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Assessing the Impact of Common Bile Duct Resection in the Surgical Management of Gallbladder Cancer

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Abstract

Background—Although radical re-resection for gallbladder cancer (GBC) has been advocated, the optimal extent of re-resection remains unknown. The current study aimed to assess the impact of common bile duct (CBD) resection on survival among patients undergoing surgery for GBC.

Methods—Patients undergoing curative-intent surgery for GBC were identified using a multi-institutional cohort of patients. Multivariable Cox-proportional hazards regression was performed to identify risk factors for a poor overall survival (OS).

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AUTHORS' CONTRIBUTIONS

Gani, Buettner, Margonis, Maithel, and Pawlik contributed in study concept and design. Buettner, Margonis, Ethun, Poultsides, Tran, Idrees, Isom, Fields, Krasnick, Weber, Salem, Martin, Scoggins, Shen, Mogal, Schmidt, Beal, Hatzaras, Shenoy, Maithel, Pawlik in acquisition of data. Gani, Buettner, Margonis, and Pawlik conducted analysis/ interpretation of data and drafting of the final manuscript. Gani, Buettner, Margonis, Ethun, Poultsides, Tran, Idrees, Isom, Fields, Krasnick, Weber, Salem, Martin, Scoggins, Shen, Mogal, Schmidt, Beal, Hatzaras, Shenoy, Maithel, and Pawlik contributed in critical review of the manuscript and final approval of the manuscript.

Results—Among the 449 patients identified, 26.9% underwent a concomitant CBD resection. The median number of lymph nodes harvested did not differ based on CBD resection (CBD, 4 [IQR: 2–9] vs. no CBD, 3 [IQR: 1–7], $P=0.108$). While patients who underwent a CBD resection had a worse OS, after adjusting for potential confounders, CBD resection did not impact OS (HR =1.40, 95%CI 0.87–2.27, $P=0.170$). Rather, the presence of advanced disease (T3: HR =3.11, 95%CI 1.22–7.96, $P=0.018$; T4: HR =7.24, 95%CI 1.70–30.85, $P=0.007$) and the presence of disease at the surgical margin (HR =2.58, 95%CI 1.26–5.31, $P=0.010$) were predictive of a worse OS.

Conclusions—CBD resection did not yield a higher lymph node count and was not associated with an improved survival. Routine CBD excision in the re-resection of GBC is unwarranted and should only be performed selectively.

Keywords

gallbladder cancer; surgical resection; common bile duct; survival

INTRODUCTION

Each year, it is estimated that 2.2 per 100,000 patients are diagnosed with gallbladder cancer (GBC) making it the sixth most common cancer of the gastrointestinal tract and the most common malignancy of the biliary tract in the United States [1,2]. Patients may be diagnosed incidentally following a routine cholecystectomy or may present late after symptoms develop [3,4]. Regardless of presentation, the best option for potential cure among patients with GBC is complete surgical resection. Prognosis following surgical resection remains poor, however, with 5-year survival ranging from 10% to 90% depending on disease factors such as tumor grade, stage of disease, and the presence of lymph node metastasis [5–7].

Surgery for GBC typically involves a partial hepatectomy that can range from resection of the gallbladder fossa to a more formal anatomic resection of segments 4b and 5 to an extended right hepatectomy [8,9]. Furthermore, any oncologic-directed operation for GBC should include a regional lymphadenectomy to assess for nodal disease to establish prognosis and the potential need for adjuvant therapy [1,10]. The role for excision of the common bile duct (CBD) is, however, more controversial [11–13]. Due to a limited body of research as well as the variation in clinical practices among Eastern and Western centers, information on the role and potential benefit of CBD resection for GBC remains limited [3,11–18]. For example, data from several previous reports have suggested that routine CBD resection be performed at the time of surgery, while other studies argue for a more selective approach [3,4,8–10,19]. Accurate data on outcomes relative to the extent of resection, including the CBD, as well as data evaluating the impact of factors on clinical outcomes may help guide decisions. Therefore, the objective of the current study was to evaluate factors associated with resection of CBD resection, as well as assess the impact of CBD on peri-operative and long-term outcomes among patients undergoing curative-intent surgical resection of GBC using a large, multi-center database.

