Published in final edited form as:

Ann Surg Oncol. 2016 September ; 23(9): 3016–3023. doi:10.1245/s10434-016-5243-y.

Prognostic Implications of Lymph Node Status for Patients With Gallbladder Cancer: A Multi-Institutional Study

Neda Amini, MD¹, Yuhree Kim, MD, MPH¹, Ana Wilson, MD¹, Georgios Antonios Margonis, MD, PhD¹, Cecilia G. Ethun, MD², George Poultsides, MD³, Thuy Tran, MD³, Kamran Idrees, MD⁴, Chelsea A. Isom, MD⁴, Ryan C. Fields, MD⁵, Bradley Krasnick, MD⁵, Sharon M. Weber, MD⁶, Ahmed Salem, MD⁶, Robert C. G. Martin, MD⁷, Charles Scoggins, MD⁷, Perry Shen, MD⁸, Harveshp D. Mogal, MD⁸, Carl Schmidt, MD⁹, Eliza Beal, MD⁹, Ioannis Hatzaras, MD¹⁰, Rivfka Shenoy, MD¹⁰, Shishir K. Maithel, MD², and Timothy M. Pawlik, MD, MPH, PhD, FACS¹

¹Division of Surgical Oncology, Department of Surgery, The Johns Hopkins Hospital, Baltimore, MD

²Division of Surgical Oncology, Department of Surgery, Winship Cancer Institute, Emory University, Atlanta, GA

³Department of Surgery, Stanford University Medical Center, Stanford, CA

⁴Division of Surgical Oncology, Department of Surgery, Vanderbilt University Medical Center, Nashville, TN

⁵Department of Surgery, Washington University School of Medicine, St. Louis, MO

⁶Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI

⁷Division of Surgical Oncology, Department of Surgery, University of Louisville, Louisville, KY

⁸Department of Surgery, Wake Forest University, Winston-Salem, NC

⁹Division of Surgical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH

¹⁰Department of Surgery, New York University, New York, NY

Abstract

Background—Although the American Joint Committee on Cancer (AJCC) classification is the most accepted lymph node (LN) staging system for gallbladder adenocarcinoma (GBA), other LN prognostic schemes have been proposed. This study sought to define the performance of the AJCC

Electronic supplementary material The online version of this article (doi:10.1245/s10434-016-5243-y) contains supplementary material, which is available to authorized users.

CONFLICT OF INTEREST Neda Amini, Yuhree Kim, Ana Wilson, Georgios Antonios Margonis, Cecilia G. Ethun, George Poultsides, Thuy Tran, Kamran Idrees, Chelsea A. Isom, Ryan C. Fields, Bradley Krasnick, Sharon M. Weber, Ahmed Salem, Robert C. G. Martin, Charles Scoggins, Perry Shen, Harveshp D. Mogal, Carl Schmidt, Eliza Beal, Ioannis Hatzaras, Rivfka Shenoy, Shishir K. Maithel, and Timothy M. Pawlik have no conflicts of interest.

LN staging system relative to the number of metastatic LNs (NMLN), the log odds of metastatic LN (LODDS), and the LN ratio (LNR).

Methods—Patients who underwent curative-intent resection for GBA between 2000 and 2015 were identified from a multi-institutional database. The prognostic performance of various LN staging systems was compared by Harrell's C and the Akaike information criterion (AIC).

Results—Altogether, 214 patients with a median age of 66.7 years (interquartile range [IQR] 56.5–73.1) were identified. A total of 1334 LNs were retrieved, with a median of 4 (IQR 2–8) LNs per patient. Patients with LN metastasis had an increased risk of death (hazard ratio [HR] 1.87; 95 % confidence interval [CI] 1.24–2.82; $P = 0.003$) and recurrence (HR 2.28; 95 % CI 1.37–3.80; $P = 0.002$). In the entire cohort, LNR, analyzed as either a continuous scale (C-index, 0.603; AIC, 803.5) or a discrete scale (C-index, 0.609; AIC, 802.2), provided better prognostic discrimination. Among the patients with four or more LNs examined, LODDS (C-index, 0.621; AIC, 363.8) had the best performance versus LNR (C-index, 0.615; AIC, 368.7), AJCC LN staging system (C-index, 0.601; AIC, 373.4), and NMLN (C-index, 0.613; AIC, 369.5).

