The Eighth Edition of the American Joint Committee on Cancer Distant Metastases Stage Classification for Metastatic Pancreatic Neuroendocrine Tumors Might Be Feasible for Metastatic Pancreatic Ductal Adenocarcinomas

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Keywords

Pancreatic neuroendocrine tumor · Pancreatic ductal adenocarcinomas · TNM staging system · Distant metastasis · Survival analysis

Abstract

Background: Significant modifications have been made to the 8th edition of the American Joint Committee on Cancer (AJCC) distant metastases (M) stage classification for metastatic pancreatic neuroendocrine tumors (PanNETs). We aimed to validate this revised classification among metastatic PanNET patients using the Surveillance, Epidemiology, and End Results database. We further sought to evaluate the feasibility of applying this classification to metastatic pancreatic neuroendocrine carcinoma (PanNEC) and pancreatic ductal adenocarcinoma (PDAC) patients. **Methods:** Stage IV pancreatic neuroendocrine neoplasm (PanNEN, including G1/G2 PanNET and G3 PanNEC classified according to the World Health Organization [WHO] 2010 grading scheme) and PDAC patients with metastatic disease diagnosed between 2010 and 2015 were identified and restaged according to the revised M stage classification for PanNET. Overall survival (OS) was compared using Kaplan-Meier analysis and

log-rank test. Uni- and multivariate Cox regression models were utilized to identify prognostic factors. **Results:** A total of 1,371 stage IV PanNEN and 634 PDAC patients were included. Among PanNEN patients, liver (75.0%) was the most common metastatic site, followed by distant lymph nodes (8.5%), lung (8.4%), bone (7.3%), and brain (1.0%). The 5-year OS for PanNET patients with M1a, M1b, and M1c stage was 44.15, 53.32, and 19.70%, respectively. However, survival comparison showed no significant difference between M1a and M1b stages among PanNET patients. Similar findings were noted after applying this classification to PanNEC patients. Multivariate analysis showed that the age at diagnosis and the number of distant metastatic sites were independent prognostic factors for metastatic PanNEN patients. Interestingly, excellent survival discrimination by M stage among stage IV PDAC patients was noted (M1a vs. M1b vs. M1c, 5-year OS: 5.42, 2.46, and 0%, respectively). **Conclusion:** Our study is the first large sample-based validation of the AJCC 8th M stage classification for PanNET. The revised classification did not effectively stratify metastatic PanNEN pa-

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tients. However, further study is warranted to validate this classification for PanNET patients according to the WHO 2017 classification. Interestingly, the revised M stage classification might be feasible for PDAC patients with metastatic disease.

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Introduction

Pancreatic neuroendocrine neoplasm (PanNEN) is a rare malignancy that represents approximately 10% of pancreatic tumors by prevalence [1]. The incidence of PanNEN has been increasing in the past decades, with an annual incidence of approximately 3.65 cases per 100,000 people [2]. Compared to pancreatic ductal adenocarcinoma (PDAC), the most common tumor of exocrine and endocrine pancreas, PanNEN is more heterogeneous, and pancreatic neuroendocrine tumor (PanNET) is generally considered to have indolent tumor biology. According to the grading classification scheme proposed by the European Neuroendocrine Tumor Society (ENETS) and adopted by the World Health Organization (WHO) classification in 2010, after incorporation of mitotic rate and/or Ki-67 index, well-differentiated (G1, G2) PanNEN is termed PanNET, while poorly-differentiated (G3) PanNEN with Ki-67 >20% is termed pancreatic neuroendocrine carcinoma (PanNEC) [3–5]. Recently, the response to therapy of those diagnosed with “well-differentiated, high-grade” PanNEN, which was considered as poorly-differentiated neoplasm under the 2010 grading scheme, was more in line with that of those with well-differentiated PanNET; the WHO 2017 grading scheme reclassified this entity as well-differentiated G3 PanNET [6]. That is, tumors with a Ki-67 labeling index >20% were subdivided into well-differentiated G3 PanNET and poorly-differentiated G3 PanNEC (see Appendix). Grade classification is a significant and independent prognostic factor for PanNEN, and several studies also indicated a discrepancy of survival outcome between patients with well-differentiated and poorly-differentiated PanNEN [4, 5, 7].

However, the majority of PanNEN patients are diagnosed at relatively advanced stage due to lack of specific symptoms. Presence of distant metastasis is an independent adverse prognostic indicator in PanNEN, and liver is the most common metastatic site [8–10]. Given that existing data are based on several studies with small sample size, the patterns of distant metastases among PanNEN patients remain unclear. It is not until 2010 that the

