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Original Article

Impact of lymph node staging systems in predicting outcome in patients with ampullary cancer

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Backgrounds/Aims: Lymph node (LN) metastasis though, is a poor prognostic factor for ampullary carcinoma (APC), the impact of Lymph node ratio (LNR) and Logarithm odds of positive lymph node (LODDS) in the long-term survival remains controversial. We evaluated the factors affecting the long-term outcome in APC patients with emphasis on LNR and LODDS. **Methods:** The prospectively collected data of 198 patients who underwent pancreatoduodenectomy for APC was analyzed after excluding 12 patients for various reasons. Factors affecting Disease specific survival (DSS) and Recurrence free survival (RFS) were analyzed with special reference to LN positivity, LNR and LODDS. **Results:** Out of 186, 117 (62.9%) patients were alive at a median follow-up of 39.5 months and 72 (38.7%) developed recurrence. The overall 5-year DSS was 59.3% & RFS 54.9%. Univariate analysis showed T-stage, tumor differentiation, perineural invasion, LN positivity, LNR and LODDS was significantly affected DSS and RFS. On multivariate analysis, perineural invasion, LN positivity, LNR and LODDS lost its significance for DSS and RFS. AUC for prediction of DSS and RFS for LNR was 0.654 ($p<0.001$) & 0.629 ($p=0.003$) respectively and for LODDS, it was 0.697 ($p<0.001$) & 0.677 ($p=0.001$) respectively. Sensitivity and specificity of LNR (0.1) for DSS were 37.7% & 83.8% and for RFS were 36.1% & 83.3%; for LODDS (−1.00), sensitivity and specificity for DSS was 62.3% and 67.5% and for RFS it was 59.7% and 66.7% respectively. **Conclusions:** LNR and LODDS although independently seem to affect the RFS and DSS, albeit have a low sensitivity and specificity in predicting DSS and RFS. **(Ann Hepatobiliary Pancreat Surg 2020;24: 484-495)**

Key Words: Periampullary; Pancreatoduodenectomy; Lymph node ratio; LODDS; Survival; Long term

INTRODUCTION

Traditionally, periampullary carcinoma (PACA) comprised of four heterogeneous tumors arising from ampulla, duodenum, pancreatic and distal bile duct. Among them, ampullary carcinoma, is the second most common variant of PACA and accounts for ~0.5% of all neoplasms arising from the gastrointestinal tract.[1] Surgical resection remains the mainstay of treatment for patients with periampullary carcinoma (PACA). The long-term survival following resection of PACA is governed by a number of factors, such as the tumor (T) differentiation, T stage, lymph node status, margin status and perineural invasion. However, these factors are reported to have varied importance among different site in periampullary tumor especially lymph node status.

Lymph node metastasis is considered to be one of the important predictors of survival in various GI malignancy.[2-7] Survival analysis can have a bias if the lymph node estimate in specimen is inaccurate. Apart from lymph node positivity, total number of LN retrieved, number of positive lymph nodes, lymph node ratio (LNR-ratio between number of positive LN and number of LN retrieved) and logarithm odds of positive lymph node (LODDS) have been suggested to have a better prognostic significance in pancreatic and periampullary carcinoma.[4,7-9]

LNR has been suggested as a prognostic marker for various cancers namely esophageal, gastric, colonic, rec-

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tal, pancreatic as well as periampullary malignancies.[2-11] However studies on ampullary tumor have suggested that number of lymph nodes involved may predict survival better than LNR while others support LNR as better prognostic marker.[12-14] Caution needs to be exercised considering the alacrity with which the proponents of LNR are proliferating. Log odds of metastatic LN (LODDS) as a LN staging method for prognostic marker was considered as an alternative since it took into consideration the status of probability of negative nodes patients also.[15-17]

The aim of our study was to critically evaluate the role of various factors with particular emphasis on LN staging methods including LNR and LODDS for prognostication of patients undergoing pancreatoduodenectomy for ampullary adenocarcinoma.

MATERIALS AND METHODS

We analyzed the data of all patients with periampullary carcinoma treated at our tertiary care referral center from January 2004 to December 2018 from a prospectively maintained database.

Inclusion criteria

All patients undergoing pancreatoduodenectomy for suspected / proven periampullary tumor were included in the study.

Exclusion criteria

The patients who had a final histopathology other than adenocarcinoma and those with distal CBD, duodenal and pancreatic variant of Periampullary carcinoma were excluded from the study. R1 resections were also excluded to avoid potential bias from inclusion of probable locally advanced tumors which were left inadvertently with positive margins.

