Research Article

Prognostic role of metastatic lymph node number and lymph node ratio in ampullary adenocarcinoma.

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Abstract

Background: The role of the metastatic-to-resected lymph nodes ratio (LNR) and the metastatic lymph node number (LNN) in the staging of ampullary carcinoma (AC) is controversial. This retrospective study evaluates the impact on survival of LNN and LNR in resected AC.

Methods: One-hundred patients who underwent pancreaticoduodenectomy with standard lymphadenectomy for AC were categorized into N1 (1-2 metastatic LNs) or N2 (≥3 metastatic LNs) and into LNR ≤0.056 or LNR>0.056 groups. Kaplan-Meier survival curves and multivariate analysis of prognostic factors were assessed.

Results: Median overall survival was 90, 36 and 36 for N0, N1 and N2 (p=0.014) and 85 and 35 months for LNR≤0.056 and LNR>0.056 (p=0.006). Median DFS was Not Reached (*NR*), 33 and 13 months for N0, N1 and N2 (p<0.001), and *NR* and 17 months for LNR≤0.056 LNR>0.056 (p<0.001). Independent prognostic factors were LNR>0.056 (HR 1.99; p=0.029), R1 margins (HR 2.4; p=0.042) and adjuvant chemotherapy (HR 1.76; p=0.044) for OS; LNN (HR 3.03 and 5.03 for N1 and N2; p=0.003), LNR>0.056 (HR 2.07; p=0.048), and tumor size ≥2cm (HR 2.73; p=0.018) for DFS.

Conclusions: Both LNR>0.056 and increasing LNN (1-2 and ≥3) should be considered in the staging of AC, as they are independent predictors of worse prognosis.

Key words: Ampulla of Vater Adenocarcinoma; lymph node ratio; TNM staging; metastatic lymph node.

INTRODUCTION

Ampullary carcinomas (AC) are rare entities that represent 0.2% of all gastrointestinal malignancies and 7% of periampullary tumors(1). AC are defined as those unequivocally originating from the anatomical structures forming the ampulla of Vater and are classified according to the World Health Organization (WHO) classification of pancreatic tumors(2). The standard of treatment is pancreaticoduodenectomy with lymphadenectomy and after resection patients with AC have a more favorable survival than other histotypes of periampullary carcinomas and pancreatic ductal adenocarcinoma(3). Among AC, the pancreaticobiliary histotype has worse survival rates than the intestinal type, although because of their frequent histological heterogeneity the clinical relevance of the histological classification is still controversial(4). The AJCC 7th Edition recommends the retrieval of a minimum of 12 lymph nodes (LNs) to adequately staging the disease(5).

Known prognostic factors are tumor size, extent of local invasion, lymph node involvement, vascular and perineural invasion, cellular differentiation, and involvement of surgical margins (R1)(6–9). More recently, new focus was put on the role of the number of metastatic lymph nodes (LNN) and the metastatic to total resected lymph nodes ratio (LNR)(10–16). The TNM staging system distinguishes between node-negative (N0) and node-positive (N1) disease. Chen et al showed that the independent prognostic factors among the various node-associated variables were nodal status and total number of harvested lymph node(17). Kang et al.(18) in 2014 proposed to modify the current N classification into a 3-tier staging system based on LNN, as this correlated inversely with survival and set the cut-off points at 0, 1 to 2 and 3 or more metastatic LNs. In 2015, Balci et al.(19) confirmed the prognostic value of LNN on a validation series, and found a correlation with lymphovascular and perineural invasion, the size of the tumor and R1. On the contrary, Pawlick et al.(20) found that the LNR was the most compelling predictor of survival compared to LNN and Hsu et al.(16) identified a LNR cut-off significantly associated with poorer outcome.

There remains a paucity of evidence in the literature regarding the role of LNN and LNR in AC. This study aimed to assess the prognostic value of LNN and LNR in a large retrospective series of patients undergoing pancreaticoduodenectomy for AC.

MATERIALS AND METHODS

Study population

All consecutive patients who underwent pancreaticoduodenectomy with standard lymphadenectomy for AC from 1998 to 2015 at Royal Marsden Hospital, London were included. The study was approved by the Institutional Review Board.

