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Short Report

Refined TNM-staging for pancreatic adenocarcinoma – Real progress or much ado about nothing?

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ABSTRACT

In order to provide optimal cancer care and prognostication, it is necessary to stage the disease. The 8th edition of the TNM-staging for exocrine pancreatic ductal adenocarcinoma (PDAC) system has refined size-based T-stages and number-based N-categories. However, several impediments to the value of this may exist. For one, even at small size (e.g. <0.5 cm), PDACs readily metastasize, making size unreliable to predict behavior. The increasing shift towards neoadjuvant treatments for both resectable and borderline PDAC, and use of conversion therapy for locally advanced disease, suggest the need for additional biological predictors. Here we discuss whether recent changes in the TNM system for PDAC are along the lines of changes seen in contemporary management. Also, with the particular aggressive biology seen in PDAC, it is questioned whether the minute details in TNM refinement represents true progress or merely shuffles the cards.

Introduction

Despite progress achieved in recent years, the survival for pancreatic ductal adenocarcinoma (PDAC) remains poor; with a mere 7–9% true survivors 5 years after diagnosis. Surgical resection remains the only curative approach, with multimodal therapies improving outcomes [1,2]. To accurately predict prognosis and decide appropriate treatment options, it is vital to describe the extent of the disease. Localized tumors have a higher survival rate compared with disseminated disease. In addition, prognostication directs the inclusion of patients in clinical studies and allows comparison of care between institutions and registries. The stratification into the correct prognostic stage group is therefore important. However, with the changes in management and the particular aggressive biology seen in PDAC, it is questioned whether such refinement represents true progress or merely shuffles the cards.

Revisions in the TNM staging system

The tumor, node and metastasis (TNM) staging system is regarded the most useful cancer staging system. There were no changes made in the 6th (2002) and 7th (2009) edition of the AJCC Cancer Staging Manual for PDAC. The 8th edition (October 2016) marked the first major revision of the T- and N-classifications (Table 1) and was made effective for patients diagnosed on or after January 1st, 2018. The 8th edition separated the exocrine from endocrine pancreatic tumors. In the present edition, the smallest tumors of the T1 type (≤2 cm) now subcategorized based on size (Fig. 1). These tumors are 'minimally invasive' and should have better outcomes. Previously staging of T2 (>2 ≤ 4 cm) and T3 (>4 cm) tumors included extra-pancreatic extension. This is difficult to define and, the T-categories are now size-based.

Further, the surgical resectability no longer define T4 tumors. Instead, the categorization includes arterial involvement, which holds an objective measure of the extent of invasion. Additionally, the N-category split into N1 and N2, due to better prognostic stratification based on the number of positive lymph nodes.

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Table 1
Changes in definitions between the 7th and 8th edition of the TNM staging System.

Category	7th edition	8th edition
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension	Tumor ≤2 cm in greatest dimension
T1a	-	Tumor ≤0.5 cm in greatest dimension
T1b	-	Tumor >0.5 cm and <1 in greatest dimension
T1c	-	Tumor 1-2 cm in greatest dimension
T2	Tumor limited to the pancreas >2 cm in greatest dimension	Tumor >2 and ≤4 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of CA or SMA	Tumor >4 cm in greatest dimension
T4	Tumor involves CA or SMA (unresectable primary tumor)	Tumor involves CA, SMA, and/or CHA, regardless of size
N1	Regional lymph node metastasis	Metastasis in 1-3 regional lymph nodes
N2	-	Metastasis in ≥4 regional lymph nodes

CA, denotes celiac axis

SMA, denotes superior mesenteric artery

CHA, denotes common hepatic artery

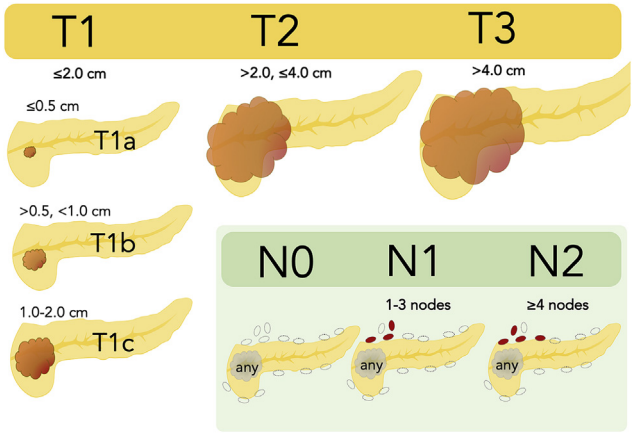

Fig. 1. Illustration of current (AJCC 8th edition) T- and N-stage. Legend: Size-based criteria for T-stages with sub-staging for T1 into T1a, T1b and T1c categories. N-stage is based on numeric differences in metastatic lymph nodes, with 3 nodes as a cut-off.

