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Impact of preoperative therapy on patterns of recurrence in pancreatic cancer

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Abstract

Background: A theoretical advantage of preoperative therapy in pancreatic adenocarcinoma is that it facilitates the early treatment of micrometastases and reduces postoperative systemic recurrence.

Methods: Medical records of 309 consecutive patients undergoing resection of adenocarcinoma in the head of the pancreas were reviewed. Survival was calculated using the Kaplan–Meier method. Associations between preoperative therapy and patterns of recurrence were determined using chi-squared analysis.

Results: Preoperative therapy was administered to 108 patients and upfront surgery was performed in 201 patients. Preoperative therapy was associated with a significantly longer median disease-free survival of 14 months compared with 12 months in patients submitted to upfront surgery ($P = 0.035$). The rate of local disease as a component of first site of recurrence was significantly lower with preoperative therapy (11.3%) than with upfront surgery (22.9%) ($P = 0.016$). Preoperative therapy was associated with a lower rate of hepatic metastasis (21.7%) than upfront surgery (34.3%) ($P = 0.026$). Preoperative therapy did not affect rates of peritoneal or pulmonary metastasis.

Conclusions: Preoperative therapy for pancreatic cancer was associated with longer disease-free survival and lower rates of local and hepatic recurrences. These data support the use of preoperative therapy to reduce systemic and local failures after resection.

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Introduction

Despite improvements in operative mortality after pancreaticoduodenectomy for pancreatic adenocarcinoma, overall survival has not improved, and most patients succumb to local and distant recurrences. Randomized controlled trials of surgical resection followed by adjuvant therapy demonstrate disease relapse rates of > 70%,[1,2] and autopsy series of patients after resection show local and distant failure rates of 75% and 88%, respectively.[3,4] The potential advantages of preoperative therapy in pancreatic cancer include improvements in the selection of patients for surgery, and the achievement of higher rates of negative-margin (R0) resection and early treatment of micrometastases.[5,6] Retrospective reports show lower local recurrence rates with preoperative therapy compared with adjuvant treatment.[7,8] The impact of preoperative therapy on distant metastases is not well defined. Recent animal and mathematical model studies suggest that most patients harbour disseminated disease at the time of diagnosis of pancreatic cancer and benefit from early systemic treatment before surgical resection.[9,10]

The aim of this study was to determine the impact of preoperative therapy on postoperative patterns of recurrence. A retrospective review was performed of 309 patients submitted to resection of adenocarcinoma in the head or uncinate process of the pancreas. Preoperative therapy was associated with significantly lower rates

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of local and hepatic recurrence, but did not affect rates of peritoneal or pulmonary metastases.

Materials and methods

The medical records of 309 consecutive patients treated for adenocarcinoma in the head or uncinate process of the pancreas at Fox Chase Cancer Center (Philadelphia, PA, USA) between September 1990 and November 2009 were reviewed. Pretreatment evaluation included contrast-enhanced computed tomography (CT) to assess resectability and exclude metastatic disease. Cytologic tissue diagnosis was obtained by fine needle aspiration under endoscopic ultrasound or, before the year 2000, CT guidance. Although preoperative multimodal therapy has been the favoured treatment strategy for localized pancreatic cancer at Fox Chase Cancer Center since 1986, many patients were submitted to surgery first if a tissue diagnosis of malignancy could not be obtained, if they refused preoperative therapy, if they had undergone previous abdominal radiation for an unrelated malignancy, and at the surgeon's discretion based on preoperative imaging.

Preoperative regimens were determined by the treating physicians. All patients treated with preoperative therapy received radiation, usually comprising standard-fractionation 50.4-Gy external beam radiation with concurrent gemcitabine or 5-fluorouracil (5-FU). If radiographic studies after preoperative chemoradiation were equivocal for resectability, patients received full-dose systemic chemotherapy and underwent resection if restaging scans showed response or stable disease. Patients receiving additional chemotherapy were treated with 5-FU or gemcitabine-based regimens.

