Langenbeck's Archives of Surgery (2019) 404:581–588
https://doi.org/10.1007/s00423-019-01807-9

ORIGINAL ARTICLE

Validation of the prognostic performance in various nodal staging systems for gallbladder cancer: results of a multicenter study

Woohyung Lee[1,2] · Chi-Young Jeong[1] · Young Hoon Kim[3] · Young Hoon Roh[3] · Myung Hee Yoon[4] · Hyung Il Seo[4] · Jeong-Ik Park[5] · Bo-Hyun Jung[5] · Dong Hoon Shin[6] · Young Il Choi[6] · Je Ho Ryu[7] · Kwang Ho Yang[7] · Chang Soo Choi[8] · Yo-Han Park[8] · Yang Won Nah[9] · Soon-Chan Hong[1]

Received: 10 February 2019 / Accepted: 17 July 2019 / Published online: 14 August 2019

Abstract

Background Although the current nodal staging system for gallbladder cancer (GBC) was changed based on the number of positive lymph nodes (PLN), it needs to be evaluated in various situations.

Methods We reviewed the clinical data for 398 patients with resected GBC and compared nodal staging systems based on the number of PLNs, the positive/retrieved LN ratio (LNR), and the log odds of positive LN (LODDS). Prognostic performance was evaluated using the C-index.

Results Subgroups were formed on the basis of an restricted cubic spline plot as follows: PLN 3 (PLN = 0, 1–2, ≥ 3); PLN 4 (PLN = 0, 1–3, ≥ 4); LNR (LNR = 0, 0–0.269, ≥ 0.27); and LODDS (LODDS < − 0.8, − 0.8–0, ≥ 0). The oncological outcome differed significantly between subgroups in each system. In all patients with GBC, PLN 4 (C-index 0.730) and PLN 3 (C-index 0.734) were the best prognostic discriminators of survival and recurrence, respectively. However, for retrieved LN (RLN) ≥ 6, LODDS was the best discriminator for survival (C-index 0.852).

Conclusion The nodal staging system based on PLN was the optimal prognostic discriminator in patients with RLN < 6, whereas the LODDS system is adequate for RLN ≥ 6. The following nodal staging system considers applying different systems according to the RLN.

Keywords Gallbladder cancer · Prognostic performance · Staging system · Restricted cubic spline model

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00423-019-01807-9) contains supplementary material, which is available to authorized users.

✉ Soon-Chan Hong
hongsc@gnu.ac.kr

[1] Department of Surgery, Gyeongsang National University Hospital, Gyeongsang National University, College of Medicine, 79 Gangnam-ro, Jinju 660-702, Republic of Korea

[2] Division of Hepato-Biliary and Pancreatic Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Ulsan, Republic of Korea

[3] Department of Surgery, Dong-A University Hospital, Dong-A University, College of Medicine, Busan, Republic of Korea

[4] Department of Surgery, Biomedical Research Institute, Pusan National University Hospital, Pusan National University, College of Medicine, Busan, Republic of Korea

[5] Department of Surgery, Haeundae Paik Hospital, Inje University, College of Medicine, Busan, Republic of Korea

[6] Department of Surgery, Kosin University Gospel Hospital, Kosin University, College of Medicine, Busan, Republic of Korea

[7] Department of Surgery, Pusan University Yangsan Hospital, Pusan University, College of Medicine, Busan, Republic of Korea

[8] Department of Surgery, College of Medicine, Inje University, Busan Paik Hospital, Busan, Republic of Korea

[9] Department of Surgery, Ulsan University Hospital, Ulsan University, College of Medicine, Ulsan, Republic of Korea

Introduction

Gallbladder cancer (GBC) is a rare gastrointestinal malignancy with a poor prognosis [1]. The known prognostic factors for worse survival include microscopic remnant tumor, lymph node (LN) metastasis, and poorly differentiated tumor [2]. LN metastasis is the strongest risk factor, even after curative resection [3, 4]. Recently, the American Joint Committee on Cancer (AJCC) 8th edition cancer staging system was presented. Major changes are tumor-invaded, perimuscular connective tissue (T2) which was divided into the peritoneal (T2a) and the hepatic (T2b) side. The patients with T2b showed more frequent nodal involvement as well as vascular and neural invasion compared with the patients with T2a in T2 GBC [5]. Furthermore, radical surgery was recommended for T2b GBC patients compared with T2a GBC patients [6]. The nodal staging system was also changed in the AJCC 8th edition. Contrary to the site of metastatic lymph nodes in the AJCC 7th edition, the new staging system was based on the number of positive LN (PLN). N1 and N2 were defined as PLN 1–3 and PLN ≥ 4 [7]. However, the adequate extent of LN dissection (LND) and the number of retrieved LN (RLN) are still controversial [8]. Furthermore, the number of RLNs differs in Western and Eastern countries. Although patients with four or more RLNs do not present a problem in applying the new staging system, the prognosis of patients with a smaller number of RLNs may be underestimated in this nodal staging system. There is a need to develop an ancillary nodal staging system for these patients. Previous studies compared the prognostic performance of various nodal staging systems. However, previous studies used arbitrary values to divide patients into subgroups [9–11]. Recently, an objective statistical method was introduced to form subgroups on the basis of dose-response relationships, termed the "restricted cubic spline" (RCS) model [12–14]. We evaluated the usefulness of the RCS model for dividing patients into subgroups in different nodal staging systems and identified the best prognostic nodal staging system for all patients with resected GBC and the patients with a small number of RLNs.

