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Revised nodal stage for pancreatic neuroendocrine tumors

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ABSTRACT

Background: Previously we have proposed a modified European Neuroendocrine Tumor Society (mENETS) staging system for pNETs, which is more suitable than either the American Joint Committee on Cancer (AJCC) or the European Neuroendocrine Tumor Society (ENETS) systems. However, it is necessary to revise the nodal stage of the mENETS system for the under representation of stage III diseases.
Methods: Nodal substages of the upper gastrointestinal organs (N0: 0 node, N1: 1–2 nodes; N2: ≥3 nodes) or the lower gastrointestinal organs (0: 0 node, N1: 1–3 nodes, and N2:≥ 4 nodes) were incorporated into the mENETS system and evaluated using the Surveillance, Epidemiology, and End Results (SEER) registry series.
Results: The mENETS classification with the upper gastrointestinal N-stage revision (stage III, 17.1%) had better proportional distribution than the mENETS classification (stage III, 8.7%) or the lower gastrointestinal N-stage revision (stage III, 14.5%). N-stage revision (N0: 0 node, N1: 1–2 nodes; N2: ≥3 nodes) was incorporated in the mENETS staging definition for further analysis. Survival curves were well separated by nodal substages. HRs of stage IIA (T3N0M0) and IIB (T1-3N1M0) of the mENETS classification with N-stage revision were similar, indicating these two substages should be attributed to stage II. Survival curves were well separated by stage using the mENETS classification with N-stage revision.
Conclusions: The mENETS classification with N-stage revision (N0: 0 node, N1: 1–2 nodes; N2: ≥3 nodes) had better prognostic value and proportional distribution than the mENETS classification for pNETs and can be used in clinical practice.

Introduction

Pancreatic neuroendocrine tumor (pNET) is a rare malignant neoplasm of pancreas with increasing incidence in recent years [1–5]. It is a highly heterogenous tumor with strikingly different outcomes (indolent and dismal) and can be categorized into different subgroups by hormonal excess syndromes (functional and non-functional), proliferative markers (grade 1, 2, and 3), and differentiation (neuroendocrine tumor and carcinoma) [1,2]. Therefore, a powerful staging system is urgently needed for pNETs to predict prognosis and aid clinical management [6].

The ENETS and the AJCC staging systems has been used to manage pNETs [2,7–11]. However, for the ENETS staging classification, the HR of death for patients with stage I tumor was similar to patients with stage IIA disease and the HR for patients with stage IIIB tumor was even lower than that for patients with stage IIIA disease [6]. For the AJCC staging system, stage III diseases are extremely under represented [6,12]. These findings indicate that both the ENETS and the AJCC staging classifications are not ideal systems for pNETs [6]. We have proposed a modified ENETS (mENETS) staging classification by maintaining the ENETS T, N, and M definitions and adopting the AJCC staging definitions, which is

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more suitable for pNETs than either the AJCC or ENETS systems. However, although the degree of lymph node invasion is confirmed to be a prognostic factor for patients with pNETs [13,14], nodal status was only divided into negative (N0) and positive (N1) across all staging systems [6]. In addition, the proportion of stage III diseases in the mENETS system was still under represented [6]. Therefore, it is necessary to incorporate substages of lymph node status into the mENETS system.

The current study was performed to determine an ideal nodal substage for pNETs using the SEER series. The application of the mENETS system with nodal staging revision was evaluated.

