

## Is Reporting of Recurrence Data Important in Pancreatic Cancer?

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**Background:** Therapeutic approaches to patients with pancreatic cancer have undergone a paradigm shift in recent years. However, little is known about the outcome of patients with recurrent pancreatic cancer who undergo treatment. The purpose of this study was to identify patients with recurrent pancreatic cancer and to determine whether treatment after recurrence had any effect on outcome.

**Methods:** A review of all patients undergoing surgical resection with curative intent revealed 70 patients with documented recurrence and complete medical records. Patients were grouped into three categories: group 1 included those who received treatment after recurrence ( $n = 45$ ), group 2 included those who were not offered treatment ( $n = 9$ ), and group 3 included those with poor performance status who received no treatment ( $n = 16$ ).

**Results:** The median overall survival for the three groups was 26, 18, and 14.5 months for groups 1, 2, and 3, respectively ( $P < .00001$ ). The median survival after recurrence was 10 months, 6 months, and 1 month, respectively, for the three groups ( $P < .0001$ ).

**Conclusions:** This is the first series we are aware of that compares the outcomes of patients who received treatment after recurrence of pancreatic cancer with the outcomes of those who received no treatment. In this series, it seems that patients who were well enough to tolerate additional therapy had a longer survival than those who received supportive care only. This may be important in the analysis of adjuvant therapy trials of pancreatic cancer with survival as an end point.

**Key Words:** Pancreatic cancer—Recurrence—Chemotherapy—Survival treatment.

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Pancreatic cancer continues to represent a significant therapeutic challenge. An estimated 30,300 cases were diagnosed in the United States in 2002 and were accompanied by 29,700 deaths.<sup>1</sup> Despite surgery with curative intent in 10% to 20% of patients, recurrence is common, with a median survival of approximately 17 months and a 5-year survival of 15% to 20%.<sup>2–4</sup> Most recurrences occur within 1 to 2 years of surgery and most commonly manifest as peritoneal or liver disease, but may also present as lung metastases.<sup>5–7</sup>

The use of chemotherapy, with or without radiotherapy, in the treatment of resectable and unresectable pancreatic cancer has been well documented.<sup>8–12</sup> In resectable patients, chemotherapy has been used alone and in combination with radiotherapy as induction therapy and in the postoperative adjuvant setting. Survival advantages have been shown with 5-fluorouracil (5-FU) combined with radiation for unresectable pancreatic cancer and, when given adjuvantly, for resected pancreatic cancer.<sup>8,9</sup> More recently, gemcitabine has been used and has shown reasonable response rates in patients with 5-FU–refractory pancreatic cancer.<sup>11</sup> In unresectable and metastatic pancreatic cancer, gemcitabine has shown a survival benefit, albeit small, when compared with 5-FU.<sup>10</sup> Perhaps more importantly, patients who received gemcitabine derived a greater clinical benefit than those who received 5-FU. Gemcitabine has also been combined with radiation in patients with unresectable pancreatic cancer, with favorable preliminary results.<sup>12</sup>

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Despite these results, little is known about the effect of treatment in the subset of patients with recurrent pancreatic cancer after previous resection with curative intent. The most recent prospective, randomized pancreatic cancer trials have not evaluated this. The purpose of this study was to evaluate the effect of treatment on patients with recurrent pancreatic cancer who had previously been treated with curative intent. It was our hypothesis that data regarding treatment after recurrence are important and that outcomes may vary depending on the type of therapy received. This information may have implications when the results of prospective trials of pancreatic cancer with survival as the primary outcome are interpreted.

## METHODS

This analysis used data from a prospective database of all patients undergoing pancreatic resection for pancreatic adenocarcinoma from 1986 to 2001 at a single institution. This included patients with tumors of the pancreatic head, body, and tail. Procedures included pancreaticoduodenectomy, total pancreaticoduodenectomy, and distal pancreatectomy. Most patients had peritoneal cytology sampled at the time of surgery as well.

The majority of patients underwent trimodality therapy that included both chemotherapy and radiotherapy in addition to surgery. Patients were treated at either Fox Chase Cancer Center or community institutions. Both preoperative and postoperative chemoradiotherapy was used. Most patients received either 5-FU or gemcitabine.

