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RESEARCH ARTICLE

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Survival benefit of lymphadenectomy for gallbladder cancer based on the therapeutic index: An analysis of the US extrahepatic biliary malignancy consortium

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Abstract

Background: The survival benefit of lymphadenectomy among patients with gallbladder cancer (GBC) remains poorly understood.

Methods: Patients who underwent resection for GBC between 2000 and 2015 were identified from a US multi-institutional database. The therapeutic index (LNM rate multiplied by 3-year overall survival [OS]) was determined to assess the survival benefit of lymphadenectomy.

Results: Among 449 patients, less than half had LNM (N = 183, 40.8%). The median number of evaluated and metastatic lymph nodes (LNs) was 3 (interquartile range [IQR]: 1-6) and 1 (IQR: 0-1), respectively. 3-year OS among patients with LNM in the entire cohort was 26.8%. The therapeutic index was lower among patients with T4 (5.9) or T1 (6.0) tumors as well as carbohydrate antigen (CA19-9) ≥200 UI/mL (6.0). Of note, a

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therapeutic index difference ≥10 was noted relative to CA19-9 (<200: 18.7 vs ≥200: 6.0), American Joint Committee on Cancer T Stage (T1: 6.0 vs T2: 17.8 vs T4: 5.9) and number of LNs examined (1-2: 6.9 vs ≥6: 16.9). Concomitant common bile duct resection was not associated with a higher therapeutic index among patients with either T2 or T3 disease. **Conclusion:** Certain clinicopathological factors including T1 or T4 tumor and CA19-9 ≥200 UI/mL were associated with a low therapeutic index. Resection of six or more LNs was associated with a meaningful therapeutic index benefit among patients with LNM.

KEYWORDS
gallbladder cancer, lymphadenectomy, therapeutic index

1 | INTRODUCTION

Although the incidence of gallbladder cancer (GBC) has decreased over the last two decades, GBC still remains the most common malignancy of the biliary tract in the United States (US).[1] Despite a generally poor prognosis among patients diagnosed with GBC, surgery remains the cornerstone of curative-intent therapy for GBC.[2] To that end, an optimal oncologic resection for GBC consists of complete tumor removal, as well as lymph node dissection (LND). LND is critical to stage patients accurately, as well as to mitigate the risk of tumor recurrence from residual lymph nodes metastasis (LNM).[3] Wang and colleagues recommended an extended LND, including retro-portal, posterosuperior pancreaticoduodenal, posteroinferior pancreaticoduodenal lymph nodes (LN), for patients with advanced GBC.[4] Nevertheless, the associated survival benefit of an extended LND has been questioned given the general dismal prognosis of patients with T3 or T4 tumor. As such, there remains a need to define whether LND has a potential survival benefit, as well as to characterize individuals who might benefit the most from LND.

The concept of the therapeutic index was first proposed by Sasako et al[5] as a simple metric to evaluate the survival benefit of lymphadenectomy for patients undergoing surgery for gastrointestinal cancers. The therapeutic index is based on the rationale that lymphadenectomy may be most important among patients with a high estimated frequency of LNM, as well as individuals who are most likely to gain a survival benefit from the ascertainment of nodal status information.[5] Nodal therapeutic index was first applied to determine the survival benefit of lymphadenectomy for gastric cancer,[6-8] and more recently has been applied to patients with colorectal and pancreatic malignancies.[9-11] Furthermore, the therapeutic index has been employed to define optimal LND in the Japanese Classification of Gastric Carcinoma guidelines, indicating the increasing adoption of this concept.[12,13] To date, the nodal therapeutic index has not been examined among patients undergoing curative-intent resection for GBC. As such, the aim of this study was to evaluate the survival benefit of LND among patients with GBC based on the therapeutic index. Additionally, we sought to identify whether common bile duct (CBD) resection, which has been suggested as a means to achieve a more thorough LND,[14] provided any additional survival benefit in terms of the nodal therapeutic index.

