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Impact of Chemotherapy and External-Beam Radiation Therapy on Outcomes among Patients with Resected Gallbladder Cancer: A Multi-institutional Analysis

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Abstract

Background—Use of adjuvant chemotherapy (CTx) and chemoradiation therapy (cXRT) for the treatment of gall-bladder cancer (GBC) remains varied. We sought to define the utilization and effect of adjuvant therapy for patients with GBC.

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Methods—Using a multi-institutional national database, 291 patients with GBC who underwent curative-intent resection between 2000 and 2015 were included. Patients with metastasis or an R2 margin were excluded.

Results—Median patient age was 66.6 years. Most patients had a T2 (46.2 %) or T3 (38.6 %) lesion, and 37.8 % of patients had lymph node (LN) metastasis. A total of 186 (63.9 %) patients underwent surgery alone, 61 (21.0 %) received CTx, and 44 (15.1 %) patients received cXRT. On multivariable analysis, factors associated with worse overall survival (OS) included T3/T4 stage [hazard ratio (HR) 1.82], LN-metastasis (HR 1.84), lymphovascular invasion (HR 2.02), perineural invasion (HR 1.42), and R1 surgical margin status (HR 2.06); all $P < 0.05$). In contrast, receipt of CTx/cXRT was associated with improved OS (CTx, HR 0.38; cXRT, HR 0.26; $P < 0.001$) compared with surgery alone. Similar results were observed for disease-free survival (DFS) (CTx, HR 0.61; cXRT, HR 0.43; $P < 0.05$). Of note, only patients with high-risk features, such as AJCC T3/T4 stage (HR 0.41), LN metastasis (HR 0.45), and R1 disease (HR 0.21) (all $P < 0.05$) derived an OS benefit from CTx/cXRT.

Conclusions—Adjuvant CTx/cXRT was utilized in 36 % of patients undergoing curative-intent resection for GBC. After adjusted analyses, CTx/cXRT were independently associated with improved long-term outcomes, but the benefit was isolated to only patients with high-risk characteristics.

Gallbladder cancer (GBC) is the fifth most common gastrointestinal cancer and one of the most aggressive gastrointestinal malignancies.¹ The American Cancer Society estimates that there will be approximately 11,000 gallbladder and extrahepatic bile duct cancer cases resulting in nearly 3,700 deaths in the United States in 2015.² Whereas complete surgical resection remains the only potentially curative treatment option for patients with GBC, the outcome of patients with advanced disease is dismal with 5-year survival ranging from 5 to 40 %.^{1,3–5} Previous studies have reported a high incidence of locoregional or distant recurrence after surgical resection for GBC, suggesting the need for additional therapeutic modalities following surgical resection.^{6,7} The role of adjuvant therapy for GBC, however, remains unclear.

Design and implementation of prospective clinical studies to assess the role of adjuvant chemotherapy (CTx) or chemoradiation therapy (cXRT) for GBC are challenging because of the rarity of the disease. One previous randomized, controlled trial reported improved overall survival among patients who received adjuvant chemotherapy, specifically among the subset of patients who underwent noncurative resections.⁸ In a separate trial, Ben-Josef et al. suggested that adjuvant chemotherapy followed by cXRT was safe and effective.⁹ While these previous studies were valuable in exploring the potential role of adjuvant therapy, most data on the topic of adjuvant therapy for GBC suffer from small, heterogeneous patient populations that mix GBC with extra- and intrahepatic cholangiocarcinoma, as well as include patients who have undergone nononcologic resections.^{10–13} Given this, we sought to evaluate the role of adjuvant CTx and cXRT among patients undergoing curative intent surgical resection for GBC using a large, multicenter, national collaborative database. Specifically, the objective of the current study was to define those factors associated with receipt of adjuvant therapy, as well as evaluate the relative treatment benefit of CTx/cXRT

versus surgery alone using propensity-matched analysis of patients undergoing curative intent resection of GBC.

