Surgery for gallbladder cancer in the US: a need for greater lymph node clearance

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Background: Gallbladder cancer (GBC) is a rare malignancy with a dismal prognosis. Often identified incidentally after laparoscopic cholecystectomy for presumably benign biliary disease, reoperation with partial hepatic resection and periportal lymph node dissection (LND) is frequently performed. The impact of lymph node (LN) clearance for GBC remains unclear.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was queried for patients diagnosed with GBC between 1988 and 2009. Survival was calculated using Kaplan-Meier method and compared using log-rank test. Multivariate analysis was performed to identify predictors of survival.

Results: A total of 11,815 patients diagnosed with GBC were identified. Cancer-directed surgery was performed in 8,436 (71.3%) patients. Optimal LN clearance (defined as ≥4 LNs) is associated with young age, advanced T-stage, no radiation therapy, and radical surgery (all <0.001). Greater LND improves survival for all stages (P<0.001). After adjusting for confounding factors, multivariable analysis of patients with node-negative disease demonstrated that early stage, greater LND, and radical surgery were strong independent predictors of survival.

Conclusions: Extensive lymphadenectomy correlates with longer survival even in node negative patients. Extensive LND should be performed in patients with GBC as many patients in the USA are undertreated.

Keywords: Gallbladder cancer (GBC); lymph node dissection (LND); lymphadenectomy; the Surveillance, Epidemiology, and End Results (SEER)

Introduction

Gallbladder cancer (GBC) is a rare but highly aggressive malignancy affecting approximately 9,810 new cases in 2012 (1). Since the advent of minimally invasive surgery, more cases are diagnosed incidentally after laparoscopic cholecystectomy for presume cholelithiasis or cholecystitis (2). The prognosis is often perceived with pessimism and nihilism given the lack of effective systemic therapy and the advanced stage with which it usually presents.

GBC is a rare and rapidly fatal disease due to its propensity for early dissemination. As a result, there have been few studies on the epidemiology of GBC. Women are three times more likely to develop GBC while significant variation is seen in the geographic distribution and prevalence of GBC (3,4). Although poorly understood, risk factors for the development of GBC include cholelithiasis, multiparity, obesity, history of typhoid infection, exposure of thoratrast, and porcelain gallbladder (3-5). A large international multi-institutional case-control study demonstrated that a history of gallbladder symptoms requiring medical attention was a major risk factor associated with GBC (6).

Surgery is widely regarded as the best treatment modality for non-metastatic GBC (7). Glenn and Jays first

proposed radical cholecystectomy with lymphadenectomy for malignant extrahepatic biliary tract tumors in 1954 (8). Later, Pack *et al.* advocated for a more aggressive approach consisting of total right hepatic lobectomy with concomitant nodal dissection for GBC (9). Given the lack of consensus, the surgical management of GBC remained controversial for many years. However, it was only until recent years that a more radical approach utilizing partial hepatic resection of the gallbladder bed with regional lymphadenectomy was advocated as standard approach for the treatment of GBC (10-12). In addition to surgical cholecystectomy with resection of gallbladder fossa (wedge hepatectomy of liver segments 4b and 5) and portal lymphadenectomy, advanced disease may necessitate major hepatectomy, resection of adjacent organs such as the pancreas, and biliary tree reconstruction. Currently, the National Comprehensive Cancer Network (NCCN recommends radical cholecystectomy with en bloc hepatic resection and regional lymph node dissection (LND) including porta hepatis, hepatoduodenal ligament, and retroduodenal nodes (13). Bile duct resection can be performed at the time of radical surgery if the tumor is resectable. For T1 tumors, simple cholecystectomy is considered curative and no further radical resection is warranted (10).

The number of LN removed has been shown to confer a substantial survival benefit in several gastrointestinal malignancies (14-18). For GBC, nodal clearance has been shown to decrease cancer-related mortality (19). In fact, nodal involvement is the strongest prognostic factor associated with long-term survival in patients undergoing radical resection for GBC. However, the extent of lymph node (LN) clearance has not been well established and remains a subject of debate. The objective of this study is to evaluate impact of more extensive LND in GBC. Using a national population-based database, the aim of this study is to determine the impact of extended LND on survival.

