Review Article

Role of laparoscopy in the surgical management of gallbladder cancer—a narrative review

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Objective: Aim of this study is to conduct a review of the available literature on the role of laparoscopy in gallbladder cancer (GBC) management.

Background: Although laparoscopic cholecystectomy is now the undisputed and widespread gold standard for benign gallbladder diseases, laparoscopic treatment of GBC is still controversial. The main international guidelines recommend an open approach, relegating laparoscopy to the mere staging purpose before definitive resection. The reasons are the risk of port-site recurrence or peritoneal dissemination due to intraoperative gallbladder perforation and the potential difficulty in achieving clear resection margins and proper lymphadenectomy. However, several articles investigating the safety and the outcomes of a laparoscopic approach have been published in the last two decades.

Methods: A literature search was performed in the PubMed database. The search words were "gallbladder cancer" AND "laparoscopic" AND ("radical" OR "extended cholecystectomy"). Language restriction was applied to include only English written articles. Studies up to March 2022 were considered. Case reports and non-comparative case series were excluded from the analysis in order to reduce biases. Twenty publications concerning laparoscopic treatment of GBC have been retrieved. Intra- and post-operative results as well as long term oncologic outcomes were reviewed. Considering the importance of the stage-adjusted therapy in GBC, the results have been presented following the American Joint Committee on Cancer (AJCC) T stage.

Conclusions: According to the current literature, laparoscopy is feasible and safe in surgical management of GBC. Long term oncological outcomes are comparable to open approach whereas laparoscopy allows less intraoperative bleeding, less postoperative morbidity and shorter length of hospital stay. Therefore, it should play an increasingly important role in the future.

Keywords: Gallbladder cancer (GBC); laparoscopy; extended cholecystectomy

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Introduction

Gallbladder cancer (GBC) is a relatively rare tumor in Western population with an annual incidence of 1.13 per 100,000 in the United States whereas it is more common in South America, Korea and Japan with annual incidence 8–10 times higher (1). However, it accounts for 80% to 95% of biliary tract malignant tumors (2). GBC has a low sensitivity to current chemo and radiation treatment and a poor prognosis, being 5-year overall survival (OS) rate 5% (1). It causes 165,000 cancer related deaths annually, which is 1.7% of all global cancer deaths (3). Radical resection is the mainstay of treatment. For patient with cancer confined to the gallbladder, stage I according to American Joint Committee on Cancer (AJCC) (4,5), 5-year OS varies from 60% to 95% whereas drops to 25% if tumor spreads to locoregional lymph nodes and to less than 2% in case of distant metastasis (1,6). Although GBC can occur incidentally after cholecystectomy for stones or polyps, most often is asymptomatic in the early stage and the diagnosis occurs in the advanced stage. Only 1 out of 5 patients is stage I at the diagnosis (1).

Surgical approach of GBC is strictly dependent on the T stage. As mentioned, Tis/T1a GBC is typically diagnosed after cholecystectomy for lithiasis and requires no further treatment (7-9). Wedge resection of the gallbladder bed or Sg4b-5 bisegmentectomy and lymph node dissection are recommended in the treatment of T1b and T2 disease (7-9). Conversely, the treatment of a locally advanced carcinoma of the gallbladder T3–T4 remains a challenge and can require major or extended hepatectomy, bile duct or major vessel resection besides to colon resection or even duodenopancreatectomy (7-9).

Laparoscopic liver resections have experienced an exponential diffusion in the last decade. International consensus conferences have confirmed that, although it is a complex surgery that requires adequate expertise both in the field of general laparoscopy and open liver surgery, it can represent an advantage for patients, especially in short-term outcomes (10,11).

Furthermore, the same consensus advocated the opportunity of making resections in the left lateral and anterior segments the standard of care (11).

Nevertheless, nearly all major international guidelines, including those of the National Comprehensive Cancer Network (NCCN) (7) and the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) (9), do not recommend laparoscopic surgery even for patients with early GBC (T≤2). The latter strongly recommends open cholecystectomy reserving laparoscopic surgery only for clinical studies with adequate informed consent. The reasons for this recommendation are the increased risk of not removing the cancer completely, gallbladder perforation with bile spillage, port site recurrence and peritoneal dissemination, relying mainly on data reported in the early 2000 or even in the late 90s (12-15).

