

National Failure of Surgical Staging for T1b Gallbladder Cancer

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ABSTRACT

Background. Current guidelines recommend radical cholecystectomy with regional lymphadenectomy (RC-RL) for patients with T1b gallbladder cancer (GBC). However, the extent to which these guidelines are followed is unclear. This study aimed to evaluate current surgical practices for T1b GBC and their implications for overall management strategies and associated outcomes.

Methods. This retrospective cohort study investigated patients identified from the National Cancer Data Base (2004–2012) with non-metastatic T1b GBC. The patients were categorized according to type of surgical treatment received: simple cholecystectomy (SC) or RC-RL. Among the patients who had lymph nodes pathologically examined, nodal status was classified as pN– or pN+. Use of any adjuvant therapy was ascertained. Overall survival (OS) was compared based on type of surgical treatment and nodal status.

Results. The cohort comprised 464 patients (247 SC and 217 RC-RL cases). The positive margin status did not differ between the two groups (6.1% for SC vs 2.3% for RC-RL; $p = 0.128$). For RC-RL, the pN+ rate was 15%. Adjuvant therapies were used more frequently in pN+ (53.1% vs 9.4% for pN–). By comparison, 10.9% of the SC patients received adjuvant therapy. The OS for RC-RL-pN– (5-years OS, 64.4%) was significantly better than for RC-RL-pN+ (5-years OS, 15.7%) or SC (5-years OS, 48.3%) ($p < 0.001$).

Conclusion. Less than 50% of the patients with a T1b GBC primary tumor undergo the recommended surgical treatment. Given that 15% of these patients have nodal metastasis and in light of the previously described benefits of adjuvant therapy for node positive GBC, failure to perform RC-RL risks incomplete staging and thus undertreatment for patients with T1b GBC.

Gallbladder cancer (GBC) is a rare but aggressive malignancy often discovered incidentally after pathologic review. In the United States, approximately 12,190 new cases of cancer of the gallbladder and nearby large bile ducts will be diagnosed in 2018, with an estimated 3790 deaths from these cancers.^{1,2} Surgical resection provides the only opportunity for curative treatment, but recurrence rates are high, and long-term survival rates are dismal.³ The 5-years survival rates are 50% for stage 1, 28% for stage 2, lower than 10% for stage 3, and lower than 5% for stage 4 cancer.¹

The National Comprehensive Cancer Network guidelines recommend radical cholecystectomy including en bloc liver resection with regional lymphadenectomy for non-metastatic tumors classified as stage T1b (invasion of the gallbladder muscle layer) or higher.⁴ Whereas aggressive surgical management of T2 and T3 GBC generally is accepted as standard treatment, some debate persists as to whether anything beyond simple cholecystectomy is truly necessary for T1b GBC.^{5,6}

The extent to which national guidelines are followed for T1b tumors remains unclear, with one study demonstrating that less than 5% of T1b patients received radical cholecystectomy before 2005.⁷ Inadequate surgical resection that fails to evaluate regional lymph nodes may lead to inaccurate disease staging, thus potentially resulting in withholding of adjuvant therapies that may be indicated. Some studies have demonstrated a survival benefit with

adjuvant therapy after surgical resection for T2 and T3 tumors, but this has not been clearly established in T1b disease.^{8,9} Adjuvant therapy also seems beneficial for patients with node-positive GBC.⁸

The main objective of our study was to use a national cancer registry to evaluate the current surgical practice pattern for T1b GBC in the United States and its implications for overall management strategies and outcomes.

METHODS

Data

This study was a retrospective cohort study using the National Cancer Database (NCDB), a nationally recognized prospective, hospital-based cancer registry sponsored by the American College of Surgeons and the American Cancer Society. The NCDB collects hospital data from more than 1500 Commission on Cancer-accredited centers in the United States including information on staging, treatment, and outcomes.¹⁰ The study was approved by the Institutional Review Board of the Baylor College of Medicine and the Michael E. DeBakey Veterans Affairs Medical Center Research and Development Committee.

Study Participants

The NCDB was queried for adult patients 18–80 years of age with a diagnosis of non-metastatic primary GBC who underwent surgical resection from 2004 to 2012. Only patients with pathologic T1b disease were included in the study. Staging was based on the American Joint Committee on Cancer staging manual.¹¹ All included patients received their entire treatment at the reporting hospital and lived more than 30 days after their diagnosis.

