (HPFs) and a Ki-67 labeling index of <3%; G2 p-NETs have 2–20 mitotic figures per 10 HPFs or a Ki-67 index of 3–20%; high-grade G3 pancreatic neuroendocrine carcinomas (p-NECs) are defined as having >20 mitotic figures per 10 HPFs or a Ki-67 index of >20%. Evolving evidence has strongly suggested that high-grade G3 p-NECs should be handled differently from well-differentiated G1/G2 p-NETs, owing to their notably different biological behavior and worse long-term outcome [12–17].

In 2010, the American Joint Committee on Cancer (AJCC) also adopted a TNM staging system for p-NENs (7th edition) [18] that was simultaneously endorsed by both the WHO [19] and the International Union for Cancer Control (UICC) [20]. Although the AJCC/UICC/WHO 2010 staging manual initially applied to pancreatic exocrine adenocarcinomas (p-EACs), it remained a significant, convenient but somewhat oversimplified classification for the prognosis of p-NENs [21–25]. Recently in 2017, AJCC/UICC updated its staging manual for p-EACs (8th edition), as well as for p-NENs that was derived from ENETS criteria [26]. However, AJCC emphasized that the newly defined 8th staging system for p-NENs should only be applied to well-differentiated tumors (G1/G2 p-NETs), while high-grade neuroendocrine carcinomas (G3 p-NECs) should be excluded and staged according to criteria for p-EACs.

The definitions of T or N stages and corresponding clinical stages in the new AJCC 2017 staging system for p-EACs have also incorporated major changes that were substantially different from those of the previous system in the AJCC 2010 manual for p-EACs or ENETS 2006 criteria for p-NENs (Table 1). Instead of being representative of "limited to" or "extends beyond" the pancreas (very difficult to determine objectively), T1, T2 and T3 stages are now defined as those with the greatest tumor dimension of ≤2 cm, >2 cm but ≤4 cm, and >4 cm, respectively. Furthermore, N stages have been revised from a binary to a tripartite classification (metastasis to 0, ≤3 and ≥ 4 regional lymph nodes). With respect to the corresponding clinical stages, in addition to tumors with T4, any N, and M0, those with any T, N2, and M0 are also grouped as Stage III.

Due to more indolent malignant behaviors, p-NENs, including G3 p-NECs, are generally considered to have better survival than p-EACs [4,5,27]. AJCC emphasized in 2017 that G3 p-NECs should be staged according to the newly defined system for p-EACs when it was unclear as to whether the change significantly improved the prognostic ability for survival of G3 p-NECs. Moreover, the new AJCC system for p-NENs was proposed only for G1/G2 p-NETs, but whether it was practical or suitable for G3 p-NECs remained to be assessed. In the present study, by analyzing the clinical characteristics and survival differences between each new AJCC stage for eligible patients at a large Chinese institution, we tested the applicability of this novel AJCC manual for G3 p-NECs. We also tried to compare the differences in the two systems for the survival analysis of G3 p-NECs, originally introduced for p-EACs and G1/G2 p-NETs. To the best of our knowledge, our study represents the first attempt to validate the two systems of the AJCC 8th staging manual for G3 p-NECs.

Table 1
The original definitions of two novel AJCC 8th TNM staging systems and present analysis for G3 p-NECs based on the data from our studying cohort (N = 104).

