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RESEARCH

Open versus laparoscopic oncologic resection for gallbladder cancer after index cholecystectomy: international multicenter comparative study

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Abstract

Background Liver resection and lymphadenectomy is a standard procedure in patients with incidental gallbladder cancer. Data regarding laparoscopic approach in this setting are scarce. The aim of this study was to compare laparoscopic and open approach in this population.

Methods This was a multicenter retrospective study including 177 patients. The primary outcome measure was overall survival (OS). The secondary outcomes measures were recurrence-free survival (RFS), lymph node yield, operative time, postoperative complications and length of hospital stay.

Results Surgery was laparoscopic in 60 (33.9%), including 18 conversions (30.0%). By intention to treat analysis, 3 and 5 year OS were 72.1% and 51.8% after laparoscopic surgery compared to 62.8% and 36.2% after open surgery ($p=0.201$). 3- and 5-year RFS were 29.1% and 19.4% after laparoscopic surgery and 28.7% and 19.1% after open surgery ($p=0.697$). Severe (grade$\geq$3) complications ($p=0.032$) and Comprehensive Complication Index (CCI; $p=0.027$) were both significantly higher after laparoscopic surgery ($p=0.032$), although length of hospital stay was significantly shorter after laparoscopic procedures both on intention-to-treat (median 6 vs. 8 days; $p=0.004$) and per protocol analysis (median 6 vs. 8 days; $p=0.004$).

Conclusions Laparoscopic approach is feasible in patients with gallbladder cancer and may shorten the duration of hospital stay.

Synopsis This retrospective cohort study suggests that laparoscopic liver resection is feasible in patients with gallbladder cancer and may shorten the duration of hospital stay. Minimally invasive procedures should be performed by surgeons experienced in laparoscopic liver surgery.

Keywords Gallbladder cancer · Length of stay · Outcomes · Complications · Laparoscopic liver resection

Abbreviations

OS	Overall survival
RFS	Recurrence-free survival
CCI	Comprehensive Complication Index
GBC	Gallbladder cancer
HCC	Hepatocellular carcinoma
OR	Oncologic resection
BMI	Body mass index
ASA	American Society of Anaesthesiologists
AJCC	American Joint Committee on Cancer
NCCN	National Comprehensive Cancer Network

Extended author information available on the last page of the article

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Introduction

Gallbladder cancer (GBC) is the most common biliary tract malignancy with rising incidence in certain populations worldwide [1]. Due to its aggressive nature prognosis is dismal which is mirrored by median survival of 10 months [2]. Surgery is the only potentially curative treatment and the preferred option in patients with resectable disease according to current guidelines [3]. However, the precise role of radical resection and its impact on overall survival is a matter of ongoing debate. The international, multicenter the OMEGA study analyzing over 3600 patients with GBC revealed that liver resection does not translate into better long-term survival. Moreover, extended resections increase perioperative morbidity and mortality [4]. Despite this, wedge resection of gallbladder bed or formal resection of segments 4b/5 with regional lymphadenectomy is still perceived to be the treatment of choice, especially in those with incidental cancers found after cholecystectomy performed for benign indications [3]. Especially in this context, application of minimally invasive approach in this population seems to be natural. So far, laparoscopic liver surgery has been widely applied in patients with colorectal liver metastases and hepatocellular carcinoma (HCC). Strong evidence exists showing that this approach translates into better short-term results without any negative impact on long-term survival [5–8]. With respect to GBC, data on application of laparoscopic surgery are less robust and they are based predominantly on single center studies [9, 10]. The aim of this study was to compare laparoscopic and open surgery in individuals with GBC based on the multicenter, international cohort of patients.