Methods

Patients, study design, and data collection

We identified patients who underwent curative intent surgery for GBC at eight tertiary referral centers between January 2000 and December 2015. The patients who underwent R2 resection, surgery without LND, or were diagnosed with T1a or T4 GBC were excluded because almost all T1a GBC patients underwent simple cholecystectomy without LND and T4 GBC was not indicated for curative resection in previous studies.

The patients underwent curative intent radical cholecystectomy including liver and LN resection. The surgeon dissected the nodes around the hepatoduodenal ligament, common hepatic artery, and retropancreas. Bile duct resection with or without hepatectomy, pancreaticoduodenectomy, or hepatopancreaticoduodenectomy was performed according to tumor invasion and its extent. To evaluate the oncological outcomes on the basis of the node status, four nodal staging systems were used: the AJCC 7th edition N stage; PLN; positive/retrieved lymph node ratio (LNR); and log odds of lymph node ratio (LODDS; LODDS = log [the number of PLN + 0.5]/[the number of negative LN + 0.5]). Because each nodal staging system contains continuous variables, except for the AJCC 7th edition nodal system, the subgroups had to be formed using the RCS model, and which was helpful in characterizing the dose-response association between continuous exposure and outcomes for nonlinear associations. The nodal staging systems were also compared with regard to the prognostic performance to identify the best nodal staging system to distinguish prognoses, and internal validation was performed through 1000 times bootstrapping with the calibration plot.

The following data were retrieved from the patients' medical records for analysis: preoperative data (age, sex, American Society of Anesthesiologists [ASA] score, and tumor markers); intraoperative data (extent of resection, operation time, and blood loss); pathological data (histological grade, RLN, PLN, and the presence of angiolymphatic, venous, and perineural invasion); and postoperative data (hospital stay and postoperative complications, which were classified using the Clavien-Dindo system) [15].

The patients were followed up twice a year with imaging studies and the measurement of tumor markers. Recurrence was evaluated according to the imaging findings. The patients with R1 resection, node metastasis, or invasion of perimuscular connective tissue underwent adjuvant chemotherapy or chemoradiotherapy [16]. This study was approved by the Institutional Review Board of each institution.

Statistical analyses

Data are expressed as means and standard deviations. The χ^2 test was used to compare categorical variables and the Student's *t* test to compare continuous variables between subgroups. We used RCS plots to determine cut-off values. The values on the *Y*-axis were estimated as the natural logarithms of the risk of disease-related death or recurrence after surgery. The inflection point represented the point of stable or reduced risk of death or recurrence and was used as the cut-off value for the subgroups in the nodal staging systems.

The multivariable Cox proportional hazards model was used to determine the prognostic factors for disease-related death or recurrence. Prognostic performances were compared with concordance statistics (C-index). Higher C-index values

are helpful in choosing a better model. In all analyses, $p < 0.05$ (two-sided) was considered statistically significant. SPSS® version 22.0 (SPSS Corp., Chicago, IL, USA) and R® statistics version 3.3.2 (R Foundation, Vienna, Austria) were used for all analyses.

Results

The number of patients included was 398, and 121 (30.4%) patients displayed nodal metastasis. The mean numbers of RLN and PLN were 6.3 and 0.7, respectively, and the mean values of LNR and LODDS were 0.14 and − 0.697, respectively. The mean patient age was 67.1 and 55.8% of the patients were female. Cholecystectomy with LND and radical cholecystectomy including liver and LN resection was performed in 190 (47.8%) and 208 patients (52.3%), respectively. CBD resection with hepaticojejunostomy, pancreaticoduodenectomy, or hepaticopancreaticoduodenectomy was performed in 18 (4.5%), one (0.3%) patient, and in one (0.3%) patient, respectively. The mean hospital stay was 10.9 days and 53 (13.3%) patients experienced postoperative complications including fluid collection (17, 4.2%), bile leakage (4, 1.0%), bleeding (7, 1.8%), wound problem (11, 2.8%), atelectasis, pneumonia (4, 1.0%), and cerebral infarction (1, 0.3%). And four (1.1%) patients experienced severe complication, which was classified using the Clavien-Dindo classification IIIb or more (Table 1). In the PLN nodal staging system, the RCS plot for survival was not stable according to PLN, and the rate of increase changed around PLN = 3 or 4. We divided the group into three subgroups on the basis of PLN = 3 or 4: the PLN 3 system comprised subgroups PLN = 0 ($n = 278$), 1–2 ($n = 79$), and ≥ 3 ($n = 41$), and the PLN 4 system comprised subgroups PLN = 0 ($n = 278$), 1–3 ($n = 94$), and ≥ 4 ($n = 26$). In the LNR staging system, the risk of disease-related death or recurrence became stable or decreased approximately 0.27 and 0.78, respectively. The decreasing risk of the subgroup LNR ≥ 0.78 was unusual. Because a previous study demonstrated that a small number of RLNs affected the analysis for LNR, we analyzed the RCS plot based on LNR for patients with RLN ≥ 2 [17]. The RCS plot for survival showed an exponential curve with no decreasing curve, and the RCS plot for recurrence showed a continuously increasing curve. Therefore, we divided the group into three subgroups, i.e., LNR = 0 ($n = 278$), 0–0.269 ($n = 43$), and ≥ 0.27 ($n = 77$). In the LODDS staging system, the first and second inflection points were observed around LODDS = − 0.8 and 0, respectively. Therefore, three subgroups were classified as LODDS = < − 0.8 ($n = 199$), − 0.8–0 ($n = 147$), and ≥ 0 ($n = 52$) (Fig. 1). Perioperative outcomes were compared among subgroups in each nodal staging system (Supplementary table 1–4).