All patients with documented recurrence were identified. Records were analyzed to determine the type of treatment received after recurrence. Patients with inadequate or ambiguous data regarding the therapy received after recurrence were excluded. In those patients who did not receive treatment after recurrence, records were reviewed to determine the reasons why they were not treated. Patients in this group were also excluded if we were unable to determine why they did not undergo treatment. Overall, 70 patients were included in the analysis. Patients were segregated into three groups for the purpose of analysis. Group 1 included those who received treatment after recurrence ( $n = 45$ ), group 2 included three patients with appropriate performance status who were not offered treatment and six patients who were offered treatment but refused ( $n = 9$ ), and group 3 included those with poor performance status at the time of recurrence who received no treatment ( $n = 16$ ).

The primary outcomes analyzed were time to recurrence, survival after recurrence, and disease-specific overall survival. A number of variables were analyzed.

These included patient age, tumor size as defined by staging criteria,<sup>13</sup> lymph node status, American Joint Committee on Cancer (AJCC) stage, tumor grade, surgical margin status, CA 19-9 level at diagnosis, type of operative procedure, peritoneal cytology at surgery, type of adjuvant chemotherapy given, preoperative versus postoperative chemotherapy, site of first recurrence, and type of treatment after recurrence (i.e., group 1, 2, or 3). Margins evaluated included the bile duct margin, the cut edge of the pancreas, the resection margin along the superior mesenteric artery/superior mesenteric vein, and the retroperitoneal margin. The retroperitoneal margin was defined as the area from the medial aspect of the duodenal sweep to the lateral aspect of the superior mesenteric vein/portal vein and is distinct from the margin along the superior mesenteric artery/superior mesenteric vein. Tumor involvement of any of these margins was considered a positive margin. The site of recurrence was defined as liver, lung, or other, which included both local and peritoneal recurrence.

Log-rank tests were performed to identify categorical variables significantly associated with time to recurrence, survival time after recurrence, and overall survival time for all patients with recurrent disease. Generalized Fisher's exact tests were used to identify categorical variables whose distributions were significantly different among the patients in groups 1, 2, and 3. A Kruskal-Wallis test was used to test for between-group differences in patient age. Cox proportional hazards models were used to evaluate the significance of the relationship between patient age and time to recurrence, survival time after recurrence, and overall survival time. Multivariate proportional hazards models were also fit to these failure-time data. Survival curves were estimated with the Kaplan-Meier method.

## RESULTS

Seventy patients were identified with biopsy-proven recurrent pancreatic cancer and complete follow-up records. The mean age was  $65 \pm 10$  years (median, 68 years), and they ranged from 41 to 83 years of age. There were 42 women (60%) and 28 men (40%). Of the 70 patients, 63 underwent pancreaticoduodenectomy (90%), 4 had a total pancreaticoduodenectomy (6%), and 3 had a distal pancreatectomy (4%).

A number of pathologic variables were analyzed. These are listed in Table 1. Tumor size was defined according to the 5th edition of the AJCC staging manual.<sup>13</sup> Tumor size was relatively equally divided, with 12 T1, 17 T2, 23 T3, and 18 T4 tumors represented. A total of 39 patients (56%) had positive lymph nodes, and 31

**TABLE 1.** Pathologic characteristics

| Variable            | n  | %  |
|---------------------|----|----|
| Tumor size          |    |    |
| T1                  | 12 | 17 |
| T2                  | 17 | 24 |
| T3                  | 23 | 33 |
| T4                  | 18 | 26 |
| Lymph node status   |    |    |
| Positive            | 39 | 56 |
| Negative            | 31 | 44 |
| AJCC stage          |    |    |
| 1                   | 19 | 26 |
| 2                   | 6  | 8  |
| 3                   | 27 | 39 |
| 4                   | 18 | 26 |
| Margin status       |    |    |
| Positive            | 39 | 56 |
| Negative            | 31 | 44 |
| Tumor grade         |    |    |
| Low                 | 9  | 13 |
| Intermediate        | 38 | 54 |
| High                | 20 | 29 |
| Not reported        | 3  | 4  |
| Peritoneal cytology |    |    |
| Positive            | 7  | 11 |
| Negative            | 58 | 89 |

AJCC, American Joint Committee on Cancer.

