Microscopic Margins and Patterns of Treatment Failure in Resected Pancreatic Adenocarcinoma

Jennifer L. Gnerlich, MD; Samuel R. Luka, MD; Anjali D. Deshpande, PhD, MPH; Bernard J. Dubray, MD; Joshua S. Weir, MS; Danielle H. Carpenter, MD; Elizabeth M. Brunt, MD; Steven M. Strasberg, MD; William G. Hawkins, MD; David C. Linehan, MD

Objective: To correlate microscopic margin status with survival and local control in a large cohort of patients from a high-volume pancreatic cancer center.

Design: Retrospective database review. A uniform procedure for margin analysis was used with 4-color inking (neck, portal vein groove, uncinate, and posterior pancreatic margin) by the surgeon in the operating room.

Setting: A tertiary care hospital.

Patients: We reviewed patients who underwent pancreaticoduodenectomy between September 1, 1997, and December 31, 2008, from a prospective, institutional database.

Main Outcome Measures: Using Cox regression models, we identified pathologic characteristics associated with local recurrence (LR) after controlling for potential confounding variables. Overall and LR-free survival curves were generated by the Kaplan-Meier method.

Results: Of 285 patients who underwent pancreaticoduodenectomy for pancreatic adenocarcinoma, 97 (34.0%) had 1 or more positive microscopic margins (uncinate, 16.5%; portal vein groove, 8.8%; neck, 7.7%; and posterior, 10.5%). A total of 198 patients (69.5%) recurred, with the first site of failure being LR only in 47 (23.7%), local plus distant recurrence in 42 (21.2%), and distant recurrence only in 109 (55.1%). Patients with LR only were significantly more likely to have lymph node involvement (adjusted hazard ratio, 2.66; 95% CI, 1.25-5.63) or a positive posterior margin (adjusted hazard ratio, 4.27; 95% CI, 2.07-8.81). Patients with a positive posterior margin had significantly poorer LR-free survival with (P < .001) or without (P = .01) lymph node involvement.

Conclusions: When systematically assessed, the incidence of positive microscopic margins is high. Positive posterior margins and lymph node involvement were each independently and significantly associated with LR.

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Pancreatic cancer is one of the most lethal malignancies.1 Multiple prognostic factors have been identified that are associated with long-term survival,2-7 but positive microscopic resection margins may be the most important independent predictor.8-17 Yeo et al10 demonstrated that patients who underwent pancreaticoduodenectomy (PD) with negative margins had 5-year survival of 26% compared with 8% for those with positive margins. However, recent studies18-23 have found that resection margin status did not affect survival, thus questioning the prognostic significance of positive microscopic margins.

Conflicting conclusions on margin status are partly attributable to the lack of a standard, uniform technique for pathologic evaluation and assessment.24 The reporting of positive microscopic margin status (R1 resection) varies considerably in the literature, from 22% to 85%,24-26 diversity in the histopathologic examination techniques and lack of standardization affect the reporting of resection margin status, with one study17 reporting a higher R1 rate after PD once a standardized protocol was implemented. Without a standardized protocol to evaluate surgical margins microscopically, there may be underreporting of positive margins.24,27

In addition, the patterns of treatment failure (eg, local and distant) after PD with curative intent are inconsistently described in the literature.28-30 It is estimated that 50% to 86% of patients with pancreatic adenocarcinoma develop recurrence locally after a presumed curative resection.29,31-33 This finding suggests that there is either gross underestimation of microscopically involved margins or that postoperative adjuvant therapy is not targeting local disease effectively. Local control has gained importance given the conflicting results regarding the effectiveness of adjuvant chemoradiotherapy in the Gastrointestinal Tumor Study Group
and European Study Group for Pancreatic Cancer trials. As many patients experience local recurrence (LR), better prediction of who may benefit from adjuvant radiotherapy would improve outcomes.

We report microscopic margin status after PD for pancreatic adenocarcinoma and its correlation with survival and local control in a large cohort of patients from a high-volume National Cancer Institute–designated Comprehensive Cancer Center. In an attempt to be consistent with the pathology reporting, we used a uniform, standardized protocol for systematic assessment of resection margin status after PD by inking 4 resection margins (neck, portal vein groove, uncinate, and posterior) with different colors. We aimed to assess the incidence of positive microscopic margin status after PD and to determine how margin status correlated with patterns of recurrence and survival.