Work-up and operative procedure

All patients underwent contrast enhanced CT scan for pre-operative staging. Pre-operative biliary drainage was done only in patients with serum bilirubin level exceeding 15 mg% or if there was an evidence of cholangitis. All patients underwent pancreatoduodenectomy and reconstruction of pancreatico-jejunostomy using by modified Blumgart's technique.[18] The extent of lymph node dissection included removal of pancreaticoduodenal, pericholedochal, periportal, along hepatic artery and lymph nodes to the right of coeliac and superior mesenteric artery. All surgeries were performed under direct supervision of two senior surgeons (PM, SS). Resection margins in the specimen at the level of bile duct, pancreatic duct, superior mesenteric artery and superior mesenteric vein were inked/marked before sending for histopathology. Resected specimens were analyzed for the location, size and differentiation of the tumor, perineural invasion (PNI), status of the lymph nodal involvement and resection margins.

Follow-up protocol included out-patient visits every 3 months in the 1st year, every 6 months for next 2 years and yearly thereafter. At each follow up complete physical examination along with blood biochemistry and ultrasound abdomen were performed. The CT scan of the abdomen was performed at 1-year and then at every 2-year intervals or when clinically indicated.

Parameters analyzed

The demographic profile and histopathological details including tumor differentiation, perineural invasion, margin status, T stage, total number of lymph nodes retrieved and the number of positive lymph nodes were reviewed and analyzed. Lymph nodes positivity was divided into N0, N1 and N2 as per AJCC 8th edition.

LNR was calculated by dividing the number of positive lymph nodes by the total number of lymph nodes retrieved. LNR was assessed as both continuous and categorical variable.

a) *LNR assessment as categorical*: LNR were categorized as: I- ≤ 0.05; II- $> 0.05/\leq 0.1$; III- $> 0.1/\leq 0.2$; IV- $> 0.2/\leq 0.3$.

b) *LNR assessment as continuous variable*: ROC curves were plotted for LNR against disease specific survival (DSS) and recurrence free survival (RFS). Area under curve, sensitivity and specificity were determined.

Logs odd of positive nodes (LODDS) was calculated by Log (*pnod*+0.5/*tnod-pnod*+0.5) where pnod is number of positive nodes while tnod is total number of examined nodes and 0.5 is added to numerator and denominator to avoid infinite number. Cut-off of LODDS were classified according in groups: LODDS1: LODDS < -3; LODDS2: $-3 \leq$ LODDS < -2; LODDS3: $-2 \leq$ LODDS < -1; LODDS4: $-1 \leq$ LODDS < 0; LODDS5: $0 \leq$ LODDS < 1.[16]

Recurrences were classified as local (nodal / tumor bed), distant (liver, peritoneum, non-regional lymph node, systemic) or both.

Survival data were obtained either from the date of the last out-patient visit or via personal communication with the patients. Deaths occurring up to 30th post-operative day were considered post-operative mortality and were excluded from the survival analysis. *Disease specific survival* was defined as the time period from start of treatment till the time of death. *Recurrence free survival* was defined as the time period from start of treatment till the time at which recurrence was detected.

Statistical analysis

Categorical variables were analyzed by Chi-square test and continuous variables with t-test or Mann-Whitney U test, where appropriate. Survival probabilities were calculated using Kaplan-Meier method and compared by Log-rank test. Cox regression was used for multivariate analysis and hazard ratios (HR) were calculated. Results were considered significant if the *p*-value was less than 0.05. Statistical analysis was performed using SPSS software (version 23 for Mac, IBM Inc., Armonk, NY, USA). Area under curve (AUC) between 0.7-0.8 was considered good predictor while AUC below 0.7 as poor predictor.

RESULTS

Five hundred and sixty six patients with periampullary carcinoma were admitted for definitive management during the study period. Among these, 364 (64.3%) patients underwent pancreatoduodenectomy while 202 (35.7%) were deemed inoperable or unresectable (metastatic disease or locally advanced tumors). The final histopathology report revealed adenocarcinoma in 321 patients while 43 patients who had other etiologies were excluded. Among 321 patients, 123 patients [Distal CBD (n=60, 18.7%), duodenal (n=37, 11.5%) and pancreatic (n=26, 8.1%)] variant of

