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Lymph Node Status After Resection for Gallbladder Adenocarcinoma: Prognostic Implications of Different Nodal Staging/Scoring Systems

NEDA AMINI, MD, GAYA SPOLVERATO, MD, YUHREE KIM, MD, MPH, ROHAN GUPTA, MD, GEORGIOS ANTONIOS MARGONIS, MD, ASLAM EJAZ, MD, and TIMOTHY M. PAWLIK, MD, MPH, PhD*

Department of Surgery, Johns Hopkins Hospital, Baltimore, Maryland

Abstract

Background and Objectives—Several lymph node (LN) staging/scoring systems have been proposed to stratify the prognosis of patients with gallbladder adenocarcinoma (GBA). We sought to define the prognostic performance of the most commonly utilized LN staging/scoring systems including AJCC/UICC N stage, lymph node ratio (LNR), log odds (LODDS), and N score, among patients with GBA.

Method—Between 2004 and 2010, 1,124 patients with GBA were identified from the Surveillance Epidemiology and End Results (SEER) database. The discriminative ability of each LN staging/scoring system was assessed using the Akaike's Information Criterion (AIC) and the Harrell's concordance index.

Results—When assessed using categorical values, LNR had a modest, improved ability to discriminate patients with regard to prognosis (C-index: 0.615; AIC: 2118.2) compared with AJCC/UICC N stage or N score and a prognostic discrimination comparable to LODDS. Among patients who had a total number of LN examined (TNLE) of 1 or 2, all the staging/scoring systems performed comparably. In contrast, among patients who had 4 TNLE, LODDS performed the best (C-index: 0.613; AIC: 303.2).

Conclusion—The performance of the different LN staging/scoring systems varied based on the TNLE. In particular, for patients who had 4 TNLE, LODDS out-performed the other staging/scoring systems.

Keywords

gallbladder; lymph node; prognosis; staging

*Correspondence to: Timothy M. Pawlik, MD, MPH, PhD, FACS, Professor of Surgery and Oncology, Chief, Division of Surgical Oncology, John L. Cameron Professor of Alimentary Surgery, Department of Surgery, Johns Hopkins Hospital, 600 N. Wolfe Street, Blalock 688, Baltimore, MD 21287. Fax: 410-502-2388. tpawlik1@jhmi.edu.

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INTRODUCTION

While gallbladder adenocarcinoma (GBA) is the sixth most common gastrointestinal malignancy, it is the most common biliary tract cancer [1,2]. In the United States, the incidence of GBA is currently estimated at 0.5 males/100,000 persons and 0.9 females/100,000 persons [3,4]. In most situations, GBA is diagnosed incidentally following a laparoscopic cholecystectomy [5,6]. The 5-year overall survival of patients with GBA is variable, ranging from 10% to 85% depending on disease stage [7,8]. Although prognosis of patients with advanced GBA remains poor, long-term survival can be expected among patients with early stage disease [9]. Surgery remains the best chance of cure for patients with GBA. For patients with T1b or higher GBA, a formal hepatic resection of liver segments 4b and 5 is generally recommended [5,6]. In addition to resection of the liver, a formal lymphadenectomy should be undertaken at the time of surgery. While the extent of lymphadenectomy sometimes can differ in Western (e.g., hilar/pericholedochal only) versus Eastern (e.g., hilar/pericholedochal plus celiac, peripancreatic, and periduodenal) series, it is clear that nodal assessment is important for accurate tumor staging [6,10–12].

