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Impact of margin status and lymphadenectomy on clinical outcomes in resected pancreatic adenocarcinoma: implications for adjuvant radiotherapy

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Background: Adjuvant chemoradiotherapy (CRT) in the treatment of pancreatic ductal adenocarcinoma (PDA) is controversial. Minimal data exists regarding the clinical significance of margin clearance distance and lymph node (LN) parameters, such as extent of dissection and LN ratio. We assessed the impact of these variables on clinical outcomes to more clearly define the subset of patients who may benefit from adjuvant radiotherapy (RT).

Methods: We identified 106 patients with resected stage 1-3 PDA from 2007-2013. Resection margins were categorized as positive (tumor at ink), ≤ 1 , or >1 mm. LN evaluation included total number examined (NE), number of positive nodes (NP), ratio of NP to NE (NR), extent of dissection, and positive periportal LNs. The impact of these variables was assessed on disease-free survival (DFS) and overall survival (OS) using multivariate cox proportional hazards modeling.

Results: In patients receiving adjuvant chemotherapy (CT) alone, greater margin clearance led to improved DFS ($P=0.0412$, HR =0.51). Range of NE was 4-37, with a mean of 19. NE was not associated with DFS or OS, yet absolute NP of 5 or more was associated with a significantly worse DFS ($P=0.005$). Whereas periportal lymphadenectomy did not result in improved DFS or OS, patients with positive periportal LN had worse clinical outcomes (DFS, $P=0.0052$; OS, $P=0.023$). The use of adjuvant CRT was associated with improved OS ($P=0.049$; HR=0.29).

Conclusions: In patients receiving adjuvant CT alone, there was a clinically significant benefit to clearing the surgical margin beyond tumor at ink. Having ≥ 5 NP and positive periportal LN led to significantly worse clinical outcomes. The addition of adjuvant RT to CT in resected PDA improved OS. A comprehensive evaluation of resection margin distance and LN parameters may identify more patients at risk for locoregional failure who may benefit from adjuvant CRT.

Keywords: Carcinoma pancreatic ductal; lymph node excision (LN excision); chemoradiotherapy adjuvant (CRT adjuvant); pancreaticoduodenectomy

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Introduction

Pancreatic ductal adenocarcinoma (PDA) carries one of the worst prognoses of all malignant neoplasms. Although its incidence is around 3% among all malignancies, it still resulted in 7% of all cancer deaths in 2014 within the United States (1). Over the last three decades, the survival rates of many cancers have had considerable improvement. However, the survival improvements in pancreatic cancer have been the worst among all malignancies (1). The best clinical outcomes are noted in the 10-20% of patients with resectable tumors, yet even in this cohort, rates of recurrence remain high suggesting increased probability of occult regional and metastatic disease. Whereas metastatic failure predominate and are noted in up to 80% of patients, local recurrence still remains an important clinical consideration representing a component of failure in 50% of patients (2). As a result, various adjuvant strategies involving chemotherapy (CT) with or without radiotherapy (RT) have been investigated over the last few decades. Randomized clinical trials have validated the benefit of adjuvant CT with improved overall survival (OS) relative to no therapy (3,4). The addition of adjuvant RT, on the other hand, has been a point of debate considering the varying and often conflicting results and criticisms of EORTC 40891, ESPAC-1 and GITSG studies (5-8). These findings have prompted others to investigate pathologic variables that may predict patterns of failure and help further define the subset of patients who may benefit from adjuvant RT.

Previous studies have also recognized multiple independent variables that have prognostic significance including tumor staging, lymph node (LN) positivity, lymphovascular and perineural invasion, tumor grade and surgical resection margin involvement (9-12). Indeed, a recent meta-analysis investigating the benefit of adjuvant therapies in PDA suggested that adjuvant chemoradiation may have a clinically relevant benefit among patients with positive resection margin (4). The distance of margin clearance and its impact on local and regional failure rates also has not been clearly established, primarily due to the lack of a uniform definition for what constitutes margin positivity (13). LN involvement is also known to be prognostic and as a result, the extent of lymphadenectomy and LN ratio has been areas of active research and debate (9,14,15). Presently, there is no clear consensus or guidelines on the number of nodes that should be examined during PDA resection, as well as the prognostic significance of number and ratio of involved nodes. Some studies

indicate that pathologic assessment of 12 or 15 nodes would provide the most accurate prognostic information, whereas others do not reveal a correlation between the numbers of nodes assessed and clinical outcomes (9,15,16). Additionally, there is very little data on whether the location of positive LN has any prognostic significance (17-19). Multiple randomized controlled trials have evaluated whether there is a survival benefit with extended resection, and most have not shown any significant survival benefit (20-23). Recent contemporary meta-analyses have also reaffirmed these findings (24,25). However, many of these trials and analyses have not specifically delineated whether periportal LN involvement from extended lymphadenectomy is prognostically relevant.