	AJCC 8th system for G3 p-NECs	AJCC 8th system for G1/G2 p-NETs
T/N/M staging definitions— (Cases)		
T1	Tumor 2 cm or less in greatest dimension — (19);	Tumors limited to pancreas, 2 cm or less in greatest dimension— (16);
T2	Tumor more than 2 cm but no more than 4 cm in greatest dimension — (28);	Tumors limited to pancreas more than 2 cm but less than 4 cm in greatest dimension — (22);
T3	Tumor more than 4 cm in greatest dimension — (42);	Tumors limited to pancreas, more than 4 cm in greatest dimension or tumors invading duodenum or bile duct — (45);
T4	Tumor involves coeliac axis, superior mesenteric artery and/or common hepatic artery — (15).	Tumors perforates visceral peritoneum (serosa) or invades other organs or adjacent structures — (21).
N0	No regional lymph node metastasis — (59);	No regional lymph node metastasis — (59);
N1	Metastases in 1–3 regional lymph nodes — (29);	Regional lymph node metastasis — (45).
N2	Metastases in 4 or more regional lymph nodes— (16).	NA.
M0	No distant metastasis — (76);	No distant metastasis — (76);
M1	Distant metastasis — (28).	Distant metastasis — (28).
Clinical staging definitions— (Cases)		
Stage I	T1 N0 M0 (A) — (8); T2 N0 M0(B) — (10);	T1 N0 M0— (7);
Stage II	T3 N0 M0(A) — (17); Any T N1 M0(B)— (13);	T2 N0 M0(A) — (8); T3 N0 M0(B) — (21);
Stage III	Any T N2 M0— (14); T4 Any N M0— (14);	T4 N0 M0(A) — (15); Any T N1 M0(B) — (25);
Stage IV	Any T Any N M1— (28).	Any T Any N M1 — (28).

Cross-tabulation of two AJCC 8th staging systems— (Cases)

For p-NETs		Stage I	Stage II	Stage III	Stage IV	Total
For p-NECs	Stage I	7	11	0	0	18
	Stage II	0	18	12	0	30
	Stage III	0	0	28	0	28
	Stage IV	0	0	0	28	28
	Total	7	29	40	28	104

Abbreviations: AJCC: American Joint Committee on Cancer; TNM: tumor-node-metastasis.
p-NECs: pancreatic neuroendocrine carcinomas; p-NETs: pancreatic neuroendocrine tumors; G: grading; T: primary tumor; N: regional lymph node; M: distant metastasis; NA: not applicable.

Materials and methods

Patient enrollment

Our study was approved by the Institutional Review Board of West China Hospital, Sichuan University, written informed consent was obtained on admission from all patients, in accordance with the general principles of the Helsinki Declaration [28]. Patients who were surgically treated and pathologically diagnosed as having p-NENs at West China Hospital of Sichuan University from January 2002 to June 2017 were systematically reviewed from their electronic or paper-based medical records. For included cases, relevant data was retrospectively collected, as we ever did [24,25]. The WHO 2010 grading classification was applied to all patients, after which patients with G1/G2 p-NETs were excluded from the present analysis. The two systems of the AJCC 8th staging manual for both

p-EACs and G1/G2 p-NETs were applied to targeted patients with high-grade G3 p-NECs.

Follow-up procedure

Follow-up was conducted by telephone, e-mail, mail or outpatient clinic review between January 2018 and June 2018, leading to potential follow-up times ranging from 13.1 months to 176.4 months, with a median of 60.6 months. There were 54 patients alive (51.9%) and 16 lost to follow-up (15.4%) on the day of last follow-up, who were censored in the final survival analysis model. We performed an overall survival (OS) analysis referring to the objectives, calculated as the number of months from the date of surgery to the date of last contact or time of death.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 22.0 software. A P value of <0.05 was considered statistically significant. Quantitative variables were reported as means with standard deviation or median, while categorical variables were presented as numbers with frequencies and proportions (%). OSs were estimated using Kaplan-Meier (K-M) methods and were compared using the log-rank test. Univariate and multivariate analyses by the Cox regression proportional hazards model were performed separately to validate the predictive value of the two AJCC 8th staging systems for OS of high-grade G3 p-NECs, as well as other prognostic factors, including age, gender, tumor location, functional status and Ki-67 labeling index. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated for each variable on multivariate analysis. Weighted Cohen's κ coefficients were computed to evaluate the inter-rater agreement of the two AJCC 8th staging systems for G3 p-NECs. When comparing the prognostic accuracy of both classifications, the Akaike information criterion (AIC) as well as the Harrell's concordance index (C-index) were calculated in the Cox regression model. AIC was defined as follows: AIC $= -2$ log maximum likelihood $+2 \times$ (the number of parameters in the model). A smaller AIC value indicated a better model for predicting outcome [29]. The C-index was calculated using R software (version 3.2.4), with a larger C-index value indicating a better model for predicting outcome [30].