Discrimination of the oncological outcomes in each nodal staging system

The median follow-up period was 26 months. The 1-, 3-, and 5-year overall survival (OS) rates were 95.8, 83.1, and 77.1%, respectively, and the 1-, 3-, and 5-year recurrence-free survival (RFS) rates were 85.3, 72.1, and 64.3%, respectively. In the AJCC 7th edition nodal staging system, the N0, N1, and N2 stages differed significantly in the 5-year OS rates (88.0, 52.8, and 0%, respectively, $p < 0.001$) and RFS rates (80.2, 27.7, and 0%, respectively, $p < 0.001$). In the PLN 3 nodal staging system, the 0, 1–2, and ≥ 3 PLN subgroups differed significantly in the 5-year OS rates (87.5, 60.4, and 34.5%, respectively, $p < 0.001$) and the RFS rates (80.2, 34.0, and 13.2%, respectively, $p < 0.001$), and with no overlapping points. In the PLN 4 system, the 0, 1–3, and ≥ 4 PLN subgroups differed significantly in the 5-year OS rates (87.5, 59.3, and 26.3%, respectively, $p < 0.001$) and the RFS rates (80.2, 29.7, and 19.0%, respectively, $p < 0.001$). In the LNR system, the LNR = 0, 0–0.269, and ≥ 0.27 subgroups differed significantly in the 5-year OS rates in patients with RLN ≥ 2 (88.2, 65.4, and 38.1%, respectively, $p < 0.001$) and with no overlapping point. The LNR subgroups also differed significantly in the 5-year RFS rates (85.0, 23.5, and 18.8%, respectively, $p < 0.001$) with no overlapping point. In the LODDS staging system, the LODDS subgroups < − 0.8, − 0.8–0, and ≥ 0 differed significantly in the 5-year OS rates (89.1, 73.2, and 46.7%, respectively, $p < 0.001$) and the RFS (80.1, 56, and 31.5%, respectively, $p < 0.001$), with no overlapping point (Fig. 2).

Comparison of the prognostic performance of different nodal staging systems

In a univariate analysis, the following factors were related to worse patient survival: carcinoembryonic antigen (CEA) ≥ 5 ng/ml; carbohydrate antigen (CA) 19–9 ≥ 37 U/ml; lymphatic invasion; venous invasion; perineural invasion; R1 resection; and advanced T stage; and LN metastasis as well (Supplementary Table 6). In the survival model, PLN 4 was the best system for discriminating prognoses, on the basis of a higher C-index (C-index 0.730). A univariate analysis of recurrence was performed using the significant factors CEA ≥ 5 ng/ml, CA 19–9 ≥ 37 U/ml, intraoperative transfusion, poorly differentiated tumor, lymphatic invasion, venous invasion, perineural invasion, R1 resection, and advanced T stage, and LN metastasis as well (Supplementary Table 7). In the recurrence model, the PLN 3 system had the best discriminating power (C-index 0.734) (Table 2). The bootstrapped calibration plot showed no difference between the observed and predicted probabilities in the PLN systems.

In the AJCC 8th edition, the recommended number of RLNs was six or more. We evaluated the oncological benefit

Table 1 Patient characteristics ($n = 398$)

	n (%) or mean ± SD
Age (years)	67.1 ± 10.3
Sex (M/F)	176 (44.2)/222 (55.8)
ASA score (I/II/III)	35 (9.2)/245 (64.1)/65 (17.0)
Preoperative CEA (ng/ml)	5.7 ± 18.2
Preoperative CA 19–9 (U/ml)	178.1 ± 916.3
Resection margin (R0/R1)	375 (94.2)/23 (5.8)
T stage (1b/2/3) (7th edition AJCC)	70 (17.6)/267 (67.1)/61 (15.3)
N stage (0/1/2) (7th edition AJCC)	277 (69.6)/115 (28.9)/6 (1.5)
No. retrieved LN	6.3 ± 5.3
No. of positive LN	0.7 ± 1.6
No. of negative LN	5.5 ± 5.1
LNR	0.14 ± 0.29
LODDS	− 0.697 ± 0.589
Cell differentiation (WD/MD/PD/UD)	176 (44.2)/125 (31.4)/49 (12.3)/6 (1.5)
Lymphatic invasion	72 (23.5)
Neural invasion	71 (20.8)
Vascular invasion	50 (14.6)
Hospital stay (days)	10.9 ± 6.8
Postoperative complication	53 (13.3)
Severe complication (CD classification≥IIIb)	4 (1.1)
Adjuvant therapy	185 (46.4)
Chemotherapy	92 (23.1)
Radiotherapy	10 (2.5)
Chemoradiotherapy	83 (20.9)

SD, standard deviation; *ASA*, American Society of Anaesthesiologists; *CEA*, carcinoembryonic antigen; *CA 19–9*, carbohydrate antigen 19–9; *AJCC*, American Joint Committee on Cancer; *LN*, lymph node; *LNR*, lymph node ratio; *LODDS*, log odds of metastatic lymph nodes; *WD*, well-differentiated; *MD*, moderately differentiated; *PD*, poorly differentiated; *UD*, undifferentiated; *CD* system, Clavien-Dindo classification system

between the RLN < 6 ($n = 160$) and RLN ≥ 6 ($n = 117$) subgroups in N0 ($n = 277$, 69.5%). However, the 5-year OS rates (86.4 vs 83.1%, $p = 0.611$) and RFS rates (73.8 vs 80.9%, $p = 0.327$) did not differ significantly between the two subgroups. Furthermore, we evaluated the similarity of the prognostic performance according to the number of the RLN. In patients with RLN ≥ 6, the LODDS system showed the best prognostic performance regarding patient survival (C-index 0.852) and recurrence (C-index 0.867) compared with other nodal staging systems (Table 3).

