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EDITORIAL

Is There a Role for Intraoperative Radiation Therapy in Patients with Resected Pancreatic Adenocarcinoma?

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The value of adjuvant radiotherapy is well established in many tumor sites and is commonly used when pathologic features of a patient's primary tumor place them at sufficiently high risk for local-regional recurrence to warrant additional intervention. The rationale for the use of adjuvant radiotherapy in such situations is the traditional shared goal of the surgical and radiation oncologist: to optimize local-regional control. Attaining local-regional control prevents the morbidity of a local recurrence, and, in some situations, improves overall survival, perhaps best exemplified in the case of postmastectomy radiotherapy for women with high-risk breast cancer.[1] For pancreatic cancer management, adjuvant radiation has been delivered through fractionated external beam radiation treatments (EBRT) and/or single-fraction high-dose intraoperative radiation therapy (IORT). IORT has the benefit of directly moving critical normal tissues of the upper abdomen away from the radiation beam.[2]

Prevention of local recurrence leading to an improvement in survival may result through a number of mechanisms. The most straightforward of these is the underappreciated fact that local recurrence, particularly at certain sites such as the head and neck, can itself lead to disease-specific mortality. Also, radiation can sterilize remaining cells able to proliferate at the local site and then metastasize, causing eventual death; this may be all the more important in light of evidence suggesting that cells can be modulated by the postoperative microenvironment to yield more a more aggressive phenotype, as has recently been suggested in breast cancer. [3–5] Another, highly intriguing, possible effect is for irradiation of local tumor cells to induce abscopal, immune-related killing effects on distant sites of micrometastases. [5,6]

Attaining local-regional control is all the more paramount when patterns of cancer failure are predominantly local-regional and/or reasonably effective chemotherapy is available to treat systemic micrometastatic disease but not sterilize local-regional disease. Therein lies the controversy over adjuvant radiotherapy (be it EBRT or IORT) for resectable pancreatic adenocarcinoma. Although clinical and autopsy series have revealed local-regional (tumor bed and regional lymph nodes) failure to be a common event (50% or greater) following pancreaticoduodenectomy, it is much less common for these failures to be in isolation with respect to distant disease and also for the local-regional failure itself to be the clear proximate cause of death.[7–9]

Acknowledging the high rates of distant failure (liver, peritoneal cavity), the value of primary radical surgery in patients with resectable disease may itself be questioned.[10] Two randomized trials provide evidence that surgery does improve long-term survival rates compared with bypass intervention or primary chemotherapy and concurrent radiation.[11,12] However, true long-term disease-free survivorship (apparent cure) is uncommon with surgery alone, and the need for effective systemic therapies is obvious. The recently reported CONKO-001 trial showed that gemcitabine following surgery delays disease failure and also likely provides higher long-term survival rates (estimated 5-year disease-free survival of 16% vs 6.5% with surgery alone).[13] Whether additional locally directed therapies beyond surgery add meaningful benefit—in the context of contemporary systemic therapy options—remains an open question. Although the role of adjuvant chemoradiotherapy was established in an early Gastrointestinal Tumor Study Group trial and through retrospective institutional reports,[14,15] the actual value of the radiation component has been called into question, most recently by the controversial ESPAC results.[16]

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What are the data regarding the benefits and toxicities of IORT ± EBRT for resectable pancreatic cancer? In this issue of the *Annals of Surgical Oncology,* investigators from the Thomas Jefferson University departments of Radiation Oncology and Surgery report their experience with 83 patients with resected pancreatic cancer treated between 1995 and 2005. Of these, 37 patients were treated with IORT; about 75% of this group also received EBRT, and 84% received adjuvant chemotherapy. In the group treated with resection but without IORT, about two-thirds underwent adjuvant EBRT and chemotherapy. IORT did not significantly increase perioperative complication rates. As patients were not randomized to the use of IORT, the authors used a propensity score adjustment in their analysis of disease control to account for differing prognostic factors between the two groups. Although IORT was associated with an odds ratio of 0.41 for local-regional recurrence, this reduction did not reach statistical significance ($P = .23$). The confidence intervals for this ratio were quite large (0.10–10.30), reflecting patient numbers. IORT was not associated with improved survival.

Institutional reports and a randomized trial have shown surgery followed by IORT to yield lower local-regional recurrence rates compared with surgery alone, although a positive impact on survival has not been readily demonstrated.[17–19] As the authors appropriately address, improvements in systemic therapy are generally necessary before prevention of local recurrence translates into a survival benefit.[20] As long as the best systemic therapy options provide only modest control of distant disease, local tumor control improvements will not translate into a survival benefit. Finally, the emergence of novel chemotherapeutic or targeted agents that impact distant metastases may also eventually impact local-regional microscopic disease control to the degree that adjuvant radiation may not be needed following R0 resection.[21]

Whether or not IORT contributes to overall survival was also evaluated in a group of patients treated at the University of Texas M.D. Anderson Cancer Center with neoadjuvant chemoradiation for radiographically resectable pancreatic cancer (no tumor involvement of the celiac axis or superior mesenteric artery with patent portal venous confluence). The authors reported local recurrence to be a component of the first site of failure in 9% in patients undergoing neoadjuvant fractionated EBRT (30–50 Gy) followed by surgery without IORT compared with 4% with the addition of IORT.[22] The contribution of neoadjuvant EBRT to surgery cannot be determined in this study. However, the risk of local recurrence without IORT was too low in this study to see a clinically meaningful benefit in survival. In part due to these results, IORT for resected pancreatic cancer was abandoned at the M.D. Anderson Cancer Center.

It is interesting to contrast these two large experiences using IORT for localized pancreatic cancer. In the current study, positive margins (R1 or R2) occurred in 30 of 83 patients (36%) overall, and the local tumor recurrence rate was numerically lower in the higher-risk IORT group (23% versus 39%). Statistical power was limited because of small numbers, but there was a suggestion that IORT improved local tumor control. In contrast, 16 of 132 patients (12%) with radiographically resectable tumors that were treated with neoadjuvant chemoradiation had positive margins (all R1) in the M.D. Anderson experience, and the crude local tumor recurrence rate was 4% with IORT and 9% without IORT. The absolute differences in the rates of positive margins and local tumor recurrence are most likely the result of differences in patient selection. However, the comparison illustrates the point that statistically nonsignificant improvements in local tumor control have been seen with the addition of IORT to resection and standard adjuvant therapies in cohorts whose combined local recurrence risk was low (<10% in the M.D. Anderson study) and moderate (30–40% in the current study). However, a local control improvement due to IORT large enough to translate into a survival benefit in pancreatic cancer is probably only possible in a cohort of the highest-risk patients (R1/R2 resections) and perhaps even then only in concert with improved systemic therapy. That hypothesis has yet to be tested.

Where does that leave us when considering the treatment of our next patient? IORT appears to reduce or at least delay local tumor recurrence in patients undergoing pancreaticoduodenectomy. The absolute local control benefit depends on the a priori risk of local recurrence. Patients undergoing R0 resection treated with standard adjuvant therapies do not appear to benefit from IORT. IORT should only be considered in patients who are judged to have incompletely resected disease (R1 or R2 resections) intraoperatively. Although a dedicated study of the impact of IORT following R1/R2 resection has not been performed, IORT should continue to be explored in this subgroup in parallel with novel systemic therapies.

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