Survival After Pancreaticoduodenectomy is not Improved by Extending Resections to Achieve Negative Margins

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Objective: This study was undertaken to determine the survival benefit of extending resections to obtain microscopically negative margins after positive intraoperative frozen sections.

Summary Background Data: The impact of residual microscopic disease after pancreaticoduodenectomy is currently a point of controversy. It is, however, generally believed that microscopically positive margins negatively impact survival and this may be improved by ultimately achieving negative margins.

Methods: Since 1995, patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma have been prospectively followed. Margin status has been codified as macro/microscopically negative (R0) or macroscopically negative/microscopically positive (R1). The impact of margin status on survival was evaluated utilizing survival curve analysis. Data are presented as median, mean ± SD where appropriate.

Results: For pancreatic adenocarcinoma, 202 patients underwent pancreaticoduodenectomy. R0 resections were achieved in 158 patients, 17 of whom required extended resections to achieve complete tumor extirpation after an initially positive intraoperative frozen section (R1 → R0). R1 resections were undertaken in 44 patients. Median survival for patients undergoing R0 resections was 21 months, 26 ± 23.4 months versus 13 months, 17 ± 21.0 months for patients undergoing R1 resections ($P = 0.02$). Median survival for patients undergoing R1 → R0 resections was 11 months, 16 ± 17.3, ($P = 0.001$). Margin status had a significant correlation with "N" stage and AJCC stage but not "T" stage.

Conclusion: Survival after pancreaticoduodenectomy is not improved by extending pancreatic resections to achieve negative margins after initially positive intraoperative frozen sections. Tumor-specific factors beyond the presence of disease at a surgical margin are responsible for the abbreviated survival seen in patients undergoing R1 resections.

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Pancreatic cancer continues to portend a poor prognosis despite advances in diagnostic imaging, endoscopic diagnosis and staging, resection techniques, and perioperative care. Numerous reports have denoted that many factors generally influence long-term survival after pancreaticoduodenectomy for pancreatic adenocarcinoma.[1-4] These factors include, among many, tumor size, tumor grade, tumor location, lymphovascular invasion, perineural invasion, number of lymph nodes containing metastatic disease, and serum CA 19-9 levels. Furthermore, utilizing the AJCC staging classification (6th edition), cancer stage, tumor stage (ie, T stage), and nodal stage (N stage) have been shown to consistently correlate with survival.[5]

Many reports have denoted the importance of complete tumor (ie, cancer) extirpation and margin status.[3–6] It is an accepted principle of surgical oncology that a positive resection margin equates to a worse prognosis. Intuitively, this is reasonable. The results of the ESPAC-1 trial support this concept, concluding margin positive resections denote a biologically more aggressive cancer.[7] More recently, the impact of margin status upon overall survival has come under question. Several reports have failed to demonstrate the deleterious impact of a margin positive resection after controlling for confounding variables.[8,9] Because of traditional concerns about margins of resections, it is conventional to obtain frozen section analysis of margins of resection intraoperatively. A positive intraoperative frozen section is generally addressed by extending resections of tumor-bearing tissues, even though the impact of margin status on overall survival remains somewhat uncertain.

This study was undertaken first to determine the impact of margin status on survival after pancreaticoduodenectomy for pancreatic adenocarcinoma and, second, to determine the impact on survival of extending resections to obtain microscopically negative margins after initially positive intraoperative frozen section margins. Our hypotheses in undertaking this study were that, margin status would impact survival after pancreaticoduodenectomy and that extending resections to achieve cancer-free margins would impart a survival advantage relative to cancer bearing (ie, positive) margins.

METHODS

With Institutional Review Board approval, data of all patients undergoing pancreaticoduodenectomy for ductal adenocarcinoma from 1995 to 2006 were reviewed. Patients undergoing pancreaticoduodenectomy for duodenal cancers, ampullary cancers, cholangiocarcinomas, mucinous cystadenomas/adenocarcinomas, intraductal papillary-mucinous neoplasm's, uncommon pancreatic cancers, and pancreatitis were excluded from this study. Preoperative evaluation included, as a minimum, a triple-phase oral and IV contrast-enhanced computed tomography scan with thin slices through the pancreas. Only patients without evidence of unresectability underwent operative exploration. Unresectable tumors on computed tomography scans were denoted by the following criteria: (1) the presence of extrapancreatic disease beyond the extent of a pancreaticoduodenectomy, (2) celiac artery or superior mesenteric artery (SMA) encasement, and (3) portal vein thrombosis or occlusion from tumor invasion.

