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

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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 are 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...
Prognostic value of LNR in DCC

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-vascular invasion.

| 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 |             |
| 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.
| Characteristic          | 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            | 0.744      |
| Age (yr)               |              |          |               |                 |            |           |           |               |                 | 0.935      |
| < 65                   | 72 (44.4)  | 65.0     | 48.3          | 63.1            | 51.0       | 48.9      | 41.3      | 49.7          | 23.0            | 0.826      |
| ≥ 65                   | 90 (55.6)  | 68.9     | 39.9          | 57.7            | 41.0       | 52.5      | 33.2      | 44.7          | 30.0            | 0.206      |
| Sex                    |              |          |               |                 |            |           |           |               |                 |           |
| Male                   | 104 (64.2) | 67.5     | 44.5          | 60.4            | 45.0       | 54.5      | 41.6      | 52.0          | 36.0            | 0.073      |
| Female                 | 58 (35.8)  | 66.2     | 45.4          | 61.9            | 41.0       | 44.0      | 31.7      | 40.5          | 16.0            |           |
| CEA (ng/mL)            |              |          |               |                 |            |           |           |               |                 |           |
| < 5.0                  | 122 (75.3) | 72.6     | 47.0          | 64.0            | 49.0       | 56.5      | 43.0      | 52.8          | 35.0            | 0.017      |
| ≥ 5.0                  | 33 (20.4)  | 51.8     | 44.4          | 55.2            | 24.0       | 32.8      | 16.4      | 21.1          | 11.0            | 0.012      |
| Not checked            | 7 (4.3)    |          |               |                 |            |           |           |               |                 |           |
| CEA (ng/mL)            |              |          |               |                 |            |           |           |               |                 |           |
| < 3.0                  | 76 (46.9)  | 77.4     | 59.8          | 73.4            | 52.0       | 64.6      | 49.9      | 59.5          | 45.0            | 0.017      |
| ≥ 3.0                  | 79 (48.8)  | 60.0     | 33.7          | 51.6            | 35.0       | 39.8      | 27.9      | 36.9          | 14.0            | 0.005      |
| Not checked            | 7 (4.3)    |          |               |                 |            |           |           |               |                 |           |
| CA19-9 (U/mL)          |              |          |               |                 |            |           |           |               |                 | 0.159      |
| < 37                   | 57 (35.2)  | 77.9     | 50.8          | 68.4            | 43.0       | 41.2      | 30.5      | 40.8          | 16.0            |           |
| ≥ 37                   | 103 (63.6) | 62.5     | 42.4          | 57.7            | 36.0       | 70.7      | 54.4      | 59.7          | 91.0            | 0.008      |
| Not checked            | 7 (4.3)    |          |               |                 |            |           |           |               |                 |           |
| CA19-9 (U/mL)          |              |          |               |                 |            |           |           |               |                 |           |
| < 78                   | 78 (48.1)  | 71.3     | 48.9          | 65.1            | 51.0       | 65.9      | 47.3      | 54.8          | 45.0            | 0.351      |
| ≥ 78                   | 82 (50.6)  | 64.5     | 42.3          | 57.9            | 39.0       | 38.2      | 29.8      | 39.4          | 14.0            | 0.008      |
| Not checked            | 2 (1.2)    |          |               |                 |            |           |           |               |                 |           |
| Operation type         |              |          |               |                 |            |           |           |               |                 |           |
| PD                     | 144 (88.9) | 68.2     | 45.9          | 62.1            | 41.0       | 51.4      | 40.4      | 49.8          | 29.0            | 0.229      |
| BDR                    | 18 (11.1)  | 56.3     | 32.8          | 38.4            | 26.0       | 47.6      | 19.0      | 29.3          | 16.0            | 0.220      |
| Combined vascular resection |            |          |               |                 |            |           |           |               |                 |           |
| No                     | 156 (96.3) | 68.0     | 45.1          | 61.3            | 45.0       | 52.4      | 39.2      | 49.1          | 29.0            | 0.314      |
| Yes                    | 6 (3.7)    | 40.0     | 40.0          | 22.6            | 15.0       | 16.7      | 16.7      | 14.5          | 7.0             | 0.126      |
| Gross appearance       |              |          |               |                 |            |           |           |               |                 |           |
| Polypoid or nodular    | 44 (27.2)  | 80.7     | 57.0          | 72.1            | 51.0       | 63.1      | 55.2      | 64.6          |                 | 0.103      |
| Infiltrative           | 118 (72.8) | 61.6     | 39.2          | 55.9            | 36.0       | 45.8      | 29.9      | 40.2          | 17.0            | 0.019      |
| Differentiation        |              |          |               |                 |            |           |           |               |                 |           |
| Well                   | 58 (35.8)  | 83.2     | 48.2          | 68.4            | 51.0       | 68.8      | 55.2      | 64.4          | 91.0            | < 0.001    |
| Moderate               | 77 (47.5)  | 67.7     | 48.5          | 63.3            | 41.0       | 47.3      | 35.5      | 43.2          | 21.0            | < 0.001    |
| 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)                                   |         |                  |           |               |                |          |     |           |           |               |                |          |     |
| ≤ 2.0                                       | 93 (57.4) | 69.6             | 46.0     | 62.6          | 49.0           | 0.623     |     | 54.9      | 39.7      | 50.1          | 35.0          | 0.228     |
| > 2.0                                       | 69 (42.6) | 63.3             | 42.7     | 58.3          | 36.0           |           |     |           |           |               |                |          |     |
| T-stage (AJCC 7th)                          |         |                  |           |               |                | 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                      | 92 (56.8) |                |           |               |                | 0.012     |     |           |           |               |                | 0.002     |
| AJCC 7th stage                              |         |                  |           |               |                | 0.061     |     |           |           |               |                | 0.004     |
| I                                            | 25 (15.4) | 27.4             | 27.4     | 57.7          | 35.0           | 47.0      | 25.6 | 37.3      | 16.0       |               |                |          |     |
| II                                           | 67 (41.3) | 55.7             | 30.0     | 48.0          | 29.0           | 35.4      | 23.5 | 33.2      | 12.0       |               |                |          |     |
| Classified as AJCC 8th                      | 92 (56.8) |                |           |               |                | 0.012     |     |           |           |               |                | 0.002     |
| 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           | 47.0      | 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          | 64.8           | 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.
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 58.5% at 5 years. The Kaplan-Meier curve and log-rank test were used to analyze the effect of clinicopathological factors on overall survival.

