

Surgical Margin Status of Patients with Pancreatic Ductal Adenocarcinoma Undergoing Surgery with Radical Intent: Risk Factors for the Survival Impact of Positive Margins

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Abstract. *Background:* For pancreatic ductal adenocarcinoma (PDAC), surgical margin status is an important pathological factor for evaluating surgical adequacy. *In this study, we attempted to investigate predictive factors for the survival impact of positive surgical margins. Materials and Methods:* From February 2004 to December 2013, 204 patients were diagnosed with PDAC and underwent surgery with radical intent; 189 patients fulfilled our selection criteria and were enrolled for analysis. *Results:* For the 189 enrolled patients with PDAC, we found male predominance (112/189, 59%) and a median age of 64 years; most patients were diagnosed with stage IIB disease ($n=115$, 61%). The positive surgical margin rate was 21% ($n=40$). Carbohydrate antigen 19-9 (CA19-9) level higher than 246 U/ml (odds ratio (OR)=2.318; 95% confidence interval (CI)=1.037-5.181 $p=0.040$) and lesion location in the uncinate process (OR=2.996; 95% CI=1.232-7.284 $p=0.015$) were the only two independent risk factors for positive surgical margins. Positive retroperitoneal soft-tissue margins were the most frequently observed (24/40, 60%). Overall, positive surgical margins had no survival impact in the 189 patients with PDAC who underwent surgery; however, positive surgical margins had an unfavorable survival impact on patients with stage IIA PDAC who underwent surgery.

Conclusion: Retroperitoneal soft-tissue was the most common site for positive surgical margins. Additionally, surgical margin positivity was more likely for tumors located in the uncinate process than for other tumors. Positive surgical margins had an unfavorable survival impact on patients with stage IIA PDAC who underwent surgery.

Pancreatic ductal adenocarcinoma (PDAC) is a dismal condition with poor prognosis. The 5-year overall survival for PDAC may be as low as 1.3% (1). This poor outcome is attributable to advanced disease at diagnosis and inefficient treatment modalities. However, surgical resection remains the mainstream treatment for both primary tumor excision and precise staging for adjuvant treatment. Unfortunately, only 15-20% patients present with resectable disease at diagnosis (2, 3). For resectable PDAC, 5-year overall survival may be improved to up to 18% (4).

For resectable PDAC, surgical margin status is an important pathological factor for evaluating surgical adequacy. However, the impact of this status on long-term clinical outcome remains debatable (5, 6). In this study, we attempted to investigate predictive factors for positive surgical margins after surgery with radical intent and the survival impact of surgical margin status.

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Key Words: Pancreatic adenocarcinoma, surgical margin, curative resection.

Materials and Methods

From February 2004 to December 2013, 204 patients were diagnosed with PDAC and underwent surgery with radical intent. Eleven patients were excluded due to involvement of the superior mesentery artery or occult distant metastasis revealed after laparotomy. Four patients with surgical mortality (4/204, 1.96%, hospital mortality within 30 days after surgery) were also excluded. Therefore, 189 patients were enrolled for analysis (Figure 1). Medical records were reviewed and analyzed; the assessed items included clinical, laboratory, and pathological findings. Conventional Whipple's

operation, pylorus-preserving pancreaticoduodenectomy, subtotal or distal pancreatectomy, or total pancreatectomy was performed as appropriate given the location of the lesion. Pathological results were reviewed. The location of the lesion was categorized into four major groups: head and neck; body; tail; and uncinate process. The investigated margins included pancreatic margins, the common bile duct margin, the duodenal margin, and the retroperitoneal soft-tissue margin. In our study, positive margins were defined either macroscopically or microscopically. A margin clearance of more than 0 mm was used to define R0 resection. Disease stage was determined based on the seventh edition of the American Joint Committee of Cancer (AJCC) staging manual (7).

Risk factors for positive surgical margin. To explore risk factors for positive surgical margins, the 189 patients were categorized into two groups: negative margins (n=149) and positive margins (n=40). Age, gender, laboratory data, tumor markers, disease stage, macroscopic pathological factors, and microscopic pathological factors were compared between these groups. Factors revealed to be significant by univariate analysis were further assessed *via* multivariate analysis.

Survival impact. Survival analysis was conducted for both groups based on individual margin status. Subgroup analyses based on disease stage were also performed. In addition to univariate analysis, multivariate Cox proportional hazard analysis was also conducted to eliminate confounding effects produced by other factors.