Conclusions—Both LODDS and LNR performed better than the AJCC LN staging system. Among the patients who had four or more LNs examined, LODDS performed better than LNR. Both LODDS and LNR should be incorporated into the AJCC LN staging system for GBA.

Lymph node (LN) status has been established as an important prognostic factor for gallbladder adenocarcinoma (GBA).^{1–4} The overall survival (OS) for patients undergoing radical resection with regional lymphadenectomy is better than for those undergoing simple cholecystectomy.^{4–6} Based on retrospective data, some investigators have suggested that in the absence of lymphadenectomy, radical resection may have a benefit compared with cholecystectomy alone.⁷ Lymph node status has been conventionally described in three ways: location of the metastatic LN, number of metastatic LNs (NMLN), and ratio of metastatic LNs to the number of retrieved LNs (LNR).^{8–11} The American Joint Committee on Cancer (AJCC) staging system, which uses the tumor node metastasis (TNM) classification, defines LN status based on the location of metastatic LN.⁹ Other studies have suggested that NMLN and LNR are more prognostic than the location of metastatic LN.^{11–13}

Many patients with GBA have a limited number of LNs harvested at the time of surgery. In fact, the total number of LNs examined (TNLE) for GBA is relatively small, with a median of one to three LNs.^{1,14} The prognosis of patients with a low LN count may not be best stratified using LNR or NMLN.^{1,7} Log odds of positives (LODDS) is a novel LN staging system calculated as the log of the ratio between metastatic LNs and negative LNs.¹⁵ Previous studies have suggested that LODDS may be superior to the LNR and AJCC systems for gastric and colon cancer.^{15–18}

Our research group reported on the performance of the LODDS staging system for GBA using the Surveillance, Epidemiology, and End Results (SEER) database.¹⁹ Despite this, data still are lacking regarding the prognostic performance of different staging systems for patients undergoing curative resection for GBA. Most previous studies have used data from a single small institution or administrative database.^{10,11,13,14,20,21} No previous study has evaluated the various LN staging systems using data from high-volume surgical institutions

in the United States. Therefore, the current study aimed to define the performance of various LN staging systems including the AJCC LN staging system, NMLN, LODDS, and LNR for a large, multi-institutional cohort of patients with GBA.

METHODS

Patient Population and Data Collection

Patients who underwent curative resection for gall-bladder cancer between January 2000 and April 2015 and who had received a lymphadenectomy were identified from a multi-institutional database (Johns Hopkins University, Stanford University, University of Wisconsin, The Ohio State University, Washington University, Vanderbilt University, New York University, University of Louisville, Wake Forest University, and Emory University). The institution review board of each institution approved this study. The study enrolled only patients who had undergone curative resection for gallbladder cancer and who had received a lymphadenectomy. Patients who had not undergone LN dissection (Nx) were excluded. Patients with gallbladder cancer other than adenocarcinoma, those with T4 disease according to AJCC 7th edition, and those with metastasis at the time of operation were excluded. Also, patients with macroscopically positive (R2) margins were excluded (Supplemental Fig. 1).

Standard demographic, laboratory, and clinicopathologic data were collected. Resection was classified as simple cholecystectomy, radical cholecystectomy, major hepatectomy, bile duct resection, or Whipple procedure. Information on the original cholecystectomy before the definitive resection was collected. Notably, the extent of lymphadenectomy was recorded according to the 7th edition of the AJCC LN staging system (N2 and N1 vs only N1). Data on neoadjuvant and adjuvant therapy also were obtained. The surgical margin after the operation was classified as R0 (microscopically negative) or R1 (microscopically positive). Vital status and date of the last follow-up visit also were collected. Recurrence was based on biopsy-proven GBA or highly suspicious imaging.

