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IRON: A retrospective international multicenter study on robotic versus laparoscopic versus open approach in gallbladder cancer

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ABSTRACT

Objective: For patients with T1b gallbladder cancer or greater, an adequate lymphadenectomy should include at least 6 nodes. Studies comparing short- and long-term outcomes of the open approach with those of laparoscopy and robotic approaches are limited, with small sample sizes, and there are none comparing laparoscopic and robotic approaches. This study compared patients who underwent robotic, laparoscopic, and open resection of gallbladder cancer, evaluating short- and long-term outcomes.
Methods: We conducted a multicenter retrospective study of patients with T1b gallbladder cancer or greater (excluding combined organ resection and T4) who underwent open, laparoscopic, and robotic liver resection and lymphadenectomy between January 2012 and December 2022. The 3 groups were matched in terms of patient baseline and disease characteristics based on propensity score matching, comparing robotic with open and robotic with laparoscopic groups.
Results: We enrolled 575 patients from 37 institutions. After propensity score matching, the median number of harvested nodes was higher in the robotic group than in the open (7 vs 5; $P = .0150$) and laparoscopic groups (7 vs 4; $P < .001$). The Pringle maneuver time was shorter with robotic resection than with laparoscopy (38 vs 59 minutes; $P = .0034$), and the robotic group also had a lower conversion rate (3% vs 14%, respectively; $P = .005$) and less estimated blood loss than open and laparoscopic resections. The perioperative morbidity and mortality rates did not differ. The robotic and laparoscopic approaches were associated with faster functional recovery than the open group. In the multivariate analysis, the factors related to the retrieval of at least 6 nodes were the robotic approach over open (odds ratio, 5.1529) and over laparoscopy (odds ratio, 6.7289) and the center experience (≥20 minimally invasive liver resections/year) (odds ratio, 4.962). After a mean follow-up of 42.6 months, overall survival and disease-free survival were not different between groups.
Conclusion: Compared with open and laparoscopic surgeries, the robotic approach for gallbladder cancer performed in a center with appropriate experience in minimally invasive surgery can provide adequate node retrieval.

Introduction

Gallbladder cancer (GbC) is the fifth most common cancer of the digestive system and the most common cancer of the biliary system, accounting for 165,000 annual cancer-related deaths

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worldwide.[1] GbC is associated with poor oncologic outcomes because of its aggressive biology, chemoresistance, and insidious onset.[2,3]

The standard of care for GbC depends on its stage. On the basis of the eighth *American Joint Committee on Cancer (AJCC) Staging Manual*, for the Tis-T1a stage, cholecystectomy is the definitive treatment, providing a high 5-year survival rate of approximately 100%.[4] For cases that are T1b or greater, cholecystectomy, liver resection, and lymphadenectomy with or without biliary resection and reconstruction are recommended.[4,5] Despite being a challenging operation associated with a high morbidity rate, this technique can achieve a 5-year survival rate of 35%.[5,6]

Over the past 20 years, the use of minimally invasive surgery in hepatobiliary malignancies has significantly expanded, providing a safe and effective treatment in most cases, with certain short-term benefits attributed mainly to its reduced invasiveness.[7–9] However, because of the limited data, performing a minimally invasive approach in GbC remains controversial.

Several retrospective studies have indicated that laparoscopic (LAP) surgery is comparable with the open technique in terms of operative time and incidence of severe complications, without significant differences in long-term oncologic outcomes.[7] In addition, other studies have shown some advantages in terms of estimated blood loss and recovery.[10–12] Nevertheless, most studies had a small sample size with heterogeneous comparative groups.[8]

The use of LAP surgery as a treatment for GbC is challenging and presents some limitations, particularly in obtaining at least 6 lymph nodes (LNs) based on some recent studies and the eighth *AJCC Staging Manual*.[4,13,14] Recently, LAP surgery has been shown to provide fewer yielded LNs in GbC compared with open surgery.[8]

The robotic (ROB) approach could offer theoretical advantages, such as filtering of hand tremors, increasing degrees of freedom in wrist articulation and 3-dimensional stereoscopic images, and eliminating the counterintuitive “fulcrum effect” observed in conventional LAP surgery.[15] These advantages may enhance the potential of the minimally invasive approach, providing even more precise dissection, thus increasing the R0 rates and enabling meticulous lymphadenectomy, with a possible superior number of LNs harvested.

Only a few studies have reported the outcomes of patients with resectable GbC who underwent ROB resection, and these studies have been highly heterogeneous, particularly regarding GbC stages, including T1a, with cholecystectomy alone as the recommended treatment, and T4 and M1 stages, whose indication of surgery remains controversial.[9,16,17]

Compared with the open approach, data on the long-term outcomes of minimally invasive GbC resection are limited. In addition, no studies have compared ROB with LAP approach in this cohort.