Data were retrospectively extracted from a prospective departmental database. Demographics and clinical characteristics included age, sex, presentation with jaundice, neoadjuvant and adjuvant therapy. Intraoperative characteristics included operation type, duration and blood losses, staging laparoscopy, 30-day mortality and postoperative complications. Pathological characteristics retrieved were tumor size, histotype, grade of differentiation, T stage, perineural invasion, the number of resected LNs and the number of metastatic LNs and surgical margins.

The cohort was categorized according to nodal status as node negative (N0) and node positive (N+). Two subgroup analyses were also conducted, using the classification published by Kang(18) and Hsu(16), respectively. In the first one, the node-positive cases were divided according to the LNN into 2 groups: N1 (1-2 metastatic LNs) or N2 (≥3 metastatic LNs). In the second one, all patients were divided into 2 groups according to LNR: LNR ≤0.056 and LNR>0.056.

AC were defined according to the World Health Organization (WHO) classification of pancreatic tumors(2). For the cases resected after 2009, the pathological staging used was the TNM classification UICC 7th Edition(5). Prior to this date previous TNM versions were used. R1 resection was defined as tumor within 1 mm of the resection margin(21). Postoperative complications were graded according to the Clavien-Dindo classification(22). The severity of pancreatic fistula was defined according to the ISGPS definition(23). In-hospital mortality was defined as mortality within 30 days of surgery. All patients were staged with a preoperative computed tomography (CT) with or without PET scan to exclude the presence of metastatic disease and were followed up after resection every 6 months up to five years.

Statistical analysis

Demographics, clinical and pathological characteristics were presented as median and IQR or frequencies.

Primary outcomes were overall survival (OS) and disease free survival (DFS). The impact of nodal status, LNN and LNR on OS and DFS was assessed. OS was defined as time from date of surgical resection to death of any cause. DFS was measured from date of surgical resection to date of recurrence. Patients without an event were censored at last follow up. Kaplan-Meier survival curves were constructed and compared across the LNN and LNR categories. Cox regression method (Hazard ratios and 95% CI) was used to compare the survival and recurrence rates between the LNN and LNR defined subgroups. Multivariable analysis was performed including all

Table 1. Cohort characteristics.

Characteristic	*Number (% or median)*
Age (years)	65 (56 – 71)
Gender	
Male	49 (49%)
Female	51 (51%)
Jaundice	76 (76%)
Preoperative stenting	61 (61%)
Tumour size (cm)	2.5 (1.5 – 3.1)
<2cm	26 (33%)
≥2cm	53 (67%)
LN retrieved	14 (9 – 19)
LN involved	1 (0 – 3)
Differentiation	
Well	12 (12%)
Moderately	45 (45%)
Poorly	43 (43%)
T staging	
T1	12 (12%)
T2	31 (31%)
T3	34 (34%)
T4	23 (23%)
N staging	
N0	38 (38%)
N1	62 (62%)
Perineural invasion	49 (49%)
Operation	
Whipple's	32 (32%)
PPPD	67 (67%)
Total pancreatectomy	1 (1%)
Staging laparoscopy	24 (24%)
Vascular resection	3 (3%)
Resection margin	
R0	89 (89%)
R1	11 (11%)
30-day Mortality	1 (1%)
ICU length of stay (days)	3 (2 – 5)
Postoperative complications	41 (41%)
Dindo-Clavien grade	
<3	32 (32%)
≥3	9 (9%)
Neoadjuvant chemotherapy	1 (1%)
Adjuvant chemotherapy	54 (54%)
Adjuvant radiotherapy	7 (7%)

variables with p<0.10 (one-tailed) at the univariate level. A *P* value <0.05 was considered as statistically significant. As LNN and LNR are inter-correlated, they were fitted in two separate multivariable models. In case of postoperative death within 30 days the patients were excluded from survival

