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EDITORIAL – GASTROINTESTINAL ONCOLOGY

The Promise of Modern Radiotherapy in Resected Pancreatic Adenocarcinoma: A Response to Bekaii-Saab et al.

Amol K. Narang, MD[1,2] and Joseph M. Herman, MD, MSc[1,2]

[1]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University School of Medicine, Baltimore, MD

Determining the optimal adjuvant management strategy for patients with resected pancreatic adenocarcinoma remains a controversial topic. In particular, defining the role for radiation continues to generate significant debate. As such, we welcome sustained investigation into whether radiation can improve oncologic outcomes after resection of pancreatic cancer. We therefore appreciate the work done by Bekaii-Saab et al. to review their institution's experience with adjuvant chemoradiation for localized pancreatic cancer in which they find no benefit on overall survival or local control when comparing patients treated with chemoradiation versus chemotherapy alone. Despite their results, we disagree with the authors' conclusion that there is "no benefit from chemoradiation over chemotherapy in the adjuvant treatment of pancreas cancer" and that "based on the available data and outside of a clinical trial, patients should be treated with chemotherapy alone following surgery."

Appreciation of the potential that modern radiotherapy may have for resected pancreatic cancer requires a historical understanding of early clinical trials that explored chemoradiation, some of which are referenced by the authors. Early institutional reports demonstrated poor local control after surgical resection of pancreatic cancer, with local failure rates of roughly 50 %.[1] As such, the Gastrointestinal Tumor Study Group (GITSG) undertook a clinical trial comparing 5-fluorouracil (5-FU)-based chemoradiation versus observation in patients undergoing Whipple resection. The chemoradiation arm experienced improved 2-year overall survival (42 vs. 15 %, $p = 0.03$), leading to widespread adoption of adjuvant chemoradiation in the United States.[2] However, this survival benefit could not be replicated in subsequent trials by the European Organization for Research and Treatment of Cancer (EORTC) and the European Study Group for Pancreatic Cancer (ESPAC), with the latter trial demonstrating the best outcomes in patients treated with chemotherapy alone.[3,4] The many pitfalls of these trials have been well documented, including slow accrual and poor trial adherence. Most importantly, radiation was delivered using AP-PA techniques in a split-course fashion to only 40 Gy. Although survival outcomes differed in these early studies, none of the three trials, including the GITSG trial, demonstrated decreased rates of local control in the chemoradiation arms, likely as a result of delivery of a suboptimal dose of radiation with nonconformal techniques using a split-course schedule that risks tumor repopulation. Therefore, the primary conclusion from these early trials should be that poorly delivered radiation likely does not affect local control and therefore has no effect on survival.

Outcomes with more conformal radiation techniques using higher doses without breaks has been explored both in the nonrandomized and randomized settings. A pooled matched-paired analysis from the Mayo Clinic and Johns Hopkins demonstrated a survival benefit of adjuvant chemoradiation when delivered to a median dose of 50.4 Gy compared to observation.[5] Moreover, RTOG 97-04, which randomized patients to initial chemotherapy with either 5-FU or gemcitabine, followed by 5-FU-based chemoradiation to 50.4 Gy, followed by additional chemotherapy with 5-FU or gemcitabine, resulted in an improved rate of local recurrence in both arms of 25–30 %.[6] This local failure rate compares favorably with historical controls despite a

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J. M. Herman, MD, MSc
e-mail: jherma15@jhmi.edu

predominance of patients with risk factors for local recurrence, including 35 % with positive margins, 66 % with positive lymph nodes, and 75 % with advanced T-stage. Although the RTOG 97-04 population was also less favorable when compared to patients enrolled on modern chemotherapy alone trials such as CONKO-001 and ESPAC-3, outcomes have been remarkably similar.[7,8] Indeed, when excluding patients from RTOG 97-04 with CA19-9 levels greater than 90, an exclusion criteria used in CONKO-001, patients from RTOG 97-04 experienced a 5-year overall survival of 34 versus 21 % for patients in CONKO-001, despite the fact that the R0 resection rate from RTOG 97-04 was only half that of CONKO-001. Additional subset analysis of RTOG 97-04 demonstrated improved survival in patients treated with radiation per protocol versus those whose radiation treatment deviated from protocol, which underscores the importance of appreciating the quality of radiation delivered when interpreting results from clinical trials.