7th edition of the American Joint Committee on Cancer (AJCC) TNM classification system for pancreatic neuroendocrine neoplasms (NENs) was included in the AJCC Staging Manual, which accepted the staging algorithm for PDAC [11]. However, in the most recent version, considering that tumor biology and prognosis are significantly different between exocrine and neuroendocrine tumors (NETs) of pancreas, the 8th edition of the AJCC TNM classification made some modifications to be consistent with the ENETS system [12]. PanNEC patients are still staged in the same manner as PDAC patients, while a novel staging system is proposed for those diagnosed with PanNET [13]. On the one hand, for stage IV patients with metastatic disease, the definition of distant metastases (M) stage has been revised for PanNET, in which patients with metastasis confined to liver are classified as M1a stage, those with metastases in at least one extrahepatic site are classified as M1b stage, and patients with both hepatic and extrahepatic metastases are M1c stage [14]. On the other hand, those with distant metastases diagnosed with PanNEC or PDAC are still generalized as M1 stage. That is, these patients diagnosed with distant metastases are considered to have similar poor prognoses regardless of metastatic sites. However, the number and patterns of specific distant metastatic sites have already been approved to be of prognostic value and incorporated into the staging protocols in various other solid tumors, including lung cancer, gastrointestinal tract NETs, and colon and rectum cancer etc. [12]. Although the prognosis for PDAC patients with distant metastasis was dismal, recent studies suggested that surgical resection combined with systemic chemotherapy may be considered for highly selected patients, especially those diagnosed with liver metastasis [15, 16]. A retrospective study by Lemke et al. [17] even found that resection of brain metastasis of PDAC has a survival benefit and suggested the surgical approach be considered for selective metastatic PDAC cases. Moreover, a recent population-based study evaluated the prognostic value of site-specific metastases for PDAC and found distinctive prognoses among patients with different metastatic sites [18]. The role of surgical resection in the management of a subset of PDAC patients with isolated liver or distant lymph node metastases was also noted. Under these circumstances, a revised M staging classification which considers the prognostic value of specific metastatic sites may help improve the treatments outcomes for PDAC patients.

To our knowledge, whether the newest M stage classification for PanNET is capable of discriminating survival between the different stages remains unclear, and

external validation based on a large sample size is lacking. Moreover, we are interested in whether this staging system is also feasible for those with PanNEC and PDAC. Therefore, in the present study, we sought to address the following objectives using the Surveillance, Epidemiology, and End Results (SEER) database [19]: (1) We aimed to validate the discrimination ability of the latest M stage classification among PanNET patients. (2) We sought to apply this M stage classification to PDAC as well as PanNEC patients and to examine its prognostic ability in these entities.

Materials and Methods

Patient Population

We used the SEER*Stat 8.3.5 software to extract data from the SEER database. All patients with a diagnosis of stage IV PanNEN according to the ICD-O-3 histology codes (<https://codes.iarc.fr/codegroup/2>) and the AJCC 7th edition staging system [11] between 2010 and 2015 were identified from the SEER database. The ICD-O-3 histology codes used in this study were consistent with a previous published study of NEN [1]. Regarding the histological grade and similar to other SEER-based studies of NEN, the WHO 2010 scheme was employed [20–22]. Patients with PanNEN were divided into two cohorts according to morphological features and Ki-67 labeling index. The cases of well-differentiated (G1/G2) PanNEN will henceforth be referred to as the PanNET cohort, and the poorly-differentiated (G3) PanNEN cases will be referred to as the PanNEC cohort. The demographic and clinicopathological data of all eligible cases, including age, race, sex, histological grade, primary tumor location, T stage, N stage (according to the 7th edition of the AJCC staging system [11]), primary site surgery, metastatic site surgery, radiotherapy, chemotherapy, specific metastatic sites, and marital status, were collected and retrospectively analyzed. To validate the prognostic ability of the revised M stage classification for PanNET patients and to estimate whether this classification could also be applied for PanNEC patients, all stage IV PanNEN patients were restaged according to the 8th edition of the AJCC Staging system for PanNET patients [12]. To further evaluate our hypothesis that the revised M staging classification for PanNET was also feasible for PDAC, 634 patients with stage IV PDAC diagnosed between 2010 and 2015 were identified in the SEER database and restaged per the AJCC 8th edition PanNET staging system. Moreover, propensity score matching (PSM) was performed for PanNEC and PDAC patients. Each patient in the PanNEC group was matched with a patient in the PDAC group. Patient characteristics were well balanced across included covariables of age at diagnosis, sex, race, N stage, histology, grade, surgery for primary site or metastatic site, radiation, and chemotherapy. Both stage IV PanNEC and PDAC patients were classified according to the M stage for PanNET patients according to the 8th TNM staging system.

Statistical Analysis

Continuous variables were compared using the Student *t* test and categorical variables using the χ^2 test. The primary endpoint

of this study was overall survival (OS), which was measured from tumor diagnosis to the date of last follow-up or death. OS values were estimated using the Kaplan-Meier method, and a log-rank test was used to assess differences in OS. Multivariate analysis was conducted using a Cox proportional hazards model to analyze the associations between clinicopathological characteristics and patient survival. Hazard ratios and 95% confidence intervals were estimated using uni- and multivariate models. To adjust for differences between stage IV PanNEC and poorly-differentiated PDAC when analyzing prognosis, a PSM analysis at a 1:1 ratio was performed. A two-side *p* value <0.05 was considered statistically significant. All statistical analyses and graphics were performed using R software version 3.5.2 (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org).