METHODS

Data Sources and Study Population

Patients diagnosed with gallbladder cancer between January 1, 2000 and December 31, 2014 were identified using data collected from the Extra-hepatic Biliary Consortium. The Extra-hepatic Biliary Consortium represents a collaborative effort among 10 high-volume, academic medical centers across the United States (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University, Stanford, California; University of Wisconsin, Milwaukee, Wisconsin; Ohio State University, Columbus, Ohio; Washington University, St. Louis, Missouri; Vanderbilt University, Nashville, Tennessee; New York University, New York, New York; University of Louisville, Louisville, Kentucky; Wake Forest University, Winston-Salem, North Carolina). Sociodemographic and clinicopathologic data were collected on all patients diagnosed with a malignancy of the biliary tract. Specifically, sociodemographic data included age, sex, and race, while clinicopathologic data included American Society of Anesthesiologists (ASA) physical performance score, preoperative functional status, tumor size, American Joint Commission on Cancer (AJCC) T-Stage, histological grade, presence of lymph node metastasis, presence of vascular and/or perineural invasion as well as the presence of disease at the final surgical resection margin (R0: no disease at resected margin, R1: presence of disease at the resected surgical margin) [20]. Tumor size, tumor grade, the presence of lymph node metastasis, and disease at the resection margin were determined using the final histopathology report. Additionally, operative details pertaining to the type and extent of surgical resection were also recorded for each patient.

Only patients undergoing a curative intent surgical resection for histologically confirmed GBC were included within the study cohort. Patients who had macroscopic disease at the resection margin (R2 disease), presence of disease within N2 nodes and patients with metastatic disease were excluded from the final analysis assessing the survival benefit of CBD resection. Incidental disease was defined as the identification of GBC following a routine cholecystectomy while non-incidental disease was defined by the suspicion of gallbladder carcinoma prior to surgery. Overall survival (OS) was calculated from the date of initial surgery to the date of death or last follow-up, as appropriate. Death was confirmed for each patient using patient records as well as social security numbers/records. This study was approved by the Johns Hopkins Institutional Review Board as well as the institutional review boards of each institution participating in the Extra-hepatic Biliary Consortium.

Statistical Analysis

Categorical variables were presented as whole numbers and percentages, and compared using Pearson's chi-squared test. Continuous variables were described as medians with interquartile (IQR) range and compared using the Kruskal–Wallis test. OS was estimated using the Kaplan–Meier method and compared between patient groups using the log–rank test. Factors associated with OS were examined using multivariable Cox proportional hazards regression analysis. Results from the multivariable analysis were presented as hazard ratios (HR) with corresponding 95% confidence intervals (95% CI). A *P*-value <0.05

was used to determine statistical significance. All analyses were performed using STATA version 14.0 (StataCorp, College Station, TX).

RESULTS

Baseline Demographic and Disease Characteristics

A total of 449 patients were identified who underwent surgical resection for GBC (Table I). The median age of all patients was 66.3 years (IQR: 57.1–73.1), while over two-thirds of patients were female (n =292, 65.0%) and white (n =305, 67.9%). Although most patients were functionally independent at the time of surgery (n =363, 80.9%), comorbidity was common among the study cohort as 63.3% (n =191) of patients were classified as either ASA physical classification grade III or IV. At the time of diagnosis, the median CA-19-9 was 26.8 units/ml (IQR: 14.5–172.6) while the median preoperative serum albumin and bilirubin were 3.7 g/dl (IQR: 3.2–4.1) and 0.7 mg/dl (IQR: 0.5–1.6), respectively. Among all patients, a radical cholecystectomy (n =343, 76.4%) was the most commonly performed operation followed by a simple cholecystectomy (n =46, 10.4%), and a more formal hepatectomy (n =46, 10.4%).

