Locally Advanced Pancreatic Cancer Treated with Radiation and 5-Fluorouracil: A First Step to Neoadjuvant Treatment?

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Key Words
Pancreatic cancer \cdot 5-Fluorouracil \cdot Neoadjuvant treatment

Abstract
Aim of the Study: In two institutions, a retrospective analysis was performed on patients with histologically proven locally advanced pancreatic cancer without distant metastases. The aim of this analysis is to assess whether chemoradiotherapy provides survival benefit for patients with locally advanced pancreatic cancer.

Methods: Forty-five patients from the Erasmus Medical Centre (Erasmus MC), Rotterdam, received 5-fluorouracil (5-FU) and radiotherapy and, 38 patients from the Academic Medical Centre Amsterdam (AMC) were offered the best supportive care. Radiotherapy consisted of 50 Gy external upper abdomen radiation in two courses, concomitant with intravenous 5-FU 25 mg/kg/24 h continuously on the first 4 days of each treatment course.

Results: The treatment protocol was completed in 38 of 45 patients (84%) without complications. Radiological response was evaluated in 38 patients. Ten patients (26%) showed a partial response, stable disease was seen in 6 (16%) patients and progressive disease in 22 (58%) patients. A second-look operation was performed in 8 of 10 patients (72%) showing a radiological response, in 3 patients the tumour could be resected. Median overall survival time for the Erasmus MC group (n = 45) was 9.8 months compared to 7.6 months when the best supportive care was given (AMC group, p = 0.04).

Conclusion: Although overall survival remains poor, treatment with 5-FU and radiotherapy might benefit some patients with locally advanced pancreatic cancer.

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Introduction

Pancreatic cancer has a dismal prognosis, with an overall 5-year survival rate of only 0–4\% [1]. At the time of presentation, approximately 40\% of the patients with pancreatic cancer already have metastatic disease; only 10–20\% of the patients are candidates for resection, and 40–50\% have locally advanced disease that is not ame-
ies are adequately randomised clinical trials [3, 7–15]. In between 9 and 13 months. However, none of these studies have shown the possible beneficial effect on survival when chemoradiotherapy was given for locally advanced pancreatic cancer. The reported median survival ranged from 80 or more [3]. Treatment consists of local radiotherapy combined with 5-fluorouracil (5-FU). The value of this combined treatment was suggested by the results of a comparative trial conducted by the Gastrointestinal Tumor Study Group (GITSG) showing better survival after a combination of 5-FU and radiotherapy, as compared to radiation alone [4, 5]. In contrast to the high response rates reported for combined modality therapy in oesophageal and rectal cancer, chemoradiotherapy for pancreatic cancer rarely achieves a complete radiographic or histopathologic response [6]. In recent years several studies have shown the possible beneficial effect on survival when chemoradiotherapy was given for locally advanced pancreatic cancer. The reported median survival ranged between 9 and 13 months. However, none of these studies are adequately randomised clinical trials [3, 7–15]. In most studies the overall survival of the treated patients was retrospectively evaluated and compared with historical controls who did not receive any form of treatment. Before initiating a prospective randomised trial we first wanted to analyse our data and consider the overall survival in relation to a group of patients who only received the best supportive care.

The aim of this analysis is to evaluate the radiologic and clinical response in all patients who started chemoradiation and to assess whether our chemoradiotherapy protocol provides survival benefit in patients with locally advanced pancreatic cancer.

### Materials and Methods

All patients with suspected locally advanced disease without metastases on computed tomography (CT) scan, underwent an explorative laparotomy at two University hospitals in the Netherlands (the EMC and the Academic Medical Centre, AMC) were studied. At the EMC all patients were offered chemoradiation, whereas at the AMC not all patients received treatment (see description below).