Variables

Surgical treatment was divided into two groups: simple cholecystectomy (SC) or radical cholecystectomy with regional lymphadenectomy (RC-RL). In this study, SC was defined based on Surgery of the Primary Site Code for “all other sites” with codes 30–59, and RC-RL was defined with code 60 (radical surgery) and/or whether scope of regional lymph node surgery was listed.

Because the NCDB reports only the most definitive operation performed, the patients in the SC group did not go on to receive re-resection. Conversely, the patients in the RC-RL group very likely included a significant proportion of patients whose cancer was detected incidentally after SC and then received re-resection. It was impossible, however, to identify these patients from the NCDB.

Adjuvant therapy was defined as any type of adjuvant therapy including chemotherapy with or without radiation. In the subset of patients who underwent lymphadenectomy, the status of the examined lymph nodes was categorized as pN+ if any lymph node was positive or pN– when all the lymph nodes were negative.

Statistical Analysis

Standard descriptive statistics were used to evaluate categorical and continuous variable distributions. The primary outcome of interest was overall survival (OS), defined as the time from diagnosis to the date of either death or last contact. The Kaplan–Meier method and log-rank tests were used to compare OS for RC-RL versus SC and separately across SC, RC-RL (pN–), and RC-RL (pN+). Logistic regression was used to determine factors associated with the performance of RC-RL. Model covariates were selected non-parsimoniously and included age, sex, race, comorbidity, treatment facility type, tumor grade, and margin status. The association between surgical approach (RC-RL vs SC) and overall risk of death was evaluated using multivariable Cox regression, with similar covariates used in the model. A *p* value lower than 0.05 was considered statistically significant. All statistical analyses were performed using STATA version 14.1 (StataCorp, College Station, TX, USA).

RESULTS

The final cohort included 464 patients, of whom 247 (53%) underwent SC and 217 (47%) underwent RC-RL. The demographic, clinical, tumor, and treatment characteristics of the final cohort are detailed in Table 1. No statistically significant differences were found in baseline demographics or comorbid status between the SC and RC-RL cohorts. The mean age was 66.2 ± 10.5 years in the SC cohort and 64.4 ± 10.4 years in the RC-RL cohort, and the gender distribution was similar between the two cohorts (male gender 32% in SC and 35% in RC-RL).

The clinical characteristics, including tumor grade and margin positivity, did not differ significantly between the two cohorts. The positive margin rates were 6.1% in the SC and 2.3% in the RC-RL cohorts (*p* = 0.128). Nearly half of all the patients had no clinical nodal stage reported. Of those who did, 10 were suspected of having nodal involvement, but only 8 patients underwent RC-RL. All 8 had demonstrated nodal disease on pathologic examination.

In the subset of RC-RL patients whose lymph nodes were evaluated and whose pathologic nodal status was known, 32 (15.0%) had positive lymph nodes (pN+) on

TABLE 1 Demographic and clinical characteristics of the study cohort

	SC (<i>n</i> = 247) <i>n</i> (%)	RC-RL (<i>n</i> = 217) <i>n</i> (%)	<i>p</i> Value
Demographics			
Mean age (years)	66.2 ± 10.5	64.4 ± 10.4	0.186
Male sex	79 (32.0)	76 (35.0)	0.489
Race			0.189
White	183 (74.1)	161 (74.2)	
Black	47 (19.0)	33 (15.2)	
Other	13 (5.3)	22 (10.1)	
Missing	4 (1.6)	1 (0.5)	
Comorbidity index			0.498
0	159 (64.4)	147 (67.7)	
1	65 (26.3)	56 (25.8)	
≥ 2	23 (9.3)	14 (6.5)	
Clinical characteristics			
Clinical T stage			0.387
1	244 (53.2)	215 (46.8)	
2	3 (1.2)	1 (0.5)	
3	0 (0)	0 (0)	
Clinical N stage			0.039
Negative (cN−)	131 (53.0)	98 (45.2)	
Positive (cN+)	2 (0.8)	8 (3.7)	
Missing	114 (46.2)	111 (51.2)	
Tumor grade			0.686
Well-differentiated	81 (32.8)	63 (29.0)	
Moderately differentiated	114 (46.2)	102 (47.0)	
Poorly differentiated	32 (13.0)	30 (13.8)	
Undifferentiated	1 (0.4)	0	
Positive surgical margin	15 (6.1)	5 (2.3)	0.128
Pathologic nodal status			N/A
Negative (pN−)	N/A	181 (83.4)	
Positive (pN+)	N/A	32 (14.8)	
Adjuvant therapy	27 (10.9)	34 (15.7)	0.132
pN−		17 (9.4)	< 0.001
pN+		17 (53.1)	
Perioperative outcomes			
Mean hospital stay (SD, days)	4.3 ± 10.3	10.0 ± 19.9	< 0.001
30-days readmission	20 (8.1)	6 (2.8)	0.044
90-days mortality	5 (2.0)	6 (2.8)	0.601