2 | METHODS

2.1 | Study population and data collection

Patients who underwent surgery for GBC between 2000 and 2015 were identified using a multi-institutional database incorporating data from ten tertiary institutions in the US (Ohio State University, Columbus, OH; Emory University, Atlanta, GA; Johns Hopkins Hospital, Baltimore, MD; New York University, New York, NY; Stanford University, Stanford, CA; University of Louisville, Louisville, KY; University of Wisconsin, Madison, WI; Vanderbilt University, Nashville, TN; Wake Forest University, Winston-Salem, NC; and Washington University, St Louis, MO). Only patients who underwent curative-intent resection for a histologically confirmed GBC were included in this study. Patients who did not have LN examined, individuals who had an R2 surgical margin, as well as patients who died within 30-days after surgery were excluded. The Institutional Review Board of each participating institution approved this study.

Patient demographic and clinicopathologic data were extracted including age, sex, race, body mass index (BMI), American Society of Anesthesiologist (ASA) class, the presence of preoperative biliary drainage, presentation (i.e. incidental vs non-incidental), preoperative serum level of carbohydrate antigen (CA) 19-9, type of liver resection, CBD resection, tumor size, American Joint Committee on Cancer (AJCC) T Stage, presence of LNM, number of LNs evaluated and LNM, tumor grade, lymphovascular or perineural invasion, as well as receipt of neoadjuvant and adjuvant therapy.

2.2 | Definition of therapeutic index

The therapeutic index of LND was calculated by multiplying the incidence of LNM by the 3-year overall survival (OS) rate of individuals with LNM among different patient cohorts, as previously reported.[7,11] Specifically, the therapeutic index was utilized to estimate the survival benefit of LND relative to different clinicopathological and LN-related

factors.[7] For example, 3-year OS was calculated among different patient groups relative to the number of LNs examined, as well as other clinicopathological factors. Based on previous studies, lymphadenectomy was considered to be meaningful when the difference of the therapeutic index was ≥10 between two groups.[6,8]

2.3 | Statistical analysis

Descriptive statistics were presented as median (interquartile range [IQR]) and frequency (%) for continuous and categorical variables, respectively. Continuous variables were compared with the Mann-Whitney U or Kruskal-Wallis tests, as appropriate. Categorical variables were compared with the χ^2 test or Fisher's exact test, as appropriate. Statistical significance was assessed at $\alpha = .05$. All analyses were performed with a multivariate normal imputation method for missing data.[15] Multivariable logistic regression was used to determine independent predictors of LNM. OS was defined as the time from date of surgery to the date of death or last follow-up. Survival analyses were performed using Kaplan-Meier curves and the difference in OS were assessed using the log-rank test. The association of clinicopathologic variables with OS was evaluated by using Cox proportional hazards regression. The multivariable model was developed based on clinically important variables as well as variables found to be significantly associated with OS on a bivariate analysis ($P < .05$). All statistical analyses were performed using SPSS, version 25 (IBM Corp, Armonk, NY) along with JMP statistical package version 14 (SAS Institute Inc, Cary, NC).

3 | RESULTS

3.1 | Patient characteristics

A total of 449 patients were identified who underwent surgical resection for GBC (Table 1). Median age at the time of surgery was 66 years old (IQR: 57-73) and roughly one-third of patients were male (N = 157, 35.0%). The majority of patients were Caucasian (N = 331, 73.7%), had ASA class more than two (N = 303, 67.5%) and were diagnosed with GBC incidentally (N = 268, 59.7%); only a subset of patients underwent biliary drainage preoperatively (N = 93, 20.7%). Preoperative median BMI and CA19-9 were 28.0 (IQR: 24.8-30.8) and 27 UI/mL (IQR 14-172), respectively. The median tumor size was 3.3 cm (IQR: 2.4-4.1). The most common procedure was IVb/V wedge liver resection (N = 318, 70.8%), whereas 22.0% (N = 99) of patients underwent cholecystectomy or bile duct resection only. Approximately one in four (N = 125, 27.8%) patients underwent CBD resection.