(44%) did not. AJCC stage grouping was skewed toward higher stages; 34% of patients had stage I or II disease, 40% were stage III, and 25% were stage IV. When the pancreatic margin status was defined, four separate sections were analyzed: (1) the pancreatic resection margin, (2) the vascular margin (superior mesenteric vein or artery) along the uncinate process, (3) the retroperitoneal margin, or (4) the bile duct margin. The margin was considered positive if any of these were involved. In this series, 38 patients (54%) had at least 1 positive margin, and 32 (46%) had negative margins. The vascular margin was the most common site of positive margins, with 95% of positive margins occurring at this location. Most patients had intermediate-grade tumors (56%); 28% had high-grade lesions, and only 13% had low-grade tumors. Peritoneal cytology was positive in 10% of patients for whom it was sent and was negative in 90%.

Treatment characteristics were also evaluated (Table 2). A total of 37 patients received preoperative chemoradiotherapy. Of these, 17 received 5-FU and 20 received gemcitabine. Thirty-three patients underwent postoperative chemoradiotherapy: 25 of these received 5-FU and 7 received gemcitabine. One patient received adjuvant therapy at an outside facility, and chemotherapy records of this treatment were unavailable. Forty-five patients underwent some form of therapy after the diagnosis of recurrence. Gemcitabine was used in 21 patients (47%), 5-FU-based therapy (including combinations with leu-

**TABLE 2.** Treatment characteristics

| Variable                              | n  | %  |
|---------------------------------------|----|----|
| Preoperative chemoradiotherapy        | 37 | 51 |
| Postoperative chemoradiotherapy       | 33 | 46 |
| Type of chemotherapy                  |    |    |
| 5-Fluorouracil                        | 42 | 58 |
| Gemcitabine                           | 27 | 38 |
| Site of first recurrence              |    |    |
| Lung                                  | 15 | 21 |
| Liver                                 | 28 | 40 |
| Other                                 | 27 | 39 |
| Chemotherapy after recurrence         |    |    |
| Yes                                   | 45 | 64 |
| No                                    | 25 | 36 |
| Type of chemotherapy after recurrence |    |    |
| Gemcitabine                           | 21 | 47 |
| 5-Fluorouracil                        | 11 | 24 |
| Other                                 | 13 | 29 |

covorin and mitomycin) was used in 11 patients (24%), and other regimens were used in 13 patients (29%). Other regimens included paclitaxel/carboplatin, irinotecan, vaccine trials, and phase I trials. Twenty-five patients did not receive any therapy after recurrence.

An analysis of variables associated with time to recurrence, survival after recurrence, and overall survival was performed for all patients with recurrent pancreatic cancer (Table 3). Tumor size ( $P = .02$ ), AJCC stage ( $P = .04$ ), and the site of first recurrence ( $P = .02$ ) were significant variables that affected the time to recurrence in a univariate analysis. The presence of lymph node metastases did not meet statistical significance ( $P = .08$ ). The site of first recurrence associated with the longest time to recurrence was the lung (median time to recurrence, 17.5 months). The liver (median, 12 months) and

**TABLE 3.** Univariate analysis of variables associated with time to recurrence, survival after recurrence, and overall survival in patients with recurrent pancreatic cancer: reported as P values by the log-rank test

| Variable                                     | Time to recurrence | Survival after recurrence | Overall survival    |
|--|--------------------|---------------------------|---------------------|
| Surgical procedure                           | NS                 | NS                        | NS                  |
| Tumor size                                   | .02                | .03                       | .03                 |
| Lymph node status                            | .08                | NS                        | NS                  |
| AJCC stage                                   | .04                | .05                       | .03                 |
| Margin status                                | NS                 | .03                       | NS                  |
| Tumor grade                                  | NS                 | NS                        | NS                  |
| Peritoneal cytology                          | NS                 | NS                        | .04                 |
| CA 19-9                                      | NS                 | NS                        | NS                  |
| Preoperative chemotherapy                    | NS                 | NS                        | NS                  |
| Postoperative chemotherapy                   | NS                 | NS                        | NS                  |
| Site of recurrence                           | .02 <sup>a</sup>   | .003 <sup>a</sup>         | .002 <sup>a</sup>   |
| Treatment after recurrence group (1, 2 or 3) | NS                 | <.0001 <sup>a</sup>       | <.0001 <sup>a</sup> |

NS, not significant; AJCC, American Joint Committee on Cancer.