Methods

The Surveillance, Epidemiology, and End Results (SEER) database is a population-based database that collects cancer incidence and survival data, consisting of approximately 28% of the United States population. The SEER database started in 1973 and has been maintained by the National Cancer Institute. Available data include patient demographics, stage, tumor features, surgery, radiation therapy, LN examination and involvement, follow-up, and cause of death. Data from the SEER program released in 2012 was utilized in

this study. The SEER database was queried to identify patients diagnosed with GBC from 1988 to 2009. Patients with gallbladder adenocarcinoma were identified based on site (C23.0). Stage was based on the 7th edition of the American Joint Commission on Cancer Staging Manual (20). The determination of stage was based on TNM, LN, and other extent of disease (EOD) data fields available in the SEER database. GBC diagnosed at autopsy was excluded from our analysis.

Summary statistics were performed to determine association between patient characteristics and LN evaluation. Age, sex, tumor size, LN evaluation, TNM stage, radiation therapy, and surgery were included in the analysis. Overall survival (OS) and cancer-specific survival (CSS) for stage I-IV were determined using Kaplan-Meier method and compared using log-rank test. Cox proportional hazard modeling was performed to determine prognostic factors. Minimal LND was defined having 1 to 3 LN evaluated and optimal LND was defined as having four or more LNs evaluated ($\geq$4 LN). Patients with stage IV or metastatic disease were excluded from multivariate survival analysis. Statistical analysis was performed using SPSS version 19.0 (IBM Inc., Chicago, IL, USA). All tests were two-tailed. Statistical significance was set at P<0.05.

Results

A total of 12,990 patients diagnosed between 1988 and 2009 were identified, of whom 11,816 patients (91%) had adequate information in the SEER database to determine clinical stage. Cancer-directed surgery, defined as simple cholecystectomy or radical resection, was performed in 8,436 out of 11,816 patients (71.3%).

Patient and tumor characteristics in our patient population are detailed in *Table 1*. The mean age of diagnosis was 71 years (median 72 years). More extensive LND was only performed in 3.3% of patients greater than 80 years, 6.1% of patients between 71 and 80 years, 9.2% of patients between 61 and 70 years, 13.2% of patients between 51 and 60 years, and 14.3% of patients younger than 50 years. The majority of patients were females. The distribution of patients based on EOD was 20.2%, 18.5%, 22.2%, and 14.8%, and 24.5% for stage I, II, IIIa, IIIb, and IV, respectively. The mean and median tumor sizes were 3.2 and 2.5 cm, respectively.

The majority of patients undergoing cancer-directed surgery did not undergo LND (62.3%). Greater LND was associated with young age, advanced T-stage, no radiation

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| Table 1 Distribution of patients undergoing lymphadenectomy				
Stratified by clinical and demographic factors	0 LN (%)	1-3 LN (%)	4+ LN (%)	P value
Age (years)				<0.001
≤50	47.3	32.0	14.3	
51-60	54.6	28.1	13.2	
61-70	57.5	23.3	9.2	
71-80	64.9	25.3	6.1	
>80	71.8	21.3	3.3	
Sex				0.706
Male	61.4	26.6	8.1	
Female	62.7	25.9	7.6	
Year of diagnosis				<0.001
1988-1992	72.2	22.5	2.0	
1993-1996	73.4	22.3	2.6	
1997-2000	65.5	25.1	5.0	
2001-2003	62.6	26.9	6.6	
2004-2006	57.0	27.9	10.4	
2007-2009	53.1	28.8	14.2	
Race				0.436
White	62.1	26.3	7.7	
Black	60.3	26.6	9.8	
Hispanic	64.0	24.9	7.3	
Asian/other	62.5	26.8	6.7	
Stage				<0.001
I	79.1	17.4	3.2	
II	72.2	19.9	7.7	
IIIa	79.9	14.9	4.9	
IIIb	0	67.4	17.7	
IV	61.2	23.3	8.0	
Radiation therapy				<0.001
Yes	65.6	24.5	6.3	
No	46.1	34.5	14.6	
Surgery				<0.001
Cholecystectomy	65.5	25.7	5.2	
Radical surgery	38.1	30.4	26.7	
LN, lymph node.				

therapy, and radical surgery. Fewer than 10% of stage I-IIIa patients underwent extensive LND before 2004 (*Figure 1*). A greater proportion of patients diagnosed with stage IIIb disease underwent more extensive LND in recent years (*Figure 2*). The mean number of LND evaluated among stage I-IIIb patients was 2.7. No LNs were recovered in 79.4%, 77.5%, and 80% of patients with stage I, II, and IIIa, respectively. Minimal LND was performed in 17.4%

of stage I, 19.9% of stage II, 14.9% of stage IIIa, and 67.4% of stage IIIb patients. More extensive LND was performed in 3.2% of stage I, 7.7% of stage II, 4.9% of stage IIIa, and 17.7% of stage IIIb patients. In all stages, greater LND was associated with longer 5-year cancer specific survival and OS (*Table 2*).

