Editorial Commentary

Improving patient stratification and selection for curative-intent treatment in localized pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) is a devastating malignancy, owing in part to the fact that most patients present with advanced disease with only 20% eligible for surgical resection. Moreover, the dismal oncologic outcomes achieved with surgery alone, coupled with the almost ubiquitous distant recurrence in operable PDAC patients, have mandated a multimodal approach for this disease. The advent of effective combination chemotherapy regimens delivered increasingly in the perioperative setting, safety and technical mastery of pancreatectomy, and growing appreciation of the molecular underpinnings in PDAC have resulted in gradual but consistent improvements in disease-specific survival and overall survival (OS) in patients with localized PDAC (1).

The evolving trend toward induction chemotherapy rather than immediate surgery, even for patients with resectable disease, underscores the need for optimal predictive tools for patient counseling and selection in the perioperative setting. This is particularly relevant since our group from the Central Pancreatic Consortium recently reported the inaccuracy and suboptimal performance of existing nomograms and prediction tools specifically for patients receiving neoadjuvant therapies (2). In this context, we reviewed with great interest the study by Habib and colleagues from Johns Hopkins Hospital which reported a prognostic model and surgical decision-making tool for curative-intent treatment of localized PDAC patients selected for neoadjuvant/perioperative chemotherapy and pancreatectomy (3). Using granular clinically and pathologically annotated datasets, this study reported on 581 patients with localized PDAC undergoing induction chemotherapy ± radiation prior to resection at a single high-volume institution with the express goal of developing a tool that allows healthcare providers to input patient-specific preoperative and postoperative factors to generate predictions for OS, recurrence-free survival (RFS), and location-specific recurrence. In this selected population of patients (88% with borderline resectable/locally advanced disease) who underwent curative-intent surgery, median OS was 29.5 months and RFS 16.6 months. Complete/marked pathologic response [College of American Pathologists (CAP) score 0, 1] was achieved in 21% of patients, while 36% had partial response (CAP score 2) and 24% had poor/no response (CAP score 3) to neoadjuvant therapy. The authors noted that the utilization of CAP scoring was inconsistent prior to 2014; as such, 19% of their cohort had unknown scores. The multivariable analysis identified several factors associated with improved survival, including receipt of 5-fluorouracil (5-FU)-based chemotherapy and ≥6 cycles of neoadjuvant chemotherapy. Factors associated with

poor prognosis in these patients reflect unfavorable biologic indicators such as poorly differentiated tumor grade, poor pathological response to chemotherapy, and nodal positivity following neoadjuvant therapies. Intriguingly, over a third of patients (36%) had local recurrence which was defined as recurrence within the resection bed or proximate remnant gland, followed by local and distant recurrence (24%). Perineural invasion and R1 resection margins were strong predictors of local-only recurrence. Liver recurrence was associated with lymphatic metastases; however, this risk was reduced with the administration of adjuvant chemotherapy.

The authors then constructed a reasonably well-calibrated decision-making tool (concordance indices of 0.68 and 0.65 for OS and RFS, respectively) encompassing both preoperative and postoperative factors that are used as input variables to predict oncologic outcomes. Preoperative factors included patient demographics (age, sex, race), baseline serum carbohydrate antigen (CA) 19-9 levels, neoadjuvant chemotherapy regimen, number of chemotherapy cycles, use of radiation therapy, type of surgical procedure, and tumor resectability. Postoperative factors encompassed tumor characteristics such as tumor grade, pathological response, tumor (T) and nodal (N) staging, perineural invasion, lymphovascular invasion, vascular resection, margin status, and receipt of adjuvant chemotherapy.

Overall, these data reinforce what we increasingly appreciate as a community invested in improving outcomes in this patient population. While clear level 1 evidence is lacking—and mature data from the PREOPANC-2 (recently presented in abstract form at ESMO 2024) and ALLIANCE-A021806 (NCT04340141) trials are eagerly awaited—the shift towards a neoadjuvant paradigm in patients with localized PDAC is predicated on the growing understanding that PDAC, even when seemingly localized on best-available imaging, is a systemic disease at presentation (4,5). Additional benefits of the neoadjuvant approach include the ability to deliver cytotoxic therapies when patients are less debilitated (*vs.* after major pancreatectomy), assessment of *in vivo* chemoresponsiveness, potentially increased ability to achieve a margin negative resection, and importantly, avoidance of non-therapeutic pancreatectomy in patients who rapidly progress on neoadjuvant treatments. Moreover, given the importance of systemic therapies, the neoadjuvant approach assures at least some delivery of these therapies since 30–50% of patients are unable to initiate and/or complete adjuvant therapy due to complicated post-operative recovery after pancreatectomy (6). This intentional selection of physiologic and biologic fitness is reflected in data from the Hopkins study. Patients who were able to tolerate longer duration (≥6 months) of more intensive neoadjuvant chemotherapy regimens (5-FU-based FOLFIRINOX) and were able to recover expeditiously enough to receive adjuvant therapy demonstrated improved survival. Conversely, surrogates of unfavorable biology (e.g., nodal positivity, modest/poor pathologic response to neoadjuvant therapy, poorly differentiated histology) were associated with worse survival.