Comparison of Patient Characteristics by Common Bile Duct Resection

Among patients who were included in the final analysis, a CBD resection was performed in 109 patients (34.2%). While patient demographics were comparable among patients who did and did not undergo a CBD resection, there were several differences in disease characteristics between the two patient groups (Table II). For example, patients who underwent a CBD resection were more likely to present with an advanced AJCC T-stage (AJCC T3 or T4: CBD, 57.0% vs. no CBD, 40.8%, $P=0.002$). Patients who underwent a CBD resection were more likely to undergo a concomitant lymphadenectomy; specifically, while 94.5% of patients who underwent a CBD resection had a least one lymph node sampled, only 81.5% of patients who did not undergo a CBD resection had a lymphadenectomy ($P<0.001$). Of note, the median number of lymph nodes harvested was comparable among patients who did and did not undergo a CBD resection (median lymph nodes harvested: CBD, 4 [IQR: 2–9] vs. no CBD, 3 [1–7], $P=0.108$). Patients who underwent CBD resection were, however, more likely to have lymph node metastasis. Specifically, among patients who underwent CBD resection, over one-half of patients (n =57, 52.3%) had lymph node metastasis versus only a third of patients (n =68, 32.4%) who did not undergo a CBD resection ($P<0.001$).

At the time of CBD resection, residual disease in the duct was found in 17 out of 121 (14.0%) patients. On final pathology, microscopic involvement of the bile duct (R1) margin was similar among patients who did (n =4) and did not (n =2) undergo CBD resection ($P=0.442$). Post-operatively, the incidence of complications was higher among patients undergoing a CBD (n =55, 48.3%) versus no CBD (n =109, 37.9%) resection ($P=0.020$).

Comparison of Risk Factors for Overall Survival

The median follow-up for the study cohort was 37.6 months (IQR: 12.3–82.1). Among all patients, median OS was 23.6 months (IQR: 12.0–88.9), while 1-, 2-, and 5-year OS were

74.9% (95%CI 69.2–79.6), 49.1% (IQR: 42.6–55.3), and 31.2% (95%CI 24.6–38.0), respectively. Several patient and disease-specific risk factors were associated with a worse OS. Specifically, on univariable analysis, the presence of lymph node metastasis, presence of disease at the time of re-resection, a greater AJCC T-stage, presence of disease at the surgical margin, advanced tumor grade, and the presence of lymphovascular or perineural invasion was associated with worse OS. Similarly, patients who underwent a CBD resection had a worse median OS (19.2 months, IQR: 9.2–33.9) compared with patients who did not undergo a CBD resection (32.4 months, IQR: 15.2–110.3, Fig. 1). However, on stratified analyses that took into account CBD resection and lymph node status, only the presence of lymph node metastasis was associated with a worse OS (Fig. 2a and b). To further investigate whether CBD resection was independently associated with OS, multivariable analyses were performed that accounted for competing clinicopathologic risk factors. After adjusting for potential confounders, an advanced AJCC T-stage (T3 vs. T1: HR =3.11, 95%CI 1.22–7.96, $P=0.018$; T4 vs. T1: HR =7.24, 95%CI 1.70–30.85, $P=0.007$) and the presence of disease at the surgical margin (HR =2.58, 95%CI 1.26–5.31, $P=0.010$) were associated with an increased risk of death following surgical resection (Table III). Of note, resection of the CBD did not impact OS (HR =1.40, 95%CI 0.87–2.27, $P=0.170$).

