pISSN: 2508-5778 • eISSN: 2508-5859
Ann Hepatobiliary Pancreat Surg 2022;26:168-177
https://doi.org/10.14701/ahbps.21-126

AHBPS
Annals of Hepato-Biliary-Pancreatic Surgery

Original Article

The prognostic value of the lymph node ratio in patients with distal cholangiocarcinoma after curative intended surgery: A single-center retrospective study

Chaeyung Oh, Hee Joon Kim, Sang Hwa Song, Eun Kyu Park, Young Hoe Hur, Yang Seok Koh, Chol Kyoon Cho

Department of Surgery, Chonnam National University Medical School, Gwangju, Korea

Backgrounds/Aims: The goal of the present study was to evaluate the prognostic value of lymph node ratio (LNR) in distal cholangiocarcinoma (DCC) after curative intended surgery.
Methods: Clinicopathological data of 162 DCC patients who underwent radical intended surgery between 2012 and 2020 were analyzed retrospectively. Prognostic factors related to overall survival (OS) and disease-free survival (DFS) were evaluated.
Results: Median OS time and DFS time were 41 and 29 months, and 5-year OS rate and DFS rate were 44.7% and 38.1%, respectively. In the univariate analysis, significant prognostic factors for OS were histologic differentiation, American Joint Committee on Cancer (AJCC) stage, positive lymph node count, LNR, R1 resection, and perineural invasion. Preoperative carcinoembryonic antigen, carbohydrate antigen 19-9, infiltrative type, histologic differentiation, AJCC stage, positive lymph node count, LNR, R1 resection, perineural invasion, and lymph-vascular invasion were significant prognostic factors for DFS in the univariate analysis. In the multivariate analysis, histologic differentiation, R1 resection, and LNR were the independent prognostic factors for both OS and DFS. The LNR ≥ 0.2 group had a significantly poor prognosis in terms of OS (hazard ratio, 3.915; $p = 0.002$) and DFS (hazard ratio, 5.840; $p < 0.001$).
Conclusions: LNR has significant value as a prognostic factor of DCC related to OS and DFS. LNR has the potential to be used as a modified staging system with furthermore studies.

Key Words: Cholangiocarcinoma; Pancreaticoduodenectomy; Lymph node ratio; Survival

INTRODUCTION

Cholangiocarcinoma is a cluster of biliary malignancies and is known to constitute 3% of all gastrointestinal cancers [1]. They are classified into three broad categories: intrahepatic cholangiocarcinoma (ICC), perihilar cholangiocarcinoma (PCC), and distal cholangiocarcinoma (DCC) based on their anatomical location [2]. Of those categories, DCC, a cholangiocarcinoma that arises from the distal or intrapancreatic bile duct, comprises 30% of all the cholangiocarcinoma [2,3]. Apart from the anatomical distinction, DCC prognosis and surgical treatment are dissimilar to ICC and PCC [4,5]. Although pancreaticoduodenectomy (PD) is known as an optimal DCC treatment [6], there're controversies on whether radical bile duct resection (BDR) is more appropriate compared with PD. A recent multi-center retrospective study concluded that bile duct segmental resection should be avoided when treating middle bile duct cancer even if R0 resection is possible [7]. However, other studies seem to have a consensus that bile duct segmental resection is an alternative surgery for the middle bile duct carcinoma and extrahepatic cholangiocarcinoma [8-10].

Distal cholangiocarcinoma prognosis is known to be poor even after surgical resection, with a 5-year survival rate of

Received: September 9, 2021, **Revised:** November 2, 2021,
Accepted: November 2, 2021

Corresponding author: Hee Joon Kim
Department of Surgery, Chonnam National University Hospital, 42 Jebong-ro, Dong-gu, Gwangju 61469, Korea
Tel: +82-62-220-6456, Fax: +82-62-227-1635, E-mail: heejoonkim@jnu.ac.kr
ORCID: https://orcid.org/0000-0002-8636-5726

18%–54% [4,5,11,12]. Lymph node metastasis is an important prognosis factor following surgical resection of DCC [13,14]. The 8th American Joint Committee on Cancer (AJCC) DCC staging system included positive numbers of lymph nodes, which is different from the 7th AJCC staging system. In the 7th AJCC staging, regional lymph node metastasis was categorized into two groups; N0, without regional lymph node metastasis, and N1, with regional lymph node metastasis. In the 8th AJCC staging, regional lymph node metastasis was categorized into three groups: N0, without regional lymph node metastasis; N1, with metastasis in one to three regional lymph nodes; and N2, with metastasis in more than 4 regional lymph nodes. However, new predictors derived from lymph node metastasis, such as positive lymph node count and the lymph node ratio (LNR), have been shown to be effective DCC prognostic indicators in recent studies [15,16]. Therefore, we conducted a single-center retrospective study focusing on lymph node metastasis as a prognostic factor for DCC. This study aimed to evaluate the prognostic value of LNR in DCC patients after curative intended resection.