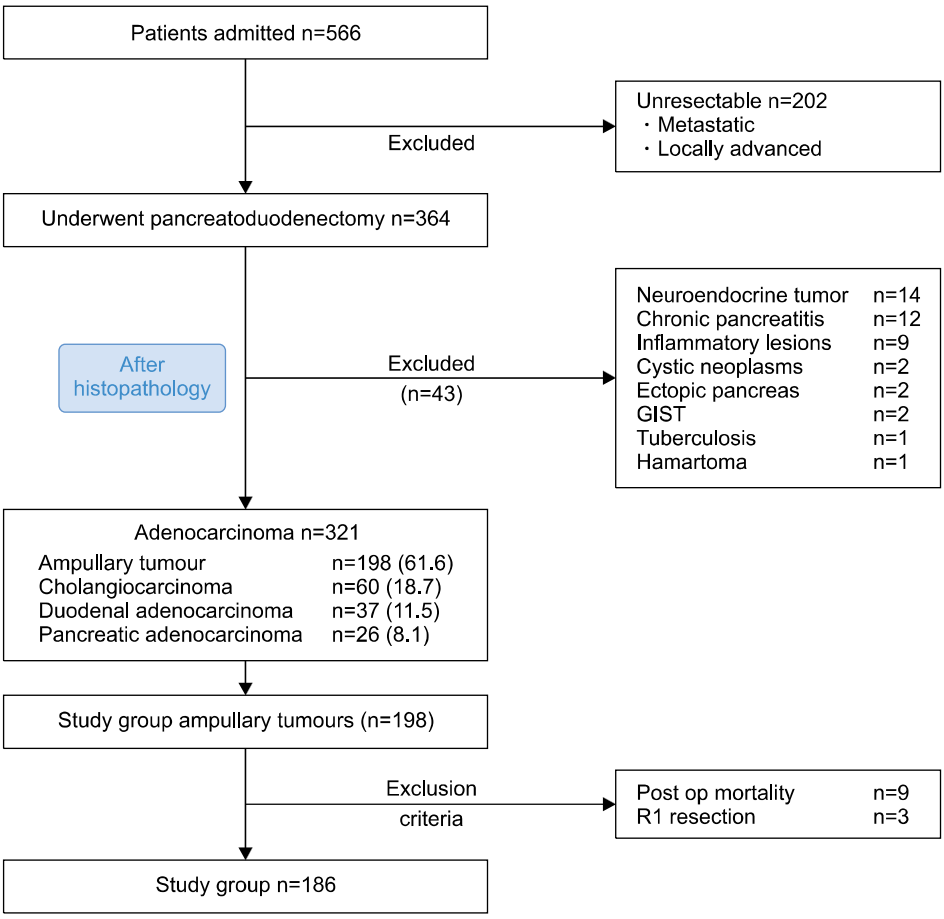

Fig. 1. Patient profile with inclusion and exclusion criteria.

PACA were excluded while one hundred ninety eight patients with ampullary tumor were reviewed. Patients with peri-operative deaths (n=9) and R1 resection (n=3) were also excluded from analysis. One hundred and eighty six patients fulfilled the study criteria and were included in the study (Fig. 1).

Demographic and pathological findings

The median age of ampullary tumor was 50 (25-78) years with male is to female ratio was 1.55. None of the patients received neoadjuvant therapy. Perineural invasion was detected in 45 (24%) patients. The poorly differentiated carcinoma comprised of 7% (n=13), whereas 47% patients had T3-4 tumors (Table 1). The lymph node positivity was found in 77 (41%) cases. The median number of lymph nodes examined was 15. The median number of LN retrieved was 14.5 among LN negative patients, while it was 16.5 for LN positive patients.

Survival

Of 186 patients who underwent resection, 117 patients (62.9%) were alive at the time of the last follow-up. Median follow-up period was 39.5 months (4-168 months). The 3-year and 5-year DSS was 72.1% and 59.3%, while RFS was 66% and 54.9% respectively. Overall 72 patients (38.7%) developed recurrence during the follow up (Table 2). Among these, 51 patients had distant metastasis alone [most common being liver (n=40, 55.5%), followed by peritoneum (n=6, 8.3%), lung (n=3, 4.2%) and brain (n=2, 2.8%)], 12 patients had local recurrence alone (16.7%), while 9 patients had recurrence at both sites (12.5%).

Table 1. Demographic and histopathological characteristics of patient's undergone resection for ampullary adenocarcinoma

Parameters	n=186 (%)
Age (years)	
≤60	158 (85)
>60	28 (15)
Sex	
Male	113 (61)
Female	73 (39)
T stage	
T1, T2	98 (53)
T3, T4	88 (47)
Differentiation	
Well differentiated	85 (46)
Moderately or poorly differentiated	101 (54)
Perineural invasion	
Negative	141 (76)
Positive	45 (24)
Lymph node	
Negative	109 (59)
Positive	77 (41)
Lymph node categorization (AJCC 8th)	
0	109 (59)
1-3	58 (31)
>3	19 (10)
Lymph node retrieved	
(≤12/>12)	71 (38)/115 (62)
(≤15/>15)	93 (50)/93 (50)
Lymph node ratio	
(<0.05/>0.05)	119 (64)/67 (36)
(<0.1/>0.1)	140 (75)/46 (25)
(<0.2/>.0.2)	158 (87)/24 (13)
(<0.3/>0.3)	176 (95)/10 (05)
Recurrence	
Present	72 (39)
Absent	114 (61)
Log-ODDS (LODDS)	
3/4/5	107/73/06

Factors effecting disease specific survival

Univariate analysis revealed T stage, tumor differentiation, perineural invasion, lymph node positivity, LNR (0.05, 0.1), number of positive lymph nodes (0/1-3/>3), and LODDS as the significant risk factors influencing DSS (Table 3). Survival curves stratified by T-stage, PNI, LODDS, differentiation, LNR (0.1) and number of positive lymph nodes (AJCC 8th ed.) are shown in Fig. 2. Tumor stage and differentiation were the significant factors on multivariate analysis (Table 3). AUC of LNR and LODDS for predicting DSS (Fig. 2) was 0.654 ($p<0.001$) and 0.697 ($p=0.001$) respectively.

