



Looking for the right TNM staging system for pancreatic neuroendocrine tumors

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Pancreatic neuroendocrine tumors (panNETs) represent a rare subgroup of neuroendocrine neoplasms (NENs) which showed an impressive increase of incidence over the last decade (1). As over the same period particularly low stage and low grade NETs had the highest increase it is plausible that small (e.g., ≤ 2 cm) panNETs incidentally detected may have had a major role thanks to the progress of imaging.

Pancreatic NENs are classified according to the grade of differentiation and proliferation index, into four categories including panNETs G1 [well differentiated (WD) with $< 3\%$ Ki-67], panNETs G2 (WD with 3–20% Ki-67), panNETs G3 (WD with $> 20\%$ Ki-67) and pancreatic neuroendocrine carcinomas (panNECs) [poorly differentiated (PD) with $> 20\%$ Ki-67] in accordance with the 2017 WHO classification (2).

For localized and locally advanced panNETs curative treatment typically consist of radical surgery of the primary tumors +/- regional nodes. Over the last 15 years several TNM staging systems were developed, including ENETS TNM 2006 and 2007, and UICC/AJCC 7th and 8th editions (3–6).

A particular criticism of AJCC TNM 7th ed. was that the stage III, defined as tumoral involvement of the celiac axis or the superior mesenteric artery (unresectable tumor) without distant metastasis, was very limited ($< 5\%$ of cases) (7), unlike pancreatic adenocarcinoma (PDAC).

ENETS TNM staging system for panNENs was reported as superior to the UICC/AJCC/WHO 2010 TNM 7th edition by Guido Rindi and co-authors (7). The

former system “perfectly allocated patients (n=1,072) in four risk groups” that showed significant differences as for survival and were equally populated, whereas the latter distinguished three groups differently populated, with most patients in stage I and a clear overlapping for stage II and III. ENETS staging system resulted more accurate than the UICC/AJCC one. However, some shortcomings of ENETS TNM were reported, including a similar prognosis between stage I and IIA and a better survival for stage IIIB than IIIA. On this basis a “modified ENETS” staging system for panNETs was proposed (8).

In 2017 AJCC updated its TNM staging system by publishing its 8th edition, that reported two separated staging systems for panNENs, one for WD panNETs (G1, G2, G3), on the basis of the ENETS 2006 TNM, and the other for PD panNECs (G3), that is the same than the PDAC staging system. For panNETs, the main changes included: (I) a size upper limit of 4 cm for the T2; (II) a specific definition of the T3, changing from a general “beyond the pancreas” to > 4 cm or invading only duodenum or common bile duct; (III) all the other adjacent structures were in the T4 together with celiac axis or the mesenteric superior artery infiltration; (IV) in addition to the T4 any-N M0, also any-T N1 M0 were classified as stage III. A main difference between PDAC/panNECs and panNETs 8th edition TNM staging system was the N category, as it was based on the number of lymph node metastases (LNM) for PDAC/panNECs, defining N0 (no LNM), N1 (1–3 LNM) and N2 (> 3 LNM), whereas it was based on

presence/absence of LNM for panNETs, defining only N0 (no LNM) versus N1 (≥ 1 LNM).

Although the AJCC TNM 8th edition was validated with large-scale studies (9) other Authors addressed the debatable nodal binary stratification by suggesting that a lymphadenectomy of at least 8 lymph-nodes is necessary to stage patients with panNETs and a trinary rather than binary stratification would be indicated. On this background Dr. Zhang and co-authors proposed a “modified” (m)TNM staging system for panNETs (10). Their study was based on a large series of patients with panNETs resected with curative intent: 825 patients from the multi-institutional database (period 2000–2016) of the US neuroendocrine tumors study group (US-NETSG) and 3,303 patients from the SEER database (period 1975–2016). The authors concluded that “the eighth TNM staging system failed to stratify patients with stage I versus IIA, stage IIB versus IIIA, and overall stage I versus II relative to long-term OS in both database”. By contrast a modified TNM staging system using N0 (no LNM), N1 (1–3 LNM), and N2 (>3 LNM) categories “was better at stratifying patients relative to long-term OS”. In fact, stage IA-B and IIA-B is included only in the ENETS staging system, whereas the AJCC TNM 8th edition reported stage I (T1 N0 M0), stage II (T2–3 N0 M0) and stage III (T4 N0 M0, any-T N1 M0). Therefore, the focus of the study regarded the stage III.

Twenty-six percent and 12% of patients had 1–3 and >3 LNM in the SEER database, respectively and 18% and 8% in the US-NETSG database, respectively. Unfortunately, it is not possible to know how many T1 were associated with N+. This would be important to know as surveillance is often proposed to non-functioning T1 (≥ 2 cm) panNET patients, as reported by the authors in the discussion. While the authors reported a “very good prognosis after surgical resection” for stage IA panNETs, with around 100% 5-year survival rate, no specific survival information was reported for T1 N1 M0 (stage IIB) and T1 N2 M0 (stage III) of the modified 8th AJCC TNM.

With their mTNM, Zhang and co-authors showed that T3 N1 (1–3 LNM) M0 panNET patients had a better survival than T4 N0 M0. However, it is unknown if T1 N1 M0 could have a better survival than T3 N0 M0 or if there is a significant difference between T3 N1 M0 and T4 N0 M0.

Another open question regards the role of the tumor grade. While it seems that “G3 neuroendocrine carcinomas” were excluded from the Zhang’s study, it is not clear if and how many “NET G3” were included. They could have a prognostic major role regardless tumor stage.

Furthermore, relapse free survival (RFS) and the related medical treatment could have impacted OS, so this unknown information would be interesting to know.

In conclusion, we think that Dr. Zhang’s study raised an important issue for panNET staging, that should be considered for future studies together with other poor prognostic factors of radically resected panNETs. Unfortunately, in clinical practice there is no current evidence to use this information for adjuvant therapeutic choice.

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Footnote

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