Methods

This was a multicenter retrospective comparative study. The study cohort consisted of 177 patients with incidental GBC managed surgically between January 2017 and June 2022 in high volume liver surgery centers located in South America (2 centers), United States of America (USA; 1 center) and Europe (6 centers). The study was conducted in accordance with the ethical standards of the Declaration of Helsinki of 1975, and the study protocol was approved by the Institutional Review Board of Medical University of Warsaw and relevant bodies in each center. Informed consent was waived by the Institutional Review Board of Medical University of Warsaw (AKBE/205/2022) due to the retrospective nature of the study. Clinical variables were extracted from the relevant databases in each participating center and sent to the Department of General, Transplant and Liver Surgery at the Medical University of Warsaw for the final analysis. Patients after cholecystectomy with incidental diagnosis of gallbladder cancer were included. Exclusion criteria comprised: (1) liver resection beyond gallbladder bed (wedge or formal segments 4b/5 resection) or other organ removal during oncologic resection (OR) (2) dissemination of the disease (3) robotic resection and (4) other malignancy. The primary outcome measure was overall survival (OS). The secondary outcome measures were recurrence-free survival (RFS), number of lymph nodes retrieved, operative time, 30-day complication rate according to the Clavien-Dindo classification, CCI and length of postoperative hospital stay. On intention-to-treat analysis (ITT), patients undergoing initially laparoscopic procedures were compared with those undergoing initially open procedures, whereas in per protocol analysis patients undergoing laparoscopically completed procedures were compared to those after either initially open or converted procedures. Surgical strategy was chosen according to the standard approach applied to patients with GBC in each participating center. Surgical approach (open or laparoscopic), scope of lymphadenectomy were decided individually by the operating surgeon or dictated by the center`s policy. Port sites were not routinely excised across the study cohort. OS was calculated from the date of OR until patient death irrespective of cause and censored at 5 years post-resection or last follow-up visit. Accordingly, RFS was calculated from the date of OR until first documented recurrence or death and censored at 5 years post-resection or last follow-up visit. Qualitative variables were presented as numbers and percentages, while quantitative variables as medians and ranges. U-Mann Whitney and Fisher or Chi^2 exact tests were used for intergroup comparisons. Survival estimates were calculated using Kaplan-Meier method and compared using log-rank test. To assess the relevant risk factors, Cox proportional hazards model and logistic regression were used. The level of significance was set at $p<0.05$. Statistical analyses were computed in STATISTICA version 13.3 (TIBCO Software Inc., Palo Alto, CA, USA).

Results

The study population comprised 177 patients including 143 women (80.8%). Median age was 66.8 years (range 32.5–86.8). Median BMI (Body mass index) was 27.2 kg/m^2 (range 18.9–48.3) and median ASA (American Society of Anaesthesiologists) score was 2 (range 1–4). In 60 cases procedure was attempted laparoscopically. 42 cases were completed by means of minimally invasive approach (70%) and conversion was needed in 18 procedures (30.0%). In 21 cases anatomic resection of segments 4b/5 was performed (11.9%). Detailed characteristics of the study cohort are

Table 1 Characteristics of the study cohort ($n=177$)

	Median (range) lub *n* (%)
Patients age (years)	66.8 (32.5–86.8)
Patient sex (female)	143 (80.8%)
BMI	27.2 (18.9–48.3)
ASA score	2 (1–4)
Ca 19−9 (U/ml)	11.6 (0.6-36557)
Operative time (minutes)	213(90–690)
Blood loss (ml)	200 (0–1500)
Anatomic 4b/5 resection	21 (11.9%)
Laparoscopic	42 (23.7%)
Conversion	18 (10.2%)
Postoperative length of stay	7 (2–38)
Tumor stage ($n=157$)	
T1a	3 (1.9%)
T1b	28 (17.8%)
T2	90 (57.3%)
T3	35 (22.3%)
T4	1 (0.6%)
Perineural invasion ($n=98$)	37 (37.7%
Lymphovascular invasion ($n=105$)	47 (44.8%)
Lymph node status (N0; $n=171$)	112 (65.5%)
Resection R0 ($n=174$)	166 (95.4%)
Number of lymph nodes removed	3 (0–25)
Complications≥3 Clavien-Dindo ($n=175$)	18 (10.3%)
CCI	20.9 (8.7–42.4)
Adjuvant chemotherapy ($n=160$)	77(48.1%)