Data presented as *n* (%), unless otherwise specified

SC Simple cholecystectomy; RC-RL radical cholecystectomy and regional lymphadenectomy

pathologic review. Of these, 53.1% received adjuvant therapy compared with 9.4% of the RC-RL patients with pN− and 10.9% of the SC patients ($p < 0.001$). The SC patients who received adjuvant therapy were more likely to have positive margins (16.7% vs 5.3%; $p = 0.032$) and a higher rate of poorly differentiated or undifferentiated tumors than those who did not (18.2% vs 8.7%, $p = 0.095$).

The characteristics of the patients who underwent RC-RL then were compared based on node-positive and node-negative disease (Table 2). The rates of pN+ disease were 11.1% for well-differentiated tumors, 10.8% for moderately differentiated tumors, and 36.7% for poorly differentiated tumors ($p = 0.016$).

In terms of facility type, academic/research hospitals were more likely to perform RC-RL for T1b GBC (58% RC-RL and 42% SC) than non-academic programs, where

TABLE 2 Demographic and clinical characteristics of RC-RL patients with pN– and pN+ tumors

	pN– (n = 181) n (%)	pN+ (n = 32) n (%)	p Value
Demographics			
Mean age (years)	64.8 ± 10.5	65.8 ± 9.7	0.592
Male	67 (37.0)	7 (21.9)	0.208
White	136 (75.1)	23 (71.9)	0.490
Comorbidity Index			0.360
0	125 (69.1)	21 (65.6)	
1	45 (24.9)	9 (21.8)	
≥ 2	11 (6.1)	2 (6.3)	
Facility type			0.731
Academic/research	78 (43.1)	17 (53.1)	
Comprehensive cancer center	69 (38.1)	11 (34.4)	
Community cancer center	19 (0.5)	2 (6.3)	
Integrated network cancer program	13 (7.2)	1 (3.1)	
Tumor grade			0.016
Well-differentiated	54 (29.8)	7 (21.9)	
Moderately differentiated	90 (49.7)	11 (34.4)	
Poorly differentiated	19 (10.5)	11 (34.4)	
Margin status			< 0.001
Negative	172 (95.0)	24 (75.0)	
Positive	1 (0.6)	4 (12.5)	
Missing	8 (4.4)	4 (12.5)	

Data presented as n (%), unless otherwise specified
 pN– Node negative on pathology; pN+ node positive on pathology; SD standard deviation

rates of RC-RL range from 35 to 48% (Fig. 1). Facility type was the only independent predictor of performance of RC-RL for T1b GBC, with academic/research hospitals more likely to follow treatment guidelines than

