Original Article

Long- and short-term outcomes for resectable gallbladder carcinoma patients treated with curative-intent laparoscopic versus open resection: a multicenter propensity score-matched comparative study

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Background: Gallbladder cancer (GBC) was once considered a contraindication for laparoscopic surgery, but it is becoming more common to use laparoscopic surgery for GBC treatment. The aim of this study was to analyze the long- and short-term outcomes of patients with more advanced T-staged GBC treated with curative intent as defined by the National Comprehensive Cancer Network (NCCN) after laparoscopic resection (LR) versus open resection (OR).

Methods: A multicenter database was used to select consecutive GBC patients treated with curative-intent resection as defined by the NCCN between 2016 and 2020. The patients were divided into the LR group and the OR group. Propensity score matching (PSM) was used to eliminate selection bias. The endpoints were overall survival (OS), progression-free survival (PFS), and short-term outcomes. Risk factors that were independently associated with OS and PFS were identified.

Results: Of 626 GBC patients treated with curative-intent resection, after PSM, 51 patients were in the LR group and 153 patients were in the OR group. The LR group had more patients who were suitable to receive adjuvant chemotherapy (AC), a longer operation time, more harvested lymph nodes, and a lower overall morbidity rate. The rates of OS and PFS were not significantly different between the two groups. AC was independently associated with better OS and PFS.

Conclusions: The overall morbidity of GBC patients after LR was lower, but the long-term outcomes between LR and OR were not significantly different. The GBC patients treated with LR were more likely to receive AC, and the use of AC after curative-intent resection of GBC helped achieve better long-term survival outcomes.

Keywords: Gallbladder cancer (GBC); laparoscopic resection (LR); morbidity; survival; adjuvant chemotherapy (AC)

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Introduction

Approximately 170,000 people worldwide each year are diagnosed with gallbladder cancer (GBC), a common cancer of the biliary tract, with most cases occurring in East Asian countries and South America (1,2). Surgery is the only treatment to achieve long-term survival (3,4). The National Comprehensive Cancer Network (NCCN) guidelines state that for all more advanced T-staged GBCs, which are resectable, *en bloc* hepatic resection + cholecystectomy + lymphadenectomy ± bile duct excision for malignant involvement is required (5). In the past, due to the high invasiveness of the tumor, complexity of the operation, and immaturity of laparoscopic surgical techniques, laparoscopic resection (LR) has been contraindicated for GBC radical resection. With improvements in the skills of surgeons and the development of new laparoscopic equipment, studies have confirmed the safety and effectiveness of laparoscopic surgery for the removal of various abdominal malignant tumors, including GBC (6,7).

Studies on LR and open curative-intent resection (OR) of GBC have suggested that LR yielded better short-term outcomes, such as shorter hospital stay, less intraoperative blood loss, fewer morbidities, and similar long-term effects compared with OR (8-11). However, almost all previously reported studies have limitations, such as performing hepatectomy in only a proportion of patients (12-18). These studies not only did not meet the current criteria from NCCN for curative-intent resection of GBC but also did not meet the homogeneity of patient selection for a cohort study due to the large differences in surgical risks between LR versus OR. Therefore, it is necessary to only include GBC patients undergoing curative resection as defined by the NCCN guidelines as the standard surgical procedures for analysis. Prospective randomized comparative studies are difficult. Propensity score matching (PSM) is a statistical method that can make different cohorts more similar in a nonrandomly selected sample by controlling differences in variables between cohorts, thereby reducing the influence

Highlight box

Key findings

- Some short-term outcomes of gallbladder cancer (GBC) patients after laparoscopic resection (LR) were better. The use of adjuvant chemotherapy (AC) after curative-intent resection of GBC helped achieve better long-term survival outcomes.

What is known and what is new?

- LR had potential advantages in hepatobiliary tumor surgery. Postoperative AC was beneficial for patients with malignant biliary tract tumors.
- Using multicenter data from more than 10 tertiary hospitals, the elimination of selective bias by propensity score matching validated the short-term advantage of LR in the treatment of GBC without affecting long-term patient survival. The survival benefit of AC in patients undergoing surgery for GBC was verified.

What is the implication, and what should change now?

- LR can be performed for suitably selected GBC patients, and AC should be performed if tolerated by patients.

of nonrandomization and improving the credibility and accuracy of the results (19-21). In addition, as most of the previously reported studies on laparoscopic GBC surgery were single-center studies, they do not represent the level of surgery across a region or country (11,13-18).

This is a retrospective study based on a multicenter database of consecutive patients from 13 hospitals who underwent curative-intent resection of GBC. PSM was used to analyze the differences in long-term and short-term outcomes of patients with GBC who underwent either curative-intent LR or OR. An additional aim of this study was to identify independent factors that influenced the long-term survival of patients after curative-intent LR or OR for GBC. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-518/rc).