Resection margins were evaluated systematically as previously described.[11] Tumours were staged after resection according to the 7th edition of the American Joint Committee on Cancer Staging Manual.[12] Postoperatively, patients were evaluated according to their history and physical examination, serum carbohydrate antigen 19-9 (CA 19-9) levels, and CT scans of the chest, abdomen and pelvis every 3–6 months for 3 years, and subsequently annually.

Local recurrence was defined as disease in the pancreatic bed, regional nodes and root of the mesentery. Distant recurrence was defined as disease in the peritoneum outside the pancreatic bed, malignant ascites, and disease in the liver, lungs or other distant organs. For the purposes of this study, only first sites of recurrence were recorded. This study was approved by the Fox Chase Cancer Center Institutional Review Board, which waived the requirement for informed consent.

Statistical analysis

Categorical variables were compared using chi-squared analysis. Continuous data were expressed as the median and range and compared using the Mann–Whitney test. Survival analysis was performed using the Kaplan–Meier method, and differences in survival were compared using the log-rank test. All statistical tests were two-sided; the significance parameter was set at $P < 0.05$. Statistical analysis was performed using SPSS Version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

Among the 309 patients who underwent resection of adenocarcinoma in the pancreatic head or uncinate process, 108 patients received preoperative therapy and 201 patients underwent surgery first. Clinicopathologic data are presented in Table 1. In the preoperative therapy group, 23 (21.3%) patients received 5-FU-based chemoradiation and 85 (78.7%) received gemcitabine-based chemoradiation. Additional preoperative chemotherapy after chemoradiation was administered in 32 patients (29.6%). In the surgery-first group, 152 (75.6%) patients received adjuvant 5-FU or gemcitabine-based regimens, including 125 (62.2%) treated with radiation as a component of adjuvant therapy. Median follow-up was 17 months (range: 1–179 months).

Preoperative therapy and patterns of recurrence

Recurrence data were available for 272 patients. The overall recurrence rate was 72.8% (198 of 272 patients) during the follow-up period. Sites of first recurrence are presented in Table 2. Local recurrence occurred in 12.1% of patients, distant recurrence in 54.4%, and both local and distant recurrence in 6.3%. The most common sites of distant recurrence were liver, peritoneum and lung. Multiple sites of first recurrence occurred in 26 (9.6%) patients.

Preoperative therapy was associated with lower rates of local and hepatic recurrence, but did not affect rates of peritoneal or pulmonary metastasis (Fig. 1). Local recurrence occurred in 11.3% (12 of 106) and 22.9% (38 of 166) of patients with and without preoperative therapy, respectively ($P = 0.016$). Hepatic recurrence occurred in 21.7% (23 of 106) and 34.3% (57 of 166) of patients with and without preoperative therapy, respectively ($P = 0.026$). Among patients treated with preoperative therapy, 19.8% (21 of 106) developed peritoneal and/or pulmonary metastases. In patients who underwent surgery first, rates of peritoneal and pulmonary metastases were 13.9% (23 of 166) and 17.5% (29 of 166), respectively.

Patterns of recurrence and other clinicopathologic factors

Perineural invasion was significantly associated with the development of peritoneal recurrence. Among the 23 patients without perineural invasion, none developed peritoneal recurrence, compared with 23 of the 142 (16.2%) patients with perineural invasion ($P = 0.037$). Perineural invasion did not affect rates of local recurrence, which occurred in 29 of 141 (20.6%) and four of 23 (17.4%) patients with and without perineural invasion, respectively ($P = 0.725$).

