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The Role of Intraoperative Radiation Therapy in Patients With Pancreatic Cancer

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Intraoperative radiation therapy (IORT) techniques allow for the delivery of high doses of radiation therapy while excluding part or all of the nearby dose-limiting sensitive structures. Therefore, the effective radiation dose is increased and local tumor control potentially improved. This is pertinent in the case of pancreatic cancer because local failure rates are as high as 50%-80% in patients with resected and locally advanced disease. Available data in patients receiving IORT after pancreaticoduodenectomy reveal an improvement in local control, though overall survival benefit is unclear. Series of patients with locally advanced pancreatic cancer also suggest pain relief, and in select studies, improved survival associated with the inclusion of IORT. At present, no phase III data clearly supports the use of IORT in the management of pancreatic cancer.
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Introduction

Given the radiation tolerance of normal tissues of the upper abdomen (liver, kidney, spinal cord, stomach, and bowel) to external beam radiotherapy (EBRT), total doses have generally been limited to 45-54 Gy in 25-30 Gy fractions. For locally advanced pancreatic cancer, this dose is inadequate, as demonstrated by the high rates of local tumor progression and poor survival seen in both prospective and retrospective studies. Local progression as first site of failure occurred in 58% of patients treated to 60 Gy with concurrent 5-fluorouracil in the second Gastrointestinal Tumor Study Group trial.[1] Similarly, the Mayo Clinic reported a local failure rate of 72% for 122 patients with unresectable pancreatic cancer treated with EBRT doses of 40-60 Gy.[2] For the minority undergoing pancreaticoduodenectomy, local failure rates of 50%-86% are seen following surgery alone.[3-7] This is, in part, owing to frequent lymphatic involvement and cancer invasion into the retroperitoneal soft tissues with an inability to achieve wide retroperitoneal soft tissue margins because of anatomical constraints such as arterial and venous vasculature.[8] The incidence of microscopic residual disease following pancreaticoduodenectomy after careful evaluation of the posterior peripancreatic soft tissue margin is reported to be as high as 40%.[9] Given these high local failure rates, attempts have been made to evaluate whether dose escalation may improve outcomes through 3-dimensional conformal EBRT, intensity-modulated radiotherapy (RT), stereotactic body RT, and intraoperative RT (IORT). This review focuses specifically on the role of IORT.

IORT and Early Studies

IORT is the delivery of RT at the time of surgery. A variety of techniques including intraoperative electron beam and high–dose rate brachytherapy IORT can accomplish this goal (Figs. 1 and 2). The advantage of IORT techniques is the delivery of high doses of RT to a targeted area while excluding part or all of the adjacent dose-limiting sensitive structures, thereby precisely increasing the effective dose to the region of the tumor.[10] This technique has been evaluated in both patients who have undergone pancreaticoduodenectomy as well as those who undergo treatment for locally advanced pancreatic cancer.

Reports of techniques similar to IORT were described as far back as the early 1900s although the modern approach to IORT was developed in the 1960s at the University of Kyoto. In these early studies, resection was followed by IORT doses of 25-30 Gy.[11] A study conducted in Japan evaluated patients treated between 1973 and 1982 to IORT doses of 20-40 Gy. An improvement in survival was seen in patients receiving IORT compared with the control arm, and nearly 50% of patients experienced relief of pain.[12] These studies prompted investigators at Massachusetts General Hospital and the Mayo Clinic to evaluate this approach in the early 1980s. Initial data from Massachusetts General on patients

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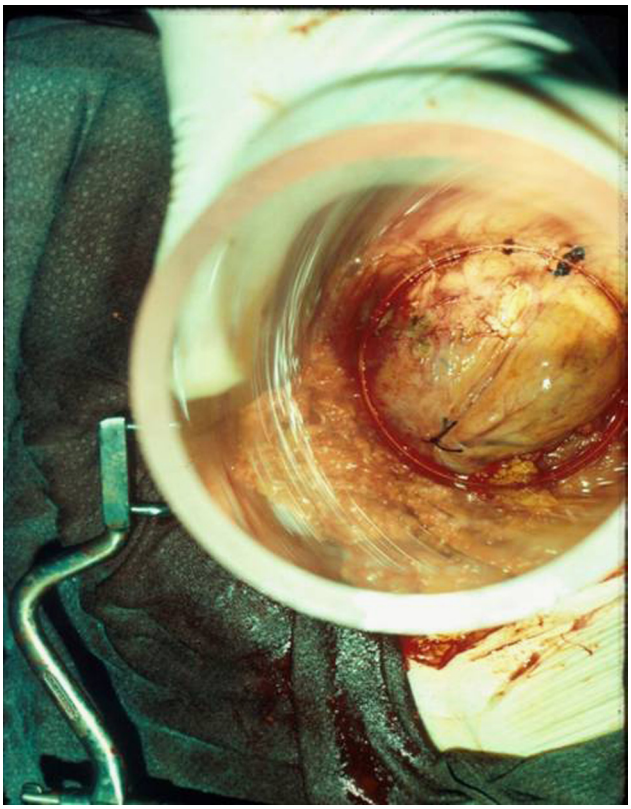