The sensitivity and the specificity for various cut-off levels of LNR and LODDS are shown in Table 4. The sensitivity for predicting DSS decreases with increasing LNR and LODDS thereby undermining its significance.

Factors affecting Recurrence free survival (RFS)

Univariate analysis revealed the T stage, tumor differentiation, lymph node positivity, LNR (0.05, 0.1), number of positive lymph nodes (0, 1-3, >3), LODDS and perineural invasion as significant risk factors influencing RFS (Table 3). On multivariate analysis, RFS was influenced by the T-stage and tumor differentiation (Table 3). Survival curves stratified as per T-stage, PNI, LODDS, differ-

Table 2. Patients and tumor characteristics and their respective 3-year and 5-year survival for disease specific survival and recurrence free survival

	Disease specific survival					Recurrence free survival				
	Deaths	3-year survival (%)	5-year survival (%)	Median survival (months)	*p*-value log rank	Recurrence	3-year RFS	5-year RFS	Median survival	*p*-value log rank
Age (years)					0.433					0.204
＜60	60	70.2	59.0	-		64	63.3	52.9	72.0	
＞60	09	82.0	60.8	-		08	81.1	66.0	-	
Male	45	72.5	53.8	-	0.516	46	65.0	52.5	-	0.661
Female	24	71.5	69.6	-		26	67.7	59.0	-	
T Stage					＜0.001					＜0.001
T1,T2	22	80.8	75.6	-		25	77.7	72.9	-	
T3,T4	47	62.5	42.7	46		47	53.1	36.3	42.0	
WD	25	85.7	73.9	-	＜0.001	26	80.3	67.6	-	0.001
MD or PD	44	58.8	43.7	42		46	52.3	42.6	39	
PNI－	42	77.8	68.1	-	＜0.001	46	69.1	62.3	-	0.001
PNI+	27	54.8	33.0	46		26	56.0	33.0	40	
N0	28	80.4	73.1	-	0.001	32	75.5	66.4	-	0.007
N1-3	32	57.0	37.2	40		32	51.1	32.5	39	
N ＞3	09	70.1	46.0	96		08	56.5	56.5	-	
LNR ≤0.05	34	76.4	69.6	-	＜0.001	37	72.9	64.3	-	0.002
LNR ＞0.05	35	64.5	40.8	46		35	54.2	37.7	42	
LNR ＜0.1	42	76.2	68.5	-	＜0.001	45	71.2	62.6	-	0.001
LNR ≥0.1	27	59.9	30.1	46		27	51.2	30.9	39	
LNR ＜0.2	57	73.3	62.3	-	0.093	60	68.6	56.7	-	0.103
LNR ≥0.2	12	63.0	40.6	44		12	48.5	43.6	36	
LNR ＜0.3	62	72.2	62.0	-	0.067	65	67.8	56.8	-	0.060
LNR ≥0.3	07	70.0	25.0	40		07	40.0	30.0	32	
LN retrieved					0.570					0.562
≤12	31	71.6	54.3	65		32	65.5	51.6	63.0	
＞12	38	72.6	63.4	-		40	66.5	57.5	-	
LN retrieved					0.625					0.240
≤15	30	72.3	56	71		43	61.5	49.2	60	
＞15	39	72.2	63.9	-		29	71.4	62.3	-	
LODDS					＜0.001					＜0.001
3	27	77.7	74.4	-		30	76.0	67.8	-	
4	37	64.7	43.5	46		37	55.4	40.7	48	
5	05	66.7	16.7	40		05	33.3	16.7	30	
LN					＜0.001					＜0.001
0	28	80.4	73.1	-		32	75.5	66.4	40	
1	41	60.5	39.3	46		40	52.9	37.8	-	

WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; PNI, perineural invasion; LN, lymph node; LNR, lymph node ratio

entiation, LNR (0.1), and number of positive lymph nodes (AJCC 8th ed.) are shown in Fig. 3 for RFS. AUC of LNR and LODDS for predicting RFS (Fig. 3) was 0.629 (p=0.003) and 0.677 (p=0.001) respectively. The sensitivity of cut off levels decreases further with increase in LNR and LODDS thereby reducing its importance (Table 4).