Data are presented as median (range) or *n* (%)

BMI- Body mass index; ASA- American Society of Anaesthesiologists; CCI-Comprehensive complication index

Table 2 Characteristics of those after procedures completed laparoscopically and the remaining patients

	Laparoscopic	Converted or open	
Patients age (years)	68.8 (36-86.8)	66.4 (32.5–85.7)	***p*=0.035**
BMI	26.8 (19.3–48.3)	27.3 (18.9–47.9)	$p=0.490$
ASA score	2.5 (1–4)	2 (1–3)	***p*=0.001**
Ca 19−9 (U/ml)	19.3 (1.8-36557)	8.8 (0.6–1807)	***p*=0.002**
Operative time (minutes)	208 (90–565)	225 (115–690)	$p=0.488$
Blood loss (ml)	200 (40-1500)	250 (0-1500)	$p=0.218$
Tumor stage (pT1)	15 (35.7%)	16 (13.9%)	***p*=0.002**
Lymph node status (N0)	30 (75%)	82 (62.6%)	$p=0.149$
Resection R0	41 (97.6%)	125 (94.7%)	$p=0.431$
Number of nodes removed	4 (0–25)	3 (0–17)	$p=0.469$
At least 3 nodes removed	31 (73.8%)	91 (69.5%)	$p=0.591$
At least 6 nodes removed	12 (28.6%)	28 (21%)	$p=0.312$
Any C-D complication	13 (30.9%)	41 (30.8%)	$p=0.988$
Complications≥3 C-D	8 (19.05%)	10 (7.52%)	***p*=0.032**
CCI	26.2 (8.7–42.4)	20.9 (8.7–42.4)	***p*=0.027**
Postoperative length of stay (days)	6 (2–30)	8 (3–38)	***p*=0.004**

All bold values by definition are significant, cause significance is when $p<0.05$

Data are presented as median (range) or *n* (%)

BMI- Body mass index; ASA- American Society of Anaesthesiologists; CCI-Comprehensive complication index; Clavien-Dindo classification

presented in Table 1. Patients in the laparoscopic group were older (median 68.8 vs. 66.4 years; $p=0.035$) had higher ASA score (median 2.5 vs. 2; $p=0.001$) and higher preoperative concentration of Ca 19−9 (median 19.3 vs. 8.8; $p=0.002$). With regard to T status, percentage of patients with early stage (pT1) tumors were more common among those whose procedures were completed using minimally invasive approach (35.7 vs. 13.9; $p=0.002$). R0 resections were achieved in vast majority of cases regardless of whether the procedure was completed laparoscopically (97.6%) or not (94.7%; $p=0.431$). Similarly, median operative time (208 vs. 225 min; $p=0.488$), as well as median blood loss (200 ml vs. 250 ml; $p=0.218$) were comparable between laparoscopic and converted or open procedures. Detailed comparison of patients undergoing purely laparoscopic resection and the remaining patients are presented in Table 2.

Long-term results (ITT analysis)

After median follow up of 52 months, in ITT analyses, OS at 3 and 5 years after all procedures attempted laparoscopically was 72.1% and 51.8%, respectively, compared to 62.8% and 36.2%, respectively, after initially open procedures ($p=0.201$; Fig. 1). The corresponding 3- and 5-year RFS rates were 29.1% and 19.4%, respectively, in the laparoscopic group and 28.7% and 19.1%, respectively, after open resections ($p=0.697$; Fig. 2).

Long-term results (per protocol analysis)

Additionally, there were no differences in 5-year OS ($p=0.288$; Fig. 3) and RFS ($p=0.905$; Fig. 4) between patients undergoing procedures completed laparoscopically (OS 53.4%; RFS 15.5%) and the remaining patients (OS 38%; RFS 20%).