Figure 1 Beam's view of an intraoperative electron beam applicator to treat a patient with locally advanced pancreatic cancer. (Color version of figure is available online.)

with unresectable pancreatic cancer receiving IORT doses of 20 Gy in combination with EBRT showed a median survival of 16.5 months, with approximately 50% of patients achieving resolution of pain after treatment.[13] A retrospective analysis of 159 patients from the Mayo Clinic treated between 1974 and 1985 evaluated IORT in addition to postoperative EBRT. An improvement in local control was seen at both 1- and 2-year time points, though no improvement in survival was seen.[2]

IORT in Resectable Disease

Given the complexity and potential morbidities related to pancreaticoduodenectomy, there was initial concern of increased toxicity with IORT in combination with surgery. Feasibility in the United States was demonstrated as early as 1983 at the National Cancer Institute, where a patient with locally advanced pancreatic cancer underwent total pancreatectomy with portal resection and IORT to the tumor bed and regional nodes, remaining disease free after nearly 20 months. Thereafter, the National Cancer Institute reported an experience evaluating 24 additional patients randomized to receive IORT (20 Gy) with EBRT (stages II-IV). Excluding 7 perioperative deaths, an improvement in local control and median survival was seen in the patients who received IORT (OS 18 vs 12 months; $P = 0.01$).[14]

Additional data using IORT following pancreatic cancer resection are limited to single- or multi-institutional

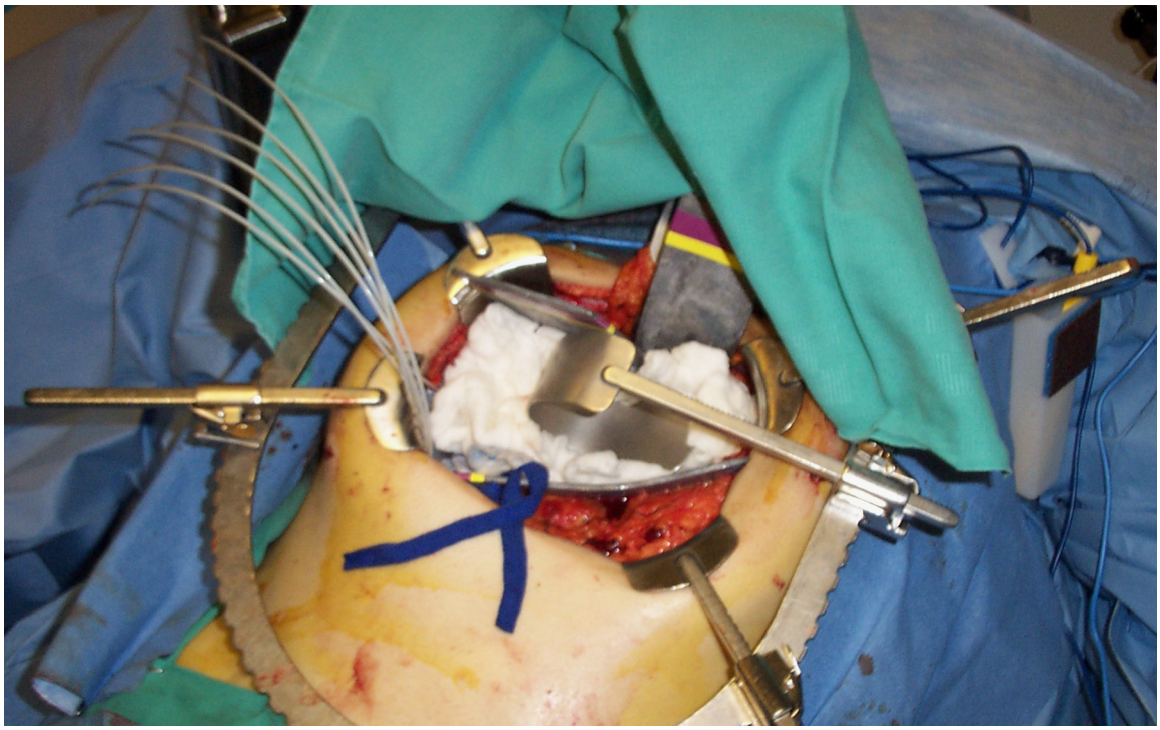

Figure 2 High–dose rate (HDR) intraoperative radiotherapy. Placement of flexible applicator in the resection tumor bed, packed to minimize applicator movement. (Color version of figure is available online.)