Rates and patterns of recurrence after curative intent resection for gallbladder cancer: a multi-institution analysis from the US Extra-hepatic Biliary Malignancy Consortium

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Abstract

Background: Gallbladder cancer is a relatively rare malignancy. The current study aimed to define the incidence and patterns of recurrence following gallbladder cancer resection.

Methods: Using a multi-institutional cohort we identified 217 patient undergoing curative intent surgery for gallbladder cancer. Patterns of recurrence were classified as locoregional and distant recurrence.

Results: At last follow-up, 76 patients (35.0%) had experienced a recurrence (locoregional only, n = 12, 15.8%; distant only, n = 50, 65.8%; locoregional and distant, n = 14, 18.4%). Median time to recurrence was 9.5 months (IQR 4.7–17.6) and was not associated with recurrence site (all p > 0.05). On multivariable analysis, T3 disease (HR = 8.44, p = 0.014), lymphovascular invasion (HR = 4.24, p < 0.001) and residual disease (HR = 2.04, p = 0.042) were associated with an increased risk of recurrence. Patients who recurred demonstrated a worse 1-, 3- and 5-year OS (1-year OS: 91.3% vs. 68.6%, p = 0.001, 3-year OS: 79.3% vs. 68.6%, p = 0.001, 3-year OS: 79.3% vs. 68.6%, p = 0.001, and 5-year OS: 75.9% vs. 16.0%, p < 0.001). After adjusting for other risk factors, recurrence was independently associated with a decreased OS (HR = 3.71, p = 0.006). Of note, receipt of adjuvant therapy was associated with improved OS (HR = 0.56, p = 0.027) among those patients who developed a tumor recurrence.

Discussion: Over one-third of patients experienced a recurrence after gallbladder cancer surgery. While chemotherapy did not decrease the rate of recurrence, patients who experienced recurrence after administration of adjuvant treatment fared better than patients who did not receive adjuvant therapy.

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Introduction

Gallbladder cancer (GBC) is a relatively rare malignancy estimated to affect approximately 10,500 patients in the United States in 2016. Many patients who present with GBC are diagnosed incidentally following a laparoscopic cholecystectomy. In fact, many cases of GBC are unapparent on gross evaluation and may initially go undiagnosed until the cholecystectomy specimens are closely examined on pathology. Another subset of patients will have non-incidental GBC and will frequently be asymptomatic, resulting in delayed diagnosis that, in turn, is associated with advanced disease. As a result, only around 10% of patients diagnosed with non-incidental GBC are eligible for potentially curative surgery. While the prognosis of patients with GBC ranges widely and depends on disease stage, prognosis can be dismal even after surgical resection. The poor prognosis associated with GBC is largely due to postoperative recurrence that can be as high as 30–65% in certain patients.

To date, only a few studies have investigated factors associated with postoperative recurrence of GB cancer. For example, lymph node metastasis, positive resection margin, moderate or poor tumor differentiation and a tumor located on the “hepatic side” have been associated with a shorter time to recurrence. Most previous studies, however, examined GBC along with other bile duct malignancies, such as cholangiocarcinoma under the ‘umbrella’ of biliary tract cancers. GBC differs, however, from other biliary tract cancers in terms of pathogenesis, surgical management and long-term outcomes. As such, the validity and applicability of these data to patients with GBC is somewhat questionable. In addition, the low incidence of GBC in most Western countries and a lack of centralized care has precluded large institutional studies. Most reports derive from Asian countries while contemporary data from the United States are lacking. In fact, one of the largest studies from a North American center comprised fewer than 100 patients with GBC. Furthermore, detailed data on recurrence are currently lacking. Given this, the objective of the current study was to define the overall incidence of recurrence following curative intent resection of GBC, as well as to characterize patterns of recurrence. Additionally, we sought to identify clinicopathologic factors associated with recurrence-free survival utilizing a large cohort of patients derived from multiple institutions in the United States.

