Intensifying local radiotherapy for pancreatic cancer—who benefits and how do we select them?

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Intraoperative radiation therapy (IORT), the delivery of radiation at the time of surgery, has a long history in the annals of the clinical management of cancer patients. The earliest attempt to irradiate tumors intraoperatively dates back to 1909 when Carl Beck drew gastric and colon cancers to the abdominal incision to expose them to ionizing radiation (1). Unfortunately, these initial efforts were unsuccessful due to limitations of beam energy, dose rate, and equipment. Renewed interest in IORT in more modern times came about from the increasing clinical experience in the US and Japan using megavoltage beams in the 1970s and 1980s and the experimental studies in large animals in the 1980s that defined the tolerance limits of normal tissues to large doses of radiation administered as a single intraoperative fraction (2,3).

The distinct advantages of IORT are the ability to expose the tumor to a high dose of radiation while physically shielding or displacing adjacent critical normal structures away from the beam path, the ability to visualize the treatment field and limit set-p uncertainties, the higher biologic effectiveness of single-fraction radiation therapy, the logistical convenience of substantially reducing the number of treatments, and the potential increased radiosensitivity of oxygenated intact tumors or freshly resected tumor beds. Despite these theoretical and practical advantages, the widespread adoption of IORT has been stymied by the lack of conclusive evidence of tangible clinical benefit in randomized studies, the logistical challenges of transporting anesthetized patients to linear accelerators, and/or the additional costs involved with shielding operating rooms when the linear accelerator is relocated to the operating room.

In recent years, there has been a resurgence of interest in IORT due to the advent of mobile IORT platforms. These include the mobile linear accelerator units with in-built shielding mechanisms delivering electron beams, the flexible high-dose rate brachytherapy applicators using Ir-192, and the miniaturized kilovoltage X-ray sources. These technological advances coincided with the increasing interest in accelerated partial breast irradiation as a convenient, cost-effective and safe treatment alternative to full-dose conventional whole breast radiation therapy for select low-risk breast cancer patients. Therefore, the last decade has witnessed an explosion in the number of cancer centers with IORT capability, the treatment of patients with IORT worldwide, and the enrollment of patients on clinical trials evaluating IORT as a viable treatment strategy. In fact, there have been more patients enrolled on a multicenter randomized international trial of breast cancer treatment with IORT *vs.* whole breast radiation than in all of the previously reported randomized IORT studies in previous decades (4). In parallel with this resurgence in IORT interest spawned by technological advances, there have been advances in chemotherapeutic management of systemic disease that has made it increasingly important to achieve effective and durable control of the primary disease with local therapies, thus providing a shot in the arm for intensification of radiation treatment via techniques such as IORT.

The accompanying article by Ashman *et al.* reports the Mayo Clinic Scottsdale experience with preoperative chemoradiation therapy combined with a mobile electron accelerator IORT for locally advanced and borderline resectable pancreatic cancer patients (5). Among 48 patients treated between 2002 and 2010 with chemoradiation therapy with the intent of resection and IORT, 31 patients underwent an attempted resection. Sixteen of these patients were able to undergo a R0/R1 resection whereas one patient underwent an R2 resection and the remaining 14 patients did not undergo resection. Twenty eight of these thirty one operated patients received IORT. Patients who had R0/R1 resections (with IORT) had significantly better

