



Status of Resection Margin in Pancreaticoduodenectomy: Is there Real Impact on Patient Survival?

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Abstract

Introduction: Pancreaticoduodenectomy (PD) is the primary curative treatment for periampullary and pancreatic head malignancies. A tumor-free resection margin (R0) is a critical prognostic factor, yet overall survival remains poor. This study aimed to assess overall survival after PD, identify histopathological factors predictive of positive margins, and compare survival between margin-positive and margin-negative patients.

Methods: A retrospective review of a prospectively maintained database was conducted for patients undergoing PD for malignant disease at a tertiary institution from January 2017 to June 2022. Patients with an ECOG status ≤ 2 were included, while those with benign disease, intraoperative metastases, or palliative procedures were excluded. Standard preoperative imaging was used for resectability assessment. Data on demographics, histopathology, and survival were analyzed using univariate analysis and Kaplan-Meier survival curves.

Results: Of 75 patients who underwent curative resection, 66 were included in the final survival analysis. The margin positivity rate was 10.8%. The most common site of margin involvement was the superior mesenteric artery (SMA) margin. Factors significantly associated with a positive resection margin were higher T-stage (T3) and the presence of perineural invasion (PNI). The mean overall survival was significantly lower in the margin-positive group compared to the margin-negative group (6.0 ± 1.5 months vs. 29.0 ± 2.8 months, $p = 0.0004$). The overall mean survival for the entire cohort was 26.9 months.

Conclusion: A positive resection margin following pancreaticoduodenectomy is associated with significantly worse overall survival and is strongly linked to advanced T-stage and perineural invasion. However, the dismal survival even in margin-negative patients underscores the aggressive biology of these tumors. Future efforts should focus on better understanding tumor biology, refining surgical approaches, and developing more effective adjuvant therapies.

Keywords: Pancreaticoduodenectomy; Resection Margin; Overall Survival; Perineural Invasion; Pancreatic Neoplasms.

Abbreviations

CI: Confidence Interval; CT: Computed Tomography; FJ: Feeding Jejunostomy; LVI: Lymphovascular Invasion; MRI: Magnetic Resonance Imaging; OS: Overall Survival; PD: Pancreaticoduodenectomy; PPPD: Pylorus-Preserving Pancreaticoduodenectomy; PNI: Perineural Invasion; PV: Portal Vein; SMA: Superior Mesenteric Artery; SMV: Superior Mesenteric Vein

Introduction

Pancreaticoduodenectomy (PD) is frequently performed for periampullary and pancreatic head malignancies. Pancreatic ductal adenocarcinoma (PDAC) is the seventh leading cause of cancer-related deaths worldwide [1]. To date, surgery with complete tumor-free resection margins (R0) combined with adjuvant chemotherapy offers the only chance for a cure, albeit with a dismal 5-year survival rate ranging from 5% to 17%.

Tumor-free resection margins are a recognized long-term prognostic factor, making a clear definition of resection margin status essential. The potential survival benefit of a negative resection margin has led to more aggressive surgery in selected patients, such as resection of the portal/superior mesenteric vein. However, the survival benefit of this approach remains unclear [2].

The most common site for a margin-positive resection in patients with portal/superior mesenteric vein involvement is the superior mesenteric artery (SMA) margin, or the posteromedial margin. This margin is often found to be infiltrated only after transecting the pancreatic neck. In such instances, resection with a positive margin may be the only option [3,4]. Consequently, the importance of determining SMA margin involvement before reaching a point of no return has led to the development of artery-first approaches to pancreaticoduodenectomy.

Although patients with margin-positive resections have decreased survival compared to margin-negative patients, the overall survival even for margin-negative patients remains dismal. The

reason for the poor overall survival in pancreatic malignancy compared to other cancers is not fully understood [5]. Thus, while margin status appears to be one factor responsible for poor survival, the underlying cause is likely the aggressive biology of the tumor itself [6].

In this study, we aimed to assess overall survival following pancreaticoduodenectomy for malignant disease, analyze the histopathological factors responsible for positive margin status after resection, and compare overall survival between margin-positive and margin-negative patients.

Materials and Methods

We performed a retrospective review of a prospectively maintained database in the Department of Surgical Gastroenterology of a tertiary teaching institution in northern India. The study included patients from January 2017 to June 2022, with follow-up until June 2023. All patients scheduled to undergo pancreaticoduodenectomy for malignant diseases were included. Patients had an ECOG performance status of 2 or less. Those who did not undergo pancreaticoduodenectomy due to intraoperatively discovered metastatic disease or who underwent surgery for palliative purposes were excluded. Pancreaticoduodenectomies performed for benign conditions, such as chronic pancreatitis, were also excluded.

