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Defining the role of systemic therapy in resectable pancreatic acinar cell carcinoma

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Abstract

Introduction: Following resection of pancreatic acinar cell carcinoma (PACC) distant recurrence remains high. We utilized the national cancer database (NCDB) to evaluate the role of systemic therapy in early-stage resected PACC.

Methods: We queried the NCDB registry from 2004 to 2015 for patients with pathologic stage I-IIB PACC. For each stage, patients who underwent surgery alone (SA) were compared to patients who received systemic and/or radiation therapy in addition to surgery (surgery + therapy [S + T]).

Results: A total of 271 patients (101 pI, 81 pIIA, and 89 pIIB) were analyzed. Of all clinically node positive patients ($n = 41$), the majority ($n = 32$, 78%) had node-positive disease at resection (pIIB). SA was performed in 112 patients (41.3%), whereas 159 (58.7%) patients received S + T. There was no difference in overall survival (OS) between S + T and SA with respect to pI or pIIA disease. In pIIB disease, S + T was associated with improved OS compared to SA (34.9 vs. 16.9 months, $p = 0.031$). Single-agent chemotherapy was associated with improved OS for pIIB disease when compared to SA (hazard ratio: 0.38, 95% confidence interval: 0.16, 0.83).

Conclusion: In resectable PACC, the survival benefit of adjuvant therapy is limited to pathologic stage IIB disease. This benefit is evident even in patients treated with single-agent chemotherapy.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

Keywords

chemotherapy; pancreas; surgical oncology

1 | INTRODUCTION

Pancreatic acinar cell carcinomas (PACC) represent 1%–2% of adult exocrine pancreatic neoplasms with peak incidence in the 6th decade of life.[1] These neoplasms are distinguished from pancreatic ductal adenocarcinoma (PDAC) both clinically and pathologically.[2,3] In contrast to PDAC, patients with PACC typically present with abdominal pain, rather than biliary obstruction, and lesions more frequently located in the body/tail of the pancreas (32.8% vs. 16.4%).[2,4] Following diagnosis, nearly 40% of PACC patients undergo surgical resection of the primary tumor, as compared with approximately 20% of patients diagnosed with PDAC.[3,5] The 5-year overall survival (OS) for resected PACC is 72% compared to 16.3% for patients with PDAC. Despite a more favorable survival following resection, distant recurrence of PACC still approaches 72%.[1] Adjuvant therapy use for PACC is increasing and current strategies are largely based on existing literature pertaining to PDAC.

Currently, adjuvant chemotherapy with modified FOLFIRINOX is standard for appropriately fit patients[6,7]; however, 40% do not complete adjuvant therapy due to postoperative morbidity, poor performance status, and/or early disease progression.[8–10] As such, the role of neoadjuvant therapy is gaining interest and is now standard of care for borderline resectable PDAC, while many institutions prefer neoadjuvant therapy for resectable disease as well.[11]

In the context of PACC, evidence is limited to case series and retrospective analyses.[1–4,12–14] Recent evidence for resectable PACC suggests improved survival with adjuvant therapy compared to resection alone, particularly in node positive disease.[13,14] The role of neoadjuvant therapy, however, is unclear. We utilized the national cancer database (NCDB) to evaluate the role of systemic therapy in early-stage resected PACC.

2 | METHODS

2.1 | Patient selection

We queried the NCDB registry between 2004 and 2015 for patients with pathologic stage I-IIB (pI-IIB) PACC. The *International Classification of Diseases for Oncology* (edition 3.2) site and histology codes were used to identify patients with acinar cell carcinoma or acinar cell cystadenocarcinoma of the pancreas (ICD-O-3.2 code 8550/3 and 8551/3, respectively). Patients with non-metastatic disease who underwent curative intent surgical resection were included. Patients with pathologic stage ≥III disease or those who underwent treatment with palliative intent, were excluded from the analysis.

2.2 | Patient characteristics and treatment cohorts

Patient characteristics included age, sex, race, Charlson–Deyo (CD) score, facility type and location. Clinicopathologic variables included tumor grade, tumor size, clinical and

pathologic T and N stages as defined by the American Joint Committee on Cancer (AJCC) staging system (6th and 7th edition), lymphovascular invasion (LVI), and margin positivity. The 6th and 7th edition of the AJCC staging system are equivalent for pancreatic cancer.[15,16] For each stage group, outcomes for patients who underwent surgery alone were compared with outcomes of patients who received systemic and/or radiation therapy in addition to surgery (neoadjuvant, perioperative, or adjuvant).

