Prognostic Validity of the American Joint Committee on Cancer Eighth Edition Staging System for Well-Differentiated Pancreatic Neuroendocrine Tumors: A Retrospective Multinational Multicenter Study

Hebin Wang
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Ding Ding
Johns Hopkins School of Medicine: Johns Hopkins University School of Medicine
Tingting Qin
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Jun Liu
Shandong Provincial Hospital
Hang Zhang
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Junfang Zhao
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Chien-Hui Wu
National Taiwan University Hospital
Ammar Javed
Johns Hopkins Hospital: Johns Hopkins Medicine
Christopher Wolfgang
Johns Hopkins Hospital: Johns Hopkins Medicine
Shiwei Guo
Changhai Hospital
Qinmin Chen
Jilin University First Hospital
Weihong Zhao
Hebei Medical University No2 Hospital: Second Hospital of Hebei Medical University
Wei Shi
Shandong Provincial Hospital
Feng Zhu
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Xingjun Guo
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Xu Li
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Feng Peng
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Ruizhi He
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Simiao Xu
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Jikuan Jin
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

Yi Wu
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Abula Nuer
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Barish Edil
The University of Oklahoma
Yu-Wen Tien
National Taiwan University
Gang Jin
Changhai Hospital
Lei Zheng
Johns Hopkins Hospital: Johns Hopkins Medicine
Jin He
Johns Hopkins Hospital: Johns Hopkins Medicine
Jianhua Liu
Hebei Medical University No2 Hospital: Second Hospital of Hebei Medical University
Yahui Liu
Jilin University First Hospital
Min Wang
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Renyi Qin (ryqin@tjh.tjmu.edu.cn)
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

---

Research

Keywords: Pancreatic neuroendocrine tumors, staging, survival, prognosis

Posted Date: October 8th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-86061/v1

Abstract

Background:

There is no widely-accepted staging system for pancreatic neuroendocrine tumors (pNETs). The aim of this study was to validate the American Joint Committee on Cancer (AJCC) 8th edition staging system for well-differentiated (G1/G2) pNETs.

Methods:

A multicenter dataset (n=1086) was used to evaluate the application of the AJCC 7th and 8th, the European Neuroendocrine Tumor Society (ENETS), and the modified ENETS (mENETS) staging systems for well-differentiated pNETs.

Results:

The proportion of patients with stage III tumors was extremely low (1.1%) according to the AJCC 7th staging system. For the ENETS staging system, patients with stage IIIA disease had worse estimated mean survival than patients with stage IIIB disease (78.9 vs. 107.3 months). When comparing with patients in stage I, the AJCC 7th, ENETS, and mENETS staging systems showed good performance in discriminating between stages; however, there was no significant difference in some stages when the reference was defined as the earlier stage. When the reference was defined as stage I or the earlier stage, there was a significant inter-stage difference in the AJCC 8th staging system.

Conclusions:

The AJCC 8th staging system is more suitable for pNETs than other TNM staging systems and may be adopted in clinical practice.

Introduction

Pancreatic neuroendocrine tumors (pNETs), which account for less than 2% of all pancreatic tumors, are a group of heterogeneous neoplasms with varying pathologic, functional, and clinical features[1, 2]. With an estimated annual worldwide incidence of 2.5 to 5 per 1,000,000 individuals, pNETs have been increasingly diagnosed over the past several decades, likely due to more accurate classification and improvements in diagnostic tools[3, 4]. Because of their rarity and heterogeneous behavior, it is difficult to stratify pNETs patients into prognostic groups using commonly accepted staging systems[5]. Thus, a robust and accurate staging system for risk stratification and survival prediction is urgently required.

In 2006, the European Neuroendocrine Tumor Society (ENETS) was the first to publish a consensus statement on the TNM staging classification of pNETs, as applied in other solid tumors[6]. Subsequently, the American Joint Committee on Cancer (AJCC) also introduced a TNM staging system for pNETs in 2010 (the AJCC 7th edition), which initially was applied to exocrine pancreatic adenocarcinoma based on studies by Bilimoria et al[5, 7]. Considering the drawbacks of these systems, Luo et al. developed a modified ENETS (mENETS) staging system, which maintained the ENETS T, N, and M definitions and adopted the AJCC system staging definitions[8]. Although several classification schemes have been proposed, there is no commonly accepted staging system (Table 1).