Therefore, a multi-institutional large-sample comparative study with both open and LAP and ROB surgical resections for GbC is warranted to fill the knowledge gap in this research field. Thus, we compared patients who underwent ROB, LAP, and open liver resection with lymphadenectomy for T1b, T2, and T3 GbC, evaluating surgical and short- and long-term oncologic outcomes.

Methods

Study design

This multicenter international observational cohort study included all consecutive patients treated at the participating centers with confirmed GbC pathologic stage of T1b, T2, and T3.[4] These patients underwent ROB, LAP, or open liver resection (with or without en bloc cholecystectomy, depending on surgical history, and with or without biliary resection, depending on its involvement) and regional standard lymphadenectomy (based on the eighth *AJCC Staging Manual*)[4] between January 2012 and December 2022. The coordinating center at Hospital del Mar Barcelona, Spain, compiled a specific pseudo-anonymized database derived from various individual databases, which were encoded by its respective center and contained relevant variables of interest.

Because of the multicenter study design, each center followed local surgical and postoperative clinical protocols. The exclusion criteria were patients operated for palliation, those with final histopathologic staging of T4, those with R2-positive resection margins (indicating macroscopic tumor remaining at the end of resection), those who underwent other organ resections concurrently (eg, pancreatic or colon resection due to suspected involvement), and those with metastatic disease (M1) during surgery.

The choice of surgical approach was based on surgeon preference, patient characteristics, and institutional resources. In the ROB group, we included those who were operated using the da Vinci Surgical System (Intuitive Surgical, Inc, Mountain View, CA).

To further mitigate bias from surgical approach selection, we opted to exclude T4 stage GbC in our analysis because they are generally preferably addressed through open surgical approaches rather than minimally invasive methods.

The primary aim was to assess whether the ROB approach can retrieve at least 6 LNs compared with LAP and open approaches for GbC resection. The secondary aim was to compare the short- and long-term oncologic outcomes of the ROB, LAP, and open groups.

Data collection and definitions

We collected data regarding preoperative patient demographics, tumor characteristics, and intraoperative and histopathologic findings. Demographic information included age (in years), sex, body mass index (BMI), the American Society of Anesthesiologists (ASA) classification, and the Charlson Comorbidity Index (CI). Complications were assessed based on the Clavien-Dindo classification and Comprehensive Complication Index (CCI).[18,19] Severe complications were defined as Clavien-Dindo grade IIIA or greater.[18] Perioperative mortality was defined as occurring either in-hospital (during primary admission) or within 90 days postoperatively. Experienced pathologists evaluated the size, stage, invasiveness, and resection margins of the resected specimens, following local or national protocols.

The surgeons categorized their patients into ROB, LAP, or open groups. Liver wedge resection was defined as resection of the liver margin in the gallbladder bed (segment 4b-5). Anatomic and nonanatomic resections were defined on the basis of the Tokyo 2020 terminology of liver anatomy and resections.[20] Staging was based on the eighth edition of the *AJCC Staging Manual* (2018) for GbC.[4] An R0 resection margin was defined as margins without microscopic disease.

Biliary resection was only indicated if the cystic duct had a positive margin. Postoperative recovery was defined as time to flatus and time to diet from the date of surgery.

The long-term outcomes, including overall survival (OS) and disease-free survival (DFS), were measured in months, are reported using Kaplan-Meier curves, and were compared over 3- and 5-year periods. The patients were followed until death, cancer recurrence, or for a maximum of 60 months. For patients who were lost to follow-up, they were censored at the last date of contact.

Participants

Participating centers were recruited through invitations sent via emails to all members of the Clinical Robotic Surgery Association.

Each center was classified on the basis of their caseload of overall liver resections (<40 or ≥40 cases/yr) or minimally invasive liver resection (including ROB and LAP approaches) (<20 or ≥20 cases/yr) and on the basis of their previous experience in ROB liver resection before entering data on ROB approach (<20 or ≥20 cases).

Ethical approval

Institutional and ethical approval was obtained from the coordinating center, Hospital del Mar of Barcelona (Spain) Ethical Committee (approval number: 2023/10969). The study was registered on ClinicalTrials.gov (identifier code NCT06061744). Informed consent was waived because of the retrospective study design. Other participating centers obtained additional institutional and national approvals as required. This study was conducted and reported following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.[21]

Statistical analyses

Data were analyzed using R (version 4.2.2; the R Foundation for Statistical Computing, Vienna, Austria). Normally and non-normally distributed variables are presented as means with standard deviation and medians with interquartile ranges, respectively. Categorical variables are presented as frequencies and proportions and were compared using the χ^2 test. Continuous data were compared using the Student's t or Mann-Whitney U test, as necessary. OS and DFS were collected on the timing and occurrence of events (death or recurrence). Time-to-event data were analyzed using Kaplan-Meier curves and compared using the log-rank test. For the propensity score–matched (PSM) cohort, the log-rank test was applied as pooled log-rank analyses of 5 strata based on the propensity score.

