

ORIGINAL ARTICLE

Redefining the R1 resection for pancreatic ductal adenocarcinoma: tumour lymph nodal burden and lymph node ratio are the only prognostic factors associated with survival

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Abstract

Introduction: The presence of positive nodal disease (LND) and the number of lymph nodes involved (LNB) are known to be significant prognostic markers for resected adenocarcinoma of the pancreas. In addition, the ratio of the number of involved nodes to the number of nodes resected known as the lymph node ratio (LNR) is emerging as an important prognostic marker. The role of the resection margin (RM) as presently defined ($R1 \leq 1$ mm) is unclear as results differ based on the dataset. The aim of this study was to assess the impact of nodal disease and a redefined RM on outcome.

Material and methods: Retrospective analysis of pancreatic head resections for adenocarcinomas from 2003–2009. The RM was re-analysed based on tumour clearance and categorized into: histopathological evidence of a tumour; ≤ 0.5 mm, ≤ 1 mm, ≤ 1.5 mm, or ≤ 2.0 mm of the actual surgical resection margin. The impact of histopathological variables on cancer-specific survival (CSS) and disease-free survival (DFS) was analysed.

Results: LND, LNB and LNR were independent prognostic markers for CSS ($P = 0.048, 0.003, 0.016$) but, did not influence DFS. A LNR < 0.143 was associated with a higher CSS [38.16 ± 4.69 versus 20.59 ± 2.20 months, $P = 0.0042$, hazard ratio (HR) 3.74 (95% confidence interval (CI) 1.52–9.23)]. An R1 RM was not associated with CSS or DFS on multivariate analysis, irrespective of the distance. LNB and LNR maintained independent significance irrespective of the size of the RM.

Conclusion: LNB and LNR are the only prognostic factors for CSS in patients with pancreatic head adenocarcinoma, but do not predict recurrence. Microscopic RMs does not seem to influence the outcome even when redefined. Further prospective studies are indicated to substantiate these findings.

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Introduction

The long-term prognosis for patients with pancreatic cancer remains dismal with 5-year survival ranging from 15–25%.^{1–4} A surgical resection offers the best chance for a cure and remains the mainstay of therapy. However, only 10–20% of patients present with resectable disease.^{5,6} Adjuvant chemotherapy has been shown to almost double the 5-year survival after a successful resection.^{7,8} The failure to significantly influence outcome in pancreatic cancer

in contrast to other site cancers reflects a lack of understanding of pancreatic tumour biology.

Numerous studies have evaluated histological parameters that predict outcome after surgery.^{3,4,9,10} While lymph node positivity, tumour stage and grade, microscopic resection margins, lymphovascular and perineural invasion and tumour size have all been associated with a poor outcome, results vary based on the dataset.^{3,4,9–11} Lymph nodal metastases is probably the most consistent factor associated with poor outcome although the exact nature of its association is as yet unclear. Three patterns of this association have been identified: (i) the presence of ≥ 1 involved nodes (LND, lymph node disease); (ii) an increasing number of

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nodes infiltrated by the tumour (LNB, lymph node burden); and (iii) an increasing ratio of the positive to examined nodes (lymph node ratio, LNR).^{1,3,12} The association between lymph nodal metastases and local disease recurrence/disease-free survival (DFS) has not been previously reported.

Although there is little doubt that an incomplete resection portends poor outcome, the significance of the negative resection margin is unclear. Currently, a resection margin >1 mm is considered negative.¹³ Unlike the data supporting the importance of a 1-mm circumferential resection margin (CRM) in rectal cancers,^{14,15} robust scientific evidence is lacking in pancreatic cancers. Further, the significance of a R0 resection in predicting outcome has been variable depending on the dataset analysed.^{3,16–24} It is likely that these outcomes may be influenced by the definition of R0, which may in itself be intrinsically flawed or, may be variably influenced by specific margins in relation to the tumour or, by the size of the study.

