Improved Survival and Local Control After Intraoperative Radiation Therapy and Postoperative Radiotherapy

A Multivariate Analysis of 46 Patients Undergoing Surgery for Pancreatic Head Cancer

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Hypothesis: Despite aggressive approaches, locoregional tumor control and survival rates for patients with cancer of the pancreatic head remain disappointing. In the present study, we address whether intraoperative and adjuvant radiotherapy may improve the prognosis for these patients.

Design: A retrospective study.

Setting: University hospital.

Patients: From February 1985 to December 1995, 46 patients with an adenocarcinoma of the pancreatic head underwent pancreatic resection. The last 26 patients also received intraoperative radiotherapy (except 5 patients) and adjuvant external beam radiation therapy.

Main Outcome Measures: Demographic data, tumor characteristics, surgical procedures, 5-year survival, and local control of disease were analyzed retrospectively.

Results: The morbidity rate was not increased by adjuvant radiation therapy; it was 43% in patients treated with surgery alone and 57% in patients treated with surgery and radiotherapy ($P=0.1$); operative mortality was 8% (n = 2) and 9% (n = 2), respectively ($P=0.8$). Overall 5-year survival and local control were 13% and 48.6%, respectively. The mean ± SD 5-year survival was 5.5% ± 5.3% (median, 10.8 months) in the surgery-alone group and 15.7% ± 8.6% (median, 14.3 months) in the surgery plus radiotherapy group ($P=0.06$); local control at 5 years was 29.8% ± 16.9% and 38.4% ± 19.9%, respectively ($P<.01$). Median metastasis-free survival was 8 and 9 months, respectively ($P=0.52$).

Multivariate analysis showed that adjuvant radiotherapy was an independent prognostic factor for survival ($P<0.01$) and local control of the disease ($P=0.03$).

Conclusion: The present study supports the role of radiotherapy combined with pancreatoduodenectomy for treatment of cancer of the pancreatic head because even if the improvement in overall survival is moderate, it is effective in improving the local control of the tumor.

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SUBJECTS AND METHODS

A retrospective cohort study was carried out on 46 patients with localized carcinoma of the pancreatic head who underwent resection between February 1985 and December 1995. In all patients ductal adenocarcinoma was diagnosed from cytologic or histologic examination findings and staged according to the Union Internationale Contre le Cancer (UICC) classification system.1

Twenty patients underwent pancreatic resection with no adjuvant therapy in the first part of our series (1985-1991); the other 26 patients underwent combined surgery and radiation therapy (1992-1995): duodenopancreatectomy, intraoperative radiation therapy (IORT), and adjuvant external beam radiation therapy (EBRT). Five patients treated with adjuvant EBRT did not receive IORT because of an inability of the linear accelerator. The operation was always performed by the same team.

At laparotomy, if the abdominal exploration excluded metastases or locally advanced pancreatic cancer, a subtotal pancreaticoduodenectomy (resection of the pancreatic head and body up to the left margin of the aorta) was performed; if possible, the entire stomach and the pylorus were preserved according to Traverso-Longmire technique.2 Pancreatic resection was always associated with lymphadenectomy extended to the hepatic portal, the common hepatic artery, the celiac trunk, the splenic vessels, the mesentericoportal trunk, and the inferior mesenteric artery.

After surgical resection, patients treated with radiation therapy had a cone of an appropriate size selected by the radiotherapist. The patients were then transferred to the linear accelerator suite. A dose of 10 Gy was delivered with a 6-MeV electron beam to the tumor bed, including the portal vein, the splenomesenteric confluence, the superior mesenteric vein up to its branches, the celiac trunk, the hepatic artery up to its division, the proximal splenic vessels, the suprarenal aorta, and the caval vein.

Four to 6 weeks postoperatively or after complete recovery, EBRT was started. A 9-MV photon beam was delivered using a box or 3-beam technique. The total dose of 50.4 Gy (International Commission on Radiological Units and Measurements, 50), subdivided into 1.8 Gy daily fractions for 3 days per week, was delivered to a target volume that included the tumor and nodal bed.

EVALUATION OF OUTCOME

In all patients, tumor-free margins in the resection specimen, depth of invasion, and regional lymph node involvement were recorded. The operative time, intraoperative blood loss, postoperative morbidity rate, hospital mortality, and overall and disease-free 5-year survival after curative resection were recorded.