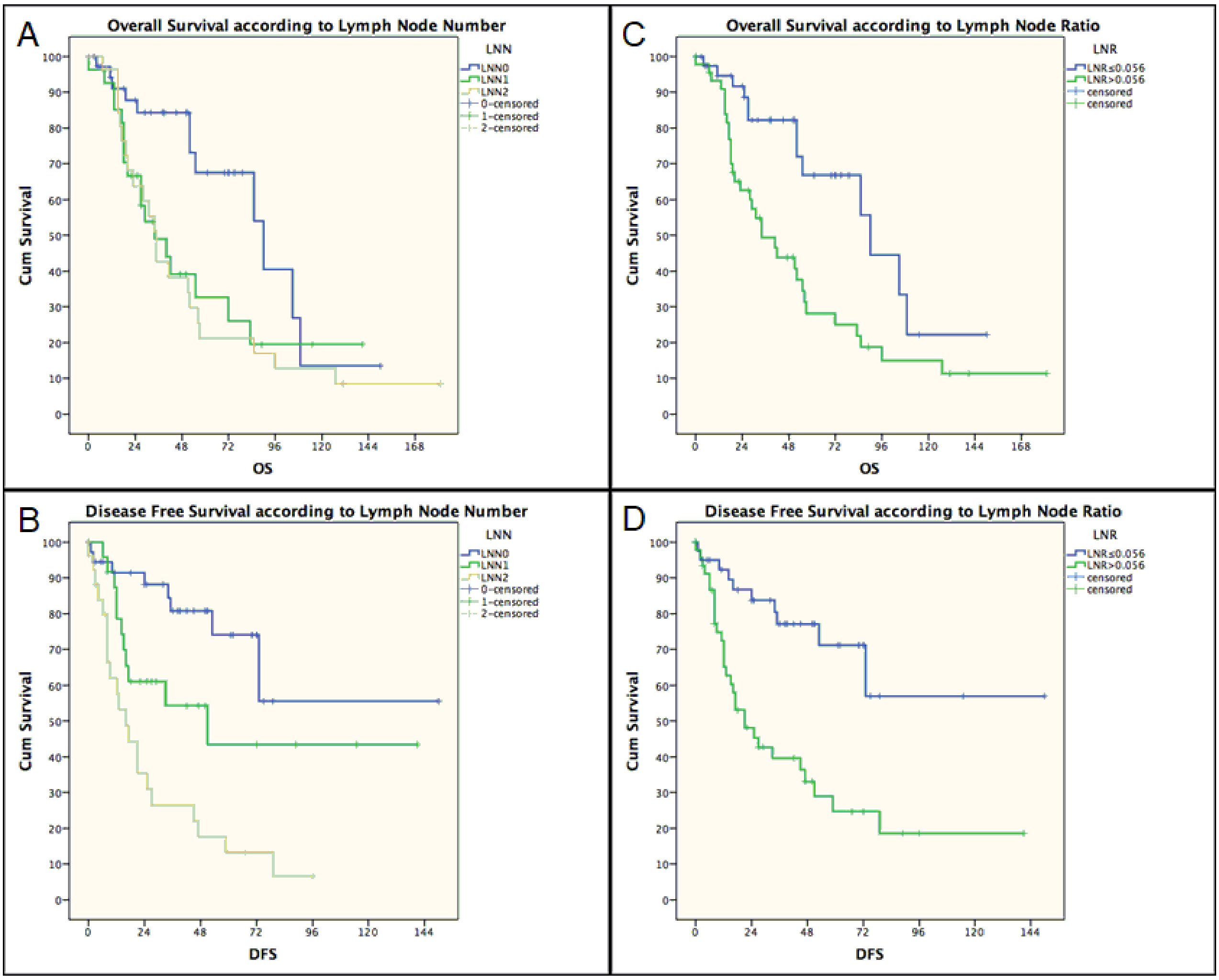

Figure 1. Kaplan Meier Curves for overall survival: patients stratified with LNN 0, N1 or N2, $p=0.014$ (A) and LNR ≤0.056 or >0.056, $p=0.006$ (C). In A there is no statistical difference between the curves N1 and N2 ($p=0.83$). Kaplan Meier Curves for disease free survival: patients stratified with LNN 0, N1 or N2, $p=0.000$ (B) and LNR ≤0.056 or >0.056, $p=0.000$ (D). The curves N1 and N2 are statistically different ($p=0.011$).

analysis. All calculations were done with IBM SPSS Statistics 20 software.

RESULTS

Clinicopathological characteristics

Overall, of 106 patients who underwent pancreaticoduodenectomy with standard lymphadenectomy for an ampullary lesion, 4 patients were excluded because the data were not complete and two patients because the pathological examination showed a benign ampulloma with no foci of invasive adenocarcinoma.

Demographics, clinical and pathological characteristics are shown in table 1. Median age at presentation was 65 and 51% of patients were female.