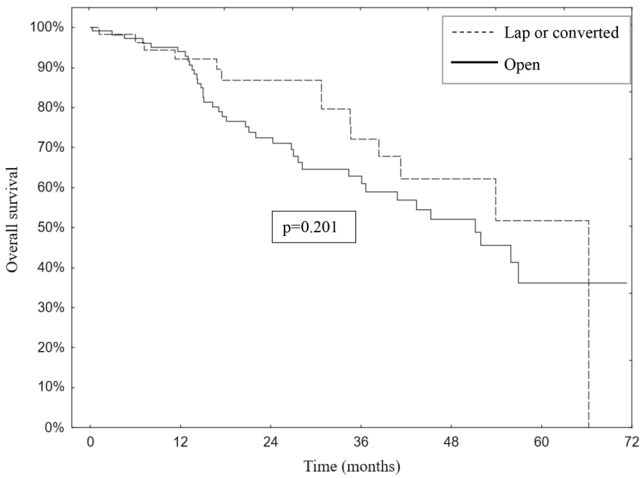

Fig. 1 Overall survival of patients based on the ITT analysis

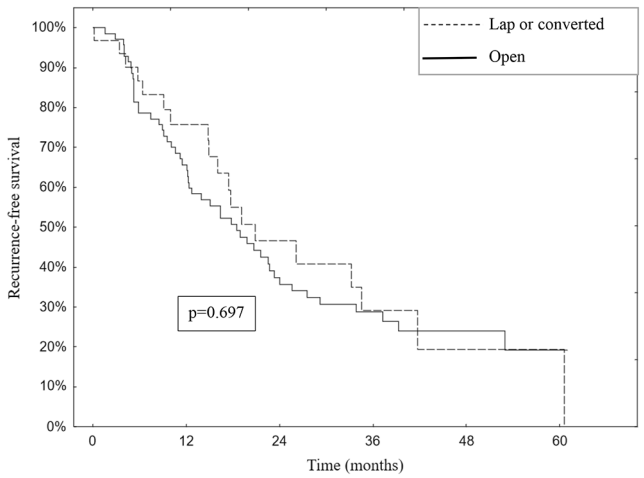

Fig. 2 Recurrence-free survival of patients based on the ITT analysis

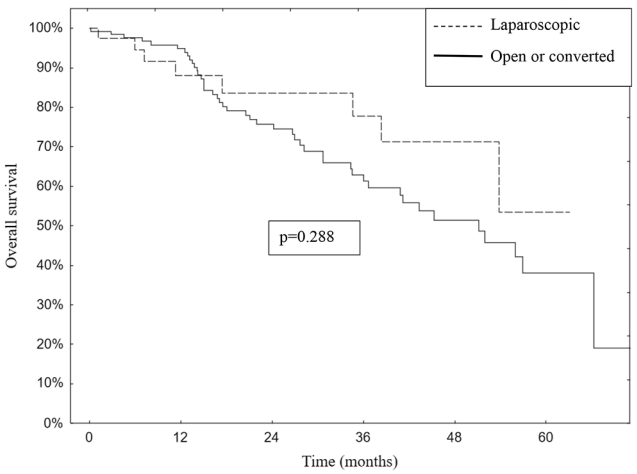

Fig. 3 Overall survival of patients based on the per-protocol analysis

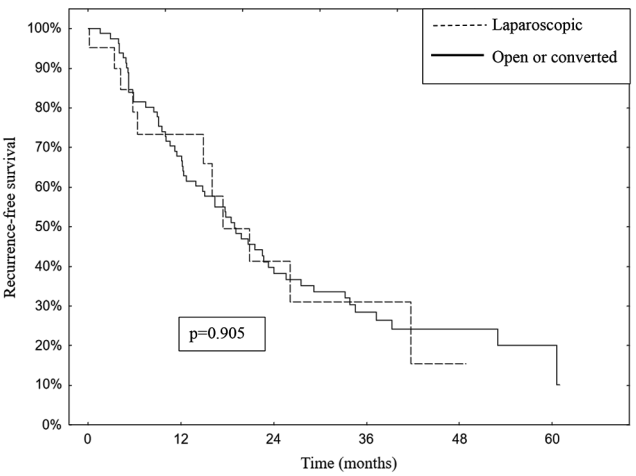

Fig. 4 Recurrence-free survival of patients based on the per-protocol analysis

Table 3 Univariable and multivariable analyses of factors related to overall survival