On pathology, most patients had T3 disease (N = 210, 46.8%), well to moderately differentiated tumors (N = 288, 64.1%), as well as lymphovascular (N = 266, 59.2%) and perineural (N = 287, 63.9%) invasion. The majority of patients did not have LNM (N = 266, 59.2%). The median number of LNs examined was 3 (IQR: 1-6), while median number of LNM was 1 (IQR: 0-1) (Table 1). A total of 123 patients (27.4%) had six or more LNs harvested.

TABLE 1 Demographic and patient characteristics in the entire cohort (N = 449)

Variable	N (%)
Age[a]	66 (57-73)
Male	157 (35.0)
Race	
Caucasian	331 (73.7)
African American	65 (14.5)
Hispanic	21 (5.3)
Asian	19 (4.2)
Other	10 (2.2)
BMI[a]	28.0 (24.8-30.8)
ASA classification	
ASA ≤2	146 (32.5)
ASA >2	303 (67.5)
Preoperative biliary drainage	93 (20.7)
Incidentally discovered	268 (59.7)
Neoadjuvant therapy	16 (3.6)
CA19-9, UI/mL[a]	27 (14-172)
Type of liver resection	
None[b]	99 (22.0)
IVb/V wedge resection	318 (70.8)
Anatomical lobectomy	32 (7.1)
Common bile duct resection	125 (27.8)
Tumor size, cm[a]	3.3 (2.4-4.1)
AJCC T stage	
T1	33 (7.4)
T2	165 (36.7)
T3	210 (46.8)
T4	41 (9.1)
Patients with LNM	183 (40.8)
Number of lymph node evaluated[a]	3 (1-6)
Number of LNM[a]	1 (0-1)
Grade	
Well to moderate	288 (64.1)
Poor to undifferentiated	161 (35.9)
Lymphovascular invasion	266 (59.2)
Perineural invasion	287 (63.9)
Adjuvant chemotherapy	230 (51.2)

Abbreviations: AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologist; BMI, body mass index; IQR, interquartile range; LNM, lymph node metastasis.
[a]Median (IQR).
[b]Cholecystectomy with or without bile duct resection.

3.2 | Clinicopathological factors associated with LNM and OS

Bivariate analysis revealed that preoperative jaundice requiring biliary stent (odds ratio [OR]: 2.34; 95% confidence interval [CI]: 1.08-5.05), preoperative CA19-9 ≥200 UI/mL (OR: 1.76; 95% CI: 1.09-2.86), and AJCC T3/4 disease (OR: 2.46; 95% CI: 1.52-3.98) were associated with higher odds of LNM. Perhaps not surprising, poor to undifferentiated tumor grade (OR: 2.33; 95% CI: 1.38-3.93),

TABLE 2 Logistic regression analysis of clinicopathological factors associated with lymph node metastasis

	Bivariate analysis		Multivariable analysis	
Variable	**OR**	**95% CI**	**OR**	**95% CI**
Age (<65)	1.82	1.13-2.93	2.06	1.21-3.50
Sex (male)	0.60	0.36-1.01		
Preoperative biliary stent	2.34	1.08-5.05		
Incidentally discovered				
No	Ref			
Yes	0.56	0.34-0.92		
CA19-9, UI/mL				
<200	Ref			
≥200	1.76	1.09-2.86		
Tumor size (cm)				
<3.0	Ref			
≥3.0	0.99	0.62-1.60		
AJCC T stage				
T1/2	Ref			
T3/4	2.46	1.52-3.98		
Grade				
Well to moderate	Ref			
Poor to undifferentiated	2.33	1.38-3.93		
Lymphovascular invasion	3.08	1.61-5.90	2.07	1.08-3.97
Perineural invasion	2.87	1.75-4.68		

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; OR, odds ratio.

lymphovascular invasion (OR: 3.08; 95% CI: 1.61-5.90), and perineural invasion (OR: 2.87; 95% CI: 1.75-4.68) were also associated with a higher likelihood of LNM, whereas individuals who had incidental GBC were at lower risk of LNM (OR: 0.56; 95% CI: 0.34-0.92). On multivariable analysis, after adjusting for all competing factors, younger age (<65 years) (OR: 2.06; 95% CI: 1.21-3.50) and lymphovascular invasion (OR: 2.07; 95% CI: 1.08-3.97) remained independent predictors of LNM (Table 2).