This paper aims to review the current role of laparoscopy for GBC surgical treatment. The final goal is to draw some conclusions about its safety, efficacy and diffusion. We present the following article in accordance with the Narrative Review reporting checklist (available at https://ls.amegroups.com/article/view/10.21037/ls-22-44/rc).

Methods

A literature search was performed in the PubMed database (*Table 1*). The search words were "gallbladder cancer" and "laparoscopic" and "radical cholecystectomy". The enquiry was restricted to articles written in English up to March 2022. References of the retrieved studies were screened for additional relevant papers. Case reports and non-comparative case series were excluded from the analysis in order to reduce biases. The articles collected are summarized in *Table 2* (2,6,16-33).

Considering the importance of the stage-adjusted therapy in GBC, the results of the review have been presented according to the AJCC T stage. Furthermore, two paragraphs about S4b-5 bisegmentectomy and about lymphadenectomy have been drafted.

Lastly, we have edited an original short video of our standard laparoscopic Sg4b-5 bisegmentectomy and regional lymphadenectomy for a case of T2 incidental GBC after laparoscopic cholecystectomy (*Video 1*).

Results

T1

According to AJCC 8th edition (5), T1 GBC is divided into T1a, for tumors invading the lamina propria, and T1b, for tumors invading the muscular layer. When the tumor is *in situ* or a T1a, simple cholecystectomy is an adequate treatment if correctly performed (negative margins and without intraoperative perforation). In this stage, the 5-year survival is >95% (34-36).

In T1b tumors, radicalization by resection of the

Table 1 The search strategy summary

Items	Specification
Date of search	30th March 2022
Databases and other sources searched	PubMed database
Search terms used	"gallbladder cancer" AND "laparoscopic" AND ("radical" OR "extended cholecystectomy")
Timeframe	From January 2011 to March 2022
Inclusion and exclusion criteria	Inclusion criteria: English written articles
	Exclusion criteria: case reports and non-comparative studies
Selection process	Two authors conducted the research independently (APF, DE) and discussed the results with two senior authors (NR, AF)
Any additional considerations, if applicable	Considering the importance of the stage-adjusted therapy in gallbladder cancer, the results were presented according to the AJCC T stage

AJCC, American Joint Committee on Cancer.

gallbladder bed or Sg4b-5 bisegmentectomy plus lymphadenectomy would appear to be related to increased survival compared to patients treated with simple cholecystectomy (7-9).

Since most patients are asymptomatic, a preoperative diagnosis of early GBC is difficult; but with the advent of laparoscopic cholecystectomy, the frequency of early GBC diagnosed intra- or postoperatively has increased. Jang *et al.* (6) sought to compare and estimate recent surgical outcomes of open and laparoscopic approach for T1 GBC in order to understand what is the optimal surgical strategy. This study demonstrated that open and laparoscopic approach had similar oncological outcomes (5-year OS rate 100% *vs.* 94.9%, P=0.982) in patients with T1a as well as T1b GBC; but in terms of intraoperative bleeding, length of the hospitalization and operative time, laparoscopy approach was better. However, considering the practical advantages of the laparoscopic approach, the latter can be a valid substitute for open surgery in the management of T1 GBC.

T2

GBC is defined as T2 if it invades perimuscular connective tissue, without infiltrating the liver. The AJCC 8th edition (5) further stratified this category into T2a (extension on the peritoneal side of the perimuscular connective tissue) and T2b (extension on the hepatic side of perimuscular connective tissue).