Lymph Node Staging Systems

In this study, NMLN indicated the number of metastatic LNs. The LNR, which ranged from 0 to 1, was the ratio of NMLN to TNLE. The LODDS was defined as the log $[(NMLN + 0.5)/(NNLN + 0.5)]$, where NNLN was the number of negative LNs, calculated by subtracting NMLN from TNLE.¹⁵ The LNR and the LODDS system were classified by comparing OS based on LNR with an interval 0.1 and LODDS with an interval 0.5.²² The LNR was categorized as Nr1 (LNR = 0), Nr2 ($0 < \text{LNR} < 0.5$), or Nr3 (LNR ≥ 0.5). The LODDS system was grouped into three classifications: LODDS1 (LODDS ≤ -3), LODDS2 ($-3 < \text{LODDS} < 0$), LODDS3 (LODDS ≥ 0). Based on previously proposed cutoff values, NMLN was grouped into three categories in subsequent analyses as follows: 0, 1 to 3, and 4 or more.¹⁰ All three LN staging systems were analyzed using these categorical cutoff values as well as continuous variables. The AJCC LN staging system was considered separately as follows: N0 (no LN metastasis), N1 (LN metastasis of the cystic duct, common bile duct, portal vein, and/or hepatic artery nodes), or N2 (LN metastasis of periaortic, pericaval, celiac, and/or superior mesenteric artery LNs).⁹ The impact of TNLE on the prognosis and

performance of the LN staging systems was examined using different TNLE cutoff points including 3, 4, 5, 6, and 7 LNs.¹⁹

Statistical Analysis

Data were presented as prevalence or median with interquartile range (IQR) as appropriate. Continuous data were tested using Mann–Whitney or Kruskal–Wallis and categorical variables using the Chi square test. The Kaplan–Meier method was used to construct survival curves and compared using the log-rank test. Patients who died within 90 days after surgery were excluded from the survival analyzes.²³ The prognostic performance of four staging systems was compared by the Harrell’s C index (c-index), which ranged from 0.5 (no discrimination) to 1 (perfect discrimination), and the Akaike information criterion (AIC), where a lower value indicated a better model fit. Whereas AIC is an established, validated method for assessing the quality-of-the-model “fit,” the c-index is used to determine the discriminatoy power of the model.²⁴ Cox regression models were constructed to evaluate the prognostic performance of the LN staging systems. All statistical analyzes were performed using STATA version 13 (StataCorp, College Station, TX, USA). A *P* value lower than 0.05 was considered significant.

RESULTS

Patient Characteristics

Altogether, 1334 LNs were retrieved from 214 patients, with a median of 4 LNs (IQR, 2–8) per patient. Among the study cohort, 98 patients (45.5 %) had LN metastasis, with a total of 271 metastatic LNs (median of 1 [IQR 1–3]). The median age of the patients was 66.7 years (IQR 56.5–73.1 years) (Table 1). The majority of the patients (82.2 %; *n* = 176) had undergone radical cholecystectomy. Notably, 130 patients (60.7 %) had undergone a simple cholecystectomy before a more definitive oncologic operation. In total, 49 patients (23.2 %) had undergone N2 dissection in addition to the N1 dissection.

Characteristics of Node Staging Systems

A strong correlation was found between TNLE and NMLN ($\rho = 0.24$; $P < 0.001$) (Supplemental Fig. 2a). The median TNLE was 3.5 (IQR 1.5–7) among the patients without LN metastasis versus 5 (IQR 3–9) among the patients who had LN metastasis ($P = 0.01$). The LN metastases were associated with AJCC T stage: 0 % for T1a, 7.15 % for T1b, 44.2 % for T2, and 57.7 % for T3 ($P = 0.001$). According to the 7th edition AJCC LN staging system, 87 of the patients (40.7 %) had N1 disease, and 11 of the patients (5.1 %) had N2 disease (Table 2). Both NMLN and TNLE were higher among the patients with N2 disease (median TNLE, 9; median NMLN, 3) than among the patients who had N1 disease (median TNLE, 5; median NMLN, 1) ($P < 0.05$ for both). The LNR and LODDS categories were equally distributed among the patients with N1 and N2 disease (Supplemental Fig. 3).

The median LNR for the patients with metastatic LN was 0.33 (IQR 0.20–0.67). The TNLE did not have a linear correlation with LNR. Notably, the median TNLE of Nr2 (7; IQR 4–12) was higher than that of Nr3 (2; IQR 2–5) ($P < 0.001$). Most of the patients had LODDS2 (*n* = 154, 71.9 %), whereas fewer patients were classified as LODDS1 (*n* = 22, 10.3 %) or

LODDS3 ($n = 38$, 17.8 %). The correlation of LODDS with LNR ($\rho = 0.81$; $P < 0.001$) was higher than with NLM ($\rho = 0.70$; $P < 0.001$) (Supplemental Figs. 2b and 2c).