Similar factors were associated with worse OS on bivariate analysis including preoperative biliary drainage (hazard ratio [HR]: 2.41; 95% CI: 1.56-3.72], preoperative CA19-9 ≥200 UI/mL (HR: 2.86; 95% CI: 2.04-4.00), tumor size ≥3.0 cm (HR: 1.91; 95% CI: 1.35-2.71), AJCC T 3/4 disease (HR: 3.24; 95% CI: 2.31-4.56), LNM (HR: 1.86; 95% CI: 1.33-2.60), poor to undifferentiated tumor grade (HR: 1.83; 95% CI: 1.31-2.55), as well as lymphovascular (HR: 2.62; 95% CI: 1.87-3.67) and perineural (HR: 2.36; 95% CI: 1.66-3.36) invasion. In contrast, patients with incidental GBC had a 48% decreased risk of death (HR: 0.52; 95% CI: 0.38-0.73). On multivariable analysis, preoperative jaundice that required a biliary stent (HR: 1.66; 95% CI: 1.03-2.68), CA19-9 ≥200 UI/mL (HR: 2.74; 95% CI: 1.87-4.00) and AJCC T 3/4 disease (HR: 2.86; 95% CI: 1.90-4.30) remained associated with worse OS (Table 3).

3.3 | Therapeutic index by perioperative factors

Patients with LNM had a 3-year OS of 26.8% (95% CI: 18.8%-36.7%) vs 50.8% (95% CI: 41.0%-60.4%) among patients without LNM

TABLE 3 Cox regression analysis of clinicopathological factors associated with overall survival

	Bivariate analysis		Multivariable analysis	
Variable	**HR**	**95% CI**	**HR**	**95% CI**
Age (<65)	1.17	0.85-1.63		
Sex (male)	0.86	0.61-1.23		
Preoperative biliary stent	2.41	1.56-3.72	1.66	1.03-2.68
Incidentally discovered				
No	Ref			
Yes	0.52	0.38-0.73		
CA19-9, UI/mL				
<200	Ref		Ref	
≥200	2.86	2.04-4.00	2.74	1.87-4.00
Tumor size, cm				
<3.0	Ref			
≥3.0	1.91	1.35-2.71		
AJCC T stage				
T1/2	Ref		Ref	
T3/4	3.24	2.31-4.56	2.86	1.90-4.30
LNM	1.86	1.33-2.60		
Grade				
Well to moderate	Ref			
Poor to undifferentiated	1.83	1.31-2.55		
Lymphovascular invasion	2.62	1.87-3.67		
Perineural invasion	2.36	1.66-3.36		

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; LNM, lymph nodes metastasis.

(Figure 1). Overall, the therapeutic index value in the entire cohort was 12.7 based on a 47.3% LNM incidence and a 3-year OS of 26.8% among patients with LNM (0.473 multiplied by 26.8). Of note, patients with T4 tumor had the worst 3-year OS (9.1%) followed by patients with CA19-9 ≥200 UI/mL (10.7%), or individuals presenting with jaundice that required a preoperatively biliary stent (13.4%). In turn, the highest therapeutic value was noted among patients with CA19-9 less than 200 UI/mL (18.7), followed by patients with tumor size less than 3.0 cm (18.3), T2 tumor (17.8) and ≥6 LNs examined