Furthermore, continued improvement in local control with radiation after resected pancreatic adenocarcinoma may be achieved through better patient selection, development of more sophisticated radiation techniques, and incorporation of novel systemic agents as radiosensitizers. Identifying those patients at greatest risk for local versus distant progression would be helpful for selectively administrating chemoradiation. One method of screening out those patients with micrometastatic disease that would not benefit from local radiation is to begin adjuvant therapy with full dose chemotherapy, followed by chemoradiation only in those patients who have not developed metastatic disease on restaging imaging. Moreover, recent work has explored potential biomarkers that may identify those patients at greater risk for local failure. Indeed, an autopsy series of consecutive patients from our institution that succumbed to pancreatic cancer demonstrated that roughly 30 % of patients most likely died from locally destructive disease, highlighting the importance of achieving better local control.[9] Interestingly, Smad-4 expression was highly correlated with the locally destructive phenotype, a finding that has also been replicated in a phase II study of chemoradiation for locally advanced pancreatic cancer.[10]

In addition to better patient selection, the development and application of more sophisticated radiation techniques may allow for both improved efficacy and decreased toxicity. Intensity-modulated radiotherapy has allowed for increased conformality of dose deposition, decreasing dose to critical organs at risk. Image guidance further improves accuracy, minimizing day-to-day variation in patient setup. By better sparing normal tissue, both technologies may allow for radiation dose escalation. Furthermore, a greater understanding of local patterns of failure may assist in identifying those areas at greatest risk for recurrence. A recent study from our institution reviewed 90 patients with resected pancreatic cancer that subsequently experienced local failure, mapping the exact location of recurrence in relation to vascular anatomy.[11] The study demonstrated that the regions at highest risk for failure encompassed a target volume that is much smaller than what has been traditionally treated. Using a more rational approach for target delineation that is based on patterns of failure may permit reduction in the size of radiation fields, which may decrease toxicity and allow for dose escalation. Another exciting new technology in radiation oncology that is increasingly being applied to pancreatic cancer is stereotactic body radiotherapy (SBRT). By administering hypofractionated treatments, SBRT drastically reduces treatment time (5 days as opposed to 5–6 weeks), decreasing the delay to full dose systemic therapy while also increasing the biologically effective dose. Early results in the locally advanced pancreatic cancer setting have been favorable, and a recent study demonstrated the feasibility of this technology in the adjuvant setting.[12] At our institution, we are exploring SBRT in the adjuvant setting in a prospective clinical trial that also incorporates the pancreatic GVAX vaccine followed by FOLFIRINOX chemotherapy.

Finally, incorporation of novel systemic agents into the chemoradiation regimen may lead to increased local efficacy. Gemcitabine has led to better outcomes than 5-FU in advanced stage patients, and its tolerability when combined with radiation has been described.[13] The combination of radiation with molecularly targeted therapies has also garnered considerable enthusiasm. Phase II data from our institution, for example, were encouraging when erlotinib was provided concurrently with capecitabine and intensity-modulated radiotherapy followed by gemcitabine and erlotinib in patients with resected pancreatic cancer.[14] Interestingly, the median overall survival for this trial was similar to that seen in the chemotherapy alone trials despite having a population of patients with significantly worse pathologic features such as lymph node involvement and margin positive resections. RTOG 08-48, an ongoing phase III trial, will better help define the role of erlotinib and standard chemoradiation in this patient population.

Certainly, the clinical relevance of local control in pancreatic cancer depends on improvements in systemic therapy, as the vast majority of patients with resected pancreatic cancer will still succumb to distant disease. However, we believe that this should not result in a nihilistic view toward the importance of local radiotherapy. As described above, the percentage of patients that experience local failure is not insignificant, and these recurrences are associated with considerable morbidity and mortality. Although early studies demonstrated little benefit of radiation on local control, the relevance of such

antiquated radiation techniques is questionable. Indeed, the authors of the current study acknowledge that the radiation techniques in their study spanned two decades and that radiation was proportionately more commonly delivered in the 1990s. We therefore believe that the results of this study should not be interpreted as a reason to abandon radiation in resected pancreatic cancer, but instead as further evidence supporting the development and better integration of modern radiotherapy with more aggressive systemic treatment. We are optimistic that by working together in a multidisciplinary fashion, we can continue to improve the quality and quantity of life of our patients with this devastating disease.

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