The ENETS staging system pointed out that patients with stage I disease had a similar prognosis to those with stage II disease[9], and the hazard ratio (HR) of death for patients with stage IIIB disease was even lower than that for patients with stage IIIA disease[10]. According to the AJCC 7th staging system, few patients would have stage III disease because pNETs seldom invade the celiac axis or the superior mesenteric artery (unresectable tumor) without distant metastasis, and patients with stage II or III disease were prognostically indistinguishable[11].

In 2017, the AJCC formally introduced a newly revised 8th staging system especially for pNETs, which was somewhat similar to the ENETS criteria, that included several significant changes[12]. First, the AJCC 8th staging system was only applied to well-differentiated pNETs, whereas poorly differentiated neuroendocrine carcinoma G3 (NEC G3) were excluded and considered according to the staging criteria for pancreatic exocrine adenocarcinoma. Second, it redefined the T, N, M, and staging system; for example, stage II and stage III was defined by combining the 2 previous subgroups of the ENETS system (stage IIA and stage IIB, and stage IIIA and stage IIIB, respectively) (Table 1).

While the new AJCC 8th staging system for well-differentiated pNETs has been validated by some studies[13, 14], validation using a large multi-center cohort has not been performed. Therefore, we utilized a multi-center database to validate the AJCC 8th staging system in the present study. To accomplish this, survival curves were compared according to the AJCC 7th and 8th, the ENETS, and the mENETS staging systems.

Materials And Methods

Patients and Data Collection

The study involved a cohort that included 1086 patients from a multi-center database comprising five Chinese centers and one American center [Wuhan Tongji hospital (n = 153), Shanghai Chang Hai hospital (n = 294), The First Hospital of Jilin University (n = 92), The Second Hospital of Hebei Medical University (n = 32), Shandong Provincial Hospital Affiliated to Shandong University (n = 32) and Johns Hopkins Hospital (n = 482)].

The main patient variables, including sex, age, tumor location, functional status, operation, type of operation, grade, T category, N category, M category, and overall survival, were all systematically collected and retrieved. We only included patients who had a pathologically confirmed diagnosis of pNET and had complete data to allow restaging per the AJCC and ENETS classifications, including T stage, nodal status, distant metastases, and follow-up data. Patients with NEC G3 tumors were excluded. Electronic datasheets were provided to all participating centers and all de-identified data were reviewed and cross-checked for inconsistencies. The study was approved by the Institutional Review Board of all participating centers.

Statistical analysis

Survival time was calculated as the number of months from the date of initial diagnosis until the date of last contact or death. Overall survival was evaluated using Kaplan-Meier curves, and log-rank tests were used to assess staging classification. Cox proportional hazards regression was performed for univariate analysis, and the HR and 95% confidence intervals (95% CI) were calculated. Multivariate analysis of each staging classification, controlling for sex, age, tumor location, functional status, type of operation, and grade, was performed using Cox proportional hazards regression. Values are expressed as number and percentage. All tests were 2-sided and statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SPSS v22.0 (IBM, Armonk, NY).

Results

Patient characteristics

In total, the study included 1086 patients from the multicenter database. Table 2 show their baseline characteristics. The median age was 54 years (mean, 53.27 years) and the proportions of male patients was 50.4%. Most patients had nonfunctioning pNETs (90.1%) and more than half (56.3%) had tumors located at the body and/or tail of the pancreas. Distal pancreatectomy and pancreaticoduodenectomy were performed in 531 (48.9%) and 398 (36.6%) patients, respectively, and laparoscopic surgery was conducted in 214 (19.7%). The median survival was 136.8 months (3-year survival rate, 90.6%; 5-year survival rate, 83.9%; 10-year survival rate, 57.6%).

TNM staging classification and survival

As shown in Fig. 1 (A and B) and Table 2, there was no significant difference in overall survival between T3 and T4 in the AJCC 7th T category and the ENETS & AJCC 8th T category (P =0.321 and p=0.645, respectively). According to the AJCC 7th T category, only 13 patients (1.2%) had T4 disease, and they exhibited abnormal survival rates (with T1 as the reference, HR = 2.772, 95% CI = 0.325 to 12.297, P =0.180). By contrast, there were significant differences in the N and M categories (HR =2.418, 95% CI = 1.809 to 3.231, P <0.001; HR =2.621, 95% CI = 1.880 to 3.654, P <0.001, respectively).