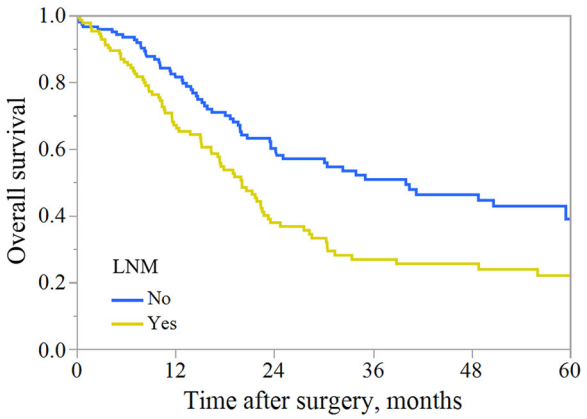

FIGURE 1 Kaplan-Meier curves demonstrating differences in overall survival among patients who did and did not have LNM in the entire cohort. LNM, lymph nodes metastasis [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Therapeutic index stratified by clinicopathological factors

Variable	Frequency of LN meta	3-y OS (%)	Therapeutic index
Overall	0.473 (133/281)	26.8	12.7
Preoperative biliary stent			
No	0.450 (112/249)	29.0	13.1
Yes	0.656 (21/32)	13.4	8.7
Incidentally discovered			
No	0.571 (53/91)	16.0	9.1
Yes	0.426 (81/190)	33.8	14.4
CA19-9, UI/mL			
<200	0.418 (71/170)	44.7	18.7
≥200	0.559 (62/111)	10.7	6.0
Tumor size, cm			
<3.0	0.474 (55/116)	38.7	18.3
≥3.0	0.473 (78/165)	19.4	9.2
AJCC T stage			
T1	0.120 (3/25)	50.0	6.0
T2	0.422 (54/128)	42.1	17.8
T3	0.586 (65/111)	18.6	10.9
T4	0.647 (11/17)	9.1	5.9
Grade			
Well to moderate	0.411 (81/197)	26.4	10.9
Poor to undifferentiated	0.619 (52/84)	26.9	16.7
Lymphovascular invasion			
No	0.322 (48/149)	43.4	14.0
Yes	0.644 (85/132)	18.9	12.2
Perineural invasion			
No	0.331 (41/124)	39.6	13.1
Yes	0.586 (92/157)	21.7	12.7
Number of LN examined			
1-2	0.374 (31/83)	18.5	6.9
3-5	0.482 (40/83)	25.3	12.2
≥6	0.539 (62/115)	31.4	16.9

Abbreviations: AJCC, American Joint Committee on Cancer; LN, lymph node; OS, overall survival.

(16.9). Interestingly, an index difference of 10 or more points was noted relative to CA19-9 (<200: 18.7 vs ≥200: 6.0), AJCC T Stage (T1: 6.0 vs T2: 17.8 vs T4: 5.9) and number of LNs examined (1-2: 6.9 vs ≥6: 16.9) (Table 4). In contrast, the lowest therapeutic value of lymphadenectomy was noted among patients with T4 disease (5.9), followed by a T1 tumor (6.0), CA19-9 ≥200 (6.0), and 1 to 2 LNs examined (6.9).

The therapeutic index was also assessed relative to CBD resection. Of note, irrespective of AJCC T category, LNM were more common among patients undergoing CBD resection (no CBD resection vs CBD resection; T2: 35.3% vs 55.8%, T3: 56.7% vs 60.8%, respectively; both $P < .05$). Patients who underwent CBD resection had a worse OS compared with patients who did not undergo CBD resection (no CBD resection vs CBD resection; T2: 56.5% vs 30.9%, T3: 12.7% vs 0%, respectively; both $P < .05$). In turn, irrespective of AJCC T category, the difference of the therapeutic index comparing patients who did and did not undergo CBD resection did not exceed

TABLE 5 Therapeutic index stratified by common bile duct resection among patients with T2 or T3 tumor

AJCC T Stage	Common bile duct resection	Frequency of LN meta	3-y OS (%)	Therapeutic index
T2	No	0.353 (30/85)	56.5	19.9
	Yes	0.558 (24/43)	30.9	17.2
T3	No	0.567 (34/60)	12.7	7.2
	Yes	0.608 (31/51)	0	0

Abbreviations: AJCC, American Joint Committee on Cancer; LN, lymph node; OS, overall survival.