Methods

Patients

This is a retrospective study with data obtained from The Biliary Surgery Branch of Elite Group of Chinese Digestive Surgery (EGCDS), which is a multicenter database established to retrospectively collect and dynamically maintain data. The data came from 13 tertiary hospitals (First Affiliated Hospital of Army Medical University, Third Affiliated Hospital of Zunyi Medical University, First Affiliated Hospital of Anhui Medical University, Affiliated Hospital of Guizhou Medical University, Jiujiang First People's Hospital, First Affiliated Hospital of Sun Yat-sen University, Henan Provincial Tumor Hospital, Capital Medical University Affiliated Beijing Friendship Hospital, First Affiliated Hospital of USTC, Lanzhou University First Affiliated Hospital, First Affiliated Hospital of Xi'an Jiaotong University, First Affiliated Hospital of Air Force Medical University, and The Second Affiliated Hospital Zhejiang University School of Medicine).

The data obtained in this study were from patients who were newly diagnosed with GBC and treated with curative-intent resection between January 2016 and December 2020. The suspicion of GBC was based on preoperative imaging examinations, such as enhanced computed tomography or magnetic resonance imaging, and tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9). The diagnosis of GBC was confirmed through postoperative pathological examination. The exclusion criteria were (I) incidental GBC; (II) Tis tumor stage or not undergoing hepatectomy; (III) loss to follow-up; (IV) missing complete variables; and (V) undergoing neoadjuvant therapy. All GBC diagnoses were confirmed by pathological examinations. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of the initiating institution, namely, the First Affiliated Hospital of Army Medical University (Approval ID: KY2022217). All patients signed an informed consent form. All participating hospitals/institutions were informed and agreed the study.

Surgical procedures

Curative-intent resection of GBC included *en bloc* hepatic resection + cholecystectomy + lymphadenectomy ± bile duct excision for malignant involvement. For tumors that invaded the macrovasculature (hepatic artery or portal vein) of the preserved portion of the liver, vascular resection and reconstruction were performed. For tumors that invaded the common hepatic duct or common bile duct, bile duct resection and cholangiojejunostomy were performed. Complete removal of tumors under gross inspection was considered curative-intent resection. Those with negative margins were considered R0 resections, and those with positive margins were considered R1 resections. As the patients came from different institutions, the surgical procedures were not completely standardized. All surgical procedures and use of instruments were determined by the individual operating surgeon based on their preferences. Both LR and OR for GBC were performed by all hospitals in this study. All hospitals performed at least 10 ORs and 2 LRs for GBC per year. All hospitals started performing LR of GBC after 2013. All surgeons involved had passed through their learning curves. The surgical procedures for LR and OR were similar; only the choice of surgical approach was different. LR conversion to OR was still analyzed as LR.

Data collection

The variables studied included age, sex, American Society of Anesthesiologists (ASA) score (12), body mass index (BMI), gallstones, diabetes mellitus, preoperative percutaneous transhepatic cholangiography and drainage (PTCD), alanine aminotransferase (ALT), max total bilirubin (TB), international normalized ratio (INR), CEA, CA19-9, tumor size, extent of hepatectomy, bile duct procedures, and vascular procedures.

Patients were dichotomized around the upper or lower limits of the normal ranges: 40 U/L for ALT, 17.1 μmol/L for max TB and last TB, 5 μg/L for CEA, and 37 U/L for CA19-9. Preoperative TB >3 mg/dL was considered preoperative jaundice. The following classifications were used for the extent of hepatectomy: wedge hepatectomy (along the margin of the tumor resection), IVB + V segment resection, and right hemihepatectomy (V–VIII segment resection). According to the World Health Organization (WHO), obesity is defined as BMI >30 kg/m^2 (22). Tumor size was determined by preoperative imaging, and other pathological variables were determined by postoperative pathological examinations. Bile duct procedures included hepatic duct or common bile duct resection and cholangiojejunostomy. Vascular procedures included vascular resection and reconstruction.

Outcomes and follow-up

Long-term outcomes were overall survival (OS) and progression-free survival (PFS). Intraoperative outcomes were operation time, blood loss, number of harvested lymph nodes (LN), and positive resection margins. Pathological outcomes were poor tumor differentiation and N and T stages based on the 8th American Joint Committee on Cancer (AJCC) staging manual (23). Postoperative outcomes were length of stay (LOS), overall morbidity, major morbidity (Clavien-Dindo grade III–IV) (24), 30-day mortality, liver failure (25), bile leakage (26), surgical site infection (SSI) (27), pleural effusion (28), abdominal bleeding (29), and seroperitoneum (30). In addition, readmissions due to adjuvant chemotherapy (AC) were recorded. All patients who were considered to have received AC were so classified based on the AC regimen recommended by the NCCN (5). The main AC regimens included gemcitabine, gemcitabine + cisplatin, and capecitabine. The dosage and timing of drug administration were determined from the package inserts and our clinical experience.