Propensity score matching

We used PSM to improve the internal validity of this study by reducing bias and heterogeneity and enhancing comparability between the treatment and control groups. The ROB approach was considered the reference group for comparison with open and LAP surgery. PSM was applied to ensure balanced characteristics among patients in all groups. Propensity score models were developed using logistic regression modeling after multiple imputations, and several models were compared based on discrimination and calibration. The final model consisted of the following covariates: sex, age, BMI, ASA score, previous abdominal surgery, CI, carbohydrate antigen 19.9, T stage, N stage, and main biliary duct resection. PSM was performed using a 1:1 greedy matching algorithm without replacement and a caliper of 0.25*standard deviations of the linear predictor. Comparisons in the matched cohort considered stratification by matched pairs; hence, McNemar χ^2 and Wilcoxon signed-rank tests were used for categorical and continuous variables.

Results

Participants

During the study period, 621 patients underwent liver resection with or without gallbladder and bile duct resection and lymphadenectomy for GbC at 37 centers, of whom 575 met the inclusion criteria (Figure 1). After PSM analysis, the 2 comparative matching groups were ROB ($n = 98$) versus open ($n = 98$) and ROB ($n = 100$) versus LAP ($n = 100$). The clinical characteristics of the matched patients were not significantly different (Tables I and II). The discrimination and calibration of the PSM models are provided in the Supplementary Figures S1–S5.

Descriptive data

Patients and baseline disease characteristics of ROB versus open and ROB versus LAP before and after PSM are presented in Tables I and II, respectively. Center expertise is shown in Table III. The number of procedures performed annually is shown in the Supplementary Figures S1–S5.

After PSM, the resection type (anatomic versus nonanatomic) and application of the Pringle maneuver were similar between the ROB and open groups. However, when comparing ROB and LAP approaches, we found that anatomic resections were more common in the ROB group (66% vs 50%; $P = .035$) (Table IV), whereas the Pringle maneuver was used more frequently in the LAP group (47% vs 31%; $P = .020$). The mean duration of the Pringle maneuver was shorter in the ROB group in both comparisons (Table IV). The ROB group had similar mean operative time and lower estimated blood loss compared with the open and LAP groups. The rate of conversion to open surgery was significantly lower in the ROB group (3% vs 14%; $P = .005$). The median CCI was lower in the ROB group than in the open group (6 vs 13; $P = .011$). Postoperative recovery was better in the ROB group, with shorter times to flatus and a regular diet, than in the open group, and shorter hospitalization length compared with the open and LAP groups (Table IV). The readmission, severe complication, or R0 margin rates did not differ.

Quality of lymphadenectomy

Table IV shows the primary outcome between the 2 comparative groups, and the median number of retrieved LNs was significantly different (ROB, 7 vs open, 5; $P = .015$; ROB, 7 vs LAP, 4; $P = .001$). The percentage of ≥6 retrieved nodes was also significantly greater in the ROB group in both comparisons (ROB, 59.18% vs open, 37.11%; $P = .002$; ROB, 59% vs LAP, 33%; $P = .001$).

In the univariable analysis, the predictive factors for retrieval of ≥6 LNs were age > 60 years, BMI ≥ 25, ASA score of 3–4, Charlson Comorbidity Index, and ≥20 previous robotic liver resections (Table V). In the multivariable analysis, the independent positive predictor for retrieval of ≥6 LNs was only a center caseload of ≥20 minimally invasive liver resections annually (odds ratio [OR], 4.962; $P = .004$) and ROB compared with open approach (OR, 5.152; $P = .019$) and LAP (OR, 6.728; $P = .0022$).

Long-term oncologic outcomes

After a mean follow-up of 42.7 months (range, 11–96 months), incision-site recurrence occurred in 3 cases (1.5%) within the minimally invasive groups (ROB, 1%; LAP, 2%) and 1 case in the open group (1%), with no differences between the groups. The 3- and 5-year OS and DFS were similar among all approaches (Figure 2). The 3-year OS in the ROB, LAP, and open groups was 62.6%, 54.7%, and 56.3%, respectively ($P = .538$).