PATIENTS AND METHODS

Patient population

DCC was defined as a cholangiocarcinoma arising from the common bile duct below the location where it meets the cystic duct and ampulla of Vater. Patients who underwent radical intended surgery for DCC at Chonnam National University Hospital and Chonnam National University Hwasun Hospital between 2012 January and 2020 December were included in the study. Radical intended surgery included PD and radical BDR. Palliative surgery and R2 resection were not included in this study. Furthermore, 90-days mortality and patients whose follow-up was lost within 3 months were also excluded. Patients' age, sex, operation type, and combined vascular resection were analyzed.

The study was approved by the Institutional Review Board of the Chonnam National University Hospital (IRB no. CNUH-2021-329). The informed consent was waived.

Clinicopathological evaluation

Each patient's clinicopathological data were obtained from electronic medical records. The evaluated preoperative factor was the patient's tumor marker level (carcinoembryonic antigen [CEA], carbohydrate antigen 19-9 [CA19-9]). The perioperative factor was the type of operation. Postoperative factors included gross tumor appearance, histologic type, tumor differentiation, tumor size, T-stage (AJCC 7th, 8th), pathological stage (AJCC 7th, 8th), assessed lymph node count, positive lymph node count, LNR, margin status, perineural invasion, and lympho-vascular invasion.

Pathological record

Macroscopic and microscopic findings were described in all the patient's pathological reports. Macroscopic findings included the tumor site, configuration, length of proximal margin and distal margin, and tumor size. Microscopic findings included histologic type, and differentiation, AJCC staging, margin involvement, perineural invasion, and lympho-vascu-

Table 1. Clinicopathological characteristics

Variable	Value
Age (yr)	69 (45–90)
Sex	
Male	104 (64.2)
Female	58 (35.8)
CEA (ng/mL)	3.03 (0.75–31.88)
CA19-9 (U/mL)	83.44 (0.1–12,000.0)
Operation type	
PD	144 (88.9)
BDR	18 (11.1)
Combined vascular resection	
No	156 (96.3)
Yes	6 (3.7)
Histologic type	
Adenocarcinoma	155 (95.7)
Papillary adenocarcinoma	2 (1.2)
Adenosquamous carcinoma	3 (1.9)
Differentiation	
Well	58 (35.8)
Moderate	77 (47.5)
Poorly	27 (16.7)
Size (cm)	2.0 (0.5–13.0)
Assessed lymph node count	15 (1–43)
Involved lymph node count	
0	103 (63.6)
1–3	44 (27.2)
≥ 4	15 (9.3)
Lymph node ratio (LNR)	
LNR = 0	103 (63.6)
0 < LNR <0.2	37 (22.8)
LNR ≥ 0.2	22 (13.6)
Margin status	
R0	148 (91.4)
R1	14 (8.6)
Adjuvant treatment	
No	112 (69.1)
Chemotherapy	40 (24.7)
Radiotherapy	4 (2.5)
CCRT	6 (3.7)

Values are presented as median (range) or number (%).
CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; PD, pancreaticoduodenectomy; BDR, bile duct resection; CCRT, concomitant chemo-radiation therapy.

https://doi.org/10.14701/ahbps.21-126

Table 2. Univariate analysis of prognostic factors for overall and disease-free survival

Characteristic	No. (%)	Overall survival					Disease-free survival				
		2 YSR (%)	5 YSR (%)	Mean ST (mon)	Median ST (mon)	Log rank *p*	2 YSR (%)	5 YSR (%)	Mean ST (mon)	Median ST (mon)	Log rank *p*
All patients	162 (100)	67.0	44.7	60.8	41.0		50.8	38.1	48.1	29.0	
Age (yr)						0.744					0.935
< 65	72 (44.4)	65.0	48.3	63.1	51.0		48.9	41.3	49.7	23.0	
≥ 65	90 (55.6)	68.9	39.9	57.7	41.0		52.5	33.2	44.7	30.0	
Sex						0.826					0.206
Male	104 (64.2)	67.5	44.5	60.4	45.0		54.5	41.6	52.0	36.0	
Female	58 (35.8)	66.2	45.4	61.9	41.0		44.0	31.7	40.5	16.0	
CEA (ng/mL)						0.073					0.012
< 5.0	122 (75.3)	72.6	47.0	64.0	49.0		56.5	43.0	52.8	35.0	
≥ 5.0	33 (20.4)	51.8	44.4	55.2	24.0		32.8	16.4	21.1	11.0	
Not checked	7 (4.3)										
CEA (ng/mL)						0.017					0.005
< 3.0	76 (46.9)	77.4	59.8	73.4	52.0		64.6	49.9	59.5	45.0	
≥ 3.0	79 (48.8)	60.0	33.7	51.6	35.0		39.8	27.9	36.9	14.0	
Not checked	7 (4.3)										
CA19-9 (U/mL)						0.159					0.008
< 37	57 (35.2)	77.9	50.8	68.4	43.0		70.7	54.4	59.7	91.0	
≥ 37	103 (63.6)	62.5	42.4	57.7	36.0		41.2	30.5	40.8	16.0	
Not checked											
CA19-9 (U/mL)						0.351					0.008
< 78	78 (48.1)	71.3	48.5	65.1	51.0		65.9	47.3	54.8	45.0	
≥ 78	82 (50.6)	64.5	42.3	57.9	39.0		38.2	29.8	39.4	14.0	
Not checked	2 (1.2)										
Operation type						0.229					0.220
PD	144 (88.9)	68.2	45.9	62.1	41.0		51.4	40.4	49.8	29.0	
BDR	18 (11.1)	56.3	32.8	38.4	26.0		47.6	19.0	29.3	16.0	
Combined vascular resection						0.314					0.126
No	156 (96.3)	68.0	45.1	61.3	45.0		52.4	39.2	49.1	29.0	
Yes	6 (3.7)	40.0	40.0	22.6	15.0		16.7	16.7	14.5	7.0	
Gross appearance						0.103					0.019
Polypoid or nodular	44 (27.2)	80.7	57.0	72.1	51.0		63.1	55.2	64.6		
Infiltrative	118 (72.8)	61.6	39.2	55.9	36.0		45.8	29.9	40.2	17.0	
Differentiation						< 0.001					< 0.001
Well	58 (35.8)	83.2	48.2	68.4	51.0		68.8	55.2	64.4	91.0	
Moderate	77 (47.5)	67.7	48.5	63.3	41.0		47.3	35.5	43.2	21.0	
Poorly	27 (16.7)	26.7	26.7	24.5	15.0		24.3	12.2	17.4	6.0	

