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Intraoperative Assessment of Pancreatic Neck Margin at the Time of Pancreaticoduodenectomy Increases Likelihood of Margin-Negative Resection in Patients with Pancreatic Cancer

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Abstract

Background—The utility of intraoperative assessment of surgical margins is often debated by experienced pancreatic surgeons. We sought to review our experience with pancreaticoduodenectomy (PD) for pancreatic cancer to determine the impact of intraoperative frozen section (FS) analysis on margin-negative resection and long-term outcome.

Material and Methods—Between 1992 and 2007, 310 consecutive patients underwent PD at our institution; 223 of these were for pancreatic cancer. Seven patients who underwent R2 resection were excluded. Charts were reviewed to determine demographics, final pathology, perioperative course, and long-term outcome. Data were compared by Fisher's exact and Student's *t* tests. Survival curves were created using the Kaplan–Meier method and compared by log-rank analysis. Predictors of margin-negative resection were determined by logistic regression analysis and predictors of survival determined by Cox proportional hazards analysis.

Results—FS analysis of pancreatic neck resection margins was obtained in 75, while no intraoperative assessment was done in 141. Although patients who underwent FS were younger (median, 62 vs. 67 years, $p=0.01$), the two groups were similar in terms of gender, comorbidities, preoperative stenting, pylorus preservation, tumor differentiation, nodal status, tumor size, length of stay, and complication rate. Margin-negative resection was more common when FS was undertaken (99% vs. 81%, $p=0.0001$). However, intraoperative FS did not significantly increase overall survival (median, 21.7 vs. 14.6, $p=0.20$). Only nodal metastasis was predictive of poor survival (median, 21.7 vs. 13.3 months, $p=0.001$).

Conclusions—Intraoperative assessment of the pancreatic neck margin status at the time of PD for pancreatic cancer increases the likelihood of obtaining a margin-negative resection.

Noteworthy is that final margin status was not predictive of survival, while only nodal metastasis was, suggesting that tumor biology is the most important factor in patients with pancreatic cancer.

Keywords

Pancreatic Cancer; RO Resection; Pancreaticoduodenectomy

Introduction

Pancreatic cancer is a lethal disease, with nearly all patients dying within 2 years of diagnosis. It is the fourth leading cause of cancer-related deaths in the USA, and it is nearly uniformly fatal with its mortality approaching its incidence. An estimated 37,000 new cases of pancreatic cancer were diagnosed in 2007, and over 33,000 succumbed to their disease.¹ Since the 1970s, the incidence of pancreatic cancer has continued to increase dramatically, with little improvement in survival. Current chemotherapy has shown only modest responses. As such, resection remains the only hope for cure, though overall survival remains dismal.^{2,3}

In the surgical treatment of pancreatic cancer, it makes sense that obtaining a margin-negative resection should be associated with improved survival.⁴ Surgeons often unreliably predict the completeness of resection, and therefore frozen section (FS) has been debated and recommended by some.^{5,6} Nevertheless, a paucity of data exists on the utility of FS analysis during pancreaticoduodenectomy (PD) for pancreatic cancer. In fact, experienced pancreatic surgeons openly disagree about the role of FS analysis during resection of pancreatic cancer. In this study, we reviewed our experience with PD for pancreatic cancer to determine the impact of FS analysis on margin-negative resection and long-term outcome. We hypothesized that failure to obtain a margin-negative resection along the surgical neck of the pancreas at the time of PD was indicative of a biologically more aggressive tumor, thus making FS analysis fruitless.

Material and Methods

Data Collection

Between 1992 and 2007, 310 consecutive patients underwent PD at the Ohio State University. After approval from the Institution Review Board, 223 patients who underwent PD for histologically confirmed pancreatic adenocarcinoma were analyzed, 89 female (41.2%) and 127 male (58.8%) with a median age of 66.0 (range, 30–84). Data were retrospectively obtained from electronic medical records, hospital and clinic charts, and pathology records. Data collected included patient age, gender, comorbidities, clinical presentation, intraoperative findings, FS findings (when applicable), degree of differentiation, tumor size, nodal status, perioperative course, complications, long-term outcome, and survival. FS margins were obtained by shaving a parallel section along the cut edge of the neck of the pancreas. Conferential deeper tissue sections were reviewed after formalin fixation and paraffin embedding of the cut margin. Similarly, in specimens where no FS was obtained, pancreatic resection margin status was determined after formalin fixation and paraffin embedding by shaving a parallel section from the cut edge of the pancreatic neck and staining with hemotoxylin and eosin. Overall survival was determined by the time from operation to death as determined by hospital records and by the Social Security Death Index (<http://www.ssdi.rootsweb.ancestry.com> as of 8/2007).