The median OS in the ROB, LAP, and open groups was 49 (95% confidence interval [CI], 16.9–42.1), 43 (95% CI, 13.7–42.6), and 46 months (95% CI, 14.3–39.2), respectively ($P = .538$) (Figure 2). The median DFS in the ROB, LAP, and open groups was 32 (95% CI, 14.1–36.1), 31 (95% CI, 8.93–35.5), and 32 months (95% CI, 21.35–42.6), respectively ($P = .516$; Figure 2).

Discussion

Over the past decade, research on GbC treatments has primarily involved small retrospective studies, with limited patient samples

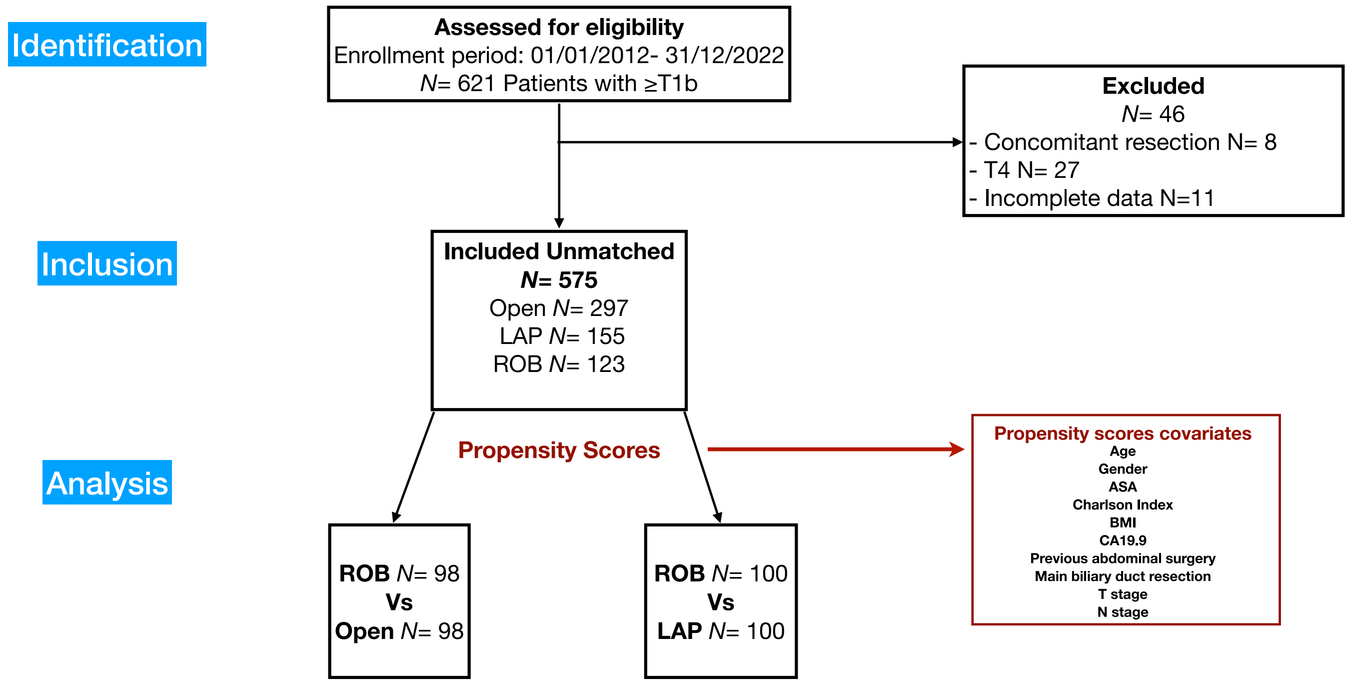

Figure 1. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flow diagram. *ASA*, American Society of Anesthesiologists; *BMI*, body mass index; *CA*, carbohydrate antigen; *LAP*, laparoscopic; *ROB*, robotic resection.

Table I
Baseline characteristics of the open versus robotic group before and after PSM

