

Editorial

Putting the Chemo in Chemoradiation for Pancreatic Cancer

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The phase II trial reported by Talamonti et al.¹ in this issue of *Annals of Surgical Oncology* is an important contribution to the literature regarding neoadjuvant therapy for pancreatic cancer. The potential benefits of neoadjuvant therapy have been discussed extensively, but the logic of this strategy may be more applicable to pancreatic cancer than to any other malignancy. Surgery for pancreatic cancer continues to carry significant morbidity and a low, but real, mortality rate, and it is associated with cure only rarely. Every attempt to use surgery only in those who may most benefit is then an irrefutably logical goal. Despite this, few multi-institutional studies using this approach have been conducted, and the authors are to be congratulated on their efforts in that regard. As does most good work, this study raises numerous important questions and challenges for future clinical neoadjuvant trials.

In the Talamonti study, 20 patients with potentially resectable pancreatic cancer received three cycles of systemic-dose gemcitabine. Radiation was delivered to a dose of 36.4 Gy during the second cycle. In contrast to traditional chemoradiation strategies for pancreatic cancer, which have emphasized using maximum tolerated doses of radiotherapy, this study design emphasized delivery of chemotherapy at the maximum tolerated dose with a reduction in the radiation dose. The regimen was well tolerated in that 19 of 20 patients completed therapy without interruption, and all received the total proscribed radiation dose. All patients were

deemed resectable after restaging, and 17 ultimately underwent resection. One patient had a complete pathologic response, and in three others, there was only residual microscopic disease in the surgical specimen.

Because the primary end points of the study were feasibility and toxicity, the results are encouraging. The authors point to the fact that the radiation schema used not only a reduced dose, but also a more limited field size, with elimination of prophylactic nodal irradiation. Despite elimination of this nodal radiation, only 35% of lymph nodes contained metastatic disease, a considerably lower number than that seen in most adjuvant studies. In the recently reported German Adjuvant Pancreatic Cancer trial, >70% of patients had positive nodes.² This raises several questions: What part of the radiotherapy is most responsible for toxicity: i.e., can radiation dosing be escalated further if the field size is diminished? If essentially only the primary tumor is being radiated, did gemcitabine alone account for the low rate of nodal disease, or is this a result of patient selection in a relatively small sample size?

Another encouraging result from the study was that only 6% of operations were associated with a microscopically positive surgical margin of resection. Positive margins have long been recognized as a poor-prognostic factor in pancreatic cancer, and positive margin rates have been looked to as one surrogate for the efficacy of neoadjuvant therapy. The incidence of positive margins is, however, related to numerous factors, including the size and location of the tumor relative to the superior mesenteric vessels, the experience of the operating surgeon, the willingness to perform resection of the superior mesenteric-portal vein confluence in the setting of involvement by tumor, and, finally, the process by which the ret-

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roperitoneal margin is defined and the specimen processed. It is unfortunate that the authors do not describe in more detail how the retroperitoneal margin was handled. This is an issue that has plagued many adjuvant studies and points to an area that should ideally be addressed prospectively during clinical trial design, particularly for multi-institutional studies. This is particularly critical because resectability and margin positivity rates have now been proposed as end points in the design of phase II neoadjuvant trials for pancreatic cancer. Finally, in this study, tumors were considered potentially resectable if there was no encasement of the superior mesenteric vessels or occlusion of the superior mesenteric-portal vein confluence. Despite this definition, it is hard to glean from the article whether several tumors abutted the vessels or whether most tumors treated in this study had a clear fat plane around them on computed tomographic scan. Without this kind of detail, the interpretation of margin status from a small study is precarious. Future studies would be improved if patients with any significant degree of superior mesenteric artery abutment were stratified or even the subject of a separate study. This group clearly has a higher incidence of both margin positivity and progression on neoadjuvant therapy. This group of "borderline resectable" patients has not been the subject of study but clearly comprises a significant number of pancreatic cancer patients who present to the surgeon. A significant percentage of patients in this study underwent vascular resection during the course of pancreaticoduodenectomy. This may have contributed to the low incidence of positive margins.

The neoadjuvant regimen used by Talamonti et al. resulted in an encouraging rate of pathologic response within the specimen, including one patient with a complete response and three others with only microscopic foci of residual disease. Given the infrequent occurrence of such responses with 5-fluorouracil (5-FU)-based chemoradiation and the lower dose of radiation used in this study, one must conclude that the results are secondary to the use of systemic-dose gemcitabine. The German Adjuvant study that used adjuvant gemcitabine reported a median disease-free survival of 14.5 months for the treatment group. The disease-free interval for all resected patients was not reported in the Talamonti study, but it was reported as 8 months for the 10 patients who had recurrence. This at least hints at the fact that, as European investigators have suggested, systemic therapy is the most important

component of adjuvant treatment for pancreatic cancer.³

For many years, neoadjuvant and adjuvant chemoradiation studies have placed their emphasis on improving radiation sensitization through the use of varying 5-FU dosing schemata and the investigation of other cytotoxic drugs such as the taxanes. It is often forgotten that the Gastrointestinal Tumor Study Group trial on which the practice of adjuvant 5-FU chemoradiation was based used 2 years of systemic-dose 5-FU in addition to the chemoradiotherapy.⁴ Given that patients with pancreatic cancer almost universally succumb to metastatic disease, it is past time that clinical trials in resectable patients more aggressively explore systemic therapy. In the past, the lack of any active agents made this difficult, but fortunately with the advent of biologically directed compounds, such investigations are now warranted and in development. A randomized phase II trial led by the Eastern Cooperative Oncology Group via the Intergroup will soon investigate the safety of gemcitabine and cetuximab, as well as gemcitabine and bevacizumab, as adjuvant therapies for pancreatic cancer. A South West Oncology Group trial currently in development will examine a neoadjuvant strategy using systemic-dose gemcitabine and oxaliplatin followed by cetuximab-based chemoradiation. The final results of Intergroup 9704 will offer significant information regarding the utility of gemcitabine as an adjuvant treatment. The Talamonti study suggests that even modestly active agents such as gemcitabine may be effective in the neoadjuvant setting when used in systemic doses. Only through investigations aimed at treating systemic disease will greater strides be made toward improving survival for pancreatic cancer patients—an achievement that is long overdue.

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