Herein, we have investigated the prognostic implications of comprehensive LN evaluation as well as surgical margin clearance in patients with resected PDA in order to assess the potential impact on clinical outcomes and their role in better defining the subset of resected patients who would benefit most from adjuvant chemoradiotherapy (CRT).

Definitions

It has been difficult to determine the prognostic significance of margin clearance during PDA resection. This is further compounded by the lack of a consensus definition of what constitutes a positive margin. Since the late 1980s, the R classification has been adapted by the International Union Against Cancer (UICC) (26). Based on these guidelines, resection margins are classified as R0, no tumor at the resection margin, R1, microscopic tumor at the resection margin and R2, macroscopic tumor involvement of margins (27). In 2002, the Royal College of Pathologists, recommended that R1 be reclassified to include the presence of tumor cells within 1 mm of ink (28). To obscure the definition of R classification even further, clinical practice and institutional differences in pathological assessment protocols commonly differ in the application and utilization of the R1 classification till this day (13,29,30). Based upon these general guidelines for the purpose of this study, we categorized resection margins as positive (tumor at ink), ≤ 1 mm from ink, or >1 mm from ink.

On the other hand, pathologic evaluation of LNs has been more uniform. LN positivity is based on pathologic assessment of resected LNs, which show microscopic evidence of tumor. LN ratio (NR) is the number of positive nodes (NP) divided numbers of nodes examined (NE).

Table 1 Patient disease specific characteristics

Variable/characteristic	N	Percentage (%)
Age, mean	68	
Sex		
Male	54	51
Female	52	49
Race		
Caucasian	79	74.5
African American	5	4.7
Asian	11	10.4
Hispanic	11	10.4
Location		
A: uncinate, head neck	90	84.9
B: body, tail	15	14.2
Combined (A + B)	1	0.1
Type of resection		
Pancreaticoduodenectomy	93	87.7
Distal pancreatectomy	13	12.3
T stage		
pT 1	2	1.9
pT 2	10	9.4
pT 3	91	85.9
pT 4	3	2.8
N stage		
pN 0	34	32.1
pN 1	72	67.9
Distance to tumor		
Positive (tumor at ink)	18	17.0
≤1 mm	50	47.2
>1 mm	38	35.8
Adjuvant therapy		
Chemotherapy	51	48.1
Chemoradiation	45	42.5
No adjuvant therapy	10	9.4
Periportal lymphadenectomy		
Yes	25	23.6
No	81	76.4
Periportal lymph nodes		
At least 1 positive lymph nodes	5	20
No positive lymph nodes	20	80

Table 1 (continued)**Table 1** (continued)

Variable/characteristic	N	Percentage (%)
Perineural invasion		
Present	94	92.2
Not present	8	7.8
Lymphovascular invasion		
Present	59	59
Not present	41	41
Tumor grade		
1	17	16.5
2	52	50.5
3	34	33.0

Periportal LNs include those nodes that around the portal vein and hepatic artery.

Methods and materials

With institutional review board approval, we identified 1,545 patients from a prospective cancer database with the diagnosis of PDA and treated at a single tertiary care center since from 1990 to 2014. Of these, comprehensive clinical and pathologic data were retrospectively collected on 106 patients with stage I-III disease who underwent up front pancreaticoduodenectomy or distal pancreatectomy from 2007 to 2014.