Baseline characteristics	Before PSM		*P* value	After PSM		*P* value
	Open, *n* = 297	ROB, *n* = 123		Open, *n* = 98	ROB, *n* = 98	
Sex, male, *n* (%)	96 (32.3)	45 (36.58)	.586	32 (32.65)	35 (35.7)	.651
Age at surgery, yr, mean (SD)	68.16 (9.88)	67.97 (11.9)	.495	66.17 (11.96)	67.83 (11.3)	.732
BMI, mean (SD)	27.83 (4.82)	25.78 (4.63)	.382	26.4 (4.87)	27.86 (4.02)	.565
ASA score, mean (SD)	2.68 (0.59)	2.21 (0.60)	.003	2.51 (0.58)	2.45 (0.63)	.685
Previous abdominal surgery, *n* (%)	121 (49.8)	60 (58.3)	.150	47 (47.9)	48 (48.9)	.732
Laparoscopy	98 (32.9)	52 (42.27)	.127	32 (32.6)	37 (37.7)	.710
Charlson Comorbidity Index, mean (SD)	2.35 (0.73)	2.51 (0.74)	.067	1.4 (0.78)	1.43 (0.75)	.901
Preoperative CA 19.9 ≥37 U/L, *n* (%)	142 (47.8)	46 (37.39)	.056	40 (40.81)	38 (38.7)	.762
Tumor invasion, *n* (%)			.083			.831
T1b	63 (20.87)	53 (43.08)		35 (35.7)	40 (40.8)	
T2	148 (49.83)	47 (38.2)		39 (39.79)	38 (38.7)	
T3	86 (28.9)	23 (18.6)		24 (24.48)	20 (20.4)	
Node, *n* (%)			.302			.857
N0	121 (59.0)	59 (67.0)		61 (62.2)	59 (60.2)	
N1	70 (34.1)	22 (25.0)		29 (29.5)	31 (31.6)	
N2	14 (6.8)	7 (8.0)		8 (8.16)	8 (8.16)	
Main biliary duct resection, *n* (%)	50 (16.8)	16 (13)	.042	13 (13.2)	12 (12.2)	.809

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CA*, carbohydrate antigen; *PSM*, propensity score matching; *ROB*, robotic resection; *SD*, standard deviation.

comparing perioperative and survival outcomes between LAP and open approaches.[7,8,17] Unfortunately, a significant knowledge gap exists when comparing the outcomes of LAP and ROB approaches. To date, only a limited number of studies (ranging from 3 to 28 patients) have focused on the outcomes of a ROB approach in GbC surgery, with none directly comparing with a LAP approach.[9,16,17]

The present international multicenter retrospective cohort study is a pioneering effort to report and compare the short- and long-term outcomes across open, LAP, and ROB (with the da Vinci System) techniques in GbC treatment. In our study, we focused solely on curative procedures. Consequently, we excluded R2 resections and T4 cases because they do not constitute curative resections. R2 resections were exceedingly rare. We also excluded most T4 cases because they were typically recommended for an open approach from the outset, thereby mitigating potential biases.

The study findings showed that the ROB approach was associated with several advantages, including a greater number of retrieved LNs, shorter Pringle maneuver times, lower estimated intraoperative blood loss, and shorter hospitalization durations compared with both open and LAP approaches. These findings were significant as they address a pressing issue in LAP treatment for GbC, which pertains to achieving adequate lymphadenectomy for improved disease stratification and staging.[22]

Table II
Baseline characteristics of the laparoscopic versus robotic group before and after PSM

Baseline characteristics	Before PSM			After PSM		
	LAP, $n = 155$	ROB, $n = 123$	P value	LAP, $n = 100$	ROB, $n = 100$	P value
Sex, male, n (%)	60 (38.7)	45 (36.58)	.623	37 (37)	38 (38)	.884
Age at surgery, yr, mean (SD)	66.46 (11.77)	67.97 (11.94)	.431	67.86 (11.17)	67.34 (11.55)	.572
BMI, mean (SD)	27.02 (5.22)	25.78 (4.63)	.167	27.22 (5.1)	27.51 (4.48)	.690
ASA score, mean (SD)	2.1 (0.65)	2.21 (0.60)	.057	2.49 (0.66)	2.45 (0.62)	.518
Previous abdominal surgery, n (%)	57 (45.2)	60 (58.3)	.068	46 (46)	49 (49)	.432
Laparoscopy	33 (21.29)	29 (23.57)	.207	29 (29)	27 (27)	.562
Charlson Comorbidity Index, mean (SD)	2.23 (0.74)	2.51 (0.74)	.282	1.41 (0.76)	1.4 (0.78)	.951
Preoperative CA 19.9 $\geq$37 U/L, n (%)	45 (29.03)	46 (37.39)	.281	32 (32)	37 (37)	.384
Tumor invasion, n (%)			.181			.416
T1b	49 (31.6)	53 (43.08)		37 (37)	40 (40)	
T2	69 (44.51)	47 (38.2)		44 (44)	45 (45)	
T3	37 (23.8)	23 (18.6)		19 (19)	15 (15)	
Node, n (%)			.742			.535
N0	64 (64.6)	59 (67.0)		58 (58)	60 (60)	
N1	29 (29.3)	22 (25.0)		36 (36)	33 (33)	
N2	6 (6.1)	7 (8.0)		6 (6)	7 (7)	
Main biliary duct resection, n (%)	13 (8.38)	16 (13)	.024	10 (10)	8 (8)	.527

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CA*, carbohydrate antigen; *LAP*, laparoscopic resection; *PSM*, propensity score matching; *ROB*, robotic resection; *SD*, standard deviation.