**METHODS**

This study was approved by the institutional review board at Washington University in St Louis and by the human studies committee of the Siteman Cancer Center. Data were retrieved from a prospective database on all the patients who underwent PD for pancreatic adenocarcinoma at Barnes-Jewish Hospital between September 1, 1997, and December 31, 2008. Patients were included in the study if they underwent either standard or pylorus-sparing PD for pancreatic adenocarcinoma confirmed by surgical pathology as consistent with ductal origin. All the periampullary cancers and those of uncertain origin were excluded.

Demographic information and patient characteristics collected in the database included age, sex, race, tobacco use, history of cancer, jaundice at presentation, and CA19-9 level. Tumor characteristics included stage at diagnosis, grade, size (<2.5 vs ≥2.5 cm), lymph node involvement (median of 15 lymph nodes evaluated per patient), lymphatic/venous/perineural invasion, and portal vein/superior mesenteric vein resection. Surgical treatment was recorded as standard PD, pylorus-sparing PD, or total pancreatectomy. Total pancreatectomies were included in the study only if the surgery was a planned PD and intraoperative assessment dictated further resection.

All the patients who underwent PD had been evaluated preoperatively and were deemed to have resectable disease. Standard preoperative workup included basic laboratory blood studies, including a CA19-9 level. Chest radiography, and pancreatic protocol computed tomography of the abdomen and pelvis with intravenous and oral contrast. A pancreatic adenocarcinoma was deemed unresectable if there were distant metastases. Patients were also considered to have unresectable regional disease if there was obvious involvement of the celiac or paraaortic nodes; greater than 30% of abutment or any evidence of narrowing of the superior mesenteric, celiac, or hepatic artery; and such great involvement of the superior mesenteric vein and tributaries that a reconstruction would be impossible.

Pancreatoduodenectomy was performed in the standard manner. We do not advocate stapling of the posterior uncinate margin because we believe that this precludes a precise superior mesenteric artery dissection. In addition, dissection and ligation of the inferior pancreatico-duodenal artery at its origin on the superior mesenteric artery is favored. Use of energy devices close to the superior mesenteric artery is avoided to reduce the chance of pseudoaneurysm formation.

A uniform, standardized procedure for margin analysis was used by the surgeon and the pathologist in the operating room.

The standardized protocol was a 4-color specimen inking: the pancreatic neck margin is black, the portal vein groove is blue, the uncinate margin is green, and the posterior margin is yellow. Two frozen sections are analyzed during the operative procedure: the pancreatic neck margin and the common bile duct margin. If the frozen section results are positive, the pancreas is resected back to negative margins. A surgical margin with malignant cells identified less than 1 mm from the margin was considered positive.

Patients were followed up by computed tomography every 6 months for the first 2 years and then yearly for 5 more years. The CA19-9 level was checked every 3 months for 2 years and then yearly for 5 more years. Follow-up information was obtained from the electronic record, the paper medical record, or the primary care physician or oncologist. Survival time was calculated by subtracting the date of death from the surgical date. Time to recurrence was calculated from the date of surgery to the date of LR, distant recurrence (DR), or LR + DR. Recurrence was determined first by evidence of disease on follow-up computed tomography. Local recurrence was defined as recurrence in the surgical bed, mesentery, periaortic soft tissue, celiac or superior mesenteric artery, pancreaticojejunal anastomosis, porta hepatis, or intercaval, periceliac, or retroperitoneal lymph nodes. Distant disease was considered to be in the omentum, peritoneum, solid organs, or pelvic lymph nodes.

Disease status at follow-up was categorized as died of disease, died of other cause, alive with disease, and no evidence of disease. Patients categorized as died of other cause had a well-documented cause of death unrelated to the cancer diagnosis and had no evidence of disease before their death. Perioperative mortality was defined as death within 30 days of the operative procedure or if the patient died in the hospital after surgery without being discharged.