Methods

Data sources and patient population

Patients undergoing surgical resection for GBC between January 01, 2000 and December 31, 2014 were identified at one of ten academic institutions participating in the Extra-hepatic Biliary Malignancies Consortium (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). Only patients undergoing a curative intent resection were included in the study population; patients presenting with metastatic disease, grossly positive surgical margins at resection (R2 disease), advanced N2 nodal disease, or AJCC 7th edition stage T4 tumors were excluded (Fig. 1).

Sociodemographic data including patient age, sex and race, as well as clinicopathologic information including American Society of Anesthesiologist (ASA) physical classification score, preoperative peak serum bilirubin, serum CA-19-9, tumor size, AJCC T-Stage, histologic grade, presence of lymph node metastasis, final resection margin, and the presence of vascular/perineural invasion were recorded. For patients with multiple lesions, tumor size was defined using the diameter of the largest tumor as per the 7th Edition of the AJCC Staging System. Similarly, histologic grade was classified according to the highest observed tumor grade and categorized as either well, moderate, or poorly differentiated. Surgical margin status and the presence of lymph node metastasis were determined using the final histopathology report. Additionally, operative details including the type and extent of surgery, as well as information pertaining to the administration of neoadjuvant and adjuvant chemotherapy and/or radiation therapy were recorded.

Recurrence of disease, recurrence-free and overall survival

The primary outcomes of interest were disease recurrence and recurrence-free survival. Tumor recurrence was defined as radiological evidence of disease or the presence of biopsy-proven disease following surgical resection. According to the site of tumor recurrence, recurrence was classified as either local (hepatic resection margin, bilioenteric anastomosis, porta hepatitis, retroperitoneal lymph nodes) or distant (intrahepatic, peritoneum, or other extra-abdominal sites). Recurrence-free survival (RFS) was calculated from the date of surgery to the date of recurrence or last follow-up. Similarly, overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up, as appropriate. For each patient, death was confirmed using hospital charts, as well as through the social security death index.

Statistical analysis

Continuous variables were reported as medians with inter-quartile range (IQR) or as means with standard deviation (SD) as appropriate and compared using Student’s t-test or the Kruskal–Wallis test. Categorical data were reported as whole numbers and proportions and then compared using Pearson’s chi-squared test. RFS and OS were estimated using the Kaplan–Meier method. Differences in RFS and OS were compared between patient groups using the log-rank test. Univariable and
multivariable Cox-proportional hazards models were constructed to determine risk factors associated with a worse RFS and OS. All variables demonstrating statistically significant associations (p < 0.05) on univariable analysis were included as independent variables in the multivariable model. Regression coefficients from the multivariable analysis were expressed as hazard ratios (HR) with corresponding 95% confidence intervals (95%CI). All analyses were conducted using STATA version 14.0 (StataCorp, College Station, TX); a p-value of <0.05 was used to define statistical significance. This study was approved by the Johns Hopkins Institutional Review Board as well as the institutional review board for each academic center participating in the Extra-hepatic Biliary Malignancy Consortium.