Statistical Analysis

Chi-square or Fisher's exact test was used for comparison between categorical variables. For continuous variables, Student's *t* test was utilized. Survival curves were constructed using the Kaplan–Meier method and compared by log-rank analysis. Patients who died in the immediate postoperative period were excluded from all survival analyses. Predictors of margin-negative resection were determined by logistic regression analysis, and associations of variables with survival were determined by multivariate Cox proportional hazards. Data are presented as median (range) unless stated otherwise.

Results

FS analysis was completed in 75 patients, while no intraoperative assessment was done in 141. In seven patients, complete extirpation of all macroscopic disease was not possible. These R2 resections were excluded from analysis. Those who did not undergo FS were significantly older than the FS group (Table 1). FS was undertaken in 12 of 25 (48%) patients age 50 or younger compared to 63 of 191 (33%) over the age of 50 ($p=0.18$). The gender distribution was similar in both groups as was comorbidities. All operations were undertaken for ductal adenocarcinoma arising in the head/uncinate process of the pancreas, and 22% of patients underwent pylorus preservation while the remaining 78% underwent standard PD with antrectomy. The two groups were similar with respect to differentiation, tumor size, T stage, and nodal status (Table 1). Postoperative length of stay was 1 day longer when no FS was undertaken, though this was not statistically significant. As well, complication rates between groups were similar. Fourteen patients required reoperation for hemorrhage (seven), wound revision (one), or intraabdominal sepsis (six) accounting for three perioperative deaths. There was no difference in the incidence of reoperation in those in which FS was or was not undertaken ($p=0.15$, 3% vs. 8.5%, respectively). Overall mortality was 5.4% and not influenced by FS. The administration of adjuvant chemotherapy and radiation was also not influenced by FS and, hence, margin status. In the 190 patients with evaluable T stage, there was no statistical difference in the number of tumors that were confined to the pancreas (i.e., T1 and T2) vs. those that invaded beyond that pancreatic parenchyma (i.e. T3).

Negative pancreatic neck margin was obtained in 74 (99%) of those undergoing FS compared to 115 (82%) with no FS ($p=0.0001$). In five of these latter cases, uncinate margin was also microscopically positive. In seven (9%), the initial FS margin was positive, and further resection was undertaken. In one patient, this required total pancreatectomy. A final negative margin was achieved in six, with one having extension of his resection far to the left of the mesenteric vessels but felt to be a poor candidate for total pancreatectomy, thus leaving a microscopically positive margin along the cut edge of the pancreas. This patient represented the only patient with a positive surgical “neck” margin on final pathology when FS was undertaken. An additional 17 patients in which FS was not undertaken had a microscopically positive retropancreatic/uncinate margin on final pathology, compared to none in the FS group. In total, complete resection (i.e., R0) was obtained in 74 (99%) when FS was undertaken compared to 99 (67%) when FS was not done ($p<0.0001$).

The size of the tumor and the tendency to undertake pylorus preservation showed a trend toward predicting R0 resection, but only intraoperative FS analysis was predictive of margin-negative resection by univariate and multivariate analysis (Table 2).

During the entire follow-up period, 59 (82%) of those in which FS was undertaken died compared to 107 (77%) in the no FS group, not including those who died in the perioperative period. Median follow-up for all remaining living patients was 16.6 months and similar in each group (Table 1). FS did not significantly increase overall survival (Fig. 1 and Table 3). Median overall survival was also similar between groups with a median of 21.7 vs. 14.6 months (Table 3). We further compared overall survival in all patients in each group found to have a margin negative, i.e., R0, resection and no significant improvement in survival when FS was obtained. Nodal status and poor differentiation of the tumors were predictive of poor survival on multivariate analysis (Table 4). FS did not significantly influence overall survival.