One patient presented with obstructive jaundice and cholangitis. The work up included a PET-CT which showed a small uptake within the liver, doubtful for metastasis or a liver abscess. In order to assess the cancer biology, he received neoadjuvant chemotherapy and he did not progress on re-staging therefore he underwent a surgical triage. An intraoperative liver biopsy with frozen section ruled out a metastasis and the patients proceeded with resection.

All procedures were performed by one of three experienced hepatopancreatobiliary surgeons. In a quarter of patients, the first step was a staging laparoscopy, which did not preclude resection. Major vascular resection was required in three patients: two cases of portal vein involvement were resected with primary closure not requiring interposition graft and a replaced right hepatic artery which required an end-to-end reconstruction. Complete resection (R0) was achieved in 89% of patients and 11 patients had microscopic positive surgical margins (R1).

Postoperative complications were observed in 41 patients and 12 patients developed a pancreatic fistula. Of these, 3 were grade C[23]. Nine cases were graded III-IV as per Dindo-Clavien: five patients had a percutaneous drainage of intraabdominal collection and one was reoperated for biliary leakage. Three patients required ICU level care for management of cardiorespiratory complications. One patient died within 30 days following the development of a grade C pancreatic fistula with sepsis and multiorgan failure.

The histotype was adenocarcinoma in all cases and a mucinous differentiation was seen in 5 patients. Median tumor size was 2.5 cm (range 1.5 – 3.1). Twenty-six (33%) patients had a tumor size <2cm and 53 (67%) ≥2cm. Pathology examination showed that 57% of patients had a high T stage (3 or 4) and 88% had a moderate or poorly grade of differentiation.

Nodal metastasis was present in 62 cases (62%). The median number of LNs involved and examined was 1 (0 – 3) and 14 (9 – 18), respectively. Dividing the cohort in patients operated prior and after 2007, there was an increase in the median number of harvested LNs from 11 (IQR 9 – 15) to 16 (IQR 10 – 23) which was statistically significant (p=0.000).

Fifty-two patients received adjuvant chemotherapy: Gemcitabine alone (n=26), Gemcitabine in a combination protocol (n=13) and non-Gemcitabine scheme (n=13). Of these, 34 patients had recurrence of disease. Radiotherapy was used as adjuvant treatment in 7 patients. Among the patients who did not receive adjuvant chemotherapy, 28 were node-negative and R0 resection, so the MDT assessment did not recommend adjuvant treatments. Among the remaining patients, eight had postoperative complication or a performance status which contraindicated further systemic treatments and 3 patients received radiotherapy only.

Overall, 51 patients out of 100 developed recurrence. Local recurrence was observed in 23 node-positive patients (out of 42 recurrences) and in 7 node-negative patients (out of 9 cases of recurrence). In the latter, only one patient had positive microscopic resection margin.

Impact of Number of metastatic lymph nodes (LNN) on survival

Thirty-eight out of 100 cases were node-negative (N0). Among the 62 node-positive cases, 28 patients were classified as N1 and 34 patients as N2. The median survival times for these groups are shown in Figure 1. Median OS was 90 months (95% CI 78.5 – 101.5) for N0, 36 months (95% CI 20.4 – 50.6) for N1 and 36 months (95% CI 23.9 – 46.0) for N2. Kaplan Meier survival curves were significantly different when compared to N0 (p=0.014) but not between N1 and N2 (p=0.83). The median DFS was Not Reached (*NR*) for N0, 33 months (95% CI *NR* – 69.4) for N1 and 13 months (95% CI 8.7 – 17.2) for N2 (p<0.001). For DFS, Kaplan Meier survival curves maintained a significant difference between N1 and N2 (p=0.01).

Impact of Lymph node ratio (LNR) on survival

Dividing the cohort of 100 patients according to LNR, 42 patients were LNR≤0.056 and 58 were LNR>0.056. Median OS was 85 months (95% CI 62.7 – 107.2) and 35 months (95% CI 25.5 – 44.4) respectively for LNR≤0.056 and LNR>0.056 (p=0.006). Median DFS was *NR* for LNR≤0.056 and 17 months (95% CI 9.1 – 24.8) for LNR>0.056 (p<0.001).

To avoid the influence of incomplete resection on survival, all Kaplan Meier curves were repeated after exclusion of patients with R1 margin, and the results did not differ significantly from the previous analysis including the entire cohort (Supplementary figure 1).

Univariate and multivariate analysis.