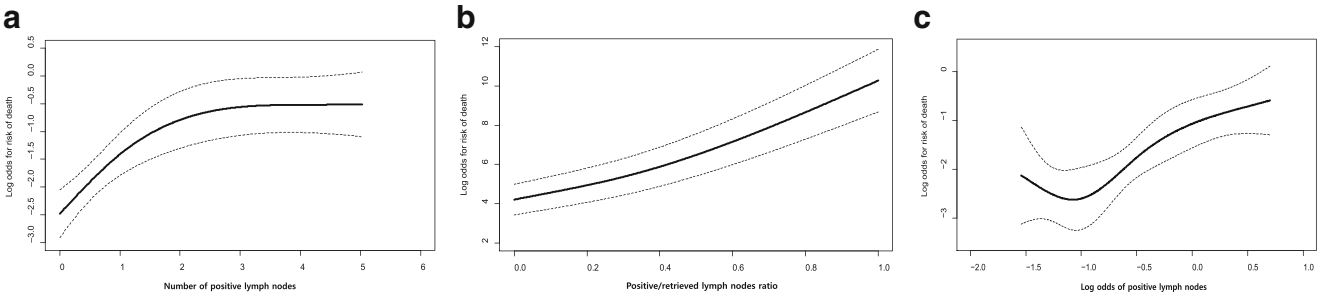

Fig. 1 Restricted cubic spline plots of survival. **a** Restricted cubic spline plot of survival showed an increasing pattern with an increasing number of positive lymph nodes. The inflection point was observed around three or four PLN. Dotted lines indicate a 95% confidence interval. **b** Restricted cubic spline plot of survival in patients with ≥ 2 retrieved lymph nodes demonstrated an exponential curve with no decreasing curve and an inflection point approximately 0.3. Dotted lines indicate a 95% confidence interval. **c** Restricted cubic spline plot of survival demonstrated an inflection point of approximately − 0.8 and 0 log odds of the positive lymph nodes. A dotted line indicates a 95% confidence interval