METHODS

Patient Selection

Patients who underwent curative resection for GBC between January 1, 2000 and April, 30 2015 were identified from a multi-institutional database (Johns Hopkins University, Stanford University, University of Wisconsin, The Ohio State University, Washington University, Vanderbilt University, New York University, University of Louisville, Wake Forest University, and Emory University). The institutional review boards at each participating institution approved this study. Only patients who underwent curative-intent surgery were included; patients with metastatic disease and those with macroscopically positive (R2) surgical margins were excluded.

Standard demographic and clinicopathologic data, including age, sex, American Society of Anesthesiologist (ASA) Physical Status Classification System, tumor size, American Joint Committee on Cancer (AJCC) stage, presence or absence of lymphovascular invasion (LVI) and perineural invasion (PNI), as well as histologic grade, were collected. Resection was classified as cholecystectomy only, radical cholecystectomy (cholecystectomy + segment 4b, 5 resection), radical cholecystectomy plus bile duct resection, formal hepatic resection or pancreatoduodenectomy. Resection margin status was categorized as microscopically negative (R0) versus microscopically positive (R1); lymph node (LN) status (no metastasis [N0], LN metastasis [N1]) also was ascertained. Perioperative details, including surgical approach, as well as information on CTx and cXRT, were collected. Vital status, date of death, or last follow-up date also were collected. Recurrence was defined as biopsy proven GBC or imaging that was high suspicious for tumor recurrence in the setting of an elevated carbohydrate antigen 19-9.

Statistical Analysis

Continuous variables were described as medians with interquartile range (IQR) and categorical variables as frequencies with percentages. Univariable comparisons for continuous variables were assessed using the Kruskal–Wallis test, whereas categorical variables were assessed using the Chi-squared or the Fisher's exact test, as appropriate. Univariable and multivariable logistic regression analysis was performed to determine associations of covariates with adjuvant CTx/cXRT. Disease-free (DFS) and overall survival (OS) outcomes were estimated using the Kaplan–Meier method; unadjusted differences in OS or DFS were assessed using the log-rank test. To account for possible confounding variables, multivariable Cox proportional hazards regression analyses and propensity score methods were utilized.^{5,14,15} The propensity score was calculated using a logistic regression model with the treatment of interest (i.e., adjuvant therapy) as the outcome measure. The propensity-matched cohorts were compared to assess the effect of CTx/cXRT versus surgery along on long-term outcome. Statistical analyses were performed with STATA version 14.0 (StataCorp, College Station, TX) and R version 3.0.3 (<http://www.r-project.org>); all tests were two-sided, and *P* value <0.05 was considered statistically significant.

RESULTS

Demographic and Clinicopathologic Characteristics

A total of 291 patients underwent resection for GBC and met inclusion criteria. The demographic and clinical characteristics of the study cohort are presented in Table 1. Median patient age was 66.6 years (IQR 56.3–73.1), most patients were white ($n = 194$, 66.7 %) and female ($n = 192$, 66.0 %). At the time of surgery, most patients underwent either radical cholecystectomy with or without bile duct resection ($n = 222$, 76.6 %). The overwhelming majority of patients ($n = 251$, 86.3 %) had at least one LN evaluated. Among these 251 patients, 110 (43.8 %) had LN metastasis, whereas 141 (56.2 %) had no nodal disease. On surgical pathology, most patients ($n = 249$, 86.2 %) had an R0 margin. The majority of tumors were AJCC T2 ($n = 122$, 46.2 %) or T3 ($n = 102$, 38.6 %); approximately one-third ($n = 82$, 33.5 %) of lesions were poor- to un-differentiated tumors.