Results

Clinicopathological Characteristics among Stage IV PanNEN Patients

As shown in Table 1, according to the WHO grading classification scheme published in 2010, 523 patients diagnosed with stage IV PanNET (384 diagnosed with G1 and 139 diagnosed with G2) and 848 patients diagnosed with stage IV PanNEC were identified. The majority of patients was of male sex, Caucasian ethnicity, from the Pacific Coast, and married. PanNET was more likely located in the body or tail and N1 stage. Regarding treatment options, 77 (9.1%) PanNEC patients received radiotherapy and 490 (57.8%) received chemotherapy. Less patients with PanNEC received surgery at the primary or metastatic site compared to G1 and G2 PanNET. Among G1 PanNET patients, 315 (82.0%) were M1a stage, 22 (5.7%) M1b stage, and 47 (12.2%) M1c stage. On the other hand, 119 (85.6%) G2 PanNET patients were diagnosed with M1a stage, 8 (5.8%) with M1b stage, and 12 (8.6%) with M1c stage. We further classified PanNEC patients according to the latest AJCC TNM staging system for PanNET. In total, 605 (71.3%) were categorized with M1a stage, 61 (7.2%) with M1b stage, and 182 (21.5%) with M1c stage.

Patterns of Distant Metastatic Sites among PanNEN Patients

Most PanNET patients had metastatic sites confined to liver, and 64 had more than one metastatic site. Similar results could be found among PanNEC patients, in whom 649 had one metastatic site and 199 had two sites or more. The details of the distribution of distant metastatic sites are presented in Table 2.

Table 1. Baseline characteristics of stage IV PanNET and PanNEC patients with metastatic disease

Characteristics	G1 PanNET (n = 384)	G2 PanNET (n = 139)	PanNEC (n = 848)	p value
Race				
White	311 (81.0%)	111 (79.9%)	676 (79.7%)	0.886
Black	45 (11.7%)	15 (10.8%)	108 (12.7%)	
Other ¹	28 (7.3%)	13 (9.4%)	64 (7.5%)	
Sex				
Female	170 (44.3%)	57 (41.0%)	351 (41.4%)	0.612
Male	214 (55.7%)	82 (59.0%)	497 (58.6%)	
CHSDA region				
East	125 (32.6%)	53 (38.1%)	328 (38.7%)	0.218
Northern Plains	36 (9.4%)	15 (10.8%)	97 (11.4%)	
Pacific Coast	205 (53.4%)	65 (46.8%)	379 (44.7%)	
Southwest	18 (4.7%)	6 (4.3%)	44 (5.2%)	
Tumor location				
Body/tail	184 (47.9%)	65 (46.8%)	328 (38.7%)	0.024
Head	101 (26.3%)	35 (25.2%)	245 (28.9%)	
Other	99 (25.8%)	39 (28.1%)	275 (32.4%)	
7th T classification				
T1	24 (6.2%)	5 (3.6%)	31 (3.7%)	<0.001
T2	112 (29.2%)	32 (23.0%)	255 (30.1%)	
T3	122 (31.8%)	60 (43.2%)	192 (22.6%)	
T4	31 (8.1%)	16 (11.5%)	96 (11.3%)	
TX	95 (24.7%)	26 (18.7%)	274 (32.3%)	
7th N classification				
N0	177 (46.1%)	57 (41.0%)	384 (45.3%)	0.005
N1	147 (38.3%)	66 (47.5%)	288 (34.0%)	
NX	60 (15.6%)	16 (11.5%)	176 (20.8%)	
8th M classification ²				
M1a	315 (82.0%)	119 (85.6%)	605 (71.3%)	<0.001
M1b	22 (5.7%)	8 (5.8%)	61 (7.2%)	
M1c	47 (12.2%)	12 (8.6%)	182 (21.5%)	
Primary site surgery				
No	269 (70.1%)	83 (59.7%)	790 (93.2%)	<0.001
Yes	115 (29.9%)	56 (40.3%)	58 (6.8%)	
Metastatic site surgery				
No	308 (80.2%)	106 (76.3%)	785 (92.6%)	<0.001
Yes	76 (19.8%)	33 (23.7%)	63 (7.4%)	
Radiotherapy				
No	364 (94.8%)	129 (92.8%)	771 (90.9%)	0.061
Yes	20 (5.2%)	10 (7.2%)	77 (9.1%)	
Chemotherapy				
No	234 (60.9%)	77 (55.4%)	358 (42.2%)	<0.001
Yes	150 (39.1%)	62 (44.6%)	490 (57.8%)	
Metastatic sites				
One	334 (87.0%)	125 (89.9%)	649 (76.5%)	<0.001
Two	43 (11.2%)	11 (7.9%)	149 (17.6%)	
More than two	7 (1.8%)	3 (2.2%)	50 (5.9%)	
Age				
>62 years	189 (49.2%)	63 (45.3%)	427 (50.4%)	0.541
≤62 years	195 (50.8%)	76 (54.7%)	421 (49.6%)	
Insurance				
No	11 (2.9%)	2 (1.4%)	29 (3.4%)	0.438
Yes	373 (97.1%)	137 (98.6%)	819 (96.6%)	
Marital status				
Married	226 (58.9%)	82 (59.0%)	504 (59.4%)	0.98
Unmarried	158 (41.1%)	57 (41.0%)	344 (40.6%)	

According to the World Health Organization grading classification scheme published in 2010, well-differentiated (G1 and G2) PanNENs are termed PanNETs, and poorly-differentiated (G3) PanNENs are regarded as PanNECs. AJCC, American Joint Committee on Cancer; CHSDA, Contract Health Service Delivery Area; PanNEC, pancreatic neuroendocrine carcinoma; PanNEN, pancreatic neuroendocrine neoplasm; PanNET, pancreatic neuroendocrine tumor. ¹ Includes American Indian, Alaska Native, and Asian/Pacific Islands. ² PanNET and PanNEC patients were restaged according to the 8th edition of the AJCC M stage classification for PanNET patients.