OS was defined as the interval from surgery to death or the last follow-up. PFS was defined as the interval from surgery to tumor recurrence, tumor metastasis, tumor progression, death or the last follow-up. All patients received a standardized follow-up regimen: once every 2–3 months within 2 years postoperatively; once every 3–4 months 3–5 years postoperatively; and once every 6 months 6 years postoperatively. Imaging, liver function and tumor serum marker assessments were performed at each follow-up. Once recurrence, metastasis or progression of the tumor was diagnosed by using the above examinations, appropriate treatment, including reresection, systemic therapy, or endoscopic nasobiliary drain (ENBD), was used. This study was censored on January 31, 2023.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, New York, USA) and R software (version 4.2.3 http://www.r-project.org/). Patients were divided into the LR group and the OR group. Considering that LR conversion to OR was a type of LR perioperative outcome, patients treated with LR conversion to OR were still considered part of the LR group. Tendency scoring was used for PSM to integrate all observed variable information to balance variables and reduce bias. Potential variables that might affect the selection of the surgical approach during the preoperative period were included in the propensity model: age, sex, ASA score, BMI, gallstones, diabetes mellitus, PTCD, ALT, Max TB, INR, CEA, CA19-9, and tumor size. Notably, in most cases, the planned surgical procedures and the actual procedures were consistent. Surgical procedures were also included in the propensity model, including the extent of hepatectomy, bile duct procedures, and vascular procedures. Propensity scores for GBC patients who underwent LR or OR were created using logistic regression estimation. A 1:3 match ratio between the two groups was applied, using the nearest-neighbor matching method with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score. The distribution of propensity scores and the standardized mean difference (SMD) were calculated to assess the effectiveness of balancing covariates between the LR and OR groups. An SMD value of <0.2 indicated negligible differences between groups.

Continuous variables with a normal distribution are expressed as mean ± standard deviation, and Student's *t*-test was used for comparisons. Continuous variables with a non-normal distribution are expressed as median and interquartile range (IQR), and the Mann-Whitney *U* test was used for comparison. Categorical variables are expressed as number (proportion), and the χ^2 test with Yates's correction or Fisher's exact test was used for comparison, as appropriate. Kaplan-Meier curves were drawn to calculate the OS and PFS rates for patients, and the log-rank test was used to compare groups. Multivariate analyses using Cox regression were performed to identify independent risk factors for OS and PFS for all GBC patients treated

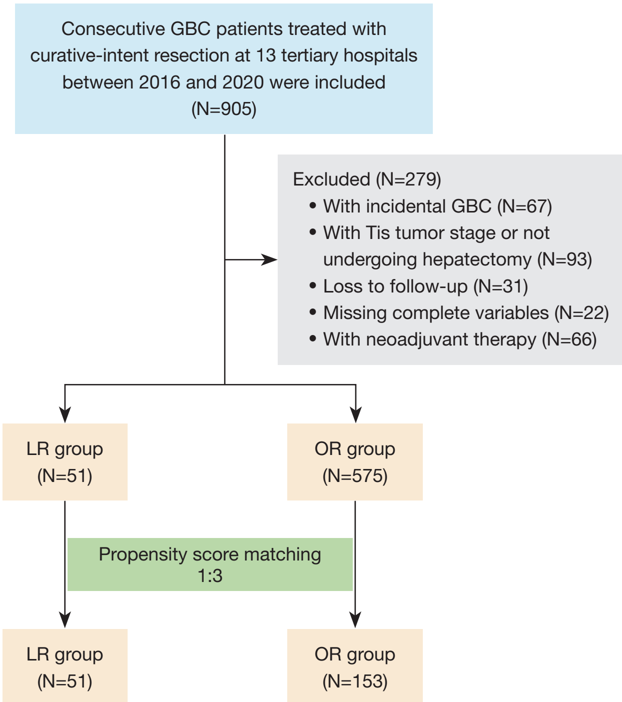

Figure 1 Patient selection. GBC, gallbladder cancer; LR, laparoscopic resection; OR, open resection.

with curative-intent resection in this study. The hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated in the univariate and multivariate analyses. A P value (two-sided) <0.05 was considered statistically significant.

Results

Patient characteristics

Of the 905 patients who were enrolled in this study, 279 patients were excluded under the preset exclusion criteria. The remaining 626 GBC patients treated with curative-intent resection were enrolled in the analytic cohort, with 51 (8.1%) patients in the LR group and 575 (91.9%) patients in the OR group (*Figure 1*). The baseline characteristics of the LR and OR groups before and after PSM are shown in *Table 1*. Before PSM, the SMD for most variables was greater than 0.2 between the two groups, and the two groups were not comparable. After PSM, there were 51 (25.0%) patients in the LR group and 153 (75.0%) patients in the OR group, and the SMD of most variables was less than 0.2 between the two groups, with nonnegligible differences in the extent of hepatectomy (SMD =0.228), and the two groups were comparable. The distributions of the propensity scores showed good overlap of the propensity score distributions between the LR and OR groups after PSM (*Figure 2*).