DISCUSSION

Prognosis following GBC remains poor with 5-year survival ranging from 10% to 90% depending on disease stage [21]. While surgery remains the best chance at long-term survival, the extent of surgery, as well as the accurate identification of patients who would benefit most from surgical resection remains controversial [1,8,9,22]. In particular, whether the CBD should be routinely excised for GBC is unclear. While some surgeons routinely recommend the resection of the extra-hepatic bile duct for GBC, other surgeons have advocated for a more selective approach given the possibility of post-CBD resection complications [15,23,24]. Most studies to date have included, however, only small single center series, with most data coming exclusively from East Asian hospitals [9,11,12,14,23,25]. The current study is important because it utilized the combined experience of 10 major hepatobiliary centers throughout the United States. In doing this, we were able to analyze a large cohort of patients with GBC to examine how often CBD resection was performed in these large tertiary centers, as well as define which factors were associated with CBD resection. Among all patients who underwent surgery, nearly one in four patients (26.9%) had a concomitant CBD resection. Interesting, while CBD resection was not associated with a higher lymph node yield, it was associated with more aggressive underlying disease such as advanced tumor stage and lymph node metastasis. In turn, although patients who underwent CBD resection had a worse OS, the effect was attributable to a greater burden of disease/more aggressive disease among patients who underwent a concomitant CBD resection. To this end, after adjusting for all other potential risk factors, CBD resection was not associated with an increased risk of death. Rather, tumor specific factors—not surgical approach—were the drivers of long-term outcome.

Several centers in Asia have advocated for routine resection of the CBD [9,11,12]. For example, Shimizu et al. proposed routine resection of the extrahepatic bile duct [9]. The authors argued that gallbladder carcinoma may often extend into the subserosa or beyond

and can invade the hepatoduodenal ligament. As such, Shumizu and coworkers advocated for routine CBD to facilitate lymphadenectomy, avoid bile duct ischemia, and increase the number of lymph nodes harvested [9]. Other studies have not, however, demonstrated similar potential benefits regarding CBD resection [13,16–18]. In a study from the Memorial Sloan Kettering Cancer center, D’Angelica and coworkers reported no difference in the number of lymph nodes harvested among patients who did and those who did not undergo a CBD resection [13]. Similarly, in the current study, we failed to find any difference in the median number of lymph nodes harvested or the median number of lymph node metastasis relative to CBD resection. In aggregate, the data suggest that resection of the CBD did not facilitate a more “thorough” lymphadenectomy, as reflected in the comparable lymph node counts among patients who did and did not undergo CBD resection.

Another theoretical benefit of CBD resection relates to survival. Several groups have proposed that radical resections that include the excision of the extra-hepatic biliary tree were associated with a survival advantage [11,14,25,26]. These surgeons point to the removal of potential occult cancer cells in the connective tissue, as well as the ability of CBD resection to address the issue of perineural invasion [11,12]. However, other investigators, including Makuuchi’s group from Japan, have questioned the survival benefit of CBD resection [23]. Citing data showing no improvement in long-term survival, and the possible increased risk of complications after a bilioenteric anastomosis, the Makuuchi group recommended preservation of the extrahepatic bile duct in radical surgery for gallbladder cancer [23]. In the current study, resection of the CBD common bile duct resection was not associated with an improvement in survival (Fig. 2). Rather patients who underwent CBD resection were more likely to have a more aggressive tumor biology (e.g., lymph node metastasis and advanced tumor stage) and, in fact, had a worse OS. Of note, after controlling for tumor-level factors, CBD was not associated with OS indicating that biological factors—not surgical approach—dictated long-term outcomes.

While not associated with increased lymph node yield or OS, CBD resection may result in an increased risk for postoperative morbidity associated with a bilioenteric anastomosis. To this point, using a multi-centric database of French patients, Fuks et al. reported no difference in recurrence-free and OS relative to CBD resection, but did demonstrate that CBD resection was associated with postoperative morbidity [15]. We similarly noted an increase in the incidence of peri-operative complications among patients who underwent CBD resection. As such, the use of CBD resection should likely be reserved for that subgroup of patients who require CBD resection to extirpate all disease in the biliary tree.

The current study should be interpreted with several limitations. As with all retrospective reports, the current study likely suffered from some selection bias that remained unaccounted even on multivariable analyses. In addition, while the use of multi-institutional data allowed for a greater sample size and more generalizable results, potential differences in clinical practices among centers could not be accounted for. However, given that each of the 10 centers were large, academic, referral centers, this variation in practices was likely negligible given the standardized practices at each center.

In conclusion, the current study demonstrates that underlying tumor biology and not the extent of surgical resection was the most important risk factor for long-term outcomes among patients with GBC. The aim for curative surgical resection should be to resect regional lymph nodes and to obtain negative surgical margins. Given that CBD resection did not yield a higher lymph node count, nor was it associated with improved long-term outcomes, a selective approach to the CBD should be employed.