Table 2. Patterns of distant metastases for patients diagnosed with stage IV PanNEN

Sites of distant metastases	Variable	PanNET (<i>n</i> = 523)	PanNEC (<i>n</i> = 848)
One site of distant metastasis	lung	8 (1.5%)	13 (1.5%)
	distant lymph node	11 (2.1%)	22 (2.6%)
	bone	5 (1.0%)	7 (0.8%)
	brain	1 (0.2%)	2 (0.2%)
	liver	434 (83.0%)	605 (71.3%)
Two sites of distant metastasis	lung and bone	0 (0.0%)	1 (0.1%)
	lung and brain	0 (0.0%)	0 (0.0%)
	distant lymph node and bone	2 (0.4%)	1 (0.1%)
	distant lymph node and brain	0 (0.0%)	1 (0.1%)
	distant lymph node and liver	16 (3.1%)	41 (4.8%)
	distant lymph node and lung	1 (0.2%)	10 (1.2%)
	liver and bone	21 (4.0%)	44 (5.2%)
	liver and brain	0 (0.0%)	2 (0.2%)
	liver and lung	14 (2.7%)	48 (5.7%)
Three sites of distant metastasis	brain and bone	0 (0.0%)	1 (0.1%)
	distant lymph node, brain, and bone	0 (0.0%)	0 (0.0%)
	distant lymph node, liver, and bone	4 (0.8%)	8 (0.9%)
	distant lymph node, liver, and lung	1 (0.2%)	14 (1.7%)
	distant lymph node, liver, and brain	0 (0.0%)	0 (0.0%)
	distant lymph node, lung, and brain	0 (0.0%)	0 (0.0%)
	distant lymph node, lung, and bone	0 (0.0%)	3 (0.4%)
	liver, brain, and bone	0 (0.0%)	0 (0.0%)
	liver, lung, and bone	3 (0.6%)	13 (1.5%)
	liver, lung, and brain	0 (0.0%)	1 (0.1%)
Four sites or more of distant metastasis	lung, brain, and bone	1 (0.2%)	0 (0.0%)
	distant lymph node, liver, brain, and bone	0 (0.0%)	0 (0.0%)
	distant lymph node, liver, lung, and bone	0 (0.0%)	4 (0.5%)
	distant lymph node, liver, lung, and brain	0 (0.0%)	2 (0.2%)
	distant lymph node, lung, brain, and bone	1 (0.2%)	0 (0.0%)
	distant lymph node, liver, lung, brain, and bone	0 (0.0%)	3 (0.4%)
Five sites or more of distant metastasis	liver, lung, brain, and bone	0 (0.0%)	2 (0.2%)

PanNEC, pancreatic neuroendocrine carcinoma; PanNEN, pancreatic neuroendocrine neoplasm; PanNET, pancreatic neuroendocrine tumor.

PanNEN Patient Survival

Figure 1a shows the OS comparison between stage IV PanNET and neuroendocrine carcinoma patients. PanNET patients had a significantly better prognosis than those with neuroendocrine carcinoma (5-year OS: 42.27 vs. 13.07%, $p < 0.001$). Among stage IV PanNET patients, those diagnosed with only one metastatic site had superior outcome compared to those with more than one site (5-year OS: 44.76 vs. 19.28%, $p < 0.001$). Regarding different M stages, as shown in Figure 1c, no significant difference was noted between M1a and M1b stages. However, survival comparison among PanNET patients with M1a versus M1c and M1b versus M1c showed significant differences.

The 5-year OS for PanNET patients with M1a, M1b, and M1c stage was 44.15, 53.32, and 19.70%, respectively. For stage IV PanNEC, patients with an increased number of metastatic sites had inferior outcomes. Specifically, the 5-year OS for patients with only one site, two sites, and three or more sites was 15.13, 9.17, and 5.65%, respectively. Kaplan-Meier curves for survival stratified by the 8th AJCC TNM staging classification are shown in Figure 2b. Patients with M1c stage disease had a significantly poorer prognosis than those with M1a stage disease (5-year OS: 7.71 vs. 15.02%, $p < 0.001$). However, Kaplan-Meier comparison between those with M1a and M1b stage only showed a tendency for significant differences.

Fig. 1. **a** Kaplan-Meier survival curves for patients with metastatic PanNET and PanNEC. **b** Kaplan-Meier survival curves for PanNET patients with only one metastatic site and more than one site. **c** Kaplan-Meier survival curves for PanNET patients with different 8th edition of the AJCC M stage classification. AJCC, American Joint Committee on Cancer; M, distant metastases; PanNEC, pancreatic neuroendocrine carcinoma; PanNET, pancreatic neuroendocrine tumor.

ence (5-year OS: 15.02 vs. 26.24%, $p = 0.118$). Similar findings were noted among patients with M1b and M1c stage.