AJCC 7th stage group and survival

According to the AJCC 7th staging classification, only 12 (1.1%) of patients had stage III tumors. Compared to patients with stage IA disease, stage III patients showed no significant difference in survival (HR = 2.076, 95% CI = 0.265 to 16.232, P =0.486). In addition, there was no significant differences between stages IIA, IIB, III, and IV when the reference was defined as the earlier stage (P =0.052, P =0.128, P =0.249, and P =0.138, respectively) (Fig. 1E and Table 2).

ENETS stage group and survival

In comparison with patients with stage I disease, a significant difference was observed across all stage groups. However, patients with stage IIIA disease had worse estimated mean survival than patients with IIIB (78.9 vs. 107.3 months). Furthermore, there were also no significant differences across stages IIIA, IIIB, and IV when the reference was defined as the earlier stage (P =0.978, P =0.411, and P =0.077, respectively) (Fig. 1F and Table 2).

mENETS stage group and survival

The mENETS staging classification showed better distinction between different stages than the AJCC 7th and ENETS systems. There was a significant difference in survival between all stage groups compared to patients with stage I disease, and the relative risk for death was correlated with advanced stage disease. Nevertheless, there were also no significant differences in stages IIB, III, and IV when the reference was defined as the earlier stage (P =0.158, P =0.691, and P =0.139, respectively) (Fig. 1G and Table 2.)

AJCC 8th stage group and survival

Because stages II and III were both previously divided into 2 previous subgroups in the ENETS system (stage IIA and stage IIB, stage IIIA and stage IIIB, respectively), the AJCC 8th staging system divided all patients into four stages. Compared with stage I disease, there was a significant difference between all stages, which was also observed when the reference was defined as the earlier stage (Fig. 1H and Table 2).

Univariate and multivariate analysis of factors associated with survival

In the univariate analysis, age ≥60 years (HR = 1.554, 95% CI = 1.156 to 2.088, P =0.003), functional status (function) (HR =0.272, 95% CI = 0.128 to 0.580, P =0.001), and grade (G2) disease (HR = 1.534, 95% CI = 1.126 to 2.091, P =0.007) were found to be significantly associated with survival (Table 2). In the multivariate analysis, different TNM staging classification (AJCC 7th system, ENETS system, mENETS system and AJCC 8th system, respectively), and age ≥60 years were identified as independent prognostic factors for overall survival (Table 3).

Discussion

Although the ENETS system is widely used in Europe, and the AJCC system in the United States[15], there is still no widely accepted staging system for pNETs as they are heterogeneous neoplasms with different clinical features, biological behaviors, and prognoses[5]. The current study used a large, multicenter database to validate the newly developed AJCC 8th staging system for well-differentiated pNETs.

The TNM staging system is widely used for solid tumor staging guidelines, including pNETs[16], with the main guidelines currently available being the AJCC 7th and 8th systems, the ENETS system, and the mENETS system. Each of these exhibits both similarities and differences.

Both the AJCC 7th and ENETS systems have been widely used in clinical practice for a long time. The AJCC 7th staging system adopted the staging system of exocrine pancreatic carcinomas for pNETs, T4 was defined as patients with involvement of the celiac axis or superior mesenteric artery (unresectable tumor), which meant that a very low proportion of patients were considered stage III (T4, any N, M0)[17]. Consistent with the literature, our multicenter cohort had a low proportion of stage III disease (1.1%). In addition, the presence of extra-pancreatic spread was difficult to assess pathologically due to the expansive growth pattern common to pNETs[13]. Furthermore, some studies found that the AJCC 7th staging system has a poor ability to differentiate between the prognoses of some subgroups. Rindi et al[18] identified 1072 pNETs patients from eight European cancer centers (1990–2007) and found no significant difference in mortality between stages IIA and IIB (death rate per 100 persons per year = 3.4 vs 3.7, respectively; HR of death = 25.2, 95% CI = 5.9 to 106.9, P = 0.84), and stages IIB and III (death rate per 100 persons per year = 3.4 and 3.4, respectively; HR of death = 25.1, 95% CI = 5.4 to 116.5, P = 1.0). Our study also exhibited similar results, where there was no significant difference across stages IIA, IIB, III, and IV when the reference was defined as the earlier stage (P = 0.052, p = 0.128, P = 0.249, and P = 0.138, respectively).