Accurate staging of cancer patients is essential to determine prognosis, tailor possible adjuvant therapy, as well as to inform surveillance strategies. One of the strongest predictors of worse long-term outcome after surgery of most gastrointestinal cancers, including GBA, is the nodal status of the regional lymph node (LN) basin [13–15]. The survival of patients with LN metastasis is worse than that of patients without LN metastasis, as patients with LN metastasis are at a 30–40% increased risk of death [13,16,17]. Several different LN staging/scoring systems have been proposed to stratify the prognosis of patients with GBA according to LN status [13,17,18]. The American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) tumor-node-metastasis (TNM) classification is the most universally accepted staging system. The latest 7th edition AJCC/UICC staging manual revised the classification of nodal status to distinguish hilar nodes (N1: lymph nodes adjacent to the cystic duct, bile duct, hepatic artery, and portal vein) from other regional nodes (N2: celiac, periduodenal, peripancreatic lymph nodes, and those along the superior mesenteric artery) [18]. Beyond the location of LN metastasis, the number of LN metastasis may also be important. For example, Sakata et al. [19] reported that patients with 4 metastatic LN have a 15% of 5-year survival compared with 62% for patients with one metastatic LN. As such, some investigators have proposed that lymph node ratio (LNR), defined as the ratio of number of metastatic LN (NMLN) relative to total number of LN examined (TNLE), may be a better indicator of the impact of LN status on survival [13,17]. Recently, two new staging systems were developed to explore the effect of negative LN as well as metastatic LN and TNLE on prognosis; the log odds of positive LN (LODDS) and the N score. The LODDS, first proposed by Wang et al. [20] in colorectal cancer and Sun et al. [21] in gastric cancer, is the natural logarithm of the ratio of the probability of metastatic to nonmetastatic LN. The “N score” proposed by Gleisner et al. [22] for colorectal cancer is a prognostic model that considers the nonlinear relationship between TNLE and number of metastatic LN.

To our knowledge, no previous study has specifically examined the discriminatory power of these various LN staging/scoring systems for GBA. We therefore sought to define the

comparative prognostic performance of some of the more commonly utilized LN staging/scoring systems including the AJCC/UICC, LNR, LODDS, and N score among patients with GBA in a large population-based cohort.

MATERIALS AND METHODS

Patient Selection

Patients who underwent resection for GBA between 2004 and 2010 were identified in the Surveillance Epidemiology and End Results (SEER) database [23]. SEER provides patient data on approximately 28% of the U.S. population that includes patient demographics, primary tumor site, tumor morphology, and disease stage at time of diagnosis, as well as treatment details and follow-up vital status. Staging data based on the 7th edition of the AJCC/UICC staging manual were available from 2004 [18,23]. GBA was identified using the International Classification of Diseases (ICD-O-3) (C239) codes [24]. Specifically, histology codes, such as 8140, 8260, 8010, 8480, 8481, 8261, 8160, 8263, 8050, 8255, 8020, 8141, 8000, 8145, 8211, 8262, 8470, and 8471 were utilized to identify patients with adenocarcinoma. Patients with histology code other than adenocarcinoma and patients with GBA diagnosed at autopsy were excluded. Only patients who underwent surgical resection for GBA were included in the study cohort. Also, patients with T4 according to AJCC/UICC 7th edition and those with metastasis at time of diagnosis were excluded.

Standard patient demographic, clinicopathologic data including size, histological grade, and historic stage were collected. The surgical procedures were determined using site-specific surgery codes or surgery of primary site codes within the SEER coding manual [23]. Simple resection was defined as “simple or total removal of the primary site” and referred to as “simple cholecystectomy” as previously published [8]. Of note, radical resection was defined as “partial or total removal of the primary site with an en bloc resection (partial or total removal) of other organs” [23]. Collaborative Stage (CS) data set was used to define tumor extension (T stage) and lymph node status (N stage). The data were analyzed according to AJCC/UICC 7th edition [18]. In addition to AJCC/UICC staging system, LN status was categorized for comparative purposes into other LN staging systems: LNR, LODDS, and N score [13,21,22].

Statistical Analysis

Demographic and clinical characteristics of the study population were reported as frequency for string variables and medians with interquartile ranges (IQR) for continuous ones. Univariable and multivariable Cox proportional hazard regression models were constructed to define which clinicopathological factors were associated with overall survival. Factors that were significant in the univariable model ($P < 0.05$) were included in the multivariable model. Kaplan–Meier estimates of survival and Cox proportional hazards models were used to determine differences in survival and explore differences in survival among the strata established by the different LN staging/scoring systems [25]. LNR was evaluated as continuous and categorical variable using the established cut-off values: Nr1: LNR = 0; Nr2: $0 < \text{LNR} \leq 0.50$, and Nr3: LNR > 0.50 according to the magnitude of the log-rank test χ^2 statistic, LODDS was calculated using the formula: $\log(\text{NMLN} + 0.5)/(\text{TNLE} - \text{NMLN})$

+0.5)[13,17,21]. LODDS was analyzed as both continuous and categorical variable. The overall survival of patients according to LODDS categories was compared using previously reported cut-off values: LODDS1: LODDS < -2; LODDS2: -2 ≤ LODDS < 0; LODDS3: LODDS ≥ 0 [21]. The N score was derived using the formula: $NMLN = 10 - \frac{NNLN}{10} + 0.05 \times (NNLN - 10)^2 + 0.2 \times (10 < NMLN - 10 < NNLN - 25)$, where NNLN was the number of negative LN [22]. As previously described, N score was analyzed as both a continuous and categorical variable with cut-off values of <6, 6–8, and >8 [22]. Finally, the impact of TNLE on prognosis was determined.