Long-Term Survival with Different Staging Systems

During a median follow-up period of 19.6 months (IQR, 8.8–37.5 months), the median OS for the entire cohort was 35.1 months. The OS was 82.6 % at 1 year, 49.5 % at 3 years, and 38.8 % at 5 years. Lymph node status was strongly associated with prognosis. The median survival of the patients with N0 was 59.5 months compared with 23.6 months for the patients who had LN metastasis (hazard ratio [HR] 1.87; 95 % confidence interval [CI] 1.24–2.82; $P = 0.003$). Even after patients with Tis and T1a disease were excluded from the analysis, the patients with N1 disease still had a worse OS than the patients without LN metastases (HR 1.82; 95 % CI 1.19–2.78; $P = 0.005$). The risk of death increased with NMLN (HR 1.20; 95 % CI 1.06–1.37; $P = 0.005$). The patients who had undergone an N2 dissection had a survival similar to that for N1 dissection (median survival: 35.1 months for N2 dissection vs 34.0 months for N1 dissection; $P = 0.11$). The survival data according to the four LN staging systems are depicted in Fig. 1. According to the AJCC LN staging system, the risk of death was higher among the patients with N1 disease than among those with N0 disease (HR 1.94; 95 % CI 1.27–2.96; $P = 0.002$) but not among those with N2 disease (HR 1.38; 95 % CI 0.54–3.50; $P = 0.50$). The 5-year survival rate according to the LNR classification was 47.3 % for Nr1, 36.2 % for Nr2, and 11.1 % for Nr3. However, Nr1 and Nr2 had overlapping survival ($P = 0.15$). The LODDS classification was able to stratify patients into three distinct prognostic cohorts: LODDS1 (70.9 %), LODDS2 (40.4 %), and LODDS3 (11.9 %). Notably, no overlap between the LODDS categories was shown ($P < 0.05$). Finally, the 5-year OS among the NMLN categories was 47.3 % for NMLN1, 29.5 % for NMLN2, and 30 % for NMLN. The survival among the NMLN2 and NMLN3 groups overlapped ($P = 0.06$).

Among the 176 patients with available data on recurrence, 68 (38.6 %) experienced recurrence. The risk of recurrence increased with each LN metastasis present (HR 1.25; 95 % CI 1.10–1.44; $P = 0.001$). Based on the AJCC LN staging system, the risk of recurrence increased with N1 disease (HR 2.22; 95 % CI 1.31–3.78; $P = 0.003$) and N2 disease (HR 2.60; 95 % CI 1.06–6.38; $P = 0.04$) versus N0 disease. The patients with N1 and N2 disease had a comparable risk of recurrence (Reference N1: HR 0.91; 95 % CI 0.38–2.18; $P = 0.83$). The 5-year recurrence-free survival (RFS) according to LNR classification was 64.9 % for Nr1, 38.3 % for Nr2, and 12.5 % for Nr3. However, the Nr2 and Nr3 patients overlapped ($P = 0.08$). The LODDS classification stratified the cohort into three distinct RFS categories: LODDS1 (80.8 %), LODDS2 (50.6 %), and LODDS3 (12.5 %) ($P < 0.001$). The 5-year RFS of NMLN categories were 64.9 % for NMLN1, 32.6 % for NMLN2, and 30 % for NMLN ($P < 0.001$).

Prognostic Performance of Different Staging Systems

In the entire cohort, LNR, as either a continuous scale (C-index, 0.603; AIC, 803.5) or a discrete scale (C-index, 0.609; AIC, 802.2), provided better discrimination for OS than the AJCC LN staging system, LODDS, or NMLN (Table 3). Although TNLE was not associated with OS or RFS, in the sensitivity analyses, the relative performance of the various LN

scoring systems was better among the patients who had four or more TNLE. In the cohort of patients with four or more TNLE, LODDS (C-index, 0.621; AIC, 363.8) had the best performance compared with the AJCC LN staging system (C-index, 0.601; AIC, 373.4), LNR (C-index, 0.615; AIC, 368.7), and NMLN (C-index, 0.613; AIC, 369.5) when assessed as categorical variables.