Table 2
The clinical features of G3 p-NECs in the present analysis.

Baseline Demographics and Tumor Characteristics	Patients (N = 104)	
	No.	%
Gender		
Female	62	59.6
Age at diagnosis, yr		
Mean ± SD	49.7 ± 11.6	
Median	51	
Range	14–86	
Tumor diameter, cm		
Mean ± SD	6.3 ± 3.3	
Median	5	
Range	1.5–12.5	
Tumor location		
Head/uncinate	45	43.3
Body/tail	59	56.7
Tumor type		
Non-functional	62	59.6
Insulinoma 30		28.8
Other functional[a]	12	11.6
Incidental diagnosis	31	29.8
Diagnostic after 2010	73	70.2
Radical resection		
Yes[b]	69	66.3
No[c]	35	33.7
Main procedure		
LRP	9	8.7
DP	28	26.9
PD	37	35.6
BP	25	24.1
Postoperative medical therapy	32	30.8
Ki67 index		
≥55%	70	67.3
<55%	34	32.7
Patients out of contact	16	15.4
Dead at last follow-up	50	48.1

Abbreviations: p-NECs: pancreatic neuroendocrine carcinomas; SD: standard deviation; LRP: local resection of pancreatic tumor; DP: distal pancreatectomy; PD: pancreaticoduodenectomy; BP: Biopsy.

[a] Including rather rare p-NECs, such as gastrinoma, vasoactive intestinal polypeptidoma, adrenocorticotropic hormone adenoma, glucagonoma, pheochromocytoma, etc.

[b] Including resections with negative surgical margins, both grossly and microscopically.

[c] Including resections all palliative and exploratory operations, as well as resections with positive surgical margins, either grossly or microscopically.

Results

Patient and tumor characteristics

As listed in Table 2, we ultimately enrolled 104 eligible patients with G3 p-NECs, including 62 females and 42 males. Radical resection (both grossly and microscopically negative surgical margins) was performed in 69, while 35 underwent either palliative or exploratory surgery or resection with positive surgical margins. When follow-up ended, 16 patients were lost contact and 50 had died.

Stages by two AJCC 8th staging systems

As Table 1 listed, in light of the new AJCC system for p-EACs, 19, 28, 42 and 15 patients with G3 p-NECs were classified to T1, T2, T3 and T4, respectively. Twenty-nine patients had metastases in 1–3 regional lymph nodes, and 16 cases had metastases in over 4 regional lymph nodes. There were 28 patients manifesting distant metastasis at surgery. In terms of corresponding clinical stages, there were 18, 30, 28 and 28 patients defined in the new AJCC Stage I, Stage II, Stage III and Stage IV, respectively. According to the new AJCC system for G1/G2 p-NETs, there were 16, 22, 45 and 21 patients distributed from T1 to T4, respectively. A total of 45 patients presented regional lymph node metastasis, and 28 had distant metastasis. With respect to corresponding clinical stages, there were 7, 29, 40 and 28 patients defined from the new AJCC Stage I to Stage IV, respectively.

Survival according to the two AJCC 8th staging systems

The estimated OS at 5 and 3 years of the whole group by K-M methods was 40.0% and 57.1%, respectively, with a median survival time (MST) of 49.6 months (95%CI: 38.2–60.9). When applying the p-EACs AJCC 8th staging system to G3 p-NECs, the estimated 5-year OSs for Stage I, Stage II, Stage III and Stage IV were 78.0%, 51.5%, not applicable (NA) and NA, respectively. The estimated OSs at 3 years for each stage were 86.7%, 76.0%, 44.5% and 20.7%, with a MST of 80.1 months (95%CI: 65.1–95.1), 61.5 months (95%CI: 47.2–75.8), 31.4 months (95%CI: 17.9–44.8) and 14.5 months (95%CI: 9.7–19.2) ($P < 0.001$; Fig. 1), respectively. Patients with G3 p-NECs classified in Stage I or Stage II had notably longer survival times than did those in Stage III or Stage IV ($P = 0.003$, $P < 0.001$; $P = 0.020$, $P < 0.001$; respectively). There were survival differences between patients with Stage I and Stage II disease ($P = 0.019$), as well as

differences between patients with Stage III and Stage IV disease (P = 0.016).