Discussion

Pancreatic cancer is generally considered a fatal disease with most being unresectable at diagnosis. The utility of FS analysis during PD has been debated by pancreatic surgeons. For those who have resectable lesions, this study supports the use of intraoperative assessment of margin status to ensure an R0 resection. Evaluating the margin intraoperatively may allow the surgeon to more effectively manage a positive margin before final pathology and thus achieve an R0 resection. However, the effect of achieving an R0 resection may not be as beneficial to survival as previously thought.

Our population of pancreatic cancer patients who underwent resection is typical of those previously reported, in their seventh decade of life with a male predominance and jaundice. Commensurate with their advanced age, more than half of patients had significant comorbidities. Patients who underwent intraoperative FS analysis of the resection margin tended to be younger. There is no clear reason for this disparity, although it does introduce the possibility of a bias that we were unable to detect in the data we collected. FS analysis in younger patients may be symbolic of a more aggressive surgical approach to complete extirpation of the tumor. As such, FS was undertaken in nearly half of patients 50 years old or younger compared to one third of patients over the age of 50, but this was not statistically significant. Otherwise, patients in each group were well matched by all other parameters measured including operative approach, tumor characteristics, perioperative events, and postoperative adjuvant treatment.

Intraoperative margin assessment significantly increased the likelihood of obtaining a negative margin at the surgical neck of the pancreas. As well, for reasons that are not clear from the data presented, the retropancreatic/uncinate margin was also more likely to be involved on final pathology when FS was not done. The retropancreatic and uncinate margins are not routinely assessed intraoperatively, since, arguably, they do not represent truly surgical margins. In other words, a microscopically positive margin in this region identified in the operating room is not likely to be surgically correctable. Interestingly, overall survival was not increased in the FS group even though a R0 resection was obtained in 99% compared to only 67% when FS was not done (Fig. 1 and Table 4). The incidence of positive margin is similar to those reported previously.⁷ Margin status was not associated with survival by univariate or multivariate analysis. As expected, poor differentiation of the tumor and positive nodes were predictive of poorer survival.

While it is well established that advances in imaging, surgical technique, and perioperative care have reduced postoperative morbidity and mortality of PD, most patients do not achieve long-term disease-free survival, even with the best of surgical care.⁸ Previous studies have indicated that an R0 resection increases long-term survival after PD, and thus, FS analysis at the time of surgery would seem to be beneficial and lead to better long-term outcomes.^{9,10} In fact, it has even been emphasized that achieving an R0 resection is one of the most powerful independent predictors of long-term survival.^{8,11} Similarly, Willett et al.¹² reported that patients in whom negative surgical margins were obtained achieved significantly longer 5-year survival (22%) than the group as a whole (13%). Similarly, results from the ESPAC-1 trial demonstrated poorer survival in patients undergoing R1 resection.¹³ However, after our review of 216 patients, we did not find an increase in overall survival, even when margin-negative R0 resection was achieved. As such, intraoperative margin assessment as a means of tailoring resection in order to achieve negative margins does not appear to impact outcome, an observation that has not been described previously. More recently, Raut et al.¹⁴ has reported similar results to our study, suggesting R0 resection does not necessarily translate into improved survival. While this may be due to

underestimation of margin status due to inconsistent pathologic analysis,^{15,16} it comes as no surprise as survival is notoriously poor given the lack of effective adjuvant therapy.

We recognize the difficulty in making definitive conclusions about the true utility of intraoperative margin assessment given the retrospective nature of this study. During the 15-year time period covered, the surgeons who undertook the majority of resections did not routinely obtain intraoperative FS analysis of the surgical neck margin. This alone could introduce a selection bias. Still, the dramatic improvement in the ability to achieve negative surgical margins with intraoperative assessment is undeniable. The impact on survival, however, is less clear.

The extension of a tumor arising from the head of the pancreas into or to the left of the surgical neck is likely indicative of a more aggressive tumor. Therefore, inability to achieve an initially negative margin after transecting the pancreas at the surgical neck during PD may be more reflective of poor biology rather than poor surgical technique. Intraoperative margin assessment, however, does play a role in providing real time feedback on the adequacy of resection allowing the surgeon the option of extending the resection to achieve negative margins for the purpose of proper stratification into clinical trials and outcomes research.