The gold standard treatment of T2 GBC is the so-called extended or radical cholecystectomy. The operation includes the removal of the gallbladder en block with a partial liver resection (anatomical or wedge resection of Sg4b-5) and regional lymphadenectomy, performed with an open approach. However, with the growing diffusion of laparoscopy in oncologic and hepatobiliopancreatic surgery, surgeons want to estimate the safety and efficacy of this minimally invasive approach in the treatment of GBC. Three studies compared these two different primary access techniques, trying to find out which one might be better: Navarro *et al.* (21), Itano *et al.* (19), and Jang *et al.* (20). These three articles agree that laparoscopic surgery is advantageous in terms of intraoperative bleeding and length of hospital stay. Navarro *et al.* also showed that the laparoscopic approach is better in terms of less complications and sooner start of adjuvant chemotherapy than open surgery. Furthermore, there was no statistically significant differences between the laparoscopy and open approach in terms of disease-free survival (DFS) (77.1% *vs.* 82.2%, P=0.641) and 5-year OS (64.6% *vs.* 80.4%, P=0.214). This study has the most reliable results because it compared oncologic outcomes using a propensity score matching analysis. Itano *et al.* showed that laparoscopic and open surgery did not show significant differences in terms of number of lymph nodes dissected (12.6 *vs.* 10.2, P=0.361) and intra-operative time (309 *vs.* 324 minutes, P=0.755).

Jang *et al.* demonstrated that frequency of postoperative complication was similar between laparoscopic and open approach (12.7% *vs.* 13.6%, P=1.000). Median follow up time reported in the article of laparoscopic group and open group was 35.2 and 38.6 months respectively. Laparoscopic approach showed significantly higher DFS

Table 2 All articles considered for review

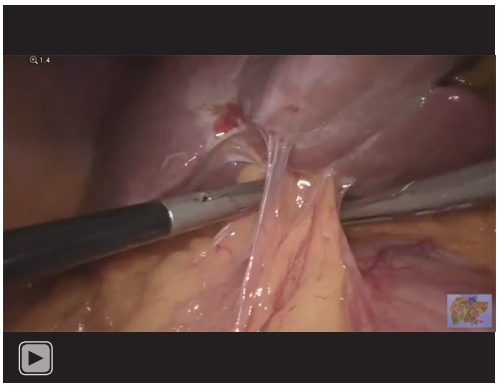
Author	Year	Study type	Number of patients		Re-resections-indication	T stage	Surgery type	LN yield	OM	MM	Operative time	Bleeding	Hospital stay	Mortality	OS	DFS	Limitations
			Open group	LPS group													
Goetze *et al.* (16)	2013	CS	200	492	Yes	iGBC T1/4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	=	=	Number of centers not defined
Zhang *et al.* (17)	2015	CS	8	20	Yes	iGBC	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	=	=	Limited patients number
Agarwal *et al.* (18)	2015	CS	46	24	No	T1b-3	EC + LN	=	=	=	OPEN	LPS	N/A	N/A	N/A	N/A	Single centre
Itano *et al.* (19)	2015	CS	14	19	No	T2	N/A	=	N/A	N/A	=	LPS	LPS	N/A	=	=	Limited patients number
Jang *et al.* (6)	2016	PSM	61	61	No	T1a/b	SC/EC	N/A	=	N/A	LPS	LPS	LPS	N/A	=	=	Prevalent number of T1a patients
Jang *et al.* (20)	2019	CS	44	55	No	T2	SC/EC + LN	=	=	N/A	=	=	LPS	=	=	=	Single centre/long period of time considered
Navarro *et al.* (21)	2020	PSM	43	43	No	T2	SC/EC + LN	=	LPS	=	N/A	LPS	LPS	N/A	=	=	More EC and extended LN in the open group
Vega *et al.* (22)	2020	CS	190	65	Yes	iGBC T1/2/3	EC/MH + LN	=	=	=	=	=	LPS	=	=	N/A	Selection bias in LPS group
Wang *et al.* (23)	2020	CS	61	45	Yes	T1b/2/3	N/A	=	LPS	N/A	=	LPS	LPS	N/A	=	=	Selection bias in LPS group
Almasri *et al.* (24)	2020	CS	445	235	No	T1-3	EC + LN	=	=	=	N/A	N/A	=	=	=	=	Number of centers not defined
D'Silva *et al.* (25)	2022	PSM	12	12	No	T2/3	N/A	=	=	=	=	=	LPS	=	=	=	Limited patients number
Dou *et al.* (26)	2022	PSM	30	30	No	T2/3	N/A	N/A	=	=	OPEN	LPS	LPS	N/A	=	=	Single centre
Dou *et al.* (27)	2020	CS	31	32	No	T1-4	EC/MH + LN	=	=	=	=	LPS	LPS	N/A	LPS	=	Selection bias in LPS group
Nag *et al.* (28)	2021	CS	38	30	No	N/A	Sg4b-5 + LN	=	=	=	=	LPS	LPS	=	=	=	Limited patients number