	Univariable		Multivariable	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.00 (0.98–1.03)	0.708		
Laparoscopic resection	1.39 (0.55–3.52)	0.492		
Ca 19−9	1.00 (1.00–1.00)	0.001	1.00 (1.00–1.00)	**0.004**
R0 vs R1/R2	2.24 (0.91–1.06)	0.051		
T1 vs T2-T4	2.84 (0.99–8.17)	0.052		
Nodal status (N0)	0.59 (0.33–1.05)	0.074		
Number of positive nodes	1.48 (1.13–1.93)	0.004		
Lymphovascular invasion	2.44 (1.23–4.86)	0.011	2.35 (1.06–5.22)	**0.036**

Multivariable analysis

On multivariable analysis the significant risk factors related to OS were concentration of Ca 19−9 ($p=0.004$) and lymphovascular invasion ($p=0.036$). Laparoscopic approach did not have any impact on long term outcomes ($p=0.492$; Table 3).

Lymph node yield

Number of retrieved lymph nodes was comparable in laparoscopic (median 4 nodes) and open or converted resections (median 3 nodes; $p=0.469$) as well as number of positive nodes (median 0 vs. 0; $p=0.347$). Accordingly, N0 status was comparable between corresponding groups (75% vs. 62.6%; $p=0.149$). At least 3 and at least 6 lymph nodes were removed in 73.8% and 28.6%, respectively, procedures completed trough laparoscopy and in 69.5% ($p=0.591$) and

21% ($p=0.312$), respectively, of either initially open or converted procedures.

Perioperative outcomes

No perioperative deaths were recorded. Uneventful postoperative course was encountered by nearly 70% of patients in both laparoscopic and open or converted cases ($p=0.988$). Among patients who experienced complications, these of grade 3 or higher according to Clavien-Dindo classification were more common in the laparoscopic group ($p=0.032$). Similarly, CCI was greater in this population ($p=0.027$). The length of hospital stay was significantly shorter after laparoscopic procedures both on ITT (median 6 vs. 8 days; $p=0.006$) and per protocol (median 6 vs. 8 days; $p=0.006$) analysis.

Discussion

This multicenter, international comparative study provides real life data corroborating efficacy of minimally invasive treatment in patients with GBC. Despite some variations in incidence and treatment of GBC in different regions worldwide, we showed that minimally invasive approach provides comparable OS and RFS compared to the standard open resections. Non-inferiority of minimally invasive surgery regarding long-term results has been already confirmed by other series including large National Cancer Database (NCDB) from USA comprising 680 patients and recent meta-analysis of Chee et al. [11–14]. However, it is worth noticing that tendency to treat less advanced cases using laparoscopic approach was observed in our cohort. Likewise, in both studies of Vega et al. and AlMasri et al. patients operated by means of laparoscopic or robotic resection had less advanced tumors according to the American Joint Committee on Cancer (AJCC) staging system [11, 13]. We believe that it reflects natural selection bias related to the early phase of implementation of minimally invasive approach in patients with GBC. What`s more, minimally invasive procedure was not associated with impaired long-term results on multivariable analysis. The only significant variables were concentration of Ca 19−9 and lymphovascular invasion. Both are well known factors linked with worse outcomes which was highlighted by others [15, 16]. The other critical parameter reflecting the quality of surgery, which is the completeness of resection (R0), was not impaired in neither study regardless of staging. In our cohort R0 resections were achieved in 95% of patients which shows the efficacy of the method and its comparable to results presented by other centers [11].

Despite this encouraging results, open approach is still commonly used by the most experienced hepatobiliary centers. It is well illustrated by the publication from the Tata Memorial Center which describes the largest single-center series of 1307 patients with GBC managed exclusively by open approach during 10 years [17]. On the other hand, gradual increase of application of laparoscopic approach reaching 70% of all operated cases is noticed by others [12].