At treatment completion and at 3-month intervals thereafter, patients were assessed using findings from complete medical history, physical examination, performance status, complete blood cell count, blood chemistry analysis, and abdominal ultrasound. At 6-month intervals, a chest radiograph and abdominal computed tomographic scan with contrast were also obtained.

STATISTICS

The survival rate was assessed, including operative deaths, from the date of laparotomy to the date of death or last follow-up. Survival curves were constructed according to the actuarial life table method. Differences between the curves were assessed using the log-rank test.13 The Fisher exact test was used when appropriate. Differences were considered significant at \( P < .05 \). All statistical computations were performed using a computer program (SPSS version 7.01; BMDP Statistical Software, Los Angeles, Calif.). Variables shown to be prognostically significant by univariate analysis were entered into a multivariate model. Multivariate analysis was applied using the Cox regression proportional hazard model.14

SURVIVAL

Survival after curative resection was evaluated in all patients. None were lost to follow-up. The median follow-up was 82 months. Thirty-eight patients (82.6%) died. Thirty-six (78.3%) patients developed some form of recurrence. Local recurrence developed in 9 patients (19.6%); 6 (30%) in the surgery-alone group and 3 (11.5%) in the surgery plus radiotherapy group. Distant metastases were observed in 30 patients (65.2%): 12 (60%) in the surgery-alone group and 18 (69%) in the surgery plus radiotherapy group.

The overall 5-year survival rate was 13%±5.4% (median, 12.5 months); 5.5%±5.3% (median, 10.8 months) in the surgery-alone group and 15.7%±8.6% (median, 14.3 months) in patients receiving adjuvant radiotherapy \( (P = .06) \) (Figure 1). Overall, local control at 3 years was 48.6%±14.5% (median, 41.4 months); 29.8%±16.9% in the surgery-alone group and 58.4%±19.9% in the adjuvant therapy group \( (P = .01) \) (Figure 2). Median metastasis-free survival was 8 and 9 months, respectively \( (P = .52) \).

MORBIDITY AND MORTALITY RATE

The incidence of postoperative complications was similar in patients treated with surgery alone and in those also receiving IORT (43% vs 57%) \( (P = .1) \) (Table 2). Seven patients (15%) required reoperation (2 in the surgery-alone group and 5 in the surgery plus radiotherapy group); 3 for bleeding (1 in the surgery-alone group and 2 in the surgery plus radiotherapy group), 1 for pancreaticojejunostomy leakage (surgery-alone group), 1 for intra-abdominal abscess (surgery-alone group), and 2 for fascial dehiscence (surgery plus radiotherapy group). The hospital mortality rate was 8% \( (n = 2) \) after pancreatic resection alone and 9% \( (n = 2) \) when associated to IORT \( (P = .8) \).
Univariate analysis showed that the poor survival rate was closely related with lymph node involvement, tumor extension, a tumor diameter greater than or equal to 2.5 cm, and male sex. In contrast, no significant differences were found in relation to age and blood transfusion as well as to the kind of therapy adopted, even if a relationship was shown between adjuvant radiotherapy and survival (Table 3). Of the factors found to be prognostically significant by univariate analysis, the Cox multivariate model confirmed not only that sex, nodal involvement, and tumor diameter were independent predictors of death, but most important, that adjuvant radiotherapy had a role in predicting survival (Table 4).

As for local control, multivariate analysis demonstrated a higher risk of local recurrence in patients who did not receive radiotherapy and in those with lymph node involvement (Table 4).

In recent years pancreatic surgery has become safer, and indications for resection have increased.17 Hospital mortality has decreased18,19 with improvements in intensive care, nutritional support, and gained experience, which resulted in a decreased operative time and blood loss.20 However, efforts to extend the operative procedure to achieve wider safety margins thus far have failed to improve survival rates for patients with cancer of the pancreatic head; in fact, the 5-year survival rate is still disappointing, ranging from 2% to 19%.21-23 Microscopic residual tumor, located at the site of the original tumor,
and distant metastases (liver, peritoneum) are the main causes of treatment failure after pancreatoduodenectomy for pancreatic carcinoma.