The aim of this study was to determine the histopathological variables that influenced the outcome with particular emphasis on the lymph node status and the resection margins (RM). The current definition of an R0 resection was redefined and the influence of specific margin status on DFS and overall survival (OS) was assessed.

Material and methods

Retrospective analysis of prospectively collected data on all patients undergoing a potentially curative pancreaticoduodenectomy for pancreatic ductal adenocarcinoma at the Royal Free hospital, London, UK, from 2003–2009. Data collected included demographic variables, details of surgery, time to recurrence or date of latest clinical review, time to death or latest clinical review and the use of adjuvant therapy.

The pancreaticoduodenectomy specimens were all dissected according to The Royal College of Pathologists (RCP) guidelines.¹³ Margins were inked prior to sectioning with different colours for each margin and the specimen sliced in the axial plane. Six different resection margins were measured microscopically and recorded, namely proximal duodenal (or gastric), distal duodenal, pancreatic, common bile duct, posterior and superior mesenteric (SMV)/ portal vein (PV) groove. A margin of >1 mm was reported as negative (R0). Distance from the tumour to the anterior surface was also noted. Other data included the type, grade and size of the cancer, the total number of nodes within the resected specimen and the total number of nodes involved with cancer. Lymph nodal disease (LND) was defined as the presence of ≥ 1 metastatic nodes, lymph nodal burden (LNB) was the number of nodes infiltrated by a tumour and the lymph nodal ratio (LNR) was the ratio of metastatic nodes to total nodes examined.

All the available histopathological specimens were re-examined by independent pathologists (J.W. and A.I.) to accurately define the R0 status based on tumour clearance and to re-categorize the R1 status based on histopathological evidence of a tumour

≤ 0.5 mm, ≤ 1 mm, ≤ 1.5 mm or ≤ 2.0 mm of the actual surgical resection margin (re-defined status).

All clinicopathological variables were correlated with cancer-specific survival (CSS) and DFS. DFS was based on the diagnosis of local or systemic recurrence identified through a combination of radiological imaging, tumour marker levels and biopsy. Local disease recurrence was confirmed either by biopsy and or the progression of lesions on subsequent follow-up scans. All patients underwent 3-monthly CT scans (chest, abdomen and pelvis) and serum tumour marker (CEA and CA19-9) analysis for at least 2 years after a surgical resection. Hence, all patients that were operated locally but followed up at other centres were excluded to ensure accuracy.

Specific exclusions included patients with adenocarcinoma arising in the background of an intraductal papillary mucinous neoplasm (IPMN), non-cancerous pathology, patients who underwent a total pancreatectomy, patients who died in the peri-operative period or within 30 days of discharge and deaths unrelated to tumour recurrence.

Statistical analysis

All the analysis was done using STATVIEW (SAS Institute Inc., Cary, NC, USA). Descriptive statistics was used to present demographic and treatment-related data. OS and DFS were univariately analysed using the Kaplan–Meier method. The log-rank test was used to compare subgroups. Factors found to be associated with $P \leq 0.1$ on univariate analysis were included in the multivariate analysis. Cox's proportional hazard was used for multivariate analysis. Statistical significance was set at $P \leq 0.05$. Lymph nodal data were analysed as both nominal and continuous variables.

Results

A total of 86 patients identified from the pathological specimen database had undergone a laparotomy for resection of a pancreatic head adenocarcinoma from 2003–2009. Of these, 70 fulfilled all the criteria to be included in the study. Sixteen (19%) patients were excluded: six distal cholangiocarcinomas (incorrect coding), three total pancreatectomies, four periampullary tumours, one peri-operative death and two adenocarcinoma with background IPMN. The clinicopathological characteristics of the cohort and the operation performed are listed in Table 1. The median follow-up period was 19.5 months (range 2.5–101.3). 24/70 (34.3%) were alive at the time of inclusion.