The variables significantly associated with decreased OS and DFS at univariate analysis, shown in Table 2, were included in the multivariable analysis fitting two models for LNR and LNN (Table 3 and 4).

In the first model (LNN), the independent prognostic factor for worse OS was the presence of R1 margins (HR 2.4; 95% CI 1.03 – 5.6; p=0.042). The LNN showed a borderline statistical significance

Table 2. Univariate analysis of risk factors associated with Overall Survival and Disease Free Survival.

Factors	*Univariate OS*			*Univariate DFS*		
	Median	95% CI	*P* Value	Median	95% CI	*P* Value
Age			0.78			0.23
<65 (n=45)	55	48.3 – 61.7		33	19.7 -46.2	
=65 more (n=54)	55	35.6 – 74.3		59	18.5 – 99.4	
Gender			0.18			0.91
Male (n=49)	85	47.8 – 122.1		47	25.2 – 68.7	
Female (n=51)	41	25.0 – 56.9		33	2.0 – 63.9	
Tumour Size			0.2			**0.007**
<2 cm (n=26)	90	18.3 – 161.6		-	-	
≥2cm (n=53)	35	21.2 – 48.7		19	1.7 – 36.3	
Differentiation			0.7			0.55
Well (n=92)	55	27.9 – 82.1		45	12.8 – 19.8	
Moderately (n=5)	52	1.1 – 102.9		24	9.8 – 4.6	
Poorly (n=3)	-			-	-	
N staging			**0.004**			**0.000**
Negative (n=38)	90	78.5 – 101.5		-	-	
Positive (n=62)	35	25.9 – 44.1		16	11.5 – 20.5	
Surgical margins			**0.003**			**0.000**
R0 (n=88)	56	39.8 – 72.2		53	28.9 – 77.0	
R1 (n=11)	35	25.9 – 44.0		9	8.0 – 9.9	
Perineural Invasion			**0.018**			**0.000**
No (n=50)	85	45.9 – 124.1		-	-	
Yes (n=49)	35	23.7 – 46.2		15	11.3 – 18.7	
Adjuvant chemotherapy			**0.025**			**0.001**
No (n=45)	83	38.7 – 127.3		73	-	
Yes (n=52)	35	8.7 – 61.2		16	9.4 – 22.6	
LNR			**0.006**			**0.000**
≤0.056 (n=42)	85	62.7 – 107.3		-	-	
>0.056 (n=58)	35	25.5 – 44.5		17	9.1 – 24.8	
LNN			**0.014**			**0.000**
N0 (n=38)	90	78.5 – 101.5				
N1 (n=28)	35	19.4 – 50.6		33	NR – 69.4	
N2 (n=34)	35	23.9 – 46.0		13	8.8 – 17.2	

Abbreviations: Metastatic to total resected Lymph Node Ratio (LNR); Lymph Node Number (LNN); Hazard Ratio (HR); Confidence Interval (CI).

(p=0.055), as the HR for N1 and N2 were 2.3 (1.1 – 4.8) and 2.2 (1.07 – 4.5) respectively, compared to node-negatives, but there was no difference between patients with 1-2 positive nodes and 3 or more positive nodes. In the second model (LNR), worse OS was associated with adjuvant chemotherapy (HR 1.76; 95% CI 1.01 – 3.07;

Table 3. Multivariate analysis of risk factors associated with Overall Survival in the two models with LNN (Model 1) and LNR (Model 2).

Factors	*Multivariate OS Model 1*			*Multivariate OS Model 2*		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Surgical margins			**0.042**			0.059
R0 (n=88)	1	-		1	-	
R1 (n=11)	2.41	1.03 – 5.64		2.28	0.97 – 5.38	
Perineural Invasion			0.97			0.90
No (n=50)	1	-		1	-	
Yes (n=49)	0.96	0.48 – 2.00		0.95	0.47 – 1.993	
Adjuvant chemotherapy			0.25			**0.044**
No (n=45)	1	-		1	-	
Yes (n=52)	1.42	0.78 – 2.58		1.76	1.01 – 3.07	
LNN			0.055		*Not included*	
N0 (n=38)	1	-				
N1 (n=28)	2.30	1.10 – 4.82				
N2 (n=34)	2.20	1.07 – 4.53				
LNR		*Not included*				**0.029**
≤0.056 (n=42)				1		
>0.056 (n=58)				1.99	1.07 – 3.69	

Abbreviations: Lymph Node Number (LNN); Hazard Ratio (HR); Confidence Interval (CI). Due to between-term collinearity, LNR and LNN were fitted in two separate multivariable models.

p=0.044) and a LNR>0.056 (HR 1.99; 95% CI 1.07 – 3.69, p=0.029).