2.3 | Statistical analysis

Statistical analysis was conducted using SAS 9.4 (SAS Institute Inc.) and SAS macros developed at the Biostatistics Shared Resource at the Winship Cancer Institute.[17] Statistical significance was set at a p value of 0.05. Descriptive analyses were performed for each variable. Patient characteristics were compared across treatment groups using chi-squared tests or Fisher's exact tests for categorical covariates and by the analysis of variance or Kruskal–Wallis tests for numerical covariates, where appropriate. The primary outcome was OS, calculated from the time of diagnosis to the time of death. Kaplan–Meier method was used to generate OS curves and the log-rank test was used for comparison of survival curves between cohorts. Univariate and multivariable Cox proportional hazard analysis for OS were performed using Firth's bias-reduced, penalized likelihood approach to account the rarity of event.[18,19]

2.4 | Data source

The NCDB is a hospital-based registry maintained by the American Cancer Society and American College of Surgeons that captures 70% of newly diagnosed cancers from more than 1500 participating facilities across the United States.[20] The NCDB has not verified and is not responsible for the statistical analysis employed here, or the conclusions drawn by the investigators.

3 | RESULTS

3.1 | Patient demographics and treatment characteristics

Among 380 524 pancreatic cancer patients identified in the NCDB participant user file from 2004 to 2015, there were 1064 cases of PACC, of which 271 met our inclusion criteria (Figure 1). Patient characteristics are listed in Table 1. Within the cohort, median age was 64 years with the majority being male patients (n = 189, 69.7%) with CD score of 0 (n = 189, 69.7%). Mean primary tumor size was 59 mm (SD ± 50) and was most often located in the pancreatic head (n = 114, 42.1%). Surgical resection alone (SA) was performed in 112 patients (41.3%), whereas 159 (58.7%) patients received systemic and/or radiation therapy in addition to surgery (surgery + therapy [S + T]). Within the S + T cohort, 14 patients received neoadjuvant therapy, 3 received perioperative therapy, and 142 received adjuvant therapy (data not shown). The node positive rate was 32.8% with margin positive resection observed in 14% of all cases. The 30- and 90-day postoperative mortality was 1.5% and 2.9%, respectively (data not shown).

The cohort consisted of 101 pathologic stage I (pI = pT1-2N0), 81 pathologic stage IIA (pIIA = pT3N0), and 89 pathologic stage IIB (pIIB = pT1-3N1) patients. Patients with pI

and pIIA disease presented most often (70.3%) with clinically node negative (cN0) disease. Clinically, node positive (cN1) disease was suspected in 4%, 6%, and 36% of patients pI, pIIA, and pIIB disease, respectively. Of all cN1 patients ($n = 41$), the majority ($n = 32$, 78%) had node-positive disease at resection (pIIB), with a concordance rate of 88% in patients who underwent surgery first (no neoadjuvant or perioperative therapy) (Figure 2). Of the 9 patients presenting with cN1 disease who were pathologically node negative (pI and pIIA), 5 patients had received neoadjuvant ($n = 4$) or perioperative therapy ($n = 1$) (data not shown).

S + T was performed in 48/101 (47.5%), 52/81 (64%), and 59/89 (66%) of patients with pI, pIIA, and pIIB disease, respectively. Patients with pI disease were more likely to undergo S + T when LVI was present (23% vs. 10.7%, $p = 0.028$). Amongst pIIA patients, those with lower CD score ($p = 0.016$) and non-private insurance ($p = 0.006$) were more likely to undergo S + T when compared to SA. Patients with pIIB disease were more likely to undergo S + T if they were under age 65 (56% vs 33%, $p = 0.044$) and had private insurance (43% vs. 20%, $p = 0.036$).

3.2 | Kaplan–Meier and univariate analysis (UVA)

In patients with pI disease, median OS was 92 months with no difference in OS between the S + T group and SA group (median OS = 98.4 months vs. 81.6 months; hazard ratio [HR]: 0.92, $p = 0.803$) (Figure 3A). These results were consistent when pI was sub-grouped into pathologic stage IA and pathologic stage IB ($p = 0.729$ and $p = 0.497$, respectively) (data not shown). Patients with pIIA disease had a median OS of 50 months with no OS difference between the S + T group and SA group (median OS = 48.2 months vs. 59.4 months; HR: 0.94, $p = 0.871$) (Figure 3B). In patients with pIIB disease, the median OS was 24.6 months and the S + T group was associated with significant improvement in OS compared to the SA group (median OS = 34.9 months vs. 16.9 months; HR: 0.54, p = 0.031) (Figure 3C).