Patient and disease specific data were obtained from electronic medical records and included consultation, clinic and procedure notes, endoscopic ultrasound, computed tomography, magnetic resonance imaging and positron emission tomography scans (*Table 1*). Post-operative disease-specific variables included type of adjuvant therapies, time to and location of recurrence, and date of death. Survival data was obtained from Medicare, SSDI, death certificates, physicians, hospice and family notification. Pathology reports of resected tumors were thoroughly analyzed for details of margin and LN involvement. Surgical resection margins were identified for pancreatic, uncinate, bile duct, vascular groove, anterior and posterior margins. The closest margin was recorded. Distance of tumor to ink was categorized as positive (tumor at ink), within 1 mm of ink, or greater than 1 mm from the inked margin. Additionally, LN characteristics included number of resected, positive and negative nodes, LN size and presence of periportal LN

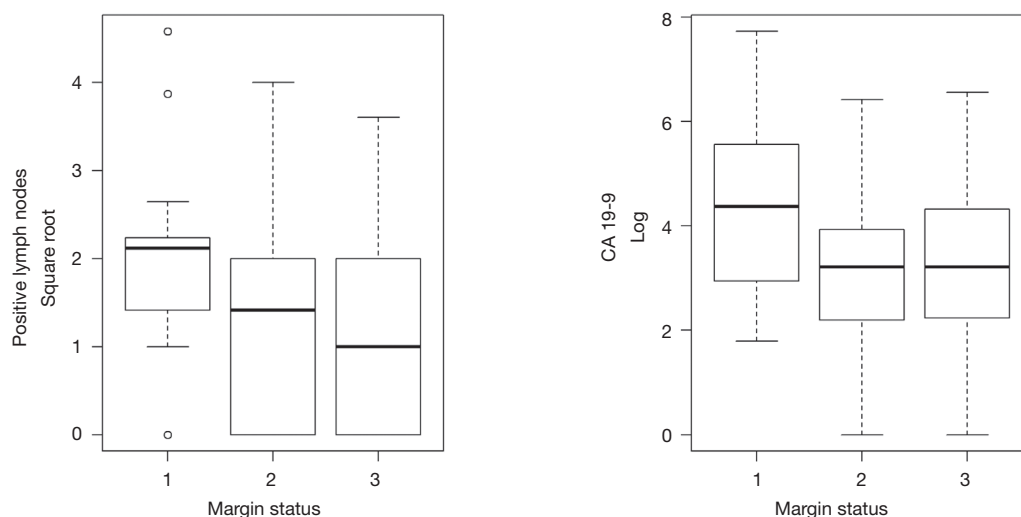


Figure 1 Margin status in correlation with lymph node positivity and CA19-9: margin status is correlated to the log of post-operative CA19-9 and the square root of node positivity. The log and square root are shown to more clearly demonstrate the correlative difference between resection margins (1, tumor at ink; 2, within 1 mm of ink; 3, greater than 1 mm from inked margin).

involvement.

In the first few years, since electronic pathology reports were available, involvement of periportal LN was not documented. Ultimately, twenty-five patients had documented periportal lymphadenectomy and histopathological evaluation of those LN.

All clinical and pathological data was collected and inputted into a new database for statistical analysis.

Statistics

One way analysis of variance (ANOVA) was used to compare the mean values of more than two continuous variables after appropriate data transformation when needed. Fisher's exact test was carried out to test for association between two categorical factors. For time to event data such as OS and disease-free survival (DFS), the log-rank test was used to compare the survival distributions between different groups and the Cox proportional hazards model was used when the predictor was continuous. Multivariable Cox model was also used to adjust for confounders when assessing a predictor of interest. Standard variable selection techniques such as stepwise selection were used in the analysis. Model diagnostics and adequacy was assessed by testing the proportional hazards assumption graphically and analytically, and Martingale and Schoenfeld residuals were used to assess model adequacy.

Results

Median follow up was 11 months (range, 1-78 months). Of the 106 patients identified, 54 were men and median age for entire cohort was 69. Ninety-three patients underwent pancreaticoduodenectomy and 13 underwent distal resections. Resection margins were identified as positive (tumor at ink), ≤ 1 mm from ink, or >1 mm from ink in 18, 50, and 38 patients, respectively. A total of 48.1% of patients received adjuvant CT alone, while 42.5% received CRT and 9.4% received no adjuvant therapy. The median number of LNs resected was 19 (range, 4-37). Periportal LNs were resected in 25 of the 106 patients and were positive in 20%. Analysis of variance demonstrated that margin status was highly correlated with NP ($P=0.012$) and post-resection CA 19-9 ($P=0.017$) (Figure 1). The median disease-free survival (DFS) for the entire cohort was 336 days (11 months) and median OS was 482 days (16 months). Patients with resection margins that were positive, ≤ 1 mm, or >1 mm had a DFS of 9.64, 12.20 and 10.57 months ($P=0.72$), respectively and median OS of 13.15, 15.91 and 16.63 months, respectively ($P=0.15$).