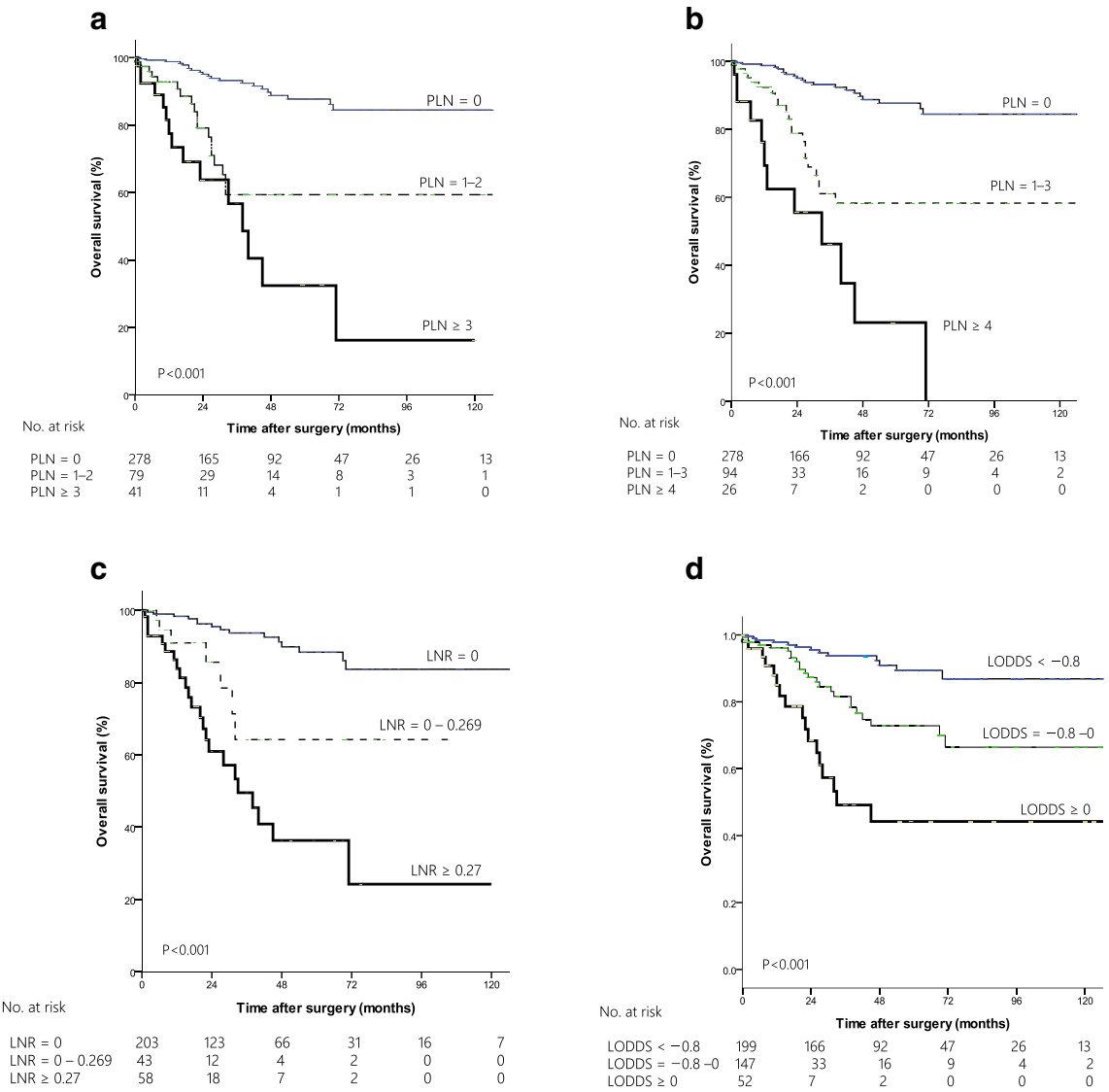

Fig. 2 Survival curves in each nodal staging system. The 5-year overall survival was compared among the subgroups in each nodal staging system using the Log-rank test. **a** Three subgroups were divided based on 0, 1–2, and ≥ 3 PLN, and the 5-year overall survival rates were statistically significantly different (87.5%, 60.4%, and 34.5%, respectively, $p < 0.001$). **b** The nodal staging system was based on four PLN. Three subgroups were defined based on 0, 1–3, and ≥ 4 PLN and the 5-year overall survival rate differed statistically significantly between them (87.5%, 59.3%, and 26.3%, respectively, $p < 0.001$). **c** Three subgroups were defined based on LNRs of 0, 0–0.269, and ≥ 0.27 and the five-year overall survival rates differed statistically significantly among these groups (88.2%, 65.4%, and 38.1%, respectively $p < 0.001$) in patients with ≥ 2 retrieved lymph nodes. **d** Three subgroups were defined based on < − 0.8, − 0.8–0, and ≥ 0 log odds of lymph nodes, and the 5-year overall survival rates were statistically significantly different in each subgroup (89.1%, 73.2%, and 46.7%, respectively, $p < 0.001$)

Discussion

GBC is the most common cancer of the biliary tract. Although its incidence is relatively low in Western countries, it is higher in several other countries, including Chile, Korea, Japan, and India [4, 6, 18]. GBC progresses aggressively and has a poor prognosis [2]. Known prognostic factors for worse survival are old age, R1 resection, nodal metastasis, and a poorly differentiated tumor [3, 19, 20], and nodal metastasis is a strong prognostic factor.

Previous nodal staging systems in the AJCC 5-7th edition emphasized the location of the PLN. This system has been established according to studies which revealed a worse prognosis in patients with PLN around the peripancreatic, celiac axis, or periaortocaval area [21, 22]. In recent NCCN guidelines, the extent of the lymph node dissection is recommended according to the location of the PLN [23]. However, recent studies revealed similar prognostic performance between the nodal staging system based on the location or numerical number and the location system has a weak discrimination power

Table 2 Oncologic discrimination according to the different nodal staging systems in patients with resected gallbladder cancer

	Overall survival					Recurrence-free survival				
	5-year OS (%)	HR	95% CI	*p* value	C-index	5-year RFS (%)	HR	95% CI	*p* value	C-index
AJCC 7th					0.724					0.718
N0	88.03*	1				80.2*	1			
N1	52.82	5.76	3.27–10.13	< 0.001		27.71	5.6	3.72–8.42	< 0.001	
N2	0	18.13	4.06–80.97	< 0.001		0	3.33	0.45–24.48	0.238	
PLN 3					0.727					0.734
0	87.58*	1				80.23*	1			
1–2	60.43	4.11	2.16–7.8	< 0.001		34.09	4.27	2.69–6.79	< 0.001	
≥ 3	34.55	9.31	4.76–18.18	< 0.001		0	9.99	5.98–16.67	< 0.001	
PLN 4 (AJCC 8th)					0.730					0.727
0	87.58*	1				80.23*	1			
1–3	59.35	4.19	2.27–7.75	< 0.001		29.77	5.04	3.28–7.74	< 0.001	
≥ 4	26.39	12.24	5.98–25.07	< 0.001		19.05	9.7	5.11–18.42	< 0.001	
LNR					0.723					0.728
0	87.58*	1				80.23*	1			
0–0.269	65.44	3.62	1.53–8.54	0.003		23.51	4.43	2.5–7.87	< 0.001	
≥ 0.27	46.97	6.49	3.63–11.62	< 0.001		27	6.28	4.05–9.73	< 0.001	
LODDS					0.689					0.682
< − 0.8	89.15*	1				80.16*	1			
− 0.8–0	73.21	2.95	1.5–5.8	0.002		56	2.46	1.53–3.95	< 0.001	
≥ 0	46.74	7.05	3.38–14.67	< 0.001		31.55	5.75	3.36–9.83	< 0.001	

OS, overall survival; *HR*, hazard ratio; *CI*, confidence interval; *RFS*, recurrence-free survival; *PLN*, number of positive lymph nodes; *LNR*, lymph node ratio; *LODDS*, log odds of positive lymph nodes

*Statistically significant difference in each subgroup in different nodal stating systems

in patients with PLN [24]. The recent nodal staging system based on PLN has the advantage of being able to discriminate the prognosis in patients with nodal metastasis [9, 25]. In this study, the PLN 4 and PLN 3 systems displayed the best prognostic performance for patient survival and recurrence, respectively. Previous studies have also shown that PLN ≥ 4 is the cut-off value for worse survival and is a prognostic factor for survival in GBC [9]. The recently published AJCC 8th edition nodal staging system is the same as the PLN 4 system [26]. However, the PLN system is insufficient to distinguish the prognoses of GBC patients with a small number of RLN.