Regional nodal metastases from the primary tumour correlated with the development of pulmonary metastases, which occurred

Table 1 Demographic data for the 309 patients submitted to resection for pancreatic adenocarcinoma

Variable	Patients, *n* (%)		*P*-value
	Preoperative therapy (*n* = 108)	No preoperative therapy (*n* = 201)	
Gender, *n* (%)			0.247
Female	44 (40.7)	118 (58.7)	
Male	64 (59.3)	83 (41.3)	
Age, years, median (range)	66 (38–84)	67 (35–91)	0.123
Year of diagnosis, *n* (%)			0.093
1990–2000	41 (38.0)	63 (31.3)	
2001–2009	67 (62.0)	138 (68.7)	
Postoperative adjuvant therapy, *n* (%)	48 (44.4)	152 (75.6)	<0.001
Preoperative CA 19-9[a], U/ml, median (range)	38 (<1–1284)	196 (<1–6928)	<0.001
Surgical procedure, *n* (%)			0.004
Pancreaticoduodenectomy	102 (94.4)	200 (99.5)	
Total pancreatectomy	6 (5.6)	1 (0.5)	
Vascular resection, *n* (%)	42 (38.9)	20 (10.0)	<0.001
Tumour size, cm, median (range)	2.5 (0–10.5)	3.0 (1.0–8.5)	0.006
Tumour stage[b], *n* (%)			<0.001
T0	7 (7.4)	0	
T1	11 (11.7)	0	
T2	4 (4.3)	4 (2.2)	
T3	72 (76.6)	181 (97.8)	
Histologic differentiation, *n* (%)			0.226
Good	4 (3.7)	20 (10.0)	
Moderate	28 (25.9)	101 (50.2)	
Poor	30 (27.8)	70 (34.8)	
Unknown/not determined	46 (42.6)	10 (5.0)	
Lymph node metastases, *n* (%)	36 (33.3)	158 (78.6)	<0.001
Perineural invasion[c], *n* (%)	44/62 (71.0)	121/127 (95.3)	<0.001
Resection margin, *n* (%)			0.591
R0	74 (68.5)	126 (62.7)	
R1	33 (30.6)	73 (36.3)	
R2	1 (0.9)	2 (1.0)	
Recurrence[c], *n* (%)	69/106 (65.1)	129/166 (77.7)	0.023

[a]Data available for 90 and 99 patients in the groups treated with and not treated with preoperative therapy, respectively.
[b]T0, complete pathologic response after preoperative therapy; data available for 94 and 185 patients in the groups treated with and not treated with preoperative therapy, respectively.
[c]Data not available for all patients, as indicated by denominator.
CA 19-9, carbohydrate antigen 19-9.

in 23.2% (38 of 164) and 11.1% (12 of 108) of patients with and without positive lymph nodes, respectively ($P = 0.012$).

Vascular resection, margin status, T-stage and tumour size did not correlate with patterns of recurrence. In patients undergoing surgery first, the receipt of postoperative radiation did not affect rates of local recurrence.

Survival

Overall survival from the date of diagnosis was 22.0 months [95% confidence interval (CI) 18.3–25.7] and 18.0 months (95% CI 16.0–20.0) in patients with and without preoperative therapy, respectively ($P = 0.045$). When analysed from the date of surgery, median overall survival was 16.0 months (95% CI 13.2–18.8) and 18.0 months (95% CI 16.2–19.8) in patients with and without preoperative therapy, respectively ($P = 0.700$). Median disease-free survival was 14.0 months (95% CI 11.3–16.7) and 12.0 months (95% CI 10.4–13.6) in patients with and without preoperative therapy, respectively ($P = 0.035$) (Fig. 2).

Median survival from the date of detection of recurrence was 10.0 months (95% CI 7.3–12.7) in patients with isolated

Table 2 Patterns of recurrence in 272 patients

First site(s) of recurrence	Patients, *n* (%)
No recurrence	74 (27.2)
Liver	60 (22.1)
Peritoneum	35 (12.9)
Lung	34 (12.5)
Local	33 (12.1)
Local and liver	7 (2.6)
Liver and lung	6 (2.2)
Bone	5 (1.8)
Other[a]	18 (6.6)

[a]Including recurrences in the liver and peritoneum (n = 3), malignant pleural effusion (n = 3), local and peritoneum recurrences (n = 2), local, liver and lung recurrences (n = 2).