Table 2. Continued

Characteristic	No. (%)	Overall survival					Disease-free survival				
		2 YSR (%)	5 YSR (%)	Mean ST (mon)	Median ST (mon)	Log rank *p*	2 YSR (%)	5 YSR (%)	Mean ST (mon)	Median ST (mon)	Log rank *p*
Size (cm)						0.623					0.228
≤ 2.0	93 (57.4)	69.6	46.0	62.6	49.0		54.9	39.7	50.1	35.0	
> 2.0	69 (42.6)	63.3	42.7	58.3	36.0		45.2	35.6	44.2	16.0	
T-stage (AJCC 7th)	92 (56.8)					0.061					0.004
T1	13 (8.0)	90.9	68.2	76.1	-		83.1	71.2	76.6	-	
T2	19 (11.7)	68.4	50.2	57.7	-		57.9	36.8	47.2	44.0	
T3	60 (37.0)	53.8	31.4	48.3	29.0		32.8	23.6	32.2	11.0	
Classified as AJCC 8th	70 (43.2)										
AJCC 7th stage	92 (56.8)					0.012					0.002
I	25 (15.4)	79.2	70.4	72.9	-		71.1	58.2	65.2	-	
II	67 (41.3)	55.7	30.0	48.0	29.0		35.4	23.5	33.2	12.0	
Classified as AJCC 8th	70 (43.2)										
Assessed LN count						0.960					0.722
< 12	52 (32.1)	65.0	45.1	61.3	49.0		52.5	39.7	49.7	35.0	
≥ 12	110 (67.9)	68.0	44.6	60.7	41.0		49.9	37.2	46.5	23.0	
Positive LN count						0.001					< 0.001
0	103 (63.6)	75.9	56.9	70.5			59.0	49.4	58.7	47.0	
1–3	44 (27.2)	55.7	27.4	47.0	35.0		47.4	25.6	37.3	16.0	
≥ 4	15 (9.3)	21.7	0.0	19.2	20.0		0.0	0.0	7.2	6.0	
LNR						< 0.001					< 0.001
0	103 (63.6)	75.9	56.9	70.5	-		59.0	49.4	58.7	47.0	
0 < LNR < 0.2	37 (22.8)	62.0	39.0	55.2	41.0		50.3	33.0	44.0	30.0	
≥ 0.2	22 (13.6)	28.1	0.0	22.2	20.0		13.6	0.0	9.0	6.0	
Margin status						< 0.001					0.005
R0	148 (91.4)	71.2	49.1	65.4	51.0		52.6	39.4	49.5	30.0	
R1	14 (8.6)	23.2	7.7	14.3	10.0		14.3	0.0	9.9	4.0	
Perineural invasion						0.033					0.021
Negative	39 (24.1)	82.5	68.8	80.3			63.8	63.8	64.8	91.0	
Positive	123 (75.9)	62.7	38.6	55.8	39.0		47.0	31.3	42.6	18.0	
Lympho-vascular invasion						0.167					0.037
Negative	122 (75.3)	70.4	47.1	63.4	49.0		54.4	42.2	52.5	35.0	
Positive	40 (24.7)	53.8	34.2	49.8	26.0		39.8	24.8	34.3	12.0	
Adjuvant treatment						0.353					0.486
No	112 (69.1)	72.1	50.8	65.5	-		52.8	40.1	50.8	29.0	
Chemotherapy	40 (24.7)	57.0	30.6	46.5	39.0		44.2	32.1	38.3	14.0	
Radiotherapy	4 (2.5)	66.7	66.7	29.0	-		66.7	66.7	25.0	-	
CCRT	6 (3.7)	27.8	27.8	32.2	18.0		44.4	44.4	38.0	9.0	

YSR, year survival rate; ST, survival time; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; PD, pancreaticoduodenectomy; BDR, bile duct resection; AJCC, American Joint Committee on Cancer; LN, lymph node; LNR, lymph node ratio; CCRT, concomitant chemo-radiation therapy; -, cannot estimate median survival time because of large proportion of censored data.