Concerns about the current staging system

The TNM system is the only universal staging system in use, but it has inherent limitations compared to other solid tumors, likely due to the particular tumor biology of PDAC.

For one, size is unreliable as a prognosticator in PDAC, as the biological behavior even in small is far more unpredictable than in most other solid tumors. Notably, in a large study of almost 59,000 patients from the SEER database, only 0.3% of patients had tumors that were ≤0.5 cm in size [3], e.g. T1a according to TNM 8th edition. Despite the small size, almost one-third (31%) had distant metastasis at time of diagnosis [3]. Clearly, this demonstrates the unreliable value of size as a prognosticator in PDAC and, moreover, point to a systemic disease from the outset. This should be taken into account in future attempts to refine staging.

Notably, 'resectability' is a subjective measure with considerable variations between institutions [4] in what constitutes inoperable or non-resectable (Fig. 2), with different definitions for both borderline and locally advanced PDAC in use. Increasingly, neoadjuvant therapy is used for resectable cancers, while still both resectable and borderline-resectable may go to upfront surgery in some centres. Evaluation of neoadjuvant therapy is unreliable, which becomes a particular issue in borderline/locally advanced cases, for which surgical exploration with multiple frozen sections from tissue surrounding vessels being performed to expand resections. For this particular group of patients, the current staging is less useful, and a biological rather than anatomical definition of resectability is called for [5]. Notably, when comparing pTNM stages, the comparison will become increasingly murky with a wide range of treatments offered across clinical stages (Fig. 2).

Of note, the TNM-staging does not take into account the resection status. Completeness of resection is of prognostic significance but is

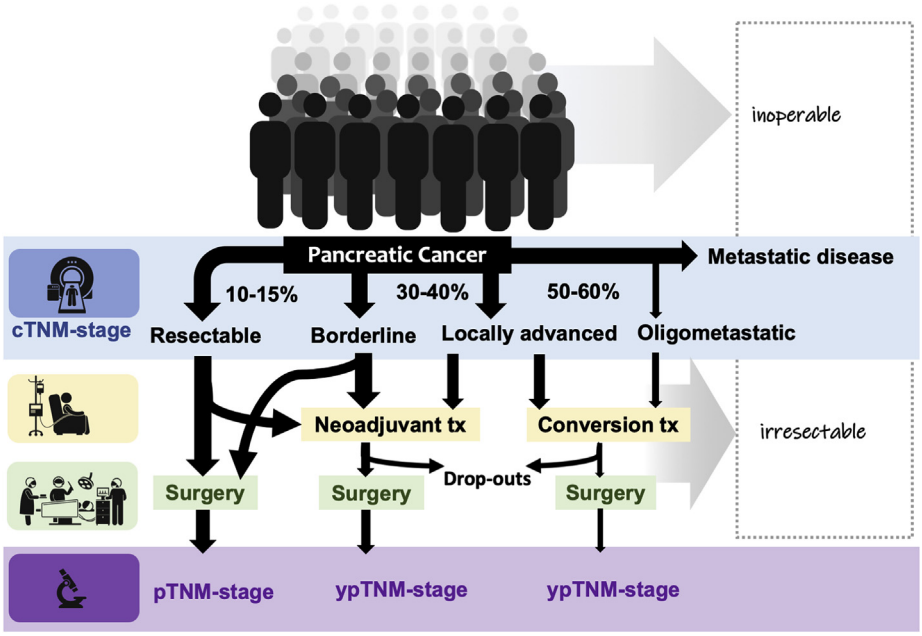

Fig. 2. Depiction of the current treatment landscape of pancreatic cancer. Legend: Any given patient may be deemed inoperable at time of diagnosis or irresectable through clinical (image-based) staging. Definitions for borderline/locally advanced cancers are floating, with variation in management. More effective systemic therapy (e.g. FOLFIRINOX) is increasingly introduced in the pre-operative setting, with more resections offered after therapy, possibly influencing the pathological TNM-staging and interpretation of its prognostic role. Better predictive and prognostic biomarkers of cancer biology are needed.

still a debated topic [6]. There is no universally accepted pathological criteria of the R-status. However, the *International Study Group of Pancreatic Surgery* (ISGPS) endorsed the definition proposed by The British Royal College of Pathologists [7]. In order to classify as R1, tumor cells should be present within 1 mm from all seven designated resection margins. The TNM 8th edition does not include resection status, but considers the margin as positive if the tumor is at or within 1 mm. However, it only takes account of the margin corresponding to the superior mesenteric artery, while the seven margins for tumor clearance in the pathology protocol. The rates of tumor involvement therefore vary significantly in the literature, due to the differing definitions of positive microscopic margins. Meta-analysis of radical resection rates shows ranges in R0-status from 70 to 80% with a 0 mm margin, diminishing to 15–24% with a $\leq$1 mm margin [8]. This in turn affects the associated survival prognostics. Strobel et al. surveyed patients after pancreaticoduodenectomy and adjuvant therapy, and found median and 5-year survival rates independently associated, in descending order, with a margin status of R0, R1 (<1 mm) or R1 (direct) [9]. Others have found that when N+ disease is present, R-status plays a lesser prognostic role [10].