When applying the new G1/G2 p-NETs staging system to G3 p-NECs, the estimated 5-year OS for Stage I to Stage IV was 75.0%, 67.6%, 23.5% and NA, respectively, while the estimated OS at 3 years for each new AJCC stage was 100.0%, 83.6%, 47.1% and 20.7%, with a MST of NA, 71.3 months (95%CI: 56.4–86.2), 31.4 months (95%CI: 14.7–48.1) and 14.5 months (95%CI: 9.7–19.2) (P < 001; Fig. 2), respectively. Patients diagnosed as having G3 p-NECs in Stage I or Stage II showed significantly better survival times than did those in Stage III or Stage IV (P = 0.010, P = 0.002; P = 0.007, P < 0.001; respectively). Comparison of survival times between Stage III and Stage IV was statistically different (P = 0.001), while survival between Stages I and II was not (P = 0.108).

Survival by the Ki67 index, surgical resection and tumor type

For different differentiated sub-groups of G3 p-NECs, the estimated OS of patients with a Ki67 index <55% were better than those with a Ki67 index ≥55% (Supplementary Fig. 1, P < 0.001). For different surgical resection of G3 p-NECs, patients with a radical resection present a much better survival than those who underwent palliative or exploratory surgery (Supplementary Fig. 2, P < 0.001). For different tumor type of G3 p-NECs, insulinoma showed statistically better survival than non-functional and other functional tumors (P = 0.002, P < 0.001; respectively), while difference between non-functional and other functional G3 p-NECs wasn't notably significant (Supplementary Fig. 3, P = 0.177).

Analyses of prognostic factors

As Table 3 indicated, patient age, tumor type and diameter and postoperative medical therapy were only statistically significant on univariate analyses (P < 0.05), while radical resection, Ki67 index and AJCC 8th staging systems currently proposed for either p-EACs or G1/G2 p-NETs were independent predictors of favorable OS for patients with G3 p-NECs on both univariate and multivariate analyses (P < 0.05).

Assessments between the two AJCC 8th staging systems

A cross-tabulation of the two new AJCC staging systems for G3 p-NECs is also displayed in Table 1. Patients with G3 p-NECs defined as Stage I (n = 18) and Stage II (n = 30) according to the new p-EACs AJCC staging criteria were distributed to Stage I (n = 7) or Stage II (n = 11) and Stage II (n = 18) or Stage III (n = 12) by the new AJCC system for G1/G2 p-NETs, whereas G1/G2 p-NETs system Stage III patients (n = 40) were distributed between p-EACs system Stage II (n = 12) and Stage III (n = 28). The weighted Cohen's κ coefficient was calculated as 0.698 (95% CI: 0.583–0.799), indicating rough agreement and moderate discrepancy (P = 0.014) between two systems. The AIC value of the AJCC 8th staging system for p-EACs was 2340.82, which is smaller than that of the AJCC system for G1/G2 p-NETs (2342.11), revealing a better prognostic stratification for the OS of G3 p-NECs. Moreover, the C-index of the AJCC 8th staging system for p-EACs was larger than that of the system for G1/G2 p-NETs [0.694(95% CI: 0.635–0.726) vs. 0.533(95% CI: 0.528–0.611); P = 0.029], suggesting more informative ability regarding patient outcome. The comparative result of the C-index was consistent with that of the AIC value, indicating that the AJCC 8th staging system for p-EACs appeared to be superior to the system for G1/G2 p-NETs in terms of OS in patients with surgically treated high-grade G3 p-NECs.