Table III
Experience of participating centers before including cases

Experience of hepatobiliary centers	No. of centers (%)
$\geq$40 liver resections/year	30 (81)
$\geq$20 minimally invasive liver resections/year	26 (70.2)
$\geq$20 previous robotic liver resections	23 (62.1)

LN metastasis is one of the most crucial prognostic factors for GbC after curative resection. Therefore, the importance of harvesting at least 6 LNs, as established by the eighth edition of the *AJCC Staging Manual*,[4,23] cannot be overstated. Thus, assessing this outcome whenever a new technology is introduced is crucial.

A recent systematic review and meta-analysis including both open and LAP approaches concluded that LAP was associated with fewer harvested LNs than open surgery.[7] This may be due to the limitations of nonarticulated laparoscopic instruments, which hinder practical dissection. Conversely, with its wider articulation ranges, the ROB technique facilitates node dissection and, consequently, a greater number of retrieved LNs. Our study supports this hypothesis, with the median number of retrieved LNs being 7 and 4 for the ROB and LAP techniques, respectively ($P = .001$). To address potential bias, we introduced the criterion of harvesting at least 6 resected LNs as an indicator of adequate lymphadenectomy. This confirmed the superiority of the ROB approach over the LAP approach. Moreover, multivariable analysis showed that the ROB approach was an independent factor associated with achieving at least 6 resected LNs compared with open (OR, 5.152) and LAP approaches (OR, 6.728). Furthermore, multivariable analysis confirmed that ROB is the approach of choice because LAP was not associated with better lymphadenectomy compared with the open approach.

Notably, despite the greater number of retrieved nodes in the ROB approach, no survival differences have been observed compared with the open and LAP groups. However, a greater odds of LN metastases among patients with $\geq$6 harvested LNs was expected, showing that this cutoff provides a more accurate staging rather than better survival.

Koh et al[24] evaluated the effect of hospital volume on liver resection results. On the basis of this study and our personal experience, we defined the groups based on precise cutoff.

The analysis showed that having experience with minimally invasive hepatectomy (at least 20 cases annually) was closely associated with achieving at least 6 resected LNs (OR, 4.962). Thus, in addition to the ROB approach, expertise at a specialized center is crucial to ensure adequate lymphadenectomy.

Although previous studies on ROB surgery for various indications have found longer operative times with the ROB approach compared with the LAP approach, our study, for the first time in the literature, showed that operative times do not differ significantly among the approaches for GbC.

Because the ROB approach is minimally invasive, we expected similar short-term outcomes in complications and patient recovery compared with the LAP approach and superior outcomes compared with open surgery. Indeed, our findings showed that the median CCI and overall recovery parameters (time to flatus and diet) of the ROB approach were superior to those of open surgery but similar to those of the LAP approach. Hospitalization length was also shorter in the ROB group than in the LAP group. This finding, along with the time to recovery, should be interpreted with caution because it might likely be due to the multicenter nature of this study, resulting from a degree of heterogeneity in discharge protocols between centers.

Moreover, our study found that the LAP approach for GbC resection was associated with greater conversion rates compared with the ROB approach (14% vs 3%, $P = .05$). Most conversions resulted from uncontrolled bleeding during lymphadenectomy, justifying the lower estimated blood loss in the ROB group compared with the LAP group (177 mL vs 205 mL, respectively, $P = .01$).

Our study's depiction of OS and DFS after minimally invasive surgery that are comparable with those after open surgery highlights the importance of presenting long-term oncologic results to confirm the oncologic effectiveness of minimally invasive GbC resection. However, the available literature is limited and controversial. Notably, several studies have reported that LAP surgery for patients with GbC leads to similar or improved treatment outcomes compared with open surgery.[7]

Incision-site recurrence has been an essential concern in minimally invasive approaches. A recent systematic review found significantly greater rates of port-site recurrence in the LAP group compared with the open approach.[7] In our series, incision-site recurrence occurred in 1.5% of the minimally invasive cases