Short-term outcomes

The short-term outcomes for the LR and OR groups before and after PSM are shown in *Table 2*. The conversion rate to open surgery in the LR group was 5.9% (3/51). Before PSM, there was no significant difference in pathological outcomes between the two groups. The LR group had more patients who were suitable for and received AC (37.3% *vs.* 14.6%, P<0.001), a longer operation time (290 *vs.* 248 min, P=0.002), more harvested LNs (7 *vs.* 5, P=0.01), and less overall morbidity (35.3% *vs.* 57.0%, P=0.004). After PSM, there was still no significant difference in pathological outcomes between the two groups. The LR group still had more patients who received AC (37.3% *vs.* 16.3%, P=0.003), more harvested LNs (7 *vs.* 4, P=0.002), a longer operation time (290 *vs.* 260 min, P=0.005), and less overall morbidity (35.3% *vs.* 57.5%, P=0.01).

Long-term outcomes

The long-term outcomes for the LR and OR groups before and after PSM are shown in *Table 2*. In the analytic cohort, the median follow-up time was 9.2 months in the LR group *vs.* 13.1 months in the OR group before PSM and 9.2 months in the LR group *vs.* 13.0 months in the OR group after PSM. Before PSM, the 3-year OS and PFS rates for the LR group were 57.4% and 50.0%, respectively, and the 3-year OS and PFS rates for the OR group were 51.9% and 40.9%. After PSM, the 3-year OS and PFS rates for the LR group were 57.4% and 50.0%, respectively, and the 3-year OS and PFS rates for the OR group were 55.5% and 43.1%.

Both before and after PSM, there was no significant difference in the OS rate or PFS rate between the two groups (before PSM: OS, P=0.38; PFS, P=0.23; after PSM: OS, P=0.50; PFS, P=0.33), as shown in *Figure 3*.

Independent risk factors for OS and PFS

Multivariate analyses indicated that stage N1/N2, stage T2, stage T3/T4, poor tumor differentiation, and positive resection margins were independently associated with worse OS and PFS for GBC patients treated with curative-intent resection and that AC was independently associated with

Table 1 Comparison of baseline characteristics between the LR and OR groups for gallbladder cancer before and after propensity score matching

Variable	Before PSM				After PSM			
	LR (n=51)	OR (n=575)	P value	SMD	LR (n=51)	OR (n=153)	P value	SMD
Age >60 years	31 (60.8)	366 (63.7)	0.80	0.059	31 (60.8)	89 (58.2)	0.87	0.053
Male	11 (21.6)	198 (34.4)	0.09	0.290	11 (21.6)	35 (22.9)	>0.99	0.031
ASA score > II grade	4 (7.8)	26 (4.5)	0.47	0.138	4 (7.8)	13 (8.5)	>0.99	0.024
BMI ≥30.0 kg/m^2	2 (3.9)	20 (3.5)	>0.99	0.023	2 (3.9)	4 (2.6)	>0.99	0.074
Gallstone	13 (25.5)	100 (17.4)	0.21	0.198	13 (25.5)	37 (24.2)	>0.99	0.030
Diabetes	6 (11.8)	42 (7.3)	0.38	0.152	6 (11.8)	10 (6.5)	0.37	0.182
Preoperative PTCD	5 (9.8)	53 (9.2)	>0.99	0.020	5 (9.8)	13 (8.5)	>0.99	0.045
ALT >40 U/L	19 (37.3)	200 (34.8)	0.84	0.052	19 (37.3)	55 (35.9)	>0.99	0.027
Max TB >17.1 μmol/L	17 (33.3)	279 (48.5)	0.053	0.313	17 (33.3)	45 (29.4)	0.73	0.085
INR >1.15	1 (2.0)	40 (7.0)	0.28	0.244	1 (2.0)	6 (3.9)	0.82	0.116
CEA >5 μg/mL	8 (15.7)	139 (24.2)	0.23	0.214	8 (15.7)	21 (13.7)	0.91	0.055
CA19-9 >37 U/L	15 (29.4)	230 (40)	0.18	0.224	15 (29.4)	35 (22.9)	0.45	0.149
Tumor size >2 cm	37 (72.5)	487 (84.7)	0.04	0.300	37 (72.5)	112 (73.2)	>0.99	0.015
Extent of hepatectomy			0.44	0.213			0.33	0.228
Wedge hepatectomy	41 (80.4)	429 (74.6)			41 (80.4)	135 (88.2)		
IVB + V segment resection	2 (3.9)	52 (9.0)			2 (3.9)	5 (3.3)		
Right hemihepatectomy	8 (15.7)	94 (16.3)			8 (15.7)	13 (8.5)		
Bile duct procedure[a]	18 (35.3)	266 (46.3)	0.17	0.225	18 (35.3)	41 (26.8)	0.33	0.184
Vascular procedure[b]	3 (5.9)	40 (7.0)	>0.99	0.044	3 (5.9)	11 (7.2)	>0.99	0.053

Values are shown as n (%). [a], bile duct procedures included hepatic duct or common bile duct resection and cholangiojejunostomy; [b], vascular procedures included vascular resection and reconstruction. LR, laparoscopic resection; OR, open resection; PSM, propensity score matching; SMD, standardized mean difference; ASA, American Society of Anesthesiologists; BMI, body mass index; PTCD, percutaneous transhepatic cholangiography and drainage; ALT, alanine aminotransferase; TB, total bilirubin; INR, international normalized ratio; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