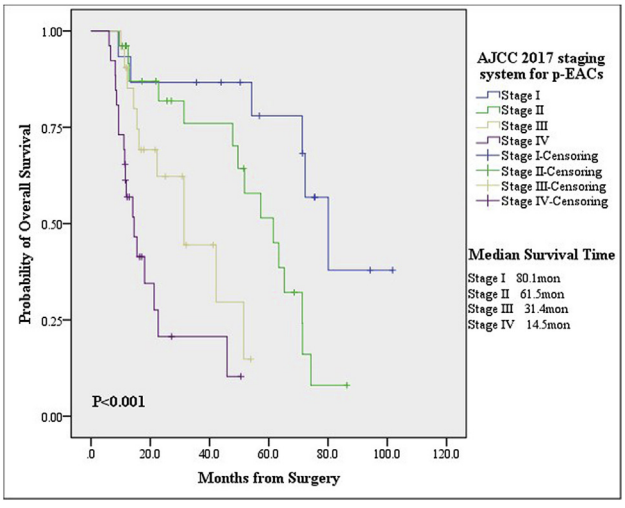

Fig. 1. Kaplan-Meier estimates for OS of G3 p-NECs, according to the AJCC 2017 staging system for p-EACs.

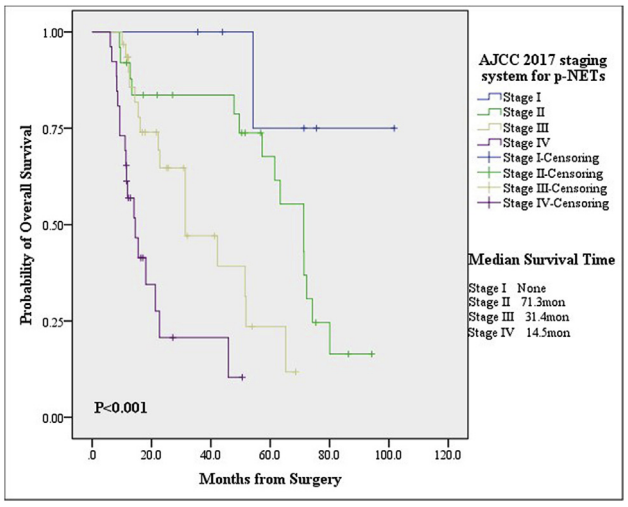

Fig. 2. Kaplan-Meier estimates for OS of G3 p-NECs, according to the AJCC 2017 staging system for G1/G2 p-NETs.

Discussion

Due to the rarity and heterogeneity of p-NENs, no consensus has been reached regarding their TNM staging system. The ENETS 2006 staging system for p-NENs has been evaluated as lacking appropriate prognostic discrimination between patients in Stage I and Stage II [10,24,25]. Moreover, due to originally being applied to p-EACs [18–20], the AJCC/UICC/WHO 2010 staging system for p-NENs (7th edition) was demonstrated to be somewhat oversimplified, for its low-proportion stratification of patients to Stage III, poor prognostic discrimination between Stage III and Stage IV, as well as inaccurate predictive abilities for survival from p-NENs [21–25].

Since 2010, several studies have demonstrated that G1/G2 p-NETs showed notably different clinical features, histological behaviors and survivals from those of G3 p-NECs [12–17]. G3 p-NECs were more likely inclined to be in late Stage III or IV, with larger tumor size, local invasion and more regional lymph node or distant metastasis at diagnosis or surgery [12–17]. Two studies by Strosberg et al. reported different 5-year OSs for three grading subgroups of p-NENs [21,22]. Qadan et al. reported 10-year OSs of

Table 3
Univariate and multivariate analysis of prognostic factors for G3 p-NECs.