Survival

CSS data were available in all 70 patients. The mean time to death was 22.90 ± 17.40 months (range: 3–101.13). On univariate analysis, the degree of differentiation ($P = 0.031$), lymphovascular invasion ($P = 0.013$), LND (presence of ≥ 1 positive nodes, $P = 0.005$) significantly affected CSS. (Table 2, Fig. 1) LNB ($P = 0.0005$), total nodes examined ($P = 0.034$) and the LNR ($P = 0.018$) were significantly associated with CSS when analysed as

Table 1 Demographic, operative and histopathological variables

Variable	Value	
Median age in years (interquartile range)	65.79 (16.77)	
Gender	Male 35; female 35	
Operation	PPPD	60 (85.70%)
	Whipples	10 (14.30%)
	Vascular resection	11 (15.70%)
Max. tumour size in mm – median (interquartile range)	30.00 (16)	
Differentiation	Well	7 (10%)
	Moderate	37 (52.90%)
	Poor	26 (37.14%)
Surgical margins	R0/R1	R0–18 (25.7%); R1–52 (74.3%)
	Anterior +ve	21 (30%)
	Posterior +ve	32 (45.70%)
	SMV/PV groove +ve	33 (47.10%)
	CBD +ve	2 (2.9%)
	Pancreatic edge +ve	2 (2.9%)
	Perineural invasion +ve	65 (92.90%)
Lymphovascular invasion +ve	38 (54.30%)	
Nodal status	Nodal status +ve	55 (78.60%)
	Median nodes examined	14 (IQR 8)
	Median +ve nodes examined	2.0 (IQR 3)

PPPD, pylorus-preserving pancreaticoduodenectomy; SMV/PV, superior mesenteric/portal vein; CBD, common bile duct.

continuous variables. On multivariate analysis only the LNB, LNR and LND maintained significance ($P = 0.0029$, 0.016 and 0.048 , respectively) (Table 2).

DFS was determined in 34 patients in whom all data were available. The mean time to recurrence was 9.89 ± 7.54 months (range: 1.27–58.35). On univariate analysis, lymphovascular invasion ($P = 0.022$) and positive lymph node status ($P = 0.016$) significantly affected DFS (Table 2).

Receiver-operator curve (ROC) analysis was used to determine the association between the LNR and CSS based on mortality during the study period. The best cut-off for LNR with regards to survival was determined at 0.143 (area under curve = 0.730). Patients with a LNR < 0.143 had a significantly higher survival than those with a higher LNR both on univariate and multivariate analyses [38.16 ± 4.69 versus 20.59 ± 2.20 months, $P = 0.0042$, hazard ratio (HR) 3.74 (95% CI 1.52–9.23)] (Fig. 1). There was no significant difference in the total number of examined nodes between these two groups ($P = 0.81$).

RM status and survival

The overall R0 resection rate based on the RCP guidelines was 25.7%, and was significantly associated with OS ($P = 0.015$) on univariate but not on multivariate analysis ($P = 0.84$). No association was found with DFS. The SMV/PV groove margin was the

most common resection margin involvement (Table 1). A significant correlation was found between lymph node and margin positivity [$P = 0.01$, OR4.50 (95% CI 1.3–15.70)]. However, subgrouping patients into node negative and node positive groups did not reveal any significant correlation between resection margin status and CSS (Table 5).

Redefining the RM status demonstrated a significant association with OS for completeness of resection (R0), and for the specific margins involving the PV/SMV groove and posterior resection margin for all groups (0.5, 1, 1.5 and 2 mm) (Table 3). However, these were not maintained on multivariate analysis.

Multivariate regression analysis confirmed that the LNR and LNB maintained their independent influence on CSS irrespective of the chosen cut-off for what was considered to be completeness of resection in all groups, whereas lymph nodal status maintained significance only for a RM status ≤ 1 and 1.5 mm (Table 4).