the threshold of 10 (T2: 19.9 vs 17.2; index difference: 2.7; T3: 7.2 vs 0; index difference: 7.2; both $P > .05$) (Table 5). Of note, the number of LNs harvested among patients with either T2 or T3 disease was comparable irrespective of whether patients underwent concomitant CBD resection (T2; no CBD resection vs CBD resection, 4 [IQR: 2-8] vs 4 [IQR: 2-9], $P = .92$; T3; no CBD resection vs CBD resection, 5 [IQR: 2-9] vs 4 [IQR: 2-8], $P = .71$; Figure 2).

4 | DISCUSSION

GBC is an aggressive malignancy of the biliary tract associated with poor outcomes.[16] Although surgery is the best chance for long-term survival among patients with GBC, 5-year OS is less than 35% even after curative-intent resection.[17] Due to the tendency of GBC to invade the surrounding lymphatics, LND has been considered an integral part of an appropriate oncologic resection.[18] The extent of LND, however, has been debated over the years with the most current AJCC guidelines recommending at least six LNs to be evaluated to appropriately stage the disease.[19] Despite the recommendations, LND still remains underperformed; in fact, only one in five patients eventually achieve the suggested LN threshold after GBC resection.[17]

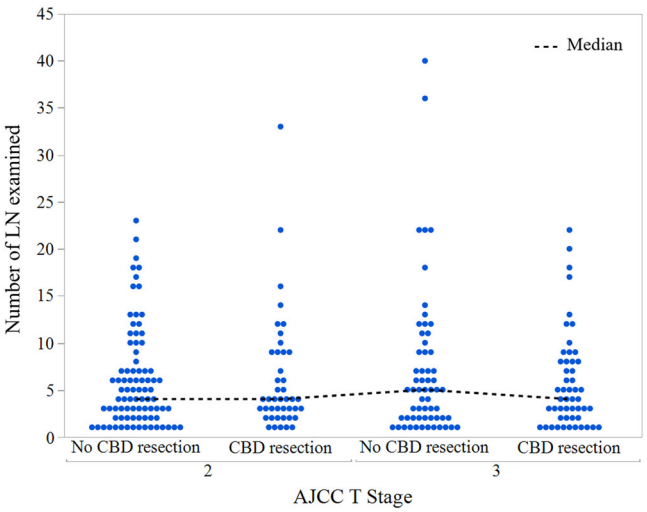

FIGURE 2 Number of LNs harvested among patients with T2 and T3 disease relative to the performance of CBD resection. LN, lymph nodes [Color figure can be viewed at wileyonlinelibrary.com]

In addition, whether extended LND is associated with a survival benefit remains a subject of debate. The current study was important because by using the US Extrahepatic Biliary Malignancy Consortium database, we identified which patients gained the most benefit from LND based on a previously established metric—the therapeutic index.[20] Of note, the highest therapeutic value of lymphadenectomy was noted among patients with CA19-9 less than 200 UI/mL (18.7), tumor size less than 3.0 cm (18.3) or T2 tumors (17.8). Interestingly, a therapeutic index interval of 10 or more —thought to represent a meaningful benefit—was noted among patients with ≥6 LN harvested compared with resection of 1 to 2 LNs (1-2: 6.9 vs ≥6: 16.9). In contrast, patients with T4 (5.9) or T1 tumors (6.0), as well as individuals with CA19-9 ≥200 UI/mL (6.0) had the lowest therapeutic value associated with LND. Perhaps of more interest, the number of LNs harvested as well as the associated the therapeutic index values among patients with T2 and T3 disease were comparable irrespective of whether patients did or did not have a concomitant CBD resection. To the best of our knowledge, this is the first study to use the therapeutic index to evaluate the survival benefit associated with LND among patients undergoing surgery for GBC.

