Role of Radiation Therapy in the Management of the Patient With Pancreatic Cancer

Review Article [1] | September 01, 1996
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Most patients who have pancreatic cancer present with advanced disease that is not amenable to surgery. For patients whose disease is amenable to surgery and who are managed with surgical resection alone, local disease control is often not achieved because of the high rate of local recurrence [9]. Therefore, additional treatment with radiation therapy is often used to improve local control of the disease. Radiation therapy is also used to treat unresectable disease, either as a palliative measure to relieve symptoms or as a neoadjuvant treatment to improve resectability.

Introduction

Treatment strategies for patients with pancreatic cancer differ based on disease stage. Standard treatment strategies for patients with T1-T2,NX,M0 disease include surgical resection and adjuvant or, less commonly, neoadjuvant chemoradiation, whereas therapy for unresectable presentations includes surgical bypass procedures, radiation therapy, and/or chemotherapy [1].

Pancreatic cancer is particularly challenging for the radiation oncologist because of the limited radiation tolerance of adjacent organs in the upper abdomen, including the kidney, liver, stomach, small bowel, and spinal cord [2]. The radiotherapy technique usually used to treat pancreatic cancer is conventional external-beam radiotherapy (EBRT), although more specialized techniques, such as intraoperative radiotherapy (IORT) and brachytherapy, have been described. Intraoperative radiotherapy involves the application of a single high dose of radiation during a surgical procedure, while brachytherapy entails the interstitial implantation of radioactive sources [1,3].

Radiation therapy can be potentiated with the use of radiosensitizing chemotherapeutic agents. One such agent, fluorouracil (5-FU), has been shown to be a radiosensitizer in vitro [4]. More recently, in vitro experiments reported by Shewach and Lawrence showed that the chemotherapeutic agent gemcita-bine (Gemzar), a deoxycytidine analog, produced increased radiation sensitivity in human colon carcinoma (HT-29) cells [5].

Resectable or Borderline Unresectable Disease

Preoperative Radiation Therapy

Pilepich and Miller examined preoperative (neoadjuvant) radiation therapy as a means of improving the efficacy of surgical resection in patients with borderline resectable or locally unresectable disease [6]. In this study, patients received 4,000 to 5,000 cGy over a 4.5- to 5-week period and were evaluated for surgery 6 weeks after radiotherapy. Of 17 patients, 11 were selected for laparotomy. At surgery, 4 of the 11 patients had metastatic disease, 1 patient was determined to be locally unresectable, and 6 patients underwent resection. Only 1 of the 6 patients experienced a clear conversion from unresectable to resectable disease. The authors concluded that radical resection was possible after preoperative radiation in some patients but that a significant number of patients should be expected to develop metastatic disease during or shortly after the radiotherapy course [6].

Ishikawa et al conducted a retrospective review of the use of preoperative irradiation in 18 patients with resectable or borderline resectable disease [7]. Patients received fractionated radiation to 5,000 cGy, terminating about 1 month prior to exploratory surgery. Measurable tumor shrinkage was noted in all 18 patients, and 16 patients underwent pancreatic resection. Although these results indicate that preoperative radiation is feasible, it is not used routinely [8].

Resectable Disease

Postoperative Radiation Therapy

Historically, surgery alone has had disappointing results in patients with pancreatic cancer. For example, Tepper et al showed that surgery for resectable disease was associated with a 5-year crude survival rate of 15% and a local recurrence rate of 50% [9]. Similar results were reported by Griffin et al [10]. Based on these findings, it was suggested that postoperative radiation therapy...
might reduce the incidence of local failure after radical surgery [9,10].
A National Cancer Institute (NCI) study compared IORT with standard postoperative radiation therapy in patients with locally confined pancreatic cancer who were undergoing either total or regional pancreatectomy [11]. Patients were randomized to receive either postoperative IORT (2,000 cGy using 9 to 12 MeV to the tumor bed and regional nodal basins) or postoperative EBRT (5,000 cGy over a period of 5 to 6 weeks). Although overall survival was similar between the treatment groups, disease-free survival and local disease control were better in the IORT-treated patients than in the EBRT-treated patients. These results suggested that IORT may provide some benefit in patients with locally confined pancreatic cancer [11].