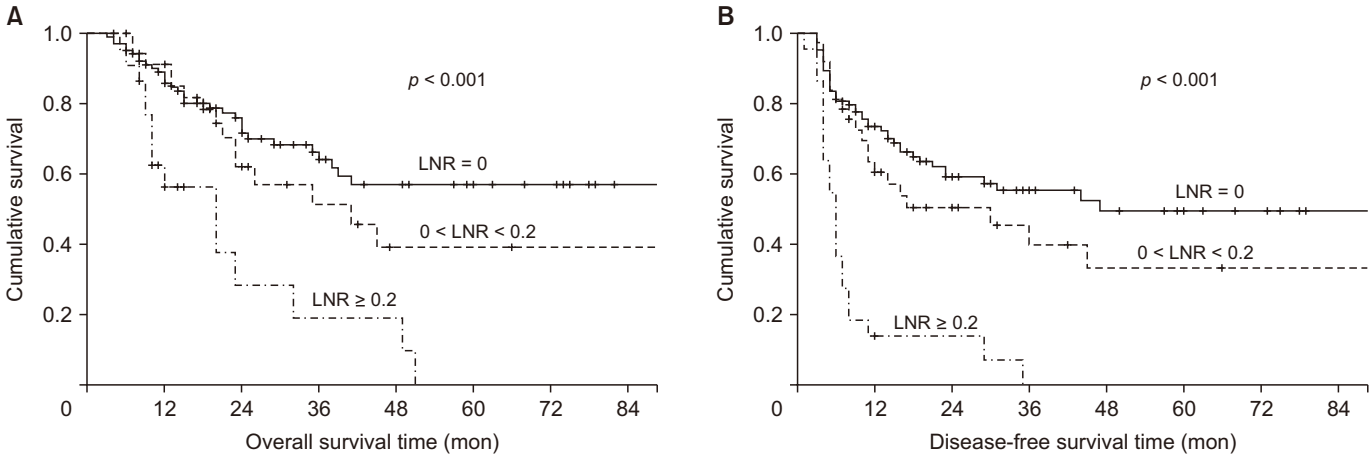

Fig. 1. Cumulative overall survival ratio according to survival time (A), and cumulative disease-free survival according to survival time (B) in the LNR groups. Significant differences of survival in the LNR group were demonstrated. LNR, lymph node ratio.

lar invasion. The total assessed lymph node count and positive lymph node count were also described in the microscopic findings. LNR was defined as the ratio of positive lymph node out of total lymph node count, and graded as LNR = 0, 0 < LNR < 0.2, and LNR ≥ 0.2. Pathological factors, mentioned above were analyzed to evaluate their impact on overall survival (OS) and disease-free survival (DFS). Pathological staging was done using the AJCC 7th edition for the patients who underwent the surgery before 2018, and the AJCC 8th edition for the patients who underwent the surgery thereafter. The T- and TNM stages of the AJCC 8th edition were excluded from our survival analysis, because of the study's small sample size and short follow-up duration.

Statistical analysis

OS and DFS were assessed using the Kaplan-Meier method. The prognostic factor was identified using the log-rank test. Factors found significant in the univariate analysis were further assessed with multivariate analysis using the Cox proportional hazard model. Positive lymph node count, classified according to the N-stage of AJCC 8th edition, was excluded from the multivariate analysis due to a linear correlation with LNR. Values of p less than 0.05 were considered to be statistically significant. The cut-off value of CEA (3.0 ng/mL), and CA19-9 (78 U/mL) were obtained using ROC curve analysis for the patients with recurrence within two years. All statistical analyses were performed using the IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Clinicopathological characteristics

Of the eligible 171 patients, 3 mortality cases and 6 cases of insufficient follow-up data were excluded. Finally, 162 patients were included in the present study; 144 (88.9%) underwent PD, and 18 (11.1%) underwent radical BDR. The total number of LNR ≥ 0.2 group was 22 (13.6%). Clinicopathological characteristics are detailed in Table 1.

Setting the cut-off value of LNR

When setting the cut-off value for LNR, we used LNR = 0 group as reference and graded others at an interval of 0.1. (0 < LNR < 0.1, 0.1 ≤ LNR < 0.2, 0.2 ≤ LNR < 0.3, 0.3 ≤ LNR < 0.4, and 0.4 ≤ LNR) In survival analysis, 0 < LNR < 0.1 and 0.1 ≤ LNR < 0.2 groups had no significant difference in the mean survival time when compared with the LNR = 0 group. LNR ≥ 0.2 group showed a significant lower survival rate compared with LNR = 0 group. So, we decided to set the cut-off value of LNR as 0.2.