median overall survival durations (23 *vs.* 10 months, P=0.002) than those who had R2 resection or no resection (with IORT). Since there were no patients without IORT who were part of the study, it remains unclear what role the IORT played in the survival outcomes achieved. It also remains unclear whether the inability of nearly half of all patients (16 of 31) to receive chemotherapy after IORT may have adversely affected overall survival of these patients. What might seem, on the surface, easier to discern is whether the additional IORT improved local control? While recognizing that comparisons to historical controls are fraught with flaws and that assessment/reporting of local control is particularly challenging in pancreatic cancer patients, the reported local failure rate of 29% in unresected patients who underwent IORT seems to compare favorably to that reported for locally advanced pancreatic cancers who do not undergo IORT. While this hints at a potential local control benefit from escalated doses of radiation to the retroperitoneal margin, given the competing risk for frequent and rapid metastatic dissemination of these aggressive tumors, it is not surprising that a potential local control benefit does not translate to a survival benefit. Similar findings were reported in a recent multi-institutional retrospective analysis of IORT for resected pancreatic cancer patients where local control was excellent but there was no improvement in overall survival (6). Undoubtedly, controlling systemic disease is of paramount importance in pancreatic cancer, but the unanswered question is whether there may be a subset of patients who might benefit from radiation dose escalation (with IORT or otherwise). Parenthetically, the issue at hand is whether we can select our patients better so as to (I) identify patients with strictly borderline/locally advanced non-metastatic disease *a priori* and treat them with chemoradiation therapy and (II) intensify this local therapy in those patients who are likely to have local tumor progression as the predominant source of disease-related mortality?

Improvements in imaging techniques have significantly enhanced our ability to identify the extent of locoregional disease in the pancreas and stratify pancreatic cancer into potentially resectable, borderline resectable, and locally advanced. Nevertheless, accurate identification of metastatic disease remains a challenge because of the frequent occurrence of occult metastatic deposits in the liver and peritoneum that are not readily visualized non-invasively by current imaging technology. We and others have addressed this therapeutic dilemma by using induction chemotherapy to either treat micrometastatic disease or give occult metastatic disease an opportunity to manifest itself on subsequent imaging (7,8). By excluding patients with metastatic disease identified on repeat imaging

after chemotherapy, the pool of patients who undergo consolidative chemoradiation therapy is enriched with those who are most likely to have localized non-metastatic disease. Concentrating a localized treatment modality on these patients offers the possibility of these patients reaping the maximum benefit of standard chemoradiation therapy. With the advent of newer chemotherapeutic regimens with greater systemic efficacy like FOLFIRINOX and gemcitabine-abraxane, this sequencing of chemotherapy followed by chemoradiation therapy may further select patients for maximum benefit from chemoradiation therapy.

The next challenge is to further select these patients for intensification of local therapy with a focal radiation boost in those patients predicted to have a pattern of failure where local relapse is the dominant site of recurrence. Indeed, there is converging evidence that, contrary to the widespread perception that all patients with pancreatic cancer die as a result of distant metastatic disease, complications of local tumor progression are a significant source of disease-related mortality. Selecting these patients for intensified radiation therapy is therefore a viable therapeutic strategy if a biomarker of local-dominant biology can be identified and validated. A recent autopsy study of pancreatic cancer patients noted that intact Smad4 expression in tumors predicts for a predominantly loco-regional failure pattern (9). This correlation was also observed in locally advanced pancreatic cancer patients treated with chemotherapy followed by chemoradiation therapy (10). This provides a rationale for potentially personalizing and intensifying radiation therapy via a focal boost in patients with intact Smad4.

In summary, the landscape of treatment strategies for pancreatic cancer is evolving and improvements in systemic therapy will necessitate improvements in local therapy as well. Selecting patients for more intense radiation therapy will require a better understanding of the biology of tumors that tend to recur locally as opposed to distantly and the deployment of techniques to achieve this intensification of radiation therapy safely and effectively. Judicious use of IORT for borderline resectable/unresectable pancreatic cancer patients will ideally be confined to patients who (I) receive induction chemotherapy, consolidation chemoradiation, and surgical resection, where possible; (II) undergo prospective collection of biomarkers (clinical, radiographic, biochemical or molecular) predictive of local-dominant biology; and (III) are monitored prospectively for toxicity. Vigilance for unique toxicities of IORT, for instance, was instrumental in identifying more pronounced mammographic changes in the tumor bed (increased calcifications and increased fat necrosis) as a result of IORT following lumpectomy for breast cancer (11). We

also envision such studies requiring the concerted effort of a consortium of centers that have IORT capabilities and expertise with pancreatic cancer management, possibly under the auspices of the American College of Surgeons Oncology Group (ACOSOG) and/or the International Society of Intraoperative Radiation Therapy (ISIORT).

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