UVA of patients with pIIB disease demonstrated additional improved OS for margin-negative resection (HR: 0.46, $p = 0.008$) and private insurance payers (HR: 0.53, $p = 0.027$). Additionally, patients with pIIB disease undergoing resection at a nonacademic center predicted worse OS compared to academic centers (HR: 1.82, $p = 0.023$) (Table 2). Only three patients with pIIB disease received either neoadjuvant or perioperative therapy, which did not allow for optimal analysis in this subgroup.

3.3 | Multivariable analysis (MVA) of pIIB disease

MVA of patients with pIIB disease continued to demonstrate significantly improved OS from S + T when compared to SA (HR: 0.39, $p < 0.001$), and margin negative resection compared to margin positive resection (HR: 0.39, $p = 0.003$). Treatment at a nonacademic center was again associated with significantly worse OS compared to academic centers (HR: 2.02, $p = 0.014$) (Table 3).

3.4 | UVA of therapy in pIIB disease

We subsequently performed UVA of pIIB patients with respect to OS for each additional therapy. Two patients who received additional therapy did not have an identified type of therapy and were therefore excluded. Using the SA group as our reference standard, we

identified significantly improved OS for chemotherapy (HR: 0.39, 95% CI: 0.19, 0.75) and radiation therapy + chemotherapy (HR: 0.54, 95% CI: 0.3, 0.96). Subset analysis of these therapies demonstrated significantly improved OS for singleagent chemotherapy (HR: 0.38, 95% CI: 0.16, 0.83) when compared to SA (Table 4).

4 | DISCUSSION

We utilized the NCDB to evaluate the role of systemic therapy in early-stage resected PACC. Our study delineates stage-specific OS for patients with resected pI-IIB PACC. The OS of patients with pI-IIA disease did not differ between S + T and SA groups. In contrast, patients with pIIB disease demonstrated significantly improved OS with S + T compared to SA. Furthermore, patients with pIIB disease who received S + T had significantly improved OS with single-agent chemotherapy when compared to SA. These findings suggest that patients with pI-IIA PACC may have limited benefit from adjuvant therapy. In addition, patients with pIIB disease appear to derive benefit from at least a single-agent chemotherapeutic regimen.

Surgical resection remains the standard of care for resectable disease and has demonstrated benefit for early-stage PACC across a variety of retrospective studies and case reports.[2,3,13,14,21–23] For patients with resected pI disease, median OS in our study was 92 months. Previous literature has not defined median OS for resected pI patients, however, 5-year survival rates are reported from 46% to 53%.[14,22] Median OS for resected pIIA and pIIB patients in our study was 50 and 24.6 months, respectively. This demonstrates a large difference in OS within pII disease and highlights the significance of nodal positivity on patient outcomes following resection.

Our findings both support and contrast those of prior NCDB studies. Similar to studies by Schmidt et al. and Patel et al.,[14] we identified margin-positive resection associated with increased risk of death in pIIB disease. In contrast, utilizing a patient cohort across all stages of PACC from 1985 to 2005, Schmidt et al.[22] found no difference in survival from adjuvant therapy on multivariable analysis.[22] More recently, however, Patel et al.[14] conducted an analysis through the NCDB of clinical stage I-II PACC from 2004 to 2015 where they identified survival benefit for adjuvant therapy over surgery alone ($p = 0.015$), particularly in the context of positive lymph nodes ($p < 0.001$).[14] While our study corroborates these findings for pIIB disease, we found limited benefit from additional therapy beyond resection in pI-IIA. This difference is likely a result of grouping patients by pathologic rather than clinical stage. Through early pathologic stage analysis, we are able to include all clinical stages that undergo resection, increasing our patient cohort. Furthermore, we exclude those patients who were upstaged to pathologic stage III or greater, who are more likely to benefit from adjuvant therapy. Additionally, we have included both neoadjuvant and perioperative therapy to broaden our inclusion criteria, which allows for more complete analysis of this patient population.

