Pancreatic Cancer: Local Success and Distant Failure

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ABSTRACT

The cure rate for pancreatic cancer remains less than 5% despite more than 20 years of clinical trials. Nevertheless, a select group of patients benefit from therapy at all stages of disease and important concepts regarding patient care have emerged. The development of agents such as gemcitabine and docetaxel have spurred a new generation of clinical trials in pancreatic cancer. An appreciation for the results of the many adjuvant and neoadjuvant trials and the application of lessons learned in the care of these patients is necessary to design the new trials. The Oncologist 1998;3:178-188

INTRODUCTION

In 1998, approximately 29,000 people in the United States will develop pancreatic adenocarcinoma, and 28,900 people will die from this tumor [1]. Unfortunately, pancreatic cancer presents as a potentially resectable tumor in only 15% of patients. Even for patients undergoing a “curative” pancreaticoduodenectomy, five-year survival remains poor at 6%-24% [2-9]. Although a select group of patients with unresectable tumors may experience 20%-25% five-year survival, the vast majority of patients develop metastatic disease within the first year of therapy. The median survival for patients with metastatic disease is a dismal three to six months.

Due to the poor survival in patients with metastatic cancer and the high incidence of post-pancreatectomy recurrence, investigators have developed programs of adjuvant and neoadjuvant therapy to treat patients. Although success with these programs has been limited, they demonstrate important principles of therapy applicable to the new generation of treatments with agents such as gemcitabine and docetaxel. This review will briefly describe the results of chemotherapy trials in metastatic pancreatic cancer. An understanding of these trials is necessary to appreciate the design of the adjuvant and neoadjuvant trials in the disease. Moreover, we will review the history of neoadjuvant and adjuvant therapy in patients with pancreatic cancer and describe how the success of future trials is dependent on the newer, active agents. Finally, we will review new directions for clinical investigation that are under way at our own institution.

METASTATIC DISEASE

Nearly all patients with pancreatic cancer will present with or develop metastatic disease. Historically, the most active single-agent chemotherapy in advanced pancreatic cancer is 5-fluorouracil (5-FU), with response rates ranging from 0%-67%. Recent trials with 5-FU combined with leucovorin show more modest partial response rates of 0%-7% [10, 11]. Nevertheless, in the absence of other active agents, 5-FU served as the cornerstone of several combination chemotherapy regimens, most notably FAM (5-FU, adriamycin, and mitomycin) and SMF (streptozocin, mitomycin, and 5-FU). When compared with supportive care alone, 5-FU-based regimens appear to offer a survival advantage of several months [12, 13]. Although higher response rates have been noted with combination regimens containing 5-FU compared with 5-FU alone, benefits in survival have been negligible (Table 1) [12-22]. Given the limited activity of 5-FU, it is not surprising that the development of successful adjuvant and neoadjuvant therapy for pancreatic cancer will require the addition of other agents with an improved cytotoxic profile. Two agents with promising activity are gemcitabine and docetaxel.

Gemcitabine is a nucleoside analog with structural similarities to cytarabine. Initial phase I studies demonstrated activity in several tumors, including pancreatic adenocarcinoma. Two phase II studies of gemcitabine in pancreatic cancer have been completed (Table 2). Casper et al. administered gemcitabine 800 mg/m² i.v. weekly for three consecutive weeks, followed by one week rest every four weeks.
Ryan, Grossbard

to chemotherapy-naive patients with advanced pancreatic cancer and noted partial responses in 11% (5/42 patients) [23]. The toxicity profile was tolerable and included a median absolute neutrophil count (ANC) nadir of $2.0 \times 10^3$ cells/µl as well as mild to moderate flu-like syndrome in all patients. Carmichael et al. administered gemcitabine 800 mg/m² in a similar schedule to chemotherapy-naive patients with advanced or metastatic pancreatic cancer, noting partial responses in 6% (2 of 34 patients) [24].