Regarding prediction of RFS, LNR (C-index, 0.614; AIC, 544.5) had a higher discrimination ability than other staging systems when assessed using categorical cutoff values. However, LODDS (C-index, 0.611; AIC, 544.4) tended to have a better discrimination than LNR (C-index, 0.610; AIC, 545.2) when assessed as a continuous variable. Similar to OS, all the staging systems showed better discrimination ability when four or more LNs were examined. Notably, LODDS (C-index, 0.660; AIC, 236.6) performed better than the other staging systems. In addition, increasing the LNR category was associated with a worse survival for T2 and T3 disease (84.2 months for T2LNR1 vs 68.2 months for T2LNR2 vs 22.8 months for T2LNR3; 20.0 months for T3LNR1 vs 20.1 months for T3LNR2 vs 13.8 months for T3LNR3; $P < 0.05$). For the LODDS system, a similar trend was noted (168.4 months for T2LODDS1 vs 68.2 months for T2LODDS2 vs 22.8 months for T2LODDS3; 25.1 months for T3LODDS1 vs 20.1 months for T3LODDS2 vs 13.8 months for T3LODDS3; $P < 0.05$).

DISCUSSION

Metastatic LN disease has been considered one of the most important prognostic factors for GBA, and because of this importance, several staging systems have been proposed.^{5,7,8,10,11,13,21,25,26} The 7th edition of the AJCC staging system, defined by LN location, is currently the most accepted LN staging system.⁹ However, previous studies have suggested that other metastatic LN criteria such as NMLN and LNR may be more important than LN location.^{11,13,20,21} In addition, more advanced statistical modeling of LN status such as LODDS has been proposed.¹⁵ To date, only one study has evaluated the various LN staging systems among patients undergoing surgery for GBA.¹⁹ This study was limited, however, because it used administrative data and focused solely on OS.¹⁹

The current study is important because it expanded on our previous work. Specifically, using a large multi-institutional database, we compared the prognostic performance of different staging systems. Notably, LNR and LODDS had a better prognostic performance than the AJCC LN staging system. In particular, among the patients with four or more TNLE, LODDS performed better for both OS and RFS. In addition, we noted that all the staging systems performed worse among the patients with fewer than four TNLE, indicating the importance of TNLE for GBA.

Similar to previous reports, we noted that LN metastasis had a significant effect on both OS and RFS.^{1,3,12} The risk of death and recurrence increased by 20 and 25 %, respectively, with each metastatic LN. Even after adjustment for competing risk factors, the likelihood of death increased with each metastatic LN. In fact, no patients with four or more LN metastases survived beyond 5 years. All four staging systems were able to classify patients into distinct prognostic groups (Fig. 1). However, LNR and LODDS outperformed the AJCC LN staging

system. Other studies have similarly suggested that LN metastatic location performed poorly in predicting long-term survival.^{8,10,12,20,21}

The AJCC LN staging has several limitations that may be related to its worse performance. For example, to determine the site of LN metastasis, the farthest LN should be considered, but the determination of lymphatic distribution is difficult to assess on the pathologic specimen. In the current study, only 11 patients (5.1 %) had N2 disease, consistent with previous data from Western series that had only a small percentage of patients with N2 disease.^{12,19} Therefore, the 7th edition of the AJCC staging system would seem not to be a good staging system for Western centers. As an alternative, some studies have suggested the use of NMLN to predict long-term survival for GBA.^{8,10,20} In the current study, the performance of NMLN for OS (C-index, 0.595; AIC, 809.4) was comparable with that of the AJCC (C-index, 0.596; AIC, 808.6). However, the performance of NMLN was superior to that of AJCC LN staging in predicting the risk of recurrence.

Negi et al.²¹ first reported the prognostic performance of LNR for gallbladder cancer. In our analytic cohort, the LNR categories overlapped in assessing both OS and RFS. Specifically, Nr1 and Nr2 had comparable OS values ($P = 0.15$) and Nr2 and Nr3 overlapped for RFS ($P = 0.85$). In contrast, the LODDS categories for OS and RFS showed no overlapping. As such, LODDS was superior to LNR in determining prognosis. Moreover, LNR does not have the ability to separate patients with the same LNR and different TNLE. For example, LNR failed to discriminate a patient with one positive LN out of one TNLE (LNR 1) from a patient with five LN metastases out of five TNLE (LNR 1). In contrast, LODDS has the ability to separate patients with different TNLE and the same LNR (Supplemental Fig. 2b).