On univariate analysis, NP (HR, 1.34; 95% CI, 1.01-1.79; $P=0.0417$), post-resection CA-19-9 above 90 (HR, 1.26; 95% CI, 1.01-1.58; $P=0.039$) and positive periportal LNs (HR, 5.00; 95% CI, 1.08-23.3; $P=0.039$) resulted in significantly lower median OS. Univariate analysis also showed similar lower median DFS with NP (HR, 1.68;

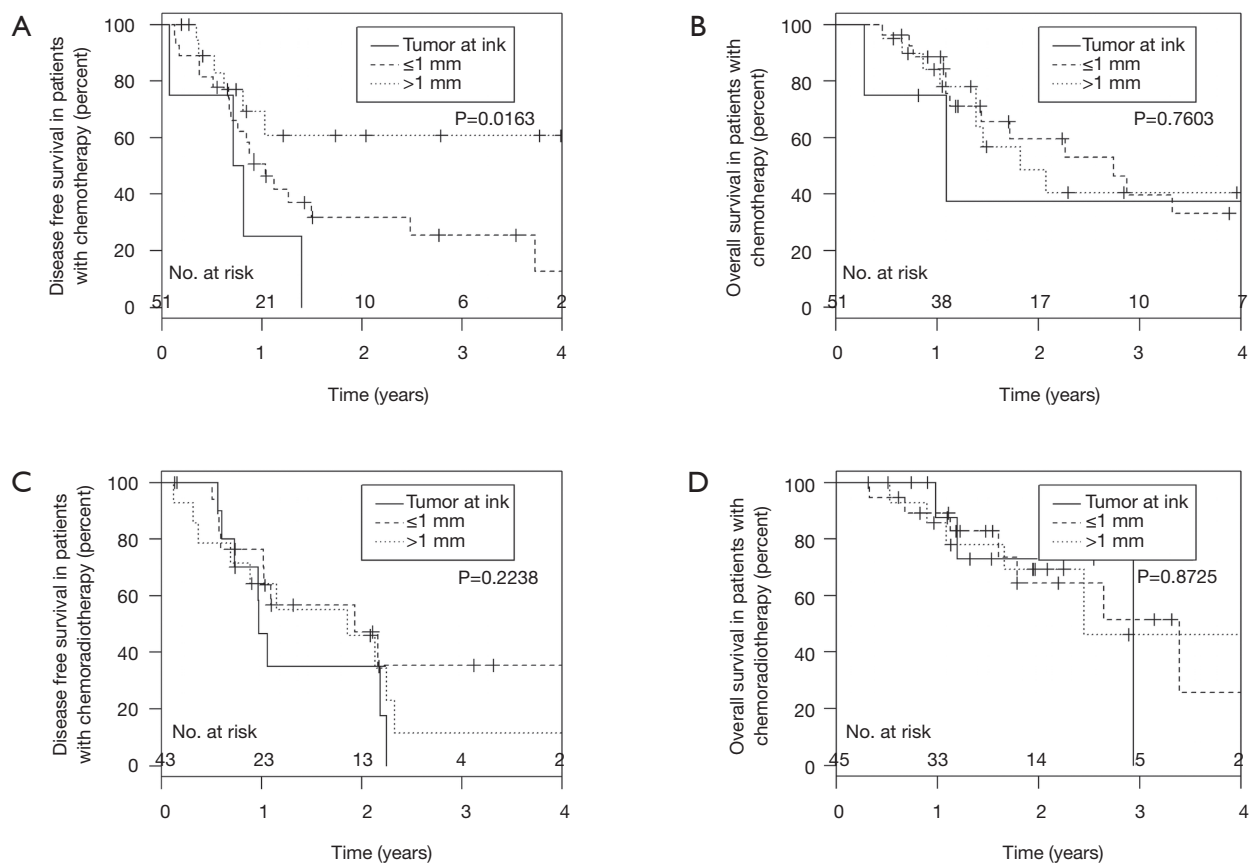


Figure 2 Disease-free survival & overall survival stratified by margin status as a function of adjuvant therapy (chemotherapy alone, A-B; chemoradiotherapy, C-D).