Gemcitabine recently has been shown to be effective in patients progressing after prior treatment with 5-FU. Rothenberg et al. administered 1,000 mg/m² gemcitabine every week for seven weeks followed by a one-week rest, and thereafter every week for three weeks followed by a one-week rest [25]. The objective response rate for patients with measurable disease was 10.5%, but 27% of patients obtained a clinical benefit which was defined as improvement in pain, performance status, or weight. Burris et al. also used clinical benefit as an endpoint in comparing 5-FU to gemcitabine as initial therapy in advanced or metastatic pancreatic cancer. One hundred twenty-six patients were randomized to receive either gemcitabine 1,000 mg/m² weekly for seven weeks followed by a week of rest, then weekly for three of every four weeks, or 5-FU 600 mg/m² weekly [22]. Of those randomized to gemcitabine, 23.8% experienced clinical benefit as compared with 4.8% of those randomized to 5-FU. Median survival was 5.65 months for gemcitabine and 4.41 months for 5-FU ($p = 0.0025$). At one year, 18% of the gemcitabine patients and 2% of the 5-FU patients were alive. Neutropenia was the most significant toxicity, with 23% of the patients receiving gemcitabine and 5% of the patients receiving 5-FU experiencing at least grade 3 neutropenia. Despite the advantages of using gemcitabine compared with 5-FU in terms of median survival and clinical benefit, all the patients randomized to gemcitabine died within 18 months. Nevertheless, the activity of gemcitabine in metastatic disease suggests that it may have a more important role in earlier stages of disease.

Similarly, docetaxel has activity in pancreatic cancer. Rougier et al. administered docetaxel 100 mg/m² every three weeks to 17 patients with advanced or metastatic pancreatic cancer [26]. Five patients (29%) with metastatic disease had partial responses, while 2/6 (33%) with locally advanced pancreatic cancer had improvement in CA 19-9, performance status, and tumor size (though not precisely measurable). All patients experienced NCI grade 3 or 4 neutropenia and no toxic deaths were reported. Abbruzzese et al. administered docetaxel 100 mg/m² every three weeks to 16 patients with metastatic disease, of whom 10 were evaluable [27]. Two patients had partial responses as well as clinical benefit (pain and performance status); two more patients experienced

<table>
<thead>
<tr>
<th>Table 1. Phase III trials of chemotherapy in advanced pancreatic cancer</th>
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<tbody>
<tr>
<td>Regimens</td>
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<tr>
<td>Control versus 5-FU, cytoxan, methotrexate, vincristine, mitomycin (Mallinson regimen) [12]</td>
</tr>
<tr>
<td>Control versus 5-FU, lomustine [14]</td>
</tr>
<tr>
<td>5-FU versus 5-FU, adriamycin versus 5-FU, adriamycin, mitomycin (FAM) [15]</td>
</tr>
<tr>
<td>5-FU versus 5-FU, adriamycin, cisplatin (FAP) versus Mallinson regimen [16]</td>
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<tr>
<td>Control versus FAM [13]</td>
</tr>
<tr>
<td>5-FU, leucovorin versus 5-FU, leucovorin, ifosfamide [17]</td>
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<tr>
<td>FAM versus streptozocin, methotrexate, 5-FU (SMF) [18]</td>
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<tr>
<td>Mitomycin, 5-FU versus SMF [19]</td>
</tr>
<tr>
<td>5-FU, methylCCNU versus 5-FU, methylCCNU, streptozocin [20]</td>
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<tr>
<td>FAM versus SMF (with 5-FU on days 1 and 8) versus SMF (with 5-FU on days 1-5) [21]</td>
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<tr>
<td>5-FU versus Gemcitabine [22]</td>
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<tr>
<td>Gemcitabine [22]</td>
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*No statistical difference for entire cohort.

<table>
<thead>
<tr>
<th>Table 2. Phase II trials in advanced pancreatic cancer</th>
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<tbody>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Cisplatin/5-FU [85]</td>
</tr>
<tr>
<td>Epirubicin/cisplatin/5-FU (ECF) [86]</td>
</tr>
<tr>
<td>Ifosfamide [87]</td>
</tr>
<tr>
<td>Irinotecan [88]</td>
</tr>
<tr>
<td>Taxol [89]</td>
</tr>
<tr>
<td>Octreotide [90]</td>
</tr>
<tr>
<td>Edatrexate [91]</td>
</tr>
<tr>
<td>Gemcitabine (chemonaive) [23]</td>
</tr>
<tr>
<td>Gemcitabine (chemonaive) [24]</td>
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<tr>
<td>Gemcitabine (5-FU refractory) [25]</td>
</tr>
<tr>
<td>Docetaxel [26]</td>
</tr>
<tr>
<td>Docetaxel [27]</td>
</tr>
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clinical benefit, but no measurable partial response. At a dose level of 100 mg/m², the median nadir ANC was 200 cells/mm³, requiring dosage reduction to 75 mg/m² in five patients.

