

Resection Margins in Carcinoma of the Head of the Pancreas

Implications for Radiation Therapy

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A retrospective review of the pathology and clinical course of 72 patients undergoing resection of carcinoma of the head of the pancreas was undertaken to identify the frequency of tumor involvement at standard surgical transection margins (stomach, duodenum, pancreas, and bile duct) as well as the peripancreatic soft tissue margin and the potential clinical significance of these findings. Of 72 patients undergoing resection, 37 patients (51%) were found to have tumor extension to the surgical margins. The most commonly involved margin was peripancreatic soft tissue (27 patients) followed by pancreatic transection line (14 patients) and bile duct transection line (4 patients). For 37 patients with tumor present at a resection margin, there were no survivors beyond 41 months. No difference in survival or local control was seen between 14 patients receiving postoperative radiation therapy and 5-fluorouracil (5-FU) compared with 23 patients not receiving additional treatment. In contrast, the 5-year actuarial survival and local control of 35 patients undergoing resection without tumor invasion to a resection margin was 22% and 43%, respectively. The 5-year survival and local control of 16 patients receiving adjuvant radiation therapy and 5-FU was 29% and 42%, respectively, whereas these figures were 18% and 31% for 19 patients not receiving adjuvant therapy ($p > 0.10$). Because residual local tumor after resection is common, preoperative radiation therapy may be beneficial in this disease. It should minimize the risk of dissemination during operative manipulation and facilitate a curative resection by promoting tumor regression. Because local failure rates approach 60% after resection and adjuvant therapy even in cases having clear resection margins, intraoperative radiation therapy to the tumor bed at the time of resection also might be considered. Protocols evaluating the feasibility and efficacy of preoperative radiation therapy and resection with intraoperative radiation therapy for patients with pancreatic cancer are underway.

Recent advances in the management of patients with carcinoma of the pancreas have included the improved identification and selection of patients for resection by

radiologic and laparoscopic techniques as well as innovations in operative and postoperative management with resultant decreasing morbidity and mortality rates.¹⁻³ Despite these gains, the 5-year survival of patients undergoing curative resection of pancreatic carcinoma is only 10% to 20%.^{1,2} Lymph node metastases, poorly differentiated histology, large tumor size, perineural spread, and vascular involvement all have been recognized as negative prognostic indicators of outcome after resection.^{4,5} Although several investigators have

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noted the poor survival of patients with tumor involvement at resection margins, there has been little emphasis on delineation of specific loci of surgical margin involvement (the transected edges of stomach, duodenum, pancreas, and bile duct and particularly the peripancreatic soft tissue) or analysis of the associated consequences. The objective of this study is to analyze the recent clinical experience and patterns of failure of patients undergoing resection of the pancreatic head for carcinoma at the Massachusetts General Hospital (MGH), with special attention to the subset of patients having involved surgical margins.

MATERIALS AND METHODS

From July of 1978 to February of 1991, 72 patients underwent resection of carcinoma of the head of the pancreas at the MGH. Most resections were performed by one surgeon (A.L.W.). There were 33 women and 39 men, with a mean age of 61 years at surgery (range, 31 to 81 years). Surgical procedures included a standard pancreaticoduodenectomy (59 patients) or pylorus-preserving pancreaticoduodenectomy (8 patients) and total pancreatectomy (5 patients). No patient had evidence of metastatic disease by physical exam, chest radiograph, computed tomography (CT) scan of the abdomen, or findings at resection.

Sixty-seven of the 72 (93%) surgical and pathologic specimens were re-reviewed by two pathologists (C.C.C., K.L.) for the presence or absence of tumor at surgical margins (pancreatic transection line, bile duct transection line, duodenum/stomach, and peripancreatic soft tissue), extent of local invasiveness (invasion into duodenum, bile duct, or peripancreatic soft tissue), histologic differentiation, lymph node metastases, and vascular involvement (tumor cells identified in either small capillary/lymphatic or medium-sized arterial/venous vessels within the specimen). Only patients with invasive pancreatic ductal adenocarcinoma of the head of the pancreas were included in this analysis, and patients with ampullary, duodenal, and distal bile duct tumors or patients with pancreatic islet cell or cystadenocarcinomas were excluded.