Results

Baseline patient characteristics
A total of 217 patients underwent curative intent resection for gallbladder cancer and met inclusion criteria (Supplemental Table 1). The median age of the cohort was 66.1 years (IQR 55.6–72.8); approximately two-thirds of patients were female (n = 142, 65.4%) and Caucasian (n = 151, 71.9%). Among all patients, the median BMI was 27.6 kg/m² (IQR 23.9–31.7) while 45.2% (n = 98) of patients presented with a BMI >30 kg/m². The overwhelming majority of patients (n = 184, 93.4%) were functionally independent on preoperative assessment; most patients presented with an ASA score of III or IV (n = 88, 57.5%). At the time of diagnosis, the median serum bilirubin and serum CA-19-9 levels were 0.6 mg/dL and 17 units/mL, respectively. Of note, 23.0% (n = 50) of patients presented with an elevated bilirubin, while one third (n = 73, 33.6%) had a high CA-19-9 (>37 units/mL). At the time of surgery, most patients underwent a radical cholecystectomy defined as the resection of segments 4b and 5 with or without a lymph node resection (n = 166, 76.5%) followed by simple cholecystectomy (cholecystectomy alone; n = 22, 10.1%), a hepatectomy with concomitant bile duct resection (n = 16, 7.4%), a bile duct resection only (n = 8, 3.7%) and a Whipple procedure (n = 5, 2.3%). Among patients who underwent a common bile duct (CBD) resection, 70.3% (n = 45) underwent a CBD resection for incidental cancer. Residual disease was noted in 50 (31.3%) patients who underwent re-resection for incidental GB cancer. Residual disease was noted locally in 8 patients, regionally in 13 patients, and observed at distant sites in 27 patients. On final histopathology, median tumor size was 30 mm (IQR 15–30); most tumors were staged as T2 tumors (n = 96, 47.5%) and were classified as moderately differentiated (n = 103, 56.9%). Of note, among the 190 patients who underwent a lymphadenectomy, lymph node metastasis was present in 78 patients (41.1%). Among the 217 patients who underwent surgery for GBC, 91 (41.9%) received adjuvant therapy; of these 91 patients, 44 (48.4%) also received adjuvant radiation therapy. A total of 87 patients received some type of adjuvant chemotherapy. Specifically, 24 patients (27.6%) received Gemcitabine alone, 22 received Gemcitabine + Cisplatin (25.3%) and 41 received other combinations of chemotherapy (47.1%).

Patterns of recurrence and factors associated with recurrence
The median follow-up for the entire cohort was 30.3 months (9.7–72.0). At the time of last follow-up, 76 (35.0%) patients had developed a tumor recurrence. Among patients who developed a
recurrence, 15.8% (n = 12) developed a local recurrence only, while 65.8% (n = 50) and 18.4% (n = 14) developed either a distant or a local plus distant recurrence, respectively. Of note, the most common site of recurrence was the liver (n = 22, 34.4%) followed by the peritoneum (n = 10, 15.6%); Fig. 2). The median time to recurrence and median recurrence-free survival among all patients were 9.5 months (IQR 4.7–17.6) and 11.2 months (IQR 4.2–29.3), respectively. Median time to recurrence was comparable among patients who developed a local, distant or local and distant recurrence (all p > 0.05, Supplemental Table 2).

Several disease-specific factors were associated with a greater risk of recurrence. Specifically, on univariable analysis, elevated serum bilirubin at presentation, the presence of disease at the surgical margin (R1), poor tumor differentiation, a higher T-stage, presence of residual disease and the presence of lymphovascular or perineural invasion were all associated with a greater risk of recurrence (all p < 0.05, Supplemental Table 3). On multivariable analysis, after adjusting for competing risk factors, higher tumor T-stage (T3 vs. T1: HR = 8.44, 95% CI 1.55–46.11, p = 0.014), the presence of residual disease at re-resection (HR = 2.04, 95% CI 1.02–4.05, p = 0.042) and the presence of lymphovascular invasion (HR = 4.24, 95% CI 1.91–9.43, p < 0.001) remained independently associated with a greater risk of recurrence (Supplemental Table 3). Of note, when examining specific patterns of recurrence, while no risk factor was associated with an increased risk of local recurrence, patients presenting with advanced AJCC T-stage (HR = 16.19, 95% CI 1.58–166.32, p = 0.019), patients with residual disease (HR = 2.35, 95% CI 1.04–5.30, p = 0.039), poorly differentiated tumors (HR = 6.63, 95% CI 1.27–34.8, p = 0.025), as well as patients with tumors characterized by lymphovascular invasion (HR = 4.98, 95% CI 2.02–12.26, p < 0.001) had an increased risk of developing a distant recurrence (Supplemental Tables 4 and 5). Interestingly, the extent of surgical resection was not associated with disease recurrence at either local or distant organs/sites (all p > 0.05).