Table IV
Outcome comparison

Approach	ROB versus open	*P* value	ROB versus LAP	*P* value
LNs retrieved, median (range)	ROB: 7 (3–14) Open: 5 (2–11)	.0150*	ROB: 7 (3–14) LAP: 4 (1–12)	<.001*
≥6 LNs retrieved, *n* (%)	ROB: 58 (59.18) Open 37 (37.75)	.002*	ROB: 59 (59) LAP: 33 (33)	<.001*
Anatomic liver resection, *n* (%)	ROB: 50 (51.02) Open: 47 (47.9)	.231	ROB: 66 (66) LAP: 50 (50)	.035*
Type of liver resection				
Wedge segments 4b-5; segments 4b+5, *n* (%)	ROB: 63 (64.3); 35 (25.7) Open: 58 (59.1); 40 (40.81)	.36	ROB: 65 (653); 35 (35) LAP: 62% (62); 38 (38)	.27
Pringle maneuver, *n* (%)	ROB: 31 (31.63) Open: 37 (37.76)	.368	ROB: 31 (31%) LAP: 47 (47)	.020*
Pringle maneuver, min, median (range)	ROB: 39 (0–60) Open: 53 (0–75)	.0461*	ROB: 38 (0–50) LAP: 59 (0–90)	.0034*
Operative time, min, mean (±SD)	ROB: 260 (±70) Open: 275 (±65)	.27	ROB: 256 (±75) LAP: 257 (±50)	.95
Intraoperative estimated blood loss, mL, mean (±SD)	ROB: 183 (±90) Open: 320 (±200)	.002*	ROB: 177 (±100) LAP: 205 (±180)	.001*
Postoperative RBC units, median (range)	ROB: 1 (0–2) Open:1 (0–2)	.139	ROB: 1 (0–2) LAP: 1 (0–2)	.421
Conversion to open, *n* (%)			ROB: 3 (3%) LAP:14 (14%)	.005*
Comprehensive complication index, median (range)	ROB: 6 (0–13) Open: 13 (0–15)	.011*	ROB: 6 (0–13) LAP: 7 (0–14)	.524
Mortality at 90 d, *n* (%)	ROB: 3 (3.06) Open: 1 (1.02)	.174	ROB: 3 (3) LAP: 4 (4)	.733
Time to flatus, d, median (range)	ROB: 2 (1–4) Open: 3 (1–6)	<.0001*	ROB: 2 (1–4) LAP: 2 (1–4)	.635
Time to regular diet, d, median (range)	ROB: 2 (2–4) Open: 4 (2–7)	<.0001*	ROB: 2 (2–5) LAP:2 (2–5)	.741
Length of stay, d, median (range)	ROB: 5 (4–12) Open: 10 (5–26)	<.0001*	ROB: 5 (4–11) LAP: 8 (4–18)	.003*
Readmission, *n* (%)	ROB: 11 (11.22) Open: 8 (8.16)	.469	ROB: 12 (12) LAP: 11 (11)	.825
Severe complication (CD ≥3,) *n* (%)	ROB: 7 (7.14) Open: 12 (12.24)	.227	ROB: 7 (7) LAP: 8 (8)	.788
R0 status, *n* (%)	ROB: 83 (89.25) Open: 82 (83.67)	.469	ROB: 88% LAP: 81%	.300
Incision-site recurrence	ROB 1 (1) Open: 1 (1)	.691	ROB: 1 (1) LAP: 2 (2)	.436

CD, Clavien Dindo; *LAP*, laparoscopic resection; *LN*, lymph node; *ROB*, robotic resection; *RBC*, red blood concentrate.
* Significant difference.

Table V
Univariate and multivariate logistic regression of factors associated with yield of ≥6 nodes

Variables	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex, female	1.44 (0.97–2.13)	.065		
Age ≥60 yr	1.68 (1.04–2.70)	.031*	0.70 (0.19–2.59)	.600
BMI ≥ 25	2.48 (1.37–4.47)	.003*	1.97 (0.81–4.75)	.131
ASA class (3–4)	1.61 (1.09–2.36)	.015*	1.59 (0.62–4.02)	.328
Charlson Comorbidity Index	1.12 (1.03–1.22)	.008*	0.97 (0.770–1.237)	.841
Anatomic liver resection	0.88 (0.58–1.35)	.579		
Experience in liver resection (≥40/yr)	1.66 (0.99–2.78)	.052		
Experience in MIS resection (≥20/yr)	2.45 (1.37–4.35)	.002*	4.96 (1.66–14.78)	.004*
Previous experience of robotic liver resection (≥20)	3.28 (2.13–5.04)	<.0001*	1.00 (0.20–4.97)	.992
Surgical approach				
ROB versus open	2.15 (1.34–3.46)	.001*	5.15 (1.31–20.24)	.019*
ROB versus LAP	2.93 (1.71–5.03)	.025*	6.72 (1.31–34.50)	.022*
LAP versus open	0.74 (0.52–0.92)	.201		
Main biliary duct resection	0.44 (0.75–2.2)	.351		
Year of surgery (2012–2017)	0.97 (0.46–1.45)	.483		

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CI*, confidence interval; *LAP*, laparoscopic resection; *LN*, lymph node; *MIS*, minimally invasive surgery; *OR*, odds ratio; *ROB*, robotic resection; *RBC*, red blood concentrate.
* Significant difference.