<sup>a</sup> Statistically significant in multivariate analysis.

other sites (median, 12 months) were less favorable. Each factor that was significantly associated with the time to recurrence was included as a covariate in a multivariate analysis. The site of first recurrence ( $P = .05$ ) was the only variable significantly associated with time to recurrence after adjusting for the other covariates in the model. Predictors of survival after recurrence in a univariate analysis included tumor size ( $P = .03$ ), AJCC stage ( $P = .05$ ), margin status ( $P = .03$ ), site of first recurrence ( $P = .003$ ), and treatment group after recurrence ( $P < .0001$ ). Again, the lung as the site of first recurrence was the most favorable outcome (median survival after recurrence, 14 months); the liver (median, 6 months) and other sites (median, 4 months) were less favorable. Variables significantly associated with the survival time after recurrence were included as covariates in a multivariate analysis. The site of recurrence ( $P < .001$ ) and the treatment group after recurrence ( $P < .001$ ) remained significant. Variables affecting overall survival by univariate analysis included tumor size ( $P = .03$ ), AJCC stage ( $P = .03$ ), peritoneal cytology at the time of surgery ( $P = .04$ ), site of first recurrence ( $P = .002$ ), and treatment group after recurrence ( $P < .0001$ ). The lung as the first site of recurrence was also most predictive of overall survival (median overall survival, 32 months). The liver (median, 17 months) and other sites (median, 20 months) had a worse outcome. Again, variables significantly associated with survival time were included as covariates in a multivariate analysis. Site of recurrence ( $P = .01$ ) and treatment group ( $P < .001$ ) were both significant after adjustment for the other factors in the model.

As noted previously, this group of 70 patients with recurrent pancreatic cancer after surgery with curative intent was divided into 3 groups based on the treatment they received after recurrence. Group 1 included those who received treatment after recurrence ( $n = 45$ ), group 2 included those with appropriate performance status who were not offered treatment or those who were offered treatment but refused ( $n = 9$ ), and group 3 included those with poor performance status who received no treatment ( $n = 16$ ). This was done in an attempt to compare survival outcomes on the basis of the type of therapy received after recurrence. Those in group 2 who were not offered any further treatment or who refused treatment all had an appropriate performance status (Eastern Cooperative Oncology Group/Zubrod performance status  $\leq 2$ ). Six patients were not offered treatment because it was not believed to be effective. Three were offered treatment and declined. The patients in group 3 had a performance status  $\geq 3$ , such that they were not thought to be well enough to tolerate additional

therapy. Of the 45 patients who received treatment after recurrence, 33 (73%) of 45 received a regimen different from what they received as adjuvant therapy. Of the 12 who received the same chemotherapy for both adjuvant and salvage therapy, 5 received gemcitabine and 7 received 5-FU. Most (six of seven) of those who received 5-FU were treated before 1994, when gemcitabine became widely available. The 45 patients who received some form of therapy after recurrence were grouped together after a preliminary analysis revealed no significant difference in survival after recurrence when comparing those who received gemcitabine (median survival after recurrence, 10 months) with those who received other types of chemotherapy (median, 9.5 months). Time to recurrence, survival after recurrence, and overall survival were calculated for each of the three groups (Table 4). The median time to recurrence was similar for all three groups at 14, 12, and 12 months for groups 1, 2, and 3, respectively. Survival after recurrence (Fig. 1) was significantly different when comparing group 1 (median survival after recurrence, 10 months), group 2 (median, 6 months), and group 3 (median, 1 month). Similarly, overall survival (Fig. 2) was better for group 1 (median overall survival, 26 months) than for group 2 (median, 18 months) or group 3 (median, 14 months).