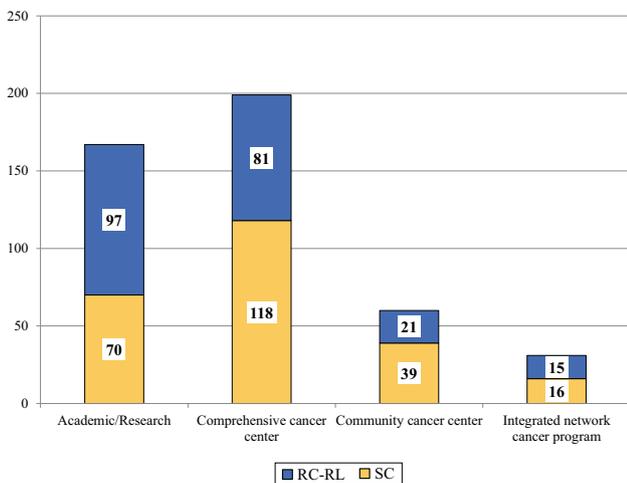


FIG. 1 Surgery by facility type. The graph represents the number of simple cholecystectomies (SC) (yellow) and radical cholecystectomies with regional lymphadenectomy (RC-RL) (blue) performed for pathologically demonstrated T1b gallbladder cancer by facility type. Data are presented as n. Missing data from 7 patients are not included (SC: n = 4; RC-RL: n = 3)

comprehensive cancer centers (odds ratio [OR], 2.33; 95% confidence interval [CI], 1.49–3.57) or community cancer centers (OR, 2.94; 95% CI, 1.54–5.56).

No patient, tumor, or treatment variable was associated with surgical approach. Tumor grade showed no association with facility type. In particular, 32.6% of well-differentiated, 36.1% of moderately differentiated, and 40.3% of poorly differentiated tumors were managed at an academic center (p = 0.243).

The 5-years OS was greater for the patients treated with RC-RL than for the patients treated with SC (57.5% vs 48.3%, respectively; p = 0.042; Fig. 2a). In the former cohort, it was better for the patients with pN– disease than for those with pN+ disease (64.5% vs 19.3%, respectively; p < 0.001; Fig. 2b). In the multivariable analysis, performance of RC-RL was associated with a 29% reduction in overall risk of death (hazard ratio [HR], 0.71; 95% CI, 0.53–0.94), whereas a higher comorbidity index and poor tumor differentiation were associated with a greater risk of death (Table 3).

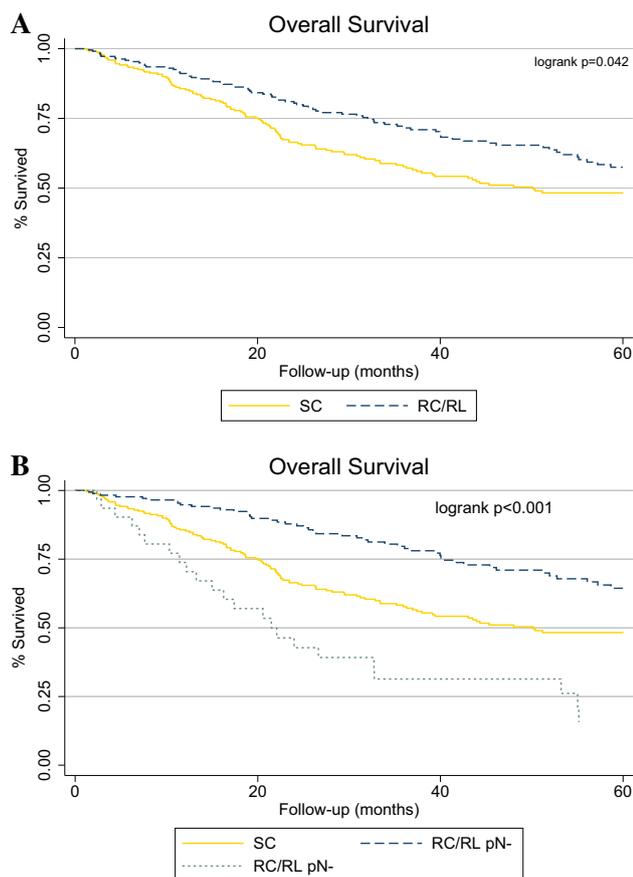


FIG. 2 The 5-years overall survival (OS) for the patients with T1b gallbladder cancer. **a** The 5-years OS for the patients who underwent radical cholecystectomy with regional lymphadenectomy (RC-RL) (57.5%) was significantly greater than for the patients who underwent simple cholecystectomy (SC) (48.3%; $p = 0.042$, log rank). **b** When the patients in the RC-RL cohort were categorized by pathologic nodal status, those with no nodal involvement (pN– RC-RL) had a better 5-years OS (64.4%) than those with nodal involvement (pN+ RC-RL; OS: 15.7%) and those in the SC cohort (SC: 48.3%; $p < 0.001$, log rank)

