Cutting Through Confusion: Multimodality Therapy in Borderline Resectable and Locally Advanced Pancreatic Cancer

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Tsai et al¹ describe the role of multimodality therapy in the treatment of borderline resectable and locally advanced pancreatic cancer. The review highlights the use of neoadjuvant therapy toward achieving the goal of resection with negative margins within a select subset of patients or, for those whom this surgical goal cannot be attained, local control of the disease without unnecessary morbidity and with prolonged survival. Central to the authors' proposal is radiographic criteria to sort patients a priori (ie, before initial treatment) into these two categories in addition to interim assessment of disease progression or response. The authors describe a treatment sequencing algorithm and timeline based on the a priori categories.

Defining Borderline Pancreatic Tumors

Over the last decade, there has been great interest in better defining borderline pancreatic tumors. Objective definitions of borderline resectable disease were proposed circa 2006.² Since then, new evidence has emerged that supports the administration of neoadjuvant therapy, and consideration of this approach is recommended in recent American Society of Clinical Oncology³ and National Comprehensive Cancer Network guidelines.⁴ In borderline patients undergoing neoadjuvant therapy and subsequent resection,

favorable results have been demonstrated, including R0 resection rates and overall survival, attributable largely to patient selection.⁵ With proven survival benefit in the metastatic setting, FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) and gemcitabine plus nanoparticle albumin-bound paclitaxel regimens have also been incorporated into neoadjuvant treatment approaches. The evolution of sequencing strategies and novel regimens for borderline and locally advanced disease suggests the need for improved patient stratification to determine the best individualized treatment approaches.

Tsai et al¹ propose imaging-based criteria to stratify patients with vascular involvement into borderline resectable and locally advanced type A or B categories. Such stratification highlights the value of standardized thin-slice pancreas protocol computerized tomography scans assessed by expert radiologists based on RECIST at both initial diagnosis and reassessment for treatment response.⁶ These distinctions are important because the current status means that systemic chemotherapy can only be accurately categorized (neoadjuvant v systemic therapy for locally advanced disease) retrospectively based on subsequent surgical decision making. Clarity of the intent of systemic therapy may help set appropriate expectations for both treating physicians and patients.

ASSOCIATED CONTENT

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Multimodality Treatment of Borderline Resectable and Locally Advanced Disease

Defining the goals of multimodality treatment for borderline resectable and locally advanced pancreatic cancers is crucial. As the treatment of pancreatic cancer shifts toward focusing on the management of both locoregional and systemic disease, the use of neoadjuvant therapies may expand. Research has demonstrated that tumor dissemination occurs before local tumor formation,⁷ from which we can extrapolate the benefits of early administration of systemic therapy. Neoadjuvant therapy allows for earlier treatment of potential metastatic disease, assessment of the patient's performance status over time and robustness in the setting of cancer-directed treatment, evaluation of tumor biology, and potential tumor downstaging to allow successful R0 resection. Indeed, the advantages of neoadjuvant therapy may not be limited to borderline or locally advanced disease. Mathematical modeling and single-institutional studies have suggested that neoadjuvant therapy may also provide benefit in both life expectancy and quality-adjusted life expectancy in patients with resectable disease.⁸

Although the use of neoadjuvant chemotherapy for borderline and locally advanced disease is gaining acceptance, the use of chemoradiotherapy in the preoperative setting remains controversial. Patients in the LAP07 randomized trial who received chemotherapy and chemoradiotherapy had improved progression-free survival (primarily because of decreased local progression) but no difference in overall survival compared with those who received chemotherapy alone.⁹ However, a recent meta-analysis of patients with localized unresectable pancreatic cancer suggests modern chemotherapy with or without radiotherapy outperforms historical controls.¹⁰

At our institution, borderline patients are preferentially treated with preoperative chemotherapy and, if successfully resected, will generally receive postoperative systemic therapy. Stereotactic radiotherapy is considered for unresectable localized lesions and R1 margin resections. We also use neoadjuvant stereotactic radiotherapy in certain situations; however, if the tumor seems clearly resectable (with or without venous reconstruction) after systemic neoadjuvant chemotherapy, we may elect to save radiotherapy for postoperative and local recurrence needs.

After several decades of stagnant treatment options, these are exciting times for the treatment of pancreatic ductal adenocarcinoma. In addition, novel sequencing strategies and

new therapeutic regimens are actively being investigated. With the burgeoning of treatment options, it is all the more critical to delineate categories of disease burden and correlate them with treatment outcomes. In this way, we in the pancreatic cancer field can ensure that an individual patient receives the best treatment tailored to his or her cancer. Tsai et al,¹ in their thoughtful analysis, provide one option for parsing the language of borderline and locally advanced ductal adenocarcinoma of the pancreas. **JOP**

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