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Fig. 1.
Comparison of overall survival by common bile duct resection.

Fig. 2. Comparison of overall survival by the presence of lymph node metastasis among patients who **(a)** underwent a common bile duct resection, **(b)** did not undergo a common bile duct resection.

TABLE I

Baseline Patient Characteristics by Common Bile Duct Resection

Characteristic	No CBD resection			CBD resection			Total	
	328	73.1%	121	26.9%	P-value	449	100.0%	
Age, years, median (IQR)	66.6	(56.8–73.29)	67.1	(58.9–72.9)	0.883	66.3	(57.1–73.1)	
Sex					0.064			
Male	123	37.5	34	28.1		157	35.0	
Female	205	62.5	87	71.9		292	65.0	
Race					0.080			
White	213	64.9	92	76.0		305	67.9	
Black	43	13.1	10	8.3		53	11.8	
Other	72	22.0	19	15.7		91	20.3	
BMI, median (IQR)	28.1	(24.3–32.7)	25.9	(22.5–29.2)		27.5	(23.7–31.4)	
ASA					0.159			
I/II	76	34.4	35	43.2		111	36.8	
III/IV	145	65.6	46	56.8		191	63.3	
Functional status					0.392			
Independent	262	79.8	101	83.5		363	80.9	
Dependent	18	5.5	3	2.5		21	4.7	
CA-19-9, median (IQR)	24.0	(15–157)	30.0	(11–281)	0.863	26.8	(14.5–172.6)	
Albumin, median (IQR)	3.7	(3.1–4.1)	3.8	(3.3–4.2)	0.239	3.7	(3.2–4.1)	
Peak bilirubin, median (IQR)	0.7	(0.5–1.3)	0.8	(0.4–4.45)	0.472	0.7	(0.5–1.6)	
Operation type					<0.001			
Radical cholecystectomy	170	51.8	9	7.4		98	21.8	
Cholecystectomy only	60	18.3	6	5.0		66	14.7	
Bile duct resection only	2	0.6	8	6.6		10	2.2	
Hepatectomy +bile duct resection	7	2.1	17	14.1		24	5.4	
Other	89	27.1	9	7.4		98	21.8	

TABLE II

Tumor and Disease-Specific Characteristics by Common Bile Duct Resection

Characteristic	No CBD resection		CBD resection		P-value	Total	
	210	65.8%	109	34.2%		319	100.0%
Tumor size, mm, median (IQR)	28	(18–47)	28	(18–47)	0.662	28	(18–47)
AJCC stage					0.002		
T1	30	14.9	3	3.1		33	11.0
T2	89	44.3	39	39.8		128	42.8
T3	72	35.8	47	48.0		119	39.8
T4	10	5.0	9	9.2		19	6.4
Lymph node metastasis					<0.001		
Nx	39	18.6	6	5.5		45	14.1
N0	103	49.1	46	42.2		149	46.7
N1	68	32.4	57	52.3		125	39.2
Margin status					0.201		
R0	181	87.0	89	81.7		270	85.2
R1	27	13.0	20	18.4		47	14.8

TABLE III

Multivariable Analysis of Factors Associated With Overall Survival

Characteristic	HR	95%CI		P-value
Age	1.01	0.99	1.03	0.171
Sex				
Male	Reference			
Female	1.00	0.64	1.58	0.994
Residual disease at Re-resection	1.47	0.93	2.33	0.102
AJCC T-stage				
T1	Reference			
T2	1.49	0.60	3.70	0.384
T3	3.11	1.22	7.96	0.018
T4	7.24	1.70	30.85	0.007
Lymph node metastasis				
N0	Reference			
Nx	2.71	1.44	5.08	0.002
N1	1.50	0.93	2.43	0.098
Margin status				
R0	Reference			
R1	2.58	1.26	5.31	0.010
CBD resection				
No CBD resection	Reference			
CBD resection	1.40	0.87	2.27	0.170