95% CI, 1.32-2.14; $P < 0.001$), post-resection CA 19-9 above 90 (HR, 1.31; 95% CI, 1.09-1.58; $P = 0.0045$) and positive periportal LNs (HR, 5.58; 95% CI, 1.45-21.5; $P = 0.012$). Although univariate analysis did not reveal a significant difference in DFS regarding margin status, there was a trend towards increased DFS as the distance in margin increased from positive (tumor at ink), ≤ 1 to > 1 mm.

Margin status adjusted for NP was a significant predictor of DFS in patients receiving adjuvant CT alone with greater margin clearance leading to improved DFS (HR, 0.31; 95% CI, 0.09-0.99; $P = 0.048$ for ≤ 1 mm, HR, 0.18; 95% CI, 0.05-0.66; $P = 0.01$ for > 1 mm, compared to positive), but did not result in a difference in OS (Figure 2). After controlling for other variables, including NP, the use of adjuvant CRT was associated with improved OS ($P = 0.03$; HR = 0.26; 95% CI, 0.08-0.88) in comparison to patients who received CT alone or no adjuvant therapy (Figure 3).

ROC analysis revealed that ≥ 5 NP to be the most accurate predictor of inferior DFS ($P = 0.005$) (AUC = 0.744).

NE was not associated with DFS or OS, yet absolute NP of 5 or more was associated with a significantly worse DFS on multivariate analysis (HR, 2.5; 95% CI, 1.49-4.47; $P \leq 0.001$; Figure 4). A median NR of 0.11 was associated with inferior DFS ($P = 0.0043$; HR = 4.04), but was not associated with OS. Whereas periportal lymphadenectomy did not result in improved DFS or OS, patients with positive periportal LN had worse clinical outcomes (DFS, $P = 0.0052$; OS, $P = 0.023$) (Figure 5).

Discussion

Given the generally poor prognosis of resected pancreatic adenocarcinoma relative to other resected malignancies, histopathology variables, including microscopic resection margin distance, LN positivity and LN location may be able to provide a prognostic information to help guide the use of adjuvant therapy, particularly RT.

Similar to previous studies, we found that LN positivity

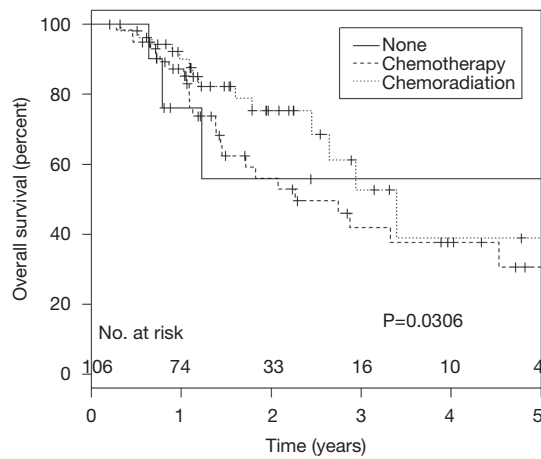


Figure 3 Overall survival comparing various adjuvant therapies: on multivariate-adjusted model comparing no adjuvant therapy, chemotherapy only and chemoradiation.

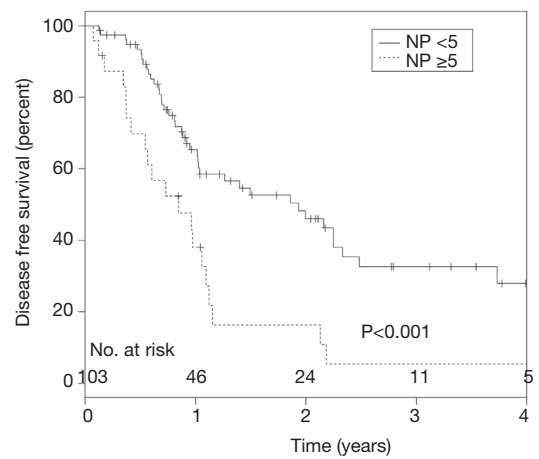


Figure 4 Disease-free survival in patients with five or more positive lymph nodes: on multivariate-adjusted model. ROC analysis determined that five positive nodes were most accurate predictor of survival.