Overall survival

The OS rate of the 162 patients was 67.0% at 2 years and

Table 3. Multivariate analysis for overall survival

Variable	p-value	HR (95% CI)
CEA ≥ 0.3 ng/mL (vs. < 0.3)	0.102	1.797 (0.890–3.627)
Differentiation (vs. well)		
Moderate	0.193	1.626 (0.782–3.378)
Poorly	< 0.001	6.477 (2.870–14.619)
AJCC 7th stage II (vs. I)	0.515	1.349 (0.548–3.322)
Lymph node ratio (vs. 0)		
0 < LNR < 0.2	0.984	0.993 (0.481–2.049)
≥ 0.2	< 0.001	4.349 (2.055–9.204)
R1 resection (vs. R0)	0.007	6.305 (1.661–23.928)
Perineural invasion	0.921	0.955 (0.381–2.392)

HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer.

Table 4. Subgroup survival analysis in the R0 group

Characteristic	No (%)	Overall survival					Disease-free survival				
		Univariate analysis			Multivariate analsysis		Univariate analysis			Multivariate analsysis	
		5 YSR (%)	Median ST (mon)	Log rank *p*	HR (95% CI)	*p*	5 YSR (%)	Median ST (mon)	Log rank *p*	HR (95% CI)	*p*
All patients	155 (100)	46.4	45.0				39.4	30.0			
Age (yr)				0.869					0.888		
< 65	71 (45.8)	49.0	51.0				41.9	23.0			
≥ 65	84 (54.2)	42.3	45.0				34.8	35.0			
Sex				0.924					0.154		
Male	98 (63.2)	46.6	45.0				43.4	44.0			
Female	57 (36.8)	46.4	51.0				32.2	16.0			
CEA (ng/mL)				0.185					0.021		
< 5.0	117 (75.5)	48.4	51.0				44.2	36.0		Reference	
≥ 5.0	31 (20.0)	47.7	24.0				17.4	11.0		1.652 (0.730–3.738)	0.228
Not checked	7 (4.5)										
CEA (ng/mL)				0.028					0.008		
< 3.0	75 (48.4)	60.8	-		Reference		50.6	89.0		Reference	
≥ 3.0	73 (47.1)	35.6	39.0		1.855 (0.9.3–3.808)	0.092	29.3	14.0		1.990 (1.057–3.746)	0.033
Not checked	7 (4.5)										
CA19-9 (U/mL)				0.181					0.010		
< 37	56 (36.1)	52.0	-				55.3	91.0		Reference	
≥ 37	97 (62.6)	44.2	39.0				31.7	16.0		1.047 (0.386–2.843)	0.928
Not checked	2 (1.3)										
CA19-9 (U/mL)				0.463					0.013		
< 78	77 (49.7)	49.3	51.0				47.9	45.0		Reference	
≥ 78	76 (49.0)	44.5	41.0				31.3	15.0		1.281 (0.708–2.318)	0.413
Not checked	2 (1.3)										
Operation type				0.389					0.353		
PD	139 (89.7)	46.7	49.0				41.1	29.0			
BDR	16 (10.3)	38.6	45.0				22.5	36.0			
Combined vascular resection				0.258					0.093		
No	149 (96.1)	46.9	49.0				40.5	31.0			
Yes	6 (3.9)	40.0	15.0				16.7	7.0			
Gross appearance				0.106					0.019		
Polypoid or nodular	43 (27.7)	58.6	-				56.5	-		Reference	
Infiltrative	112 (72.3)	40.8	38.0				30.8	19.0		1.931 (0.994–3.748)	0.052
Differentiation				< 0.001					< 0.001		
Well	54 (34.8)	51.6	-		Reference		57.7	91.0		Reference	
Moderate	75 (48.4)	49.2	41.0		1.515 (0.728–3.154)	0.267	36.4	23.0		1.885 (0.957–3.712)	0.067
Poorly	26 (16.8)	27.8	15.0		7.230 (3.104–16.839)	< 0.001	12.6	6.0		5.650 (2.518–12.678)	< 0.001