Factors Associated with Receipt of Adjuvant Therapy

Postoperatively, 105 (36.1 %) patients received adjuvant therapy (CTx: $n = 61$, 21.0 % vs. cXRT: $n = 44$, 15.1 %), whereas 186 (63.9 %) patients underwent surgery only. Among those 84 patients who were available for the data on the type of adjuvant chemotherapy, the majority of patients received Gemcitabine alone ($n = 30$, 35.7 %) or Gemcitabine plus Cisplatin ($n = 27$, 32.1 %); approximately one-third ($n = 27$, 32.1 %) of patients received other regimens. On univariable analysis, factors associated with an increased likelihood to receive adjuvant therapy included patient specific factors, such as lower ASA score, as well as tumor-specific factors, including N1 disease, presence of LVI, as well as worse tumor grade (Table 2). After controlling for competing risk factors on multivariable analysis, patients with N1 disease remained roughly three times more likely to receive adjuvant therapy compared with patients who had N0 disease [odds ratio (OR) 3.06, 95 % confidence interval (CI) 1.57–2.95; $P = 0.001$]. Similarly, the presence of LVI was associated with a fivefold increased odds of receiving adjuvant therapy (OR 5.16, 95 % CI 2.51–10.58; $P < 0.001$). In contrast, patients with more medical comorbidities were less likely to receive adjuvant therapy (ASA 3–4: OR 0.33, 95 % CI 0.17–0.65; $P = 0.001$). Interestingly, independent of clinical factors, adjuvant therapy administration increased across the time periods examined (reference, 2000–2005: 2006–2010, OR 7.18, 95 % CI 3.00–17.19 vs. 2011–2015, OR 8.99, 95 % CI 3.74–21.63; both $P < 0.001$). Among those patients with T3/T4 disease, LN metastasis (OR 1.77, 95 % CI 1.01–3.10; $P = 0.04$) and the year of surgery (reference, 2000–2005: 2006–2010, OR 5.01, 95 % CI 1.62–15.51; $P = 0.005$ vs. 2011–2015, OR 8.06, 95 % CI 2.61–24.84; $P < 0.001$) were associated with the receipt of adjuvant therapy. No factor was specifically associated with receipt of CTx versus cXRT (all $P > 0.05$).

Diseasefree Survival and Overall Survival After Resection for GBC

Median follow-up was 26.1 months. At the time of last follow-up, 90 (39.0 %) patients had recurred with a median DFS of 19.8 months (95 % CI 17.0–24.5). Data on patterns of recurrence were available for 83 (28.5 %) patients (local only, $n = 14$ vs. local + distant recurrence, $n = 18$ vs. distant only $n = 51$). On multivariable analysis, T3/T4 disease [hazard ratio (HR) 1.74, 95 % CI 1.17–2.59; $P = 0.006$], N1 disease (HR 1.65, 95 % CI 1.14–2.38; P

= 0.008), LVI (HR 2.02, 95 % CI 1.37–2.99; $P < 0.001$), R1 margin status (HR 1.61, 95 % CI 1.03–2.52; $P = 0.036$), and postoperative complications (HR 1.48, 95 % CI 1.03–2.12; $P = 0.032$) were all associated with worse DFS (Table 3a). Adjuvant CTx (HR 0.61, 95 % CI 0.39–0.98; $P = 0.041$) and cXRT (HR 0.43, 95 % CI 0.27–0.68; $P < 0.001$) also were associated with improved DFS on multivariable analyses.

Median OS was 28.3 months (95 % CI 22.4–34.0) with 1-, 3-, and 5-year OS of 76.7, 42.2, and 33.0 %, respectively. Similar to DFS, T3/T4 diseases (HR 1.82, 95 % CI 1.17–2.81; $P = 0.007$), tumor size (>3 cm: HR 1.26, 95 % CI 1.13–2.38; $P = 0.01$), N1 disease (HR 1.84, 95 % CI 1.24–2.73; $P = 0.002$), LVI (HR 2.02, 95 % CI 1.33–3.06; $P = 0.001$), R1 margin status (HR 2.06, 95 % CI 1.31–3.25; $P = 0.002$), and postoperative complications (HR 1.76, 95 % CI 1.20–2.56; $P = 0.013$) were associated with worse OS (Table 3b). After controlling for these factors, adjuvant CTx (HR 0.38, 95 % CI 0.23–0.65; $P < 0.001$) and cXRT (HR 0.26, 95 % CI 0.15–0.43; $P < 0.001$) remained associated with a decreased risk of death. Because interaction between adjuvant therapy and margin status was noted, sensitivity analyses were done, including this interaction term. When the interaction term was included in the multivariable analysis, adjuvant CTx (HR 0.46, 95 % CI 0.26–0.82; $P = 0.008$) and cXRT (HR 0.33, 95 % CI 0.19–0.59; $P < 0.001$) remained associated with improved OS, however only cXRT (HR 0.56, 95 % CI 0.34–0.92; $P = 0.021$) was associated with improved DFS.