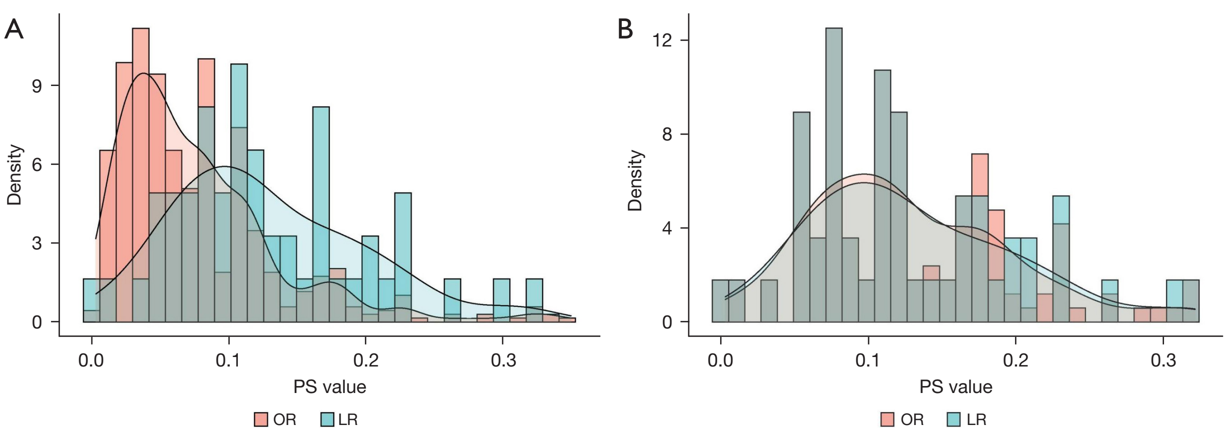

Figure 2 Distribution of the propensity scores for gallbladder cancer between the LR and OR groups before (A) and after (B) propensity score matching. LR, laparoscopic resection; OR, open resection; PS, propensity score.

Table 2 Outcomes of gallbladder cancer in the LR and OR groups before and after propensity score matching

Outcome	Before PSM			After PSM		
	LR (n=51)	OR (n=575)	P value	LR (n=51)	OR (n=153)	P value
Pathological outcomes						
Poor differentiation	17 (33.3)	181 (31.5)	0.69	17 (33.3)	56 (36.6)	0.80
N stage			0.48			0.42
N0	26 (51.0)	271 (47.1)		26 (51.0)	78 (51.0)	
N1	18 (35.3)	247 (43.0)		18 (35.3)	63 (41.2)	
N2	7 (13.7)	57 (9.9)		7 (13.7)	12 (7.8)	
T stage			0.06			0.055
T1	24 (47.1)	227 (39.5)		24 (47.1)	91 (59.5)	
T2	15 (29.4)	262 (45.6)		15 (29.4)	46 (30.1)	
T3/T4	12 (23.5)	86 (15.0)		12 (23.5)	16 (10.5)	
Adjuvant chemotherapy	19 (37.3)	84 (14.6)	<0.001	19 (37.3)	25 (16.3)	0.003
Intra-operative outcomes						
Operation time, min	290 [249, 380]	248 [190, 339]	0.002	290 [249, 380]	260 [190, 330]	0.005
Blood loss, mL	200 [100, 400]	200 [100, 400]	0.21	200 [100, 400]	200 [100, 400]	0.74
LN yield	7 [3, 11]	5 [2, 9]	0.01	7 [3, 11]	4 [1, 8]	0.002
Short-term outcomes						
LOS, days	9.0 [7.00, 15.50]	9.0 [7.00, 14.00]	0.16	9.0 [7.00, 15.50]	9.0 [7.00, 14. 00]	0.44
Overall morbidity	18 (35.3)	328 (57.0)	0.004	18 (35.3)	88 (57.5)	0.01
Major morbidity	9 (17.6)	149 (25.9)	0.26	9 (17.6)	48 (31.4)	0.09
Liver failure	2 (3.9)	31 (5.4)	0.90	2 (3.9)	15 (9.8)	0.31
Bile leakage	2 (3.9)	28 (4.9)	>0.99	2 (3.9)	7 (4.6)	>0.99
SSI	4 (7.8)	85 (14.8)	0.25	4 (7.8)	17 (11.1)	0.69
Pleural effusion	3 (5.9)	58 (10.1)	0.47	3 (5.9)	19 (12.4)	0.30
Abdominal bleeding	1 (2.0)	15 (2.6)	>0.99	1 (2.0)	3 (2.0)	>0.99
Seroperitoneum	2 (3.9)	67 (11.7)	0.15	2 (3.9)	19 (12.4)	0.14
Positive margins	8 (15.7)	89 (15.5)	>0.99	8 (15.7)	18 (11.8)	0.63
Mortality	2 (3.9)	34 (5.9)	0.79	2 (3.9)	8 (5.2)	>0.99
Long-term outcomes						
Time of follow-up, months	9.2 [4.28, 16.95]	13.1 [5.33, 25.28]	0.07	9.2 [4.28, 16.95]	13.0 [6.07, 29.43]	0.20
3-year OS, %	57.4	51.9	0.38	57.4	55.5	0.50
3-year PFS, %	50.0	40.9	0.23	50.0	43.1	0.33