Discussion

This study reaffirms the adverse prognostic effect of lymph nodal metastases on survival after a pancreatic head resection for ductal adenocarcinoma. This study has shown that LND, LNB and LNR independently influence outcome. However, these findings are not entirely consistent with previous studies and opinion is still guarded as to the exact nature of the relationship between lymph nodal metastases and outcome.^{1,3,12}

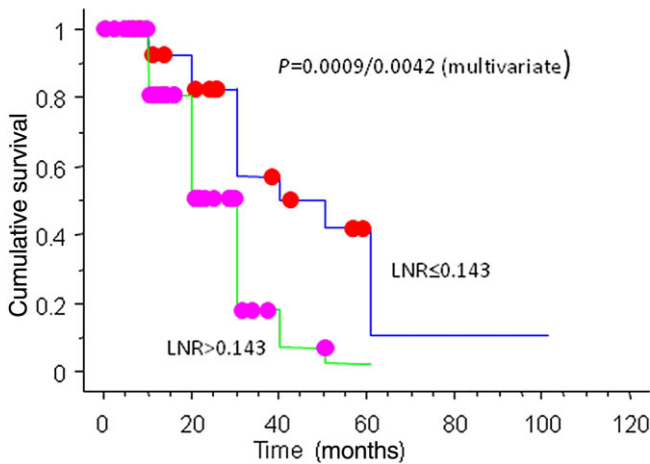
A number of retrospective studies have analysed the relationship between survival and extent of lymph node assessment after resection of pancreatic tumours.^{1,12,25} An inadequate surgical lymphadenectomy or pathological assessment would understage patients owing to the potential of missing metastatic nodes. A large review of 1666 patients within the Surveillance, Epidemiology and End results (SEER) database for pancreatic cancer suggested that an attempt to harvest and resect at least 15 lymph nodes was essential for accurate staging.²⁶ Higher nodal yields were not associated with significant survival differences at any stage.²⁶ Similarly, a study by the Memorial Sloan–Kettering Cancer Centre group showed that a lymph node harvest of 12 nodes provided accurate survival estimates in patients with node negative disease.¹ The median nodes examined in this study was 14 (IQR 8) and, unlike the SEER database study, there was no significant difference in the total number of nodes examined between the nodes positive and nodes negative group [median 15.0 (range: 3–49) versus 10.0 (range: 4–25); $P = 0.140$].

It has been suggested that the use of LND alone or LNB may carry the bias of an inadequate lymphadenectomy or histopathological examination. Previous studies in both colorectal and gastric cancer have shown that a ratio-based classification of lymph nodes was far superior to LNB and LND in predicting survival.^{27–29} The same seems to be true for pancreatic tumours where the LNR is emerging as the candidate marker for prognosis as opposed to the LND or LNB.^{1,12,25} These data showed that a LNR ≥ 0.143 was associated with reduced survival [HR 3.74 (95%

Table 2 Impact of demographic, surgical and histopathological variables on survival

Variables	Overall survival			Disease-free survival			
		Median OS (IQR) – mths	Univariate P-value	Multivariate P-value	Median OS (IQR) – months	Univariate P-value	Multivariate P-value
Gender			0.618			0.819	
Vascular resection			0.674			0.678	
Type of reconstruction			0.754			0.844	
Tumour size			0.13			0.955	
Differentiation (Binomial Variable)	Well/Mod	18.57 (16.65)	0.031	0.161	7.42 (6.37)	0.06	0.30
	Poorly	13.53 (19.68)			6.08 (6.08)		
Neural invasion			0.973			0.631	
Lymphovascular invasion	–ve	24.26 (26.56)	0.013	0.631	8.3 (13.1)	0.022	0.155
	+ve	16.37 (15.65)			7.42 (7.0)		
SMV/PV groove invasion	–ve	19.57 (27.98)	0.065	0.167		0.363	
	+ve	14.47 (18.84)					
Resection status (R0/R1)	–ve	22.43 (28.53)	0.015	0.840		0.301	
	+ve	16.30 (18.48)					
Ant. margin status			0.275			0.838	
Post. margin status	–ve	18.57 (22.58)	0.062	0.652		0.012	0.292
	+ve	16.30 (17.78)					
CBD margin			0.762			0.507	
+ve lymph node status	–ve	26.13 (32.26)	0.005	0.048	10.34 (17.52)	0.016	0.075
	+ve	16.30 (16.27)			7.10 (6.80)		
Lymph node ratio (LNR)*			0.018	0.016		0.287	
Lymph node burden (LNB)*			0.0005	0.0029		0.207	
Total nodes*			0.034	0.106		0.444	

CBD, common bile duct; LNR, lymph node ratio; LNB, lymph node burden.