The effect of adjuvant CTx or cXRT on DFS and OS was most pronounced among patients with high-risk features, including T3–T4 tumors, N1 disease, as well as an R1 surgical margin. For example, the risk of recurrence decreased by roughly 40–65 % with adjuvant therapy among patients who had high-risk features, such as T3/T4 disease (HR 0.56, 95 % CI 0.36–0.87; $P < 0.001$), LN metastasis (HR 0.59, 95 % CI 0.37–0.93; $P = 0.001$), and R1 margin (HR 0.34, 95 % CI 0.16–0.73; $P = 0.001$). A similar OS benefit for adjuvant therapy was noted among patients with high-risk features (Fig. 1). In contrast, CTx or cXRT did not confer a DFS or OS benefit among patients with T1/T2 tumors, N0 disease, or among patients who had an R0 margin (all $P > 0.05$).

Lastly, propensity-matched analyses were undertaken to minimize confounding by indication and to create more balanced cohorts of patients who received adjuvant therapy versus surgery alone. After propensity-matching for T stage, nodal disease, presence/absence of LVI, histologic grade, and surgical margin status, the propensity-matched cohort included 61 patients who received adjuvant therapy versus 72 patients who had surgery alone. Following matching, clinicopathologic factors, including age, sex, T stage, tumor size, nodal status, LVI, PVI, histologic grade, and margin status, were comparable in the adjuvant versus no adjuvant groups (Supplemental Fig. 1). On propensity-matched analysis, the benefit of adjuvant CTx/cXRT therapy among patients with high-risk features remained significant (Fig. 2).

DISCUSSION

GBC is one of the most aggressive gastrointestinal cancers as locoregional and distant recurrence after surgical resection for GBC is common.^{7,16–20} As such, chemotherapy

and/or radiation therapy has been considered in the adjuvant setting to improve locoregional control as well as treat any possible residual systemic tumor burden. The role of adjuvant therapy for GBC remains unclear and somewhat controversial.^{16,21} Most previous studies were limited due to small sample size, single institutional experiences, as well as heterogeneous study populations.^{11,18,19,22} The current study is important because it reports one of the largest, multi-institutional experiences on the surgical management of GBC in the United States. More importantly, using both multivariable and propensity-matched analyses, we demonstrated a potential benefit of adjuvant therapy for patients with GBC. Specifically, adjuvant CTx/cXRT was associated with a decreased risk of recurrence and long-term death, even after controlling for other competing patient- and tumor-specific risk factors. Of note, the benefit of adjuvant therapy was most pronounced among those patients with more adverse prognostic features such as advanced T stage, LN metastasis, and an R1 surgical margin. Data from the current study are consistent and support current National Comprehensive Cancer Network (NCCN) guidelines.

In the current cohort, adjuvant therapy was utilized in roughly one-third of patients undergoing curative-intent resection for GBC. Perhaps as expected, receipt of adjuvant therapy was associated with certain patient and clinicopathologic factors. Specifically, while patient age was not associated with receipt of adjuvant therapy, ASA classification was strongly associated with the likelihood of a patient to receive postoperative therapy. In fact, patients with an ASA score of 3–4 were 70 % less likely to receive adjuvant therapy. These data are consistent with reports from the medical oncology literature, which suggest that older patients can benefit from chemotherapy and age alone should not be utilized to exclude patients.²³ Assessments of frailty and comorbidity such as the ASA classification also may be useful tools when consider adjuvant therapy, although clinical decision needs to be individualized for each patient. Not surprisingly, tumor-specific factors also were associated with receipt of adjuvant therapy. In particular, patients who had tumors characterized by LVI and LN metastasis were up to three to five times more likely to receive adjuvant therapy versus surgery alone. Previous studies have similarly demonstrated that disease characteristics, including LN metastasis, moderately-poorly differentiated tumors, and disease extending to the liver or other adjacent organs were associated with a higher likelihood of adjuvant therapy administration.⁵

