Radiation Therapy in Resectable/Resected Pancreatic Adenocarcinomas: Clearing Up the Fog

July 11, 2011
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Surgical resection remains the sole modality that has proven capable of "curing" pancreatic cancer. Still, despite improvements in surgical techniques and in perioperative morbidity at experienced surgical centers, the most optimistic 5-year survival numbers for resected pancreatic cancers hover in the 20% to 25% range, with median survivals in the 20- to 22-month range. Given that curative surgical resection is generally advised only in a carefully selected minority of patients (usually 10% to 15% of all diagnosed pancreatic cancers), it is incumbent on the oncologic community to strive for better outcomes for those with this disease. Since combined-modality treatments are associated with the most successful outcomes in practically every type of gastrointestinal (GI) cancer, comprehensive, rather than exclusive, treatments will likely generate any advances in local as well as systemic control in pancreatic cancer as well. The article by Palta et al examines the prevailing literature on adjuvant radiotherapy (RT), chemotherapy, combined-modality treatment, and neoadjuvant therapy for resectable pancreatic cancer, and it once again highlights the relative equivalence (and therefore overall lack of improvement) of varying regimens and the dichotomy between European and US treatment paradigms. It also offers food for thought regarding potential alternative approaches that may enhance our ability to achieve truly curative resections, and it outlines current trial designs attempting to resolve these complex issues.

With the original Gastrointestinal Tumor Study Group (GITSG) trial demonstrating a clear superiority for adjuvant chemoradiotherapy (CRT) over surgery alone[1] (despite limitations that are well documented in the Palta et al review), this regimen became the accepted treatment of choice, unchallenged until the publication of two somewhat controversial European trials at the turn of the millennium. The European Organisation for Research and Treatment of Cancer (EORTC) 40891 trial, in its original form, demonstrated no benefit for adjuvant CRT in resected pancreatic head or periampullary carcinomas.[2] Notwithstanding limitations in technique similar to those of the GITSG study (outdated RT technique, split-course RT, and low total RT dose delivery), we and others have previously noted how a different analytical perspective actually suggests that this was, in fact, a positive trial supporting the findings of the GITSG study.[3,4] The European Study Group for Pancreatic Cancer (ESPAC)-1 study[5] has generated much controversy and analysis (once again summarized in the article by Palta et al), and some would argue is the epitome of how complex trials with poor quality control and "dealer's choice" enrollment strategies can result in greater confusion rather than clarity. Nevertheless, despite the overwhelming absence of evidence against the use of RT in the adjuvant setting for pancreatic cancer, it has been replaced by a chemotherapy-only approach in many parts of Europe. While further chemotherapy-alone trials have since been developed and published, and while they have largely supported the use of gemcitabine in the adjuvant setting, local recurrence rates have been far worse and overall survival no better than previously reported.[6,7]

In the United States, however, RT continues to play a role in the adjuvant management of resected pancreatic cancer, with a recently reported trial (Radiation Therapy Oncology Group [RTOG] 9704[8,9]) as well as a currently accruing study (RTOG 0848) addressing the role of modern RT techniques as well as newer chemotherapy/targeted therapy regimens. The impact of RT "quality" on local control and its potentially associated impact on survival in the adjuvant setting was first assessed prospectively in RTOG 9704. In this study, modern three-dimensional (3-D) RT, when delivered per protocol, was associated with an improvement in patient outcomes.[10] While radiation oncologists continue to make strides in improving the efficacy and tolerability of RT, including through recently reported results with intensity-modulated radiotherapy (IMRT),[11,12] our impact on patient outcome may be limited by the success, or lack of success, of our colleagues in surgical and medical oncology. Specifically, the challenge of improving the likelihood both of R0 vs R1/R2
resections and of the development of systemic therapy associated with a truly incremental benefit in survival in the adjuvant setting needs to be met head-on. Multiple studies have demonstrated that the patients who are most likely to benefit from adjuvant RT are those who have had R0 resections and who have received adequate adjuvant chemotherapy. Unfortunately, the proportion of patients undergoing R1 resections remains high in modern reports (range, 19% to 45%).[6,8,13] Patients who have had R1 resections tend to have inferior median survival compared with those who have had R0 resections (range, 8 to 18 months vs 20 to 25 months). It is therefore imperative that surgeons and multi-disciplinary teams rely on improved CT/MRI and functional imaging to appropriately select those patients who are likely to benefit from neoadjuvant therapy.[14] Several studies have demonstrated a higher likelihood of tumor downstaging and subsequent R0 resections following neoadjuvant therapy in patients with borderline resectable disease.[15,16] In such borderline cases, neoadjuvant combined-modality therapy should be strongly considered. Such discussions may be challenging and will require timely consideration; a multidisciplinary forum is more likely to facilitate such discussions and thus to be associated with the potential for improved outcome for patients with pancreatic cancer.[17]

Despite the previous widespread acceptance of gemcitabine as the drug of choice in the neoadjuvant/adjuvant treatment of pancreatic cancer, RTOG 9704 associated it with only a marginal, non-significant improvement in 5-year survival. However, the recently reported success of the FOLFIRINOX regimen (oxaliplatin, irinotecan, leucovorin, and fluorouracil) in metastatic pancreatic cancer has generated tremendous excitement regarding the potential for using this regimen in the definitive setting.[18] Although it is imperative to point out that the patients who received this chemotherapeutic regimen were inherently selected out for higher performance status due to the toxicity associated with it, the publication of these results may, nevertheless, represent a tremendous improvement in systemic options available to patients in the neoadjuvant or adjuvant setting.

Notwithstanding the dichotomy in treatment paradigms on the two sides of the Atlantic, it is clear that we have a long way to go in the fight against even the most "favorable" pancreatic adenocarcinoma. Improvements in surgical and radiation techniques have yielded more tolerable treatment options, and the development of novel systemic strategies is well underway. However, no single modality has yet proven definitively adequate. The oncology community must, therefore, learn from successful combined-modality experiences to create an "inclusionary," rather than "exclusionary,"" environment for protocol development. Working in our respective silos has not, and will not, benefit the patients we strive to serve. The currently accruing phase III RTOG 0848/EORTC study is an example of one such strategy: patients with resected pancreatic head carcinomas are allowed to receive systemic dosing of adjuvant chemotherapy, and those demonstrating no recurrence 4 to 6 months later have the opportunity to receive adjuvant RT in a randomized fashion. In addition, this study will be addressing, in a randomized fashion, the role of erlotinib (Tarceva) in the adjuvant setting. The integration of modern surgical, medical, and radiation oncology expertise in such studies will, hopefully, allow us to make strides in improving the rather dismal outcomes that have been seen in this disease thus far, as well as providing greater hope for our patients in the future.

Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

References:
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