Of the 72 patients undergoing resection, 39 patients received postoperative radiation therapy. Patients typically received 40 Gy to 50 Gy in 22 to 28 fractions of 1.8-Gy fractions over 5 to 6 weeks by techniques previously described.^{6,7} In addition, patients usually received intravenous 5-fluorouracil (500 mg/m²/day) for 3 consecutive days during the first and last weeks of radiation therapy.

After resection, patients were evaluated for local failure, distant metastases, and survival after resection. Local failure was defined as a recurrence occurring in the

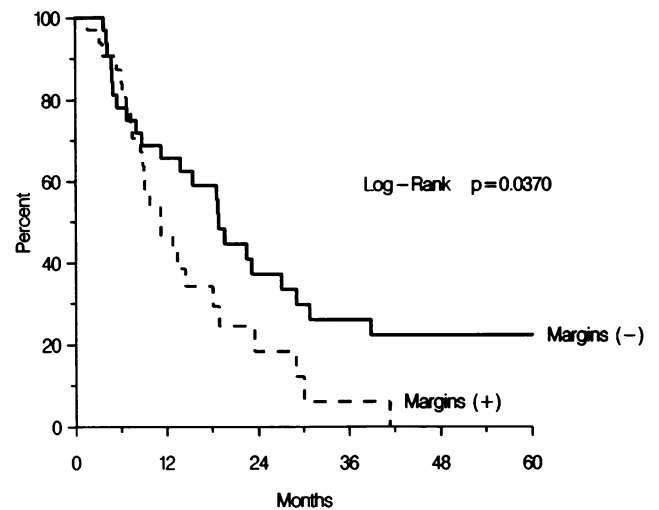


Figure 1. Actuarial survival of patients with carcinoma of the head of pancreas after resection based on margin status.

tumor bed or para-aortic lymphatics. Patterns of failure were determined principally by clinical and radiologic evaluation and less commonly by re-exploration or by autopsy. Mean and median follow-up times were 17 and 11 months, respectively. Actuarial local control and overall survival rates were estimated by Kaplan-Meier curves.⁸ The log-rank test was used to detect differences between Kaplan-Meier curves. The patterns of failure of 11 patients dying of pancreatic cancer could not be accurately determined. Although included in the survival analyses, these patients were censored in local control and distant metastatic evaluations.

RESULTS

Of the 72 patients undergoing resection, 37 patients (51%) were found on pathologic evaluation to have tumor involvement at a resection margin. The most commonly involved resection margin was peripancreatic soft tissue (27 patients) followed by pancreatic transection line (14 patients) and bile duct transection line (4 patients). No patient was found to have tumor involvement at the stomach or duodenal transection surfaces; therefore, these two subgroups are combined in further analyses. Of the 27 patients with tumor involvement of the peripancreatic soft tissue margin, 8 patients also had tumor extension to the pancreatic or bile duct transection margin.

The 5-year actuarial survival, local control, and freedom from distant metastases for all 72 patients was 13%, 34%, and 29%, respectively. There were four postoperative deaths. For the 35 patients having negative resection margins, the 5-year actuarial survival, local control, and freedom from distant metastases were 22%, 43%, and 37%, respectively (Figs. 1 through 3). In contrast, the

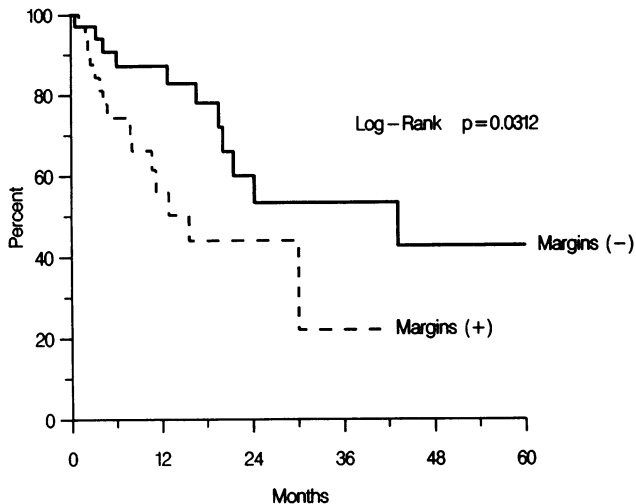


Figure 2. Actuarial local control of patients with carcinoma of the head of pancreas after resection based on margin status.