Beyond their documented activity as single agents in metastatic pancreatic cancer, gemcitabine and docetaxel may have a role as potent radiosensitizers. Preclinical studies of gemcitabine have shown potent radiosensitization effects in human colon and pancreatic cancer cell lines [28-31]. These effects parallel the intracellular depletion of dATP. The radiosensitization effect had no correlation with dFdCTP and dFdCMP incorporation into DNA, suggesting that the inhibition of ribonucleotide reductase is the key mechanism of action [30]. Similarly, docetaxel has potent radiosensitizing effects in vitro and in vivo [32-34].

Preliminary data from clinical trials with gemcitabine and concomitant radiation are promising. Eisbruch et al. administered gemcitabine 300 mg/m² every week during radiotherapy to eight patients with head and neck cancer [35]. Seven patients had at least grade 3 skin toxicity, and all patients had grade 3 mucositis. Seven of eight patients had clinical and pathological complete responses. Furthermore, tumor biopsies obtained after the gemcitabine infusion documented intracellular levels of phosphorylated gemcitabine equivalent to those levels shown to be radiation sensitizing in vitro. Merlano et al. combined gemcitabine 800 mg/m² days 5, 12, and 19 every 28 days, cisplatin 20 mg/m² days 1-5 every 28 days, and radiation weeks 2, 3, 4 and 6, 7, 8 to patients with head and neck cancer [36]. All of the initial four patients treated demonstrated a complete response to therapy. Grade 3 or 4 mucositis occurred in all four patients treated, and grade 4 hematologic toxicity occurred in three of eight courses.

Mauer et al. performed a phase I study of docetaxel and concomitant radiotherapy in 29 patients with advanced nonsmall cell lung cancer or esophageal cancer [37]. Neutropenia and esophagitis were the dose-limiting toxicities, and the maximum tolerated dose of docetaxel was 20 mg/m² weekly. Masters et al. administered docetaxel once every three weeks with concomitant chest radiotherapy in patients with non-small cell lung cancer, and the maximum tolerated dose was 60 mg/m² [38]. Although these studies are preliminary in nature, the initial results appear to support the in vitro data suggesting radiosensitization by these two agents. Ongoing studies are defining the role of these agents with concurrent radiation.

**Adjuvant Therapy of Resected Pancreatic Cancer**

Pursuing earlier studies showing that radiation effects were potentiated by fluoropyrimidines, investigators at the Mayo Clinic and Montreal General Hospital demonstrated successful results 30 years ago combining radiation therapy and chemotherapy in gastrointestinal malignancies, particularly gastric, pancreatic, and rectal cancers [39-44]. In 1974, the Gastrointestinal Tumor Study Group (GITSG) began a study of adjuvant combined-modality therapy in patients with resected pancreatic cancer. This study, however, was terminated after eight years due to very slow accrual [45]. Patients with adenocarcinoma of the pancreas who had undergone a curative resection were randomized to either observation or combined-modality therapy with 40 Gy of radiation delivered by split course and concurrent 5-FU. The 5-FU was given as a bolus injection at a dose of 500 mg/m² on the first three days of radiation therapy and then as weekly maintenance for two years or until disease progression. Forty-three patients were available for analysis, and median survival for the treatment group was 20 months, compared with 11 months for the control group ($p = 0.03$).

This study has been criticized extensively for several reasons, including its prolonged accrual time, early termination, small number of events, and the inclusion of patients with poor performance status—44% of patients had an ECOG performance status of 2 or 3. Nevertheless, it remains the only prospective, randomized trial of postoperative multimodality therapy in pancreatic cancer. This beneficial effect of adjuvant multimodality therapy in the first two years has been supported by several retrospective and prospective series (Table 3) [3, 8, 46, 47]. Five-year survival, however, does not appear to be dramatically improved, suggesting that adjuvant therapy only delays recurrence of tumor.