Several studies have reported that adjuvant therapy is associated with improved outcomes following surgery for GBC; however, other research have reported no correlation between adjuvant therapy and long-term survival.^{12,24,25} Given that data regarding the benefit of adjuvant treatment for GBC vary widely, adequate control of baseline demographic and clinical characteristics among patients receiving adjuvant therapy versus surgery alone is critical to evaluate the impact of adjuvant therapy.³ In the current study, we utilized both multivariable and propensity-matched analyses to minimize confounding by indication. While such methods cannot completely eliminate residual bias, these statistical techniques can markedly improve the comparability of the groups being assessed (Supplemental Fig. 1). Using these techniques, we found that adjuvant CTx/cXRT were independent factors associated with improved long-term outcomes. Of note, the benefit of adjuvant therapy was isolated only to patients with high-risk GBC features (i.e., T3–T4, N1, and R1 surgical margins). These findings were consistent with the data reported by Ben-Josef et al. in a

single-arm phase II trial in which the authors reported a survival benefit of adjuvant cXRT only among patients with resected GBC or extrahepatic cholangiocarcinoma that was T2, N1, or R1.⁹ Other observational studies have similarly demonstrated that the benefit of adjuvant therapy for GBC is most pronounced among that subset patients with T2, N1, and R1 disease.^{3,11,21,25}

Radiotherapy is commonly administered with concurrent chemotherapy, and most studies that have reported a benefit of adjuvant radiotherapy included patients treated with concurrent chemotherapy.^{1,4,16} As noted in the current study, the locoregional benefit of adjuvant cXRT may be only relevant when systemic control of disease also is addressed, as the majority of recurrences (86 %) were distant in nature. Given that distant recurrence is more common than locoregional recurrence, CTx has been proposed as a more effective adjuvant strategy than cXRT.^{7,8} To this end, Horgan et al. reported that patients receiving adjuvant cXRT and systemic CTx derived greater benefit than radiation therapy alone.²⁵ Other investigators have similarly argued that adjuvant cXRT provides an incremental survival benefit over CTx alone.²¹ Collectively, data from the current study as well as previous reports suggest that administration of systemic CTx with the integration of cXRT may be the optimal adjuvant strategy for patients with resected GBC characterized by high-risk features.^{1,5,9,26}

Several limitations should be considered when interpreting the data. The collaboration among multiple different institutions limited the ability to standardize treatment criteria. However, the multi-institutional study design increased the generalizability of the results. In addition, as with all nonrandomized retrospective studies, control of confounding variables was challenging. Although the use of multivariable analyses and propensity-matching allowed us to control for measurable confounders, unknown or unmeasured confounders could not be taken into account. In turn, there was likely some residual bias. While the current study noted a strong association between adjuvant therapy and certain subsets of patients, only a randomized trial truly can assess the relative benefit of adjuvant therapy in these different subset of patients. The data, however, do highlight the potential benefit of adjuvant therapy and the need to better examine its effect in patients with GBC. In addition, incomplete information on recurrence pattern limited the analysis to assess further the correlation between recurrence patterns and adjuvant therapy. Finally, given that only seven patients underwent radiation therapy alone, the effect of adjuvant radiation therapy and CTx therapy was analyzed as a composite endpoint, thereby not allowing us to define the effect of either therapy alone.

In conclusion, following curative intent resection of GBC, roughly one-third of patients received adjuvant CTx/cXRT. After adjusting for varied clinicopathologic factors in the no adjuvant versus adjuvant GBC cohorts using multivariable and propensity-matching, CTx/cXRT remained independently associated with a long-term benefit. The benefit of adjuvant therapy was most pronounced among patients with high-risk features, including T3/T4 tumors, N1 disease, and R1 surgical margins. As such, patients with GBC and these high-risk features should be considered for adjuvant therapy.

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FIG. 1.