The literature is scarce with regards to additional systemic and locoregional therapies for resectable PACC. Most reviews of the topic are limited by sample size and encompass both resectable and unresectable disease. A systematic review identified disease control rates (DCR) for gemcitabine-based (0%–50%)[13,24–26] or fluoropyrimidine-based (33%–

67%)[13,26,27] chemotherapy regimens, while DCR for surgical resection with concurrent chemoradiation neared 100% for up to 80 months.[2,13,27,28] In regards to surgically resected disease, a case series of 14 patients by Glazer et al.[13] demonstrated significantly improved survival with adjuvant radiation therapy compared to surgery alone (HR: 0.05, $p = 0.03$). However, the small sample size of this study limits its clinical applicability. In our analysis of resected patients with pIIB disease, those who received chemotherapy as well as radiation therapy + chemotherapy, demonstrated significantly improved OS compared to SA. Further stratification identified benefit from at least single-agent chemotherapy when compared to SA. This is an important finding as it demonstrates that if patients are unable to receive multiagent chemotherapy, administration of single-agent chemotherapy does predict improved OS compared to SA in patients with pIIB disease.

Pancreatic resection carries a high morbidity rate and in the context of PDAC, approximately 40% of patients do not receive adjuvant therapy.[29] Neoadjuvant therapy provides potential benefit of decreased tumor size, improved margin negative resection rate, targeting of micrometastatic disease and ensuring patients receive systemic therapy as part of their management due to a large proportion of patients being unable to receive therapy after surgery. As such, neoadjuvant therapy has been proposed for resectable PDAC and has shown promise in recent phase II/III randomized controlled trials.[30,31] Few studies have investigated the effect of neoadjuvant therapy in resectable PACC.[12] Our S + T cohort included patients who underwent neoadjuvant, perioperative, and adjuvant therapy. Due to sample size, we were unable to separate these groups for analysis. Our study demonstrates that the majority ($n = 32/41$, 78%) of clinically node positive patients have node positive disease at resection. After removing patients who underwent neoadjuvant or perioperative therapy, this correlation increased to 88% (30/34). Based on these results we would propose that the presence of clinically node positive disease on initial staging imaging could be a useful tool to guide patient selection for neoadjuvant therapy in PACC patients.

Our study has several limitations that should be recognized. First, this is a retrospective design that can be subject to selection bias. We combined neoadjuvant, perioperative, and adjuvant therapies into a single cohort due to very small numbers of patients within each of these treatment groups, which would make subsequent analysis suboptimal. In addition, the agents used, dosing and duration of systemic therapy is not delineated in the NCDB. As such, we cannot make any definite conclusion in relation to the impact of single-agent or multiagent chemotherapy. Furthermore, there may be significant selection bias between patients who did and did not receive chemotherapy. Patients who did not receive adjuvant chemotherapy may have had a more complicated postoperative course or other comorbidities that would independently limit their survival. Despite these limitations, our study is the first large, comprehensive pathologic stage-specific analysis of resectable PACC and provides detailed insight into patient populations that will benefit from additional therapy.

5 | CONCLUSION

In patients undergoing surgical resection for pancreatic acinar cell carcinoma, the association of adjuvant therapy with improved OS is limited to patients with pathologic stage IIB disease. Furthermore, the possible benefit of adjuvant chemotherapy is evident

even in patients treated with singleagent chemotherapy, which may be useful as there are a number of patients who cannot tolerate multiagent chemotherapy after resection. Most patients who present with clinically node positive disease have pathologically positive nodes at resection, and this may be useful in patient selection for neoadjuvant therapy. Future studies should focus on defining the role of neoadjuvant therapy in patients with pancreatic acinar cell carcinoma with clinically node positive disease.