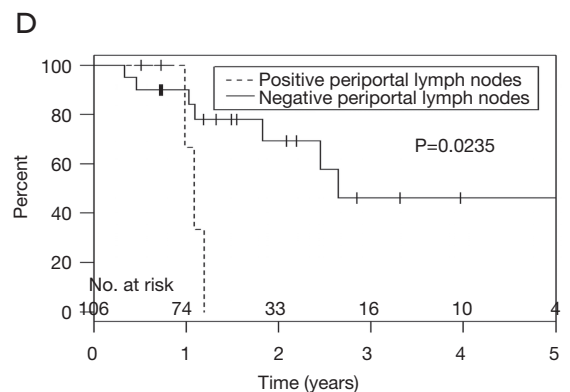
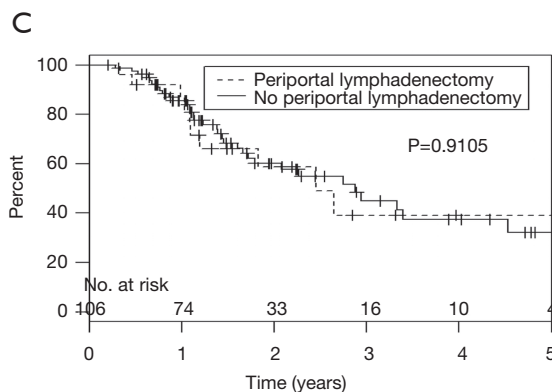
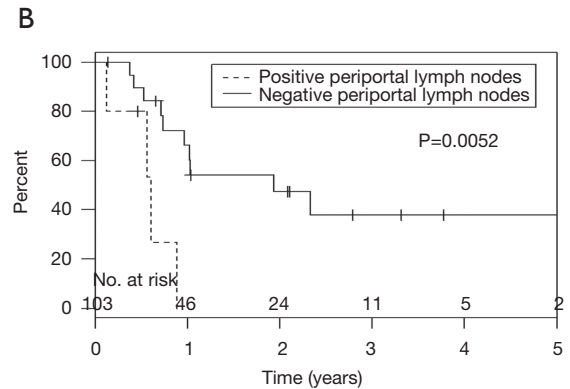
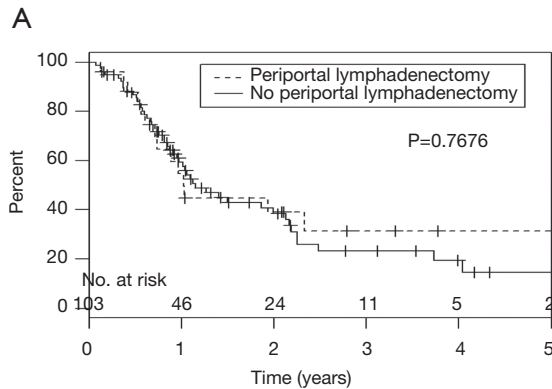


Figure 5 DFS and OS of periportal lymphadenectomy and patients with positive periportal lymph nodes: DFS and OS in patients who underwent periportal lymphadenectomy *vs.* those who did not (A and C, respectively). DFS and OS in patients who underwent periportal lymphadenectomy with positive periportal lymph nodes *vs.* those with negative periportal lymph nodes (B and D, respectively). DFS, disease-free survival; OS, overall survival.

and elevated post operative CA 19-9, individually portend a poor prognosis regarding disease free and OS. However, our study also provides insight into variables less frequently analyzed variables, such as involved periportal lymphadenopathy. Although multiple previous studies (20-25) have assessed clinical outcomes associated with extended lymphadenectomy, none specifically addressed whether the location of involved LNs removed during extended dissection offered prognostic value. Our study similarly concluded that extended dissection does not offer any survival benefit compared to standard dissection as periportal lymphadenectomy did not result in improved DFS or OS. However, contrary to previously reported data, we noted that periportal LN involvement was prognostic of a poor clinical outcome. In our cohort, periportal LN evaluation was limited to 25 % of the patients. In spite of this limitation, the impact of positive periportal adenopathy on OS and DFS was quite significant. No patients with positive periportal LN were alive 1.5 years from diagnosis and DFS did not exceed 12 months. Whereas dissection of periportal LNs as part of pancreaticoduodenectomy remains an area of investigation, our data suggest that reporting of periportal LNs and associated involvement may provide crucial prognostic information. Many potential questions arise regarding the role of adjuvant therapy within this subgroup and we recommend periportal LN involvement be evaluated by larger and more comprehensive studies. Additionally, a standardized approach to evaluating these LNs should be considered.

