Studies of intraoperative radiotherapy in carcinoma of the pancreas

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Summary

Intraoperative radiotherapy (IORT) involves the administration of therapeutic radiation to malignancies during surgical procedures. IORT permits high dose delivery to tumors with the simultaneous reduction of radiation exposure to normal tissues, which may be directly shielded or operatively mobilized from the treatment volume. IORT has been investigated in various intra-abdominal malignancies, including carcinoma of the pancreas. Techniques of IORT were initially developed in Japan during the 1970's. Reports of therapeutic benefit in some patients with unresectable pancreatic cancer encouraged further examinations by various institutions in the United States. Experiences at the Massachusetts General Hospital in the early 1980's suggested that IORT enhanced survival in selected patients with locally advanced but non-metastatic disease. However, subsequent investigations by a variety of institutions, including the Mayo Clinic, failed to establish any conclusive evidence that IORT significantly prolonged the survival enhancement of unresectable pancreatic cancer patients. A prospective multi-institutional study carried out by the Radiation Therapy Oncology Group (RTOG) showed an 8-month median survival, similar to conventional therapy and indicating that IORT failed to prolong survival. However, the RTOG did show that IORT rapidly and consistently palliated the severe visceral pain which often accompanied pancreatic cancer. By 1990, some institutions had explored IORT as an adjunct to pancreatectomy, in patients with resectable tumors. Studies typically involved highly selected uncontrolled patients but did suggest that IORT could enhance local disease control and, in some cases, overall survival, when performed in conjunction with pancreatic resection. IORT appeared to be most conspicuously beneficial when used with extended radical resections. A small prospectively randomized trial conducted at the National Cancer Institute showed significant improvement in local disease control in patients receiving IORT compared with patients receiving conventional external beam postoperative radiotherapy after resection. Current evidence suggests that IORT may have an important palliative role in patients with unresectable pancreatic cancers, ameliorating visceral pain and promoting local control of the primary tumor; however, IORT appears to have no significant effect on overall survival. For patients with resectable disease, especially patients with locally extensive tumor, IORT appears to have benefit in enhancing disease control and in some cases survival. It is reasonable to further explore the potential role of IORT in pancreatic cancer, especially as a component of multimodal therapy, since IORT's demonstrated enhancement of local control could be an important factor in eventual disease control.

Key words: cancer, intraoperative radiotherapy, malignancy, pancreas, radiation, therapy

Background

Carcinoma of the pancreas frequently is a devastating disease, which often results in the death of patients in spite of all types or intensity of treatment. Pancreatic cancer is the fourth leading cause of mortality from malignant disease in the United States [1], with an overall five-year survival rate under 5% [2]. This dismal prognosis is to the natural history of the disease which disseminates early and results in incurable stages by the time of clinical presentation, to the lack of sufficiently sensitive screening and diagnostic techniques to consistently enable diagnosis at early stages which are the most likely to be cured, and to the paucity of effective therapeutic agents for advanced disease.

Pancreatic cancer most commonly presents at advanced stages. Various chemotherapeutic agents and regimens have shown activity against carcinoma of the pancreas. However, clinically meaningful responses resulting in obvious disease regression or significant prolongation of survival are uncommonly seen. A frequent feature characterizing end-stage carcinoma of the pancreas is the inexorable progression of local disease which produces anorexia, gastric outlet dyskinesis, and unremitting visceral pain. Typically, systemic therapy produces little relief of these difficult symptoms. Radiation therapy sometimes has palliative benefit in ameliorating visceral pain and in stabilizing the size of the primary tumor mass within the pancreas. Consequently, radiotherapy is utilized with great regularity in the management of advanced pancreatic cancer. Unfortunately, it can be difficult to effectively deliver high doses of radiation to pancreatic tumors, and conventional abdominal radiotherapy is often poorly tolerated by debilitated patients with the disease.

Surgical resection currently is the only therapeutic modality capable of curing pancreatic cancer, although long-term survival is expected only in relatively small numbers of patients. In a review of 2,398 resected patients published in the late 1980's, Gudjonsson found only a 3.8% five-year survival rate [2]. In highly-selected patients undergoing surgery performed in centers specializing in pancreatic resection, cure rates can be somewhat improved. Five-year survival rates of 18% to 25% have been recently reported.
[3—5]. Such improvements in long-term survival have been mainly attributed to declining morbidity and mortality following pancreatic resection rather than to improvements in the scope or efficacy of surgical resection itself [6—8].