Pancreaticoduodenectomy was undertaken in a standard fashion with pylorus preservation whenever possible. The celiac trunk and the SMA were skeletonized with removal of all pancreatic and nodal tissue to the right of the vessels, ventral to the vessels, and dorsal to the vessels. The portal vein and the distal superior mesenteric vein were skeletonized routinely and were resected when necessary to achieve complete tumor extirpation. Intraoperative frozen section analysis was routinely obtained for the common bile duct/common hepatic duct margin and pancreatic neck margin. Other margins underwent intraoperative frozen section analysis as

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indicated by operative findings. All patients underwent extended resections in response to a positive intraoperative margin. The decision to further extend resections after a second or subsequent positive intraoperative margin was at the discretion of the attending surgeon. No patients underwent total pancreatectomy to achieve complete tumor extirpation. All margins were evaluated on permanent section.

A R0 resection was defined as the macroscopic and microscopic absence of cancer cells at all resection margins on permanent sections. The microscopic presence of malignant cells at any margin of resection on permanent section was designated as a R1 resection. No patients in this report had gross residual cancer upon completion of pancreaticoduodenectomy (ie, R2 resection).

Adjuvant therapy was applied to all patients able and willing to receive it, irrespective of final margin status or stage. Adjuvant therapy was not protocol driven and generally consisted of chemoradiation therapy for 6 weeks followed by chemotherapy for 3 to 6 months after resection.

All patients were followed up until death. The primary end point of this study is survival. Survival is defined as the time interval from pancreaticoduodenectomy to death. The impact of margin status on survival was evaluated utilizing survival curve analysis. To emphasize the relative importance of the earlier portions of the survival curves given the relatively short survival of patients with pancreatic cancer, Kaplan-Meier survival curves were analyzed using a Gehan-Breslow test, although significance was not different when analyzed by the Mantel-Cox test. Data are presented as median, mean ± SD where appropriate. Significance was accepted with 95% confidence.

RESULTS

Patient Demographic Data

Since 1995, 687 patients have undergone pancreaticoduodenectomies at the University of South Florida. Of these resections, 202 (29%) were undertaken on patients with a histologic diagnosis of pancreatic ductal adenocarcinoma. Complete tumor extirpation (ie, R0 resection) was achieved in 158 patients (78%). Residual microscopic disease was present at one or more permanent surgical margin in 44 patients (22%). For patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma, demographic data and tumor characteristics are depicted in Table 1. Median survival for all patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma was 17 months, 22 ± 20.2 months with 26% of patients currently alive.

TABLE 1. Demographic Data for Patients Undergoing Pancreaticoduodenectomy for Pancreatic Adenocarcinoma

Tumor Extirpation	N	% Male	Age Median (Mean ± SD)
Complete (R0) with margins initially negative	141	51	68 yr (67 ± 10.6)
Complete (R0) with margins initially positive	17	59	61 yr (62 ± 5.9)
Incomplete (R1)	44	52	66 yr (66 ± 8.6)

Survival

Complete Tumor Extirpation

Complete tumor extirpation was achieved in 158 patients and they experienced a median survival of 21 months, 26 ± 23 months. Of these patients, 17 (11%) had positive intraoperative margins by frozen section analysis and underwent extended resections to achieve complete tumor extirpation.

Of 158 patients undergoing complete tumor extirpation, 91% received adjuvant therapy. Of 141 patients with initial margins negative by frozen section, 90% underwent adjuvant therapy. Median survival for 141 patients with initial margins negative by frozen section was 22 months, 27 ± 20 months. Adjuvant therapy did not significantly prolong survival; median survival for patients receiving adjuvant therapy versus those not receiving adjuvant therapy (21 months, 25 ± 21.8 months vs. 22 months, 26 ± 22.2 months). All patients with complete tumor extirpation undergoing extended resections for initially positive frozen section margins received adjuvant therapy; their median survival was 11 months, 16 ± 17.3 months. Among patients undergoing complete tumor extirpation, patients with initially negative intraoperative margins lived longer than patients with initially positive intraoperative margins by survival curve analysis ($P = 0.001$), and by Mann-Whitney U test ($P = 0.02$) (Table 2).

Of the 141 patients undergoing R0 pancreaticoduodenectomies with negative intraoperative frozen section margins, 29 patients underwent extensions of conventional pancreaticoduodenectomy, including portal vein/superior mesenteric vein resections in 28 and a colon resection in 1. For the 17 patients undergoing R0 resections after initially positive intraoperative frozen sections, 16 patients underwent further resections of positive pancreatic neck margins, 2 underwent additional resections of positive bile duct margins, and 9 patients underwent extensions of conventional pancreaticoduodenectomy, including portal vein/superior mesenteric vein resections in 7, hepatic artery resections and reconstructions in 2, a colon resection in 1, and an inferior vena cava resection in 1.