The discriminative ability of each model was assessed using the Akaike's Information Criterion (AIC) and the Harrell's concordance index (*c*-statistic) [26,27]. AIC is a log likelihood of model fitness whereby the optimal model (e.g., one that is both parsimonious and accurate) is associated with a lower AIC value. For Harrell's *c*-statistic, a value of *c* = 0.5 indicates no predictive ability as compared with chance, whereas a value of 1 indicates perfect discrimination. All analyses were carried out through STATA version 12.0 (StataCorp, College Station, Texas). All tests were two-sided and a *P*-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Overall, 1,124 patients with GBA, who met inclusion criteria, were identified from the SEER database (Table I). Median age was 73 years (IQR: 63–81) and the majority of patients were female (*n* = 801; 71.3%). The median tumor size was 2.5 cm (IQR: 1.7–4). At the time of diagnosis, most of the patients (*n* = 626; 56.2%) had “localized” tumors based on historic stage; most patients (*n* = 737; 68.9%) had T2 or T3 stage disease according to the 7th edition AJCC/UICC staging classification. The majority of patients (*n* = 384; 41.4%) had a moderately differentiated tumor. Overall, no lymph nodes were examined (Nx) in 58.9% patients, while 462 patients had at least one lymph node evaluated. Among patients who underwent a “radical resection” based on the SEER variable, 76.9% (*n* = 80) of patients had at least one lymph node evaluated. In contrast, only 37.2% (*n* = 367) who had a simple cholecystectomy had at least one lymph node evaluated. Among patients who had at least one lymph node evaluated, the median TNLE was 1 (IQR: 1–3). Only 19.9% (*n* = 92) patients had ≥ 4 lymph nodes evaluated. Of those patients who had at least one lymph node examined, 203 (43.7%) had nodal metastasis. Specifically, according to the 7th edition AJCC/UICC nodal staging system, 197 (42.6%) had N1 but only six (1.3%) patients had N2 disease. There was no difference in the TNLE examined among patients who did (median 2, IQR: 1–4) and did not (median 1, IQR: 1–3) have lymph node metastasis (*P* = 0.15). While 260 (56.3%) patients had a LNR of 0, 71 (15.4%) were N_r2 (LNR ≤ 0.5) and 131 (28.4%) were N_r3 (LNR > 0.5), respectively. Most patients had a LODDS2 (*n* = 263; 56.9%); while some patients had a LODDS1 (*n* = 50; 10.8%) or LODDS3 (*n* = 149; 32.3%). Of note, patients were relatively equally distributed with regard to the different N score categories (Table II).

The median, 3- and 5- year survival were 25 months, 39.6% and 25.6%, respectively. Factors most strongly associated with survival included T stage and nodal status (Table III).

In assessing the prognostic discrimination of the T stage classification system, only patients without nodal or metastatic disease (N0M0) were considered. T stage discriminated survival among patients with T1, T2, and T3 disease (49 months vs. 27 months vs. 13 months, respectively; $P < 0.001$). Overall, patients with T3 disease had more than a two-fold increased risk of death (HR 2.25; 95% CI 1.75–2.91) compared with patients who had T1 tumors ($P < 0.001$). LN status was also strongly associated with long-term survival. Patients with N0 disease had a median survival of 42 months compared with 15 months for N1 disease; the six patients with N2 disease, paradoxically, had a longer median survival of 62 months ($P < 0.001$). Risk of death incrementally increased with N1 (HR 1.97; 95% CI 1.49–2.59) disease compared with N0 disease, but not N2 disease (HR 1.01; 95% CI 0.37–2.77). In addition, the risk of death increased with each metastatic lymph node (HR 1.18; 95% CI 1.06–1.31; $P = 0.002$). Specifically, patients with 1–2 LN metastasis had a two-fold higher risk of death compared with patients without LN (HR 1.98; 95% CI: 1.50–2.62; $P < 0.001$). TNLE did not, however, impact prognosis. The risk of death did not change with each lymph node examined among patients with N0 (HR 0.97; 95% CI 0.92–1.04; $P = 0.45$) or N1/N2 disease (HR 0.96; 95% CI 0.92–1.01; $P = 0.10$).