Even when a potentially curative pancreatectomy is performed, local disease recurrence is common and is seen in over 50% of resected patients [9]. Radiation therapy is widely utilized to promote the local control of a variety of malignancies as an adjunct to surgical resection. Combined with concomitant 5-fluorouracil chemotherapy, postoperative irradiation following pancreatectomy has been demonstrated to improve the survival of resected patients compared to surgery alone in multi-institutional prospectively controlled clinical trials [10]. The toxicity of radiotherapy to the upper abdomen is however considerable and is often poorly tolerated, therefore somewhat limiting the applicability of routine irradiation for resected patients.

Intraoperative radiotherapy (IORT) is a modality for allowing irradiation of tumors or of tissues potentially harboring malignant cells at the time of surgery. IORT theoretically permits the delivery of high radiation doses to regions of malignant disease, which can be operatively exposed at the time of surgery. Simultaneously, IORT permits the sparing of radiation exposure to radiosensitive normal tissues in the region of the tumor volume. Normal tissues may be operatively mobilized out of the radiation volume or may be operatively directly shielded. IORT therefore permits the delivery of high radiation doses while lowering the risk of radiation-related toxicity. Because of the generally poor tolerance of conventional radiotherapy by patients with carcinoma of the pancreas, IORT has generated considerable interest as a potential therapeutic modality in pancreatic cancer treatment.

**Methods of intraoperative radiation**

IORT involves methods to deliver maximum doses of radiation to regions at risk for harboring neoplastic cells while simultaneously attempting to spare normal tissues in the region from potentially damaging radiation exposure. IORT is delivered as a single radiation fraction during surgery, with operative exposure of tumor and with attempts to physically displace or to shield normal tissues from the delivered irradiation volume.

The majority of institutions performing IORT have physically separate operating and radiotherapy suites, necessitating patient transfer for the surgical and radiotherapeutic phases of treatment. A patient undergoing IORT is explored in the operating room, with appropriate tumor resection and exposure of tissues at risk for containing residual tumor. Following tumor resection and delineation of the regions to be irradiated, the surgical incision is temporarily closed and protected from contamination. While maintaining anesthesia, the patient is then transported to the radiotherapy treatment room. With the patient positioned on the radiation treatment table, the incision is reopened, and the radiation field is defined, typically making liberal use of self-retaining retractors to maintaining exposure. The treatment volume is then constructed by placement of treatment applicators (typically acrylic or stainless steel cylinders of various sizes), which serve primarily to collimate the IORT treatment beam and secondarily to prevent mobile viscera such as intestine from falling into the treatment volume. The patient is then irradiated, a process requiring usually less than five minutes, while surgical and radiotherapeutic personnel leave the room. During the delivery of IORT, the patient is remotely monitored electronically. Following irradiation, the treatment applicator is removed, completing the IORT procedure. Remaining surgery is then conducted in the radiation treatment room for simple incision closures. If extensive is surgery required, such as reconstruction of the gastrointestinal tract, the patient is transported back to the operating theater for completion of the operative procedure.

Some institutions have a dedicated IORT suite, a combination operating and radiotherapy room, which simplifies the logistics of IORT delivery by eliminating the need to transport patients under anesthesia between physically separated surgical and radiotherapeutic facilities. Most institutions performing IORT utilize electron beam radiation in order to limit the radiation dose to radiosensitive normal structures which might underlie regions of tumor which are irradiated. High-energy electron radiation from a linear accelerator has a steep fall-off in dose at tissue depths which are precisely defined by the electron energy. X-ray and photon radiation, because of deep tissue penetration and the consequent possibility of unacceptably high dose delivery to tissues deep to tumor, are poorly suited to intraoperative applications and are uncommonly used for IORT procedures.
Intraoperative radiotherapy in carcinoma of the pancreas

Since the initial investigations of intraoperative radiotherapy during its developmental phases, IORT has been considered as a potential approach to the treatment of pancreatic cancer. Since higher radiation doses can be delivered to the pancreas than achievable by conventional techniques, IORT theoretically could promote local disease control in pancreatic malignancies. Early IORT experiences included examinations of the feasibility of treating advanced pancreatic malignancies and the resultant effect on disease control.

An early pilot series was reported by Goldson [13] in which 19 patients with advanced pancreatic cancer received IORT. The feasibility of delivering IORT to pancreatic neoplasms was demonstrated. There were no obvious toxicities associated with the technique, although no patient survived sufficiently long to suggest any therapeutic benefit. A larger Japanese experience of 108 patients with locally advanced and metastatic pancreatic cancer demonstrated no IORT-associated complications. The median survival for the overall group was 6 months [14]. The Massachusetts General Hospital (MGH) accumulated a series of 16 patients with unresectable pancreatic cancer treated with IORT in combination with conventional external beam radiotherapy (EBRT). These patients showed an encouraging median survival of 18 months [15]. Based on the anecdotal early experiences, many investigators felt there was ample suggestion of a possible benefit of IORT in pancreatic cancer. Various institutions accumulated information attempting to define the therapeutic role of IORT in pancreatic cancer, both in locally advanced and in locally confined stages. Although few studies represented prospectively controlled clinical trials which, by their nature, precisely define the value of any new therapy compared with the standard, various clinical series were sufficient to establish several tentative conclusions concerning the applicability and utility of IORT in carcinoma of the pancreas.