The ENETS system's ability to predict the prognosis of specific groups of patients was considered to be possibly superior to the AJCC 7th system. However, some studies have suggested that ENETS system cannot appropriately discriminate the prognoses of stage I and stage II patients[9], and predicted some abnormal survival outcomes between stages IIIA and IIIB[10]. Luo et al.[8] investigated the SEER database (N = 2529 patients) and a multicenter database (N = 1143 patients) and confirmed that patients with stage I disease had a similar prognosis to those with stage IIA disease (with stage I as the reference: SEER series, HR = 0.99, P = 0 .955; multicenter series, HR = 1.41, *P* = 0.337) using the ENETS staging system. In addition, the HR of death for patients with stage IIIA disease was even higher than that for patients with stage IIIB disease (with stage I as the reference: SEER series, HR of death = 2.87 vs. 2.77, respectively; multicentric series, HR of death = 4.56 vs. 4.25, respectively). In our study, there were no significant differences in stages IIIA, IIIB, and IV when the reference was defined as the previous stage (*P* = 0.978, *P* = 0.411, and *P* = 0.077, respectively).

Maintaining the ENETS's T, N, and M definitions and adopting the AJCC system's staging definitions, Luo et al.[4] developed the mENETS, which solved the problem of the low proportion of patients of stage III in the AJCC 7th staging system and the poor differentiation between stages I stage II in the ENETS staging system. However, it became clear that the system showed poor ability to distinguish between the prognoses of stages IA and IB. Meanwhile, the prognostic difference between IIB stage III stage was slightly worse than other subgroups. In the present study, there was also no significant difference across stages IIB, III, and IV when the reference was defined as the previous stage (*P* = 0.158, *P* = 0.691 and *P* = 0.139, respectively). Thus, the use of complex staging methods may not have much added value when considering diagnoses in the clinical setting.

In 2017, the AJCC 8th staging system, which followed the ENETS's definition of T and simplified the original staging criteria, was introduced by the AJCC specifically for well-differentiated pNETs. The AJCC 8th staging system was no longer suitable for poorly differentiated neuroendocrine carcinoma (G3), which have a significantly worse prognosis, and divided all patients into four stages. In fact, some studies have confirmed that there was no significant difference in survival between patients with stage IIIA or IIIB disease according to the ENETS system[13]. Thus, simplifying and merging some subgroups may be acceptable and may be more practical for determining the clinical prognosis of patients with pNETs. In this study, we confirmed that the AJCC 8th staging system succeeded in classifying patients into 4 significantly different staging groups using our multicenter database, and the relative risk for death was closely correlated with advanced stage disease.

Eschewing the TNM staging system, the World Health Organization published their histologic grade (G) classification based on Ki-67 expression and mitotic counts. The classification was principally to be used for prognostic stratification and determining the adjuvant chemotherapy strategy according to the accurate measurement of proliferation[14]. In the present study, patients with G1 disease exhibited a better estimated 5-year survival rate than patients with G2 (87.1% vs. 81.6%), and histologic grade was found to be associated with overall survival in the univariate analysis (G2: HR = 1.534, 95% CI = 1.126 to 2.091, *P* = 0.007). The functional status of pNETs also has a significant effect on the prognosis. Studies have confirmed that functional pNETs have better prognoses than non-functional pNETs[19]. Consistent with the literature, the estimated 5-year survival rate of patients with functional and non-functional pNETs in our study were 95.0% and 82.5%, respectively. Functional status was also identified as significant positive prognostic factor in the univariate analysis (HR = 0.272, 95% CI = 0.128 to 0.580, *P* = 0.001).

Although the AJCC 8th staging system is superior to other TNM staging systems and may bring a unified consensus on TNM staging, it failed to include the histologic grade and functional status, which ultimately lead to its limitations in prognosis prediction. Therefore, a new stage classification combining the TNM staging system and G grade is needed to help guide therapeutic decisions. Furthermore, novel surveillance guidelines need to be developed and trialed.

The major limitation of this study was the retrospective nature of the data analysis. Furthermore, the lack of postoperative course data and postoperative chemotherapy information, among other variables, meant that their significance could not be assessed out. Furthermore, since some patients underwent enucleation, the postoperative lymph node assessment may not be accurate.

Conclusions

The AJCC 8th staging system is more suitable for pNETs compared to the AJCC 7th, the ENETS, and the mENETS staging systems, and may be adopted in clinical practice. Using this novel system, a consensus on the TNM staging classification of pNETs may soon be reached.