Values are shown as n (%) or median [interquartile range] unless otherwise indicated. LR, laparoscopic resection; OR, open resection; PSM, propensity score matching; LN, lymph node; LOS, length of stay; SSI, surgical site infection; OS, overall survival; PFS, progression-free survival.

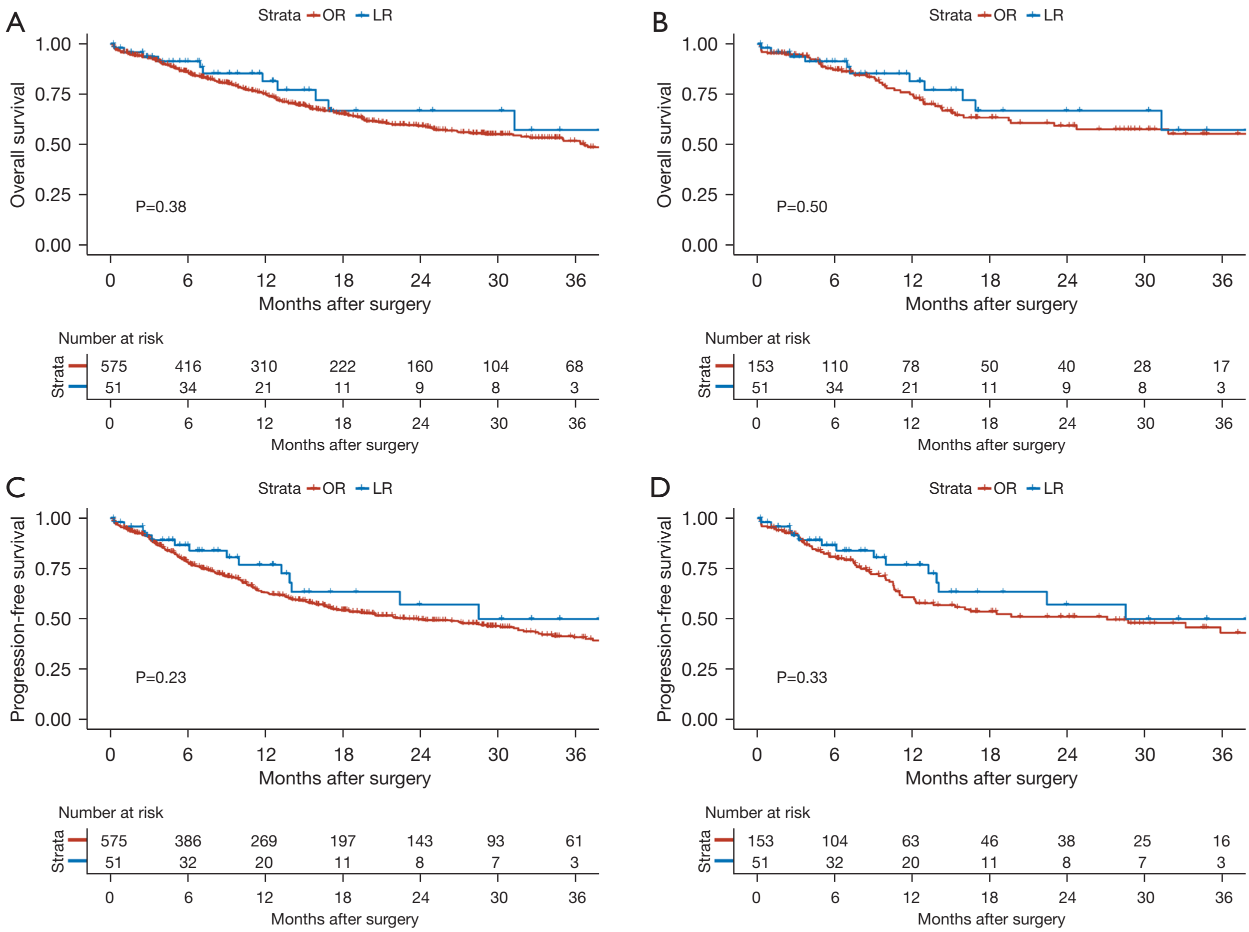

Figure 3 Kaplan-Meier curves for OS and PFS rates for patients with gallbladder cancer in the LR and OR groups before (A, OS; C, PFS) and after (B, OS; D, PFS) propensity score matching. LR, laparoscopic resection; OR, open resection; OS, overall survival; PFS, progression-free survival.

better OS and PFS for GBC patients treated with curative-intent resection (OS, HR: 0.593; 95% CI: 0.363–0.969; 5-year OS rate: 58.3% *vs.* 40.6%; PFS, HR: 0.540; 95% CI: 0.347–0.840; 5-year PFS rate: 51.5% *vs.* 32.9%) (*Table 3*).

