Stage Classification and Prognosis Assessment in Localized Pancreatic Cancer: It Takes Two to Tango

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Although the 5-year survival of patients diagnosed with localized pancreatic ductal adenocarcinoma (PDAC) has increased from 32% to 44% over the 2018-2023 period,[1,2] predicting the probability of cure and selecting the optimal therapeutic strategy in individual patients remains extremely difficult. Anatomical disease extent, especially regarding vascular involvement, is mostly perceived as a technical challenge for the surgeon to achieve a R0 resection; similarly, patient's performance status (PS) and comorbidities are perceived as factors altering the risk/benefit ratio of surgical intervention. Other factors, such as duration of symptoms and carbohydrate antigen (CA) 19-9 levels, are usually considered a proxy for risk of occult disease dissemination, potentially nullifying the curative potential of surgery. In the article that accompanies this editorial, Dekker et al[3] set out to validate the prognostic value of anatomy, CA 19-9, and PS (ABC factors)[4,5] in a retrospective data set of 1,835 patients with localized PDAC treated with initial modified fluorouracil with leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX) at five high-volume pancreatic cancer centers in the United States and the Netherlands, between 2012 and 2019. At multivariable Cox proportional hazards analysis, each of the ABC factors demonstrated independent prognostic value in terms of overall survival; when combined in a simplified clinical point score (1 point for each poor ABC factor and 2 points for locally advanced [LA] disease), five different groups of patients with nonmetastatic PDAC with 5-year survival rates ranging from 4.8% to 47% were discriminated. Thus, the authors suggest that staging of patients with localized PDAC at diagnosis should be based on anatomy, CA 19-9, and PS.[3]

The National Cancer Institute's (NCI) Dictionary of Cancer Terms defines staging as the process of performing examinations and tests to learn the extent of the cancer within the body.[6] Disease burden, reflected by cancer stage and codified using the TNM classification,[7,8] is arguably the most important determinant of prognosis in patients with cancer.[9,10] However, cancer staging not only serves to determine prognosis but also to guide patient care, to assist in evaluating treatment results, to enable cancer research and the exchange of information between different centers, and to support global cancer control activities. It has long been recognized that many factors, besides anatomical extent of disease, can contribute to prognosis. Many attempts at including additional prognostic factors in staging classifications have been made, leading to the development of a separate Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging system for human papillomavirus-related oropharyngeal cancer[11] or the inclusion of the levels of serum tumor markers in the prognostic group classification of testicular cancer.[12] More complex prognostic staging systems, incorporating TNM parameters along with additional prognostic clinicopathological factors, have been proposed, for example, for metastatic breast cancer.[13] Although potentially important to facilitate a more accurate determination of prognosis, such attempts may be fraught by the inconsistent use of terms and definitions, resulting in uncertainty and confusion, rather than precision. This may limit the utility of the TNM classification, particularly in geographical regions in which the necessary biomarker tests are unavailable.[7,14]

To address the issues of consistency and universal utility and considering the multifaceted purpose of TNM staging and the interests of multiple stakeholders relying on cancer staging, a Global Consultation on Cancer Staging was held in 2017, under the auspices of the UICC, the US NCI, and the Centers for Disease Control and Prevention.[15,16] A unanimous consensus was reached that anatomical extent of disease should be considered and presented separately from other prognostic factors but could still be combined with other factors in the framework of *prognostic groups*. From a terminology standpoint, agreement was reached on the following

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THE TAKEAWAY

In the article that accompanies this editorial, Dekker et al[3] propose that staging of patients with localized pancreatic ductal adenocarcinoma (PDAC) at diagnosis should be based on anatomy, cancer antigen 19-9, and performance status (ABC factors). The data presented show that, in a population of patients with clinically localized PDAC who underwent primary modified fluorouracil with leucovorin, irinotecan, and oxaliplatin treatment, ABC factors bear independent prognostic value for overall survival, and their combination could be used to predict individual patients' clinical outcomes, discuss treatment options, and define the overall therapeutic strategy.

definitions: the terms *stage* and *anatomical stage group* are applied by UICC and AJCC, respectively, to describe the anatomical extent of disease; the terms *prognostic group* and *prognostic stage group* are applied by UICC and AJCC, respectively, to describe classifications that incorporate prognostic factors in addition to the anatomical extent of disease.[15] According to such terminology, the ABC system would fall in the *prognostic group* or *prognostic stage group* rather than in the *stage* or *anatomical stage group* category.