Surgical procedure and postoperative treatment

The decision to offer surgery was based on standard preoperative evaluation, primarily computed tomography (CT) and magnetic resonance imaging (MRI) when necessary. Endoscopic ultrasonography was rarely used. Resectability criteria were:

- Absence of distant disease,
- Absence of locally advanced disease, defined as involvement of the superior mesenteric artery (SMA), common hepatic artery, or celiac trunk, or involvement of the portal vein (PV)/superior mesenteric vein (SMV) of less than 180°.

The surgical approach—classical PD or pylorus-preserving pancreaticoduodenectomy (PPPD)—was based on the surgeon's preference and disease origin. For patients with intraoperative findings of local advanced disease adjacent to the SMV or PV exceeding 180°, resection and reconstruction were performed if an R0 resection was deemed feasible.

Pancreaticojejunostomy was performed according to surgeon preference (e.g., Cattel-Warren duct-to-mucosa, Heidelberg duct-to-mucosa, or dunking technique). Pancreaticogastrostomy was not performed in any case. Hepaticojejunostomy was performed using a modified Blumgart technique, followed by gastrojejunostomy or duodenojejunostomy. A feeding jejunostomy (FJ) was routinely placed.

Data analysis

Data were analyzed using IBM SPSS Statistics v.16 for Windows (IBM, Armonk, NY). Recorded factors were evaluated by univariate analysis for their association with positive margin status. Descriptive statistics were used for categorical data (frequency and percentage) and quantitative data (mean, median, interquartile range). The study population was divided into margin-positive and margin-negative groups for analysis.

Categorical variables were compared using the Chi-square or Fisher's exact test. Continuous variables were analyzed with the t-test or Mann-Whitney U test. Results are reported as p-values with 95% confidence intervals (CI). The impact of margin status on overall survival (OS) was examined using the Kaplan-Meier method with log-rank testing. A p-value ≤ 0.05 was considered statistically significant.

Results and Discussion

Demographics and clinical data

Seventy-five patients underwent curative surgical resection for periampullary and pancreatic malignancy during the study period. Sixty-six were included in the final survival analysis. Nine patients

were excluded: eight died within 30 days of the procedure due to surgical complications, and one had a final histopathology of tuberculosis. The study group was 53% female, with an age range of 21 to 72 years and a mean age of 50.1 years. Nearly 85% of the population was between 35 and 65 years old. The most common tumor site was the periampullary region.

There were no significant differences in demographic parameters between the margin-positive and margin-negative groups.

Histopathology and outcomes

Overall

The final histology was adenocarcinoma in all but three patients; the other pathologies were a mixed adenoneuroendocrine tumor and two neuroendocrine tumors of the ampullary region. Histopathology confirmed the ampulla as the most common site of tumor origin (n=55) (Table 1). Microscopic margin positivity was found in 8 patients (10.8%). Six patients had involvement of the SMA margin, four had posterior surface margin involvement, and one had only pancreatic neck margin involvement. Three patients had both posterior and SMA margins positive. There were no R2 resections.

Twelve patients were lost to follow-up. Fifty-four patients were followed for a median duration of 13 months post-surgery (range: 2–50). Thirty-three patients died during follow-up, and 21 remain alive. The mean overall survival (OS) was 26.9 ± 2.7 months (95% CI: 21.6–32.3 months).

Group-wise analysis

Histopathological tumor characteristics, namely location, T-status, and perineural invasion (PNI), were significantly associated with margin-positive status. PNI was significantly associated with margin-positive tumors, but lymphovascular invasion (LVI) was not. Tumor grade and N-stage were comparable between the groups. The mean overall survival was significantly different between the margin-positive and margin-negative groups (6.0 ± 1.5 months, 95% CI: 2.0–11.0 vs. 29.0 ± 2.8 months, 95% CI: 23.5–34.5; $p = 0.0004$) (Figure 1).

Table 1: Comparison between Demographic and Histopathological features between two groups.

	All patients n (%)	Margin Positive n (%)	Margin Negative n (%)	p value
Age	50.1 ± 11.4	48.3 ± 10.4	50.3 ± 11.7	0.65
Male	31 (47)	4 (50)	27 (46.6)	0.85
Female	35 (53)	4 (50)	31 (53.4)	
Site of tumor				
Ampulla	55 (83)	2 (25)	53 (91.9)	<0.0001
Distal CBD	3 (4.5)	1 (12.5)	2 (3.4)	
Pancreatic Head	7(10.6)	5 (62.5)	2 (3.4)	
Duodenal	1(1.5)	0	1 (1.7)	
pT				0.02
1	1 (1.5)	0	1 (1.7)	
2	32 (48.5)	0	32 (55.1)	
3	32 (48.5)	8 (100)	24 (41.2)	
4	1 (1.5)	0	1 (1.7)	0.182
pN				
0	34 (51.5)	2 (25)	32 (55.2)	
1	15 (22.7)	2 (25)	13 (22.4)	0.102
2	17 (25.8)	4 (50)	13 (22.4)	
LVI	38 (57.6)	8 (100)	30 (51.7)	0.008
PNI	22 (33.3)	6 (75)	16 (27.6)	
Tumor Grade				
Well Differentiated	18 (27.3)	2 (25)	16 (27.6)	0.48
Mod Differentiated	40 (60.6)	4 (50)	36 (62.1)	
Poorly Differentiated	8 (12.1)	2 (25)	6 (10.3)	