Incomplete Tumor Extirpation

Residual microscopic disease was present at 1 or more surgical margins (R1 resection) in 44 patients. Of the patients, 48% had positive margins at the pancreatic neck, 39% had positive peripheral pancreatic margins, 36% had positive bile duct margins, 27% had positive margins along the uncinate margin/SMA, and 11% had positive margins in a resected piece of portal vein. All patients with positive margins at the pancreatic neck and/or bile duct underwent

TABLE 2. Survival After Pancreaticoduodenectomy for Pancreatic Adenocarcinoma for Patients Undergoing Complete Tumor Extirpation With Negative Intraoperative Frozen Sections (R0), for Patients Undergoing Complete Tumor Extirpation After Further Resections Because of Positive Intraoperative Frozen Sections (R1 → R0), and for Patients With Residual Microscopic Disease (R1)

Margin Status	Patients	% Receiving Adjuvant Therapy	Survival Median (Mean ± SD)	*P* Relative to R0 Resections
R0	141	90	21 mo (26 ± 23.4 mo)	N/A
R1 → R0	17	100	11 mo (16 ± 17.3 mo)	$P = 0.001$
R1	44	100	13 mo (17 ± 21.0 mo)	$P = 0.02$

further excisions, often multiple, to obtain clean margins which failed to do so. In addition, 17 patients underwent extensions of conventional pancreaticoduodenectomy after initial positive intraoperative margins and yet they had persistent positive margins; 13 underwent portal vein or SMV resections, 2 underwent hepatic artery excisions, 1 underwent extended small bowel resection, and 1 underwent hemigastrectomy.

All patients with residual microscopic disease (ie, R1 resections) underwent adjuvant therapy; they experienced a median survival of 13 months, 17 ± 21.0 months. Patients undergoing R1 resections had shorter survivals than patients undergoing R0 resections with initially negative margins by survival curve analysis ($P = 0.02$) and by Mann-Whitney U test ($P = 0.001$) (Table 2). Patients undergoing R1 resections lived as long as patients undergoing R0 resections after initially positive margins by frozen section (survival curve analysis, $P = 0.91$) and by Mann-Whitney U test ($P = 0.91$).

Factors Influencing Margin Status

Patients undergoing R0 resections had tumors ranging from T1 to T3 (Table 3); the majority of tumors were T3. This is true whether initial frozen section margins were negative or positive (Table 3). Patients undergoing R1 resections had tumors ranging from T1 to T3 (Table 3); 64% of tumors were T3. T stage did not correlate with margin status. Furthermore, T stage did not correlate with survival for patients undergoing R0 resections, R0 resections after initially positive margins by frozen section analysis, or R1 resections (Fig. 1).

Among patients undergoing R0 resections, 52% had nodal metastases; 48% with negative initial frozen section margins had nodal metastases. For patients with initially positive intraoperative margins undergoing extended resections to achieve complete tumor extirpation, 87% had nodal metastasis. Among patients undergoing R1 resections, 61% had nodal metastases. Patients with positive intraoperative of final margins were more likely to have nodal metastases ($r = 0.39$, $P < 0.0001$). Patients undergoing R0 resections had improved survival without nodal metastases (Fig. 2). This is not true for patients with initially positive margins undergoing R0 resections or patients undergoing R1 resections; survival in these patients was unaffected by the presence or absence of nodal metastasis.

Patients with more advanced stage malignancies were more likely to have positive margins ($r = 0.32$, $P < 0.0001$). However, survival was not different among the stages of the cancers (Fig. 3).

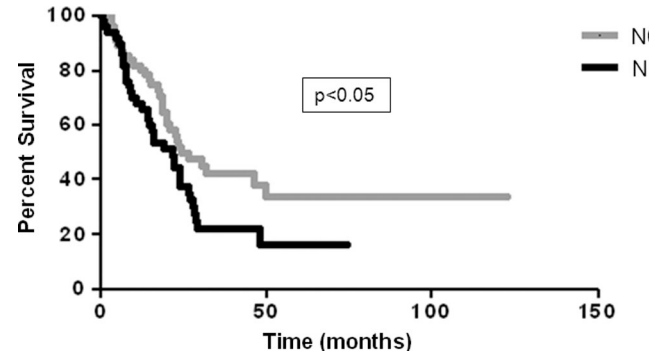

FIGURE 2. Patients undergoing R0 resections with initially negative intraoperative margins had improved survival without nodal metastases (N = 141).