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Figure 1.
Overall survival in patients with pancreatic cancer following PD. No significant differences in overall survival was seen when frozen section was undertaken.

Table 1

Demographic and Clinicopathologic Characteristics in Patients Undergoing PD with or without Intraoperative Frozen Section Assessment of Surgical Margin

	Frozen, n=75	No frozen, n=141	p value
Age, median (range)	62.0 (39–81)	67.0 (30–85)	0.01
Gender	F 28 (37%) M 47 (63%)	F 61 (43%) M 80 (57%)	N.S.
Comorbidities	47 (63%)	91 (65%)	N.S.
Jaundice	67 (89%)	122 (87%)	N.S.
Pain	34 (45%)	57 (40%)	N.S.
Pylorus preservation	21 (28%)	26 (18%)	N.S.
Differentiation			
Well	5 (6.7%)	10 (6.8%)	
Moderately	43 (57.3%)	70 (59.6%)	N.S.
Poor	22 (29.3%)	49 (34.8%)	
Unknown	5 (6.7%)	12 (8.5%)	
Tumor size (cm)	3 (0–8)	3.5 (0.8–8)	N.S.
T stage ^a			
T1/T2	12 (16%)	23 (16.3%)	N.S.
T3	55 (73.3%)	20 (70.9%)	
Node positive	48 (64%)	92 (65.2%)	N.S.
LOS (days)	12.9	14	N.S.
Post-op death	3 (4%)	8 (5.7%)	N.S.
Complications			
Total No.	53	98	
Patients	32 (42.6%)	63 (44.7%)	N.S.
Chemotherapy			
Yes	33 (44%)	49 (34.8%)	
No	12 (16%)	43 (30.5%)	N.S.
Unknown	30 (40%)	49 (34.8%)	
Radiation			
Yes	24 (32%)	33 (23.4%)	
No	17 (22.7%)	48 (34.0%)	N.S.
Unknown	34 (45.3%)	60 (42.6%)	
Follow-up (mean, SD, median) (months)	34.1, 32.4, 18.9	33.5, 39.3, 16.6	N.S.

SD Standard deviation

^aT stage was unknown in 25 (seven in FS group and 18 in no FS group) and were excluded from this analysis

Table 2

Predictors of Negative Pancreatic Neck Margin Resection in Patients Undergoing PD

Variable	Univariate <i>p</i> value	Multivariate <i>p</i> value
Frozen section	0.001	0.001 RR 27.9 (95% CI 43.7–209)
Age	0.856	–
Gender	0.955	–
Comorbidities	0.346	–
Preoperative stent	0.960	–
Tumor size	0.055	0.209
Differentiation	0.647	–
T stage	0.859	–
Node positivity	0.981	–
Pylorus Preservation	0.060	0.110

Only variables with greatest potential to affect overall survival (i.e., $p \leq 0.2$) were included in multivariate logistic regression analysis

RR Relative risk, *CI* confidence interval

Table 3

Median, 2 and 5-Year Overall Survival in All Patients with Pancreatic Cancer Following PD

	Median survival (months)	2 year survival (%)	5 year survival (%)
Frozen section	21.7	38.6	8.2
No frozen section	14.6	29.2	11.4

The use of frozen section analysis did not significantly improve overall survival ($p=0.28$)

Table 4

Univariate and Multivariate Analysis of Variables to Predict Overall Survival

Variable	Univariate <i>p</i> value	Multivariate <i>p</i> value
Frozen section analysis	0.278	–
Age	0.258	–
Gender	0.949	–
Comorbidities	0.428	–
Complications	0.415	–
Pre-operative stent	0.166	0.596
Tumor size	0.442	–
Differentiation	0.034	0.014 RR 2.23 (95% CI 1.18–4.24)
T stage	0.420	–
Nodes	0.001	0.003 RR 1.79 (95% CI 1.20–2.43)
Margin status	0.099	0.228
Pylorus preservation	0.106	0.716

Only variables with potential to affect overall survival (i.e. $p \leq 0.2$) were included in Cox proportional hazards model.

RR Relative risk, *CI* confidence interval