Kaplan–Meier survival curves among patients comparing surgical resection plus adjuvant therapy to surgical resection alone for gallbladder cancer: disease-free survival stratified by **a** T stage, **c** lymph node status, and **e** surgical margin, and overall survival stratified by **b** T stage, **d** lymph node status, and **f** surgical margin

FIG. 2.

Kaplan–Meier survival curves among propensity-matched cohort comparing surgical resection plus adjuvant therapy to surgical resection alone for gallbladder cancer: disease-free survival among patients with **a** T3–T4 stage, **c** N1 disease, and **e** R1 margin, and overall survival stratified by **b** T3–T4 stage, **d** N1 disease, and **f** R1 margin

TABLE 1
Baseline characteristics of 291 patients who underwent curative resection for gallbladder cancer

Characteristic	Total (<i>n</i> = 291)	Surgery only (<i>n</i> = 186)	Surgery + chemo (<i>n</i> = 61)	Surgery + cXRT (<i>n</i> = 44)	<i>P</i>
Age (year)	66.6 (56.3–73.1)	67.7 (56.9–74.0)	64.5 (56.3–73.2)	63.9 (55.3–69.3)	0.122
Sex					0.842
Female	192 (66.0)	122 (65.6)	42 (68.9)	28 (63.6)	
Male	99 (34.0)	64 (34.4)	19 (31.1)	16 (36.4)	
Race					0.114
Other/unknown	61 (21.0)	42 (22.6)	15 (24.6)	4 (9.1)	
White	194 (66.7)	125 (67.2)	35 (57.4)	34 (77.3)	
Black	36 (12.4)	19 (10.2)	11 (18.0)	6 (13.6)	
BMI, Kg/m ²	27.6 (23.5–31.7)	27.1 (23.1–31.0)	28.5 (24.5–32.7)	28.3 (25.1–32.4)	0.335
ASA (<i>n</i> = 199)					0.135
1–2	81 (40.7)	43 (35.2)	23 (47.9)	15 (51.7)	
3–4	118 (59.3)	79 (64.8)	25 (52.1)	14 (48.3)	
Preoperative bilirubin	0.6 (0.5–1.0)	0.6 (0.5–1.1)	0.5 (0.4–0.9)	0.6 (0.4–1.2)	0.043
Preoperative INR	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	0.925
Preoperative albumin	3.8 (3.4–4.2)	3.7 (3.1–4.2)	4.0 (3.6–4.2)	4.0 (3.8–4.2)	0.005
Preoperative platelet	253 (203–327)	259 (200.5–330)	253 (216–326)	247 (203–325)	0.935
Jaundice (<i>n</i> = 261)	39 (14.9)	26 (16.5)	5 (8.3)	8 (18.6)	0.247
Preoperative creatinine	0.8 (0.7–1.0)	0.9 (0.7–1.0)	0.8 (0.7–1.0)	0.8 (0.6–0.9)	0.031
Type of resection (<i>n</i> = 290)					0.225
Bile duct resection only	9 (3.1)	8 (4.3)	1 (1.6)	0 (0.0)	
Cholecystectomy only	30 (10.3)	25 (13.5)	4 (6.6)	1 (2.3)	
Radical cholecystectomy	222 (76.6)	137 (74.1)	48 (78.7)	37 (84.1)	
Hepatectomy + bile duct resection	21 (7.2)	11 (5.9)	6 (9.8)	4 (9.1)	
Whipple	8 (2.8)	4 (2.2)	2 (3.3)	2 (4.5)	
Resection method (<i>n</i> = 289)					0.159
Open	272 (94.1)	172 (92.5)	57 (95.0)	43 (100.0)	
MIS	17 (5.9)	14 (7.5)	3 (5.0)	0 (0.0)	
EBL	300 (150–500)	300 (200–500)	200 (150–400)	300 (200–600)	0.167