Variables potentially affecting OS were analyzed using uni- and multivariate Cox proportional hazards analysis. Table 3 shows that for stage IV PanNET patients, age ≤ 62 years, primary site surgery, and less metastatic sites were associated with a better prognosis ($p < 0.05$). For patients

with stage IV PanNEC, in addition to the variables mentioned above, early lymph node stage, chemotherapy, and being married at diagnosis were identified as protective factors.

To further elucidate whether the revised M stage for PanNET was also suitable for PanNEC or PDAC patients, PSM was performed; the demographic features and clinicopathological characteristics of these patients are shown

Fig. 2. a Kaplan-Meier survival curves for PanNEC patients with different number of metastatic sites. **b** Kaplan-Meier survival curves for PanNEC patients stratified by the 8th edition of the AJCC M stage classification for PanNET. AJCC, American Joint Committee on Cancer; M, distant metastases; PanNEC, pancreatic neuroendocrine carcinoma; PanNET, pancreatic neuroendocrine tumor.

in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000502382). After PSM, PDAC patients had a significantly inferior prognosis compared to PanNEC patients (5-year OS: 2.27 vs. 24.11%, $p < 0.001$; Fig. 3a). Interestingly, when these patients were stratified by the revised M stage classification, PDAC patients with more advanced stage had significantly poorer outcomes (M1a vs. M1b vs. M1c, 5-year OS: 4.90, 2.45, and 0%, respectively; the results of internal comparison are shown in Fig. 3b). For stage IV PDAC and PanNEC patients with the same M stage, discrepancies in survival outcomes were found among those with M1a and M1c stage, but not for M1b stage patients. Moreover, to further validate the prognostic ability of the revised M stage classification for PDAC, 634 stage IV PDAC patients, regardless of histological grade, were identified. As shown in online supplementary Table 2, the most common metastatic site for these patients was liver (480, 75.7%), followed by lung (171, 27.0%), distant lymph nodes (91, 14.4%), bone (53, 8.4%), and brain (4, 0.6%). After adjustment for other potential prognostic covariate variables, the novel classification was significantly associated with OS (M1a vs. M1b vs. M1c, 2-year OS: 15.85, 6.86, and 2.44%, respectively; 5-year OS: 5.42, 2.46, and 0%, respectively; the results of internal comparison are shown in online suppl. Fig. 1).

Discussion

PanNEN consists of a group of heterogeneous neoplasms, including functional and nonfunctional tumors, and a considerable percentage of them have distant metastases at the time of diagnosis [23]. The 8th edition of the AJCC TNM staging system distinguished PanNET from PanNEC and revised the M stage classification. This study is the first large population-based validation of the latest M staging system for stage IV PanNET. Our study indicated that for PanNET patients with distant metastases, the discrimination of the revised M stage classification was not significant. However, after applying the revised M stage classification for PanNET to PanNEC and PDAC, we accidentally found that the staging system could effectively stratify PDAC patients, but not PanNEC patients. Moreover, our study revealed the patterns of the distant metastatic sites of PanNEN patients and suggested the prognostic factors for OS among this entity, which can help guide clinicians to better manage these patients.

There are now two widely used staging systems for PanNEN patients: the ENETS and the AJCC staging classification. Recently, due to the inability of these systems to discriminate between intermediate stages, other researchers proposed a modified staging algorithm [24]. However, all of the aforementioned classifications

Table 3. Uni- and multivariate Cox regression analysis for PanNET and PanNEC patients