More recently, a retrospective study by Zerbi et al examined the impact of IORT following surgical resection [12]. Patients either underwent resection alone (47 patients) or resection and IORT at a dose of 12.5 to 20 Gy (43 patients). Whereas 1-, 2-, and 3-year survival rates and median disease-free survival did not differ significantly between the treatment groups, local recurrence was significantly reduced in patients who underwent resection plus IORT (27% of patients), as compared with those who had a resection only (56% of patients; P less than .01 by the chi-square and Mantel-Cox tests).

Although these results provide some support for the concept of adding of IORT to surgical resection to enhance local control, it should be noted that no survival benefit was observed. Selection factors may have contributed to the improved local control observed, and IORT remains investigational in this context [12].

**Postoperative Radiation Therapy Plus Chemotherapy**

In 1985, the Gastrointestinal Tumor Study Group (GITSG) reported the results of a randomized trial that compared surgical resection alone (N = 22) with surgical resection followed by radiation therapy plus chemotherapy (N = 21) [13]. Postoperative radiation therapy (EBRT) consisted of 4,000 cGy given in two courses of 2,000 cGy each, and chemotherapy consisted of IV 5-FU at 500 mg/m² daily during the first 3 days of each 2,000-cGy course of radiation. One month after the completion of radiation therapy, chemotherapy was continued weekly for up to 2 years or until recurrence. Accrual into the trial was slow due to the concern that patients would not tolerate surgery plus radiation and chemotherapy [14]. Nevertheless, this study demonstrated that surgery plus adjuvant radiation and chemotherapy significantly improved survival compared with surgery alone (median survival, 20 vs 11 months; P = .03 using a one-sided log-rank test) [13].

The results of the initial GITSG trial led to the design of a confirmatory trial in which an additional 30 patients received surgery plus radiation and chemotherapy [15]. Median survival was 18 months, which was similar to that observed for the adjuvant therapy group (20 months) in the initial trial. Two-year actuarial survival was 46% for the confirmatory trial patients who received adjuvant therapy, 43% for the initial trial patients who received adjuvant therapy, and only 18% for the initial trial patients who received surgery alone (Figure 1). The results of both studies supported the benefit of surgery plus radiation and chemotherapy in patients with resected pancreatic cancer [16]. The GITSG concluded that "... the combined use of radiation therapy and fluorouracil as adjuvant therapy after curative resection is effective and is preferred to no adjuvant therapy [15]." However, the use of adjuvant radiation therapy and chemotherapy has been slow to gain acceptance. Reluctance to use this treatment regimen reflects a variety of concerns, including the possibility that patients with positive surgical margins may not benefit from this treatment regimen [17], and doubt surrounding the GITSG study results due to the low patient numbers (N = 43) and lengthy recruitment time [2].

However, more-recent data continue to support the GITSG results [18]. In addition, efforts at improving postoperative adjuvant radiation therapy by using hepatic radiation and continuous-infusion 5-FU have been initiated, but whether these efforts will result in improved outcomes with acceptable toxicity is unknown [19]. Decisions about whether or not to use adjuvant therapy for patients with resectable pancreatic cancer should be made on a case-by-case basis [1].

**Locally Unresectable Disease**

**Radiation Therapy**

Haslam et al examined the impact of radiation administered to 29 patients with unresectable pancreatic cancer [20]. Radiotherapy generally consisted of 6,000 cGy given in three sequential treatments of 2,000 cGy in 10 fractions over 2 weeks, followed by 2-week intervals of rest. Fifteen of these patients also received chemotherapy, and some patients underwent palliative bypass procedures.
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Good palliation was achieved in 45% of these patients. At 2.5 years after diagnosis, 21% of the patients were alive. Although this study suggested that radiation therapy may be advantageous for patients with locally unresectable disease, it was limited by its retrospective design and indiscriminate use of chemotherapy and bypass procedures [20].

In a study reported by Dobelbower et al, 40 patients with locally unresectable pancreatic cancer received radiation therapy (5,900 to 7,000 cGy over a 7- to 9-week period) [21]. Twelve of the patients also received chemotherapy. The projected 1-year survival rate was 49%, similar to that for patients with resectable disease who were treated with surgery of curative intent. Shibamoto et al reported that radiation therapy confers a survival advantage [22]. In patients with unresectable lesions but no distant metastases, survival was longer in patients who received radiation than in historical controls who did not (P = .00003).