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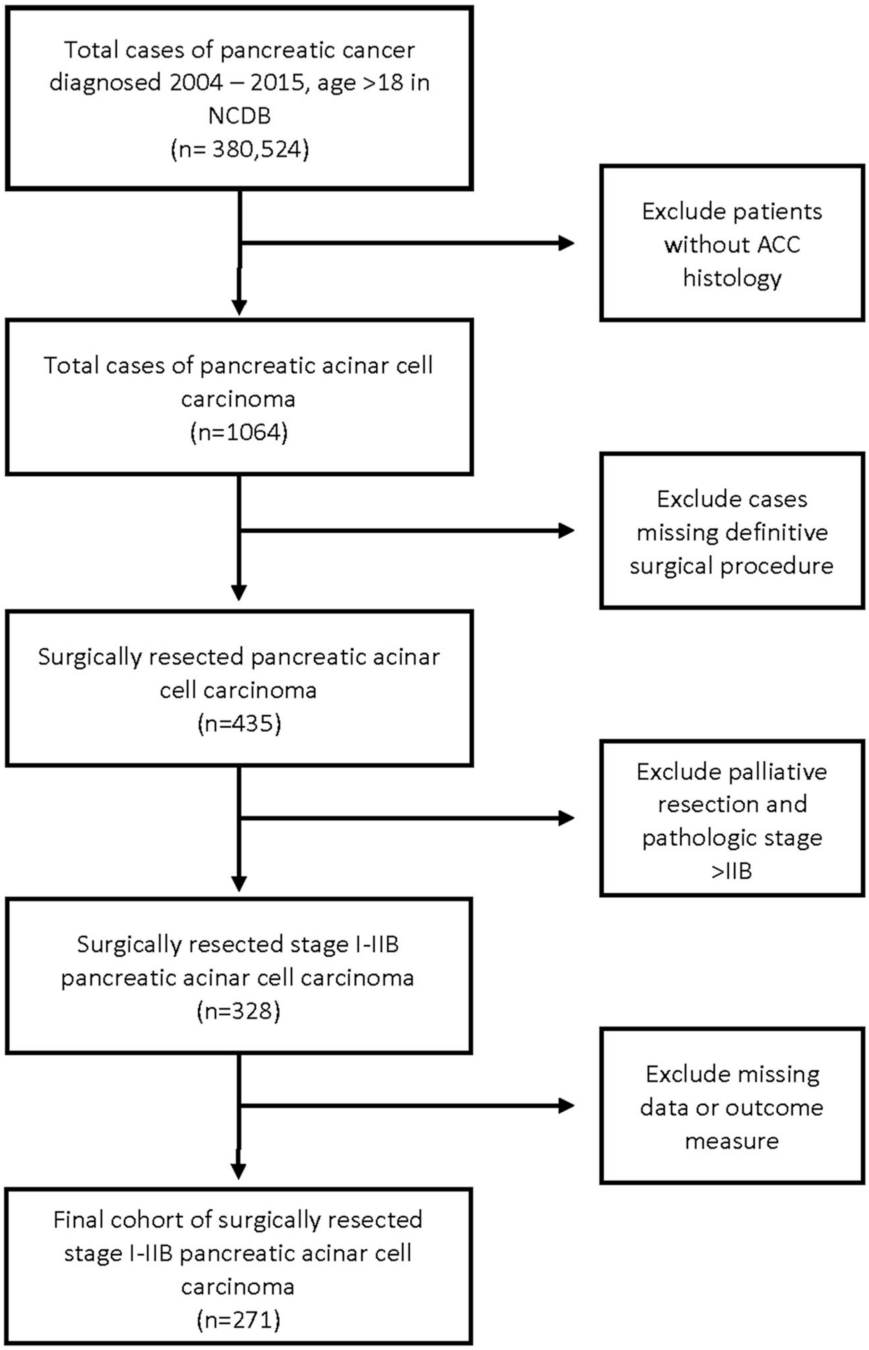