Statistical procedures. The threshold for statistical significance was defined as $p < 0.05$. Continuous variables were analyzed using the independent Student's *t*-test, whereas categorical variables were assessed using the Pearson chi-square test. Multivariate analysis was performed *via* logistic regression. Survival analysis was conducted using both a log-rank test (univariate) and a Cox hazards model (multivariate). SPSS v.21 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. A value of $p < 0.05$ was considered statistically significant.

Results

Table I summarizes the demographic data, disease status, surgical method, and margin status for the study cohort. Male predominance (n=112, 59%) and a median age of 64 years were observed. Most lesions were located in the head and neck (n=132, 70%), and most of the surgical procedures were pancreaticoduodenectomies, either conventional (n=102, 54%) or pylorus-preserving (n=62, 33%). Most patients in the study cohort were diagnosed with stage IIB PDAC (n=115, 61%). The rate of surgical margin positivity was 21% (n=40).

Univariate analysis revealed that high carbohydrate antigen 19-9 (CA19-9) level and lesion location in the uncinate process were significantly associated with positive surgical margin (Table II). Subsequent multivariate analysis demonstrated that both factors [specifically, CA19-9 level higher than 246 U/ml (OR=2.318; 95% CI=1.037-5.181 $p=0.040$) and lesion location in the uncinate process

Table I. Demographic data of the patients included in this study.

Characteristic	Value
Gender, n (%)	
Male	112 (59%)
Female	77 (41%)
Age, years	
Median (IQR)	64 (56-73)
Stage, n (%)	
IA	2 (1%)
IB	15 (8%)
IIA	57 (30%)
IIB	115 (61%)
Operative method, n (%)	
PD	102 (54%)
PPPD	62 (33%)
Other*	25 (13%)
Tumor location, n (%)	
Head or neck	132 (70%)
Uncinate process	34 (18%)
Body	16 (8%)
Tail	7 (4%)
Resection margin, n (%)	
Positive	40 (21%)
Negative	149 (79%)

IQR: Interquartile range; PD: pancreaticoduodenectomy; PPPD: pylorus-preserving pancreaticoduodenectomy; *subtotal and distal pancreatectomy, n=22; total pancreatectomy, n=3.

(OR=2.996; 95% CI=1.232-7.284 $p=0.015$)] were independently associated with positive surgical margins.

Retroperitoneal soft-tissue margins were the most commonly observed positive surgical margins (n=24; 24/40, 60%). When the site of the primary tumor was considered (Table III), the risk of a positive retroperitoneal soft-tissue margin was higher for patients with tumors in the uncinate process (92%) than for those with tumor in other locations (50%).

Patients with negative surgical margins (n=149) had overall survival similar to that of patients with positive surgical margins (n=40) (Figure 2). Because of the small number of patients with stage IA or stage IB PDAC, only analyses of stage IIA (n=57) and stage IIB (n=114) were performed using the Cox proportional hazards model. The factors used for analysis included age, gender, tumor location, CA19-9 level, tumor size, histology, mitotic count, lymph node ratio, lymphatic invasion, vascular invasion, peri-neural invasion, margin status, and chemotherapy application. Negative surgical margins, normal CA19-9 level, and well-differentiated histology were the three independent factors that favored survival for those with stage IIA disease (Table IV). No independent factors that significantly affected survival were identified for those with stage IIB disease (Table V).

Table II. Univariate analysis of predictive factors for resection margin status.