Table 2 (*continued*)

Table 2 (*continued*)

Author	Year	Study type	Number of patients		Re-resections-indication	T stage	Surgery type	LN yield	OM	MM	Operative time	Bleeding	Hospital stay	Mortality	OS	DFS	Limitations
			Open group	LPS group													
Han *et al.* (29)	2019	ExpC	N/A	N/A	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Expert opinion
Yoon *et al.* (30)	2019	Sur-Rev	N/A	N/A	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Expert opinion
Zhao *et al.* (31)	2018	SRMA	710	770	No	N/A	N/A	N/A	N//A	N/A	N/A	LPS	LPS	N/A	LPS	=	All retrospective and small sample size studies
Feng *et al.* (32)	2020	SRMA	455	613	No	N/A	N/A	=	=	N/A	=	=	LPS	N/A	=	=	Limited number of included studies/ all retrospective
Lv *et al.* (33)	2021	SRMA	2,179	1,523	No	T1-4	N/A	=	LPS	N/A	=	LPS	LPS	N/A	=	=	All retrospective and small sample size studies
Zhang *et al.* (2)	2020	SRMA	367	287	No	T1-2-3	N/A	=	=	N/A	LPS	LPS	LPS	=	LPS	=	All retrospective and small sample size studies

CS, comparative study; PSM, propensity score matched analysis; ExpC, expert consensus; Sur-Rev, international survey of expert surgeons and literature review; SRMA, systematic review and meta-analysis; N/A, not available; iGBC, incidental gallbladder cancer; EC, "extended cholecystectomy" denotes wedge resection or anatomical resection of Sg4b-5; LN, lymphadenectomy; SC, "simple cholecystectomy" denotes removal of gallbladder alone; MH, major hepatectomy; OM, overall morbidity; MM, major morbidity; LPS denotes statistically significant results in favor of the laparoscopic approach; OPEN denotes statistically significant results in favor of the open approach; OS, overall survival; DFS, disease-free survival; Sg4b-5, Sg4b-5 anatomical bisegmentectomy; = denotes that there are not statistically significant differences between open and laparoscopic.



Video 1 Sg4b-5 bisegmentectomy and regional lymphadenectomy for a case of T2 incidental gallbladder cancer after laparoscopic cholecystectomy.

(P=0.0171). However, when cases were stratified according to the lymph node (LN) status (T2N0 and T2N1), there was no statistically significant difference in terms of DFS between two groups. This result might be explained by the relative higher number of T2N0 cases in the laparoscopic group. There was no significant difference in terms of OS (P=0.116). Besides, the port site metastasis rate in this article was nil.

In conclusion, although the laparoscopic approach requires more experienced technique to be performed effectively and safely, the results obtained from the analysis of these three studies have shown that it is not inferior to the open one.

T3-4

According to AJCC 8th edition (5), GBC is classified T3 if it perforates the serosal and/or directly invades the liver or one other adjacent organ or structure. It is T4 if it invades the main portal vein or hepatic artery or more than one extrahepatic organ or structure. In case of T3-4 GBC, surgery may include bile duct resection with hepatico-jejunal anastomosis, right hepatectomy with possible extension to segment 4 or caudate lobe, portal vein or hepatic artery resection and reconstruction, colic resection or even pancreaticoduodenectomy. Most of the papers in the literature concerning laparoscopic approach in GBC are focused on the early stage of the disease or incidental GBC. Therefore, studies investigating the efficacy of laparoscopic surgery for advanced GBC are limited.