First proposed by Sasako et al,[5] the therapeutic index is a simple metric that evaluates the therapeutic value of LND in different stations or among patients with certain clinicopathologic characteristics. The rationale of therapeutic index is that LND should be performed among patients with the highest incidence of LNM who could derive a benefit from LND.[5] While LND is performed to adequately stage the disease and limit the locoregional tumor spread, the therapeutic index focuses more on the latter and aids in the identification of patients who will benefit the most from LND. Although the therapeutic index was first proposed in the treatment of gastric cancer,[6-8] investigators have recently applied this concept to different types of malignancies, including colorectal and pancreatic cancer as well as intrahepatic cholangiocarcinoma.[9-11] Nevertheless, to date, the nodal therapeutic index has not been examined among patients undergoing resection for GBC.

Lymphadenectomy is critical in adequately staging the disease and determining adjuvant chemotherapy and postoperative surveillance strategies. Currently, the National Comprehensive Cancer Network (NCCN) guidelines recommend radical cholecystectomy with en bloc liver resection and complete LN resection in the region of porta hepatis for GBC staged T1b or higher.[18] Despite the important role of LND in the adequate staging of disease, LND has been debated mainly for patients with advanced GBC due to their poor associated outcomes. For example, while Sakata et al[21] advocated for radical LND among selected patients with positive LNs and R0 resection, other investigators have reported that radical LND may not improve the long-term outcomes of patients with advanced GBC.[22-24] In addition, routine LND may increase the complication rates, especially among patients undergoing extensive LND for the para-aortic nodal disease.[24] As such, there remains a need to identify which patients will receive the most benefit from LND. The current study revealed that the survival benefit—as calculated by the therapeutic index—was only modest among patients with T4 tumors (5.9) and CA19-9 ≥200 UI/mL (6.0), indicating that these factors likely reflect a systemic rather than a local spread of the tumor. Indeed, patients with CA19-9 ≥200 UI/mL had a 3-year OS as low as 10.7%, while the respective survival rate for patients with T4 disease was only 9.1%. In contrast, patients with T1 disease and CA19-9 less than 200 UI/mL had a relatively favorable 3-year OS of 50.0% and 44.7%, respectively. Of note, an index difference of more than 10 was noted relative to CA19-9 (<200: 18.7 vs ≥200: 6.0) and AJCC T Stage (T1: 6.0 vs T2: 17.8), which has been considered to represent a meaningful benefit.[6,8] Collectively, these data suggest that patients with CA19-9 less than 200 UI/mL and T2 tumors derive the most benefit from LND associated with GBC resection. In addition, the data from the current study suggest that LND may not be as beneficial to facilitate the staging of the disease or provide a survival benefit for patients with more aggressive characteristics, such as CA 19-9 more than 200 UI/mL or more advanced disease (ie, T4 tumors).

Several studies have demonstrated a relationship between the number of harvested LNs with appropriate disease staging and, in turn, accurate prognostication.[17,25] For example, Ito et al[25] reported that survival of patients classified as N0 based on less than six LNs harvested was significantly worse than that of N0 patients based on ≥6 LNs harvested. In addition, an analysis of the Surveillance, Epidemiology, and End Result database reported that among patients with stage I, II, and IIIA disease, longer survival was observed when four LNs, four or five LNs, and six LNs were evaluated, respectively.[26] While the recommended number of LNs to evaluate for GBC was 3 in the 6th edition of the AJCC staging manual,[27] the most current 8th AJCC edition recommends at least six LNs be evaluated to adequately stage patients with GBC.[19] Nevertheless, several studies have reported significant variations in the number of LNs harvested by surgeons in the United States. For example, a previous study from our group reported that among 6531 patients undergoing surgery for GBC in the National Cancer Database, only 21.1% of patients had the recommended LN threshold of six or more LNs.[17] Similarly, in a different report by Leigh et al[28] approximately 80% of patients undergoing portal lymphadenectomy for GBC ≥pT1b did not have six or more LNs examined. The current study revealed that only 27.4% (n = 123) of patients had six or more LNs harvested suggesting that surgeons still need to improve LN sampling when treating patients with GBC as the latest guidelines suggest. Of note, inadequate LN evaluation may lead to inaccurate GBC staging and errors in assessing prognosis, risk of recurrence, and recommendations about adjuvant therapy.[18] In addition, by utilizing the concept of the therapeutic index, the current study revealed that the therapeutic value increased with an increasing number of LNs evaluated. Indeed, while the therapeutic index increased from 6.9 to 12.2 when 1 to 2 and 3 to 5 LNs were evaluated, respectively, a meaningful therapeutic value was noted among patients with resection of six or more LNs examined (16.9) (6 LN: 16.9 vs 1-2 LN: 6.9). This is in line with the 8th edition of the AJCC staging manual that recommends ≥6 LNs be evaluated to stage GBC properly.[19] In addition, apart from appropriate disease staging, the current data suggest that six or more LNs should also be the optimal