Variables	PanNET						PanNEC					
	univariate analysis			multivariate analysis			univariate analysis			multivariate analysis		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age												
>62 years	ref.			ref.			ref.			ref.		
≤62 years	0.51	0.38–0.69	<0.001	0.55	0.41–0.75	<0.001	0.64	0.54–0.76	<0.001	0.66	0.56–0.79	<0.001
Race												
White	ref.			–			ref.			–		
Black	0.86	0.53–1.38	0.530	–	–	–	1.16	0.91–1.47	0.243	–	–	–
Other	1.12	0.67–1.87	0.673	–	–	–	0.97	0.70–1.33	0.830	–	–	–
Sex												
Female	ref.			–			ref.			–		
Male	1.13	0.84–1.51	0.421	–	–	–	1.09	0.92–1.29	0.334	–	–	–
CHSDA region												
East	ref.			–			ref.			–		
Northern Plains	0.66	0.37–1.17	0.159	–	–	–	0.87	0.65–1.15	0.332	–	–	–
Pacific Coast	0.78	0.57–1.06	0.110	–	–	–	1.01	0.84–1.22	0.885	–	–	–
Southwest	0.83	0.42–1.66	0.603	–	–	–	0.96	0.64–1.44	0.850	–	–	–
Tumor location												
Body/tail	ref.			–			ref.			–		
Head	1.01	0.71–1.44	0.953	–	–	–	1.20	0.98–1.47	0.079	–	–	–
Other	1.13	0.80–1.60	0.486	–	–	–	1.20	0.98–1.46	0.073	–	–	–
Histological grade ¹												
G1	ref.			–			–			–		
G2	0.90	0.64–1.26	0.532	–	–	–	–			–		
Limited to the pancreas												
Yes	ref.			–			ref.			–		
No	0.82	0.57–1.16	0.259	–	–	–	0.88	0.71–1.08	0.217	–	–	–
Unknown	1.62	1.12–2.34	0.010	–	–	–	1.23	1.00–1.50	0.047	–	–	–
7th T classification												
T1	ref.			–			ref.			–		
T2	0.87	0.44–1.73	0.701	–	–	–	1.42	0.88–2.28	0.150	–	–	–
T3	0.70	0.35–1.37	0.293	–	–	–	1.12	0.69–1.82	0.651	–	–	–
T4	0.88	0.40–1.93	0.744	–	–	–	1.36	0.81–2.28	0.239	–	–	–
TX	1.45	0.74–2.84	0.279	–	–	–	1.67	1.04–2.67	0.034	–	–	–
7th N classification												
N0	ref.			–			ref.			ref.		
N1	0.86	0.62–1.19	0.372	–	–	–	1.20	1.10–1.31	0.035	1.23	1.11–1.36	0.044
NX	1.52	1.03–2.25	0.036	–	–	–	1.47	1.19–1.82	<0.001	1.37	1.08–1.74	0.008
Primary site surgery												
No	ref.			ref.			ref.			ref.		
Yes	0.34	0.23–0.49	<0.001	0.47	0.30–0.75	0.001	0.37	0.24–0.56	<0.001	0.43	0.27–0.68	<0.001
Metastatic site surgery												
No	ref.			ref.			ref.			ref.		
Yes	0.37	0.23–0.58	<0.001	0.69	0.40–1.18	0.177	0.59	0.41–0.84	0.003	0.85	0.58–1.26	0.425
Radiotherapy												
No	ref.			–			ref.			–		
Yes	1.15	0.62–2.11	0.662	–	–	–	1.00	0.75–1.35	0.977	–	–	–
Chemotherapy												
No	ref.			–			ref.			ref.		
Yes	1.07	0.80–1.43	0.649	–	–	–	0.75	0.64–0.89	0.001	0.72	0.61–0.86	<0.001
Metastatic sites												
One	ref.			ref.			ref.			ref.		
Two	1.64	1.06–2.55	0.027	1.47	0.94–2.30	0.095	1.46	1.18–1.81	0.001	1.34	1.08–1.68	0.008
More than two	2.92	1.29–6.62	0.010	2.43	1.07–5.56	0.035	2.60	1.90–3.55	<0.001	2.66	1.92–3.68	<0.001
Insurance												
No	ref.			–			ref.			–		
Yes	2.48	0.62–10.01	0.201	–	–	–	0.91	0.58–1.42	0.681	–	–	–
Marital status												
Married	ref.			–			ref.			ref.		
Unmarried	0.91	0.67–1.22	0.515	–	–	–	1.54	1.30–1.82	<0.001	1.46	1.23–1.73	<0.001

CHSDA, Contract Health Service Delivery Area; CI, confidence interval; HR, hazard ratio; PanNEC, pancreatic neuroendocrine carcinoma; PanNET, pancreatic neuroendocrine tumor. ¹ The histological grade of PanNET patients was classified according to the World Health Organization Classification of Tumours of the Digestive System, published in 2010.

Fig. 3. a Kaplan-Meier survival curves for patients with metastatic PanNEC and G3/G4 PDAC after PSM. **b** Kaplan-Meier survival curves for PanNEC and G3/G4 PDAC patients stratified by the 8th edition of the AJCC M stage classification for PanNET. AJCC, American Joint Committee on Cancer; M, distant metastases; PanNEC, pancreatic neuroendocrine carcinoma; PanNET, pancreatic neuroendocrine tumor; PDAC, pancreatic ductal adenocarcinoma.

vaguely categorized PanNEN patients with M1 stage as stage IV. The newest AJCC staging system was released in 2017; Kamarajah et al. [25] validated its ability in PDAC patients and found similar concordance indices between the 7th and 8th edition systems. However, only those undergoing surgery and with nonmetastatic disease were included in this study; thus, the study could not provide information about the survival discrimination of this system among advanced-stage patients. For PanNET patients with metastatic disease, the 8th edition of the AJCC staging system separated them into M1a, M1b, and M1c stage based on the staging system for gastrointestinal originated NET patients, while their PanNEC competitors were still staged by the AJCC staging system for PDAC. However, the discriminative ability of the revised system has not been assessed using a nationally representative dataset. In the present study, we identified eligible PanNEN and PDAC patients and restaged them according to the newest M stage classification for PanNET patients. Our results showed that the OS of M1b stage PanNET patients had a tendency to be better than that of those with M1a stage, which suggested that the revised classification might harbor innate weaknesses. Similar findings were extracted when we applied the M staging system for PanNET to PanNEC. Kaplan-Mei-

er survival comparisons showed no significant differences between M1a versus M1b stage and M1b versus M1c stage. However, we surprisingly found that this classification showed excellent survival discrimination by M stage among stage IV PDAC patients. PDAC is a lethal disease and considered to be the leading cause of cancer-related death. Most PDAC patients are diagnosed at advanced stages. Liver, peritoneal cavity, and lung metastasis is the most common form of distant metastasis for these patients. However, it has been reported that for PDAC patients with liver metastasis, aggressive surgical approaches, including liver resection, might improve survival, especially in those with oligometastasis [26]. Moreover, in the present study, significant prognostic differences for PDAC patients stratified by the novel M classification were observed. This prognostic algorithm might be able to reflect the biology of this entity, stratify patients according to their risk, and support the clinician in making appropriate treatment decisions.