Table 3 Prognostic performance based on the C-index according to the different nodal staging systems in gallbladder patients with retrieved lymph nodes ≥ 6

	Overall survival	Recurrence-free survival
PLN 3	0.817	0.842
PLN 4 (AJCC 8th)	0.819	0.844
LNR	0.809	0.834
LODDS	0.852	0.867

PLN, number of positive lymph nodes; *LNR*, lymph node ratio; *LODDS*, log odds of positive lymph nodes

Only 12% of GBC patients had retrieved RLN 6 or more [27]. Validation of the current nodal staging system is needed as well as the establishment of ancillary nodal staging systems in various situations.

Theoretically, LNR is an excellent nodal index for discriminating prognoses. Previous studies have shown discordant LNR cut-off values for GBC, such as 0.13 or 0.5 [9–11, 28]. In this study, we identified LNR = 0.27 as the cut-off value. Furthermore, this nodal index was appropriate for patients with RLN ≥ 2. LNR may be inappropriate for prediction of the prognosis in all GBC patients. In particular, the prognosis may be underestimated in patients with small numbers of RLN [29]. Another study showed that limited LND may not detect skip metastases [10]. In the present study, 19 (4.7%) patients showed one PLN with one RLN. After exclusion of the patients with RLN = 1, the LNR system showed significant differences in the oncological outcomes between subgroups. In this respect, small number of RLN may be associated with underestimation of the nodal status in patients with GBC. The LNR system is suitable for node-positive patients with sufficient RLN, whereas it is insufficient for discriminating the prognoses of patients with a small number of RLN.

In patients with a small number of RLN, the LODDS system may be a reasonable option. LODDS calculates the odds

of negative and positive LN. A value of 0.5 is added to both the numerator and denominator to avoid singularity [30, 31]. Previous studies have shown that the LODDS system is a better model than the LNR system in breast cancer and gastric cancer patients with limited numbers of RLN [17, 30, 32]. This is because the denominator in LODDS is smaller than the denominator in LNR in patients with limited RLN [17]. In this study, LODDS was more prognostic than other nodal staging systems in large RLN subgroup. However, LODDS may be helpful in this situation. In the PLN 3 or 4 system, the number of RLN is not important for definite nodal staging. However, in case of a large number of RLN, ratio is more important than a simple number of PLN. LNR and LODDS are suitable in this situation and LODDS is more prognostic in this study. Furthermore, real-world practice showed different number of RLN according to the countries [4, 6, 27]. In this study, 46.5% of all patients were retrieved with an LN of six or more. However, another study showed 12% of an RLN of six or more. Considering the discordant practice, if the nodal staging system shows a different prognosis according to RLN, RLN must be considered in the selection of the nodal staging system. In this study, the LODDS system showed more prognostic in RLN ≥ 6, whereas the PLN system was universal in all GBC patients. Therefore, the PLN system is adequate for the patients with an RLN < 6, and LODDS system is suitable for RLN ≥ 6. It is also important to set the guidelines to acquire the appropriate number of lymph nodes, but it is also important to apply different systems depending on the number of lymph nodes obtained.

This study had several limitations. Because GBC is a rare disease, we did not prepare a subset for validation of various nodal staging systems. We did not evaluate the effectiveness of adjuvant therapy on the basis of the various nodal staging systems because there were missing data. This study showed discrepant results compared with previous studies. The authors showed that LNR and LODDS were better than the PLN system in all patient cohorts. However, the present study showed that the PLN system had the best discriminating power in the survival and recurrence in all patients. A previous study showed that LODDS was the best in patients with 4 or more RLN. Similar results were presented in our study. The LODDS system was the best in patients with 6 or more RLN. A larger study is required to confirm these results in nodal staging systems.

In conclusion, the PLN 4 and PLN 3 systems showed the best discriminating power for survival and recurrence, respectively, in all resected GBC patients. However, the LODDS system was the best predictive model in patients with RLN ≥ 6. The following nodal staging system should be considered when applying different systems according to RLN.

Acknowledgments The authors thank the members of the Busan-Ulsan-Kyeungnam HBP Surgery Study Group of Korea for cooperating in this study and for providing the clinicopathologic information for the patients with gallbladder cancer.