Assessing Various LN Staging/Scoring Systems: Impact on Survival

The 7th edition AJCC/UICC N system failed to discriminate patients into distinct prognostic cohorts. While patients with N0 disease had a better 5-year survival (36.7%) compared with N1 disease (12.8%), the long-term survival of the six patients with N2 disease (62.5%) was surprising longer than either N0 or N1 patients ($P = 0.19$) (Fig. 1a). Regarding LNR categories, the 5-year overall survival was 36.2% for Nr1, 20.4% for Nr2, and 12.9% for Nr3 ($P < 0.001$) (Fig. 1b). The 5-year overall survival of the different LODDS categories was: 39.4% for LODDS1, 33.3% for LODDS2, and 12.2% for LODDS3 (Fig. 1c); of note, the LODDS1 and LODDS2 categories failed to discriminate prognosis among these patients ($P = 0.24$). Finally, the 5-year overall survival of the different N score stage categories was 32.8% for N score 0–6, 30.8% for N score 6–8, and 13.4% for N score >8 ; however, N score groups 1 and 2 had overlapping survival curves ($P = 0.26$) (Fig. 1d). When assessed using categorical cut-off values, LNR had a modest improved ability to discriminate patients with regard to prognosis (C-index: 0.615; AIC: 2118.2) compared with AJCC/UICC N stage (C-index: 0.598; AIC: 2120.3) or N score (C-index: 0.607; AIC: 2121.0) and a somewhat comparable prognostic discrimination to LODDS (C-index: 0.613; AIC: 2117.3) (Table IV). Similarly, when LN status was modeled as a continuous variable, LNR (C-index: 0.612; AIC: 2117.9) performed better than N score (C-index: 0.607; AIC: 2125.8) and LODDS (C-index: 0.609; AIC: 2120.1).

The relative performance of the different LN staging/scoring systems varied based on the TNLE. For example, among patients who had 1 or 2 TNLE, the AJCC/UICC, LODDS and N score staging/scoring systems all performed comparably (LNR, C-index: 0.615; AIC: 1344.0 vs. AJCC/UICC, C-index: 0.624; AIC: 1342.1 vs. LODDS: 0.621; AIC: 1343.7 vs. N score, C-index: 0.621; AIC: 1344.5). In contrast, among patients who had 4 TNLE, LODDS performed the best (LODDS, C-index: 0.613; AIC: 303.2 vs. AJCC/UICC: 0.556; AIC: 306.4 vs. LNR: 0.567; AIC: 308.3 vs. N score, C-index: 0.486; AIC: 309.0). The relationship between the number of metastatic nodes, LNR, LODDS, and N score staging

systems was evaluated using scatter plots (Figs. 2 and 3). The correlation between the prognostic power of the various scoring systems and number of LN metastasis was not linear. For example, the prognostic accuracy of N score and LODDS increased with the number of LN metastasis, suggesting that N score and LODDS correlated with number of LN metastasis, and the correlation was more prominent among those with number of LN metastasis less than four (Fig. 2). Similarly, the correlation between the value of N score or LODDS and LNR was close, but it was not linear (Fig. 3). Interestingly, when the LNR was 0 or 1, N score and LODDS showed heterogeneous distribution, indicating that the N score and LODDS system may have more discriminatory power among patients with LNR 0 or 1.