Characteristic		Surgical margin status		p-Value
		Negative (N=149)	Positive (N=40)	
Age, years	Mean±SD	63.84±11.16	64.38±10.44	0.455
Gender	Male/female	89/60	23/17	0.799
AST (U/I)	Mean±SD	79.13±88.51	84.92±105.57	0.732
ALT (U/I)	Mean±SD	115.28±137.98	123.53±156.57	0.753
Bil.irubin (mg/dl)	Total	4.74±5.15	4.04±5.17	0.454
	Direct	2.98±3.28	2.42±3.11	0.401
ALK-P (U/I)	Mean±SD	273.81±363.17	220.12±186.25	0.421
Amylase (U/I)	Mean±SD	152±135.95	129.43±130.66	0.508
Lipase (U/I)	Mean±SD	225.9±34.16	331.29±173.35	0.367
Albumin (g/dl)	Mean±SD	3.81±0.64	3.77±0.57	0.729
CEA (ng/ml)	Mean±SD	15.86±96.05	9.9±32.80	0.723
	>5/≤5 ng/ml	35/95	12/22	0.336
CA19-9 (U/ml)	Mean±SD	4151.29±33977.14	858.45±1093.14	0.579
	>246/≤246 U/ml	21/12	57/75	0.035
Tumor size	Mean±SD	3.19±1.31	3.23±1.56	0.860
Tumor size	>2/≤2 cm	122/27	31/8	0.733
T-Stage	T1	3 (100%)	0 (0%)	0.273
	T2	18 (90%)	2 (10%)	
	T3	128 (77%)	38 (23%)	
Positive LN	Mean±SD	1.65±1.97	1.52±2.48	0.721
N-Stage	N0	61 (79%)	16 (21%)	0.914
	N1	88 (79%)	24 (21%)	
LNR	0	60 (80%)	15 (20%)	0.888
	0<LNR≤0.2	54 (78%)	15 (22%)	
	0.2<LNR ≤0.4	18 (75%)	6 (25%)	
	LNR>0.4	16 (84%)	3 (16%)	
Histology	Adenocarcinoma	3 (75%)	1 (25%)	0.233
	Well-differentiated	15 (94%)	1 (6%)	
	ModerateIy differentiated	109 (76%)	35 (24%)	
	Poorly differentiated	22 (88%)	3 (12%)	
Mitotic count	Low	76 (81%)	18 (19%)	0.644
	Intermediate	2 (67%)	1 (33%)	
	Moderate	39 (72%)	15 (28%)	
	High	10 (77%)	3 (23%)	
Vascular invasion	Yes:no	38: 91	6: 31	0.140
Lymphatic invasion	Yes:no	61: 69	12: 25	0.135
Peri-neural invasion	Yes:no	115: 14	33: 4	1.000
Tumor stage	IA	2 (100%)	0 (0%)	0.706
	IB	13 (87%)	2 (13%)	
	IIA	43 (75%)	14 (25%)	
	IIB	91 (79%)	24 (21%)	
Operative method	PD	82 (80%)	20 (20%)	0.239
	PPPD	45 (73%)	17 (27%)	
	Other/total*	22 (88%)	3 (12%)	
Tumor location	Head or neck	109 (83%)	23 (17%)	0.138
	Uncinate	22 (65%)	12 (35%)	
	Body	12 (75%)	4 (25%)	
	Tail	6 (86%)	1 (14%)	
Uncinate vs. other	Uncinate	22 (65%)	12 (35%)	0.027
	Other	127 (82%)	28 (18%)	

AST: Aspartate aminotransferase; ALT: alanine transaminase; Bil: bilirubin; ALK-P: alkaline phosphatase; CEA: carcinoembryonic antigen; CA 19-9: Carbohydrate Antigen 19-9; LN: lymph node; LNR: lymph node raatio; PD: pancreaticoduodenectomy, classical type; PPPD: pylorus-preserving pancreatoduodenectomy; *total pancreatectomy.

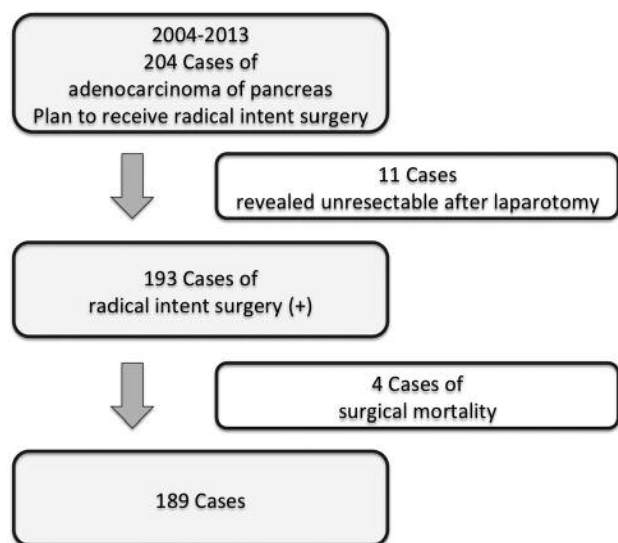


Figure 1. Flowchart of study subject selection.

Discussion

PDAC is a disease with a dismal outcome, and surgical resection is the only method for improving survival. In the seventh edition of the AJCC staging manual, PDAC of stages IA, IB, IIA and IIB is categorized as resectable. In contrast, stage III and stage IV PDAC are categorized as borderline resectable or unresectable. For most pathological diagnoses for malignancies, clearance of the resection margin is an index of surgical quality and an indicator of prognosis. In our study, we attempted to investigate the impact of margin status on overall survival.