In 2020, Dou *et al.* (27) published a retrospective monocentric series of 63 consecutive patients who underwent radical surgery for GBC. The authors performed a subgroup analysis focusing on T3. Thirty-five patients were considered, 15 in the laparoscopic group and 20 in the open group. Laparoscopic resection was associated with significative less intraoperative bleeding whereas operation length, number of LNs yield, positive margin on liver parenchymal, LN metastasis, vascular invasion, post-operative morbidity, 30 and 90 days post-operative mortality and length of hospital stay did not differ significantly between groups. Intriguingly, the OS Kaplan-Meier curves comparison demonstrated a significant survival benefit in the laparoscopic group (P=0.023). The authors explain this result with a clearer visual of the operation field which gives the surgeon a magnified view of the anatomic structures facilitating surgical manipulation and reducing intraoperative bleeding. It is worth admitting that it's not rigorous to draw conclusions on such a small number of studies and patients. However, a systematic review conducted by Zhang *et al.* (2) including Dou and other 3 studies with a total of 86 cases (33 laparoscopic and 53 open) confirmed this finding with 1- and 2-year OS rates significantly higher in the laparoscopic group of patients.

Goetze *et al.* (16) analyzing German Registry data from 837 patients with incidental gallbladder carcinoma after cholecystectomy showed that laparoscopy was as safe as the open technique regardless of T stage. Considering only the T3 patient, 5-year survival rate for laparoscopic cholecystectomy, primary open approach, and intraoperative conversion were 24, 6 and 11% respectively (log-rank test, P=0.001).

Furthermore, in 2022, Dou *et al.* (26) conducted another study focusing the analysis on T2–T3 patients using the propensity score matching in order to overcome selection bias due to the retrospective setting of the study. Although the length of operation was increased in the laparoscopic group, intraoperative bleeding and length of hospital stay were decreased. Post-operative morbidity, mortality and 1-, 2-, 3-year OS rate were comparable. At multivariate analysis T stage, vascular invasion and tumor differentiation were identified to be independent risk factors of OS. Besides, the authors reported no case of port-site metastasis and explain the result with preoperative recognition of the GBC, cautious operative manipulation, en bloc resection of gallbladder and liver parenchymal, and use of plastic bag for specimen extraction.

Despite the small number of available studies, laparoscopy seems to achieve intra and postoperative safety

as well as oncological adequacy even for locally advanced GBC. Pathological factors, rather than laparoscopic or open approach, are the key factors determining the long-term patient's OS. However, it is worth to admit that caution must be used in drawing conclusions about the safety of laparoscopic approach in advanced GBC. As already mentioned, surgical operations in these stages can be demolitive and demanding. Radical oncology and patient safety must always be the primary objective. Therefore, although laparoscopy should not be excluded a priori, it should be considered only in highly selected cases and in high volume tertiary referral centers. Besides, even in case of an open resection, a diagnostic laparoscopy with staging intent is mandatory as the first step of the operation in order to rule out peritoneal carcinomatosis or liver metastasis. As a matter of fact, the former is not always obvious at preoperative imaging. Staging laparoscopy might avoid useless laparotomy in patients with metastatic disease.

Incidental GB cancer (iGBC)

iGBC is defined as a carcinoma of the gallbladder unexpectedly discovered in the definitive histopathological report of a cholecystectomy performed in patients in whom malignancy is not suspected preoperatively. Laparoscopic cholecystectomy is increasingly diffused for benign diseases of the gallbladder such as lithiasis, polyps or adenomyomas. Therefore, even though the reported incidence of iGBC after laparoscopic cholecystectomy is 0.2–1%, it is currently detected more and more frequently (34).