As a result of the rarity of this disease, several small-sample retrospective studies reported that the liver is the first involved organ when patients with PanNEN develop metastatic disease [9, 10]. However, the patterns of distant metastases among these entities are

rarely evaluated in population-based studies. Our study suggested that for stage IV PanNEN patients with M1 stage, 82.4% of PanNET and 70.8% of PanNEC patients had liver metastases, which was consistent with previous studies [23, 27]. Regarding extrahepatic metastases, among PanNET patients, bone accounts for 6.2% of cases followed by distant lymph node (6.0%), lung (4.8%), and brain (0.5%). For PanNEC patients, lung was the most common extrahepatic metastatic site (10.3%) followed by distant lymph node (9.8%), bone (7.8%), and brain (1.3%). Regarding the number of distant metastatic sites, 87.8% of PanNET and 76.5% of PanNEC patients had only one distant metastatic site at the time of diagnoses. Moreover, those diagnosed with multiple metastatic sites had significantly inferior outcomes compared to those with a single metastatic site. The prognostic value of the number of distant metastatic sites has been suggested in many other solid tumors [28–30], and our findings were consistent with those of previous studies.

Multivariate analysis showed that age at diagnosis and surgery at the primary site were associated with OS among stage IV PanNEN patients. The impact of age at prognosis could be explained by the disparities in the tolerance to aggressive treatment modalities. Previous studies suggested that older patients were less likely to tolerate aggressive treatment modalities with curative intent. Even if they received treatment, elderly patients were also more likely to have comorbidity [31, 32]. The value of primary site surgery for patients with metastatic disease has been shown for other carcinomas [33]. A recent SEER analysis also indicated that PanNEN patients could benefit from surgery even when metastases occurred [2]. Our study confirmed the value of surgery at the primary site among metastatic PanNEN patients. Moreover, according to the National Comprehensive Cancer Network (NCCN) guidelines, if surgical tolerance is acceptable, surgical resection of both the primary tumor and liver metastases should be considered for PanNEN patients with limited hepatic disease [34]. For selected patients, noncurative debulking resection could also be acceptable, which suggests the importance of local treatment of the primary site for metastatic PanNEN patients. However, given that a large amount of patients in the current study did not undergo surgery and considering the high rate of recurrence after surgical resection, the role of systemic therapy needs to be estimated. For PanNEC patients, our study showed that patients who received chemotherapy had significantly better OS than those who did not. Although the evidence of cytotoxic therapy

among advanced PanNEN patients was not sufficiently strong, it was recommended as an option for patients with unresectable or metastatic disease in the NCCN guidelines. Streptozocin- and temozolomide-based therapies have great antitumor activities in PanNEN, but there is no consensus on which regimen is the best [35, 36].

Several limitations should be acknowledged in this SEER-based analysis. The main limitation is the classification of PanNEN. Patients diagnosed with G3 NET (according to the WHO 2017 scheme), the so-called “well-differentiated, high-grade” tumors, were identified as PanNEC in this study (based on the WHO 2010 scheme). The WHO 2010 classification system allowed the staging of PanNEN with consistent criteria throughout the present study period. However, according to the WHO 2017 classification, G3 PanNENs are subdivided into well-differentiated G3 NETs and poorly-differentiated G3 neuroendocrine carcinomas by using very accurate criteria (manual Ki-67 measurement instead of eyeballing and morphological assessment of well-differentiated versus poorly-differentiated morphology) [6]. We acknowledge that due to the retrospective nature of this study and lack of information about Ki-67 labelling index in the SEER database, we could not reclassify those diagnosed with G3 PanNET according to the newest WHO classification. However, in the present study, we aimed to evaluate the feasibility of applying the novel M stage classification proposed by AJCC for PanNET to metastatic PanNEC. That is, both the well-differentiated NENs (G1, G2, and G3 PanNET according to the 2017 WHO scheme) and poorly-differentiated PanNENs (the “true” G3 PanNECs according to the 2017 WHO scheme) were restaged. The revision of the definition of well-differentiated NEN (PanNET) did not affect our findings. We hope to have the opportunity to reclassify the PanNEN patients treated in a real-world setting according to the 2017 WHO scheme and to validate the prognostic value of the 8th edition of the M classification in the future. Secondly, only five site-specific distant metastases at initial diagnosis were recorded in the SEER database between 2010 and 2015. It has been reported that metastases to other sites, such as peritoneum, may also occur in metastatic PanNEN. However, due to the lack of information in the database, we could not assess the prognostic value of this site of distant metastases. Thirdly, the site, but not the exact number of distant metastases, was reported in the database. However, in other solid tumors such as lung carcinoma, the 8th edition has revised the definition of M stage and fo-