Methods

Patients

Pathologically confirmed pNET cases were retrieved from the SEER database (from 1973 to 2012). Patients were collected on the basis of International Classification of Diseases for Oncology, 2nd and 3rd editions (ICD-O-2/3) for tumors of the pancreas: C25.0 to C25.9. The following ICD-0-3 diagnosis codes were used for retrieving: carcinoid tumor (8240), neuroendocrine carcinoid (8246), islet-cell adenocarcinoma (8150), malignant beta-cell tumor (8151), malignant alpha-cell tumor (8152), G-cell tumor (8153), VIPoma (8155), malignant somatostatinoma (8156), malignant enteroglucagonoma (8157), argentaffin carcinoid tumor (8241), enterochromaffin cell tumor (8242), mucocarcinoid tumor (8243), and atypical carcinoid tumor (8249). TNM data were collected on the basis of the following codes: derived the American Joint Committee on Cancer (AJCC) stage group 6th ed (2004+), derived AJCC stage group 7th ed (2010+), derived SS1977 (2004+), collaborative stage (cs) tumor size 2004, cs extension 2004, cs lymph nodes 2004, cs mets at dx2004, Regional nodes positive (1988+), and Regional nodes examined (1988+). Patients were included only if they had complete information to allow restaging per the mENETS classifications and the revised N-stage. Baseline clinicopathologic characteristics including age, gender, operation, location of the primary tumor, functional status, and grade were retrieved. The study protocol was authorized by the local institutional review board.

N-stage revision

Previously we have proposed a mENETS staging classification by maintaining the ENETS T, N, and M definitions and adopting the AJCC staging definitions (Table 1) [6]. In the study, node stage was substaged by the definition for the upper gastrointestinal organs (N0:0 node, N1: 1–2 nodes, and N2: ≥3 nodes) or the definition for the lower gastrointestinal organs and pancreatic adenocarcinoma (N0:0 node, N1: 1–3 nodes, and N2: ≥4 nodes) [12,15]. N2 substage (TxN2M0) was included in stage III. Outcome separation and stage distribution were used to select a better N-stage protocol from protocols of upper and lower gastrointestinal organs.

Statistical analyses

Survival period was determined from date of initial diagnosis until date of death or last contact. Overall survival (OS) analyses were examined using Kaplan-Meier curves. Multivariate analysis of mENETS staging classification or the mENETS classification with N-stage revision controlling for age, gender, differentiation, tumor location, and functioning was analyzed using Cox proportional hazards regression. HRs and 95% CIs were calculated. Model comparisons were on the basis of the Harrell C statistic. Statistical analysis was performed using STATA 12.0 software (STATA, College Station, TX). A 2-sided $p < 0.05$ was defined as statistical significance.

Table 1
The modified European Neuroendocrine Tumors Society (mENETS) staging definitions and mENETS with the upper gastrointestinal N-stage revision for pancreatic neuroendocrine tumors with cross-tabulation of stage distributions.

mENETS		mENETS with N-stage revision	
T1	Tumor limited to the pancreas,< 2 cm	T1	Tumor limited to the pancreas,< 2 cm
T2	Tumor limited to the pancreas, 2–4 cm	T2	Tumor limited to the pancreas, 2–4 cm
T3	Tumor limited to the pancreas, > 4 cm, or invading duodenum or common bile duct	T3	Tumor limited to the pancreas, > 4 cm, or invading duodenum or common bile duct
T4	Tumor invades adjacent structures	T4	Tumor invades adjacent structures
N0	No regional lymph node metastasis	N0	No regional lymph node metastasis
N1	Regional lymph node metastasis	N1	Metastasis in 1–2 regional lymph nodes
		N2	Metastasis in ≥3 regional lymph nodes
M0	No distant metastasis	M0	No distant metastasis
M1	Distant metastasis	M1	Distant metastasis

mENETS				mENETS with N-stage revision			
Stage	T	N	M	Stage	T	N	M
IA	T1	N0	M0	IA	T1	N0	M0
IB	T2	N0	M0	IB	T2	N0	M0
IIA	T3	N0	M0	IIA	T3	N0	M0
IIB	T1-3	N1	M0	IIB	T1-3	N1	M0
III	T4	Any N	M0	III	Any T	N2	M0
					T4	Any N	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

Edition		mENETS with N-stage revision					
		IA	IB	IIA	IIB	III	IV
mENETS	IA	421	0	0	0	0	0
	IB	0	388	0	0	0	0
	IIA	0	0	406	0	0	0
	IIB	0	0	0	285	210	0
	III	0	0	0	0	217	0
	IV	0	0	0	0	0	573

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