Intraoperative radiotherapy in unresectable carcinoma of the pancreas

A considerable proportion of the early clinical experiences with IORT in treating locally advanced unresectable pancreatic carcinoma was accumulated at MGH. The initial series reported by MGH included 15 patients with pancreatic cancer [15]. All patients were demonstrated a laparotomy to have locally unresectable disease and to have no visceral or peritoneal metastases. Patients received IORT to the primary tumor at doses of 15-20 Gy. Patients also received 45-50 Gy conventional external beam radiotherapy to the upper abdomen, often with concomitant chemotherapy. The observed median survival of 17 months was approximately double the expected survival for a similar patient group treated by conventional radiation and chemotherapy. More than half of the IORT patients appeared to have local control of the primary lesion, with no demonstrated evidence of local progression during the follow-up period. MGH treated additional patients and reported a similar median survival of 17 months [16]. However, a fall in median survival was observed to 12 months, as MGH began to accumulate larger numbers of patients with unresectable pancreatic cancer, possibly in so doing treating patient group which was less select but more representative of pancreatic cancer patients as a whole.

Early experiences with IORT in unresectable pancreatic cancer were accumulated at the Mayo Clinic [17]. Forty-four patients with locally unresectable pancreatic cancers and no obvious distant metastases received 20 Gy IORT to the primary lesion and 45-50 Gy fractionated external beam radiotherapy. Overall median survival was 11 months, compared with a 9-month median survival expected for a similar group treated conventionally. Disease progression was clinically documented in 71% of patients treated with IORT, although only 7% were considered to have progressed within the IORT field.

In an effort to critically examine the potential role of IORT in the treatment of patients with unresectable pancreatic cancer, a phase I-II multi-institutional trial was conducted by the Radiation Therapy Oncology Group (RTOG). Patients with locally unresectable but nonmetastatic pancreatic carcinoma underwent laparotomy with the delivery of IORT 917-22 Gy to the primary. Postoperative external beam radiotherapy (50 Gy) was delivered concomitantly with 5-fluorouracil chemotherapy. Fifty-one patients were treated. The median survival was 9 months, with a two-year survival of 6% [18]. The trial noted the frequent control of visceral pain by IORT. However, no evidence emerged of any substantial prolongation of survival associated with IORT administration.

Intraoperative radiotherapy combined with pancreatic resection

Because of the surgical complexities involved with pancreatic resections, some investigators examining IORT in its early developmental stages expressed concern that the addition of IORT to pancreatectomy could result in increased or unexpected toxicity. However, the technical feasibility of the use of IORT in combination with pancreatic resections for cancer was demonstrated by 1983 at the National Cancer Institute (NCI), where a patient with advanced cancer was reported to be disease-free for more than 19 months following extended pancreatectomy with portal vein resection and intraoperative radiotherapy delivered to the resection bed and regional nodal basins [19]. Because of the complexities of delivering IORT in combination with extensive pancreatic surgery, a significant experience was slow to accumulate using IORT as an adjunct to pancreatectomy.

Kyoto University explored the use of IORT with pancreatic resection [20—21]. Twenty-three patients underwent pancreatectomy for localized disease and had IORT (25-30 Gy) delivered to the resection bed. Most patients had additional conventional external beam radiotherapy pre- or postoperatively (total EBRT dose 60-70 Gy). The five-year survival was 19%. Eighteen patients had resections which were considered noncurative because of disease extension or...
nodal involvement. These patients received IORT and EBRT in addition to suboptimal resection of the primary tumors. The patients receiving IORT had a median survival of 14 months, significantly greater than the 4-month median survival of a comparative series of noncuratively-resected patients who received no radiotherapy.

Hiraoka and colleagues at Kumamoto University reported 12 pancreatic cancer patients who underwent pancreatectomy with adjunctive IORT (30 Gy), comparing the clinical results with 12 patients undergoing similar resections without radiotherapy [22]. There were four treatment-related deaths in the total series, but no deaths occurred in patients receiving IORT. At 12 months, 50% of IORT patients were alive, compared with only 25% of resection alone patients. In a subsequent report, Hiraoka treated 16 patients with extended pancreatectomy, including wide nodal dissection and portal vein resection, and delivered IORT (30 Gy) to the resection bed [23]. A comparison group of nine patients underwent extended pancreatectomy alone. At 5 years, 29% of IORT patients were alive, compared to none of the non-IORT patients.