Of the 103 (16.5%) patients who received AC, the most common AC regimens were gemcitabine [34 (33.0%) patients], gemcitabine + cisplatin [21 (20.4%) patients], and capecitabine [20 (19.4%) patients].

Discussion

This is the first multicenter study to use PSM to analyze the long-term and short-term outcomes of patients with GBC treated with laparoscopic and open curative-intent resection. In addition, this study identified independent risk factors affecting OS and PFS after curative-intent resection of GBC. In this study, after PSM, there were no significant differences in OS or PFS in GBC patients who underwent either LR or OR, but LR was associated with fewer overall morbidities and more harvested LNs. In addition, this study confirmed that AC prolonged OS and PFS in patients after curative-intent resection of GBC.

Of the intraoperative outcomes, after PSM, the number of harvested LNs in the LR group was significantly higher than that in the OR group. As GBC is often accompanied by LN metastasis, regional LN dissection is a critical step in curative-intent resection of GBC (31). Previous studies indicated that laparoscopic surgery for GBC did not increase the number of LNs harvested (18,32), whereas the results of this study showed that laparoscopic surgery for GBC increased the number of harvested LNs. The laparoscopic camera not only allows local magnification but

Table 3 Multivariable analyses of independent risk factors for overall survival and progression-free survival of patients with gallbladder cancer

Variable	Comparison	Overall survival		Progression-free survival	
		P value	HR (95% CI)	P value	HR (95% CI)
Surgical approach	LR *vs.* OR	0.63	0.858 (0.463–1.591)	0.54	0.845 (0.489–1.458)
N stage	N1/N2 *vs.* N0	0.001	1.606 (1.214–2.125)	0.001	1.540 (1.202–1.974)
T stage	T2 *vs.* T1	0.04	1.313 (1.052–1.795)	0.01	1.441 (1.093–1.900)
	T3/T4 *vs.* T1	0.005	1.773 (1.189–2.645)	0.03	1.523 (1.050–2.209)
Poor differentiation	Yes *vs.* No	0.047	1.332 (1.091–1.782)	0.048	1.330 (1.077–1.663)
Adjuvant chemotherapy	Yes *vs.* No	0.04	0.593 (0.363–0.969)	0.006	0.540 (0.347–0.840)
Positive margins	Yes *vs.* No	<0.001	2.091 (1.475–2.965)	<0.001	2.083 (1.535–2.827)

HR, hazard ratio; CI, confidence interval; LR, laparoscopic resection; OR, open resection.

also facilitates reaching areas that cannot be seen by human eyes in OR, leading to more LNs being removed under laparoscopy. Notably, a greater number of LNs dissected may not mean more benefit to patients. Many immune cells and immune factors in LNs can resist tumor invasion and initially defend against tumors. If tumor cells invade LNs, immune cells such as lymphocytes and macrophages will initiate an immune response to attack and eliminate tumor cells (33-35). Therefore, in the future, it is necessary to actively study the appropriate LN yield for different patients to improve the long-term effects of surgery in GBC patients.

Of the postoperative outcomes, the rate of overall morbidity after PSM was significantly lower in the LR group than in the OR group. Many studies have suggested that the morbidity rates did not differ between GBC patients who underwent laparoscopic surgery or open surgery (18,32), which can be related to the selection of patients. In our study, patients from 2016 to 2020 were selected. During this period, the high-throughput hepatobiliary centers in this study had already developed very mature laparoscopic hepatectomy, bile duct resection, and bile duct-jejunostomy techniques and had started performing laparoscopic vascular resection + reconstruction. As for most other laparoscopic oncological surgeries, such as laparoscopic pancreaticoduodenectomy, the advantages of laparoscopic surgery gradually become apparent after technological maturity, including (I) developing surgical instruments that can be inserted through small incisions, eliminating the need for extensive trauma to surrounding tissues, and thereby reducing tissue damage; (II) improving the surgical field of vision so that surgical steps can be clearly visualized; and (III) visualizing deep tissues, hemostasis, repair and other procedures have become more precise and accurate (36-38). These advances result in significantly less morbidity of LR than OR after curative-intent resection of GBC.