Abbreviations

pNETs
pancreatic neuroendocrine tumors
AJCC
American Joint Committee on Cancer
ENETS
European Neuroendocrine Tumor Society
mENETS
modified European Neuroendocrine Tumor Society
HR
hazard ratio

Declarations

Ethics approval and consent to participate

The current study was conducted in accordance with the Declaration of Helsinki principles and was approved by the Ethics Review Board of the Tongji Hospital of Huazhong University of Science and Technology. (Approval number: TJ-JRB20190418).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by grants from The National Natural Science Foundation of China (81772950 to RY Q, 81773160 to MW, 81702792 to SM X, 81502633 to XL, 81602475 to XJ G, 81874205 to FZ); Tongji Hospital Clinical Research Flagship Program (2019CR203) to RY Q; Hubei Natural Science Foundation (2017CFB467), National Key Research and Development Program of China (2019TFC1315905) and Tongji Hospital Science Fund for Distinguished Young Scholars (2017) to MW. The authors declare no relevant conflicts of interest.

Authors' contributions

HBW, JHL, YHL, MW, and RYQ designed the study. JL, HZ, JFZ, CHW, AJ, CW, SWG, QMC, WHZ, WS, FZ, XJG, XL, FP, RZH, SMX, JKJ, AN, BE, YWT, GJ, LZ, and JH collated the data. HBW, DD, TTQ, and MW carried out data analyses and produced the initial draft of the manuscript. HBW, JHL, YHL, MW, and RYQ contributed to drafting the manuscript. All authors have read and approved the final submitted manuscript.

Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

References

1. Hallet J, Law CHL, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2015;121(4):589–97.
2. Yao JC, Eisner MP, Leary C, Dagohoy C, Phan A, Rashid A, et al. Population-based study of islet cell carcinoma. Ann Surg Oncol. 2007;14(12):3492–500.

3. Fitzgerald TL, Hickner ZJ, Schmitz M, Kort EJ. Changing incidence of pancreatic neoplasms: a 16-year review of statewide tumor registry. Pancreas. 2008;37(2):134–8.
4. Keutgen XM, Nilubol N, Kebebew E. Malignant-functioning neuroendocrine tumors of the pancreas: A survival analysis. Surgery. 2016;159(5):1382–9.
5. 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(4):558–63.
6. Rindi G, Klöppel 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(4):395–401.
7. 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(2):204–12.
8. 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;35(3):274–80.
9. 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(23):7798–803.
10. 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(6):824–33.
11. 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(10):764–77.
12. Yang M, Zhang Y, Zeng L, Ke N-W, Tan C-L, Tian B-l, et al. Prognostic Validity of the American Joint Committee on Cancer Eighth Edition TNM Staging System for Surgically Treated and Well-Differentiated Pancreatic Neuroendocrine Tumors: A Comprehensive Analysis of 254 Consecutive Patients From a Large Chinese Institution. Pancreas. 2019;48(5):613–21.
13. You Y, Jang JY, Kim SC, Yoon YS, Park JS, Cho CK, et al. Validation of the 8th AJCC Cancer Staging System for Pancreas Neuroendocrine Tumors Using Korean Nationwide Surgery Database. Cancer Res Treat. 2019;51(4):1639–52.
14. Choe J, Kim KW, Kim HJ, Kim DW, Kim KP, Hong SM, et al. What Is New in the 2017 World Health Organization Classification and 8th American Joint Committee on Cancer Staging System for Pancreatic Neuroendocrine Neoplasms? Korean J Radiol. 2019;20(1):5–17.
15. Klöppel G, Rindi G, Perren A, Komminoth P, Klimstra DS. The ENETS and AJCC/UICC TNM classifications of the neuroendocrine tumors of the gastrointestinal tract and the pancreas: a statement. Virchows Arch. 2010;456(6):595–7.
16. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93–9.
17. Kamarajah SK, Burns WR, Frankel TL, Cho CS, Nathan H. Validation of the American Joint Commission on Cancer (AJCC) 8th Edition Staging System for Patients with Pancreatic Adenocarcinoma: A Surveillance, Epidemiology and End Results (SEER) Analysis. Ann Surg Oncol. 2017;24(7):2023–30.
18. 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(10):764–77.
19. Ishida H, Lam AK-Y. Pancreatic neuroendocrine neoplasms: The latest surgical and medical treatment strategies based on the current World Health Organization classification. Crit Rev Oncol Hematol. 2020;145:102835.

Tables

Table 1. Staging definition of the various staging systems for pancreatic neuroendocrine tumor.