DISCUSSION

Pancreatoduodenectomy remains the mainstay of treatment for patients with periampullary carcinoma, since it has the potential to offer cure and provide long-term survival. We report 59.3% 5-year DSS and 54.9% 5-year RFS in patients with ampullary variant of periampullary

Table 3. Multivariate analysis of potential risk factors affecting DSS and RFS

	DSS				RFS			
	HR (95% CI)	Univariate *p*-value	HR (95% CI)	Multivariate *p*-value	HR (95% CI)	Univariate *p*-value	HR (95% CI)	Multivariate *p*-value
Age (years)					0.621 (0.298-1.296)			
＜60	0.755 (0.374-1.523)	0.433	-	-		0.204	-	-
＞60								
Sex					0.898(0.555-1.453)			
Male	0.849 (0.517-1.393)	0.516	-	-		0.661	-	-
Female								
T1, T2	2.808 (1.692-4.661)	＜0.001	1.986 (1.089-3.623)	0.025	2.553 (1.571-4.151)	＜0.001	2.060 (1.173-3.620)	0.012
T3, T4								
WD	2.451 (1.480-4.058)	＜0.001	2.379 (1.414-4.003)	0.001	2.284 (1.396-3.738)	0.001	2.256 (1.361-3.741)	0.002
MD or PD								
PNI+	2.439 (1.503-3.959)	＜0.001	1.499 (0.890-2.525)	0.128	2.190 (1.352-3.546)	0.001	1.302 (0.772-2.196)	0.322
PNI−								
LN 0/1	2.796 (1.722-4.541)	＜0.001			2.323 (1.456-3.708)	＜0.001		
LN 0/1-3/＞3	1.695 (1.252-2.295)	0.001	1.101 (0.698-1.737)	0.680	1.520 (1.122-2.058)	0.007	0.943 (0.561-1.584)	0.824
LNR ≥0.05	2.366 (1.472-3.805)	＜0.001			2.111 (1.328-3.357)	0.002	-	-
LNR ＜0.05								
LNR ≥0.1	2.540 (1.560-4.136)	＜0.001	1.538 (0.929-2.547)	0.095	2.326 (1.439-3.761)	0.001	1.758 (0.806-3.837)	0.156
LNR ＜0.1								
LNR ≥0.2	1.706 (0.915-3.182)	0.093			1.675 (0.901-3.114)	0.103	-	-
LNR ＜0.2								
LNR ≥0.3	2.082 (0.950-4.563)	0.067			2.119 (0.969-4.630)	0.060		
LNR ＜0.3								
LODDS GROUP	2.101 (1.448-3.048)	＜0.001	1.355 (0.792-2.319)	0.268	1.987 (1.368-2.886)	＜0.001	1.658 (0.987-2.741)	0.060
LN retrieved ≥12	0.871 (542-1.402)	0.570	-	-	0.871 (0.547-1.388)	0.562	-	-
LN retrieved ＜12								
LN retrieved ≥15	0.888 (0.551-1.431)	0.625	-	-	0.754 (0.471-1.208)	0.240	-	-
LN retrieved ＜15								

WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; PNI, perineural invasion; LN, lymph node; LNR, lymph node ratio