Characteristic	Total (n = 291)	Surgery only (n = 186)	Surgery + chemo (n = 61)	Surgery + cXRT (n = 44)	P
Transfusion (n = 273)	41 (15.0)	31 (17.7)	5 (8.5)	5 (12.8)	0.21
Tumor size, mm	30.0 (20.0–48.0)	28.5 (15.0–45.0)	28.0 (17.0–49.0)	36.0 (25.0–50.0)	0.059
Margin (n = 289)					0.609
R0	249 (86.2)	159 (86.4)	54 (88.5)	36 (81.8)	
R1	40 (13.8)	25 (13.6)	7 (11.5)	8 (18.2)	
Tumor grade (n = 245)					0.04
Well differentiated	30 (12.2)	25 (16.4)	1 (1.8)	4 (10.8)	
Moderately differentiated	133 (54.3)	83 (54.6)	32 (57.1)	18 (48.6)	
Poorly to undifferentiated	82 (33.5)	44 (28.9)	23 (41.1)	15 (40.5)	
T stage (n = 264)					0.057
1	24 (9.1)	22 (13.3)	1 (1.7)	1 (2.6)	
2	122 (46.2)	75 (45.2)	30 (50.8)	17 (43.6)	
3	102 (38.6)	61 (36.7)	22 (37.3)	19 (48.7)	
4	16 (6.1)	8 (4.8)	6 (10.2)	2 (5.1)	
LV1 (n = 167)	80 (47.9)	35 (36.1)	25 (58.1)	20 (74.1)	0.001
PNI (n = 168)	89 (53.0)	45 (45.9)	22 (55.0)	22 (73.3)	0.03
Lymph node					<0.001
N0	141 (48.5)	105 (56.5)	21 (34.4)	15 (34.1)	
N1	110 (37.8)	50 (26.9)	36 (59.0)	24 (54.5)	
Nx	40 (13.7)	31 (16.7)	4 (6.6)	5 (11.4)	

ASA American Society of Anesthesiologist; MIS minimally invasive surgery; EBL estimated blood loss; LV lymphovascular invasion; PNI/perineural invasion

TABLE 2

Various factors associated with receipt of adjuvant therapy

	Univariable			Multivariable		
	OR	(95 % CI)	P value	OR	(95 % CI)	P value
Age (year)						
65	Ref			Ref		
> 65	0.67	0.41–1.08	0.099	0.61	0.33–1.11	0.108
Sex						
Female	Ref			Ref		
Male	0.95	0.57–1.58	0.853	1.69	0.87–3.26	0.119
Race						
Other/unknown	Ref			Ref		
White	1.22	0.66–2.26	0.527	0.91	0.41–1.99	0.809
Black	1.98	0.85–4.63	0.116	1.38	0.48–4.02	0.55
ASA						
1–2	Ref			Ref		
3–4	0.56	0.31–1.00	0.049	0.33	0.17–0.65	0.001
Tumor grade						
Well to moderately differentiated	Ref			Ref		
Poorly to undifferentiated	3.01	1.08–8.37	0.035	1.34	0.71–2.54	0.571
T stage						
1–2	Ref			Ref		
3–4	1.41	0.85–2.32	0.184	1.22	0.61–2.46	0.571
Margin						
R0	Ref			Ref		
R1	1.06	0.53–2.11	0.869	1.04	0.39–2.77	0.939
Resection method						
MIS	Ref			Ref		
Open	2.71	0.76–9.67	0.124	3.25	0.71–14.93	0.13
Size	1	0.99–1.02	0.402	0.99	0.98–1.00	0.14
Lymph node status						

	Univariable			Multivariable		
	OR	(95 % CI)	P value	OR	(95 % CI)	P value
N0	Ref			Ref		
N1	3.50	2.05–5.96	<0.001	3.06	1.57–2.95	0.001
Nx	0.85	0.37–1.95	0.696	0.94	0.34–2.55	0.898
LVI	3.19	1.68–6.05	<0.001	5.16	2.51–10.58	<0.001
PNI	1.99	1.06–3.73	0.031	0.91	0.44–1.90	0.808
Complication						
No	Ref			Ref		
Yes	0.68	0.41–1.13	0.134	0.67	0.34–1.29	0.228
Year						
2000–2005	Ref			Ref		
2006–2010	3.27	1.62–6.58	0.001	7.18	3.00–17.19	<0.001
2011–2015	4.06	2.04–8.07	<0.001	8.99	3.74–21.63	<0.001

