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EDITORIAL – PANCREATIC TUMORS

Multimodality Therapy in Operable Pancreatic Cancer: Should We Sequence Surgery Last?

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The dismal oncologic outcomes with surgery alone and the near-universal distant failure in patients with operable pancreatic ductal adenocarcinoma (PDAC)[1] have mandated a multimodality approach for this disease. The advent of increasingly effective combination chemotherapy regimens[2–8] delivered in the adjuvant, and now neoadjuvant settings, perioperative safety and technical mastery of pancreatectomy, and growing appreciation of the molecular underpinnings in PDAC[9–11] have resulted in gradual but consistent improvements in disease-specific survival and overall survival (OS) over the last decade, although much work lies ahead.

Paramount to the continued progress in the field is the pressing issue of multimodality treatment sequencing in operable PDAC. Adjuvant therapy with modified FOLFIRINOX has recently been established as a new benchmark in the fittest patients completing the Darwinian selection process of tolerating major pancreatectomy, avoiding major perioperative complications, and being eligible for timely adjuvant therapy initiation.[3] In parallel, strategies to deliver these systemic regimens, with or without radiation, in the neoadjuvant setting are increasingly popular.[12–15] The most compelling rationale for this approach is the growing understanding that PDAC, even when appearing localized on best-available imaging, is a systemic disease at presentation.[16,17] Additional benefits of the neoadjuvant approach include the ability to deliver cytotoxic therapies when patients are less debilitated (vs. following major pancreatectomy), assess in vivo chemoresponsiveness, potentially increase the ability to achieve a margin negative resection and importantly, avoid nontherapeutic pancreatectomy in patients who rapidly progress on neoadjuvant treatments.[1,18] 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 postoperative recovery after pancreatectomy.[19]

Based on these factors, proponents of neoadjuvant treatment sequencing have advocated for total neoadjuvant therapy (TNT)—where all the prescribed nonsurgical treatment modalities (induction chemotherapy with or without consolidative chemoradiation therapy) are delivered prior to surgery.[1, 13,18] Recent reports suggest that increased cycles of neoadjuvant therapy and receipt of TNT are associated with improved margin-negative resection rates, node-negative pathology, augmented rates of major and complete pathologic response, and a signal for improved survival compared with perioperative treatment sequencing in patients completing all prescribed therapy.[12,13] However, the trepidation associated with a TNT approach is that surgeons may miss a biologic "window" to operate, and that the physical and physiologic toll of extended systemic treatments may manifest in attrition of patients who would otherwise be candidates for surgery.

In this edition, Kim and colleagues build on a strong tradition of neoadjuvant treatment sequencing for operable PDAC at the Medical College of Wisconsin (MCW) to describe their experience with TNT for operable PDAC.[20] They retrospectively reviewed a cohort of 541 potentially operable PDAC patients [42% resectable, 58% borderline resectable (BR)] treated at MCW in two "eras:" (1) an earlier

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paradigm [prior to August 2017, n = 452 (84%)], where patients received neoadjuvant chemoradiotherapy (CRT) with concurrent gemcitabine or capecitabine and BR patients received 2 months of induction chemotherapy followed by CRT prior to surgery [termed shorter course neoadjuvant therapy (SNT)], and (2) a more contemporary paradigm [after August 2017, n = 89 (16%)], where resectable/BR patients received 4 months of induction chemotherapy followed by CRT (termed TNT). Notwithstanding the use of more variable and dated regimens in the SNT cohort, TNT patients were more likely to achieve pathologic complete response (pCR; 8% vs. 4%, $p < 0.01$) and less likely to have poor/absent pathologic response (2% vs. 26%, $p < 0.01$) compared with SNT patients. Other clinicopathologic variables (e.g., nodal status, perineural invasion, perioperative complications) were not statistically different between the groups. In their cohort, receipt of $\geq$ 5 months of nonsurgical therapy (TNT or perioperative) was associated with improved OS and a decreased risk of death by 40% on multivariable survival modeling. Notably, patients receiving TNT were more likely to receive at least 5 months of nonsurgical therapy compared with SNT counterparts (67% vs. 45%, $p < 0.01$). Despite the higher rates of venous resection in the TNT cohort, suggesting potentially more anatomically unfavorable disease compared with SNT patients, TNT was associated with improved rates of pCR and reduced incidence of poor pathologic response. These results are consistent with recent reports from the Central Pancreas Consortium (CPC), showing that increased cycles of neoadjuvant FOLFIRINOX chemotherapy were associated with increased rates of pCR and OS.[21] Although the present MCW study was likely underpowered to detect a difference in survival between TNT and SNT arms, data from the CPC has shown that major pathologic response following neoadjuvant therapy is associated with improved locoregional recurrence-free, metastasis-free, and OS in patients with localized PDAC.[20] Taken together, these data indicate that completion of increasingly effective TNT results in increased rates of major pathologic response and is a laudable oncologic goal in operable PDAC.