Variable	MST(mon.)	Univariate Analysis	AJCC 8th edition for p-EACs Multivariate Analysis[a]	AJCC 8th edition for p-NETs Multivariate Analysis[a]
		HR 95%CI P	HR 95%CI P	HR 95%CI P
Gender				
Male	46.2			
Female	60.6	1.593 0.868–2.922 0.133		
Age, yr.				
<Median	54.5			
≥Median	34.8	0.210 0.104–0.425 **0.031**	1.003 0.949–1.061 0.906	1.028 0.986–1.073 0.192
Tumor location				
Head/uncinate	53.4			
Body/tail	61.1	1.215 0.718–2.152 0.247		
Tumor greatest diameter		**0.042**	0.083	0.115
≤2 cm	71.4			
>2 cm but ≤4 cm	52.6	0.245 0.134–0.372 **0.027**	1.135 0.834–1.238 0.432	1.242 0.925–1.437 0.772
>4 cm	44.1	1.625 0.819–1.253 0.178	1.024 0.592–0.923 **0.041**	1.004 0.763–1.082 0.058
Tumor type		**0.024**	0.176	0.254
Insulinoma	71.4			
Non-functional	42.2	0.714 0.523–0.975 **0.034**	0.785 0.559–1.102 0.161	0.766 0.537–1.093 0.141
Other functional	14.4	1.244 0.621–0.997 **0.046**	1.255 0.789–1.354 0.351	1.346 1.575–1.368 0.361
Diagnosis				
Incidental	49.4			
Symptomatic	53.6	2.124 0.836–1.415 0.327		
Radical resection				
Yes	61.5			
No	15.5	0.446 0.313 −0.636 < **0.001**	0.598 0.402–0.888 **0.011**	0.574 0.387–0.849 **0.006**
Postoperative medical therapy				
Yes	64.2			
No	41.7	0.531 0.554–1.142 **0.046**	0.425 0.513–0.742 0.075	0.624 0.616–0.847 0.092
Ki67 index				
<55%	71.3			
≥55%	22.7	0.497 0.347 −0.712 < **0.001**	0.703 0.450–1.098 **0.021**	0.524 0.316–0.838 **0.017**
Staging by AJCC 8th edition for p-EACs		**<0.001**	**0.027**	
I	80.1			
II	61.5	0.211 0.100 −0.446 < **0.001**	0.258 0.194–0.421 **0.021**	
III	31.4	0.646 0.385–1.084 0.098	0.536 0.454–1.004 **0.029**	
IV	14.5	1.736 0.968–3.111 0.064	1.223 0.912–2.389 **0.074**	
Staging by AJCC 8th edition for p-NETs		**<0.001**		**0.041**
I	NA			
II	71.3	0.136 0.030 −0.619 < **0.001**		0.452 0.937–2.103 **0.038**
III	31.4	0.622 0.323–1.286 0.213		1.623 1.112–2.825 0.102
IV	14.5	1.960 0.998–3.848 0.051		1.824 1.235–3.126 **0.036**

Abbreviation: WHO: World Health Organization; G3 p-NECs: grading 3 pancreatic neuroendocrine carcinomas; MST: median survival time; HR: hazard ratio; CI: confidence interval; AJCC: American Joint Committee On Cancer; NA: not applicable.

[a] The potential prognostic value of two stages by AJCC 8th edition for p-EACs and p-NETs for predicting the OS of G3 p-NECs was evaluated in separate Cox hazard models.

71% for G1, 53% for G2 and 33% for G3 [31]. Recently, a study from the United Kingdom demonstrated 5-year OSs of 87%, 78% and 29% for G1, G2 and G3 p-NENs, respectively [32]. As a result, many new practical guidelines suggested that different treatment strategies should be adopted for various grading sub-groups of p-NENs [14,33–35]. For example, somatostatin analogs have been recommended as first-line medical therapy for both functional and non-functional progressive G1/G2 p-NETs, alone or in combination with molecular targeted drugs such as sunitinib and everolimus, while platinum-based chemotherapies were the first choice for G3 p-NECs, similar to the medical treatment for p-EACs [35].