From the perspective of surgical oncology, optimal margin clearance of solid tumors is the primary objective. However, positive margin status is sometimes inevitable. In our study, the rate of margin positivity was 21%. In previous reports, positive margin rates among PDAC patients undergoing resection with radical intent ranged from 14% to 60% (8). In our study, we found that high serum CA19-9 level and tumor location in the uncinate process were factors predictive of margin positivity. Furthermore, our analyses indicated that CA19-9 was an independent risk factor. Based on our receiver operating characteristics curve analysis, the optimal cutoff value of CA19-9 for prediction of positive surgical margins was 246 U/ml. CA19-9 has been reported to be a useful biochemical marker for diagnosing pancreatic cancer (9) and a predictor of overall survival for patients with resectable PDAC (10). Therefore, CA19-9 should be regarded as a predictive marker for positive surgical margins that has versatile clinical applications. Furthermore, our report found that the incidence of margin positivity was elevated for

Table III. Positivity of soft-tissue margins in different tumor locations.

Location	Positive soft-tissue margin, n (%)	p-Value
Head or neck	11 (48%)	0.247
Uncinate	10 (92%)	
Body	2 (50%)	
Tail	1 (100%)	
Uncinate vs. other		0.074

patients with tumors located in the uncinate process (Table II). Our series included 34 patients (17.9%) with a tumor in an uncinate location. However, the incidence of surgical margin positivity was much higher in this group than among patients with non-uncinate lesions (35% versus 18%). Retroperitoneal soft-tissue margins were the most common location for positive surgical margins, accounting for 60% of our cases with such margins. This result was consistent with the corresponding percentages of 80% (11) and 73% (8) reported in prior studies that also suggested that the retroperitoneal soft tissue is the most common site of positive surgical margins. In addition, our results (Table III) also showed a trend that positive retroperitoneal soft-tissue margins were more common for those with tumors primarily located in the uncinate process than for other tumors ($p=0.074$).

For years, studies have attempted to elucidate factors that influence survival for patients with PDAC. Various risk factors, including preoperative biliary stent, CA19-9 level, blood transfusion, R0 resection, tumor size, absence of lymph node or distant metastases, and peri-neural infiltration, have been discussed (16). For a surgical oncologist, R0 resection may be the most important consideration. Certain studies have demonstrated that surgical margin affects survival (17-19), although this effect was not observed in other investigations (5, 11, 20, 21). One study even proposed that repeated resection for margin clearance did not improve outcome (22). One possible reason for these inconsistent research results is lack of standardization of margin definitions (23, 24); another potential reason is the evolution of more efficient adjuvant chemotherapy regimens. In our study, adjuvant chemotherapy regimens were not unified but were instead chosen based on physicians' preferences and patient tolerance. All of these factors may have influenced the results of individual studies.

For patients with cancer, different pathological stages can indicate different survival statuses; staging systems exist for this reason. The main purpose of our work was to evaluate the impact of positive signal margins on survival. Therefore, in our study, it is reasonable to conduct subgroup analysis based on cancer stage, using multivariate analysis to eliminate the confounding effects of other factors. For patients with stage IIA PDAC, surgical margin, tumor size, CA19-9 level,

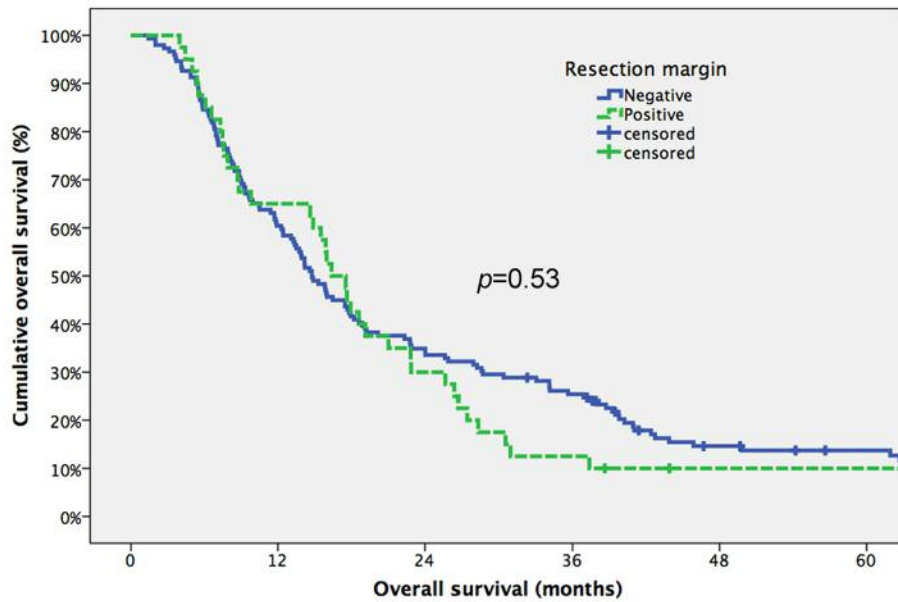


Figure 2. Survival curves for patients with negative and positive resection margins.