	AJCC 7th stage system			ENETS, mENETS and AJCC 8th stage system			
T1	Limited to the pancreas, Z ≤ 2 cm in greatest dimension			Tumor limited to the pancreas, < 2 cm			
T2	Limited to the pancreas, > 2 cm in greatest dimension			Tumor limited to the pancreas, 2–4 cm			
T3	Beyond the pancreas but without involvement of the superior mesenteric artery			Tumor limited to the pancreas, > 4 cm, or invading the duodenum or common bile duct			
T4	Involvement of the celiac axis or superior mesenteric artery (unresectable tumor)			Tumor invades adjacent organs (stomach, spleen. colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery)			
N0	No regional lymph node metastasis						
N1	Regional lymph node metastasis						
M0	No distant metastasis						
M1	Distant metastasis (M1a§: metastasis confined to liver; M1b§: metastasis in at least one extrahepatic site; M1c§: both hepatic and extrahepatic metastases)						
AJCC 7th and mENETS stages				ENETS and AJCC 8th stages			
Stage	T	N	M	Stage	T	N	M
IA	T1	N0	M0	I	T1	N0	M0
IB	T2	N0	M0	II(A) ¶	T2	N0	M0
IIA	T3	N0	M0	II(B) ¶	T3	N0	M0
IIB	T1-3	N1	M0	III(A) ¶	T4	N0	M0
III	T4	Any N	M0	III(B) ¶	Any T	N1	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

AJCC, American Joint Committee on Cancer; ENETS, European Neuroendocrine Tumors Society; mENETS, modified ENETS; T, primary tumor; N, lymph nodes; M, distant metastasis. § M1a, M1b and M1c are only used in the AJCC 8th stage system. ¶ Stage II (A/B) and III (A/B) are only used in the ENETS system.

Table 2. Baseline clinicopathologic characteristics and univariate analysis of prognostic factors for overall survival.

	Multicenter database (n = 1086)		Univariate analysis			
	No.	%	HR	95% CI	P value	
Sex						
Male	547	50.4	1			
Female	539	49.6	0.802	0.600-1.072	0.136	
Age, years						
< 60	726	66.9	1			
≥ 60	360	33.1	1.554	1.156–2.088	0.003	
Tumor location					0.079	
Head/uncinate	450	41.4	1			
Body/tail	611	56.3	0.732	0.547–0.979	0.035	
Other	25	2.3	0.539	0.170–1.713	0.295	
Functional status						
Nonfunctional	978	90.1	1			
functional	108	9.9	0.272	0.128–0.580	0.001	
Operation					0.054	
Pancreaticoduodenectomy	398	36.6	1			
Distal pancreatectomy	531	48.9	0.710	0.523–0.965	0.029	
Enucleation	153	14.1	0.574	0.354–0.932	0.025	
Others	4	0.4	0	0	0.944	
Type of operation						
Open	872	80.3	1			
Laparoscopic	214	19.7	1.121	0.772–1.629	0.548	
Grade						
G1	483	44.5	1			
G2	603	55.5	1.534	1.126–2.091	0.007	
AJCC 7th T category					< 0.001	
T1	335	30.8	1			
T2	433	39.9	3.524	1.956–6.347	< 0.001	
T3	305	28.1	5.634	3.147–10.086	< 0.001	0.002§
T4	13	1.2	2.772	0.325–12.297	0.180	0.321§
ENETS& AJCC 8th T category					< 0.001	
T1	315	29.0	1			
T2	410	37.8	3.261	1.764–6.029	< 0.001	
T3	256	23.6	5.618	3.066–10.296	< 0.001	0.001§
T4	105	9.7	6.365	3.030-13.371	< 0.001	0.645§