https://doi.org/10.14701/ahbps.21-126

Table 4. Continued

Characteristic	No (%)	Overall survival					Disease-free survival				
		Univariate analysis			Multivariate analsysis		Univariate analysis			Multivariate analsysis	
		5 YSR (%)	Median ST (mon)	Log rank *p*	HR (95% CI)	*p*	5 YSR (%)	Median ST (mon)	Log rank *p*	HR (95% CI)	*p*
Size (cm)				0.517					0.219		
≤ 2.0	88 (56.8)	48.5	51.0				41.2	36.0			
> 2.0	67 (43.2)	43.4	38.0				36.6	21.0			
T-stage (AJCC 7th)				0.049					0.003		
T1	13 (8.4)	68.2	-		Reference		71.2	-		Reference	
T2	17 (11.0)	56.6	-		1.291 (0.284–5.870)	0.741	41.1	44.0		1.381 (0.305–6.258)	0.675
T3	59 (38.1)	31.9	29.0		1.407 (0.220–8.985)	0.718	24.0	11.0		1.690 (0.227–12.536)	0.608
Classified as AJCC 8th	66 (42.6)										
AJCC 7th stage				0.009					0.001		
I	24 (15.5)	73.7	-		Reference		60.6	-		Reference	
II	65 (41.9)	31.0	32.0		1.256 (0.244–6.474)	0.785	24.2	12.0		1.746 (0.755–4.037)	0.192
Classified as AJCC 8th	66 (42.6)										
Assessed LN count				0.912					0.877		
< 12	51 (32.9)	46.8	49.0				40.7	35.0			
≥ 12	104 (67.1)	46.3	41.0				38.3	29.0			
Positive LN count				0.004					< 0.001		
0	100 (64.5)	57.9	-		Reference		49.8	47.0		Reference	
1–3	41 (26.5)	29.5	41.0		1.158 (0.586–2.288)	0.672	27.7	29.0			
≥ 4	14 (9.0)	0.0	20.0		6.473 (2.276–18.406)	< 0.001	0.0	6.0			
LNR				< 0.001					< 0.001		
0	100 (64.5)	57.9	-		Reference		49.8	47.0		Reference	
0 < LNR < 0.2	34 (21.9)	42.8	41.0		1.002 (0.471–2.132)	0.996	36.3	30.0		0.761 (0.378–1.531)	0.443
≥ 0.2	21 (13.5)	0.0	20.0		3.091 (1.356–7.046)	0.007	0.0	6.0		3.394 (1.524–7.560)	0.003
Perineural invasion				0.050					0.036		
Negative	39 (25.2)	68.8	-		Reference		63.8	91.0		Reference	
Positive	116 (74.8)	40.4	41.0		0.931 (0.371–2.335)	0.88	32.6	23.0		1.176 (0.518–2.671)	0.698
Lympho-vascular invasion				0.135					0.038		
Negative	117 (75.5)	48.6	51.0				43.2	35.0		Reference	
Positive	38 (24.5)	37.0	35.0				27.0	12.0		1.144 (0.539–2.426)	0.727
Adjuvant treatment				0.493					0.585		
No	108 (69.7)	52.8	-				41.8	30.0			
Chemotherapy	39 (25.2)	31.3	39.0				33.0	14.0			
Radiotherapy	3 (1.9)	50.0	23.0				50.0	11.0			
CCRT	5 (3.2)	40.0	18.0				53.3	-			

YSR, year survival rate; ST, survival time; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; PD, pancreaticoduodenectomy; BDR, bile duct resection; AJCC, American Joint Committee on Cancer; LN, lymph node; LNR, lymph node ratio; CCRT, concomitant chemo-radiation therapy; -, cannot estimate median survival time because of large proportion of censored data.

44.7% at 5 years. Mean and median OS time was 60.8 months and 41.0 months, respectively. In the univariate analysis, histologic differentiation, AJCC 7th stage, margin status, and perineural invasion were the prognostic factors for OS (Table 2). The LNR ≥ 0.2 group demonstrated a significantly poor prognosis (Fig. 1A). In the multivariate analysis, histologic differentiation, margin status, and LNR were independent significant prognostic factors (Table 3).

Since the margin status showed significant OS and DFS showed a significant prognostic value (Table 2), we conducted subgroup analysis in the R0 group. Poorly differentiated group (when compared with well-differentiated group), lymph node count four or more (compared with lymph node count 0), and LNR ≥ 0.2 (when compared with LNR = 0), were significant prognostic factors for OS (Table 4).

Disease-free survival

The DFS rate of the 162 patients was 50.8% at 2 years, and 38.1% at 5 years. Mean and median DFS time was 48.1 and 29.0 months, respectively. In the univariate analysis, preoperative CEA ≥ 5.0 ng/mL, preoperative CEA ≥ 3.0 ng/mL, preoperative CA19-9 ≥ 37 U/mL, preoperative CA19-9 ≥ 78 U/mL, infiltrative gross type, differentiation, T-stage/TNM stage of AJCC 7th edition, positive lymph node count, LNR, margin status, PNI, and LVI were the prognostic factors for DFS. The three LNR groups significantly correlated with the DFS prognosis in the univariate analysis (Fig. 1B and Table 2) In multivariate analysis, preoperative CEA ≥ 5.0 ng/mL, poorly differentiated carcinoma, LNR ≥ 0.2, and R1 resection were determined as independent poor prognostic factors (Table 5).

In the subgroup analysis of the R0 group, CEA 3.0 ng/mL or more, poorly differentiated group (when compared with the well-differentiated group), and LNR ≥ 0.2 (when compared with LNR = 0), were significant prognostic factors for DFS (Table 4).

Table 5. Multivariate analysis for disease-free survival

Variable	*p*-value	HR (95% CI)
CEA ≥ 5.0 ng/mL	0.018	2.275 (1.155–4.481)
CEA ≥ 3.0 ng/mL	0.480	1.305 (0.623–2.733)
CA19-9 ≥ 37 U/mL	0.629	1.177 (0.607–2.283)
CA19-9 ≥ 78 U/mL	0.863	1.078 (0.459–2.531)
Infiltrative gross type	0.446	1.306 (0.657–2.597)
Differentiation (vs. well)		
Moderate	0.052	1.954 (0.995–3.839)
Poorly	0.001	3.890 (1.756-8.048)
T-stage (AJCC 7th) (vs. T1)		
T2	0.506	1.583 (0.409–6.130)
T3	0.065	3.127 (0.933–10.483)
AJCC 7th stage II (vs. stage I)	0.697	0.735 (0.156–3.469)
Lymph node ratio (vs. 0)		
0 < LNR < 0.2	0.388	0.740 (0.374–1.465)
≥ 0.2	0.001	3.760 (1.756–8.048)
R1 resection	< 0.001	13.579 (3.179–58.001)
Perineural invasion	0.724	1.168 (0.493–2.768)
Lympho-vascular invasion	0.694	0.854 (0.389–1.875)

HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; AJCC, American Joint Committee on Cancer.