Table IV. Cox's proportional hazards analysis in patients with stage IIA disease.

Factor	Hazard ratio (95% CI)	p-Value
Age		
Per year increase	1.004 (0.958-1.052)	0.869
Gender		
M vs. F	1.589 (0.675-3.742)	0.289
Tumor size		
Per cm increase	0.506 (0.230-1.113)	0.090
Tumor location		
Uncinate vs. non-uncinate	0.883 (0.287-2.711)	0.827
CA19-9		
Per U/ml increase	1.000 (1.000-1.001)	0.008
Resection margin		
Positive vs. negative	4.839 (1.700-13.772)	0.003
Chemotherapy		
No vs. yes	1.471 (0.609-3.557)	0.391
LNR		
Per unit increase	0.595 (0.080-4.431)	0.613
Histology		
Moderately vs. well-differentiated	0.018 (0.001-0.215)	0.002
Poorly vs. well-differentiated	0.027 (0.003-0.261)	0.002
Mitotic count		
Intermediate vs. low	0.000 (0.000-)	0.978
Moderate vs. low	0.785 (0.304-2.032)	0.618
High vs. low	0.091 (0.007-1.109)	0.060
Vascular invasion		
Yes vs. no	1.163 (0.526-2.570)	0.709
Lymphatic invasion		
Yes vs. no	0.832 (0.352-1.965)	0.675
Peri-neural invasion		
Yes vs. no	0.772 (0.170-3.512)	0.112

CA 19-9: Carbohydrate antigen 19-9; LNR: lymph node ratio.

Table V. Cox's proportional hazards analysis in patients with stage IIB disease.

Factor	Hazard ratio (95% CI)	p-Value
Age		
Per year increase	0.984 (0.961-1.007)	0.169
Gender		
M vs. F	0.723 (0.413-1.265)	0.255
Tumor size		
Per cm increase	1.146 (0.850-1.545)	0.372
Tumor location		
Uncinate/non-uncinate	0.945 (0.500-1.784)	0.860
CA19-9		
Per U/ml increase	1.000 (1.000-1.000)	0.201
Resection margin		
Positive vs. negative	0.696 (0.345-1.406)	0.313
Chemotherapy		
No vs. yes	1.401 (0.808-2.428)	0.230
LNR		
Per unit increase	4.475 (0.849-23.580)	0.077
Histology		
Moderately vs. well-differentiated	2.047 (0.769-5.446)	0.152
Poorly vs. well-differentiated	2.322 (0.616-8.756)	0.214
Mitotic count		
Intermediate vs. low	0.460 (0.097-2.172)	0.327
Moderate vs. low	1.394 (0.786-2.471)	0.256
High vs. low	0.710 (0.232-2.172)	0.548
Vascular invasion		
Yes vs. no	1.805 (0.988-3.297)	0.055
Lymphatic invasion		
Yes vs. no	0.979 (0.532-1.801)	0.946
Peri-neural invasion		
Yes vs. no	0.622 (0.242-1.597)	0.323

CA 19-9: Carbohydrate antigen 19-9; LNR: lymph node ratio.

and histology were all independent factors for survival. For patients with stage IIB PDAC, no independent factors for survival were identified. Because pancreatic cancer has been recognized as a systemic disease (25, 26), different disease stages may reflect different extents of involvement. This phenomenon may explain our observations. For stage IIA disease, a positive surgical margin was an independent factor for survival; for stage IIB disease, no local factors for survival were identified. Stage IIA PDAC should be regarded as a more localized condition for which the surgical margin affects survival. Pancreatic surgeons should attempt to perform radical surgery for PDAC by stage IIA in order to achieve favorable survival outcomes.

Our study had several limitations. The study period was almost 10 years. Treatment of PDAC has improved during this period with respect to both surgical techniques and systemic treatment. This evolution in treatment may have produced detectable or undetectable survival benefits. In addition, the definition of a positive surgical margin and the standard procedure for pathological examination of the resection margin may have incorporated additional biases into our study. These potential biases render it difficult to compare different studies on this topic.

Conclusion

In our study, we found that the retroperitoneal soft tissue is the most common location for positive margins among patients with PDAC who underwent surgery. In addition, positive margins were more common for tumors located in the uncinate process than for other tumors. With respect to survival impact, positive surgical margins had a negative impact on survival of patients with stage II PDAC who underwent surgery.

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