The decision as to whether to use radiation therapy in the patient with locally unresectable disease should include consideration of the extent of the tumor, the extent of normal tissue exposure to the radiation fields, and the patient's baseline medical and nutritional status [1]. Specialized and experimental radiation therapy techniques, including hyperfractionated EBRT, IORT, brachytherapy, high-linear-energy-transfer radiation, and charged-particle irradiation, have been considered [23-30]. The extent to which these approaches may be helpful will depend on whether they enhance locoregional control with acceptable morbidity to normal tissues and whether such enhanced control results in improved survival and quality of life.

Radiation Therapy Plus Chemotherapy
Combining 5-FU with radiation therapy may augment the effects seen with radiation therapy alone [31]. A GITSG study compared the effectiveness of radiation alone (6,000 cGy), radiation (4,000 cGy) plus 5-FU, and radiation (6,000 cGy) plus 5-FU in 194 patients with locally unresectable pancreatic cancer [32,33]. Fluorouracil was administered at a dosage of 500 mg/m² IV on each of the first 3 days of the radiation therapy course and was subsequently continued indefinitely.

After 106 patients were randomized, the radiation-therapy group was discontinued because it was found to have a significantly inferior survival rate than survival in either group that received radiation plus 5-FU (P less than .01 by the log-rank test; Figure 2). Therefore, all remaining patients were randomized to one of the radiation-chemotherapy groups.

When survival was analyzed for the second phase of the study, the higher radiation dose plus 5-FU appeared to be superior to the lower radiation dose plus 5-FU; however, this difference was not statistically significant (P = .19 by the log-rank test). In fact, at 15 months the survival curves for these two treatment regimens overlapped. This study demonstrated the benefits of combined radiation and 5-FU therapy compared with radiation alone in patients with pancreatic cancer confined to the pancreas and peripancreatic area [32,33].

Klaassen et al of the Eastern Cooperative Oncology Group (ECOG) studied 5-FU alone (600 mg/m² IV weekly) vs 5-FU plus radiation therapy (4,000 cGy) in patients with locally unresectable disease [34]. Median survival was equivalent for the two treatment groups. In the 91 patients analyzed, median survival was 8.2 months with 5-FU (N = 44) vs 8.3 months with 5-FU plus radiation (N = 47). These results suggested that patients with locally unresectable pancreatic cancer should receive 5-FU alone, because this regimen produced results similar to those obtained with 5-FU plus radiation.

A subsequent study by the GITSG disputed the results of Klaassen et al and confirmed the advantage of radiation plus chemotherapy over chemotherapy alone [35]. This study compared radiation plus combination chemotherapy (streptozocin, mitomycin, and 5-FU [SMF]) with combination chemotherapy alone. Radiation plus chemotherapy resulted in a 1-year survival rate of 41%, as compared with 19% for chemotherapy alone (P less than .02) [35].

As a result of the GITSG trial and other studies, radiation therapy plus chemotherapy has been used to improve local control and influence survival in patients with locally unresectable pancreatic cancer.

Future Directions
Novel combinations and means of administering radiation therapy and chemotherapy may yield better local control and survival for patients with resectable and locally unresectable disease [36,37]. Recent studies suggest that preoperative administration of radiation plus chemotherapy may be of benefit in selected patients [38-40], but additional study is needed to confirm these results.

Chemotherapeutic agents other than 5-FU that may provide synergistic effects when combined with radiation include mitomycin and cisplatin (Platinol). In addition, gemcitabine, a deoxycytidine analog currently in clinical trials,* has produced increased radiation sensitivity in human colon carcinoma.
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Pancreatic cancer remains difficult to treat. Current data support the use of adjuvant radiation plus chemotherapy following surgical resection. For patients with locally unresectable pancreatic cancer, data from the GITSG and other groups also support the use of radiation plus chemotherapy for palliation. Continued research into the role of radiation therapy in the treatment of pancreatic cancer is clearly warranted.

References:
23. Leichman L, Seydel HG, Stablein D, for the Gastrointestinal Tumor Study Group: Continuous


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