To determine whether any underlying differences existed among the three groups, an analysis of variables among the three groups was performed. Variables that were significantly different among the three groups included margin status ( $P = .01$ ), peritoneal cytology ( $P = .01$ ), and AJCC stage ( $P = .05$ ). There was not a significant difference in the pattern of recurrence among groups. Between-group differences in survival time after recurrence and overall survival time were assessed after adjustment for the effects of margin status, peritoneal cytology, and AJCC stage by using multivariate Cox proportional hazards models. Survival after recurrence remained statistically different when group 1 was compared with both group 2 ( $P = .01$ ) and group 3 ( $P = .02$ ). The difference in overall survival remained significant between group 1 and group 2 ( $P = .03$ ), but groups 1 and 3 were not significantly different.

**TABLE 4.** Median time to recurrence, survival after recurrence, and overall survival by group

| Variable                       | Group 1 | Group 2 | Group 3 | <i>P</i> value |
|--------------------------------|---------|---------|---------|----------------|
| Time to recurrence (mo)        | 14      | 12      | 12      | NS             |
| Survival after recurrence (mo) | 10      | 6       | 1       | <.0001         |
| Overall survival (mo)          | 26      | 18      | 14      | <.0001         |

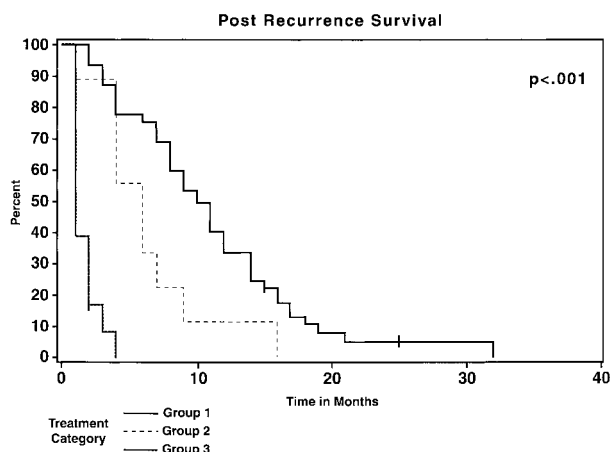


FIG. 1. Kaplan-Meier actuarial survival curve comparing survival after recurrence by treatment group.

## DISCUSSION

Treatment of advanced and metastatic pancreatic cancer has undergone a change in philosophy in the last 10 years. Before reports showing a clinical benefit associated with gemcitabine, 5-FU was the most widely used agent for advanced pancreatic cancer, and published response rates were no higher than 20%.<sup>14,15</sup> Gemcitabine has been shown to have clinical benefit in 5-FU-refractory advanced pancreatic cancer.<sup>11</sup> More recently, gemcitabine was compared with 5-FU in a prospective, randomized trial of patients with advanced pancreatic cancer.<sup>10</sup> Patients treated with gemcitabine derived greater clinical benefit than those treated with 5-FU and also had an improvement in survival, although this was small. This laid the groundwork for modern treatment strategies, most of which include gemcitabine.

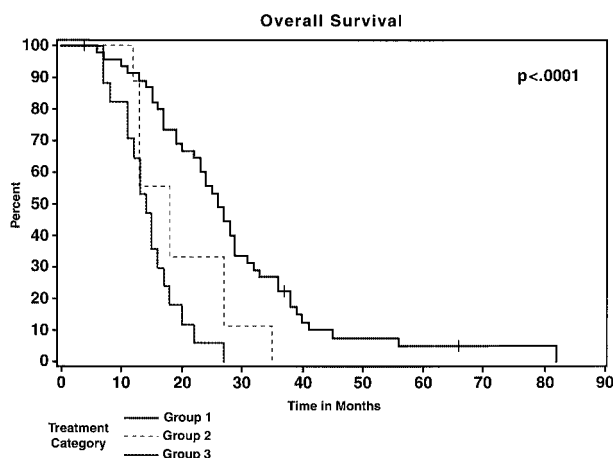


FIG. 2. Kaplan-Meier actuarial survival curves comparing overall survival by treatment group.