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)      | 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 analysis | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |   |   |
|                                |        | 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              | 0.869          | 39.4             | 30.0 |               |               |               |               |     |
| **Age (yr)**                    |        |                |                   |               |                 |     |                |               |               |               |     |
| < 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**                         |        |                |                   |               |                 |     |                |               |               |               |     |
| 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)**                 |        |                |                   |               |                 |     |                |               |               |               |     |
| < 5.0                           | 117 (75.5) | 48.4          | 51.0              |               | 44.2             | 36.0 |               |               |               |               | 0.021|
| ≥ 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) | 0.185          |                   |               | 0.028             | 0.008 |               |               |               |               |     |
| **CEA (ng/mL)**                 |        |                |                   |               |                 |     |                |               |               |               |     |
| < 3.0                           | 75 (48.4) | 60.8          | -                 |               | Reference        |     |                |               |               |               | 0.010|
| ≥ 3.0                           | 73 (47.1) | 35.6          | 39.0              | 1.855 (0.9.3–3.808) | 0.092 |     |                |               |               |               | 0.990 (1.957–3.746) | 0.033 |
| Not checked                     | 7 (4.5) | 0.181          |                   |               | 0.028             | 0.008 |               |               |               |               |     |
| **CA19-9 (U/mL)**               |        |                |                   |               |                 |     |                |               |               |               |     |
| < 37                            | 56 (36.1) | 52.0          | -                 |               | 55.3             | 91.0 | Reference |               |               |               |     |
| ≥ 37                            | 97 (62.6) | 44.2          | 39.0              | 1.047 (0.386–2.843) | 0.092 |     |                |               |               |               | 0.928 | (0.708–2.318) | 0.413 |
| Not checked                     | 2 (1.3) | 0.463          |                   |               | 0.013             |     |                |               |               |               | 0.163 |
| **Operation type**              |        |                |                   |               |                 |     |                |               |               |               | 0.013 |
| PD                              | 139 (89.7) | 46.7          | 49.0              | 0.389          | 41.1             | 29.0 |               |               |               |               | 0.353 |
| BDR                             | 16 (10.3) | 38.6          | 45.0              |               | 22.5             | 36.0 |               |               |               |               |     |
| **Combined vascular resection** |        |                |                   |               |                 |     |                |               |               |               | 0.006 |
| No                              | 149 (96.1) | 46.9          | 49.0              | 0.258          | 40.5             | 31.0 |               |               |               |               | 0.093 |
| Yes                             | 6 (3.9) | 40.0          | 15.0              |               | 16.7             | 7.0 |               |               |               |               |     |
| **Gross appearance**            |        |                |                   |               |                 |     |                |               |               |               | 0.019 |
| Polypoid or nodular             | 43 (27.7) | 58.6          | -                 | 0.106          | 56.5             | - | Reference |               |               |               |     |
| Infiltrative                    | 112 (72.3) | 40.8          | 38.0              |               | 30.8             | 19.0 | 1.931 (0.994–3.748) | 0.052 |     |
| **Differentiation**             |        |                |                   |               |                 |     |                |               |               |               | < 0.01 |
| Well                            | 54 (34.8) | 51.6          | -                 |               | Reference        |     |                |               |               |               | 0.001 |
| Moderate                        | 75 (48.4) | 49.2          | 41.0              | 1.515 (0.728–3.154) | 0.267 |     |                |               |               |               | 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 |     |
Table 4. Continued