DISCUSSION

Among patients with a primary gastrointestinal malignancy, LN status remains one of the most important factors associated with prognosis. Over the last decade, there has been a gradual evolution on how clinicians utilize data on LN status to make predictions about long-term survival [28–31]. Traditionally, metastatic nodal disease was simply categorized as absent (N0) or present (N1) [32]. Recently, in the 7th edition AJCC/UICC, an N2 category was created to differentiate the actual location of any metastatic nodes [18]. Other investigators have noted, however, that the TNLE needs to be taken into account to avoid stage migration and possible under-staging [11,13,17]. While LNR takes into account TNLE, it can be problematic because the numerator (NMLN) is not independent from the denominator (TNLE) [22]. As such, other LN scoring systems, such as LODDS and N score, have been proposed by our group and others [20–22]. While these different LN staging/scoring systems have been investigated to varying degrees for other malignancies [33–35], a comprehensive evaluation of their relative performance among patients with gallbladder cancer does not exist. As such, the current paper is important because we are the first to define the comparative prognostic performance of AJCC/UICC, LNR, LODDS, and N score among patients with GBA in a large U.S. population-based cohort. The issues of how to interpret LN data in patients with GBA may be particularly relevant as TNLE is often low. In the current study, we found that the relative performance of the different LN staging/scoring systems varied based on the TNLE. While the different staging/scoring systems performed comparably among patients with a low TNLE, LODDS out-performed the other staging/scoring systems among patients who had ≥ 4 TNLE.

LN status has been recognized as an important prognostic factor for GBA patients [36]. Clinical guidelines recommend lymphadenectomy even for early stage T1b GBA in order to evaluate accurately the nodal basin [37,38]. In the current study, we similarly noted that the presence of N1 disease was associated with an almost two-fold increase in death compared with N0 disease (Table III). Unexpectedly, N2 disease was not associated with a worse survival. These data need to be interpreted with caution, however, as only six patients in the SEER analytic dataset had N2 disease. The reason for the paucity of N2 patients is probably multifactorial and may be related to both patient selection, as well as the overall rarity in which these nodal basins are sampled. These data do suggest that the applicability of the N2 category may be limited in the Western experience. Beyond the N2 category, we also noted that the AJCC/UICC staging system in general performed poorly especially among those patients who had ≥ 4 TNLE (C-index: 0.556). Because of the relative poor performance of

the AJCC/UICC, other investigators have suggested the use of LNR. Several previous studies have been reported on LNR for GBA [11,39]. For example, Choi et al. [39] noted that LNR predicted disease-free survival even after controlling for competing risk factors, especially in stage IIIB patients. In a different study, Shirai and colleagues noted, however, that the NMLN better predicted patient outcome than either location (N1 or N2) or LNR [39]. In the current study, we noted that while LNR performed comparably to the AJCC/UICC staging system among patients who had only 1 or 2 TNLE, LNR performed poorly among patients who had ≥ 4 TNLE (C-index: 0.567) (Table IV). In particular, patients with an LNR 0 or 1 (e.g., either “all” negative or “all” positive nodes) were not adequately staged with a simple ratio (Fig. 3).

Several investigators have advocated LODDS as a better means to utilize LN data to stratify patients with regard to survival [21,33]. LODDS is defined as the natural logarithm of the ratio of the probability of a LN to contain metastasis versus the probability of a LN to be free of metastatic disease. Reporting on patients with gastric cancer, Sun et al. [21] found that the LODDS system was more reliable than the AJCC/UICC staging system in stratifying patient survival. In a separate study examining patients with colon cancer, our group proposed a novel “N score,” which is a prognostic model that takes into account the differential impact of TNLE among patients with and without LN metastasis, as well as the possible nonlinear interaction between TNLE and NMLN [22]. In this study, Gleisner et al. [22] demonstrated that the N score had the best prognostic accuracy, as it was not affected by underlying differences in TNLE. While LODDS and the N score have been applied to other malignancies, to our knowledge, neither of these LN scoring systems had previously been evaluated among patients with GBA. We found that LODDS and N score did not always out-perform AJCC/UICC or LNR among patients undergoing surgery for GBA. In fact, among patients who had limited TNLE, the prognostic accuracy of LODDS and N score were no different than AJCC/UICC or LNR. Patients who had ≥ 4 TNLE, however, were indeed better stratified with regard to prognosis using LODDS (LODDS, C-index: 0.613; AIC: 303.2 vs. AJCC/UICC: 0.556; AIC: 306.4 vs. LNR: 0.567; AIC: 308.3 vs. N score, C-index: 0.486; AIC: 309.0). In addition, we found that LODDS and the N score were able to identify residual prognostic heterogeneity among patients with either LNR 0 or 1 (Fig. 3). The maximal prognostic power of LNR likely resides in discriminating patients with variable ratios of NMLN-to-TNLE (i.e., $LNR > 0$ and < 1). LNR is less effective in stratifying patients with a whole number integer LNR, since a LNR of 0 fails to provide accurate information on TNLE (0 NMLN divide by any TNLE is always 0) or NMLN (if NMLN and TNLE are the same, LNR will be always be 1 regardless of the actual TNLE). As such, as our data suggest other nodal scoring systems such as LODDS or N-score may be more applicable and relevant to these subsets of patients.