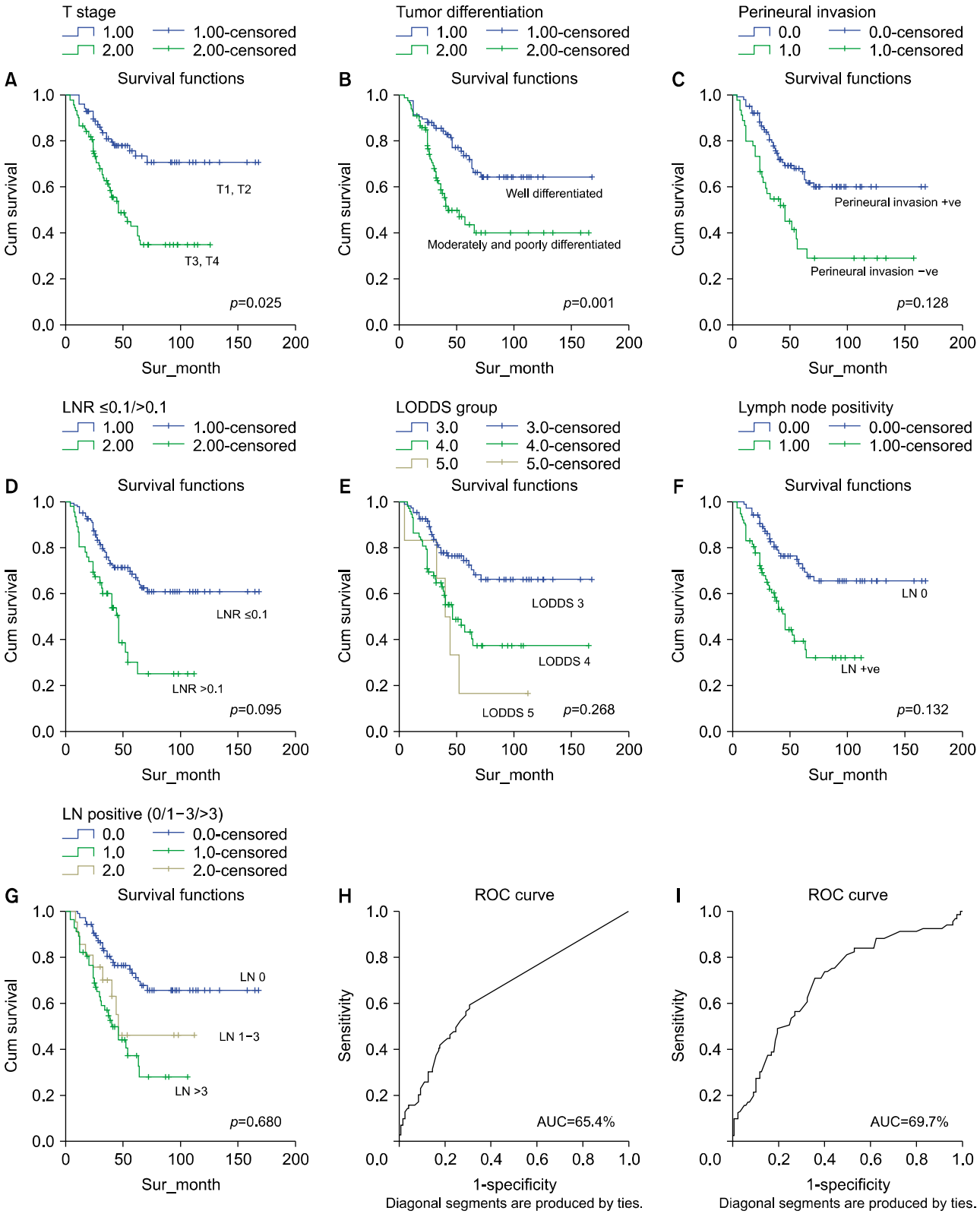

Fig. 2. (A and B) Depicting significantly better disease specific survival (DSS) in patients with T1/T2 stage and well differentiated ampullary tumors; (C-G) DSS is worse with patients with Perineural invasion, lymph node ratio (LNR) of >0.1, LODDS cut off at 4 & 5, lymph node positive disease, and >3 L.N positive, however not statistically significant; (H) ROC curves showing DSS prediction by LNR. AUC was 0.654 for DSS with *p*-value of <0.001; (I) ROC curves showing DSS prediction by LODDS. AUC was 0.697 for DSS with *p*-value of <0.001.

Table 4. Sensitivity and specificity of LNR and LODDS ratio for predicting DSS and RFS (from ROC curve)

LNR	DSS		RFS	
	Sensitivity	Specificity	Sensitivity	Specificity
−1.96	37.7	83.8	36.1	83.3
−1.00	18.8	91.5	18.1	91.2
−0.49	10.1	97.4	9.7	97.4
	AREA- 0.654		AREA- 0.629	
LODDS ratio	DSS		RFS	
	Sensitivity	Specificity	Sensitivity	Specificity
−1.96	100	9	100	9
−1.00	62.3	67.5	59.7	66.7
−0.49	20.3	90.6	19.4	90.4
	AREA- 0.697		AREA- 0.677	

carcinoma undergoing curative resection. The better survival is similar to that reported by Sakata et al. which is 64% at 5 years but significantly higher when compared to Farid et al. (5 year actuarial survival 27%)[10] and Lee et al. (median survival 28-31 months).[9,12] The rationale behind the better survival in our series could be attributed two folds. Firstly, there was only ampullary tumors in our analysis, which are essentially known to have a better survival whereas pancreatic head tumors with their dismal prognosis were higher in the studies by Lee et al.[9] and Farid et al.[10,19] Secondly, the number of patients with lymph node positive disease (41%) in our study was lower as compared to that reported by Farid et al. (68%),[10] Hurtuk et al. (62%),[20] Hatzaras et al. (58%)[21] & Falconi et al. (50%).[22]

T-stage and tumor differentiation had significant impact on DSS & RFS in both univariate and multivariate analysis. Apart from this, patients with T3/T4 disease had significant recurrence as compared to T1/T2 disease ($p < 0.001$). The negative impact of tumor differentiation has been reported by Kim et al.[23] and Doepker et al.[24] as well. The various aspects of lymph nodes staging system such as LN positivity, number of LN retrieved, number of positive lymph nodes (N0, N1 and N2) (AJCC 8th ed.), LNR and LODDS needs to be examined to assess the actual impact of lymph node involvement on the prognosis of ampullary carcinoma.

Lymph node positivity has been reported as a marker of poor prognosis in patients undergoing pancreatoduodenectomy.[20,21,25,26] Pancreatic head tumors had been the preponderant tumors in the above-mentioned studies. However, in our study, LN positivity failed to reach statistical significance for DSS & RFS on multivariate analysis and our results are in conformity with Farid et al.[10] & Choi et al.[27] Doepker et al.[24] in their study on 106 ampullary tumors found LN positivity not to be significant predictor for overall survival but was significant in predicting recurrence on multivariate analysis.