($n = 3$). Nonetheless, tumor dissemination is not specific to minimally invasive surgery and can also occur in the open approach. In our series, one case of tumor dissemination was identified in the open group, with no statistically significant differences between the LAP and ROB approaches. The low incidence of incision-site recurrences in our study may be due to the recognition of

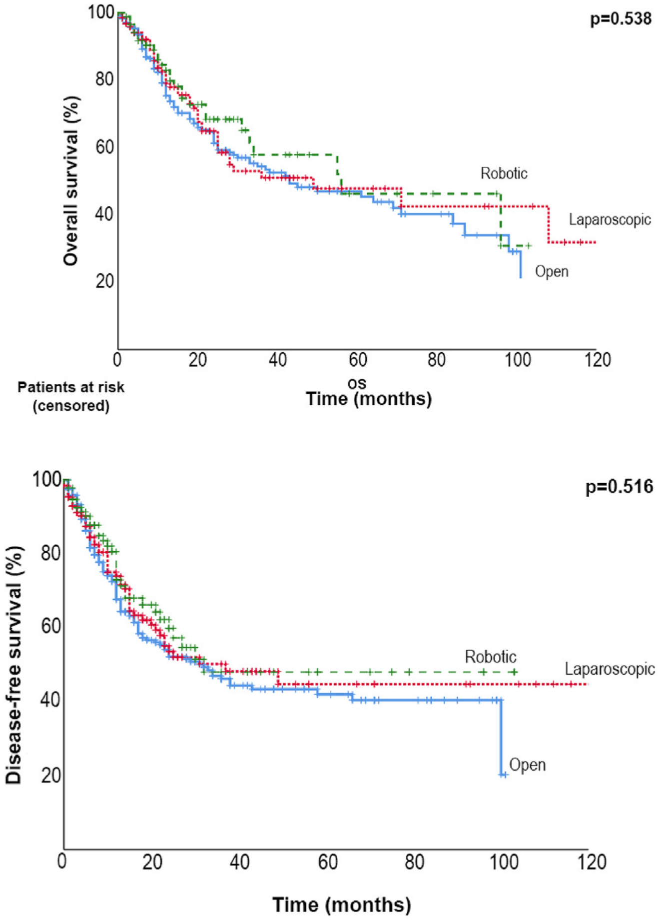

Figure 2. Kaplan-Meier plot for overall survival and disease-free survival in the robotic, laparoscopic, and open groups.

preoperative malignancy, use of precautionary surgical techniques, en bloc resection of the gallbladder and liver parenchyma, and use of plastic bags for specimen removal.

Study limitations

However, our study has several limitations. The retrospective nature of our study hindered the inclusion of quality-of-life and cost-related analyses and could lead to selection biases. The high cost of the ROB approach is a notable drawback, and future studies should assess the impact of the therapy on patients' well-being, including cost-effectiveness. In addition, local protocols influenced adjuvant therapy choice (chemotherapy alone or in combination with radiotherapy), introducing an inevitable further source of bias.

Furthermore, we included patients who had undergone surgery since 2012 in the sample, when recommendations of resecting at least 6 nodes had not been published. Considering that the AJCC recommendations of harvesting at least 6 nodes was published only in 2018,[4] a potential bias of the number of resected nodes can be the year of surgery. Thus, we included in the multivariable analysis the year of the procedure, before and after 2017, which was not related to the number of resected nodes.

Finally, including a large number of centers introduced some heterogeneity in the procedures within the open and minimally invasive approaches, including the device type used and hybrid versus pure robotic techniques or hand-assisted laparoscopic procedures. Because a consensus definition of a hybrid approach remains ambiguous in the literature, we sought to determine the predominant approach used, and the surgeons categorized their patients within 1 of the 3 subgroups.

Despite these limitations, the international multicenter design of this extensive study is a notable strength because it provides a large sample size to compare different surgical approaches in treating GbC, providing new evidence on outcomes after minimally invasive GbC surgery. The implementation of a robust PSM approach involving 10 variables further helped mitigate the inherent bias associated with retrospective multicenter studies. The main findings of this study highlight the need for prospective studies to further evaluate our conclusions.

In conclusion, this study highlights the potential benefits of the ROB approach over LAP and open surgery in treating GbC. Our findings provide valuable insight into the superiority of the ROB approach in terms of LN retrieval, mainly over the LAP approach. Furthermore, this study paves the way for future research to serve as a benchmark and contribute to the development of a comprehensive reference for GbC surgical treatment. Finally, this study's findings emphasize the potential advantages of the ROB approach in GbC surgery and encourage further research and standardization in the field.

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Conflict of Interest/Disclosure

The authors have no relevant financial disclosures.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [https://doi.org/10.1016/j.surg.2024.05.045].

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