cused not only on the number of involved organs, but also on the number of distant metastases. The impact of the exact number of distant metastases in PanNEN patients should be estimated in the future. Furthermore, given the limited number of patients undergoing surgery, we did not have sufficient information to restage them according to the newest definition of tumor size (T) and nodal status (N) stage. The feasibility of T and N stage of the 8th edition staging system for PanNEN should be evaluated in future studies. Meanwhile, as suggested in previous research, some pM0 patients may include case with cM1, because pathologists did not assess metastatic site without specimens, and in consistent coding practice data loss is found [37]. In addition, in clinical practice, many metastatic lesions in PanNET are resectable and pathologically confirmed. On the other hand, most of those in PanNEC and PDAC are not surgically resected. These patients had the opportunity to encounter the so-called stage migration. Therefore, the accuracy of M category might be different between PanNET and PDAC. However, as we mentioned above, it was hard to obtain an adequate number of patients staged after surgical resection. Moreover, the large sample size of this study and the quality control of the SEER database made the result of our study convincing. In addition, as previously mentioned, systemic options, such as biologically targeted agents (everolimus or sunitinib) and somatostatin analogs (octreotide or lanreotide), have been recommended for metastatic PanNEN patients based on the results of several randomized studies [38, 39]. However, information related to systemic options was not recorded in the SEER database, which hindered us from identifying their prognostic value among metastatic PanNEN patients. According to the WHO 2017 scheme, the proliferation index Ki-67 is recommended to be measured manually with printed photos. Moreover, the cutoff values of G1 and G2 PanNET have also been revised in this classification. We hypothesize that the missing significant difference between the PanNET groups diagnosed with M1a and M1b might become statistically significant if the Ki-67 index is re-evaluated manually. Furthermore, if the Ki-67 index was measured based on metastatic sites, the grade classification might be inaccurate. We also acknowledge that, since the proper definition of pancreatic neoplasm represents a challenge for expert pathologists in the field, it would be better to have a centralized pathology revision. However, the SEER database is limited by its lack of central pathological review. The SEER data are also limited in relation to the recording of several relevant features

for the metastatic process, such as tumor size as well as vessel and nerve neoplastic involvement. Last but not the least, considering the high mortality and morbidity rate intrinsically given by pancreas surgery, disease- or relapse-free survival might be more feasible regarding metastases history. We did not use disease- or relapse-free survival because of the limitation of the SEER database, and recommend that further studies look into the prognoses of PanNEN patients with metastatic disease by using these endpoints.

In conclusion, our study was the first to use a large population-based dataset to validate the 8th edition of the AJCC M stage classification for metastatic PanNET patients. Based on the WHO 2010 classification for PanNEN (employed by the 8th edition of the AJCC TNM staging system), we found that the revised M stage classification is not sufficiently feasible based on this work. We further applied this classification to PanNEC and PDAC patients and found that the revised M classification showed excellent discriminative ability among PDAC patients. Our study indicated that the 8th edition of the AJCC M stage classification for metastatic PanNET could represent an effective staging instrument for PDAC, providing evidence for the revision of the next edition of the TNM staging system. However, since the classification of G3 PanNEN has been revised in the newest WHO system, further study is warranted to validate this M stage classification for PanNET patients according to the WHO 2017 classification.

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Statement of Ethics

The Institutional Review Board of Fudan University Shanghai Cancer Center approved this study. As this study is based on a publicly available database without identifying patient information, informed consent was not needed. This article does not contain any studies with human participants or animals performed by any of the authors.

Disclosure Statement

None of the authors report any conflict of interest.

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Author Contributions

J. Wen and J. Chen contributed to the study design. J. Wen, J. Chen, D. Liu, and X. Xu collected the study data. J. Wen and J. Chen contributed to data analysis and interpretation. All authors contributed to manuscript writing. M. Fan and Z. Zhang reviewed the manuscript and contributed to quality control. All authors reviewed the manuscript and approved the final version.

Data Availability

The present study was based on the publicly available SEER database (<https://seer.cancer.gov>), and permission was received from the National Cancer Institute to access the database for the purposes of research (private SEER ID 13499-Nov2016).

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Appendix

	Ki-67 index	Mitotic index
WHO Classification 2010 for NENs		
<i>Well-differentiated NENs</i>		
Neuroendocrine tumor (NET) G1	≤2%	<2/10 HPF
Neuroendocrine tumor (NET) G2	3–20%	2–20/10 HPF
<i>Poorly-differentiated NENs</i>		
Neuroendocrine tumor (NEC) G3	>20%	>20/10 HPF
WHO Classification 2017 for PanNENs		
<i>Well-differentiated NENs</i>		
Neuroendocrine tumor (NET) G1	≤2%	<2/10 HPF
Neuroendocrine tumor (NET) G2	3–20%	2–20/10 HPF
Neuroendocrine tumor (NET) G3	>20%	>20/10 HPF
<i>Poorly-differentiated NENs</i>		
Neuroendocrine tumor (NEC) G3	>20%	>20/10 HPF

HPF, high-power fields; NENs, neuroendocrine neoplasms; PanNENs, pancreatic neuroendocrine neoplasms.

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