The goal of this review was to evaluate factors affecting outcome in patients with recurrent pancreatic cancer and attempt to determine whether treatment after recurrence has any effect on survival. This was in response to recent adjuvant therapy trials of pancreatic cancer that did not examine recurrence data.<sup>16</sup> This report represents the first study we are aware of that evaluates the outcome of patients with recurrent pancreatic cancer who had previously been resected with curative intent. We identified three distinct groups of patients on the basis of their status at the time of recurrence and the treatment they received after recurrence. We found that survival after tumor recurrence and overall survival were significantly better in the group of patients who received treatment of any kind after their disease recurred (median survival after recurrence, 10 months) than in the group of patients who were not offered treatment or who refused treatment (median, 6 months). The third group of patients, those who did not have an adequate performance status at the time of recurrence to be considered for therapy, did poorly (median, 1 month), as expected. It is important to note that this survival benefit remained the same when differences between these two groups were taken into account. In the group of patients who received treatment after recurrence, the type of chemotherapy received did not have any effect on survival. Another interesting finding of this study is the effect that the site of first recurrence had on the time to recurrence, survival after recurrence, and overall survival. An isolated recurrence in the lung certainly corresponds to longer survival after recurrence (median, 14 months) and longer overall survival (median, 32 months) than a recurrence in the liver (median, 6 and 17 months, respectively) or other locations (median, 6 and 20 months, respectively). It seems from these data that the pattern of recurrence may be as important as the type of treatment received after recurrence.

Univariate analysis of variables associated with survival after recurrence and overall survival revealed several factors that correlated with survival. Survival after recurrence was affected by tumor size, AJCC stage, margin status, site of first recurrence, and type of treatment received after recurrence. Factors significantly associated with overall survival included tumor size, AJCC stage, peritoneal cytology, site of recurrence, and treatment group after recurrence. In the multivariate analysis, the only variables that affected survival after recurrence and overall survival were the site of first recurrence and the type of treatment received after recurrence. Margin status had an effect on survival after recurrence but had no effect on overall survival, as has been seen in other series.<sup>4,17</sup> It is possible that this is confounded by the

selection of a group of patients who had complete records and whose disease recurred. If all patients were included, a positive margin might have been associated with a decrease in overall survival. However, in a large review from our institution focusing on the pancreatic margin at resection, the overall rate of a positive margin was 62%, which is consistent with what we see in this series.<sup>18</sup> Similarly, tumor grade and lymph node status had no effect on survival, as has been reported by others.<sup>4,16</sup> This may also be related to selection bias. Another interesting finding was the association between the site of first recurrence and survival. In this series, it seems that tumors that recurred in the lung initially had a much more favorable prognosis than other sites, including the liver and peritoneum.

Identifying the reason for improved survival in this group of patients undergoing therapy after recurrence is difficult. The retrospective nature of this report and the small sample size in the group that was not offered (or refused) treatment make it difficult to draw definitive conclusions from this study. It is unlikely that the difference in survival can be ascribed to a treatment effect alone. Although some benefit from chemotherapy may have been realized, results of trials using gemcitabine or 5-FU in patients with advanced disease would suggest that the benefit is likely to be small.<sup>8,10</sup> Another possible explanation is the level of supportive care patients received after the diagnosis of recurrence. We have no way of quantifying this in our report, but it is certainly possible that the patients who underwent treatment were more aggressively supported than those who were not being actively treated. This alone may have had bearing on the difference in survival among groups.

Another interesting point of discussion is the implication these results may have on prospective trials of pancreatic cancer with survival as the primary end point. The recently reported European Study Group for Pancreatic Cancer trial, which compared chemoradiotherapy, chemotherapy, and observation alone after curative surgical resection for pancreatic adenocarcinoma, is one such study.<sup>16</sup> Although randomization occurred among treatment groups, no data were kept regarding patterns of recurrence and the treatment received after recurrence. The results from this review suggest that both of these may have important implications on overall survival. It is conceivable that differences may exist among groups in both the site of recurrence and therapy after recurrence despite randomization. This may have an effect on the outcome of such trials.

Recurrent pancreatic cancer remains a significant therapeutic challenge. Little has been written about the effect of treatment on these patients, most of whom have previously been treated with chemotherapy. Although this

issue remains unsettled, data from the treatment of patients with advanced disease at presentation would suggest that meaningful palliation may be realized. As chemotherapy continues to improve, this is likely to become more important.

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