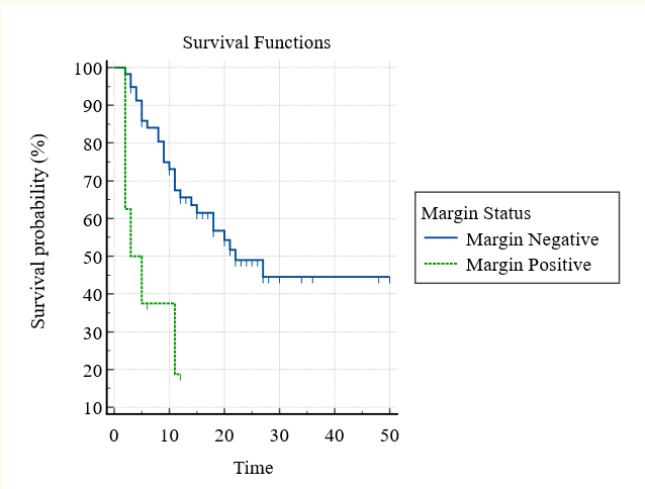


Figure 1: Kaplan Meier curve for overall survival; Margin positive and margin negative.

On univariate analysis, gender, tumor grade, PNI, LVI, and T-stage were not associated with a statistically significant decrease in survival ($p > 0.05$) (Table 2).

Discussion

Pancreaticoduodenectomy is the only curative option for pancreatic head, duodenal, and distal common bile duct malignancies.

Table 2: Median survival Analysis for Pancreaticoduodenectomy patients.

Prognostic Variable	Median Survival (months)	95 % CI	p value
Gender			0.53
Male	22	11-22	
Female	18	99-27	
Lymph Node			0.52
Positive	20	10-27	
Negative	21	10-22	
PNI			0.09
Present	14	6-22	
Absent	27	12-27	
LVI			0.53
Present	18	11-22	
Absent	27	9-27	
High grade tumor			0.13
Present	11	2-20	
Absent	22	11--27	

Prognosis for periampullary adenocarcinomas varies with the primary tumor’s origin; pancreatic adenocarcinoma has the worst prognosis (5-year survival of 5-20%), while duodenal adenocarcinoma has the best (5-year survival of 30-40%). Important prognostic indicators include non-pancreatic primary cancers, negative lymph node status, a low number of positive lymph nodes, smaller tumor size, curative resection, well-differentiated tumors, and no invasion of the extrapancreatic nerve plexus.

The overall survival in our study was 26.9 months, consistent with a similar study from MSKCC of 596 patients, which reported a median survival of 24 months [7].

Our margin positivity rate of 10% is low compared to Western studies, which range from 12% to 87.9% [8-12]. This is likely be-

cause the majority of our patients had ampullary malignancies, whereas Western cohorts often include a higher proportion of borderline resectable pancreatic cancers, which account for higher positive margin rates.

Our study shows a significantly decreased survival of 6 months in margin-positive patients compared to 29 months in margin-negative patients. This survival in our margin-positive cohort is lower than the 12-15 months reported in existing literature [10,13]. The reason may be delayed postoperative recovery and poor performance status, resulting in an inability to receive adjuvant chemotherapy. In our study, pancreatic head adenocarcinoma was significantly associated with SMA margin involvement, consistent with existing literature.

Higher T-stage (T3) and PNI were significant factors associated with positive margins. This is likely because PNI is a characteristic feature of PDAC, present in 70% to 95% of resected specimens, and is often an early event in cancer progression [14,15].

This study has several limitations. Its retrospective, single-center nature and the relatively small number of patients limit the generalizability of the findings. All positive margin statuses were grouped together regardless of the tumor-to-margin distance, preventing further sub-analysis. Furthermore, the lack of detailed follow-up data made it impossible to ascertain whether mortality was due to recurrence or other causes.

Conclusion

The prognosis following pancreaticoduodenectomy remains dismal despite improved postoperative care and the advent of new chemotherapeutic agents. In this study, margin-positive status was associated with significantly decreased overall survival and was linked to higher T-stage (T3) and the presence of PNI. The poor survival even in margin-negative patients underscores the need for a better understanding of tumor biology in the periampullary region, a re-evaluation of surgical approaches, and the development of novel chemotherapy regimens tailored to the tumor's biological aggressiveness [16,17].

The patients undergoing pancreaticoduodenectomy may need to assess the activation of the anti-aging gene Sirtuin 1 that is critical to the survival of surgical patients. The patients may need to consume Sirtuin 1 activators versus Sirtuin 1 inhibitors to avoid multiple organ disease syndrome and various chronic diseases [18-20].

Conflict of Interest

No Conflict of interest between the authors.

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