Two groups were compared for statistical analysis: patients with positive surgical margins and patients with negative surgical margins. In addition, the first site of treatment failure (LR only, DR only, or LR + DR) and any recurrence were correlated with the site of positive microscopic margins. The categories of any LR and any DR were created to encompass all the LRs (LR only and LR + DR) and DRS (DR only and LR + DR), respectively. χ² Tests were used to compare the distribution of patient demographics, tumor characteristics, and patterns of treatment failure with positive resection margins. Cox proportional hazards regression models were used to generate crude hazard ratios (HRs) and adjusted HRs (aHRs) and 95% CIs. Characteristics that were found to be associated with recurrence status in χ² analysis with
a P ≤ .10 were included in multivariate models. Kaplan-Meier survival curves were generated, and log-rank tests were used to compare differences in overall and LR-free survival between the positive and negative margin groups. Median survival times and times to recurrence were calculated and compared between the positive and negative margin groups using the Mann-Whitney test. A commercially available statistical software program (SPSS, version 16.0; SPSS Inc) was used for all the analyses, and P < .05 was considered statistically significant.

RESULTS

Six hundred eighty-four patients at Barnes-Jewish Hospital underwent PD between September 1, 1997, and December 31, 2008. There was pathologic confirmation of pancreatic adenocarcinoma in 354 patients. Fifty-six patients did not have complete recurrence data recorded and were excluded from the study. Perioperative mortality occurred in 13 patients (3.7%), and they were excluded from the study. Thus, 285 patients who underwent PD for pancreatic adenocarcinoma with complete follow-up were included in this study.

The mean age of the study patients was 64.6 years (age range, 36-85 years). Patients were most likely to have a clinical stage IIB (67%) or IIA (20%) tumor at initial evaluation. Tumor diameter on pathologic evaluation was at least 2.5 cm in 64.9% of patients, and most patients (68.8%) had lymph node involvement. Most patients (88.1%) underwent standard PD, whereas only 4.9% underwent pylorus-sparing PD. Total pancreatectomy was performed in 7.0% of patients as dictated by intraoperative frozen section analysis. Vascular resection was performed in 74 patients (26.0%). Patient, tumor, and treatment characteristics are listed in Table 1.
Of the 285 patients in this study, 188 (66.0%) had all 4 margins negative (a complete R0 resection) and 97 (34.0%) had 1 or more positive margins. Of those 97 patients, 74 had 1 positive margin, 19 had 2 positive margins, and 4 had 3 positive margins. In total, there were 124 positive margins: 47 uncinate, 30 posterior, 25 portal vein groove, and 22 neck (Table 1).

Mean follow-up in the study was 32.4 months (median, 19.7 months). Of the 285 patients, 87 (30.5%) had no recurrence of disease and 198 (69.5%) had recurrence. Of the patients who recurred, 109 (55.1%) had DR only, 47 (23.7%) had LR only, and 42 (21.2%) had LR + DR as the first site of recurrence on follow-up imaging studies. At the end of follow-up, 184 patients (64.6%) had died of disease, 58 (20.4%) had no evidence of disease, 14 (4.9%) were alive with disease, and 29 (10.2%) had died of other causes. Thirty-eight of the 97 patients (39.2%) with positive margins had LR (ie, any LR = LR only and LR + DR), whereas 51 of 188 patients (27.1%) with negative margins had LR (Table 2).

Univariate analysis of tumor and treatment characteristics was then performed by recurrence status (Table 2). No significant correlation was noted of microscopic margins with tumor stage, grade, or CA19-9 level (data not shown). Patients with any positive margins were more likely to have lymph node involvement, lymphatic invasion, and venous invasion and to have undergone vascular resection compared with patients who had negative margins (P < .05 for all). On subset analysis of the 4 margin sites, patients with a positive posterior margin were more likely to have lymphatic invasion (P < .02), patients with a positive uncinate margin were more likely to have a large tumor (≥2.5 cm) and lymph node involvement (P < .03 for both), and patients with a positive portal vein groove margin were more likely to have venous invasion and vascular resection (P < .02 for both). A significantly higher percentage of patients with any positive margin were more likely to have LR (LR only or any LR) (P < .04). However, subset analysis demonstrated that it was only a positive posterior margin that significantly correlated with LR (LR only or any LR) as a first site of recurrence (P < .01 for both). No significant association of positive microscopic margins with DR or LR + DR was noted.