JSHBPS, NCCN and ESMO guidelines recommend oncological extended re-resection, comprising Sg4b-5 bisegmentectomy or gallbladder bed resection along with hepatic pedicle lymphadenectomy, for all T1b or greater tumor, cystic duct or LN involvement, vascular or perineural invasion (7-9). An appropriate staging with MRI or CT scan is mandatory before the operation and the optimal time interval for the re-resection seems to be from 4 to 8 weeks after the cholecystectomy (37). Port site resection, in case of gallbladder removed without a bag, is advocated only by ESMO whereas JSHBPS discourage it because, in case of port site metastasis, the disease has already spread to the peritoneum (38). Laparoscopy is not even mentioned in the above guidelines as a surgical approach after finding an iGBC. Only the NCCN guidelines state "consider staging laparoscopy" as the first step of the "re-resection" (39).

Vega *et al.* (22) in a multicentre retrospective observational cohort study on 255 patients who underwent hepatic re-resection after iGBC (65 laparoscopic, 190 open) investigated long-term oncological outcomes. The statistical analysis was conducted with the inverse probability of treatment weighting (IPTW) using propensity scoring in order to minimize selection bias. In this study recurrence free survival (RFS) incidence was higher in the laparoscopic group (P=0.038) and OS did not differ between groups. Independent predictors of worse RFS were one to three positive nodes, at least four positive nodes, and residual cancer whereas independent predictors of worse OS were at least four positive nodes, blood loss at least 500 mL and residual cancer. Furthermore, length of hospital stay was shorter after laparoscopic re-resection (median 4 *vs.* 6 days; P<0.001) and port site resection was not associated with improved OS or RFS. Wang *et al.* conducted a similar study on 106 patients with iGBC (45 laparoscopic, 61 open). They found better 1- and 5-year OS with less intraoperative blood loss, lower complication rate and lower duration of hospital stay in the laparoscopic group. Goetze *et al.* (16) queried the German Registry of iGBC in order to draw a definitive conclusion about the safety of LC in iGBC, giving a good snapshot of clinical practice about this issue in German, Switzerland and Austria as well. The scholars analyzed 834 patients affected by iGBC, divided into three groups according to the surgical approach used for cholecystectomy (492 laparoscopic, 200 open, 142 laparoscopic converted to open) and they stratified the results according to the T stage as well. Open cholecystectomy was associated with slightly better 5-year OS in T1 stage disease although the difference did not achieve statistical significance (P>0.05). However, considering T2 and T3 stage disease laparoscopy was associated with a significantly better 5-year survival rate (P=0.002 and P=0.01 respectively). Furthermore, a subgroup analysis conducted on patients who have not undergone re-resection after the finding of an iGBC revealed a significant survival benefit in the laparoscopic group (P<0.0001).

Besides, the same study reported a comparable rate of intraoperative accidental gallbladder perforation (23% *vs.* 21%). The perforation rate was significantly higher in the conversion group (35%, P=0.006) and this might have been one of the reasons for the conversion. Port site metastasis rate was 6.1%, 3.5% and 2.8% in the laparoscopic, open and conversion group respectively. However, the overall recurrence rate did not differ significantly in the three groups (30% *vs.* 36% *vs.* 30%).

In conclusion, laparoscopic re-resection for iGBC seems to be feasible and safe with short e long term outcome comparable or even better than the open approach.

Furthermore, the primary access technique (laparoscopy or open) for the initial cholecystectomy does not affect the prognosis.

Sg4b-5

In case of preoperative diagnosed GBC or iGBC with T stage ≥ 1b, the surgical options are wedge resection of Sg4b-5 or anatomic Sg4b-5 bi-segmentectomy along with regional lymphadenectomy. No difference has been demonstrated in terms of short- and long-term results, so the surgeon's practices and preferences matter. However, GBC progression to the liver is thought to occur via gallbladder veins, which flow into the portal veins of segments 4a and 5. Thus, some authors suggest anatomic Sg4b-5 bi-segmentectomy in order to remove potential not macroscopically visible metastasis of the liver (28,40,41). Anatomical segmentectomies and bisegmentectomies with laparoscopic approach are challenging procedures as reported by many difficulty scores such as Kawaguchi *et al.* score (42). Nag *et al.* (28) compared 30 laparoscopic and 38 open S4b-5 bi-segmentectomy for GBC. The authors showed that laparoscopic surgery was associated with less blood loss (158 *vs.* 219 mL, P=0.006) and shorter hospital stay (6.4 *vs.* 9 days, P=0.0001) compared to open surgery. No differences were found in terms of intra-operative time (286 *vs.* 274 min, P=0.565), mean overall (51 *vs.* 46.4 months, P=0.457) and recurrence-free survival (48.6 *vs.* 46.6 months, P=0.352). The complication rate was slightly lower in the laparoscopic group (16.6% *vs.* 31.5% P=0.259), but the difference was not statistically significant. Despite the promising results, which suggest an advantage of laparoscopy Nag *et al.* study has several limitations. The limited number of patients and the retrospective observational design require caution in results interpretation. Further studies on larger patient populations are needed to draw more solid conclusions.