	Multicenter database (n = 1086)		Univariate analysis			
N category						
N0	838	77.2	1			
N1	248	22.8	2.418	1.809–3.231	< 0.001	
M category						
M0	973	89.6	1			
M1	113	10.4	2.621	1.880–3.654	< 0.001	
AJCC 7th stage group					< 0.001	
IA	294	27.1	1			
IB	306	28.2	2.984	1.493–5.964	0.002	
IIA	180	16.6	4.729	2.323–9.625	< 0.001	0.052§
IIB	181	16.7	6.644	3.379–13.063	< 0.001	0.128§
III	12	1.1	2.076	0.265–16.232	0.486	0.249§
IV	113	10.4	9.315	4.697–17.471	< 0.001	0.138§
ENETS stage group					< 0.001	
I	279	25.7	1			
IIA	310	28.5	2.597	1.293–5.219	0.007	
IIB	128	11.8	4.376	2.130–8.990	< 0.001	0.035§
IIIA	69	6.4	4.322	1.563–11.948	0.005	0.978§
IIIB	187	17.2	6.178	3.145–12.136	< 0.001	0.411§
IV	113	10.4	8.778	4.426–17.410	< 0.001	0.077§
mENETS stage group					< 0.001	
IA	279	25.7	1			
IB	310	28.5	2.594	1.291–5.213	0.007	
IIA	128	11.8	4.371	2.127–8.979	< 0.001	0.035§
IIB	162	14.9	6.078	3.077–12.044	< 0.001	0.158§
III	94	8.7	5.314	2.248–12.563	< 0.001	0.691§
IV	113	10.4	8.771	4.422–17.396	< 0.001	0.139§
AJCC 8th stage group					< 0.001	
I	279	25.7	1			
II	438	40.3	3.145	1.617–6.119	< 0.001	
III	256	23.6	5.925	3.033–11.573	< 0.001	< 0.001§
IV	113	10.4	8.762	4.417–17.379	< 0.001	0.044§

AJCC, American Joint Committee on Cancer; ENETS, European Neuroendocrine Tumors Society; mENETS, modified ENETS; T, primary tumor; N, lymph nodes; M, distant metastasis; CI, confidence interval; HR, hazard ratio. § p-values with the earlier stage as the reference.

Table 3. Multivariate analysis of prognostic factors for overall survival.

	AJCC 7th system multivariable analysis			ENETS system multivariable analysis			mENETS system multivariable analysis			AJCC 8th system multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Sex												
Male	1			1			1			1		
Female	0.836	0.321–1.125	0.237	0.839	0.326–1.129	0.246	0.833	0.619–1.122	0.229	0.808	0.602–1.084	0.154
Age, years												
< 60	1			1			1			1		
≥ 60	1.493	1.107–2.014	0.009	1.500	1.112–2.024	0.008	1.498	1.111–2.022	0.008	1.506	1.117–2.032	0.007
Tumor location												
Head/uncinate	1			1			1			1		
Body/tail	0.841	0.625–1.132	0.254	0.830	0.616–1.118	0.220	0.818	0.606–1.103	0.187	0.811	0.604–1.090	0.165
Other	0.558	0.169–1.844	0.338	0.565	0.171–1.868	0.349	0.560	0.169–1.855	0.343	0.645	0.199–2.093	0.465
Functional status												
Nonfunctional	1			1			1			1		
Functional	0.510	0.235–1.106	0.088	0.504	0.233–1.092	0.082	0.498	0.230–1.079	0.077	0.494	0.228–1.070	0.074
Type of operation												
Open	1			1			1			1		
Laparoscopic	0.957	0.655–1.399	0.820	0.955	0.654–1.395	0.813	0.953	0.653–1.393	0.805	0.969	0.663–1.414	0.869
Grade												
G1	1			1			1			1		
G2	1.283	0.934–1.761	0.124	1.288	0.937–1.770	0.119	1.281	0.932–1.761	0.127	1.322	0.965–1.812	0.083
AJCC 7th stage group												
IA	1											
IB	2.744	1.367–5.511	0.005									
IIA	4.060	1.975–8.346	< 0.001									
IIB	5.248	2.639–10.434	< 0.001									
III	2.051	0.261–16.097	0.495									
IV	7.675	3.820-15.417	< 0.001									

	AJCC 7th system multivariable analysis	ENETS system multivariable analysis			mENETS system multivariable analysis			AJCC 8th system multivariable analysis		
ENETS stage group										
I		1								
IIA		2.412	1.196–4.866	0.014						
IIB		3.696	1.777–7.685	< 0.001						
IIIA		3.906	1.401–10.892	0.009						
IIIB		4.912	2.475–9.750	< 0.001						
IV		7.223	3.595–14.512	< 0.001						
mENETS stage group										
IA					1					
IB					2.408	1.193–4.858	0.014			
IIA					3.685	1.772–7.662	< 0.001			
IIB					4.749	2.378–9.482	< 0.001			
III					4.885	2.049–11.649	< 0.001			
IV					7.208	3.588–14.482	< 0.001			
AJCC 8th stage group										
I								1		
II								2.817	1.441–5.507	0.002
III								4.757	2.415–9.369	< 0.001
IV								7.135	3.553–14.328	< 0.001

AJCC, American Joint Committee on Cancer; ENETS, European Neuroendocrine Tumors Society; mENETS, modified ENETS; T, primary tumor; N, lymph nodes; M, distant metastasis.