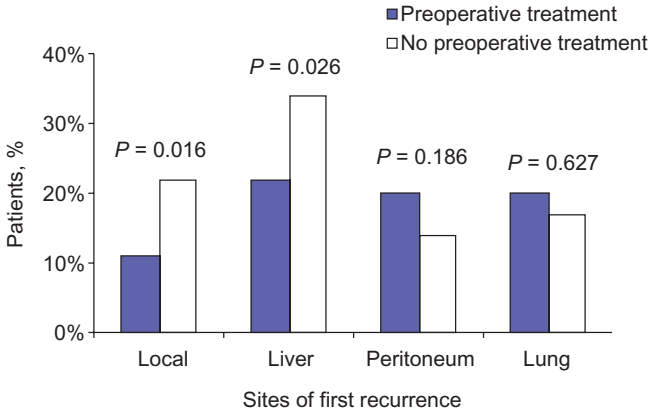

Figure 1 Sites of first recurrence after pancreatic resection in 272 patients, with (n = 106) and without (n = 166) preoperative therapy

pulmonary metastases as the first recurrence, 8.0 months (95% CI 6.3–9.7) in patients with hepatic metastases, 7.0 months (95% CI 6.2–7.8) in patients with local recurrence, and 3.0 months (95% CI 2.2–3.8) in patients with peritoneal metastases (P < 0.001) (Fig. 3).

Discussion

The putative benefits of preoperative therapy for pancreatic adenocarcinoma include early treatment of micrometastases, higher R0 resection rates, and improved selection of patients for potentially morbid surgery.[5,6] This study evaluated the ability of preoperative therapy to eradicate micrometastases and its impact on postoperative patterns of recurrence. Consistent with prior reports, the most common sites of postoperative disease relapse were the liver, peritoneum, local sites and lung.[13,14] Patients treated with preoperative therapy had longer disease-free survival and lower rates of local and hepatic recurrence than patients submitted to upfront surgery. However, preoperative therapy did not

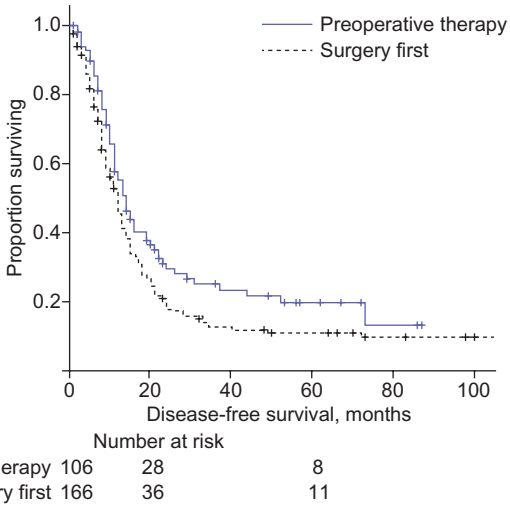

Figure 2 Disease-free survival after pancreatic resection was longer in 106 patients treated with preoperative therapy than in 166 patients who underwent immediate surgery (P = 0.035)

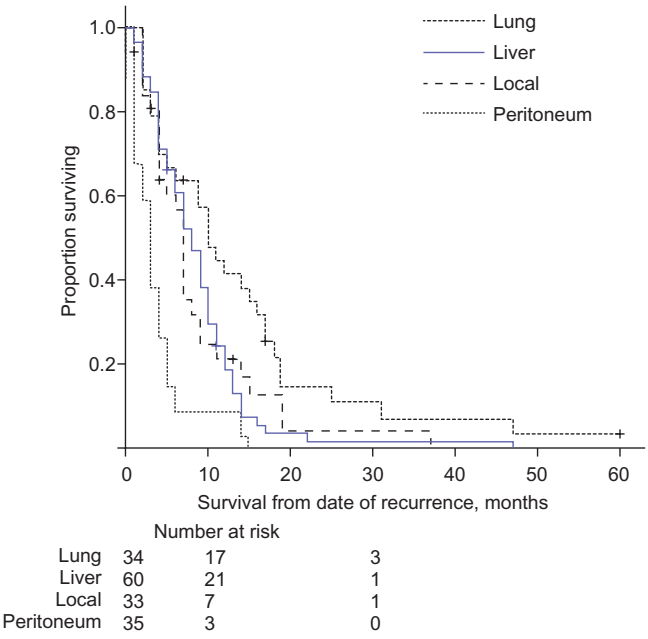

Figure 3 Survival from the date of detection of recurrence was longest in patients with pulmonary metastases and shortest in those with peritoneal recurrence (P < 0.001)