While these aforementioned prognostic factors are not entirely unique, the study by Habib *et al.* does add to the taxonomy of prognostic and predictive models in patients with localized PDAC. It highlights the complexity of predicting outcomes for PDAC and adds to the body of literature that continues to reveal that outcomes cannot be dictated to a single variable, but rather that the constellation of tumor and treatment variables must be integrated to understand a patient's unique tumor biology. This landscape of modeling PDAC outcomes is quite vast, with numerous models developed over the years and a review published in 2019 identifying as many as 21 different models aimed at predicting outcomes in PDAC patients (7). However, as noted by Habib *et al*, the absence of neoadjuvant therapy-related factors in previous prognostic models is a major limitation, and the current study clearly addresses this unmet need in the field. Furthermore, previous models have not typically included granular site-specific recurrence patterns, although some, like the study by La Torre *et al.*, offered predictions for early recurrence (8).

It is somewhat surprising that the most common site (36% of patients) of disease recurrence was within the local resection bed or proximal remnant gland, despite the margin negative rate being impressively high at 82%. In fact, <30% of patients in this series had distant-only recurrence, a striking departure from other reports in similar populations (9,10). This may reflect a disproportionate refinement of locally "confined" biology in patients undergoing the Darwinian selection process of neoadjuvant therapy and curative-intent pancreatectomy. Other limitations warrant emphasis. First, the primary constraint is the lack of external validation. As for any model created using a single-institution series, the current prognostic model will need to undergo external validation before widespread use. Second, we found it challenging to easily access the tool online, which hinders its value as a handy model for everyday use. Third, as we gain deeper insight into the molecular underpinnings of the disease, spurring the development

of molecular-based signatures to predict treatment responsiveness (11,12), the next generation of predictive and prognostic tools—even in patients with localized disease—must attempt to incorporate these molecular data to provide a comprehensive understanding of treatment-related trajectories. Widespread utilization of next-generation sequencing (NGS) technologies holds much promise in allowing tailored approaches to treatment decision-making, and matching therapies to tumors with actionable alterations—as established by the Know Your Tumor registry study—is expected to become commonplace (13). Finally, as mentioned previously, this model continues to rely on post-treatment and post-operative factors for improved discriminatory power. However, the pursuit for a clinically relevant model that will effectively guide treatment in a neoadjuvant paradigm needs to include variables available *prior* to completion of intended therapies. Only then can we truly tailor the intended course of treatment.

A pressing lacuna remains. In the dynamic landscape of PDAC management, where multidisciplinary approaches and novel systemic therapies are increasingly taking precedence, there is an urgent need to integrate a nuanced understanding of tumor biology/immunology to clinical decision making. Despite strides in neoadjuvant therapy efficacy, a significant subset of patients display inadequate pathological response or even progression of disease while on treatment (3), highlighting a crucial area for improvement in both predictive models and treatment strategies. For example, recent developments underscore the predictive value of immunological biomarkers in PDAC, particularly the role of pre-chemotherapy neutrophil-to-lymphocyte ratio (NLR) and its dynamics during treatment in influencing pathological response and overall outcomes—as reported by our group (14). Such immunologic and molecular determinants wield considerable influence over chemosensitivity and outcomes by orchestrating intricate crosstalk within the complex PDAC tumor microenvironment, dictating the delicate balance between a chemoresistant, immune-excluded stromal landscape *vs.* chemoreceptive biology (15). Therefore, while the study in question is a step in the right direction by integrating neoadjuvant therapy-derived clinical metrics into PDAC prognostic modeling, the ultimate aspiration of such decision-making models will require the incorporation of NGS, spatial biomarkers, and molecular determinants of therapeutic resistance in order to be truly comprehensive and paradigm-shifting.

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