Whether these same results could be obtained without radiation has been the subject of considerable debate. A European trial of adjuvant chemotherapy with FAM (5-FU, adriamycin, and mitomycin) revealed a statistically significant prolongation in median survival for the treatment group (23 months versus 11 months, $p = 0.02$), but no improvement in actuarial survival at three and five years [4]. Ishikawa et al. treated 27 patients after pancreatectomy with concomitant portal vein and hepatic vein infusion of 5-FU for 28-35 days [48]. The initially reported three-year survival rate of 51% and the cumulative rate of death from hepatic metastases of 8% were significantly lower than their historical controls. A recent update of these patients has shown a very durable survival curve with a 41% five-year survival [49]. At the MGH Cancer Center, we are prospectively evaluating the role of portal vein 5-FU after pancreatectomy (Fig. 1).

The role of adjuvant therapy will be refined further when the results of a large, prospective multi-institutional European trial are published. This study randomizes patients after pancreatectomy to one of four arms: 40 Gy radiation with 5-FU, six months of 5-FU and leucovorin, a combination of those arms, or observation [50]. Future intergroup studies will evaluate the role of gemcitabine in the adjuvant setting.
Off-protocol treatment with radiation and 5-FU appears to offer the best chance at delaying recurrence in the first two years, but long-term survival is not dramatically affected.

**Locally Advanced Pancreatic Cancer**

In the absence of distant metastases, resection of pancreatic cancer is often limited by the tumor’s involvement of adjacent structures, particularly the vessels of the celiac axis. The GITSG evaluated the role of combined modality therapy for locally advanced pancreatic cancer (Table 4). Beginning in 1974, investigators through the GITSG randomized patients with locally advanced adenocarcinoma of the pancreas to receive 60 Gy of external beam radiation, 60 Gy of radiation with 5-FU, or 40 Gy of radiation with 5-FU (Table 3) [51, 52]. The radiation-alone arm was discontinued after 106 patients were enrolled, as both the median time to progression and overall survival were significantly less when compared with the combined modality arms ($p < 0.02$). An additional 88 patients were enrolled in the two combined modality arms. The differences between the combined modality arms in time to progression and overall survival were not statistically significant, although a trend toward improved survival was seen with 60 Gy of radiation. Based on these studies, 5-FU and concurrent radiation became the standard of care for locally advanced pancreatic cancer. Over the next decade, several randomized trials attempted to improve on this regimen with either different radiosensitizers, combination therapy, or chemotherapy alone.
After demonstrating that combined modality therapy was better than radiation alone, the GITSG examined whether radiation with concurrent adriamycin was better than radiation with concurrent 5-FU [53]. Patients randomized to the 5-FU arm received 60 Gy of external beam radiation in three split courses (20 Gy over two weeks followed by a two-week break). The 5-FU was administered as a 500 mg/m² bolus infusion on the first three days of each radiation course and then weekly until progression of disease. Patients randomized to the adriamycin arm received a continuous course of 40 Gy radiation and 15 mg/m² adriamycin every week while on radiation and then eight cycles of 60 mg/m² adriamycin. After completing adriamycin, patients were maintained on weekly 5-FU until disease progression. A total of 157 patients were randomized, and the median survival was similar in each arm (37 weeks on the 5-FU arm and 33 weeks on the adriamycin arm). Toxicity was significantly worse for patients receiving adriamycin and consisted primarily of hematologic toxicity. Based on an earlier GITSG study of SMF demonstrating a 15% response rate in metastatic disease [21], the GITSG studied whether the addition of radiation and 5-FU to SMF chemotherapy was beneficial for patients with locally advanced disease [54]. Forty-eight patients with unresectable carcinoma of the pancreas were randomized to either SMF or combined modality therapy (CMT) followed by SMF. There was a statistically significant improvement in overall survival in the combined modality arm. Importantly, only patients treated with CMT experienced survival beyond 18 months (Table 4).

Investigators at the ECOG addressed a similar question regarding the additive benefit of radiation therapy to 5-FU for locally advanced pancreatic cancer. They randomized patients to receive either 5-FU 600 mg/m² weekly for an indefinite period or 40 Gy radiation with 5-FU 600 mg/m² given on the first three days of radiation followed by maintenance 5-FU 600 mg/m² weekly [55]. Ninety-one patients were randomized, and there was no significant difference in time to progression or overall survival between the two arms. The investigators concluded that 5-FU was equivalent to CMT in the setting of locally advanced disease. Alternatively, the proponents of CMT argued that the dose of 5-FU and radiation in this study was inadequate to produce significant effects and that only intensive treatment with both chemotherapy and radiation would produce lasting benefit.