3-year actuarial survival, local control, and freedom from distant metastases of 37 patients with tumor involvement at resection margins was 6%, 22%, and 19%, respectively (Figs. 1 through 3). There were no survivors beyond 41 months for patients with tumors invasive of a resection margin. The differences in survival and local control based on margin status were statistically significant at $p < 0.05$.

Further examination of survival, local control, and freedom from distant metastases stratified by the parameters of histologic differentiation, lymph node status, and vascular involvement for patients having clear or involved resection margins is summarized in Table 1. Because survival did not exceed 41 months among patients with positive resection margins, 2-year actuarial statistics were used. For patients having tumors with no involvement of margins, the pathologic features of well or moderately well-differentiated histology or no vascular involvement were statistically significant favorable prognostic factors (Table 1). Although patient numbers were small, the 2- and 5-year survival of six patients with tumors exhibiting no vascular involvement was surprisingly high at 83%. Among patients with tumor involvement at a resection margin, there were no statistically significant prognostic factors, with the odd exception that patients with lymph node metastases appeared to have a superior survival than patients without this. Local control and freedom from distant metastases were not statistically different between these two subsets, however.

The 5-year survival, local control, and freedom from distant metastases of 16 patients receiving adjuvant radiation therapy with uninvolved resection margins was 29%, 42%, and 49%, respectively, whereas these figures

were 18%, 31%, and 31%, respectively, for patients not receiving adjuvant therapy (Figs. 4 through 6). Although the results were superior for patients receiving adjuvant therapy compared with patients not receiving adjuvant treatment, these differences were not statistically significant. For patients with tumor present at the resection margin, there was no difference in survival, local control, or freedom from distant metastases based on administration of postoperative radiation therapy and 5-FU (Figs. 4 through 6).

DISCUSSION

Traditionally, the true surgical resection margins of a pancreaticoduodenectomy have been considered to be the transection lines of the stomach and duodenum, the pancreas, and the distal bile duct, whereas for patients undergoing a total pancreatectomy, standard margins would include the stomach, duodenum, and distal bile duct. In this analysis, the tumors of 16 patients were noted to have extended to the transected margin of the pancreas or bile duct. No patient was observed to have tumor extension to margins of the stomach or duodenum. In contrast, the degree of tumor invasion through the pancreatic capsule into peripancreatic soft tissues is not routinely documented. The pancreatic capsule and peripancreatic soft tissues may not be strictly regarded as a surgical resection margins because they are not transected with the scalpel. Instead, these may be more appropriately considered dissection margins that must be mobilized to permit removal of the transected tissues. Nevertheless, these are relevant margins in that tumors may

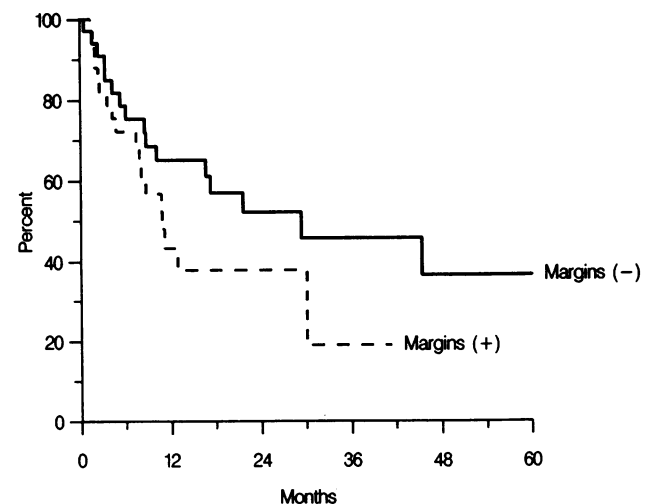


Figure 3. Actuarial freedom from distant metastases of patients with carcinoma of the head of pancreas after resection based on margin status.