TABLE 3. "T" Stage for Patients Undergoing Pancreaticoduodenectomy for Pancreatic Adenocarcinoma Stratified by Margin Status: Patients Undergoing Complete Tumor Extirpation With Negative Intraoperative Frozen Sections (RO), Patients Undergoing Complete Tumor Extirpation After Further Resections Because of Initially Positive Intraoperative Frozen Sections (R1 → R0), and Patients With Residual Microscopic Disease (R1)

	"T" Stage (AJCC, 6th Edition)		
Margin Status	**T1**	**T2**	**T3**
R0	11%	30%	59%
R1 → R0	0%	27%	73%
R1	10%	26%	64%

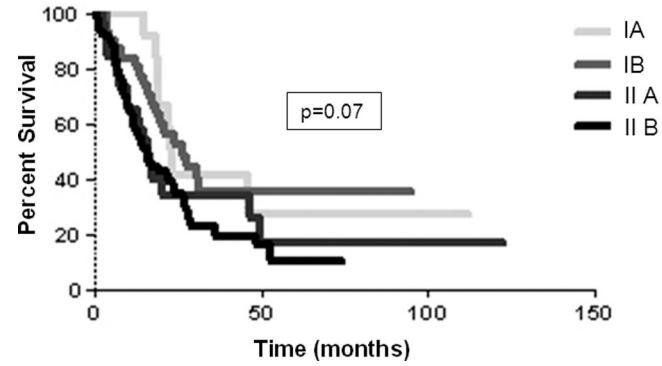

FIGURE 3. Survival after pancreaticoduodenectomy for pancreatic adenocarcinoma was not impacted by AJCC stage.

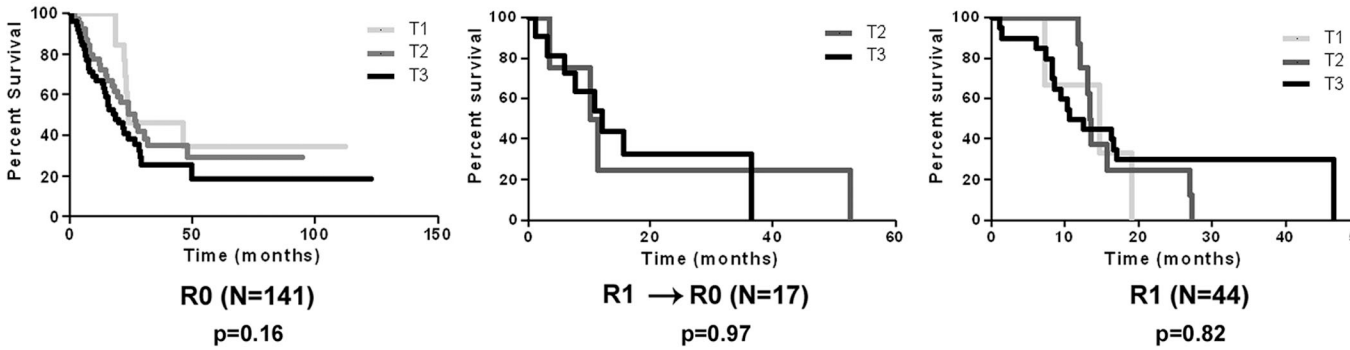

FIGURE 1. "T" stage does not predict survival in patients with initially negative intraoperative margins (R0), in patients with initially positive intraoperative margins further resected to ultimately negative margins (R1 → R0), or in patients with residual microscopic disease (R1).

Because of small numbers in some stages stratified by margin status, impact of margin status on survival by stage cannot be determined.

DISCUSSION

Complete operative resection remains the only potential cure for pancreatic adenocarcinoma. Despite best efforts, survival after resection remains generally poor. This study documents that the presence of malignancy at a surgical margin is foreboding. Surprisingly, achieving a margin free of malignancy after an initially positive margin offers no survival advantage. Though negative margins denote a favorable prognosis in general, obviously, survival after pancreaticoduodenectomy for patients with initially positive margins involves more than the absence or presence of malignancy at their ultimate surgical margins. "Chasing" involved margins to obtain margins free of malignancy seems to be a futile undertaking.