Comprehensive LN analysis revealed ≥ 5 positive nodes to be the most accurate predictor of inferior DFS when analyzed as a continuous variable. Previous studies have shown a significant linear relationship between survival and up to 8 involved LNs, however the median nodes examined of that cohort was 17, where our median was 19 (9). In spite of this, absolute number of nodes examined was not associated with DFS or OS, mirroring similar results seen in Riediger *et al.* (15). Analysis of LN ratio showed a median of 0.11 was associated with inferior DFS, but did not impact OS.

Degree of margin clearance was an important predictor of DFS, particularly in patients receiving CT. Interestingly, this was not seen in the subgroup of patients receiving RT (Figure 2). A meta-analysis by Stocken *et al.* (4) revealed that CT resulted in improved clinical outcome only in the subgroup of patients with negative resection margins, and this benefit was mitigated in the presence of residual microscopic disease. Chang *et al.* (31) have hypothesized

that the risk associated with local disease burden, in particular following an R1 resection, may not be overcome with CT alone, as this subset experienced clinical benefit following treatment with RT. Similar to our data, these results are further supported by the retrospective series by Herman *et al.* (32) which showed that irrespective of margin involvement, there was no difference in outcomes following receipt of adjuvant 5-FU based RT. Our results also suggest that reporting microscopic margin status at intervals of 1 mm distances may influence prognosis. The trend observed indicates that grouping of R0 and R1 resections according to the UICC definition maybe insufficient to properly stratify patients with PDA. Many previous studies have also had similar difficulty in showing the prognostic significance of R1 resection on both univariate and multivariate analysis (30). It is interesting to note that previous studies reporting resection margins vary vastly in the incidence of R1 resections (20% to 80%) (13). In our cohort, resection margins classified utilizing the Royal College of Pathologists and UICC definitions resulted in R1 resection rates of 64% and 17%, respectively, thereby underscoring the need for a universally accepted and clinically relevant definition of what constitutes a high-risk resection margin (13,30,33).

In our contemporary cohort, we also found that the addition of adjuvant RT to CT compared to those patients who received CT alone showed significant survival benefit. Multivariate analysis with margin status both included and removed in the statistical model provided similar outcomes with regards to OS. Previous meta-analysis (4) looking at the role of adjuvant RT in resected PDA had not shown significant benefit in OS, however they did suggest that among patients with positive resection margins, there was greater benefit of chemoradiation versus CT alone. We had relatively similar numbers of patients that received CT alone and chemoradiation and in our study population as whole, there was a clear clinical survival benefit by the addition of adjuvant RT. In a similar retrospective study by Sohn *et al.* (34) chemoradiation was found to a significant predictor of clinical outcome and mirroring our recent conclusions.

Despite our confirmatory findings and novel results, we recognize that there are limitations to our study. Our analysis was retrospective from a single institution experience. Some patients within our cohort lacked complete follow-up data, though this was small portion of the entire study population. In our evaluation of pathology reports, we found variability regarding the data reported.

It was not until more recent pathological assessments that reporting had become more standardized. This is important because, a larger sample size with consistent margin reporting may reveal an even more significant impact on OS and DFS. Regardless, our study represents a contemporary evaluation of resected pancreatic adenocarcinoma patients and includes a broad analysis of multiple prognostic variables and their interrelationships.

Conclusions

In conclusion, we found that periportal nodal status is a valuable prognostic indicator that requires further investigation. With regards to margin status, we discovered that there is important and relevant clinical difference in evaluating margins at 1mm intervals and that the UICC definition of R1 resection maybe inadequate as a prognostic tool. Our data also suggests that the addition of adjuvant radiation therapy to CT in resected PDA, improves OS and this supports the role of RT in advanced PDA. Furthermore, the variability of resection rates and outcomes among previous studies, including our own, may in large part be due to the lack of a uniform histopathology evaluation protocol and margin resection definition. Our study supports the standardization of pathological evaluation of margin status and LN assessment among institutions. In the future, larger studies utilizing a standardized approach to histopathology evaluation may provide a clearer picture of which variables play a greater role in prognosis and help identify which subset of patients will benefit more from adjuvant CRT.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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