Months	0	12	24	36	48	60
LNR ≤ 0.14	28	22	13	8	5	1
LNR > 0.14	42	30	11	3	1	0

Figure 1 Influence of the lymph node ratio (LNR) stratification on overall survival (OS) – Kaplan–Meier survival curves and the numbers at the risk table

CI 1.52–9.23)]. Unlike this study, an association between LNB and LND has not been a consistent finding in previous studies, and this disparity can be explained as a result of a number of clinical and pathological differences in the datasets.^{1,3,4,9,10,12} As it stands, LNR appears to be the most consistent marker for stratification of prognosis.

The majority of reported series have included tumours not confined to the head of the pancreas, tumours other than ductal adenocarcinomas, and above all there appears to be a huge difference in the reporting of a resection margin status suggesting inconsistent reporting of histopathological specimens.^{1,12,16,25,30–32} The large population-based study by Slidell *et al.* included histological variants such as adenosquamous and signet ring cell carcinomas; the biology of these are likely to differ influencing the outcome.³² Numerous other studies reporting on lymph nodes included resections for tumours in the head, body and tail, requiring anatomically varied resections. Their patterns of spread are different, as are their outcomes.^{1,12,25,29} Such confounding variables have been eliminated in this dataset. Unlike previous studies, this dataset included a homogenous population of patients with primary adenocarcinoma of the head of the pancreas who have undergone a pancreaticoduodenectomy alone.

Table 3 Impact of varying the resection margin (RM) status on cancer-specific survival (CSS) and disease-free survival (DFS) (re-reported specimens)

Margin value (mm)	Margin site	OS		DFS	
		Univariate P-value	Multivariate P-value	Univariate P-value	Multivariate P-value
≤0.5	Ant. margin	0.708		0.837	
	Post. margin	0.196		0.097	0.683
	SMV groove	0.051	0.130	0.156	
	R0/R1	0.064	0.846	0.670	
≤1.0	Ant. margin	0.275		0.838	
	Post. margin	0.062	0.652	0.012	0.292
	SMV groove	0.065	0.167	0.363	
	R0/R1	0.015	0.840	0.301	
≤1.5	Ant. margin	0.163		0.461	
	Post. margin	0.087	0.486	0.066	0.963
	SMV groove	0.062	0.115	0.536	
	R0/R1	0.016	0.810	0.267	
≤2.0	Ant. margin	0.179		0.575	
	Post. margin	0.11		0.106	
	SMV groove	0.031	0.093	0.544	
	R0/R1	0.007	0.54	0.262	

OS, overall survival.

Table 4 Influence of the redefined resection margin status on the association between lymph nodal positivity (LNP), lymph node burden (LNB), lymph node ratio (LNR) and cancer-specific Survival (CSS)

Resection margin (R0 defined as under)	LNP Multivariate P-value	LNB Multivariate P-value	LNR Multivariate P-value
≤0.5	0.105	0.007	0.032
≤1.0	0.048	0.0029	0.016
≤1.5	0.041	0.003	0.010
≤2.0	0.156	0.004	0.018

The redefined resection margins significantly impacts CSS on univariate analyses (Table 3). This along with other significant factors (Table 2) has been incorporated in the multivariate model to assess whether the Lymph node status retains significance irrespective of the redefined margins.