Table 1. TWO-YEAR ACTUARIAL SURVIVAL, LOCAL CONTROL, AND FREEDOM FROM DISTANT METASTASES FOR PATIENTS WITH INVOLVED OR UNINVOLVED RESECTION MARGINS STRATIFIED BY HISTOPATHOLOGIC FEATURES

| Comparison | No. of Patients | | Survival (%) | | Local Control (%) | | Freedom From Distant Metastases (%) | |
|---------------------------------|-----------------|------|--------------|------|-------------------|------|-------------------------------------|------|
| | (M+) | (M-) | (M+) | (M-) | (M+) | (M-) | (M+) | (M-) |
| Overall | 37 | 35 | 18 | 37† | 44 | 60† | 38 | 52 |
| Differentiation | | | | | | | | |
| Well/moderately well | 28 | 20 | 20 | 49 | 39 | 80† | 43 | 65 |
| Poor (1 patient unevaluable) | 8 | 15 | 21 | 19 | 69 | 30 | 29 | 34 |
| Lymph node metastases | | | | | | | | |
| Yes | 27 | 20 | 28† | 20 | 46 | 55 | 44 | 48 |
| No (1 patient unevaluable) | 10 | 14 | 0 | 61 | 39 | 64 | 17 | 61 |
| Vascular involvement | | | | | | | | |
| Yes | 31 | 27 | 23 | 27† | 40 | 52 | 34 | 48 |
| No (4 patients unevaluable) | 4 | 6 | 25 | 83 | 50 | 83 | 75 | 67 |

* Log-rank based on total N.

† p < 0.05.

M+, patients with tumors with involved resection margins; M-, patients with tumors with uninvolved resection margins.

potentially involve the major vessels and retroperitoneal tissues, where there may be anatomic and technical limitations to further excision of tissue. On histopathologic examination, the tumors of 27 patients (38%) were observed to have tumor extension to the edge of the peripancreatic soft tissues. As the data from this study indicate, patients with tumors involving either standard surgical margins or the peripancreatic soft tissue margins represent a large percentage of patients undergoing re-

section. This observation is particularly significant because these patients have a universally fatal outcome with high rates of local failure, distant metastases, and no long-term survivors. In addition to standard margins, evaluation of the extent of tumor invasion through the pancreatic capsule with inking of the peripancreatic soft tissue surface of the resection specimen to determine the status of this margin should be an integral component of pathologic examination.

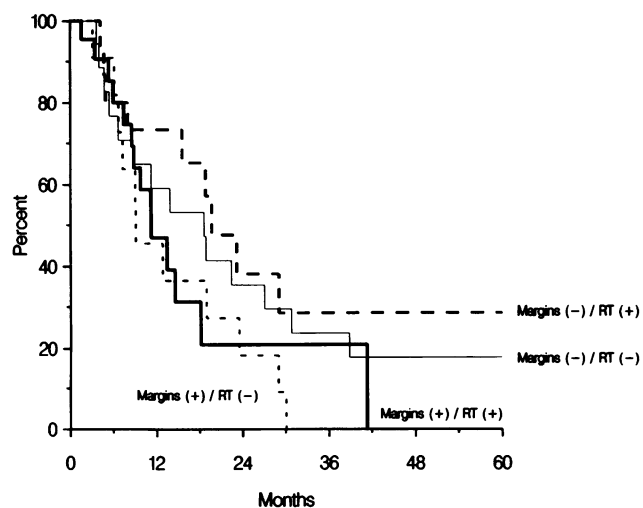


Figure 4. Actuarial survival of patients with carcinoma of the head of pancreas after resection based on margin status and radiation therapy.