The current study had several limitations that need to be considered. As with all administrative datasets, the SEER dataset has inherent restrictions [40]. Specific operative details regarding the extent of lymphadenectomy performed at the time of surgery were not available. The objective of the current study was not to evaluate the impact of operative LN dissection; rather, we sought to determine the comparative prognostic performance of various LN staging/scoring systems based on the actual nodes that were harvested. In addition, while we utilized a large, national U.S. cohort, over one-half of patients with GBA

had no LN evaluated (58.9%). In turn, we had to exclude all Nx patients from the analysis, which in turn limited the analytic cohort and may have limited the statistical power of the analyses.

Our group had previously reported that compliance with National Comprehensive Cancer Network (NCCN) guidelines for gallbladder cancer was poor [8]. In fact, we previously noted that only about 10–13% of patients with GBA underwent radical resection/hepatectomy. These previous data are consistent with the current report in which we noted a radical resection incidence of about 10%. It is important to emphasize that most patients with GBA (i.e., T1b) should be considered inadequately staged when a formal oncologic surgical procedure has not been performed. In turn, one needs to be cautious to interpret the current data, which were characterized by treatment decisions made not in compliance with the NCCN guidelines. The current data do, however, reflect the “real world” treatment of GBA on a population-based level, making the data generalizable and applicable to many clinical settings.

CONCLUSIONS

Among patients with GBA undergoing surgical resection, less than one-half had no LN evaluated. The incidence of LN evaluation was, however, much higher ($\approx 80\%$) among patients who underwent a “radical resection.” While LN status was strongly associated with overall survival, the different LN staging/scoring systems demonstrated variable accuracy in predicting prognosis. Specifically, the relative performance of the different LN staging/scoring systems varied based on the TNLE. Among patients who had 1 or 2 TNLE, the different staging/scoring systems all performed comparably. In contrast, for those patients who had 4 TNLE, LODDS out-performed the other staging/scoring systems. These data may have implications for how pathological LN data should be interpreted in the post-operative setting following surgery for GBA.

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Fig. 1. Kaplan–Meier survival curves stratified by LN categories according to (a) 7th edition AJCC/UICC, (b) LNR, (c) LODDS, and (d) N score.

Fig. 2.
The distribution of (a) N score and (b) LODDS according to number of metastatic lymph nodes.

Fig. 3.
The distribution of (a) N score and (b) LODDS according to LNR.

TABLE I**Demographics and Tumor Characteristics for Gallbladder Patients**

	No. of patients (n = 1,124)
Age (years), median (IQR)	73 (63–81)
<60	217 (19.3)
60	907 (80.7)
Sex	
F	801 (71.3)
M	323 (28.7)
Race	
White	850 (75.6)
Black	122 (10.9)
Other	152 (13.5)
Year of diagnosis	
2004–2006	510 (45.4)
2007–2008	302 (26.9)
2009–2010	312 (27.7)
AJCC T (n = 1,070)	
Tis	107 (10.0)
T1a	73 (6.8)
T1b	110 (10.3)
T1-not specified	43 (4.0)
T2	426 (39.8)
T3	311 (29.1)
AJCC N	
N0	259 (23.0)
N1	197 (17.5)
N2	6 (0.5)
Nx	662 (58.9)
AJCC TNM (n = 400)	
I	59 (14.7)
II	121 (30.3)
III	214 (53.5)
IV ^a	6 (1.5)
Tumor size, cm, median (IQR)	2.5 (1.7–4.0)
3 cm	393 (63.0)
>3 cm	231 (37.0)
Histological grade (n = 928)	
Well differentiated	199 (21.4)
Moderately differentiated	384 (41.4)
Poorly differentiated	345 (37.2)
Historic stage (n = 1,115)	

No. of patients (n = 1,124)	
In situ	107 (9.6)
Localized	626 (56.2)
Regional	288 (25.8)
Distant	94 (8.4)
Type of surgery	
Simple cholecystectomy	987 (87.8)
Radical resection	104 (9.3)
Surgery (not specified)	33 (2.9)
TNLE, median (IQR)	1 (1–3)
NMLN, median (IQR)	0 (0–1)

TNLE, total number of lymph nodes examined; NMLN, number of metastatic lymph nodes.