Patients with N1 and N2 positive lymph nodes had poor DSS and RFS on univariate analysis but it failed to reach statistical significance on multivariate analysis. Sakata et al.[12] demonstrated that presence of ≥4 positive LN predicted the outcome better than LN ratio for ampullary cancers. The significance of the number of positive lymph nodes, is still moot, though it's relevance has been reported by some authors in the past.[27,28] Kang et al.[29] reviewed more than 1000 patients with ampullary tumors and proposed the modification in nodal staging according to number of metastatic LN into 3 tier. Consequently, in the current TNM staging system for ampullary carcinoma metastatic lymph nodes have been sub classified on the basis of their number. We classified the number of positive LN retrieved as per AJCC 8th classification but did not find it consequential in multivariate analysis.

The effect of number of lymph nodes retrieved on long-term survival has also been studied with some support in literature.[22,28] However, our study including the one by Farid et al.[10] did not find total lymph node yield to be of any prognostic significance. Number of retrieved lymph nodes when stratified into N0 or N1 disease, did not affect survival, whether the cut-off level was kept at 12 or 15 lymph nodes. This though, does not diminish the importance of maximal lymph node retrieval; as adequate lymph node removal is still essential for proper staging of the disease besides eluding the stage migration effect.

Previous studies have tried to validate LNR as a categorical variable by either using cut-off levels[10,25] or by grouping them.[4,9,20,22] Farid et al.[10] & Shamseddine et al.[28] found the LNR >0.2 to be an important factor in determining prognosis. The study by Shamseddine et al.[28] was limited by the small sample size (n=80) & a low lymph node yield (median n=9). Pawlik et al.,[4] Lee et al.,[9] Hurtuk et al.[20] & Falconi et al.[22] found that as the LNR groups increased, the survival decreased proportionately. While Sakata et al.,[12] Sierzega et al.[13] and Murakami et