A recent study by Murikami *et al.* factored in the role of adjuvant chemotherapy and showed that LNB and lymph node positivity status predicted outcome, but not LNR.³³ A key contributor to their observations may have been the fact that an extended lymphadenectomy was performed in the vast majority of their patient cohort (mean number of nodes examined was 29), perhaps allowing a better nodal staging of the disease. As the chemotherapy practice was variable, we could not include data in our analysis. Randomized controlled trials have confirmed the positive effect of chemotherapy on survival and is likely to influence the results.^{8,19}

This study also shows that lymph nodal metastasis is not a marker for early recurrence as evidenced by the lack of an association between LND, LNB and LNR, and DFS. This finding assumes significance as most previous studies reporting on the prognostic significance of lymph nodes take into account the CSS but not DFS. As routine surveillance does not improve outcome even if metastases are detected early, estimation of DFS is often inaccurate. Owing to our surveillance policy of 3 monthly CT scanning even in patients not receiving adjuvant therapy, we could determine DFS. However, the numbers were significantly smaller than those analysed for CSS owing to our referral practice. This lack of an association between lymph nodal status and DFS suggests that patients with lymph node metastases do not recur earlier than those without, but once recurrence occurs they succumb faster. This could result from differences in tumour biology, differential sites of metastases or possibly the tendency of these tumours to de-differentiate as recurrence manifests. It would be interesting to compare the sites of recurrence in these groups of patients. We acknowledge the limitations of our study in that the dataset for the DFS group is significantly smaller than the CSS group and hence, the possibility of a type2 error.

Previous studies have shown a variable effect of the RM on survival. Differences in pathological reporting, surgical technique, definition of positivity and group stratification affects outcome analyses.³⁴ Additionally, margin positivity has not been shown to be significant on multivariate analysis in a number of studies.³⁴ Campbell *et al.* reviewed the histology of 128 patients undergoing a pancreatic resection for adenocarcinoma reported

as having an R1 resection.³⁵ Of these, 57 (45%) were based on equivocal margins (tumour involvement within 1 mm of, but not directly reaching, one or more resection margins). There was no difference in survival between the equivocal and unequivocal groups. All R1 resections had a poorer survival as compared with R0 resections on univariate but not on multivariate analysis. Menon *et al.* demonstrated that R1 resections adversely affected survival on univariate analysis alone.³⁶ R0 resection rates of 15–30% is noted in centres that use the RCP guidelines for pathological reporting; the rate in this study is 25.7%.^{36,37} In contrast, the reported R0 resection rates from the US are much higher (55–85%) suggesting a difference in pathological staging standards.^{1,12,25,31} In spite of these differences in pathological reporting, RM status was not associated with survival on multivariate analyses in any of these studies. This would suggest that the RM is not a significant prognostic factor for survival. Interestingly in our dataset, there is a significant correlation between lymph node and margin positivity ($P = 0.001$). Further 78% of this dataset had positive lymph node disease. This could suggest that lymph node positivity has a stronger influence on outcome as compared with RM status. When the RM in node negative patients alone was examined no significance was found in the outcome between R0 and R1 resections on univariate analysis (Table 5). However, the numbers were too small for any meaningful interpretation of and the chance of a type2 error is highly likely.

Redefining the resection margin did not impact the prognostic significance on multivariate analysis. Incorporating the margin status into a multivariate analysis showed that the LNR and LNB maintained their significance throughout all margin sizes, whereas the lymph nodal positivity status was variable depending upon the margin cutoff. This suggests that the LNR and LNB are better prognostic indicators than the RM.⁴

Conclusion

This study is the first report to demonstrate a clear and independent association of tumour lymph node burden and the LNR with OS irrespective of the resection margin status as it stands currently or, if redefined. The presence of LND did not seem to affect DFS. However, the small size of the study and the lack of chemotherapy data might significantly influence the results. Hence, large

controlled prospective studies to define the exact relationship between lymph nodes and RM, and outcome are indicated.

Conflicts of interest

None declared.

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Table 5 Impact of the resection margin (RM) status on cancer-specific survival (CSS) among node -ve and node +ve patients analysed individually

Nodal status	Number of patients (%)	R0/R1 status [Number of patients (%)]		Impact of R0/R1 status on CSS (P-value)
		R0	R1	
Negative	15 (21.5)	7 (53)	8 (47)	0.20
Positive	55 (78.5)	11 (20)	44 (80)	0.80

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