^a AJCC stage IV: only N2M0.

TABLE II

Number of Positive Nodes, Total Examined Nodes, and 5-Year Survival According to Different Lymph Nodes Staging System

	N (%)	NMLN ^a	TNLE ^a	5-year overall survival (%)
AJCC 7th				
N0	259 (56.1)	0 (0–0)	1 (1–3)	36.7
N1	197 (42.6)	1 (1–2)	2 (1–4)	12.8
N2	6 (1.3)	2 (1–2)	2 (1–2)	62.5
LNR				
0	260 (56.3)	0 (0–0)	1 (1–3)	36.2
>0 and 0.5	71 (15.4)	1 (1–2)	5 (3–9)	20.4
>0.5	131 (28.4)	1 (1–2)	1 (1–2)	12.9
LODDS				
< -2	50 (10.8)	0 (0–0)	8 (6–12)	39.4
-2 and <0	263 (56.9)	0 (0–0)	1 (1–3)	33.3
0	149 (32.3)	1 (1–2)	1 (1–2)	12.2
N score				
6	154 (33.3)	0 (0–0)	4 (2–8)	32.8
>6 and 8	176 (38.1)	0 (0–0)	1 (1–1)	30.8
>8	132 (28.6)	1 (1–2)	1 (1–2)	13.4

NMLN, number of metastatic lymph nodes; TNLE, total number of lymph nodes examined.

^aMedian (IQR).

TABLE III
Univariable and Multivariable Cox Proportional Hazards Regression Analysis for Overall Survival

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, y	1.00 (1.00–1.01)	0.21	—	—
Male sex	1.28 (1.06–1.54)	0.01	1.47 (0.99–2.17)	0.05
Tumor size	1.06 (1.01–1.12)	0.03	0.96 (0.87–1.05)	0.37
AJCC T				
T1	Ref		Ref	
T2	1.51 (1.17–1.96)	0.002	2.85 (0.84–9.65)	0.09
T3	2.25 (1.75–2.91)	<0.001	4.61 (1.35–15.77)	0.02
AJCC N ^a				
N0	Ref		Ref	
N1	1.97 (1.49–2.59)	<0.001	2.64 (1.28–5.44)	0.01
N2	1.01 (0.37–2.77)	0.98	0.62 (0.10–3.77)	0.61
AJCC TNM				
I	Ref		Ref	
II	1.51 (0.83–2.72)	0.18	0.56 (0.14–2.32)	0.43
III	2.65 (1.55–4.53)	<0.001	0.48 (0.11–2.08)	0.32
IV	1.43 (0.47–4.32)	0.53	—	—
NMLN	1.18 (1.06–1.31)	0.002	0.99 (0.83–1.17)	0.88
TNLE	0.97 (0.94–1.01)	0.12	—	—

NMLN, number of metastatic lymph nodes; TNLE, total number of lymph nodes examined.

^aNx patients (n = 662) were excluded.

TABLE IV
Prognostic Performance of Different Lymph Node Staging Systems Before and After Stratifying for Total Number of Lymph Nodes Evaluated

	Number of lymph nodes examined					
	All		<4		4	
	C-Index	AIC	C-Index	AIC	C-Index	AIC
AJCC N 7th	0.598	2120.3	0.609	1603.9	0.556	306.4
LNR (continuous)	0.612	2117.9	0.616	1601.8	0.568	307.2
LODDS (continuous)	0.609	2120.1	0.620	1601.1	0.593	306.2
N score (continuous)	0.607	2125.8	0.624	1603.0	0.583	306.5
LNR (categorical)	0.615	2118.2	0.618	1602.5	0.567	308.3
LODDS (categorical)	0.613	2117.3	0.617	1600.1	0.613	303.2
N score (categorical)	0.607	2121.0	0.630	1599.1	0.486	309.0