Author contributions Study conception and design: Lee, Jeong, YH Kim, Yoon, Hong. Acquisition of data: Lee, KW Kim, Jung, Yang. Analysis and interpretation of data: Lee, Seo, Choi, Ryu, Hong, CS choi, Nah. Drafting of manuscript: Lee, Jeong, JI Park, Chu, Ryu, Shin. Critical revision: Lee, Jeong, Roh, Shin, Hong.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Chan E, Berlin J (2015) Biliary tract cancers: understudied and poorly understood. J Clin Oncol 33(16):1845–1848. https://doi.org/10.1200/JCO.2014.59.7591
2. Aloia TA, Jarufe N, Javle M, Maithel SK, Roa JC, Adsay V, Coimbra FJ, Jarnagin WR (2015) Gallbladder cancer: expert consensus statement. HPB (Oxford) 17(8):681–690. https://doi.org/10.1111/hpb.12444
3. Chen C, Geng Z, Shen H, Song H, Zhao Y, Zhang G, Li W, Ma L, Wang L (2016) Long-term outcomes and prognostic factors in advanced gallbladder cancer: focus on the advanced T stage. PLoS One 11(11):e0166361. https://doi.org/10.1371/journal.pone.0166361
4. Lee SE, Kim KS, Kim WB, Kim IG, Nah YW, Ryu DH, Park JS, Yoon MH, Cho JY, Hong TH, Hwang DW, Choi DW, Korean Association of H-B, Pancreas S (2014) Practical guidelines for the surgical treatment of gallbladder cancer. J Korean Med Sci 29(10):1333–1340. https://doi.org/10.3346/jkms.2014.29.10.1333
5. Shindoh J, de Aretxabala X, Aloia TA, Roa JC, Roa I, Zimmitti G, Javle M, Conrad C, Maru DM, Aoki T, Vigano L, Ribero D, Kokudo N, Capussotti L, Vauthey JN (2015) Tumor location is a strong predictor of tumor progression and survival in T2 gallbladder cancer: an international multicenter study. Ann Surg 261(4):733–739. https://doi.org/10.1097/SLA.0000000000000728
6. Lee W, Jeong CY, Jang JY, Kim YH, Roh YH, Kim KW, Kang SH, Yoon MH, Seo HI, Yun SP, Park JI, Jung BH, Shin DH, Choi YI, Moon HH, Chu CW, Ryu JH, Yang K, Park YM, Hong SC (2017) Do hepatic-sided tumors require more extensive resection than peritoneal-sided tumors in patients with T2 gallbladder cancer? Results of a retrospective multicenter study. Surgery 162:515–524. https://doi.org/10.1016/j.surg.2017.05.004
7. Chun YS, Pawlik TM, Vauthey JN (2018) 8th edition of the AJCC Cancer staging manual: pancreas and hepatobiliary cancers. Ann Surg Oncol 25(4):845–847. https://doi.org/10.1245/s10434-017-6025-x
8. Sternby Eilard M, Lundgren L, Cahlin C, Strandell A, Svanberg T, Sandstrom P (2017) Surgical treatment for gallbladder cancer - a systematic literature review. Scand J Gastroenterol 52(5):505–514. https://doi.org/10.1080/00365521.2017.1284895