The independent prognostic factors for worse DFS in the first model were a tumor size ≥2cm (HR 2.73; 95% CI 1.19 – 6.28; p=0.018) and LNN, for which HR (95% CI) were 3.03 (1.09 – 8.40) and 5.03 (1.98 – 12.80) for N1 and N2, respectively (p=0.003). In the second model, the size of tumor ≥2cm was again an independent prognostic factor (HR 2.44; 95% CI 1.06 – 5.63; p=0.035) along with a LNR>0.056 (HR 2.07; 95% CI 1.01 – 4.27; p=0.048).

DISCUSSION

The present study confirms that in AC both the presence and the burden of nodal involvement are important prognostic factors. The frequency of nodal metastasis in our series was 62%, which is slightly higher than the rates of 45-50% reported in the literature(10,12,16,19). Kang et al.(18) found that AC patients with greater LNN had worse OS and proposed a new nodal substaging accordingly. The most recent 8th TNM AJCC/UICC Edition uses the same N categories(24). A recent validation study confirmed that these proposed N categories segregate patient survival well(25). Using the same subgrouping in our study, we had consistent results. Nonetheless, in our series the hazard ratios for N1 and N2 were not statistically different for OS, while the presence of 3 or more metastatic LNs was associated with shorter DFS compared to those with up to 2 LNs involved (p<0.001). These patients tend to have a higher rate of local recurrence than

Table 4. Multivariate analysis of risk factors associated with Disease Free Survival in the two models with LNN (Model 1) and LNR (Model 2).

Factors	*Multivariate DFS Model 1*			*Multivariate DFS Model 2*		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Tumour Size			**0.018**			**0.035**
<2 cm (n=26)	1			1		
≥2cm (n=53)	2.73	1.19 – 6.28		2.44	1.06 - 5.63	
Surgical margins			0.054			0.061
R0 (n=88)	1			1		
R1 (n=11)	2.48	0.98 – 6.24		2.41	0.96 – 6.05	
Perineural Invasion			0.93			0.38
No (n=50)	1			1		
Yes (n=49)	0.96	0.38 – 2.40		1.47	0.61 – 3.53	
Adjuvant chemotherapy			0.48			0.064
No (n=45)	1			1		
Yes (n=52)	1.33	0.59 – 3.01		1.99	0.96 – 4.11	
LNN			**0.003**		*Not included*	
N0 (n=38)	1					
N1 (n=28)	3.03	1.09 – 8.40				
N2 (n=34)	5.03	1.98 – 12.80				
LNR		*Not included*				**0.048**
≤0.056 (n=42)				1		
>0.056 (n=58)				2.07	1.01 – 4.27	

Abbreviations: Lymph Node Ratio (LNR); Hazard Ratio (HR); Confidence Interval (CI). Due to between-term collinearity, LNR and LNN were fitted in two separate multivariable models.

patients with none or 1-2 metastatic LNs.

The importance of LNR in the prognostic stratification of patients has already been established for gastric, esophageal, colonic and pancreatic cancer(20,26–30). A recent paper evaluated a prognostic nomogram staging system integrating age, grade, T stage and LNR for pancreatic ductal adenocarcinoma (PDAC) and compared this to the TNM staging system AJCC 8th Edition. They proved that LNR in PDAC was a robust prognostic predictor for resected patients and the LNR-based nomogram had a superior performance in predicting survival than the AJCC 8th Edition of the TNM staging system(30).

Falconi et al.(10) showed in 2008 that LNR and more than 16 resected nodes are independent prognostic factors for survival and tumor recurrence. Recently, Hsu et al.(16) identified a cut-off of LNR >0.056 as an independent predictor of poor overall and disease free survival in a large series of 212 patients. This value was chosen in our series to divide the patients in two groups in an attempt to provide an external validation of this LNR cut off in a geographically different population. This cut off might not be appropriate to other series but only a meta-analysis including various cut offs would suggest the most suitable value. The recent studies focused on LNR did not compare its impact on survival to other node-associated variables such as the LNN. In our study, we analyzed the impact on survival of both LNN and LNR. The subanalysis using the same LNR cut-off identified by Hsu et al. showed that a higher LNR correlated with worse OS and was also strongly associated with shorter median DFS (p<0.001). On the contrary, the increasing number of metastatic lymph nodes was not a significant predictor of worse OS, with similar HR for patients with 1 to 2 and 3 or more positive LNs. Similar result was shown when R1 patients were excluded from survival analysis.