As such, proponents of the TNT paradigm—including our group—believe it is the most efficient way to deliver the entirety of the prescribed systemic chemotherapy schedule (typically 6 months) in patients with localized PDAC. However, attrition on neoadjuvant therapy precluding surgical resection remains a legitimate concern with this approach. In the MCW experience, this attrition rate was $\sim$ 30% in both the SNT and TNT cohorts, recapitulating recently published data from the Southwest Oncology Group (SWOG) 1505 randomized trial.[14] Importantly, the rates of surgical resection and the proportion of patients who either developed metastatic disease or did not undergo surgery due to a decline in performance status was not statistically different between SNT and TNT arms, suggesting that extended upfront nonsurgical treatment is not associated with an appreciable loss in the biologic or physiologic "window" to operate.

The authors are to be congratulated not only for this study, but also for their long-standing commitment to the neoadjuvant paradigm in potentially operable PDAC. An important aspect of this study, in contrast to other recently published studies of neoadjuvant therapy, is their inclusion of consecutive patients with resectable/BR PDAC selected for neoadjuvant therapy, allowing for an intention-to-treat analysis as well as an appreciation of the study denominator.[22] The reported median OS of 26 months for the entire cohort provides an important survival benchmark for neoadjuvant therapy in PDAC based on this intention-to-treat analysis. This favorable survival duration further reflects the oncologic value of treating localized PDAC patients with systemic therapy first whenever possible, regardless of resectability status.

Several additional points in this study bear emphasis. First, as alluded to previously, it is possible that the improvement in pathologic response observed with TNT is attributable to increased utilization of modern chemotherapy regimens (e.g., FOLFIRINOX, gemcitabine/nab-paclitaxel) in this cohort. Second, although variations exist, the typical total neoadjuvant chemotherapy schedule utilized at our and other institutions is generally 6 months. The TNT cohort in this study received only 4 months of induction chemotherapy, followed by CRT with concurrent gemcitabine or capecitabine. Empirically, such radiosensitizing chemo-monotherapy with long-course radiotherapy likely does not achieve the systemic dose/efficacy of combination chemotherapy, thereby prioritizing local over systemic control earlier in the treatment course. It is well known that systemic failure remains the Achilles heel even in completely resected PDAC, and it is unclear whether the lack of improvement in overall survival in the TNT versus SNT cohorts in this study are in part related to higher rates of distant recurrence owing to "inadequate" systemic therapy upfront. To this end, patterns of failure between TNT and SNT cohorts are not reported in this study. Third, the routine application of radiotherapy for potentially operable PDAC can be strongly debated. Several randomized trials have indicated the lack of OS benefit for radiotherapy in these patients.[23,24] In fact, the neoadjuvant CRT arm in the recent Alliance for Clinical Oncology trial A021501 (NCT02839343) was dropped after an interim analysis deemed this approach futile in achieving the desired R0 resection endpoint.[25] Furthermore, our recent CPC study revealed no difference in survival when comparing patients who received any neoadjuvant radiotherapy with those treated with neoadjuvant chemotherapy alone.[20] Other than long-entrenched institutional practice patterns and preference, one must question the routine incorporation of radiotherapy in the

design of future TNT regimens in patients with resectable/BR PDAC. Finally, these data reinforce that, regardless of the treatment sequencing strategy, patients with operable PDAC likely fare best when receiving ≥ 5 months of multimodality, nonsurgical therapy in addition to complete margin-negative resection. It is less surprising, therefore, that receipt of 5+ months on nonsurgical therapy—and not TNT sequencing per se—was associated with improved survival in this cohort. Indeed, the ability to withstand 5 or more months of nonsurgical therapy, not progress with metastatic disease, and maintain performance status throughout this period in order to undergo surgical resection, is perhaps as much an exercise in Darwinian selection as distilling the fittest patients for toxic adjuvant therapy following major pancreatectomy. Notwithstanding, these and accumulating data may underscore the fact that the optimal strategy to allow patients to complete all components of multimodality therapy may be to sequence surgery last in potentially operable PDAC.

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