Beginning in 1985, Bruckner and colleagues pursued a course of intensive chemotherapy with concurrent radiation therapy in patients with locally advanced adenocarcinoma of the pancreas. Patients received 5-FU, streptozocin, and cisplatin with concurrent radiation therapy (Table 4) [56]. Thirty-five patients were entered into the study over ten years. There were six complete responses and nine partial responses, for an overall response rate of 43%. Nine of the fifteen responders underwent surgical exploration, two had pathologic complete responses, and three had complete surgical resection. The median survival time for the entire group was 15 months, and the two-year survival was 26%. Toxicity in this study was moderate, with 15% of patients requiring hospitalization for stomatitis; however, grade 4 hematologic toxicity was uncommon. Slow accrual to this trial raises obvious questions regarding selection bias. Therefore, it is difficult to draw conclusions regarding the benefit of intensive CMT for locally advanced disease.

Recent studies in gastrointestinal malignancies have focused on the benefits of continuous-infusion 5-FU as a radiosensitizer. Whittington et al. studied twenty-five patients with recurrent, residual, or unresectable carcinoma of the pancreas or biliary tract with continuous-infusion 5-FU administered in a phase I dose escalation beginning at 200 mg/m² along with concurrent radiation therapy [57]. The dose of 5-FU was escalated in 25 mg/m² increments. The progression-free survival at one year was 40%, and the median survival was 11.9 months. Of note, 18% of patients were alive at two years and three of 25 patients were alive without evidence of progression at 18, 34, and 44 months, respectively. The authors recommended a 5-FU dose of 250 mg/m² by continuous infusion for future studies, as gastrointestinal toxicity was dose-limiting at higher doses.

Table 4. Locally advanced pancreatic cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patients</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG 1979*</td>
<td>40 Gy + 5-FU</td>
<td>83</td>
<td>36.5 weeks</td>
</tr>
<tr>
<td></td>
<td>60 Gy + 5-FU</td>
<td>86</td>
<td>49.4 weeks</td>
</tr>
<tr>
<td></td>
<td>60 Gy alone</td>
<td>25</td>
<td>22.9 weeks</td>
</tr>
<tr>
<td>GITSG 1985</td>
<td>60 Gy + 5-FU</td>
<td>79</td>
<td>37 weeks</td>
</tr>
<tr>
<td></td>
<td>40 Gy + adriamycin</td>
<td>78</td>
<td>33 weeks</td>
</tr>
<tr>
<td>GITSG 1988*</td>
<td>SMF</td>
<td>24</td>
<td>32 weeks</td>
</tr>
<tr>
<td></td>
<td>CMT(A) + SMF</td>
<td>24</td>
<td>42 weeks</td>
</tr>
<tr>
<td>ECOG 1985</td>
<td>5-FU</td>
<td>44</td>
<td>8.2 months</td>
</tr>
<tr>
<td></td>
<td>CMT(B) + 5-FU</td>
<td>47</td>
<td>8.3 months</td>
</tr>
<tr>
<td>Bruckner et al.</td>
<td>5-FU, STZ, CDDP, XRT</td>
<td>35</td>
<td>15 months</td>
</tr>
</tbody>
</table>

SMF = streptozocin 1 g/m² q 8 weeks, mitomycin 10 mg/m² q 8 weeks, 5-FU 600 mg/m² on days 1, 8, 29, 36.
CMT(A) = 54 Gy radiation and 5-FU on days 1-3, 28-30 followed by SMF.
CMT(B) = 40 Gy radiation and 5-FU 600 mg/m² days 1-3 followed by 5-FU 600 mg/m² weekly.
*The difference between single modality and combined modality arms was statistically significant.