Nagakawa et al25 deem that an extensive dissection of the retroperitoneum and extrapancreatic nerve plexus is necessary for curative resection of cancer of the pancreas, and local recurrence rate of pancreatic bed often involved by tumor extension can be lower.26-28 However, single cancer cells and cancer cell clumps cannot always be eradicated by surgery alone, and serious nutritional disorders (diarrhea) have appeared following this procedure.29

For these reasons, the use of adjuvant treatment such as chemotherapy, IORT, and postoperative EBRT has been proposed.30-32 The standard adjuvant therapy of pancreatic adenocarcinoma treated with curative resection is still controversial. The role of radiotherapy with or without chemotherapy in resectable pancreatic cancer has yielded interesting results.15,30,32 Studies by the Gastrointestinal Tumor Study Group have shown improvement in survival with a combination of EBRT and fluorouracil chemotherapy, reporting a median survival of 18 months.33 However, single cancer cells and cancer cell clumps cannot always be eradicated by surgery alone, and serious nutritional disorders (diarrhea) have appeared following this procedure.29

Table 3. Univariate Analysis of Clinical and Pathological Variables After Curative Resection of Carcinoma of the Pancreatic Head in 46 Patients*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>5-Year Survival Rate, %</th>
<th>Median Survival, mo</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>6.0</td>
<td>11.8</td>
<td>.47</td>
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<td>Sex</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>19</td>
<td>0</td>
<td>11.0</td>
<td>&lt;.01</td>
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<td>F</td>
<td>27</td>
<td>21.0</td>
<td>20.8</td>
<td>...</td>
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<tr>
<td>Transfusion (units of PRBC), mL</td>
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<td>&gt;300</td>
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<td>9.8</td>
<td>11.0</td>
<td>...</td>
</tr>
<tr>
<td>T4</td>
<td>7</td>
<td>0</td>
<td>15.5</td>
<td>...</td>
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<td>Lymph node involvement</td>
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<td>21.0</td>
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<tr>
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<td>0</td>
<td>10.8</td>
<td>&lt;.01</td>
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<td>Tumor diameter, cm</td>
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<td>.06</td>
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<td>Surgery + radiotherapy</td>
<td>26</td>
<td>15.7</td>
<td>14.3</td>
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</tbody>
</table>

* Ellipses indicate not applicable; PRBC, packed red blood cells; and NE, not evaluable. Tumor stages are according to the Union Internationale Contre le Cancer classification system.

As demonstrated in our experience, the combination of IORT and EBRT as adjuvant therapy can be delivered safely to patients as part of a planned combined modality approach for radical resection of carcinoma of the head of the pancreas.15,46 Moreover, in this study morbidity and mortality rates in patients who received IORT were similar to those who underwent surgery alone.

In the attempt to identify important factors in predicting long-term survival, multiple variables were evaluated. Age, type of resection, and blood transfusion did not influence survival. On the contrary, in patients with tumors ≥2.5 cm or less in diameter, no lymph node involvement, and stage T1 and T2 tumors, the survival was significantly prolonged. As given in Table 3, women surviving the operation seemed to have a somewhat better prognosis than men (P.<.01). Similar observations were made in other series33,41 reporting a correlation between female sex and a less-advanced stage of the tumor, but similar findings were not confirmed in the present study. The absence of statistical correlation between status of tumor margins and outcome is probably due to the small number of patients with microscopic residual disease.

Although use of adjuvant radiotherapy was not shown to be statistically significant by the univariate analysis, there was a trend toward a longer survival period in patients who received combined radiosurgical treatment. The adjuvant treatment group had a longer median overall survival (14.3 months) than patients who received surgery alone (10.8 months), and the 5-year survival in the surgery plus radiotherapy group was 3 times (15.7%) as high as that of the surgery-alone group (5.5%). The local control rate in the surgery plus radiotherapy group was significantly higher than in surgery-alone group (58.4% vs 29.8%, P.<.009), while the metastasis-free survival remained low in both (P.=.52). Adjuvant radiotherapy was confirmed to be a major determinant of survival and local control of the disease when evaluated by the Cox proportional hazard model.

In summary, the present study was not randomized; therefore, far-reaching conclusions cannot be drawn.
However, our results support the utility of radiation therapy following pancreatectoduodenectomy in the treatment of pancreatic cancer because the findings represent an effective way to improve local control of tumor and, most likely, survival. Other therapeutic options such as neoadjuvant and adjuvant chemoradiotherapy might further increase survival after pancreatectoduodenectomy, reducing the incidence of distant metastases.

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REFERENCES