Overall survival by recurrence
Among all patients, median overall survival was 16.1 months (IQR 10.1–28.3) while the 1-, 3- and 5-year survival estimates for all patients were 80.4% (95% CI 73.5–85.7), 53.7% (95% CI 44.9–61.7) and 43.7% (95% CI 34.2–52.7), respectively. Patients who developed a recurrence following surgical resection demonstrated worse survival compared with patients who did not develop a recurrence (Fig. 3). Specifically, estimates of 1-, 3- and 5-year survival were lower for patients who developed a recurrence compared with patients who did not develop a recurrence (1-year OS: 91.3% vs. 68.6%, p = 0.001, 3-year OS: 79.3% vs. 28.7%, p < 0.001, and 5-year OS: 75.9% vs. 16.0%, p < 0.001). Interestingly, no differences in OS were observed, however, by the site of recurrence as patients who developed either local or distant recurrence had comparable OS (all p > 0.05). To further explore the relationship between recurrence and OS, additional sub-analyses were performed. Interestingly, while the administration of adjuvant therapy was not associated with improved OS among the full cohort, when stratified by the development of disease recurrence, the receipt of adjuvant therapy was associated with 44% improved OS (HR = 0.56, 95% CI 0.32–0.93, p = 0.027; Fig. 4a–b) among those patients who developed a tumor recurrence. This effect was more pronounced among patients who received adjuvant chemotherapy compared with adjuvant radiation therapy (Fig. 4c–d).

Factors associated with receipt of adjuvant therapy on multivariate analysis included advanced tumor stage (T3 disease) (OR = 5.81, 95% CI 1.10–30.60, p = 0.038). Similarly, patients with lymph node metastases were also more likely to receive adjuvant treatment (OR = 3.54, 95% CI 1.17–10.73, p = 0.025) (Supplemental Table 6).

Factors associated with OS on univariable analysis included presence of disease at the surgical margin (HR = 3.25, 95% CI 1.87–5.65, p < 0.001), a higher tumor grade (poorly differentiated vs. well differentiated: HR = 2.56, 95% CI 1.05–6.23, p = 0.038), an advanced AJCC T-stage (T3 vs. T1: HR = 6.67, 95% CI 2.07–21.51, p = 0.002), the presence of lymphovascular invasion (HR = 2.56, 95% CI 1.63–3.93, p < 0.001) or perineural invasion (HR = 2.67, 95% CI 1.71–4.15, p < 0.001), disease recurrence (HR = 6.08, 95% CI 3.57–10.36, p < 0.001) and the presence of disease at the time of re-resection (HR = 1.98, 95% CI 1.14–3.44, p = 0.015) (Supplemental Table 7). On multivariable Cox proportional hazard regression analysis, after adjusting for patient demographics and disease-related factors, while the presence of residual disease at re-operation was not associated with an increased risk of worse OS (HR = 1.32, 95% CI 0.66–2.65, p = 0.430), subsequent recurrence after curative intent surgery was associated with almost 4-fold greater risk of a worse OS (HR = 3.71, 95% CI 1.46–9.42, p = 0.006).