Bruckner regimen: two or three 28-day cycles of 5-FU 1,000 mg/m² on days 1-4, streptozocin 300 mg/m² on days 1, 2, 3, cisplatin 100 mg/m² on day 3, XRT 2 cGy/d on days 1-5, 8-12 to a total dose of 54 Gy. All patients were assessed for resectability at this point and then given maintenance 5-FU 600 mg/m² and leucovorin 200 mg/m² q 14 days × 1 year or until disease progression.
At the Dana-Farber/Partners Cancer Care, we currently are enrolling patients with locally advanced disease in a phase I study of gemcitabine, 5-FU, and concomitant radiation therapy (Fig. 1). In this study, the dose of 5-FU is 200 mg/m²/d, and gemcitabine is given weekly at a starting dose of 100 mg/m². Off-protocol radiation therapy with continuous-infusion 5-FU probably offers the best chance at delay- ing progression while maintaining a tolerable toxicity profile. More intensive therapy should be limited to an investigational setting.

**NEOADJUVANT THERAPY**

In an attempt to improve overall survival and tumor resectability, investigators at several centers have pursued preoperative therapy. There are potential advantages to neoadjuvant therapy for patients with pancreatic cancer. The morbidity of a pancreaticoduodenectomy can lead to a lengthy recovery, limiting the ability to deliver adjuvant therapy to many patients. Yeo et al. reported that only 72% of patients eligible for adjuvant postoperative chemoradiotherapy received therapy [8]. Furthermore, 35% of the treatment group were alive at two years compared with 0% of the nontreatment group, despite the lack of any identifiable poor prognostic characteristics in this group.

Delaying therapy to the postoperative setting also raises several theoretical concerns. Radiation is more effective on well-oxygenated cells, and surgery can alter the vascular supply of residual disease. Tumor manipulation at the time of surgery may lead to peritoneal seeding, a frequent site of relapse. Moreover, preoperative therapy avoids the morbidity and mortality of pancreatectomy in those patients with aggressive disease who are destined to progress quickly. One can safely assume that these patients had micrometastatic disease which became clinically evident quickly. One can safely assume that these patients had micrometastatic disease which became clinically evident preoperatively.

Additionally, positive retroperitoneal margins and nodal status at the time of pancreaticoduodenectomy are poor prognostic factors. A retrospective review of patients with pancreatic cancer who underwent resection at the Massachusetts General Hospital demonstrated that 51% of the patients had positive margins. The three-year survival for patients with positive margins was 6%, which was significantly less than the 22% three-year survival for patients with negative margins [58]. A series of pancreaticoduodenectomy from Johns Hopkins and Memorial Sloan-Kettering Cancer Center revealed that five-year survival for patients with negative nodes was 57% and 35%, respectively, while the five-year survival for patients with positive nodes was 7% and 9%, respectively [5, 59]. Neoadjuvant therapy may reduce the percentage of positive margins and lymph nodes, perhaps leading to a more favorable outcome.

Early reports of neoadjuvant therapy demonstrated that operative morbidity and mortality were not affected adversely [60-62]. Jessup et al. treated sixteen patients with adenocarcinoma of the pancreas deemed unresectable by exploratory laparotomy or abdominal CT [63]. Patients received 45 Gy of external beam radiation and concurrent 5-FU 225 mg/m² by continuous infusion. Two patients had rapid progression while on therapy. Restaging four to six weeks after completion of combined modality therapy demonstrated distant metastases in three patients and 11 potentially resectable patients. Ten patients were taken to surgery, and only two were resectable. Overall survival for the entire cohort was 9.6 months. These patients were compared to 24 control patients who were considered resectable on initial staging. Fifteen of 24 patients had potentially curable resections, and the overall survival was 12.2 months. This study demonstrated the safety of preoperative therapy and the potential to convert unresectable disease into resectable disease. However, there was no obvious improvement in outcome.

In an attempt to demonstrate benefit in those patients with resectable disease, Evans et al. at MD Anderson Cancer Center treated 28 potentially resectable patients with preoperative 5-FU and radiation [64]. At restaging, one patient had lung metastases and four had liver metastases. Six patients had unresectable disease at laparotomy, while 17 patients underwent pancreaticoduodenectomy. It is reasonable to assume that those patients who progressed during the brief duration of neoadjuvant therapy had occult micrometastatic disease at presentation and that this disease would not have been cured surgically. Therefore, preoperative therapy in this cohort of potentially resectable patients spared 39% the morbidity and mortality associated with resection.