At both centres locally advanced disease was defined as tumour growth in the mesenteric root (superior mesenteric vein and/or portal vein, hepatic or superior mesenteric artery confirmed by biopsy at vessel location), transverse mesocolon or mesentry of the small bowel (at the ligament of Treitz), and positive regional lymph nodes at stations other than those to be removed en bloc with the pancreaticoduodenectomy. The resectable nodes are described by the Japanese Pancreas Society classification [16] (Table 1). Histopathological biopsies of the primary tumour were obtained during operation in all cases to confirm the diagnosis. In addition, biopsies of suspected lymph nodes outside the resection area were taken. For this study, only patients with tumours of <6 cm and a Karnofsky performance status of >80 points were included. Positive lymph nodes (proven by biopsy) had to be located within the radiation field, otherwise patients were excluded.

Between May 1982 and January 1998, 45 of 190 patients with incurable disease had locally advanced pancreatic cancer without metastases. They were offered combined radiotherapy and 5-FU after discharge from hospital at the EMC. In order to compare the results of chemoradiotherapy at the EMC, patients who underwent a bypass between 1992 and 1998 at the AMC for locally advanced disease and were only observed after discharge from hospital were selected. Of the 82 patients with locally advanced disease during this time period, 16 patients were excluded since they had histologically proven positive lymph nodes outside the radiation field. Forty-four patients (study group, SG) underwent either high-dose radiotherapy (n = 20), chemoradiation (n = 4) or chemotherapy alone (n = 4) in trial settings. The remaining 38 patients (excluded group, EG) served either as controls or did not participate in any study. To eliminate any selection bias, the SG was compared with the EG. Postoperative complications were comparable (SG vs. EG, 34 vs. 23%, p = 0.367) as was the case for postoperative hospital

### Table 1. Lymph node group classification by the Japanese Pancreatic Society [16]

<table>
<thead>
<tr>
<th>Group</th>
<th>Carcinoma of the pancreatic head</th>
<th>Carcinoma of the pancreatic body-tail</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13, 17</td>
<td>8, 11, 18</td>
</tr>
<tr>
<td>2</td>
<td>6, 8, 12, 14</td>
<td>7, 9, 14, 15</td>
</tr>
<tr>
<td>3</td>
<td>1, 2, 3, 4, 5, 7, 9, 10, 11, 15, 16, 18</td>
<td>5, 6, 12, 13, 17, 17, 16, 16</td>
</tr>
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Numbers and names of lymph nodes: 1 = right cardinal; 2 = left cardinal; 3 = along the lesser curvature of the stomach; 4 = along the greater curvature of the stomach; 5 = suprapyloric; 6 = infrapyloric; 7 = along the left gastric artery; 8 = along the common hepatic artery; 9 = around the celiac artery; 10 = splenic hilum; 11 = along the splenic artery; 12 = in the hepatoduodenal ligament; 13 = on the posterior surface of the pancreatic head; 14 = along the superior mesenteric artery; 15 = along the middle colic artery; 16 = around the abdominal aorta; 17 = on the anterior surface of the pancreatic head; 18 = along the inferior margin of the pancreatic body-tail.
stay (SG vs. EG, 10 vs. 11 days, \( p = 0.204 \)) and tumour size (SG vs. EG, 3.6 vs. 3.5 cm, \( p = 0.461 \)). The Karnofsky performance status was >80 points for both SG and EG. The whole group of patients from the AMC is also described in detail elsewhere [9, 15, 17].

Radiotherapy

Radiotherapy was given according to the EMC Daniel den Hoed Clinic protocol consisting of 50-Gy external beam radiotherapy in 2 courses, with a split-course of 2–3 weeks, combined with intravenous 5-FU. Radiotherapy started at a mean of 48 days postoperatively. Until the end of the 1980s 5-FU was given in a dose of 375 mg/m² as a bolus injection 4–6 h before radiation on the first 4 days of each treatment course. Since 1990, and currently, 5-FU has been given as a continuous infusion in a dose of 25 mg/kg/24 h, with a maximum of 1,500 mg, the first 4 days of both radiation courses. This protocol was developed on the basis of the results of GITSG [16, 17]. The choice of radiation dose of 50 Gy was a compromise between the 40- and 60-Gy doses used in the GITSG study. By using the 50-Gy dose in fractions of 2 Gy, the actual treatment time was limited to 5 weeks. A treatment split of 2–3 weeks was considered valuable to allow acute reactions to therapy to subside.