In light of the stratification of patients into prognostic groups for survival analysis of p-NENs, patients were defined by all classifications as a whole entity, possibly not accurately reflecting the outcome of patients with varying grading features. Recently in 2017, the AJCC made major updates on staging this disease which stated clearly that its staging system for p-NENs should be applied only to G1/G2 p-NETs and that G3 p-NECs should be classified according to the criteria for p-EACs. To the best of our knowledge, to date, there has been no study evaluating the application of this new manual to G3 p-NECs. Whether these changes have significantly improved the prognostic ability for the survival of G3 p-NECs was unclear.

With eligible data from our institution, we first validated and compared the application of the two new staging systems in the AJCC 8th manual to survival analysis of G3 p-NECs, proposed for p-EACs and G1/G2 p-NETs. In the present study, with the major changes in the definitions of T stage, N stage and corresponding clinical stage as described previously, both systems for p-EACs and G1/G2 p-NETs classified eligible patients into four prognostic groups, with statistically different stage distributions for OS of G3 p-NECs ($P < 0.05$). In addition, the system for p-EACs significantly discriminated the survival difference of G3 p-NECs between Stage I and Stage II ($P = 0.019$), while the system for G1/G2 p-NETs did not

(P = 0.108), suggesting that the former system provided more appropriate and practical prognostic discrimination between each new AJCC stage. The consistent results of the AIC with the C-index value when comparing the two systems indicated that the AJCC 8th staging system for p-EACs was superior when applied to G3 p-NECs for its better prognostic stratification and more accurate predicting ability for OS of G3 p-NECs.

Recent studies have focused on the heterogeneous behaviors of G3 p-NECs. Sorbye et al. [36,37] reported G3 p-NECs consisting of well-differentiated tumors that had a Ki-67 index <55% and did not respond to platinum-based chemotherapy, and poorly differentiated tumors that had a Ki-67 index ≥55% and responded well to platinum-based chemotherapy. Basturk et al. [38], Kim et al. [39] and Chen [40] also described G3 p-NECs containing two distinct neoplasm sub-groups that could be further separated morphologically into well-differentiated G3 p-NETs and poorly differentiated G3 p-NECs, with different Ki-67 indices, histological features, clinical manifestations, treatment responses and prognoses. Similarly, we identified two sub-groups of G3 p-NECs in the present study. Seventy patients were diagnosed as having G3 p-NECs with a Ki-67 index ≥55%, with significantly worse prognosis than those with a Ki-67 index <55% (Supplementary Fig. 1). We also found by Cox hazard model that the Ki-67 index was an independent predictor of favorable OS for G3 p-NECs.

The major limitations of this study were the retrospective nature of the data analysis and the duration over which patients were recruited. Furthermore, AJCC accepted the WHO 2010 grading scheme in its 8th staging manual which regarded all G3 p-NECs as an entirety. This might ignore the heterogeneity of G3 p-NECs with morphologically different-differentiated subgroups, which might be the potential defect of AJCC 8th staging manual and should be further studied or revised in the later AJCC 9th staging manual. In addition, as a sub-group of p-NENs, G3 p-NECs were very rare. There were limited numbers of certain groups when subdivided by the new AJCC stage system. The statistical significance of our findings was influenced by the small number of patients when performing the survival analysis. Therefore, in-depth and prospectively designed studies with large volumes are needed to validate our results.

Conclusion

Based on the analysis from our center, we validated the use of two TNM staging systems in the AJCC 8th manual to G3 p-NECs. We demonstrated that both classifications for p-EACs and G1/G2 p-NETs were prognostic factors for OS of patients with G3 p-NECs. However, the system originally applied to p-EACs appeared to be superior in performance due to its better prognostic stratification and more accurate predicting ability. Our results supported the wide application of this new AJCC system to G3 p-NECs in clinical practice.

Conflicts of interest and source of funding

We declared that we had no conflict of interest among the authors. This research was sponsored by the 1.3.5. Project Disiplines of Excellence, West China Hospital, Sichuan University.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.01.010.

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