Although survival in these pilot trials was poor, they demonstrated the possible benefit of neoadjuvant therapy in two groups of patients. The first group contains patients with chemo-sensitive and radiation-sensitive cancer who are assured delivery of treatment in a safe and efficient manner unencumbered by the morbidity of surgery. The second group consists of those patients with very aggressive disease in whom a pancreaticoduodenectomy has little hope of prolonging survival and only exposes patients to the morbidity of surgery. Recently, experiences at the ECOG and the MD Anderson Cancer Center confirmed these benefits [65, 66].

Investigators at ECOG treated fifty-three patients with potentially resectable disease. Patients received 50.4 Gy of external beam radiation with concurrent 5-FU 1,000 mg/m²/d by 96-h continuous infusion on days 2-5 and 29-32 [65]. Nine patients (17%) had local tumor progression or distant metastases on restaging. Seventeen patients (32%) were found to have metastatic or locally advanced disease at the time of surgery, and only 45% received a potentially curable
pancreaticoduodenectomy. The overall survivals for patients who developed progressive disease on restaging versus those patients deemed unresectable at laparotomy were five and eight months, respectively. The overall survival for patients undergoing resection was 15.7 months. Only three of the 24 patients who underwent pancreaticoduodenectomy experienced a local recurrence, and none of these occurred without the concomitant presence of distant metastases. The liver and peritoneum were the most frequent sites of relapse.

At the MD Anderson Cancer Center, 144 patients with resectable pancreatic cancer were prospectively followed. Ninety-one patients with an identifiable mass in the head of the pancreas on abdominal CT and a positive cytologic diagnosis were treated preoperatively with 5-FU and radiation [66]. Preoperative therapy consisted of either a standard fractionation scheme of radiation therapy or a rapid fractionation scheme. The standard fractionation scheme delivered a total of 50.4 Gy in 1.8 Gy fractions with 5-FU 300 mg/m² by continuous infusion five days per week. The rapid fractionation scheme delivered a total of 30 Gy in 3 Gy fractions with continuous-infusion 5-FU and allowed a surgical resection one month earlier than standard fractionation. Some patients received intraoperative radiotherapy (IORT) at the time of resection. For the 53 patients who did not have an identifiable mass in the head of the pancreas or cytologic findings diagnostic for pancreatic cancer preoperatively, an immediate attempt at resection was undertaken. Postoperatively, 50.4 Gy of radiation and 5-FU 300 mg/m²/d by continuous infusion five days per week was administered. Survival for patients who received preoperative therapy was not significantly different from that of patients who received postoperative therapy (19 versus 22 months, respectively).

Although this series from the MD Anderson Cancer Center makes comparisons between heterogeneous treatment groups and selects patients for preoperative therapy that have a better prognosis (head of the pancreas versus body/tail of the pancreas), several important concepts have emerged: A) 26% of patients in the preoperative therapy group were found to have progressive disease at the time of restaging and were spared a pancreaticoduodenectomy. The median survival for all patients not undergoing a pancreaticoduodenectomy was 7.2 months. B) Preoperative chemoradiation and pancreaticoduodenectomy prevented local recurrence, possibly due to a decreased rate of positive retroperitoneal margins. C) A significant percentage of patients taken directly to pancreaticoduodenectomy (24%) did not receive adjuvant therapy because of delayed recovery from treatment. Although preoperative therapy with 5-FU and radiation may not improve survival when compared with postoperative therapy, it does ensure delivery of therapy to those patients who might benefit and prevents surgical therapy for a large portion of patients with rapidly progressive disease.

IORT

For patients with tumors resistant to chemotherapy and radiation, local and distant progression occurs rapidly. Overcoming this inherent resistance will require newer agents to both control distant disease and sensitize local tumors to radiation. Inherent tumor resistance to radiotherapy has prompted attempts to control local disease by using higher doses of radiation in the form of IORT.

IORT can deliver high doses of radiation directly to the tumor or tumor bed, thus optimizing dose and minimizing toxicity to surrounding tissues. Morbidity, however, includes the need for laparotomy and the inability to resect tissues that have been exposed to IORT. Therefore, IORT is used as adjuvant therapy immediately after a resection, or as an attempt to improve local control in patients with unresectable disease. Multiple institutions have reported their experiences with IORT in both resectable and locally advanced pancreatic cancer (Table 5) [7, 9, 67-76]. There is little evidence that overall survival is improved with IORT, as it is similar to that reported in a series of conventional combined modality therapy. Local control may be slightly better after IORT, but the vast majority of patients still develop distant metastases [7, 68, 69, 71].