9. Amini N, Kim Y, Wilson A, Margonis GA, Ethun CG, Poultsides G, Tran T, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Maithel SK, Pawlik TM (2016) Prognostic implications of lymph node status for patients with gallbladder cancer: a multi-institutional study. Ann Surg Oncol 23(9): 3016–3023. https://doi.org/10.1245/s10434-016-5243-y
10. Birnbaum DJ, Vigano L, Russolillo N, Langella S, Ferrero A, Capussotti L (2015) Lymph node metastases in patients undergoing surgery for a gallbladder cancer. Extension of the lymph node dissection and prognostic value of the lymph node ratio. Ann Surg Oncol 22(3):811–818. https://doi.org/10.1245/s10434-014-4044-4
11. Kim SH, Chong JU, Lim JH, Choi GH, Kang CM, Choi JS, Lee WJ, Kim KS (2016) Optimal assessment of lymph node status in gallbladder cancer. Eur J Surg Oncol 42(2):205–210. https://doi.org/10.1016/j.ejso.2015.10.013
12. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L, Yan H, Lee SF, Mony P, Devanath A, Rosengren A, Lopez-Jaramillo P, Diaz R, Avezum A, Lanas F, Yusoff K, Iqbal R, Ilow R, Mohammadifard N, Gulec S, Yusufali AH, Kruger L, Yusuf R, Chifamba J, Kabali C, Dagenais G, Lear SA, Teo K, Yusuf S, Investigators P (2014) Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med 371(7):612–623. https://doi.org/10.1056/NEJMoa1311889
13. Warensjo E, Byberg L, Melhus H, Gedeborg R, Mallmin H, Wolk A, Michaelsson K (2011) Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study. BMJ 342: d1473. https://doi.org/10.1136/bmj.d1473
14. Lee W, Han HS, Ahn S, Yoon YS, Cho JY, Choi Y (2018) Correlation between resection margin and disease recurrence with a restricted cubic spline model in patients with resected hepatocellular carcinoma. Dig Surg 35(6):520–531. https://doi.org/10.1159/000485805
15. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240(2):205–213. https://doi.org/10.1097/01.sla.0000133083.54934.ae
16. Horgan AM, Amir E, Walter T, Knox JJ (2012) Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol 30(16):1934–1940. https://doi.org/10.1200/JCO.2011.40.5381
17. Chen LJ, Chung KP, Chang YJ, Chang YJ (2015) Ratio and log odds of positive lymph nodes in breast cancer patients with mastectomy. Surg Oncol 24(3):239–247. https://doi.org/10.1016/j.suronc.2015.05.001
18. Coburn NG, Cleary SP, Tan JC, Law CH (2008) Surgery for gallbladder cancer: a population-based analysis. J Am Coll Surg 207(3):371–382. https://doi.org/10.1016/j.jamcollsurg.2008.02.031
19. Cai ZQ, Guo P, Si SB, Geng ZM, Chen C, Cong LL (2017) Analysis of prognostic factors for survival after surgery for gallbladder cancer based on a Bayesian network. Sci Rep 7(1):293. https://doi.org/10.1038/s41598-017-00491-3
20. Cziupka K, Partecke LI, Mirow L, Heidecke CD, Emde C, Hoffmann W, Siewert U, van den Berg N, von Bernstorff W, Stier A (2012) Outcomes and prognostic factors in gallbladder cancer: a single-centre experience. Langenbeck's Arch Surg 397(6):899–907. https://doi.org/10.1007/s00423-012-0950-8
21. Kokudo N, Makuuchi M, Natori T, Sakamoto Y, Yamamoto J, Seki M, Noie T, Sugawara Y, Imamura H, Asahara S, Ikari T (2003) Strategies for surgical treatment of gallbladder carcinoma based on information available before resection. Arch Surg 138(7):741–750; discussion 750. https://doi.org/10.1001/archsurg.138.7.741
22. Miyazaki M, Yoshitomi H, Miyakawa S, Uesaka K, Unno M, Endo I, Ota T, Ohtsuka M, Kinoshita H, Shimada K, Shimizu H, Tabata M, Chijiiwa K, Nagino M, Hirano S, Wakai T, Wada K, Isayama H, Okusaka T, Tsuyuguchi T, Fujita N, Furuse J, Yamao K, Murakami K, Yamazaki H, Kijima H, Nakanuma Y, Yoshida M, Takayashiki T, Takada T (2015) Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition. J Hepatobiliary Pancreat Sci 22(4):249–273. https://doi.org/10.1002/jhbp.233
23. Benson AB 3rd, D'Angelica MI, Abbott DE, Abrams TA, Alberts SR, Saenz DA, Are C, Brown DB, Chang DT, Covey AM, Hawkins W, Iyer R, Jacob R, Karachristos A, Kelley RK, Kim R, Palta M, Park JO, Sahai V, Schefter T, Schmidt C, Sicklick JK, Singh G, Sohal D, Stein S, Tian GG, Vauthey JN, Venook AP, Zhu AX, Hoffmann KG, Darlow S (2017) NCCN guidelines insights: hepatobiliary cancers, version 1.2017. J Natl Compr Cancer Netw 15(5):563–573
24. Negi SS, Singh A, Chaudhary A (2011) Lymph nodal involvement as prognostic factor in gallbladder cancer: location, count or ratio? J Gastrointest Surg 15(6):1017–1025. https://doi.org/10.1007/s11605-011-1528-4
25. Pandey D (2012) Technical description of a regional lymphadenectomy in radical surgery for gallbladder cancer. HPB (Oxford) 14(3): 216–219. https://doi.org/10.1111/j.1477-2574.2011.00430.x
26. Mahul B, Amin SBE, Brookland RK, Jessup JM, Greene FL, Brierley JD, Byrd DR (2017) AJCC cancer staging manual eighth edition.
27. Lee AJ, Chiang YJ, Lee JE, Conrad C, Chun YS, Aloia TA, Vauthey JN, Tzeng CD (2018) Validation of American joint committee on cancer eighth staging system for gallbladder cancer and its lymphadenectomy guidelines. J Surg Res 230:148–154. https://doi.org/10.1016/j.jss.2018.04.067
28. Choi BG, Kim CY, Cho SH, Kim HJ, Koh YS, Kim JC, Cho CK, Kim HJ, Hur YH (2013) Impact of lymph node ratio as a valuable prognostic factor in gallbladder carcinoma, focusing on stage IIIB gallbladder carcinoma. J Korean Surg Soc 84(3):168–177. https://doi.org/10.4174/jkss.2013.84.3.168
29. Ito H, Ito K, D'Angelica M, Gonen M, Klimstra D, Allen P, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR (2011) Accurate staging for gallbladder cancer: implications for surgical therapy and pathological assessment. Ann Surg 254(2):320–325. https://doi.org/10.1097/SLA.0b013e31822238d8
30. Aurello P, Petrucciani N, Nigri GR, La Torre M, Magistri P, Tierno S, D'Angelo F, Ramacciato G (2014) Log odds of positive lymph nodes (LODDS): what are their role in the prognostic assessment of gastric adenocarcinoma? J Gastrointest Surg 18(7):1254–1260. https://doi.org/10.1007/s11605-014-2539-8
31. Tez M, Altundag K (2017) Log odds of metastatic lymph nodes (LODDS) or negative to positive lymph node ratio? Surgery 162: 461. https://doi.org/10.1016/j.surg.2017.01.021
32. Bagante F, Tran T, Spolverato G, Ruzzenente A, Buttner S, Ethun CG, Groot Koerkamp B, Conci S, Idrees K, Isom CA, Fields RC, Krasnick B, Weber SM, Salem A, Martin RC, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Vitiello G, JN IJ, Maithel SK, Poultsides G, Guglielmi A, Pawlik TM (2016) Perihilar cholangiocarcinoma: number of nodes examined and optimal lymph node prognostic scheme. J Am Coll Surg 222(5):750–759 e752. https://doi.org/10.1016/j.jamcollsurg.2016.02.012