Univariate analysis of tumor and treatment characteristics was then performed by recurrence status (eTable; http://www.archsurg.com). Patients with any type of recurrence were more likely to have a large tumor size (≥2.5 cm), lymph node involvement, lymphatic invasion, venous invasion, tumor stage IIA or IIB, and poorly differentiated tumors (P < .01 for all). Patients who had LR (LR only or any LR) were more likely to have lymph node involvement, and patients who had DR (DR only or any DR) were more likely to have venous invasion (P < .05 for both). Patients who were diagnosed as having LR + DR as a first site of recurrence were significantly more likely to have a large tumor size (≥2.5 cm) (P < .01). On subset analysis of the 4 resected margin sites, patients who...
Patients with any positive microscopic margins were significantly more likely to have poorer LR-free survival compared with patients who had negative margins \( (P = .005) \) (Figure 3A). In a subset analysis, only patients with a positive posterior margin were significantly more likely to have poorer LR-free survival \( (P < .001) \) (Figure 3B). The other 3 margins (uncinate, neck, and portal vein groove) showed no significant association with LR-free survival.

Lymph node involvement also showed a strong association with LR. Therefore, LR-free survival curves were generated for positive margin status and were stratified by lymph node status. Patients with any positive microscopic surgical margins were significantly more likely to have poorer LR-free survival only if there was lymph node involvement \( (P = .04) \) (Figure 4). To verify that lymph node involvement was not the sole predictor of LR, a similar comparison was performed for posterior margin status. As shown in Figure 5, patients with a positive posterior margin were significantly more likely to have poorer LR-free survival with \( (P < .001) \) and without \( (P = .01) \) lymph node involvement. The same relationship holds true when evaluating any LR (data not shown). Although lymph node involvement is significantly associated with LR, a positive posterior margin is independently and significantly associated with LR.

Pancreatic cancer is an aggressive disease with poor long-term survival and early recurrence. Patients with a positive surgical margin have median survival of less than a year, a result similar to that of patients without operative intervention. \(^{15,45} \) The continued controversy regarding microscopic margins and survival in pancreatic adenocarcinoma largely relates to the lack of standardized assessment of surgical margins. \(^{24} \) First, there are many studies that were unable to accurately differentiate R0 and R1 resections because the data were not analyzed in a prospective manner, and surgeons likely underreport R1 re-

### Table 3. Crude and Adjusted Hazard Ratios (HRs) for Local Recurrence in Patients Who Underwent Pancreaticoduodenectomy for Pancreatic Adenocarcinoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Local Recurrence Only</th>
<th>Any Local Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td>Tumor size ((\geq 2.5 \text{ vs} &lt; 2.5 \text{ cm}))</td>
<td>2.34 (1.56-6.73) (^b)</td>
<td>2.66 (1.25-5.63) (^b)</td>
</tr>
<tr>
<td>Lymph node involvement (yes vs no)</td>
<td>4.38 (2.20-8.71) (^b)</td>
<td>4.27 (2.07-8.81) (^b)</td>
</tr>
<tr>
<td>Posterior margin (yes vs no)</td>
<td>1.50 (0.75-3.02)</td>
<td>1.19 (0.59-2.42)</td>
</tr>
<tr>
<td>Uncinate margin (yes vs no)</td>
<td>2.13 (0.76-5.97)</td>
<td>1.88 (0.64-5.54)</td>
</tr>
<tr>
<td>Portal vein groove margin (yes vs no)</td>
<td>2.48 (1.11-5.55)</td>
<td>1.63 (0.70-3.78)</td>
</tr>
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</table>

\(^a\) The crude HR columns contain variables that have \( \chi^2 P < .10 \) with the outcome local recurrence (LR) only or any LR. Jaundice, stage, grade, size, lymph node involvement, and positive margin site were included in the adjusted model. The crude HR shows the association between each variable alone and the outcome LR only or any LR. Every variable in the crude HR column was then entered into a multivariate model to show the adjusted HR for each variable with all the other variables in the model.