The NCI attempted a prospective, randomized trial of IORT in pancreatic cancer. Pre-resection, 55 patients were Table 5. Phase II studies of IORT in pancreatic cancer

<table>
<thead>
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<th>Group</th>
<th>Patients</th>
<th>Median survival (mo)</th>
<th>2-yr. survival</th>
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<tbody>
<tr>
<td>MGH [67]</td>
<td>68 LA</td>
<td>13</td>
<td>12%</td>
</tr>
<tr>
<td>Mayo Clinic [68]</td>
<td>37 LA</td>
<td>13.6</td>
<td>12%</td>
</tr>
<tr>
<td>Mayo Clinic [69]*</td>
<td>27 LA</td>
<td>14.9</td>
<td>27%</td>
</tr>
<tr>
<td>Mayo Clinic [69]**</td>
<td>56 LA</td>
<td>10.5</td>
<td>6%</td>
</tr>
<tr>
<td>Japan [70]</td>
<td>31 LA</td>
<td>8.2</td>
<td>14%</td>
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<td>Kentucky [71]</td>
<td>49 LA</td>
<td>16</td>
<td>22%</td>
</tr>
<tr>
<td>Milan [7]</td>
<td>43 LA</td>
<td>19</td>
<td>24%</td>
</tr>
<tr>
<td>Germany [72]</td>
<td>12 CR</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>NCI [73]</td>
<td>26 CR</td>
<td>18</td>
<td>NA</td>
</tr>
<tr>
<td>MD Anderson [9]</td>
<td>39 CR</td>
<td>19</td>
<td>19% (4-yr.)</td>
</tr>
<tr>
<td>Thomas Jefferson Univ. [74]</td>
<td>14 CR</td>
<td>16</td>
<td>15.5% (5-yr.)</td>
</tr>
<tr>
<td>Toledo, OH [75]</td>
<td>10 CR</td>
<td>17.5</td>
<td>30%</td>
</tr>
<tr>
<td>Lyon, France [76]</td>
<td>25 CR</td>
<td>NA</td>
<td>20%</td>
</tr>
</tbody>
</table>

LA = locally advanced, unresectable. 
CR = post-complete resection.
*EBRT + chemotherapy→IORT.
**IORT→EBRT + chemotherapy.
entered in the study, but only 24 were eligible after resection. There was a trend toward better survival in the IORT group, but due to the small number of patients in each arm, no conclusions could be drawn from the study [77]. The NCI also reported the results of a prospective, randomized trial of IORT in locally advanced pancreatic cancer. Again, a small number of patients (23) were randomized and no significant differences in local control, disease-free survival, or overall survival were detected [78]. The role of IORT remains to be explored in further investigational studies.

CONCLUSION

After many years of clinical research in pancreatic cancer, several important principles have emerged. Combined modality therapy with radiation and 5-FU offers the best chance for delaying progression in patients with resectable and locally advanced pancreatic cancer. Most patients, however, succumb to metastatic disease due to the inherent resistance of these tumors to radiation and chemotherapy. Long-term survivors consist of those patients who have completely resected tumors, receive aggressive pre- or postoperative combined modality therapy, and have negative margins and lymph nodes demonstrated on pathology. The immediate future of clinical trials in pancreatic cancer will attempt to improve on local control and survival by adding gemcitabine and docetaxel to adjuvant and neoadjuvant programs. At Dana-Farber/Partners Cancer Care, our pancreatic cancer program currently has several trials evaluating the role of these new agents (Fig. 1). For patients with resectable disease, postoperative portal vein chemotherapy followed by combined modality therapy is offered. For patients with locally advanced disease at presentation, patients are enrolled in a phase I trial of gemcitabine, 5-FU, and concomitant radiation therapy. In the metastatic setting, we have an ongoing phase I/II trial of gemcitabine and docetaxel given concomitantly. Future efforts also will focus on administration of monoclonal antibody against HER-2/neu, as this protein is overexpressed in approximately 50% of pancreatic cancers [79-84]. Through these efforts, we hope to develop new regimens which improve the survival of our patients with locally advanced and metastatic pancreatic cancer.

REFERENCES


Anonymous. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of