DISCUSSION

The median assessed lymph node count was 16.7 and nodal metastasis was found in 36.4% of the patients this was similar to the results of previous studies (20%–60%) [4,5,15-17]. Andrianello et al. [18] reviewed the data of 1,490 cases of DCC after PD in the States. The median OS time was 31 months and the 5-year survival rate was 18%. Lyu et al. [19] reviewed the data of 123 patients with DCC after PD in a single center in China. The 5-year OS rate was 31.5%. In the present study, the mean OS time was 60.8 months and the 5-year OS rate was 44.7%. Better mean OS time and the 5-year OS rate is thought to be as a result of lesser lymph node involvement in our study. While patients with no lymph node involvement were 45.6% in Andrianello et al. [18] study, and 58.5% in Lyu et al. [19] study, in our study, 63.6% of the patients had no lymph node metastasis.

Lymph node metastasis is one of the most important risk factors for poor prognosis in DCC patients after surgery. Byrling et al. [20] showed that lymph node metastasis was the only independent risk factor for long-term survival of DCC patients. Kiriyama et al. [16] reviewed the data of 370 DCC patients who underwent PD in 24 centers in Japan. The 3-year survival rate of patients without lymph node metastasis was significantly higher than that of patients with lymph node metastasis. Lyu et al. [19] also showed that the long-term prognosis of patients without lymph node metastasis was better than that of patients with lymph node metastasis.

Previous studies have suggested different LNR cut-off values. Kiriyama et al. [16] reported that LNR greater than 0.17 was associated with shorter median survival. Li et al. [21] suggested 0.45 as the LNR cut-off value of predicting worse survival. Oshiro et al. [22] showed that an LNR cutoff value of 0.2 was an independent risk factor for predicting prognosis. You et al. [23] performed a retrospective analysis for 251 DCC patients who underwent surgery in four centers in South Korea. This study found that LNR of 0.1 or higher predicted the OS of DCC more accurately than that of the AJCC 7th and AJCC 8th editions.

In the present study, multivariate analysis showed that histologic type, R1 resection, and LNR ≥ 0.2 were significant prognostic factors for both OS and DFS; the LNR findings were consistent with those of our present study which showed that LNR is a significant prognostic value for DCC. However, the studies showed different LNR cutoff values.

Ito et al. [24] reported that the number of lymph nodes was more than 12 for all the DCC patients who had undergone

PD for DCC. Lyu et al. [19] reported that the cutoff of the total lymph node count was 24. In our study, the median total lymph node count was 16.7 and a total of 13 patients out of 162 had less than five lymph nodes dissected.

Our study has limitations; a small-sized retrospective study of a single-center. However, our findings on LNR's significant prognostic value for DCC were consistent with previous studies. Large and multicenter research studies should be conducted for more accurate results.

In conclusion, LNR has a significant value as a prognostic factor of DCC related to OS and DFS after radical intended surgery. LNR has the potential to be used as a modified staging system with furthermore studies.

FUNDING

None.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Chaeyung Oh, https://orcid.org/0000-0003-1290-1837
Hee Joon Kim, https://orcid.org/0000-0002-8636-5726
Sang Hwa Song, https://orcid.org/0000-0003-4726-8461
Eun Kyu Park, https://orcid.org/0000-0001-7242-4855
Young Hoe Hur, https://orcid.org/0000-0003-1089-2033
Yang Seok Koh, https://orcid.org/0000-0002-0368-5389
Chol Kyoon Cho, https://orcid.org/0000-0001-8457-7314

AUTHOR CONTRIBUTIONS

Conceptualization: HJK. Data curation: CO, SHS, EKP. Methodology: CO, HJK, YHH. Visualization: HJK. Writing - original draft: CYO. Writing - review & editing: HJK, YSK, CKC.