Pathological pancreatic cancer staging introduced by the 8th TNM edition has been widely validated and recognized as resulting in more balanced distribution among stages, enhanced prognostic discrimination (particularly of lymph node categories), and an overall better balance between simplicity, ease of use, and prognostic ability.[17-21] Clinical TNM staging in localized pancreatic cancer, however, remains an unresolved challenge. Clinical T status on the basis of tumor diameter can be difficult to assess because of poor visibility of some tumors and vague tumor boundaries on cross-sectional imaging. Clinical staging of regional nodes has only modest accuracy: Pathologically positive nodes are missed by imaging in more than half of the cases,[22] and EUS-guided biopsy of suspicious lymph nodes is rarely performed because of the little influence nodal status has on therapeutic decision making. As a result, the discriminatory value of both the seventh and eighth clinical TNM staging system for overall and pancreatic cancer–specific survival is very limited for stages IB-III.[22,23] In that respect, validation of the commonly used, surgically oriented, anatomical classification in the three subcategories of resectable, borderline resectable, and LA, on the basis of the extent of vascular involvement,[4,24] is a welcome addition to our knowledge and bears important value for the multidisciplinary evaluation of patients with nonmetastatic PDAC. The addition of disease-related (CA 19-9 serum levels) and patient-related (PS according to WHO) factors may certainly help gauge individual patients' disease trajectory and long-term outcome, as the authors demonstrate. However, the interpretation and generalizability of the results of composite classifications of this type is typically hampered by the inherent potential for confusion regarding the relative relevance of individual prognostic elements. A first element of potential confusion, partially compensated for by the sensitivity analysis presented in the TAPS consortium series, is the possible relationship of additional prognostic factors (eg, CA 19-9 levels or WHO PS) with anatomical extent of disease or their dependence on other potentially confounding factors (eg, genetically determined inability to produce CA 19-9 or its spurious elevation in jaundiced patients). Second, hybrid classifications (or, in general, prognostic nomograms) may not be generalizable across the full spectrum of disease and may only apply to selected anatomy and time-dependent scenarios.[25-28] This is clearly the case for the analysis presented in Dekker et al,[3] which was conducted, by design, only in patients with localized disease who had been deemed fit enough to receive a rather challenging therapeutic regimen (mFOLFIRINOX); indeed, the age of the population studied was younger than 70 years, and WHO PS 2-3 patients were a tiny minority (4%), not reflecting the entire spectrum of potential patients with newly diagnosed PDAC. In that respect, the generalizability of their findings remains restricted to a relatively narrow population of patients with localized pancreatic cancer, for whom a decision to administer primary mFOLFIRINOX has already been made, independent of the ABC factors.

Assessing prognosis in heterogeneous patient populations (eg, combining cases with primary and recurrent, recurrent and metastatic, or resectable and unresectable disease) is another major cause of incorrect use of terminology and inconsistency in result reporting. In the experience presented by the TAPS consortium, a mixed population of resectable and unresectable patients was considered; LA disease, for which surgical resection is seldom considered an option (limited to fit patients responding to induction chemotherapy) by current guidelines,[24,29] accounted for 52% of the overall population and was progressively more represented from 0% in prognostic groups 0 and 1 to 37% in group 2, 85% in group 3, and 100% in group 4; as expected, the proportion of patients who received surgery decreased from 84% to 67%, 44%, 17%, and 13% across prognostic groups 0 to 4, respectively. This raises the question of the potentially confounding prognostic effects of treatment. While it must be acknowledged that neither UICC nor AJCC recommend taking treatment response or subsequent treatment into account in multivariate analysis when defining clinical stage groupings,[7,14] the influence of

potentially curative treatment (such as surgery) in modifying disease trajectories and prognosis cannot be denied and plays a fundamental role when discussing available treatment options with patients and caregivers.[30] In this context, rather than being used as an additional prognostic factor for patients with newly diagnosed PDAC, including the impact of surgery in the multivariate prognostic model could have helped sort out whether ABC factors are prognostic per se (ie, informative of the likely outcome of cancer, independent of treatment) or predictive of the probability of undergoing curative surgery. Indeed, considering the reciprocal relationships between anatomical extent of disease (stage, A factor) and radical surgery, for example by formally testing the interaction between such terms and exploring the stage by treatment interaction term for prognostic discrimination, would be of great help to define the role that should be given to individual ABC factors, when discussing prognosis, on one hand, and treatment choices, on the other.

Overall, the data presented by Dekker et al[3] importantly add to our knowledge; however, keeping anatomical staging separate from the prognostic refinement achievable with the additional use of CA 19-9 and WHO PS would probably render the ABC factors more useful to define the therapeutic path and discuss its potential impact in individual patients. Understanding of which population of patients with pancreatic cancer this approach would best be applied, particularly since emerging data are challenging FOLFIRINOX as a universal standard for neoadjuvant treatment of localized PDAC,[31] would require further analysis of the data and extensive external validation, across the entire disease spectrum.

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