The choice between LNN and LNR as best predictor of prognosis is still under debate. Sakata et al.(13) addressed the problem in 2011. Using different reference ranges, they compared the prognostic power of LNN and LNR and concluded that LNN better predicts outcomes after resection. However, the results were probably limited by the small size of the series, technical variations among the cases and the choice of different subclassifications for their analysis. Our study is monoinstitutional and all patients received standardized treatment. To validate data from the literature, our reference ranges have been aligned to those previously published(16,18). At multivariable analysis, only LNR was an independent prognostic factor for OS, whereas in the LNN subanalysis, N1 and N2 did not show a difference in OS. Both LNN and LNR were independent predictors of shorter DFS, along with a tumor size ≥2cm. This was reflected in the Kaplan-Meier curves for DFS were the subgroups discriminated well.

At present, there is limited evidence on the role for adjuvant therapy in resectable peri-ampullary cancer(31–33). A recent review on adjuvant treatments following curative surgery for peri-ampullary adenocarcinoma did not found a significant difference in the 5-year overall survival between patients who underwent surgery alone or with associated adjuvant therapy(33). A retrospective series from the Mayo clinic on the other hand showed improved survival for resected patients receiving adjuvant chemo-radiotherapy, especially in stages IIB or higher(34). Adjuvant treatments have added costs in terms of complications and poor quality of life, and should only be offered in advanced or high risk patients. A standard core set for the parameters defining the high-risk patient has not yet been agreed(31). In addition to LNN, the LNR gives information about the biology of the tumor and the adequacy of the lymphadenectomy. Improvement in the staging of resected AC allows better discussion with the patient about the treatment strategy and the improves the accuracy in the analysis of data in view of studies aiming to identify the future role of neoadjuvant strategies.

We acknowledge that this study has some limitations including its retrospective nature spanning over a period of 17 years, with various changes in the classification of this cancer. On the other hand, all the versions of the TNM staging system until and included UICC version 7 classify the nodal involvement in absent (N0) and present (N1) and the cohort we present in this study will serve as a historical cohort for future studies including cases classified with the new 8th edition UICC TNM staging system, where the nodal staging is divided in N0, N1 (1-2 LNs) and N2 (3 or more LNs)(24). This study is an attempt to confirm whether the LNR is more accurate than LNN in predicting survival. Another limitation is the small sample size of this study. In order to demonstrate a difference in overall survival according to the lymph node status with a power of 80% the required number of events is 91 with a sample of 220 patients, therefore the present study is underpowered and does not allow to draw a conclusion. To overcome the problem, a meta-analysis would be useful to confirm the prognostic role of LNN and LNR and to suggest the most suitable cut off value for LNR.

In PDAC, it was recently shown that the number of examined lymph nodes was imperfect as a survival predictor as this depends on surgical techniques. On the other hand, LNR was not associated with the extent of the lymphadenectomy and could allow patients to benefit from surgery without the added risk of postoperative complications and at the same time have an accurate evaluation of the survival risks(30). The lymph node ratio is simple to calculate postoperatively and should be considered for practical purposes in the stratification of patients for adjuvant treatment, as only higher risk patients should be offered adjuvant treatments. Furthermore, the use of both LNN and LNR in the staging and prognosis of resected AC can help to offer patients a personalized pathway and follow-up.

CONCLUSIONS

The present study confirmed that nodal status is of primary importance in the assessment of prognosis of resected AC. In our study, a LNR >0.056 was an independent prognostic factor of worse OS, while predictors of decreased DFS were an increasing number of metastatic nodes (1-2 and ≥3) and a lymph node ratio >0.056. These two parameters should be both considered in the staging of AC, as the LNR can add information on survival and help in the selection of candidates for adjuvant treatments and tailored follow up.

Abbreviations

AC	Ampullary Carcinoma
DFS	Disease Free Survival
LNN	Lymph Node Number
LNR	Lymph Node Ratio
OS	Overall Survival
WHO	World Health Organization

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