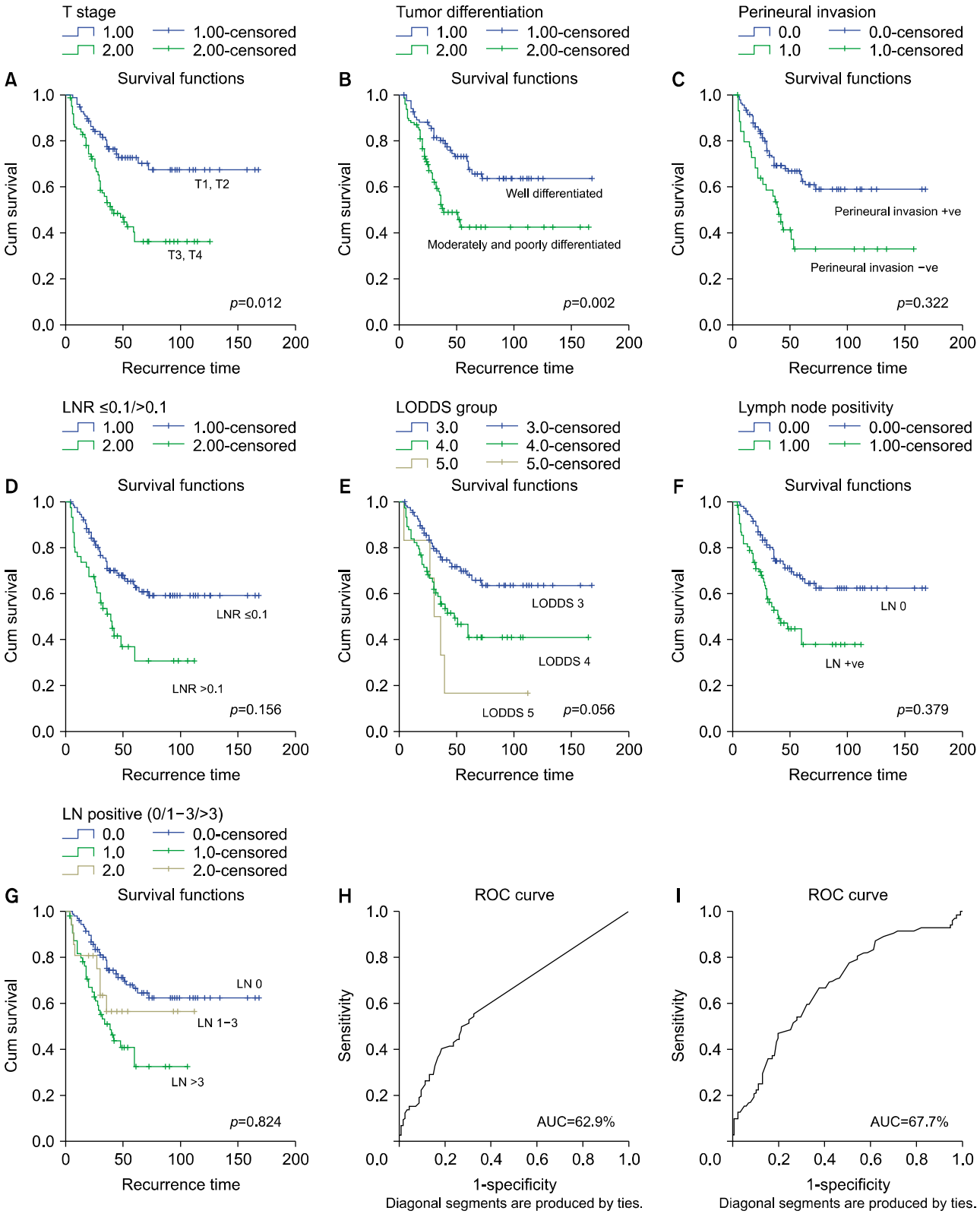

Fig. 3. (A and B) Depicting significantly lower recurrence free survival (RFS) in patients with T1/T2 stage and well differentiated ampullary tumor; (C-G) RFS is worse in patients with Perineural invasion, lymph node ration of >0.1, LODDS cut off at 4 & 5, lymph node positivity, and >3 L.N. positive, however not statistically significant; (H) ROC curves showing RFS prediction by LNR. AUC was 0.629 for RFS with *p*-value of 0.003; (I) ROC curves showing RFS prediction by LODDS. AUC was 0.677 for RFS with *p*-value of <0.001.

al.[30] have dissuaded its use as a prognostic marker, Sakata et al.[12] suggested that LNR may be useful when the median lymph node yield is low, as these patients may not have been adequately staged. We found LNR cut-off levels of 0.1 as having highest chi- square value amongst the LNR strata and a good predictor of RFS (p=0.001) & DSS (p=0.001) but failed to show any statistical significance on multivariate analysis whereas Doepker et al.[24] also found LNR of 0.1 as significant predictor for OS and RFS in univariate analysis. We aver that since the number of lymph node involved is a continuous variable, it would be apt to analyze it as a continuous variable using ROC curve rather as a categorical variable. LNR with cut-off value of 0.1 showed a low sensitivity (DSS-37.7%, RFS-36.1%) & low specificity (DSS-83.8%, RFS-83.3%), with AUC of 0.654 for DSS ($p<0.001$) & 0.629 for RFS (p=0.003). Though LNR has shown a low sensitivity & specificity and a smaller AUC, p-values were significant for prediction of DSS & RFS. House et al.[8] demonstrated that LN ratio >0.18 was a strong predictor of survival in pancreatic cancer when evaluated as continuous variable while Berger et al.[31] reported that statistical significance was lost when LNR was examined as a continuous variable (p=0.06). Tol et al.[11] showed that LNR was a common predictor of poor survival for CBD, ampullary and pancreatic cancer.

Further, He et al.[16] analyzed a total of 205 patients undergoing surgical resection for periampullary adenocarcinoma. In their study LODDS was able to stratify patients into various subgroups with significant differences of both DSS and RFS and based on the ROC curves, LODDS outperformed LNR and other LN staging systems in predicting DSS and RFS. In our study the predictive power of LODDS and LNR was almost the same for DSS, AUC being 0.697 and 0.677 for DSS and RFS respectively. However, in multi-variate analysis, both the lymph node stratifications did not reach statistical significance. Morales-Oyarvide et al.[15] evaluated 600 patients who underwent surgical resection for pancreatic ductal adenocarcinoma (both head and body tail) and concluded that Lymph node ratio and LODDS were associated with a stepwise increase in the hazards for recurrence (Ptrend 1/4 0.004 and 0.005, respectively). In this study, 49% patients had R1/R2 resection, including both head & body tail tumors vis a vis our study where in only patients undergoing PD were ampullary.

Our study is limited by the retrospective analysis of data and a non-inclusion of few variables due to missing data in some patients. These include specific histologic subtype intestinal or pancreatobiliary variant and data related administration of adjuvant therapy especially in earlier patients in our series. However, the strengths of our study are the inclusion of both RFS and DSS in the analysis. Secondly, we evaluated LNR both as a continuous and categorical variable, and LODDS unlike most other studies that have either not examined RFS or have studied LNR solely as a categorical variable.

In conclusion, lymph node positivity and the number of positive nodes in ampullary tumors, unlike other abdominal malignancies lose their significance as a predictor of survival on multivariate analysis. LNR when analyzed as a continuous variable is able to predict DSS and RFS but when analyzed as a categorical variable, fails to show similar significance. Further studies are required to validate this concept since the sensitivity and specificity of LNR and LODDS for ampullary tumors is low.

CONFLICT OF INTEREST

None of the authors have any potential conflicts to disclose.

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