FIGURE 1.
Flow diagram of selection criteria

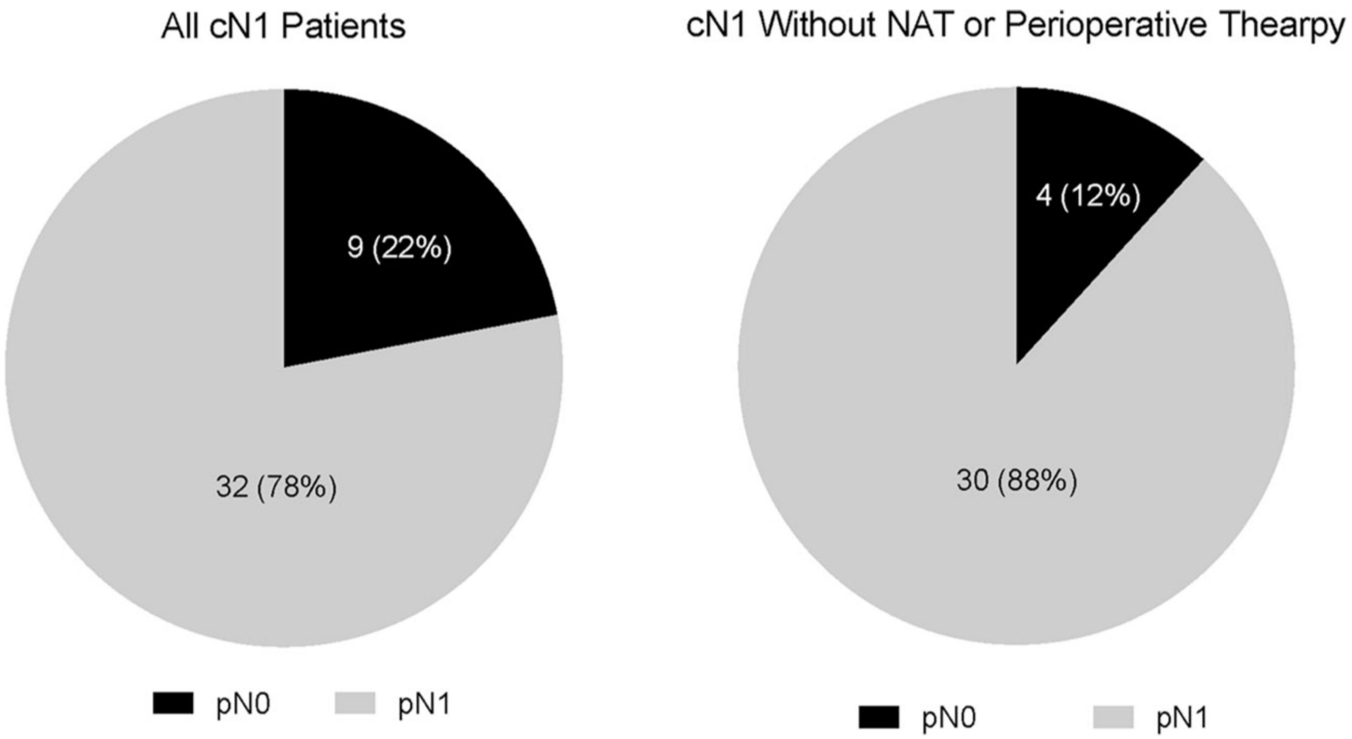

FIGURE 2.
Pie charts of cN1 positive patients with pN0 and pN1 disease at resection

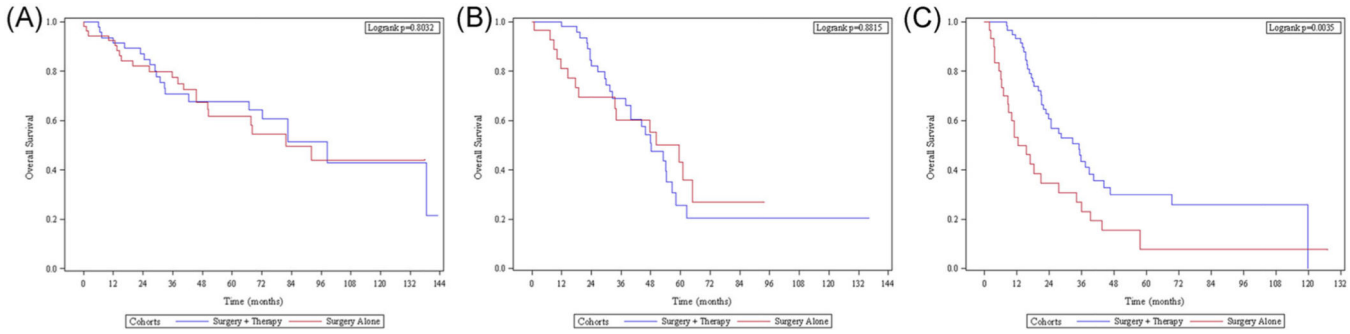

FIGURE 3.

Kaplan–Meier analysis of surgery + therapy versus surgery alone for resected (A) pI, (B) pIIA, and (C) pIIB PACC. PACC, pancreatic acinar cell carcinoma