As for long-term outcomes, there was no significant difference in the OS or PFS after PSM between the LR group and the OR group. There is still concern among some surgeons about the possibility of direct and/or indirect implantation of tumor cells at surgical port sites, leading to port site recurrence (39). Forcibly extracting a tumor (specimen) without using a protective bag during laparoscopic surgery, contacting surgical instruments contaminated with tumor cells, or dislodging tumor cells to the port site during the inflation process can cause tumor cells to directly and/or indirectly implant at the port site (40,41). Many previous studies confirmed that port site recurrence resulted in a survival time that was significantly worse for GBC patients after laparoscopic surgery than after open surgery (42-44). Although the prospective database was not designed to include information on port site recurrence, the results of this study did indirectly reflect the extremely low rate of port site recurrence in GBC patients who underwent LR, and it did not affect PFS. This may be related to advances in surgical instruments and the routine use of a "specimen bag" in laparoscopic surgery to remove excised tissues. Based on our experience in clinical practice, and under the context of curative-intent resection, avoiding bile leakage and routine use of a "specimen bag" to extract specimens minimized port site recurrence and improved the long-term results of surgery. The results of many previous single-center studies are consistent with the results of this study when laparoscopic surgery is compared with open surgery, laparoscopic surgery does not reduce the long-term survival outcomes of GBC patients (8-11).

Cox regression models of OS and PFS confirmed that N1/N2, T2, T3/T4, poor tumor differentiation, and positive resection margins were independently associated with poor OS and PFS after curative-intent resection for GBC patients and that AC was independently associated with improved OS and PFS. In a previous study on risk factors for OS after curative-intent resection of GBC, N1/N2, T2, T3/T4, poor differentiation, and positive resection margin were identified as independent risk factors for poor OS (45). In the past, there has been much controversy about whether adjuvant therapy should be performed after radical resection of GBC. On the one hand, several phase III trials and retrospective studies of biliary tract tumors (cholangiocarcinoma and/or GBC) have failed to demonstrate AC to be effective for patients with resected biliary tract tumors (46-49). On the other hand, a recent phase III trial found a significant improvement in OS, suggesting that adjuvant S-1 could be considered a standard of treatment for resected biliary tract cancer for Asian patients (50). However, the studies mentioned above included all biliary tumors and did not specifically focus on GBC. Considering the heterogeneity of tumors, it would be more valuable to study GBC separately, as this would provide more valuable guidance for the AC strategy of GBC patients treated with curative resection. A recently published randomized phase III trial that enrolled 508 patients with resected pancreaticobiliary tumors, including 140 patients with GBC, demonstrated that AC was effective in resected GBC, significantly improving 5-year disease-free survival (51), and this is the only randomized phase III study that has demonstrated the efficacy of AC in resected GBC. At present, the NCCN guidelines clearly state that for resectable GBC, adjuvant therapy and monitoring are needed after surgery (5).

In this study, AC significantly improved the 5-year OS and 5-year PFS rates of patients with resected GBC. As the recurrence of GBC usually involves distant metastasis, intravenous infusion of chemotherapeutic drugs after GBC resection can remove not only small residual tumor cells next to the tumor but also tumor cells that have spread to other organs and tissues of the patient. This is a possible mechanism to explain why AC is beneficial for the long-term survival of patients with resected GBC. Additionally, this study found that the LR group had more patients who received AC. This phenomenon may be related to its lower rate of morbidity. Postoperative morbidity could impact the patient's physical condition, leading to a reduced tolerance to AC and a lower AC usage rate. Performing surgery through a laparoscopic approach could reduce the occurrence of morbidity, allowing more patients to receive AC. This may be a pathway to improving long-term survival for patients by selecting the surgical approach. However, this is only a speculative hypothesis based on the results, so it should be tested in larger prospective studies.

Notably, neoadjuvant chemotherapy (NAC) has gradually played a more important role in the comprehensive management of malignant tumors. Given the high mortality rate and malignant potential associated with GBC, it is crucial to prioritize NAC for cases in the advanced stage (52,53). While aggressive surgical approaches, such as vascular resection and reconstruction, could lead to a complete cure, the emphasis should be on AC for patients facing advanced stages of GBC. In this context, the comprehensive management strategy would involve not only formidable surgical interventions but also a well-considered approach to adjuvant therapies, recognizing their importance in improving outcomes for patients with advanced GBC.

This study has the following limitations. First, there was a large difference in the number of patients in the LR and OR groups. This was because LR of GBC is an operation that has only been carried out in recent years. Second, this study has the shortcomings inherent to retrospective studies, although this study employed PSM between the two groups to minimize selection bias. Third, we did not conduct an analysis on the type of AC used. In this study, all types of AC were grouped together, although the two regimens used most often were gemcitabine and gemcitabine + cisplatin. The types of AC used still need to be further investigated. Fourth, although the laparoscopic procedures used in all the participating centers were mature, different hospitals had different surgical techniques and levels. All the surgeons had passed the LR learning curve, and the operation time and overall morbidity rate were similar in different years (Figure S1).

Conclusions

LR performed for curative-intent resection of GBC reduced the risk of overall morbidity after surgery, increased the number of harvested LNs, and did not affect the long-term survival of patients. Postoperative AC prolonged the survival outcomes of patients after GBC resection. The data show that in high-throughput hepatobiliary centers, LR can be performed for suitably selected GBC patients, and AC should be performed if tolerated by patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the initiating institution, namely, the First Affiliated Hospital of Army Medical University (Approval ID: KY2022217), and all patients signed an informed consent form. All participating hospitals/institutions were informed and agreed with the study.

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