In order to determine the impact of LN clearance in patients with node-negative (stage I-IIIa) disease,
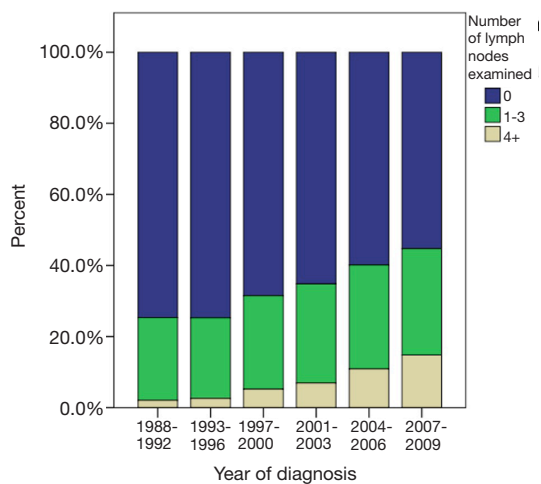
Figure 1 Trend in number of lymph nodes examined by year of diagnosis (stage I-IIIa).
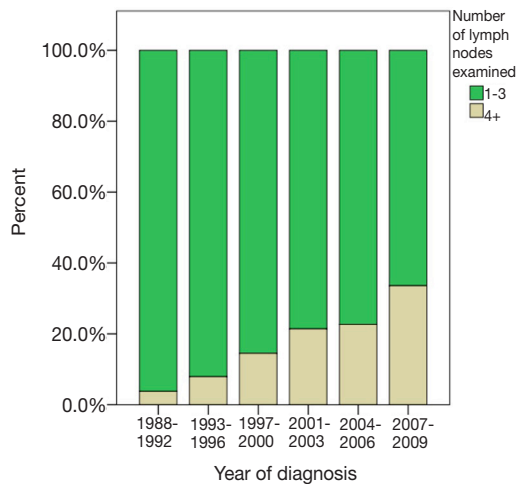
Figure 2 Trend in number of lymph nodes examined by year of diagnosis (stage IIIb).

Table 2 Kaplan-Meier survival estimates by AJCC stage

Number LN examined	Overall survival (OS)				Cancer-specific survival (CSS)			
	1-year survival (%)	5-year survival (%)	Mean (mos)	P value	1-year survival (%)	5-year survival (%)	Mean (mos)	P value
Stage I				<0.001				<0.001
0 LN	69.8	35.9	70.3		78.6	56.7	141.2	
1-3 LN	81.8	49.5	103.0		89.8	69.2	180.0	
4+ LN	87.9	60.4	105.0		89.9	65.2	124.0	
Stage II				<0.001				<0.001
0 LN	57.8	21.9	49.0		68.2	36.9	94.2	
1-3 LN	79.2	40.0	75.5		84.7	56.0	117.3	
4+ LN	88.8	72.3	135.8		90.4	76.9	165.6	
Stage IIIa				<0.001				<0.001
0 LN	34.2	7.3	20.4		40.3	12.8	34.6	
1-3 LN	59.5	19.2	39.4		61.6	26.3	59.0	
4+ LN	64.5	35.8	56.5		68.0	46.7	70.4	
Stage IIIb				<0.001				<0.001
0 LN								
1-3 LN	26.6	4.3	30.3		52.9	16.5	47.9	
4+ LN	42.6	11.6	51.8		71.9	24.0	59.2	
Stage IV				<0.001				<0.001
0 LN	11.1	1.0	6.8		13.2	2.4	8.7	
1-3 LN	26.6	4.3	12.1		30.2	5.7	15.0	
4+ LN	42.6	11.6	26.1		42.6	14.0	29.7	

LN, lymph node; AJCC, American Joint Commission on Cancer.