DISCUSSION

Guidelines recommend aggressive management for GBC in light of its propensity for early spread to lymph nodes and its dismal prognosis in advanced stages. Surgery offers the only chance for cure but also serves an important role in the staging of this disease. In this context, we found that less than half of the patients with pathologically proven T1b GBC received the recommended surgical treatment of RC-RL, and when they did, 15% had demonstrated nodal involvement. In turn, the patients with positive lymph nodes were much more likely to receive adjuvant therapy than those whose lymph nodes were negative, or importantly, those whose lymph nodes were never evaluated in the first place as a result of substandard surgical resection.

TABLE 3 Multivariable analysis for overall survival (OS)

	HR	95% CI	<i>p</i> Value
Surgical approach			
SC (ref)			
RC-RL	0.71	0.53–0.94	0.019
Demographics			
Age ≤ 55 (ref)			
Age 55.1–60	0.84	0.47–1.50	0.551
Age 60.1–70	0.79	0.47–1.32	0.369
Age > 70	1.24	0.75–2.05	0.410
Female (ref)			
Male	0.85	0.64–1.11	0.230
White race (ref)			
Black	1.19	0.81–1.75	0.36
Other	2.48	1.55–3.98	< 0.001
Comorbidity Index 0 (ref)			
1	1.46	1.03–2.07	0.033
2+	2.35	1.48–3.72	< 0.001
Facility type			
Academic/research (ref)			
Comprehensive cancer center	1.20	0.84–1.71	0.327
Community cancer center	0.99	0.59–1.66	0.965
Integrated network cancer program	0.92	0.50–1.70	0.786
Tumor grade			
Well-differentiated (ref)			
Moderately differentiated	1.13	0.79–1.61	0.497
Poorly differentiated	2.84	1.80–4.48	< 0.001
Margin status			
Negative (ref)			
Positive	1.12	0.87–1.46	0.373

Data presented as *n* (%), unless otherwise specified

RC-RL Radical cholecystectomy and regional lymphadenectomy; pN– node-negative on pathology; pN+ node-positive on pathology

In 2006, Benson et al.¹² published clinical practice guidelines for hepatobiliary cancers, establishing RC-RL as the standard of care for T1b GBC. These guidelines were based mainly on retrospective studies that demonstrated better survival for patients who underwent RC-RL than for those who received SC for higher T and N stages of disease. Although these guidelines have been available for more than a decade, our study demonstrated poor compliance in current surgical practice, with less than 50% of patients with T1b GBC having received the recommended care, although this rate seems to have improved from past reports.

In 2008, Jensen et al.⁷ examined Surveillance, Epidemiology, and End Results (SEER) data from 1988 to 2004 and found that the rate of radical cholecystectomy

was only 4.5% for patients with T1b GBC. Aggressive surgical management has been advocated for early-stage disease, particularly T1b disease, given the high rate of residual disease and the benefit of lymph node evaluation. At re-resection for GBC initially staged as T1, Pawlik et al.¹³ found residual disease in 37.5% and lymph node metastasis in 12.5% of cases. Furthermore, Jensen et al.¹⁴ argued that lymph node evaluation had more prognostic value than the radical resection itself.

Indeed, failure to assess the regional lymph nodes can result in understaging of GBC. In our series, nearly 15% of the patients with T1b GBC whose lymph nodes were evaluated demonstrated regional nodal spread, a rate comparable with that reported in the literature for T1b disease.^{7,13,14} Although the risk of nodal involvement was especially high for poorly differentiated tumors in our series, it still was 11% for well and moderately differentiated GBCs. Likewise, even if the eight patients with clinically suspicious lymph nodes were excluded, the rate of perhaps occult nodal disease would still be 11.7% (24/205) in the remaining RC-RL patients with known pN status.

Given this sizable risk of lymph node involvement in T1b disease, the significance of accurate surgical staging for this group of patients is all the more important. With lymph node evaluation, the staging of T1b GBC could drastically change from stage 1 to stage 3 or 4, portending a much poorer prognosis and indicating a need to consider adjuvant therapy for patients with a suitable performance status.