TABLE 1

Descriptive statistics by pathologic stage for resected PACC

Covariate	Level	Stage I		*p* value	Stage IIA		*p* value	Stage IIB		*p* value
		S + T *N* = 48	SA *N* = 53		S + T *N* = 52	SA *N* = 29		S + T *N* = 59	SA *N* = 30	
Age	<65	26 (54.17)	24 (45.28)	0.373	25 (48.08)	12 (41.38)	0.562	33 (55.93)	10 (33.33)	0.044
	≥65	22 (45.83)	29 (54.72)		27 (51.92)	17 (58.62)		26 (44.07)	20 (66.67)	
Sex	Male	29 (60.42)	29 (54.72)	0.563	37 (71.15)	26 (89.66)	0.092	46 (77.97)	21 (70)	0.41
	Female	19 (39.58)	24 (45.28)		15 (28.85)	3 (10.34)		13 (22.03)	9 (30)	
Race	White	40 (83.33)	40 (75.47)	0.331	45 (86.54)	26 (89.66)	1	53 (89.83)	27 (90)	1
	Others	8 (16.67)	13 (24.53)		7 (13.46)	3 (10.34)		6 (10.17)	3 (10)	
Facility type	Others	17 (37.78)	25 (49.02)	0.268	27 (55.1)	10 (35.71)	0.101	20 (35.09)	11 (36.67)	0.884
	Academics	28 (62.22)	26 (50.98)		22 (44.9)	18 (64.29)		37 (64.91)	19 (63.33)	
Charlson-Deyo Score	0	32 (66.67)	37 (69.81)	0.896	42 (80.77)	15 (51.72)	0.016	42 (71.19)	20 (66.67)	0.677
	1	12 (25)	13 (24.53)		7 (13.46)	11 (37.93)		13 (22.03)	9 (30)	
	2+	4 (8.33)	3 (5.66)		3 (5.77)	3 (10.34)		4 (6.78)	1 (3.33)	
Primary payor	Others	27 (56.25)	31 (58.49)	0.82	31 (59.62)	8 (27.59)	0.006	34 (57.63)	24 (80)	0.036
	Private	21 (43.75)	22 (41.51)		21 (40.38)	21 (72.41)		25 (42.37)	6 (20)	
Grade	Well differentiated	7 (30.43)	9 (36)	0.92	1 (4.55)	4 (26.67)	0.212	2 (4.88)	2 (9.52)	0.334
	Moderately differentiated	11 (47.83)	11 (44)		14 (63.64)	7 (46.67)		19 (46.34)	6 (28.57)	
	Poorly differentiated/ undifferentiated	5 (21.74)	5 (20)		7 (31.82)	4 (26.67)		20 (48.78)	13 (61.9)	
AJCC clinical T	c0	1 (2.13)	0 (0)	0.392	1 (1.92)	3 (10.34)	0.498	2 (3.45)	1 (3.45)	0.271
	c1	9 (19.15)	6 (11.76)		15 (28.85)	8 (27.59)		27 (46.55)	7 (24.14)	
	c2	19 (40.43)	26 (50.98)		21 (40.38)	10 (34.48)		17 (29.31)	12 (41.38)	
	c3	6 (12.77)	3 (5.88)		2 (3.85)	0 (0)		2 (3.45)	1 (3.45)	
	cX	12 (25.53)	16 (31.37)		13 (25)	8 (27.59)		10 (17.24)	8 (27.59)	
AJCC clinical N	c0	33 (70.21)	38 (73.08)	0.651	34 (65.38)	23 (79.31)	0.484	25 (43.1)	14 (50)	0.783

Covariate	Level	Stage I		*p* value	Stage IIA		*p* value	Stage IIB		*p* value
		S + T *N* = 48	SA *N* = 53		S + T *N* = 52	SA *N* = 29		S + T *N* = 59	SA *N* = 30	
	c1	3 (6.38)	1 (1.92)		4 (7.69)	1 (3.45)		23 (39.66)	9 (32.14)	
	cX	11 (23.4)	13 (25)		14 (26.92)	5 (17.24)		10 (17.24)	5 (17.86)	
Lymph vascular invasion, 2010	Not present	14 (53.85)	24 (85.71)	0.03	18 (51.43)	8 (42.11)	0.584	9 (20.93)	3 (17.65)	1
	Present	6 (23.08)	3 (10.71)		13 (37.14)	10 (52.63)		29 (67.44)	12 (70.59)	
	Unknown	6 (23.08)	1 (3.57)		4 (11.43)	1 (5.26)		5 (11.63)	2 (11.76)	
Primary site	Others	31 (64.58)	36 (67.92)	0.723	33 (63.46)	19 (65.52)	0.853	27 (45.76)	12 (40)	0.604
	Head	17 (35.42)	17 (32.08)		19 (36.54)	10 (34.48)		32 (54.24)	18 (60)	
Surgical margin	Negative	44 (93.62)	53 (100)	0.062	38 (76)	23 (92)	0.122	44 (74.58)	23 (79.31)	0.624
	Positive	3 (6.38)	0 (0)		12 (24)	2 (8)		15 (25.42)	6 (20.69)	
Tumor size	>4	18 (37.5)	23 (43.4)	0.547	36 (69.23	18 (62.07)	0.512	32 (54.24)	19 (63.33)	0.412
	≤4	30 (62.5)	30 (56.6)		16 (30.77)	11 (37.93)		27 (45.76)	11 (36.67)	

Abbreviations: PACC, pancreatic acinar cell carcinoma; SA, surgery alone; S + T, surgery + therapy.

