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PREOPERATIVE CHEMORADIATION FOR BORDERLINE RESECTABLE PANCREATIC CANCER: THE NEW STANDARD?

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“Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.” –

Winston Churchill, 1942

We and others have long championed the administration of systemic chemotherapy and/or radiation therapy prior to pancreatectomy for localized pancreatic cancer with the goals of facilitating margin-negative resection, eradicating occult systemic disease, enhancing local control, and maximizing patient survival, while sparing those patients with an irreversibly poor physiologic status or evolving metastatic disease what would otherwise be a futile operation [1]. An enlarging body of preclinical and clinical evidence has supported the efficacy of this approach, and the National Comprehensive Cancer Network [2] and American Society of Clinical Oncology [3] now recommend this strategy for some patients with localized cancers, including those with borderline resectable tumors at risk for a margin-positive resection. Nonetheless, some continue to argue that pancreatectomy should routinely be performed *de novo* on the basis that delaying surgery risks losing the opportunity for the only curative treatment modality—and that no randomized data exists to justify that risk. In this issue of *Annals of Surgery*, Drs. Jang and colleagues report the results of a prospective, randomized, multi-institutional study in which patients with borderline resectable pancreatic cancer who were randomly selected to receive gemcitabine-based chemoradiation prior to pancreatectomy survived significantly longer than patients randomly assigned to surgery primarily. So, does that end this debate?

Before answering that question, we must acknowledge that the study team responsible for this clinical trial deserve an enormous amount of credit. A major obstacle to the successful conduct of prospective studies of preoperative therapy for pancreatic cancer has historically been physicians’ strong bias against disrupting the surgical standard of care; previously published studies that randomized patients to preoperative chemoradiation or surgery closed prematurely, not due a positive statistical signal at interim analysis (as in this trial), but rather because of challenges accruing sufficient numbers of patients [4, 5]. Perhaps for this reason, the relevant literature largely consists of single-arm trials and single-institution anecdotal series [6]. This study by Jang *et al.* illustrates that preconceived biases must often

be set aside, and collaboration with other institutions and investigators need to be sought, so that robust trials can be conducted to answer the most important questions in clinical oncology, including the current one. This study also demonstrates that surgeons can be extraordinarily successful leading such trials.

It should also be emphasized that the basic design of this study includes elements that demonstrate the extent to which Dr. Jang and colleagues considered additional sources of potential bias and took measures to reduce them. The study randomized patients between two treatment arms. The intention-to-treat primary analysis was based on an objective survival endpoint instead of resection rate—a more commonly evaluated metric that is particularly prone to confounding by surgical decision-making. Predefined radiographic criteria were used to define eligibility, and each patient's scans were reviewed by dedicated radiologists within each hospital prior to enrollment (although regrettably studies from the four enrolling sites were not reviewed centrally by a single reviewer). Standard criteria to determine the role for surgery were clearly and prospectively described. Furthermore, the technical conduct of surgery, including the extent of vascular dissection and lymphadenectomy, was mandated by protocol. These design elements are critical to the interpretation of investigations of preoperative therapy for pancreatic cancer, particularly in the multi-institutional setting [6, 7].

Therefore, given that this was a reasonably well-conducted, prospective clinical trial, should we conclude that all patients with borderline resectable pancreatic cancer should be treated with preoperative gemcitabine-based chemoradiation? Not really, as important questions remain. Foremost among them is the role of preoperative systemic chemotherapy in this setting, as no patient enrolled on this trial received it. Only 63% of the patients who initiated preoperative chemoradiation on protocol underwent subsequent pancreatectomy, in large part due to metastatic disease progression, and the majority of postoperative recurrences developed at sites remote from the resected primary tumor. Systemic treatment regimens now used routinely for patients with advanced pancreatic cancer are associated with objective response rates as high as 32%, and exert cytotoxic effects both upon the primary tumor as well as the micrometastatic disease assumed to exist in essentially all patients [8, 9]. Furthermore, systemic therapy delivered postoperatively to patients with resected pancreatic cancer has proven survival benefit [10]. For these reasons, preoperative systemic doses of chemotherapy—delivered either prior to chemoradiation to select patients with evolving metastases, as routinely employed in the locally advanced setting [11], or even as a replacement for chemoradiation—has significant appeal. In this regard it should be recognized that radiation therapy may sterilize the oncologically-critical superior mesenteric artery margin and increase the possibility for achieving negative margins at surgery [12], as suggested by data from this trial. However, whether or not chemoradiation can prolong survival of patients with localized cancer is the subject of ongoing debate [11, 13]. And, to the extent that preoperative radiation may have benefit, future studies should consider existing alternatives to conventional chemoradiation that appear to yield rates of local control equivalent to those associated with conventional chemoradiation using dosing schedules as short as 5 days [14]. Alliance for Clinical Trials in Oncology Trial A021501, which randomizes patients with borderline resectable cancer to preoperative FOLFIRINOX or to FOLFIRINOX followed by stereotactic body radiotherapy, was designed to

characterize the role of a modern preoperative radiation regimen in this setting and should help address these issues [15].

Furthermore, though the results of this study are clearly instructive, they should not be overgeneralized to suggest that all patients with borderline resectable pancreatic cancer should be treated exclusively with gemcitabine-based chemoradiation—or indeed any single preoperative regimen. The criteria that Dr. Jang and colleagues used to define borderline resectable cancer are generally accepted and reasonable, but are based only upon the radiographic relationship between the primary tumor and the major mesenteric vasculature. Other clinical factors must be considered when making treatment decisions. At our institution, all patients with borderline resectable pancreatic cancer are seen by a coordinated, multidisciplinary team. Each patient's physiologic status, comorbidity profile, lifestyle and support system, access to healthcare, and the anticipated natural history of his or her systemic burden of disease as estimated by serum levels of CA 19-9 or the presence or absence of suspicious radiographic findings, are carefully evaluated. Following this comprehensive evaluation, collaborative treatment recommendations are generated that weigh the perceived risks and benefits of systemic chemotherapy, radiation therapy, and the duration of time within which these treatments will be administered. A clinical classification of localized pancreatic cancer that takes such considerations into account has been used at our institution for the past decade and has served to inform the development of more recently published treatment guidelines [3, 16, 17].

The management of patients with borderline resectable pancreatic cancer is one of the most significant biological and technical challenges in oncology. To date, patients have been treated with algorithms largely based upon consensus guidelines and low-level data. This study by Dr. Jang et al. provides initial randomized data that support a role for preoperative chemoradiation in this setting. We still have a long way to go, and many important questions remain unanswered; properly designed clinical trials—led by surgeons—are needed to answer them.

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