affect overall survival from the date of surgery or the frequency of peritoneal or pulmonary failures.

Local relapse as a component of first site of recurrence occurred in 11.3% and 22.9% of patients treated with and without preoperative therapy, respectively. The lower incidence of local failure with preoperative therapy in part reflects a significant downstaging effect. Although patients treated with

preoperative therapy had locally more advanced tumours, as is reflected in the higher need in this group for total pancreatectomy and vascular resection, their resected pathologic specimens exhibited a smaller tumour size, as well as a lower incidence of positive lymph nodes, and perineural and extrapancreatic invasion. Furthermore, 7.4% of patients treated with preoperative therapy exhibited a complete pathologic response, which has been shown to be independently associated with prolonged survival.[15] Other investigators have also demonstrated that preoperative therapy is associated with a downstaging effect and lower local recurrence.[7,8]

Hepatic metastases as a component of first site of relapse occurred in 21.7% of patients treated with preoperative therapy, compared with 34.3% with upfront surgery. Recent *in vivo* and mathematical modelling studies demonstrate that most patients harbour micrometastases at the time of diagnosis of pancreatic cancer and benefit from therapy that reduces cell proliferation earlier in the course of treatment.[9,10] Amikura *et al.* calculated tumour doubling times and observed that radiographically occult liver metastases are often present at the time of pancreatectomy.[16] Thus, the lower incidence of hepatic recurrence with preoperative therapy is partly attributable to better methods of selecting patients for surgery which allow the identification of patients with initially occult micrometastases that become radiographically evident after preoperative treatment.

Preoperative therapy did not improve rates of peritoneal or pulmonary recurrence or overall survival from the date of surgery. Barbier *et al.* also observed that preoperative therapy did not result in higher overall survival, despite an improvement in local control.[8] Cytotoxic drug delivery is inefficient in the peritoneal cavity,[17] and gemcitabine and 5-FU may be ineffective in eradicating pancreatic cancer cells in the peritoneum.

Data on recurrence were available for 272 of the 309 patients, which highlights the fact that a retrospective review of recurrence after resection of pancreatic cancer is limited by incomplete radiology and clinician reports. In addition, the present study analysed first sites(s) of recurrence because many patients do not undergo further imaging to detect subsequent sites of disease after their initial diagnosis of recurrence. Other limitations of this study include its retrospective nature, heterogeneous patient population, which included multiple pre- and postoperative chemotherapy and chemoradiation regimens, and non-standardized methods of assessing resectability. Patients were treated before the recently published consensus statement on definitions of resectable and borderline resectable pancreatic cancer.[18] In addition, the present group did not have sufficient data to perform an intent-to-treat analysis: data on the number of patients who started preoperative therapy and were not resected were lacking. In early trials of preoperative therapy in pancreatic cancer, this group observed resectability rates of between 38% and 67%.[19,20] Undoubtedly, patient selection contributed to the improved disease-free survival after resection in patients who received preoperative therapy.

In conclusion, preoperative therapy was associated with longer disease-free survival and lower rates of local and hepatic recurrence. Overall survival from the date of pancreatectomy and rates of pulmonary and peritoneal relapse were not affected by the receipt of preoperative therapy. In pancreatic adenocarcinoma, preoperative therapy is recommended to reduce local and hepatic failures after resection, and improved systemic therapies are required to control peritoneal and pulmonary recurrences.

Conflicts of interest

None declared.

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