An adequate number of harvested LNs is a critical to ensuring accurate staging.^{12,13,19} The minimum number of TNLE for other malignancies such as pancreatic cancer and colorectal cancer have been defined.^{27–30} However, this number is controversial for GBA. The 6th edition of the AJCC LN staging system recommended three TNLE, but this recommendation was omitted in the 7th edition.³¹ Asian centers typically have a higher number of TNLE than Western centers. As such, most Asian studies recommend that at least six LNs be examined for gallbladder cancer.^{4,10,20}

In the current study, TNLE was not associated with OS or RFS. However, the LN staging systems performed better with four or more TNLE than with fewer than four TNLE, suggesting that at least four LNs should be examined. Although some of the differences among AJCC, LNR, and LODDS were indeed small in the examination of the entire cohort, the data demonstrated that all the staging systems performed better when four or more LNs were examined. In addition, the differences in the accuracy of certain staging systems were more pronounced with four or more TNLE than with fewer than four TNLE. For example, the c-index for LODDS to predict OS was only 0.595 for fewer than four TNLE compared with a higher c-index of 0.621 for four or more TNLE. Similarly, in the assessment of RFS, the c-index of the AJCC staging was only 0.571 for fewer than four TNLE compared with a much higher c-index of 0.624 for four or more TNLE. As such, the data highlight the importance of examining four or more nodes to improve overall accurate staging of patients with GBA.

Several limitations of this study should be considered in the interpretation of our data. Data were gathered from 10 academic institutions. Therefore, the surgical technique and the extent of lymphadenectomy varied and were not standard. For example, a small subset of patients ($n = 49$) had an N2 dissection, which is used for stage 4b disease and is a relative contraindication to surgery by some clinicians. Kondo et al.³² had reported, however, a survival benefit for N2 dissections when no para-aortic LN metastasis was evident. In fact, these authors reported that when there was no distant metastasis and the para-aortic nodes were negative, the postoperative survival for patients with positive regional nodes alone, including N2 nodes, was comparable with that for patients with N0 dissections.

In the current study, patients with N2 had a 5-year OS of 35.6 %, comparable with the 35.7 % survival rate noted for patients with N1 disease who underwent complete resection. As such, surgery for patients with N2 disease may be justified for carefully selected patients. Whereas “vital status” was available for all the patients, detailed data on recurrence was not available for a subset of the patients (38/214). Although the lack of inclusion of these patients may have biased the RFS analysis, this is unlikely given that the data likely were missing at random.

In conclusion, the use of LNR and LODDS demonstrated prognostic superiority over the AJCC LN staging system, with LODDS having the best discrimination ability, especially among patients with a high TNLE. Although our data should be validated in other series, LNR and LODDS should be considered in determining the prognostic impact of LN status among patients with GBA.

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FIG. 1.

Kaplan-Meier curves stratified by **a** 7th edition of AJCC lymph node staging, **b** lymph node ratio (LNR), **c** log odds of metastatic lymph node (LODDS), and **d** number of metastatic lymph nodes (NMLN)

TABLE 1

Characteristics of 214 patients who underwent curative resection for gallbladder adenocarcinoma

	No. of patients (<i>n</i> = 214)
Median age: years (IQR)	66.7 (56.5–73.1)
Female	146 (68.2)
Comorbidities	
Diabetes (<i>n</i> = 186)	48 (25.8)
CHF (<i>n</i> = 185)	10 (5.4)
Chronic renal failure (<i>n</i> = 186)	1 (0.5)
Preoperative laboratory	
Total bilirubin: mg/dl (IQR)	0.6 (0.4–0.8)
Total albumin: g/dl (IQR)	3.9 (2.5–4.3)
AJCC T stage (<i>n</i> = 196)	
Tis	4 (2.0)
T1a	5 (2.6)
T1b	14 (7.1)
T2	95 (48.5)
T3	78 (39.8)
AJCC N stage	
N0	116 (54.2)
N1	87 (40.7)
N2	11 (5.1)
AJCC TNM stage (<i>n</i> = 196)	
0	3 (1.5)
1	18 (9.1)
2	53 (26.9)
3	112 (56.9)
4B*	11 (5.6)
Median tumor size: cm (IQR)	3.0 (2.0–4.5)
Histologic grade (<i>n</i> = 183)	
Well differentiated	22 (12.0)
Moderately differentiated	100 (54.7)
Poorly differentiated	61 (33.3)
Type of surgery	
Cholecystectomy	10 (4.7)
Radical cholecystectomy	176 (82.2)
Right hepatectomy with bile duct resection	5 (2.3)
Extended right hepatectomy with bile duct resection	6 (2.8)
Right trisectorectomy with bile duct resection	4 (1.9)
Bile duct resection only	7 (3.3)
Whipple procedure	6 (2.8)
Previous cholecystectomy	130 (60.7)