| Characteristic                  | No (% ) | Overall survival | Disease-free survival |
|---------------------------------|---------|------------------|-----------------------|
|                                 |         | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
|                                 |         | 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) ≤ 2.0                 | 88 (56.8) | 48.5 | 51.0 | 0.517 | 0.219 | 41.2 | 36.0 |
| > 2.0                           | 67 (43.2) | 43.4 | 38.0 | 0.049 | 0.003 | 36.6 | 21.0 |
| T-stage (AJCC 7th)              |          |        |                |          |        |        |          |                |
| 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 stage    | 66 (42.6) |        |                |          |        |        |          |                |
| AJCC 7th stage                  |          |        |                |          |        |        |          |                |
| 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 stage    | 66 (42.6) |        |                |          |        |        |          |                |
| Assessed LN count               |          |        |                |          |        |        |          |                |
| < 12                            | 51 (32.9) | 46.8 | 49.0 | 0.912 | 0.877 | 40.7 | 35.0 |
| ≥ 12                            | 104 (67.1) | 46.3 | 41.0 | 0.004 | < 0.001 | 38.3 | 29.0 |
| Positive LN count               |          |        |                |          |        |        |          |                |
| 0                               | 100 (64.5) | 57.9 | -   | Reference | 49.8 | 47.0 | Reference |
| 1–3                             | 41 (26.5) | 29.5 | 41.0 | 1.145 (0.276–8.460) | 0.007 | 0.20 | 4.01 | 6.0 |
| ≥ 4                             | 14 (9.0)  | 0.0  | 20.0 | 6.347 (2.276–18.406) | < 0.001 | 0.0  | 6.0 |
| LNR                             |          |        |                |          |        |        |          |                |
| 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 (0.241–2.312) | 0.996 | 36.3 | 30.0 | 0.761 (0.378–1.531) | 0.443 |
| ≥ 0.2                           | 21 (13.5) | 0.0  | 20.0 | 3.001 (1.356–7.046) | 0.001 | 0.0  | 6.0 | 3.394 (1.524–7.560) | 0.003 |
| Perineural invasion             |          |        |                |          |        |        |          |                |
| 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        |          |        |                |          |        |        |          |                |
| Negative                        | 117 (75.5) | 48.6 | 51.0 | 0.135 | 0.038 | 43.2 | 35.0 | Reference |
| Positive                        | 38 (24.5) | 37.0 | 35.0 | 0.036 | 0.036 | 27.0 | 12.0 | 1.144 (0.539–2.426) | 0.727 |
| Adjuvant treatment              |          |        |                |          |        |        |          |                |
| No                              | 108 (69.7) | 52.8 | -   | 0.493 | 0.585 | 41.8 | 30.0 |
| Chemotherapy                    | 39 (25.2) | 31.3 | 39.0 | 0.500 | 0.500 | 33.0 | 14.0 |
| Radiotherapy                    | 3 (1.9)  | 50.0 | 23.0 | 0.500 | 0.500 | 50.0 | 11.0 |
| CCRT                            | 5 (3.2)  | 40.0 | 18.0 | 53.3 | - | 1.144 (0.539–2.426) | 0.727 |

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).

**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 58.3% 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. Os-hiro 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

**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.

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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 further studies.

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**CONFLICT OF INTEREST**

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

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

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