Figures

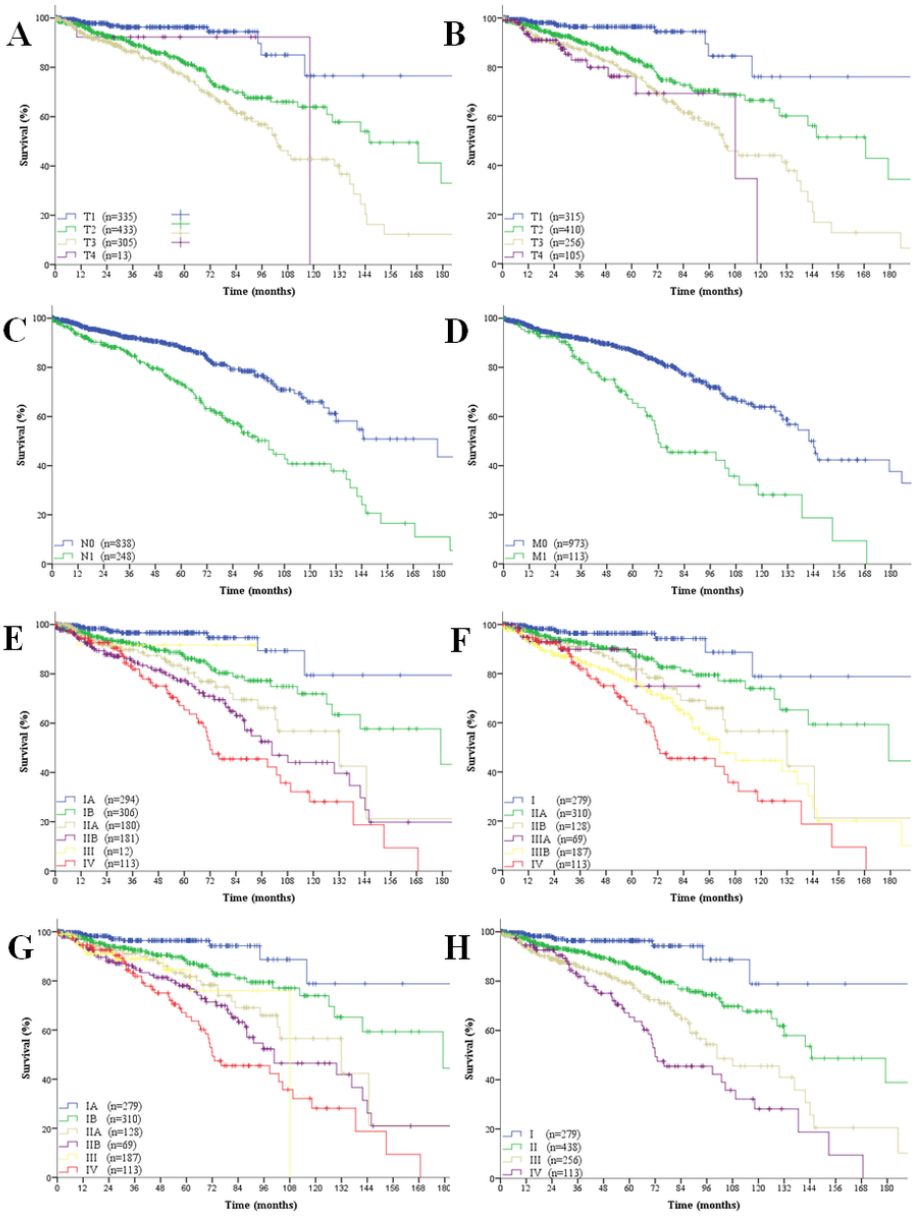

Figure 1

Kaplan-Meier analysis of overall survival. (A) T category of the American Joint Committee on Cancer (AJCC) 7th edition, (B) T category of the European Neuroendocrine Tumor Society (ENETS) and AJCC 8th edition, (C) N category, (D) M category, (E) 7th AJCC stage group, (F) ENETS stage group, (G) modified ENETS (mENETS) stage group, (H) 8th AJCC stage group.