One of the most challenging aspects with regard to treatment of biliary tract cancers is an optimal lymph node dissection. Strong evidence support routine removal of regional lymph nodes defined as those in the hepatoduodenal ligament, gastrohepatic and retroduodenal according to the National Comprehensive Cancer Network (NCCN) guidelines [18]. Lymphadenectomy provides at least crucial staging information [19], notwithstanding metaanalysis of Widmann et al. revealed that proper lymph node dissection translates into better survival in patients with T1b, T2 and T3 tumors [20]. Other large series confirm this observation [21]. Despite significance of this procedure, one-quarter of patients undergoing surgery for GBC have no lymph node assessment according to the analysis of over 2000 GBC cancer cases recorded in the NCDB database [22].

Currently, at least 6 nodes are recommended for proper staging, however benchmark value was set at the lower level of 4 lymph nodes [23]. In our group of laparoscopic procedures median number of lymph nodes removed was 4 and 28% of cases were completed with at least 6 nodes recovered which was slightly better compared to open procedures, albeit not statistically significant. These results are in line with large, national analyses and abovementioned benchmarks [22, 23]. Our study confirms equivalent lymph node yield between laparoscopic and open resections, thus it provides another evidence highlighting the quality of lymphadenectomy in patients with GBC managed by minimally invasive approach. Median number of 4 nodes removed during laparoscopic resections in our data could be perceived as even more important finding. This observation stems from the analysis of large database underlines the significance of this threshold as a more reasonable goal during the radical surgery, as removal of 6 nodes is challenging in most cases [24].

Another very important benefit associated with laparoscopic surgery is decreased number of complications and faster postoperative recovery, thus ERAS Society recommends this approach in patients undergoing liver resections [25]. Most of patients in our cohort (70%) had an uneventful postoperative course. However, in patients who encountered complications those of grade≥3 were more common in laparoscopic group, thus CCI was greater accordingly which is contrary to other recently published series [26]. This unexpected observation may have a few explanations.

Firstly, small number of events may be responsible for type 1 error. On the other hand, in our unselected, international, multicenter cohort we present reality of implementation of the minimally invasive approach to the patients with GBC with the natural learning-curve effect [27]. Another rationale behind this result is that patients in the laparoscopic group were older and had more comorbidities which was reflected by the significantly greater ASA score compared to their open counterparts. It seems plausible, as ASA score is well-described factor linked to increased morbidity after liver surgery [28]. Despite this, postoperative hospital stay was significantly shorter after laparoscopic procedures which is perceived to be one of the main advantages of the minimally invasive approach and corresponds to other series and meta-analyses which have been published so far [10, 11, 20, 29].

Our results should be interpreted with caution and some limitations must be acknowledged. Firstly, it is a retrospective study with its natural, inherent selection bias. Additionally, intra and postoperative management were not standardized among centers which potentially could influence the results of our study. Scope of lymph node dissection was not precisely defined. Thus, variations between centers regarding extent of lymphadenectomy could be the additional source of bias. Some data were lacking, including reasons behind conversions and detailed analysis of complications beyond their grading according to the Clavien-Dindo classification. Nevertheless, the strength of this study is the thorough assessment of the early phase of implementation of minimally invasive approach in patients with GBC in the multicenter, international setting with adequate follow-up, including comprehensive analysis of the relevant end-points. What is more, it is one of the largest multicenter studies describing role of the laparoscopic surgery in patients with GBC analyzed so far.

Conclusions

Laparoscopic approach is feasible for OR in patients with incidental gallbladder cancer and may shorten the duration of hospital stay. However, minimally invasive procedures should be performed by surgeons experienced in laparoscopic liver surgery, due to potential risk of increased morbidity in the early phase of implementation of this complex procedure.

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Data availability The data will be available upon reasonable request.

Declarations

Ethics approval and consent to participate The Institutional Review Board of the Medical University of Warsaw approved that no further approval for retrospective analyses is needed.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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