We are aware that today this treatment technique is suboptimal, but at that time it was considered acceptable according to the GITSG data. The first course consisted of 13 × 2 Gy, followed after the split by 12 × 2 Gy, 5 days/week. The radiation technique involved multiple-field treatment planning using CT. Megavoltage energy of 25 MV was preferred, although occasionally 4, 6 or 8 MV was used. Three-field plans using wedges were more common.

The target volume comprised the tumour and first lymph node stations as seen on the planning CT, adding 10 mm for the planning target volume.

The main concern was protection of the kidneys (a renography was always performed) and spinal cord. Technical details of the radiotherapy protocol have been previously published [18]. According to our protocol, one third of the kidneys should not receive a dose of >20 Gy, taking renography also into account. The maximal radiation dose accepted for the spinal cord was 50 Gy. Toxicity was scored according to the common toxicity criteria scale (CTC) of the World Health Organisation.

After completion of chemoradiotherapy, patients were given a 2-month break before re-staging, to allow recovery of blood counts, side effects of radiation, and overall functional activity. In the treatment group tumour size on restaging CT was compared to the initial CT tumour size only by measuring.

Response Assessment

CT scan was planned 2 months after the chemoradiotherapy regimen had been completed.

Partial response was defined as a decrease in tumour size of >50% for at least 4 weeks without disease progression at another site. Bi-dimensionally measurable tumours must have had a 50% decrease in tumour size, as measured by multiplication of the greatest diameter by the perpendicular diameter, whereas uni-dimensional tumours must have had a 30% decrease at linear tumour measurement. Stable disease was defined as no significant change in measurable or evaluable disease for at least 4 weeks, no appearance of new areas of malignant disease, and no decrease in malignant disease of >50% or increase of >25%. Progression was defined as a >25% increase in area of any malignant lesion measuring >2 cm², or the appearance of any new lesion at another site.

After chemoradiotherapy resection specimens were evaluated for size, tumour margins, degree of differentiation and lymph node status.

Statistics

Survival was calculated from the date of operation until October 2002, on an actuarial basis using the Kaplan-Meier method. Comparison of survival was done only for patients with pancreatic adenocarcinoma, using the log-rank test. To test for differences between SG and EG, the \( \chi^2 \) test or Mann-Whitney test was used. Two-sided \( p \) values of <0.05 were considered significant.

Results

Patients’ characteristics are listed in table 2. There were no significant differences regarding age, sex and tumour characteristics between both groups. Use of gastro/biliary bypass and preoperative stents differs between both groups (see Discussion).

As far as could be defined, no ampullary tumours were included in this study. A majority of patients had locally advanced disease due to direct tumour invasion either in large vessels or transverse mesocolon found during explorative laparotomy.

Toxicity

Thirty-eight of 45 patients (85%) completed the planned regimen of chemoradiotherapy. Three patients (7%) discontinued treatment: in 1 patient treatment was discontinued due to non-reversible haematological (grade-III) toxicity, and 2 patients refused further treatment because of severe (grade-III) nausea and vomiting. Neither grade-IV toxicity nor treatment-related deaths were observed. Details of toxicity grade for all patients who started chemoradiotherapy are summarised in table 3.

Radiological Tumour Response

Four patients stopped treatment due to development of malignant ascites, proven by cytology during chemoradiotherapy. For 38 patients who received the full treatment, evaluation of local tumour response was planned 2 months after the chemoradiotherapy regimen had been completed. Ten patients (10/38; 26%) showed a partial response on CT scan, 6 (6/38; 16%) had stable local disease and 22 (22/38; 58%) showed tumour progression at either local or distant sites. Locoregional progression was found in 11 patients (24%), liver metastases were found in 11 patients (24%). Three of 22 patients with progressive disease developed concomitant metastases else-
where: 1 patient developed lung metastases; 1 patient bone metastases, and 1 patient developed peritoneal metastases.