REFERENCES

1. Gonzalez RS, Bagci P, Basturk O, Reid MD, Balci S, Knight JH, et al. Intrapancreatic distal common bile duct carcinoma: analysis, staging considerations, and comparison with pancreatic ductal and ampullary adenocarcinomas. Mod Pathol 2016;29:1358-1369.
2. Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463-473; discussion 473-475.
3. Launois B, Reding R, Lebeau G, Buard JL. Surgery for hilar cholangiocarcinoma: French experience in a collective survey of 552 extrahepatic bile duct cancers. J Hepatobiliary Pancreat Surg 2000;7:128-134.
4. Murakami Y, Uemura K, Sudo T, Hashimoto Y, Nakashima A, Kondo N, et al. Prognostic factors after surgical resection for intrahepatic, hilar, and distal cholangiocarcinoma. Ann Surg Oncol 2011;18:651-658.
5. Kim BH, Kim K, Chie EK, Kwon J, Jang JY, Kim SW, et al. Long-term outcome of distal cholangiocarcinoma after pancreaticoduodenectomy followed by adjuvant chemoradiotherapy: a 15-year experience in a single institution. Cancer Res Treat 2017;49:473-483.
6. Strijker M, Belkouz A, Van Der Geest LG, Van Gulik TM, Van Hooft JE, De Meijer VE, et al. Treatment and survival of resected and unresected distal cholangiocarcinoma: a nationwide study. Acta Oncol 2019;58:1048-1055.
7. Hayashi H, Jang JY, Kim KS, Choi JS, Takahara T, Choi SH, et al. Comparison of pancreaticoduodenectomy and bile duct resection for middle bile duct cancer: a multi-center collaborating study of Japan and Korea. J Hepatobiliary Pancreat Sci 2020;27:289-298.
8. Lee HG, Lee SH, Yoo DD, Paik KY, Heo JS, Choi SH, et al. Carcinoma of the middle bile duct: is bile duct segmental resection appropriate? World J Gastroenterol 2009;15:5966-5971.
9. Schreuder AM, Engelsman AF, Van Roessel S, Verheij J, Besselink MG, Van Gulik TM, et al. Treatment of mid-bile duct carcinoma: local resection or pancreatoduodenectomy? Eur J Surg Oncol 2019;45:2180-2187.
10. Akita M, Ajiki T, Ueno K, Tsugawa D, Tanaka M, Kido M, et al. Benefits and limitations of middle bile duct segmental resection for extrahepatic cholangiocarcinoma. Hepatobiliary Pancreat Dis Int 2020;19:147-152.
11. Komaya K, Ebata T, Shirai K, Ohira S, Morofuji N, Akutagawa A, et al. Recurrence after resection with curative intent for distal cholangiocarcinoma. Br J Surg 2017;104:426-433.
12. Ercolani G, Dazzi A, Giovinazzo F, Ruzzenente A, Bassi C, Guglielmi A, et al. Intrahepatic, peri-hilar and distal cholangiocarcinoma: three different locations of the same tumor or three different tumors? Eur J Surg Oncol 2015;41:1162-1169.
13. Sakata J, Wakai T, Matsuda Y, Ohashi T, Hirose Y, Ichikawa H, et al. Comparison of number versus ratio of positive lymph nodes in the assessment of lymph node status in extrahepatic cholangiocarcinoma. Ann Surg Oncol 2016;23:225-234.
14. Kim HJ, Kim CY, Hur YH, Koh YS, Kim JC, Kim HJ, et al. Prognostic factors for survival after curative resection of distal cholangiocarcinoma: perineural invasion and lymphovascular invasion. Surg Today 2014;44:1879-1886.
15. Kawai M, Tani M, Kobayashi Y, Tsuji T, Tabuse K, Horiuchi T, et al. The ratio between metastatic and examined lymph nodes is an independent prognostic factor for patients with resectable middle and distal bile duct carcinoma. Am J Surg 2010;199:447-452.
16. Kiriyama M, Ebata T, Aoba T, Kaneoka Y, Arai T, Shimizu Y, et al. Prognostic impact of lymph node metastasis in distal cholangiocarcinoma. Br J Surg 2015;102:399-406.
17. Murakami Y, Uemura K, Hayashidani Y, Sudo T, Ohge H, Sueda T. Pancreatoduodenectomy for distal cholangiocarcinoma: prognostic impact of lymph node metastasis. World J Surg 2007;31:337-342; discussion 343-344.

18. Andrianello S, Paiella S, Allegrini V, Ramera M, Pulvirenti A, Malleo G, et al. Pancreaticoduodenectomy for distal cholangiocarcinoma: surgical results, prognostic factors, and long-term follow-up. Langenbecks Arch Surg 2015;400:623-628.
19. Lyu S, Li L, Zhao X, Ren Z, Cao D, He Q. Prognostic impact of lymph node parameters in distal cholangiocarcinoma after pancreaticoduodenectomy. World J Surg Oncol 2020;18:262.
20. Byrling J, Andersson R, Sasor A, Lindell G, Ansari D, Nilsson J, et al. Outcome and evaluation of prognostic factors after pancreaticoduodenectomy for distal cholangiocarcinoma. Ann Gastroenterol 2017;30:571-577.
21. Li X, Lin H, Sun Y, Gong J, Feng H, Tu J. Prognostic significance of the lymph node ratio in surgical patients with distal cholangiocarcinoma. J Surg Res 2019;236:2-11.
22. Oshiro Y, Sasaki R, Kobayashi A, Murata S, Fukunaga K, Kondo T, et al. Prognostic relevance of the lymph node ratio in surgical patients with extrahepatic cholangiocarcinoma. Eur J Surg Oncol 2011;37:60-64.
23. You Y, Shin YC, Choi DW, Heo JS, Shin SH, Kim N, et al. Proposed modification of staging for distal cholangiocarcinoma based on the lymph node ratio using Korean Multicenter Database. Cancers (Basel) 2020;12:762.
24. Ito K, Ito H, Allen PJ, Gonen M, Klimstra D, D'Angelica MI, et al. Adequate lymph node assessment for extrahepatic bile duct adenocarcinoma. Ann Surg 2010;251:675-681.