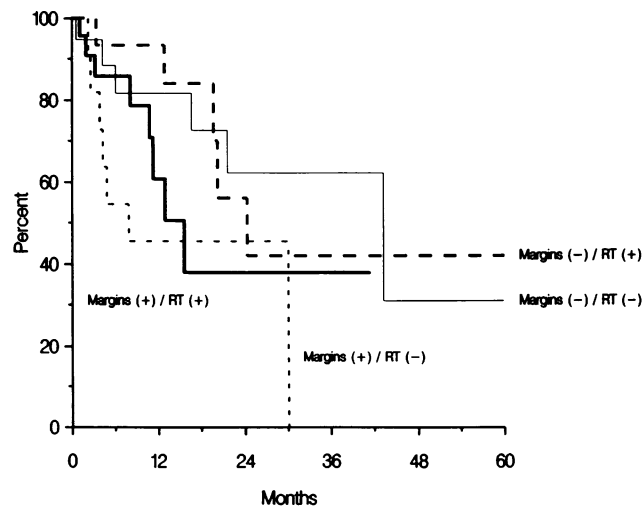


Figure 5. Actuarial local control of patients with carcinoma of the head of pancreas after resection based on margin status and radiation therapy.

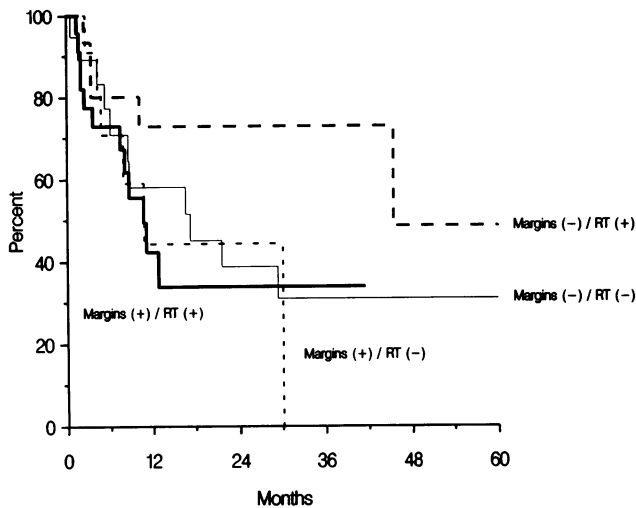


Figure 6. Actuarial freedom from distant metastases with carcinoma of the head of pancreas after resection based on margin status and radiation therapy.

The 5-year actuarial survival, local control, and freedom from distant metastases of all 35 patients undergoing resection with uninvolved resection margins was 22%, 43%, and 37%, respectively. After the Gastrointestinal Study Group study found a survival benefit for patients with completely resected pancreatic carcinomas receiving adjuvant postoperative radiation therapy with 5-FU compared with surgical control, all patients since 1985 have routinely received postoperative radiation therapy with 5-FU.^{9,10} The 5-year survival, local control, and freedom from distant metastases was 29%, 42%, and 49%, respectively, for 16 patients receiving adjuvant treatment compared with 18%, 31%, and 31%, respectively, for those not irradiated. Although these figures are similar to or superior to those reported by other investigators, further efforts to improve on these results seem appropriate.^{9,10}

For patients with pancreatic carcinoma, it is well recognized that intraoperative biopsy or dissection of the pancreas may result in tumor dissemination and implantation with the subsequent development of peritoneal metastases.^{1,3} As the current study has demonstrated, a high percentage of patients will have residual local disease by pathologic examination after resection because of the local invasiveness of pancreatic cancer and anatomic constraints limiting wide *en bloc* resections. To minimize the risk of dissemination during operative manipulation and to facilitate a curative resection by promoting tumor regression, preoperative external beam radiation therapy (45 to 50.4 Gy in 25 to 28 fractions) to the pancreas and regional lymphatics combined with 5-FU may confer benefits superior to those of postoperative irradiation. Data from a small series of patients treated at Tufts in

this fashion indicate that this approach is feasible without added surgical complications.¹¹ Because local failure rates approach 60% after resection and adjuvant external beam radiation therapy for patients with tumors having clear resection margins, intraoperative radiation therapy (10 to 15 Gy) to the tumor bed at the time of resection should be further examined. Such an approach would permit total radiation doses of 60 to 65 Gy to the surgical bed, further increasing the chance for local control. The triad of preoperative external beam radiation therapy, surgical resection, and intraoperative radiation therapy has resulted in improved local control and survival for patients with locally advanced rectal cancer.¹² Clinical investigations to evaluate the feasibility and efficacy of moderate to high-dose preoperative radiation therapy and resection with intraoperative radiation therapy in patients with pancreatic cancer are currently underway at the Massachusetts General Hospital.

Acknowledgments

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