	No. of patients (<i>n</i> = 214)
N2 dissection (<i>n</i> = 211)	49 (23.2)
Median TNLE per patient (IQR)	4 (2–8)
Median NMLN per patient (IQR)	1 (1–3)
Margin statuses	
R0	194 (90.6)
R1	20 (9.4)
Neoadjuvant chemotherapy (<i>n</i> = 211)	8 (3.8)
Neoadjuvant radiotherapy (<i>n</i> = 209)	3 (1.4)
Adjuvant chemotherapy (<i>n</i> = 172)	79 (45.9)
Adjuvant radiotherapy (<i>n</i> = 168)	41 (24.4)

IQR interquartile range, *CHF* congestive heart failure, *AJCC* American Joint Committee on Cancer, *TNM* tumor node metastasis, *TNLE* total number of lymph nodes examined, *NMLN* number of metastatic lymph nodes

TABLE 2

Type of nodal dissection, number of metastatic lymph nodes (NMLN), total lymph nodes examined (TNLE), 5-year overall survival (OS), and 5-year recurrence-free survival (RFS) according to different staging systems

	<i>n</i> (%)	N2 dissection	Median NMLN (IQR)	Median TNLE (IQR)	5-Year OS (%)	5-Year RFS (%)
AJCC 7th edition						
N0	116 (54.2)	29 (25.7) *	0 *	3.5 (1.5–7) *	47.3 *	64.9 *
N1	87 (40.7)	9 (10.3)	1 (1–2)	5 (3–9)	26.4	28.8
N2	11 (5.1)	11 (100)	3 (2–7)	9 (6–12)	35.6	37.5
LNR						
0	116 (54.2)	29 (25.7)	0 *	3.5 (1.5–7) *	47.3 *	64.9 *
>0 to <0.5	60 (28.0)	15 (25.4)	1 (1–2)	7 (4–12)	36.2	38.3
0.5	38 (17.8)	5 (13.2)	2 (1–3)	2 (2–5)	11.1	12.5
LODDS						
–3	22 (10.3)	12 (54.6) *	0	12 (11–18) *	70.9 *	80.8 *
–3 to 0	154 (71.9)	32 (21.2)	0 (0–1)	4 (2–7)	40.4	50.6
0	38 (17.8)	5 (13.2)	2 (1–3)	2 (2–5)	11.9	12.5
NMLN						
0	116 (54.2)	29 (25.7)	0 *	3.5 (1.5–7) *	47.3	64.9 *
1 to 3	85 (39.7)	16 (18.8)	1 (1–2)	4 (2–8)	29.5	32.6
4	13 (6.1)	4 (30.8)	5 (5–7)	11 (8–22)	0	0

IQR interquartile range, *AJCC* American Joint Committee on Cancer, *LNR* lymph node ratio, *LODDS* log odds of metastatic lymph node

* Significant *P* value between values in each column (*P* < 0.05)

TABLE 3

Prognostic performance of different lymph node staging systems before and after stratification for total number of lymph nodes examined

	Overall survival				Recurrence-free survival			
	Total cohort		TNLE < 4		Total cohort		TNLE < 4	
	C-index	AIC	C-index	AIC	C-index	AIC	C-index	AIC
AJCC LN staging	0.596	808.6	0.596	309.9	0.601	373.4	0.571	221.8
LNR (continuous)	0.603	803.5	0.606	307.9	0.601	369.5	0.579	219.4
LODDS (continuous)	0.588	804.5	0.586	310.2	0.604	368.1	0.572	220.8
NMLN (continuous)	0.595	809.4	0.596	310.1	0.604	371.3	0.566	221.6
LNR (categorical)	0.609	802.2	0.602	308.9	0.615	368.7	0.586	220.3
LODDS (categorical)	0.604	799.0	0.595	307.7	0.621	363.8	0.592	218.5
NMLN (categorical)	0.599	806.2	0.593	308.1	0.613	369.5	0.567	219.8
								240.2

TNLE total number of lymph nodes examined, AIC akaike information criterion, AJCC American Joint Committee on Cancer, LNR lymph node, LODDS log odds of metastatic lymph node, NMLN number of metastatic lymph nodes