Eight of 10 patients who had shown tumour regression but were free of metastatic disease on CT scan underwent a second-look operation between 4 and 6 months after chemoradiotherapy. Two patients refused surgical re-exploration because of their general condition. In 3 patients resection could be performed. Definitive histological diagnosis demonstrated that all tumours were adenocarcinomas, two resections were radical (R-0) and one was an non-radical (R-1). Overall in only 2 patients (5%) of the total group who started chemoradiotherapy could curative resection be performed. The remaining patients failed to demonstrate adequate tumour regression to be considered resectable at the second-look laparotomy.

**Survival**

The overall median survival for the EMC group (n = 45, including 3 resected patients) that received radiotherapy and 5-FU was 9.8 (CI 7.6–12.0) and 7.6 (CI 6.2–9.0) months for the AMC control group (n = 38; p = 0.046). The survival curve is shown in figure 1. Survival of the 3 patients who underwent resection for adenocarcinoma was 11, 15, and 157 months. If these 3 patients are not included in the survival analysis, then the median survival is 9.2 (CI 6.35–12.05) in the EMC group (n = 42) vs. 7.6 months in the AMC group (p = 0.1).

**Discussion**

In the Netherlands surgery for pancreatic cancer is partly centralized in two major centres, the AMC and the EMC. This study was designed to evaluate the radiologic and clinical response to chemoradiotherapy, which rou-
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tinely was offered to patients with locally advanced pancreatic cancer at the EMC. The overall survival of these patients was compared with a group of similar patients who received best supportive care at the AMC. Of the 45 patients who started our chemoradiation protocol, 38 patients (84%) received full treatment.

Toxicity associated with chemoradiotherapy was relatively low. Three patients had grade-III toxicity and 4 patients developed malignant ascites during therapy. Grade-III–IV haematological toxicity was observed in 6.5% of the patients. Nausea was the most common non-haematological toxicity with this treatment; 25% of the patients experienced this adverse effect and 2 patients refused to continue treatment. This is similar to the toxicity reported by other studies using 5-FU radiotherapy regimens [4, 5, 7, 8, 10–12, 14, 19–27].

There was a significant difference in bypass surgery and use of biliary stents. In the AMC every patient with locally advanced disease underwent a double bypass in a trial setting [28, 29]. In the EMC only patients with signs of obstruction peri- and postoperatively underwent a bypass. That explains the difference between both groups. Differences in the use of preoperative stents can also be explained by the different policies in both institutions. In the EMC a stent is used only when patients have clinical and laboratory signs of obstructive jaundice. In the AMC every patient is given a preoperative stent.

Already 2 months after completion of the chemoradiation 22 patients (58%) showed progression of disease. In this study 26% of patients showed a response and 16% had stable disease after 2 months which is again comparable to international results [3, 7–9, 11, 12, 19, 21, 30–35]. However, only 2 patients (5%) of the total group underwent a radical (R0) resection. Distant metastases, especially in the liver (11 patients in this study), are the most important cause of death in pancreatic cancer [24–26], and were found in 11 patients in this study 2 months after finishing chemoradiotherapy. Eight patients who had shown tumour regression underwent a second-look laparotomy followed by resection in 3 patients. All 3 patients had histopathologically proven adenocarcinoma after resection. In 2 cases had R0 resections and 1 had an nonradical (R1) resection. Median survival for these 3 patients was 83 months (11, 15, and >157 months, still alive). Remarkably, 2 patients were not found to have positive resection margins or positive lymph nodes, which suggests that preoperative chemoradiotherapy may yield pathologic down-staging for patients with locally advanced pancreatic cancer.

Pilepich and Miller [26] also described this concept of down-staging. They performed second-look laparotomy in 11 of 17 patients after preoperative irradiation. The tumour could be resected in 6 of them, and 2 patients were still alive after 5 years. However, in this small series the resectability at first laparotomy was in doubt for at least 5 patients [26].