Cox proportional hazard regression analysis of factors associated with (a) disease-free survival and (b) overall survival after resection for gallbladder cancer

TABLE 3

	Univariate			Multivariate		
	HR	(95 % CI)	P value	HR	(95 % CI)	P value
(a)						
Age						
65	Ref			Ref		
> 65	1.09	0.80–1.49	0.595	1.08	0.77–1.52	0.658
Sex						
Female	Ref			Ref		
Male	0.91	0.66–1.26	0.569	0.93	0.66–1.32	0.697
Lymph positive						
N0	Ref			Ref		
N1	1.79	1.28–4.50	0.001	1.65	1.14–2.38	0.008
Nx	1.27	0.77–2.10	0.342	1.39	0.80–2.41	0.245
T stage						
1–2	Ref			Ref		
3–4	2.92	2.12–4.02	< 0.001	1.74	1.17–2.59	0.006
Adjuvant therapy						
No	Ref			Ref		
Chemo only	0.95	0.63–1.44	0.825	0.61	0.39–0.98	0.041
Chemoradiotherapy	0.87	0.57–1.31	0.504	0.43	0.27–0.68	< 0.001
Complication						
No	Ref			Ref		
Yes	1.92	1.40–2.64	< 0.001	1.48	1.03–2.12	0.032
Margin						
R0	Ref			Ref		
R1	3.12	2.12–4.60	< 0.001	1.61	1.03–2.52	0.036
Tumor grade						
Well to moderately differentiated	Ref			Ref		

	Univariate			Multivariate		
	HR	(95 % CI)	P value	HR	(95 % CI)	P value
Poorly to undifferentiated	1.65	1.20–2.27	0.002	1.18	0.83–1.68	0.362
Size						
3cm	Ref			Ref		
> 3cm	1.85	1.36–2.53	<0.001	1.26	0.90–1.78	0.178
LVI	2.48	1.80–3.41	<0.001	2.02	1.37–2.99	<0.001
PNI	2.09	1.52–2.88	<0.001	1.38	0.92–2.08	0.124
Year	0.99	0.95–1.03	0.56	1.02	0.98–1.07	0.313
(b)						
Age						
65	Ref			Ref		
> 65	1.25	0.89–1.74	0.192	1.32	0.91–1.90	0.143
Sex						
Female	Ref			Ref		
Male	0.87	0.62–1.24	0.451	0.86	0.59–1.24	0.421
Lymph positive						
N0	Ref			Ref		
N1	1.76	1.24–2.50	0.002	1.84	1.24–2.73	0.002
Nx	1.3	0.76–2.23	0.34	1.55	0.85–2.83	0.148
T stage						
1–2	Ref			Ref		
3–4	3.1	2.17–4.45	<0.001	1.82	1.17–2.81	0.007
Adjuvant therapy						
No	Ref			Ref		
Chemo only	0.74	0.47–1.16	0.186	0.38	0.23–0.65	<0.001
Chemoradiotherapy	0.69	0.44–1.07	0.098	0.26	0.15–0.43	<0.001
Complication						
No	Ref			Ref		
Yes	2.42	1.68–3.48	<0.001	1.76	1.20–2.56	0.013
Margin						
R0	Ref			Ref		

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	Univariate			Multivariate		
	HR	(95 % CI)	P value	HR	(95 % CI)	P value
R1	3.50	2.36–5.18	<0.001	2.06	1.31–3.25	0.002
Tumor grade						
Well to moderately differentiated	Ref			Ref		
Poorly to undifferentiated	1.68	1.17–2.40	0.005	1.21	0.83–1.77	0.319
Size						
3cm	Ref			Ref		
> 3cm	1.88	1.24–2.85	0.003	1.26	1.13–2.38	0.01
LVI	2.24	1.45–3.46	<0.001	2.02	1.33–3.06	0.001
PNI	2.27	1.44–3.57	<0.001	1.42	0.91–2.22	0.12
Year	0.98	0.93–1.02	0.27	1.02	0.97–1.07	0.408