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Table 3 Multivariate regression analysis—OS

Entire cohort	Hazard ratio (HR)	CI	P value
Age			
Per year	1.013	1.009-1.016	<0.001
Gender			
Male	Ref		
Female	0.888	0.821-0.961	0.003
Race			
White	Ref		0.698
Black	1.041	0.918-1.180	0.533
Hispanic	0.981	0.892-1.078	0.688
Other	0.951	0.845-1.069	0.398
Stage			
I	1 (Ref)		<0.001
II	1.608	1.433-1.806	
IIIa	3.693	3.328-4.098	
Extent of lymph node dissection (LND)			
0 LN	1 (Ref)		<0.001
1-3 LN	0.590	0.528-0.660	
>4 LN	0.392	0.330-0.465	
Surgery			
Simple	1 (Ref)		0.009
Radical	1.171	1.041-1.316	
OS, overall survival; LN, lymph node.			

multivariate analysis using Cox regression hazard modeling was performed. This revealed that early stage, removal of ≥4 LN, and radical resection were the most important independent predictors of survival (*Table 3*). However, subgroup analysis on stage I patients demonstrated that extent of LND did not significantly reduce risk of cancer-related mortality [hazard ratio (HR) 0.854; CI, 0.496-1.470, P=0.570].

Discussion

Early diagnosis and surgical resection provide the only chance for a cure for early stage GBC. Since the mid-1990s, there has also been more evidence supporting aggressive hepatic resection with lymphadenectomy for GBC (10,12,21). However, the extent of LND remains a subject of debate for GBC. In recent years, the number of recommended LND for GBC ranges from 1 to 6 LN (19,20,22-24). In the current study, we demonstrated that a greater number of LNs examined correlated with improved survival. Despite some survival benefit associated with greater LND, we found that LND remains underperformed in the United States. Only 7.7% patients had 4 or more LN examined, whereas 62.3% had no LND and 26.1% had minimal LND (1-3 nodes removed). Inadequate LN will likely increase the risk of locoregional recurrence as well as lead to inaccurate GBC staging and stage migration.

The importance of adequate LN assessment in accurate staging and survival is shown in other gastrointestinal malignancies. Current recommendations for colon cancer require sampling a minimum of 12 LN whereas other several studies suggest that more than 12 LNs (25-28). For pancreatic cancer, recent studies suggest that sampling at least 15 LN is required for accurate staging of pancreatic adenocarcinoma (29,30). As nodal involvement is a known poor prognostic factor for GBC, there is an increasing need to perform adequate lymphadenectomy in order to improve staging and identify node-positive patients who may benefit from adjuvant therapy after curative resection.

Currently, no consensus has been established regarding the appropriate extent of resection for GBC. Several series advocate for hepatic resection and regional LND over simple cholecystectomy to avoid residual disease and positive margins (11,31). More aggressive surgical interventions, including major hepatectomy and biliary tree reconstruction, have been advocated in some studies (10,32,33). While major hepatic resection is not mandatory in all GBC cases, it is still unclear if non-anatomic resection of segments IVb and V affects GBC survival. Theoretically, dissection of the gallbladder off the liver during simple cholecystectomy may violate the subserosal plane, thereby leaving behind microscopically positive disease (34). However, D'Angelica *et al.* suggested that the extent of resection did not necessarily improve survival outcomes; instead, survival is dictated by tumor biology and stage (11). Pawlik *et al.* suggested margin status was associated with survival, not extent of anatomical or non-anatomical hepatectomy (34). Furthermore, it is unclear whether or not radical resection is worthwhile for early T1 GBC. While some consider simple cholecystectomy as curative for early T1 disease, a recent study advocates for concomitant LND for early T1 disease (35). While the extent of LND was an independent predictor of survival in the current study, we noted similar survival rates in stage I patients who had either 1-3 or greater than 4 LN examined. Given the conflicting reports in the literature, further investigation is warranted to determine the value of radical cholecystectomy with lymphadenectomy for early GBC.

There are limitations to our study. The details on the extent of tumor resection (i.e., extent of hepatectomy, biliary tree reconstruction) are not available in the SEER database for GBC. Even though margin status is an important determinant of survival, margin status is not available in the current database. Data on recurrence and chemotherapy are also not available in the SEER database. Furthermore, although we assessed only node-negative patients in our multivariate survival analysis, stage migration remains a critical mechanism for the profound effect of the total number of LNs examined on survival. Nevertheless, our current analysis of the SEER database provides generalizable results on the role of lymphadenectomy for GBC.

In summary, more extensive lymphadenectomy (at least four or more nodes) correlates with improved survival in patients with GBC. Given the majority of patients with GBC are still undertreated in the US, greater efforts should be taken to retrieve adequate LN in patients with GBC. Given its prognostic importance, extent of lymphadenectomy will likely be an emerging quality metric for GBC in the future.

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Footnote

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