Editorial

Progress in TNM staging of pancreatic neuroendocrine tumors

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In recent years, staging classifications for well-differentiated pancreatic neuroendocrine tumors (NETs) have evolved significantly (1-3). Historical classifications, which attempted to combine clinical, pathological, and radiographic findings, were found to be overly complex. It was not until 2006 that Rindi *et al.* proposed a standard four-stage TNM classification, which was subsequently endorsed by the European Neuroendocrine Tumor Society (ENETS) (4). The T stage distinguished between tumors smaller than 2 cm (T1), 2–4 cm (T2), >4 cm or invading duodenum/bile ducts (T3), and invading adjacent structures (T4). N and M stages were defined simply by the presence or absence of regional lymph nodes and distant metastases (*Figure 1A*). The American Joint Committee on Cancer (AJCC) seventh edition adopted a different TNM classification in 2010, derived from the staging for pancreatic adenocarcinoma. In this classification, T1 referred to a tumor <2 cm, T2 referred to a tumor >2 cm, T3 referred to disease extending beyond the pancreas, and T4 referred to the invasion of the celiac axis or SMA (unresectable). As in the ENETS classification, N and M stage were defined simply by the presence or absence of metastases (*Figure 1B*).

Although both staging classifications were prognostic in aggregate, there were manifest problems in their ability to provide adequate prognostic stratification (5). These inadequacies were identified in a 2016 analysis of the Surveillance, Epidemiology, and End-Results (SEER) database and a multicentric analysis of Chinese and US institutions in which prognostic overlap was found between ENETS stages I and II and also between AJCC stages III and IV (3). Moreover, the percentage of patients with AJCC stage III (locally advanced, unresectable) was only 2.2%, reflecting the relative rarity of this presentation in pancreatic NETs. This analysis proposed a relatively simple modification: adoption of the ENETS T-definitions but the use of the AJCC stage groupings. This change resulted in a more robust prognostic classification than either the ENETS or the AJCC staging systems. Unfortunately, this proposal was not published in time for the AJCC eighth edition [2018], which adopted the ENETS classification without modification.

With this background in mind, the new modified eighth AJCC staging classification proposed by Zhang *et al.* published in the *Annals of Surgery*, offers an even more accurate prognostic staging classification (*Figure 2*) (6). It retains the ENETS/AJCC T-definitions but adjusts stages: for example, stage IIA (T2N0) becomes stage IB. More importantly, the new modified staging recommendation adds a new N2 category, defined as the involvement of ≥4 locoregional lymph nodes. The new proposal was tested on data from the SEER registry and validated in a multi-institutional database: the US Neuroendocrine Tumor Study Group (US-NETSG), which analyzed 825 patients who underwent curative-intent resection for grade 1 and 2 pancreatic NETs between the years 2000 and 2016. In both the SEER and US-NETSG databases, the new TNM classification resulted in a statistically significant separation of 5-year overall survival outcomes between each stage ($P<0.001$ and $P<0.05$ for all stage comparisons within the SEER and US-NETSG respectively).

One might inquire about the significance of this research: why is an accurate staging system important for pancreatic NETs? One answer is that understanding how stage correlates with risk of post-surgical recurrence

A

T1 Tumor limited to the pancreas, <2cm
T2 Tumor limited to the pancreas 2-4 cm
T3 Tumor limited to the pancreas size >4 cm or invading duodenum or bile duct.
T4 Tumor invading adjacent organs or the wall of large vessels

N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M0 No distant metastasis
M1 Distant metastasis

Stage	T	N	M
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Any T	N1	M0
IV	Any T	Any N	M1

B

T1 Tumor limited to the pancreas, <2cm
T2 Tumor limited to the pancreas >2cm
T3 Tumor extends beyond the pancreas but no involvement of the celiac axis or SMA
T4 Tumor involves the celiac axis or the SMA (unresectable)

N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M0 No distant metastasis
M1 Distant metastasis

Stage	T	N	M
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

Figure 1 ENETS (A) and AJCC 7th Edition (B) TNM staging of pancreatic NETs. ENETS, European Neuroendocrine Tumor Society; NETs, neuroendocrine tumors.

T1 Tumor limited to the pancreas, <2cm
T2 Tumor limited to the pancreas 2-4 cm
T3 Tumor limited to the pancreas size >4 cm or invading duodenum or bile duct.
T4 Tumor invading adjacent organs or the wall of large vessels

N0 No regional lymph node metastasis
N1 1-3 regional lymph node metastases
N2 ≥ 4 regional lymph node metastases

M0 No distant metastasis
M1 Distant metastasis

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

Figure 2 Proposed TNM classification for pancreatic NETs (6). NETs, neuroendocrine tumors.

and overall survival is critical as we consider the potential role of adjuvant therapy. To target adjuvant therapy to the appropriate population of patients, we need robust information on recurrence risk (already addressed by the US-NETSG and other investigators) and stage-based survival (7). Tumor grade, based on the ki-67 proliferative index and mitotic rate, is another important prognostic factor, also analyzed extensively by the US-NETSG and other groups.

In the future, molecular determinants of prognosis will undoubtedly gain in importance. One of these is a mutation in DAXX, an oncogenic driver mutation in pancreatic NETs, which seems to predict malignant behavior among patients with small, localized tumors (8). Circulating molecular

markers will also contribute to risk stratification (9). Determination of which small (<2 cm), low-grade, asymptomatic tumors can be monitored safely (as opposed to resected) is a key challenge facing physicians who treat NETs (10).

In summary, Zhang and colleagues who participated in the design and validation of a new modified TNM staging system for pancreatic NETs have made significant progress in developing a new classification that stratifies survival between each stage in a statistically significant fashion. The ninth AJCC staging committee should adopt this robust yet straightforward staging classification.

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