In an analysis of the SEER database, Tran and Nissen¹⁵ argued that “nodal involvement is the strongest prognostic factor associated with long-term survival in patients undergoing radical resection for GBC.” In their study, the authors examined the extent of lymph node dissection from 1988 to 2010 and found that the majority of patients (62.3%) undergoing cancer-directed surgery did not undergo lymph node dissection, and that 77% of those who did had only one to three lymph nodes retrieved.¹⁵ Given the implications of inadequate lymph node evaluation, it is imperative that T1b GBC patients receive appropriate surgical resection (patient condition permitting) to improve staging and to identify patients who may benefit from adjuvant therapy.

In our study, the rate of adjuvant therapy receipt among the patients who underwent SC and never had their lymph nodes assessed (10.9%) did not differ from that among patients who underwent RC-RL with negative lymph nodes (9.4%; $p = 0.67$), but was significantly lower than that among patients found to have positive lymph nodes at the time of RC-RL (53.1%; $p < 0.001$). The reasons for administering adjuvant therapy to patients in the SC cohort are unclear but may include an attempt at treating more

aggressive tumor biology (e.g., poor differentiation) or suboptimal surgical outcomes (e.g., positive surgical margins or incomplete surgical staging).

In an expert consensus statement from the American Hepato-Pancreato-Biliary Association, RC-RL was recommended for patients with T1b-3 GBC, and adjuvant therapy appeared to improve survival for patients with high-risk features such as higher T stage (T3 or T4), node-positive disease (N1 or N2), or positive margins.¹⁶ The panel emphasized that the role of adjuvant therapy for patients with T1b and T2 disease remained unknown because the literature on this subject included patients who received SC and did not have their nodal status appropriately evaluated. Our group previously demonstrated a survival benefit for lymph node-positive GBC patients who received surgery and adjuvant therapy, particularly adjuvant chemoradiation.⁸ With a growing literature supporting the use of adjuvant therapy for node-positive GBC, a failure to assess lymph nodes for patients with T1b GBC ultimately risks under treatment for the 12% to 15% of patients with nodal involvement who might derive a survival benefit from adjuvant therapy.

Our study had several limitations. First, it was a retrospective study using a national cancer registry that is limited by its predefined variables. No specific procedural code exists for simple or radical cholecystectomy. Instead, we defined these procedures using a combination of procedural codes under the “all other sites” disease site category. Although we suspect that most of the tumors in this data set were detected incidentally after cholecystectomy, we were unable to determine this definitively because only the most definitive operation is listed in the NCDB. To avoid the potential that these patients might have gone on to receive re-resection at a different hospital, we made sure to include only patients who received their diagnosis and all their treatment at the reporting facility. It should be noted, however, that survival does not appear to differ between patients who undergo definitive radical resection at the time of their original operation and those who require re-resection after first undergoing an SC.¹⁷

Second, we were unable to distinguish the exact tumor location on the gallbladder, especially in relation to the liver bed. Others have previously studied the tumor location in T2 GBC, concluding that tumors on the hepatic side had worse survival and higher rates of locoregional recurrence than tumors on the peritoneal side,¹⁸ and that treatment of peritoneal and hepatic-side T2 tumors may require different surgical approaches.^{19,20} The same concept could apply to T1b tumors, although due to the relative rarity of this cancer, a prospective randomized trial or institutional series likely will not be adequately powered to answer this question.

Third, although our analysis seemed to support a survival benefit of RC-RL over SC, this should be interpreted with caution because this type of comparison inherently involves non-addressable unmeasured biases. Still, our data align with those from a decision analytic Markov modeling of surgical treatment for T1 GBC which concluded that RC-RL was associated with a survival benefit for most patients with T1b GBC.²¹ Finally, we lacked data on disease recurrence.

CONCLUSION

Although it appears that the rate of radical cholecystectomy and regional lymphadenectomy for T1b GBC is increasing overall, we report a high rate of failure to comply with guidelines that may lead to under staging for as many as 15% of patients. In light of data supporting the use of adjuvant therapy, and radiation in particular, for patients with node-positive disease, efforts to improve the quality of care for patients with T1b GBC should focus on improving adherence to existing practice guidelines for medically fit patients so those who might benefit most from adjuvant therapy can be identified.

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DISCLOSURE There are no conflicts of interest.

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