Validation of the 8th edition

The changes in the 8th edition were mainly based on a multi-institutional study from three centres in the United States [11]. Using the Surveillance, Epidemiology and End Results (SEER) database (2004–2013) [12], the 8th edition proved discriminatory abilities similar to that of the 7th edition but allowed for a finer stratification of patients with resected tumors based on nodal involvement. The study revealed similar survival rates for patients staged as IIA (T3N0M0) or IIB (T1-3N1M0) until 20 months, before diverging. This suggests lymphatic spread has a delayed impact on survival. However, based on recurrence patterns investigated in the ESPAC-4 trial [13], there was no survival difference in the pattern of recurrence, as either local recurrence or distant metastasis, in terms of overall survival.

Further validation using data derived from patients with resected pancreatic cancer from Europe and the United States, confirmed that the 8th edition over all provides a moderately increased prognostic accuracy in surgically treated patients, compared with the previous 7th edition [14]. The revised T-stages were poorly associated with survival, especially in node-negative patients. As a group, the node-negative patients pose the greatest challenge in prognostication, yet, the new N stage was prognostic, showing accurate discrimination of survival.

However, reports of conflicting findings exist. Schlitter et al. found that all pT-stages, as defined in the 8th edition, showed greatly improved discriminative powers with significant overall differences in survival [15]. The latter study also found conflicting outcome regarding node status, where the N1 and N2 categories of the 8th edition resulted in no observed prognostic difference. This in contrast to prior findings, where the finer stratification of node-status appears to be prognostically significant [14].

Controversies

Primarily designed to assess the burden of disease, the TNM-system currently fulfills several purposes, such as cancer surveillance, deciding eligibility for clinical trials, and guiding treatment and prognostication. However, it is evident that other factors, including various aspects of tumor biology, molecular pathways and biological mechanisms contribute to prognosis [16,17]. None of these are currently included in the classification. Consequently it is important to recognize the inherent limitations in the TNM-system to predict patient outcomes [18].

After neoadjuvant treatment and subsequent surgical care, the grade/degree of regression (equal to tumor response) can be determined using the *y*pTNM staging (Fig. 1). No single tumor regression grading system has been agreed on, although consensus work is ongoing. In real-life, the clinican will have to rely on re-staging by cross-sectional imaging after completed neoadjuvant treatment. Again, large institutional variation exists in what defines ‘unresectable’ and ‘non-operable’. Also, it is rare to have complete

(<3–4%) and even major response (some 10–15%) on imaging, as most will have stable disease (40–60%) and some progress (20–25%) during treatment [19,20]. As both clinical (image-based) and pathological response is difficult to predict, biochemical response by means of change in CA19-9 is used as a surrogate biomarker that is related to neoadjuvant response and prognosis [21–23].

Current and future biomarkers

Circulating tumor DNA (ctDNA) can be detected already when pancreatic tumors are deemed resectable [24]. Further, a liquid biopsy test detecting ctDNA for KRAS gene mutations, combined with other protein markers, identified nearly two-thirds of pancreatic tumors without evidence of distant metastasis, at the time of surgery [25]. Similar results have been found when studying exosomes [26]. Increasingly sensitive and specific detection tools will conceivably result in non-invasive tests for early stage pancreatic cancer [27].

Currently there is no consensus regarding the number or classification of molecular subtypes based on gene expression data in PDAC, but agreement to at least two subtypes (so-called 'basal-like' and 'classical') have been reached [28]. These two have considerable differences in prognosis, with basal-like having more poorly differentiated tumors and shorter overall survival compared to the classical type [28]. Ongoing investigations into molecular alterations (such as GATA expression) could identify potential predictive biomarkers or help elucidate which tumor types would respond better to either gemcitabine or FOLFIRINOX regimens [28].

Whether such biomarkers will become part of future staging systems for PDAC, in order to incorporate tumor biology and cancer behavior to personalized and guided treatment, remains to be investigated. The need is evident, as resection currently is the only curative approach, and early detection prior to metastasis is paramount for long-term survival.

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Declaration of competing interest

None.

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