\(^b\) In the multivariate models, a 95% CI that does not include 1.00 is considered statistically significant.
sections. This leads to misclassification of margin status and potentially inaccurate analysis. Second, the lack of uniform assessment of the pathologic specimens makes interinstitutional comparability difficult. Katz et al\textsuperscript{46} cite that only 15\% of studies document communication between the surgeon and the pathologist regarding orientation of the specimen and that only 66\% document inking of the specimen. We propose a standardized system of 4-color specimen inking that the surgeon applies in the operating room in conjunction with a pathologist, ensuring communication between the surgeon and the pathologist. Inking of the posterior margin supports reliable documentation of this retroperitoneal margin, found in this study and others to be of importance but is inconsistently described in studies.\textsuperscript{46}

Whereas many studies have focused on DR after PD, few have analyzed the factors contributing to LR. The present study showed that 24\% of patients who recurred had LR only as their first site of recurrence. When considering patients who had any LR (LR only and LR + DR) as their first site of recurrence, 45\% of patients had LR as part of their first site of recurrence. The fact that almost half of the patients recurred locally after PD implies that local control plays an important role in the treatment of pancreatic adenocarcinoma.

In a multivariate analysis, the presence of a positive posterior surgical margin and lymph node involvement were the only factors strongly associated with LR. Unlike other recently published studies,\textsuperscript{36-47} showing that margin status was not independently associated with LR, we found just the opposite (aHR, 4.27; 95\% CI, 2.07-8.81). Lymph node involvement has also been associated with poor long-term survival.\textsuperscript{19,48} Asiyanbola et al\textsuperscript{47} reported that patients with more than 5 positive lymph nodes had a 2.5-fold increased
risk of LR. The present study also showed that lymph node involvement was significantly associated with LR only (aHR, 2.66; 95% CI, 1.25-5.63). Because 68.8% of the patients had lymph node involvement, the association of lymph node involvement with LR is not inconsequential.

To ensure that lymph node involvement was not the driving force behind LR when surgical margins were positive, a subset analysis was performed on each of the 4 margin sites stratified by lymph node status to determine whether resection margin had any independent effect on local disease. Only patients with a positive posterior margin had significantly poorer LR-free survival compared with patients with a negative margin regardless of lymph node involvement. This result is not surprising; the posterior margin is the hardest margin to control for surgically. Unlike the neck margin, the posterior surgical resection cannot be extended more posteriorly to ensure an adequate negative surgical margin. Because more radical resection with extensive lymphadenectomy has not increased survival, there is a greater need to look at the effectiveness of adjuvant therapies on local control.

The present study had the advantage of using a prospective database in which pathologic findings were entered soon after being determined by the pathologist. Barnes-Jewish Hospital was also a major referral center, and a high volume of PDs were performed every year, allowing us to perform statistical analysis with a large number of patients. A major limitation of this study is the lack of high-fidelity data regarding adjuvant treatment received. The standard adjuvant treatment for patients treated at Barnes-Jewish Hospital is 2 cycles of systemic chemotherapy followed by restaging and the addition of chemoradiotherapy if there is no evidence of DR. Because most of the surgically resected patients received their adjuvant treatment elsewhere, detailed information on dose, frequency, and completeness of planned treatment is not captured in the database. Without this type of detailed data on adjuvant treatment, we cannot draw any conclusions about the effect that chemotherapy or radiotherapy has on LR.

Local control is important for long-term survival after PD for pancreatic adenocarcinoma. This study is distinct because we found that the posterior margin, in particular, is strongly associated with LR. By having a standardized approach to preoperative staging, surgical techniques, and pathologic assessment of surgical margins, future studies will be better able to compare patients and select subgroups that may preferentially benefit from different treatment modalities. A more methodical approach to the evaluation of patients with pancreatic adenocarcinoma is paramount to the improvement of care in this difficult disease.

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Correspondence: David C. Linehan, MD, Section of Hepato-Pancreato-Biliary and GI Surgery, Department of Surgery, Barnes-Jewish Hospital/Washington University School of Medicine, 660 S Euclid Ave, PO Box 8109, St Louis, MO 63110 (linehand@wudosis.wustl.edu).

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Online-Only Material: The eTable is available at http://www.archsurg.com.