Discussion
Gallbladder carcinoma (GBC) is a rare malignancy in the Western world.17 As a result, it is an understudied disease and data pertaining to long-term outcomes after resection of GBC is limited.18–20 As a result, this study provides valuable insights from a multi-institutional analysis from the US Extra-hepatic Biliary Malignancy Consortium, HPB (2016), http://dx.doi.org/10.1016/j.hpb.2016.05.016
The two main patterns of recurrence observed after curative intent resection of GBC are locoregional and distant disease. Locoregional recurrence along the hepatic resection margin or in the porta hepatitis likely arises from residual microscopic disease or from tumor spread via lymphatic flow along the Glissonian pedicles. On the other hand, intrahepatic and distant recurrence more likely results from hematogenous spread through the cystic veins. In the present study, among patients who recurred, a distant recurrence occurred in the majority of patients (65.8%). Specifically, the most common site of recurrence was the liver (34.4%); less common sites included the peritoneum and lung (Fig. 2). These observations may have important implications regarding the optimal surveillance strategy following GBC resection. In line with these findings, the Memorial Sloan Kettering Cancer Center (MSKCC) group reported that among patients with GBC who recurred, 85% (41 of 48) experienced initial disease recurrence at a distant site, with or without a concomitant locoregional recurrence. While the most common site of distant metastasis in the MSKCC study was the peritoneum, Kim et al. noted that distant intrahepatic recurrence was the most common site of distant recurrence – consistent with findings in the current study. Furthermore, Aramaki et al. and others reported that recurrence was most frequent in intra-abdominal organs, such as the liver. Of note, time to recurrence and survival after recurrence were comparable among patients who experienced locoregional versus distant recurrence. Similarly, others have shown that the site of initial disease recurrence had no apparent impact on survival.

Another interesting finding was that the administration of adjuvant therapy was not associated with recurrence risk. Previously, other investigators reported the negligible impact of adjuvant treatment on risk of recurrence. For example, Kim et al. reported no difference in disease-free survival between the no-adjuvant therapy and adjuvant therapy groups. To this end, we found that adjuvant therapy failed to improve the risk of survival in the overall cohort. Nonetheless, patients who had previously been offered adjuvant treatment and subsequently recurred, fared better than patients who recurred after surgery alone. Although this finding may be related to selection bias as
medically fit patients with a better tumor biology might have been commonly offered adjuvant treatment, use of adjuvant therapy was more common among high-risk patients. In fact, patients who received adjuvant treatment had more advanced disease and were more likely to have lymph node metastases (Supplemental Table 6). O’Connell et al. had previously noted that colon cancer patients who had a recurrence following adjuvant therapy had a different prognosis than patients who progressed after surgery alone. In contrast to patients who received chemotherapy, the use of adjuvant radiotherapy alone was not associated with a survival benefit. The etiology of these disparate results may be multifactorial, but is likely a result of variations in how patients were selected and analyzed. Future studies are needed to better define the role of adjuvant chemotherapy and radiotherapy following curative intent surgery for GBC.

Several limitations should be considered when interpreting our findings. As with all retrospective studies, there was undoubtedly a degree of selection, as well as treatment bias. Because data were gathered from 10 academic institutions, treatment approaches may have been affected by selection and center bias. In addition, 12.8% of patients did not have lymph node sampling. For this reason, we did not formally use the tumor, node, metastasis (TNM) staging system in our analysis.

Figure 4 Comparison of Kaplan–Meier estimates for overall survival by (a) adjuvant therapy among all patients (b) adjuvant therapy among patients who developed a disease recurrence (c) adjuvant chemotherapy among patients who developed a disease recurrence, and (d) adjuvant radiation therapy among patients who developed a disease recurrence.
To mitigate this limitation, we performed a sub-analysis after excluding patients who did not have LN evaluation (Supplemental Table 8). Of note, the results did not change. In addition, data pertaining to the treatment of recurrences were not available in the current study. Finally, despite harnessing the collective experience of 10 major health care centers in the United States, our sample size was still relatively small (n = 200). In turn, this may have limited some analyses and increased the risk of a Type II statistical error.

Collectively, in the largest Western study reported to date, nearly one-third of patients who underwent curative intent surgery for GBC experienced a recurrence. Most patients recurred within 2 years following surgery and the most common site of spread was the liver. Therefore, intensive follow-up aimed at the early time period following surgery may be advisable. Because median time to recurrence was comparable among patients who developed a local or a distant recurrence, comprehensive follow-up imaging studies (e.g., liver, lung, etc.) are important. These data should help inform surveillance strategies and discussions around prognosis for patients undergoing curative intent surgery for GBC.

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Conflict of interest
None to declare.

References

Appendix A. Supplementary data
Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2016.05.016.