Zerbi et al. from the University of Milan reported a comparison study involving IORT in patients with resectable pancreatic cancer between 1985 and 1993 [24]. A total of 90 patients underwent pancreatecoduodenectomy. IORT (13-20 Gy) was delivered to the tumor bed in 43 patients. No IORT was given to 47 patients. No postoperative adjunctive radiotherapy or chemotherapy was administered to either patient group. Tumor size, adequacy of resection, morbidity, and mortality were similar between IORT and non-IORT patients. IORT significantly improved the median time to relapse (13 months for IORT patients, 8 months for surgery alone patients). Similarly, IORT enhanced the local disease control rate (27% local recurrence for IORT patients, 57% for surgery alone patients). Overall survival was higher in IORT patients (71%) compared to surgery alone (49%). At one year IORT patients had a 71% survival, compared with 49% for surgery alone patients; at two years, IORT survival was 24%, non-IORT. The observed survival differences were not statistically significant because of small patient numbers.

A prospectively randomized controlled clinical trial of IORT in resectable pancreatic cancer was performed at the National Cancer Institute (NCI). Twenty-four patients with resected pancreatic adenocarcinomas were randomized to receive IORT (20 Gy) to the resection bed or to receive standard control treatment. Standard therapy was defined as resection alone for patients with disease confined within the pancreatic capsule; standard therapy also included postoperative external beam radiotherapy (45-55 Gy) for patients with extrapancreatic extension or nodal disease. Study patients had locally advanced disease which would be considered unresectable by conventional criteria; however, patients were able to undergo extensive exirpative surgery to grossly remove the primary tumor, procedures frequently requiring extensive resections including portions of the portal vascular system. Because of the particularly extensive surgical procedures, the toxicity was considerable. The overall perioperative mortality was 27% and morbidity was 71%, although the mortality and morbidity did not differ statistically between IORT and control groups. The median survival of IORT patients was 18 months, compared to 12 months for control patients. Local recurrences occurred in all of 12 control patients (100%) but only in four of 12 IORT patients (33%). One IORT patient remained alive without evidence of disease more than 15 years following therapy at the NCI. Because of small patient numbers, statistically significant survival differences were not reached between IORT and control groups.

Conclusions
At present, intraoperative radiotherapy must be considered an experimental treatment. Available clinical information suggests that the use of IORT permits higher doses of radiation to be delivered to intra-abdominal sites than conventional fractionated techniques, with reduced radiation-related toxicity to most normal tissues. This higher total dose delivers appears to enhance local control rates, compared to conventional radiation. Thus, IORT can theoretically enhance therapeutic results for locally aggressive tumors, such as pancreatic carcinoma, which are difficult to treat and which are difficult to irradiate by conventional means because of limited radiation tolerance of surrounding normal tissues.

In unresectable pancreatic cancers, IORT has been demonstrated to improve local tumor control without significant toxicities, although no survival advantage has resulted from the enhanced local control. IORT can effectively and rapidly palliate the visceral pain which frequently accompanies locally advanced pancreatic cancers and consequently does have benefit to some patients. Further investigations appear warranted of IORT in unresectable pancreatic cancer where IORT is combined with other regional and systemic modalities.

For resectable pancreatic cancers, available studies indicate that the combination of IORT with pancreatectomy is feasible and does not lead to increased morbidity or mortality compared to surgical resection alone. IORT consistently enhances local tumor control in pancreatic resection beds. Major improvements in survival have been seen in some series combining IORT with pancreatectomy. Certain institutions have failed to show that IORT consistently enhances survival following pancreatic resection, but total experiences in the adjunctive use of IORT have been rather limited in number. It seems reasonable to speculate that the enhanced local control provided by IORT may have an important survival benefit. It is likely that the enhancement of survival provided by improved local control may become more apparent when effective systemic therapeutic adjuncts are discovered which reduce the incidence of widespread metastases, the usual clinical finding of pancreatic cancer late in its course.

In institutions with the capability to deliver IORT, intraoperative irradiation should be considered routinely in patients with locally advanced pancreatic carcinomas which appear technically possible to resect. Alternatively in centers without the capability to deliver IORT, referral of patients with to IORT facilities should be contemplated. The application of IORT in such patients should be performed in
the context of approved trials designed to evaluate the efficacy and toxicity of IORT in specific clinical situations. The referral and inclusion of patients with pancreatic malignancies will be important in final assessments of the overall role of intraoperative radiotherapy in comprehensive cancer treatment.

References


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