Recently Kastl et al. [36] described a combination of radiotherapy, chemotherapy and mitomycin which was given to 27 patients with locally advanced pancreatic cancer. A second-look re-laparotomy was performed in 16 patients. In 10 patients the tumour could be resected. Although this study shows an improved resectability, median survival remained poor (9 months) [36].

Although these groups are very similar (table 2), care must be taken when drawing conclusions because selection bias might have occurred. The control group may be partly selected in terms of patients who did not prefer radiotherapy, for instance, due to general conditions. High-dose radiotherapy (70–72 Gy) without subsequent chemotherapy was offered in a phase-II study at the AMC to evaluate the effect of radiotherapy on pain control [9, 15]. So the control group in our study consisted of patients in a poor condition and therefore it is even more surpris-

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Fig. 1. Overall survival in patients with locally advanced pancreatic cancer.

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ing that the benefit from chemoradiotherapy in mean survival is so poor. The radiotherapy group in the AMC study had a median survival time of 11 months (10 months from the start of radiotherapy) which is comparable with the results in the EMC group [9].

This study shows a small survival benefit for patients with unresectable locally advanced adenocarcinoma of the pancreas treated with radiotherapy and 5-FU (9.8 vs. 7.6 months in the control group, \( p = 0.046 \)). This is comparable to results published in international literature in which survival ranges from 9 to 14 months [3, 7–12, 14, 19–23, 30–37].

In a recent trial, Ishii et al. [10] reported the results of 20 patients who were treated with 5-FU (200 mg/m\(^2\)/day) infusion + radiotherapy (50.4 Gy over 25 fractions) for locally advanced pancreatic cancer similar to those reported in this study. Ten percent of their patients achieved partial radiographic response and the tumour remained stable in 80%. The median overall survival was 10.3 months [10].

A more recent randomised trial of 31 patients by Shin-chi et al. [12] found a significantly better survival for the patients treated with external beam radiotherapy and continuous 5-FU (13.4 vs. 6.4 months). However, as in our study their survival curves separate immediately after surgery. The difference at this point is 7 months, suggesting a worse prognosis for the control group at the time of admission [12].

In a study by de Lange et al. [38] gemcitabine radiotherapy was found to yield a similar median survival (10 months). In some studies cisplatin is found to have some value when added to the 5-FU or gemcitabine regimens [31, 38]. The rationale for this addition is that 5-FU and gemcitabine are primarily used as a radio-sensitisers and therefore have a local effect; cisplatin might help to target the disease more effectively at distant locations of (micro-)metastases.

Of the studies discussed above only one [12] was designed as a randomised clinical trial; however, the results should be interpreted with caution because only 31 patients were enrolled and an adequate power analysis was lacking. All other studies are cohort studies.

According to the present study, we cannot conclude that there is a clear benefit using 5-FU and radiotherapy for patients with locally advanced pancreatic cancer. The significant difference in survival appearing in figure 1 is most likely due to the worse prognosis of patients who did not receive radiotherapy. The beneficial effect of chemoradiotherapy should be expected after a few months so that the two curves would only begin to separate some time after the completion of treatment. In fact, the curves separate immediately after surgery, making the conclusion viable that a worse prognosis is most obviously the reason for this significant difference. Despite some positive reports in the literature there is no first level evidence that subscribes the positive effect of chemoradiotherapy in patients with locally advanced pancreatic carcinoma. To draw final conclusions, randomised clinical trials are necessary. The lack of efficacy of the above-mentioned modalities raises the question whether further modifications of this multimodality approach could lead to better clinical results. Data from the MD Anderson Hospital showed promising results for patients with resectable pancreatic cancer treated with either rapid fractionation chemoradiotherapy and intra-operative chemoradiotherapy [39]. They reported an overall median survival of 19 months which compares favourably with recently reported series of patients treated by pancreaticoduodenectomy alone, and to those treated with combined postoperative adjuvant 5-FU-based chemoradiotherapy (median survival 11–20 months). However, in patients with locally advanced pancreatic carcinoma no similar positive results with 5-FU and radiotherapy alone have been reported yet.
References