TABLE 2

Univariate analysis of resected pathologic stage IIB PACC

Univariate analysis of pathologic stage IIB				
			OS	
Covariate	**Level**	***N***	**Hazard ratio (95% CI)**	***p* value**
Cohorts	Surgery + therapy	59	0.47 (0.28–0.79)	0.004
	Surgery alone	30	–	–
Age	≥65	46	1.51 (0.91–2.50)	0.111
	<65	43	–	–
Sex	Female	22	1.16 (0.66–2.04)	0.597
	Male	67	–	–
Race	Others	9	0.89 (0.38–2.06)	0.78
	White	80	–	–
Facility type	Others	31	1.82 (1.08–3.05)	0.023
	Academics	56	–	–
Charlson-Deyo	1	22	1.23 (0.69–2.19)	0.487
Score	2+	5	2.84 (0.98–8.23)	0.054
	0	62	–	–
Primary payor	Private	31	0.53 (0.30–0.93)	0.027
	Others	58	–	–
Grade	Moderately differentiated	25	0.96 (0.27–3.39)	0.944
	Poorly differentiated/ undifferentiated	33	1.51 (0.44–5.18)	0.513
	Well differentiated	4	–	–
LVI, 2010	Present	41	0.57 (0.26–1.22)	0.146

Univariate analysis of pathologic stage IIB

			OS	
Covariate	**Level**	***N***	**Hazard ratio (95% CI)**	***p* value**
	Unknown	7	0.88 (0.29–2.63)	0.818
	Not present	12	–	–
Primary site	Others	39	1.15 (0.69–1.92)	0.581
	Head	50	–	–
Surgical margin	Negative	67	0.46 (0.26–0.82)	0.008
	Positive	21	–	–
Tumor size	>4	51	1.30 (0.78–2.18)	0.312
	≤4	–	–	

Abbreviations: CI, confidence interval; OS, overall survival; PACC, pancreatic acinar cell carcinoma.

TABLE 3

Multivariable analysis of resected pathologic stage IIB PACC

Multivariable analysis of pathologic stage IIB			
		OS	
Covariate	**Level**	**Hazard ratio (95% CI)**	***p* value**
Cohorts	Surgery + therapy	0.39 (0.23–0.68)	<0.001
	Surgery alone	–	–
Race	Others	0.77 (0.29–2.05)	0.699
	White	–	–
Primary payor	Others	1.60 (0.89–2.88)	0.12
	Private	–	–
Facility type	Others	2.02 (1.15–3.55)	0.014
	Academics	–	–
Charlson-Deyo Score	1	1.08 (0.59–1.99)	0.805
	2+	2.75 (0.90–8.37)	0.075
	0	–	–
Primary site	Others	1.30 (0.73–2.32)	0.378
	Head	–	–
Surgical margin	Negative	0.39 (0.21–0.72)	0.003
	Positive	–	–
Tumor size	>4	1.08 (0.61–1.92)	0.781
	≤4	–	–

Abbreviations: CI, confidence interval; OS, overall survival; PACC, pancreatic acinar cell carcinoma.

TABLE 4

Univariate analysis of additional therapy for resected pIIB PACC

			OS		
Cohort	**Treatment**	***N***	**Hazard ratio (95% CI)**	**HR *p* value**	**Log-rank *p* value**
Grouped	Chemotherapy	22	0.39 (0.19–0.75)	0.007	0.010
	Radiation +che- motherapy	33	0.54 (0.30–0.96)	0.038	
	Surgery alone	30	–	–	
Subset	Single-agent chemotherapy	13	0.38 (0.16–0.83)	0.025	0.099
	Multiagent chemotherapy	9	0.47 (0.17–1.09)	0.114	
	Radiation + single-agent chemotherapy	19	0.64 (0.32–1.22)	0.193	
	Radiation + multiagent chemotherapy	14	0.50 (0.22–1.02)	0.075	
	Radiation only	2	0.54 (0.11–1.70)	0.372	
	Surgery alone	30	–	–	

Note: Firth's penalized maximum likelihood estimation was used.

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.