The patients in this report are typical of patients with pancreatic cancer in the United States. Most have advanced tumors (ie, T3 tumors) at the time of resection. Nodal metastases are common. Most patients are of stage IIB, reflecting advanced T stage and/or nodal metastases; many patients had both. Over three-quarter of patients undergoing pancreaticoduodenectomy underwent R0 resections. Surprisingly, and inexplicably, extensive measures undertaken to initially obtain free margins seem rewarded with relatively prolonged survival, whereas the same measures after initially obtaining a margin containing malignancy seem to lead to relatively abbreviated survival. Undertaking risky measures (eg, portal vein or SMA resections) to achieve free margins after failing to first do so seems inappropriate, whereas undertaking them to initially achieve free margins seems worthwhile and advisable. Plausible explanations for this apparent discrepancy are; (1) peritoneal seeding with tumor transection or (2) resecting tumors with indistinct margins reflects insidious invasion (ie, biologically aggressive tumors). Notably, we did not demonstrate a relationship between tumor size and margin status. Margin status does not reflect tumor size. However, we have demonstrated a correlation between nodal involvement and positive margins, which also suggests that margin status is a reflection of aggressive tumor biology. In addition, patients undergoing resections with either an initially positive intraoperative margin resected to R0 or patients with ultimately positive margins (R1) were nearly twice as likely to undergo a major portovenous resection during initial tumor extirpation, again reflecting aggressive tumor biology.

AJCC, T stage, N stage, and overall stage are conventionally believed to predict survival after pancreaticoduodenectomy for adenocarcinoma. When these are stratified by margin status, T stage is not a factor in survival. Nodal status, however, does predict survival for patients undergoing complete tumor extirpation with initially negative frozen section margins. For patients with initially positive intraoperative margins or margins positive on final sections, nodal metastasis had no impact on survival suggesting factors beyond nodal staging are ultimately determining patient survival. However, survival in these patients is generally so poor that usual or customary "prognostic factors" may lose significance. For example, in this data set, AJCC stage did not significantly impact survival, though numbers in earlier stages were small.

Others have studied the impact of margin status on survival after pancreaticoduodenectomy and demonstrated deleterious effects of a positive margin on overall survival.[10–13] We agree, but our finding that outcome is not improved by extending resections to achieve negative margins complicates conclusions of studies denoting the notorious impact of positive margins. Our data indicate that margin status is less a function of tumor size or operative technique and more a surrogate marker for aggressive tumor biology, which portends an extremely poor prognosis. In this context, it is of no surprise that extending resections to achieve negative margins imparts no improvement in overall survival. These results are in agreement with Neoptolemos and Geer, who each suggest a microscopically positive margin is linked to the underlying biologic phenotype.[7,14] In effect, tumors resected with a positive margin behave similarly to poorly differentiated tumors and tumors with lymphatic metastasis, the later relationship we herein have demonstrated. As well, extended lymphadenectomy has failed to demonstrate any survival advantage over standard lymphadenectomy in each of 4 prospective trials, again emphasizing that extensive resection does not change outcome.[15–17] On the contrary, Schmidt et al found that extending resections to total pancreatectomy following an isolated positive pancreatic neck margin did impart a survival advantage relative to patients undergoing R1 resections, despite greater than 60% nodal positivity in patients undergoing total pancreatectomy.[19] In the context of our own data, this study suggests that patients undergoing resections with an initially positive margin have multifocal pancreatic disease, although to our knowledge no such pathologic relationship has ever reliably been demonstrated.

In all 17 patients undergoing initial R1 resections subsequently extended to R0 resections, we believed that we were initially undertaking R0 resections. If difficulty was encountered in creating a plane between the neck of the pancreas and the portal vein, portovenous resection was undertaken. Likewise, the pancreas was transected at the neck or further distally beyond palpable tumor. Our judgment, however, based upon preoperative imaging and intraoperative inspection and palpation, failed. These patients died of recurrent/progressive disease in about 1 year and we believe they were doomed to failure because of aggressive tumor biology.

Patients undergoing complete tumor extirpation with initial margins of resection negative for malignancy by frozen section do best, even if extensive measures are required to initially obtain margins free of malignancy. Unfortunately, even with margins free of malignancy survival is generally disappointing, suggesting that pancreatic adenocarcinoma becomes a systemic disease early for the majority of patients. Patients undergoing less than complete tumor extirpation have particularly poor survival. Notably, survival after pancreaticoduodenectomy is not improved by extending resections to achieve negative margins after positive intraoperative frozen sections, suggesting the importance of "tumor specific" factors beyond the specific size of the tumor (ie, T stage). Patients with positive margins and even those with initially positive margins have different tumors and different cancers than patients whose tumors are initially resected to "negative" margins. How and why they are different is currently a point of conjecture. Although margin status is important, it is undoubtedly a surrogate marker for tumor specific issues, such as the infiltrating nature of the tumor and/or aggressive tumor biology.

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