number of LNs to resect with regard to survival benefit associated with LND according to the therapeutic index.

The route of the lymphatic drainage from the gallbladder is known to be via the cystic duct and CBD towards the retro-duodenal and para-aortic LNs.[29] As such, data from previous studies have suggested that routine CBD resection should be performed at the time of surgery[30,31]; yet, other investigators have argued for a more selective approach.[32,33] For example, Shimizu et al[30] advocated for routine CBD resection when performing surgery for GBC given that half of the patients (22/44, 50.0%) without preoperative jaundice were eventually found to have a microscopic invasion of the hepatoduodenal ligament. On the other hand, Gani et al[34] noted that CBD resection did not yield a higher LN count among patients undergoing surgery for GBC. In addition, concomitant CBD was not associated with improved survival (HR: 1.40; 95% CI: 0.87-2.27) after adjusting for all potential confounders.[34] Similarly, the current study revealed than CBD was not associated with a higher LN number among patients with either T2 or T3 disease (Figure 2). In addition, the current study evaluated the therapeutic index of LND for patients with T2 or T3 tumors stratified by the performance of concomitant CBD resection. Of note, a higher incidence of LNM was noted (55.8% vs 35.3%; $P = .037$) among T2 patients who underwent prophylactic CBD resection, yet 3-year OS was comparable among patients with and without CBD resection (30.9% vs 56.5%; log-rank $P = .28$), which translated into comparable therapeutic values of LND between the two groups (therapeutic index; no CBD resection: 19.9 vs CBD resection: 17.2). On the other hand, while a subset of patients with T3 tumors underwent CBD resection due to disease invasion, neither patients nor those without CBD resection demonstrated a high associated therapeutic value of LND (therapeutic index; no CBD resection: 7.2 vs CBD resection: 0). Collectively, these findings suggest that routine CBD resection is not associated with a higher LN yield and improved survival, which is in line with the NCCN guidelines.[18] As such, according to the therapeutic index, routine CBD excision in the resection of GBC is not warranted and should only be performed on a case-by-case basis.

The current study had several limitations that should be considered when interpreting the results. Due to the nature of the metric, it was not feasible to determine the cut-off value of the therapeutic index associated with a significant benefit of LND for a certain patient group; rather, by using the index, we were able to compare subgroups of patients in terms of the relative therapeutic value of LND.[9] In addition, while the multiinstitutional nature of the study was a strength, there may be heterogeneity in patient selection, surgical techniques, and perioperative management according to individual center practices. Finally, given that the therapeutic index is calculated by multiplying the frequency of LNM and long-term survival of patients with LNM, the therapeutic value determined by this metric may change overtime along with changes in the rates of systematic therapy employed including neoadjuvant or adjuvant chemotherapy.[35-37] In addition, information on adjuvant therapy and its potential impact on survival were not included in the analysis of the therapeutic index.

In conclusion, the survival benefit derived from lymphadenectomy was modest among patients with T1 or T4 tumors as well as CA19-9 ≥200 UI/mL. Resection of six or more LNs was associated with the highest therapeutic value among patients undergoing surgery for GBC. In addition, CBD resection for T2 and T3 patients did not provide any additional survival benefit in terms of therapeutic index and was not associated with a higher number of harvested LNs.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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