Lymphadenectomy

Lymph node status is one of most important prognostic factors in GBC (43-45), strongly related to DFS and OS. NCCN (7), ESMO (8) and AJCC (4,5) guidelines recommend performing the hepatic pedicle lymphadenectomy even though without specifying the exact extension of the dissection. However, according to the 8th edition of AJCC (4,5), it is mandatory to retrieve a number of LN ≥6 for a proper lymphadenectomy. In case of 1–3 positive LN the stage is N1 whereas it's N2 in case of 4 or more positive nodes. Furthermore, several papers suggest to perform a D2 LN dissection including posterosuperior retro pancreatic LN (station 13), along with bile duct, portal vein, proper and common hepatic artery LN (stations 12b, 12p, 12a and 8 respectively) as well as right celiac nodes (station 9) (46-48). Although technically demanding, D2 laparoscopic lymphadenectomy for GBC is feasible and safe. Besides, it is associated with lower blood loss, less intra- and postoperative blood transfusions and shorter hospital stay compared to open as shown in a propensity-score-based case match analysis by Ratti *et al.* (48). Thirteen articles of the present review, reporting data about the number of LN harvested, confirm these findings (2,18-26,28,32,33). There is no statistically difference between open and laparoscopic approach in terms of number of LN, OS and DFS. Laparoscopy allows less bleeding, less blood transfusions and shorter length of stay. These heartening results clash with other data from the United States National Cancer Database (NCBD). Kemp Bohan *et al.* (49) conducted an analysis on 2302 non-metastatic patients from 2006 to 2015 who underwent GBC resection. Despite the inherent limitations of using the NCBD the results provide a good snapshot of the US practice in that recent period. Only 59.1% of patients with pT1b-T3 disease had an associated lymphadenectomy and, if LN dissection was performed, only 23.9% (n=310) had ≥6 LN harvested. The lymphadenectomy rate was significantly higher at academic/research centers and patients treated at these centers showed independent survival benefit.

The study also confirmed that lymphadenectomy independently reduced the risk of mortality in the overall cohort by 48%. Besides, patients who did not receive LN dissection had roughly the same OS of those with node positive. Those results might be explained by the improved staging and more accurate prognostication of the disease conferred by the lymphadenectomy. However, Kemp Bohan *et al.* article once again strengthens the evidence on the importance of lymphadenectomy in GBC treatment. Moreover, the data clearly show that GBC surgical management is demanding and requires specific expertise and technical skills. Therefore, patients must be addressed in tertiary high-volume referral centers. Otherwise, the risk is to receive a suboptimal treatment.

In conclusion, despite high-quality studies lacking, laparoscopic and open lymphadenectomy in GBC has similar oncologic outcomes but laparoscopy has better short-term outcomes. However, hepatic pedicle

lymphadenectomy is still not routinely performed in several peripheral centers, affecting patient OS (50,51).

Discussion

In this narrative review, data from the most recent articles regarding laparoscopic surgical treatment of GBC were analyzed.

As often happens in surgical issues, especially about rare tumors such as GBC, there are several papers in literature but high-quality evidence, obtainable with randomized controlled trials, is lacking.

Currently, there is a kind of paradox in surgical treatment of GBC. From one hand the official guidelines [JSHBPS (9), NCCN (7) and ESMO (8)] clearly recommend open surgical approach in all cases of resectable GBC, relegating laparoscopy to the mere staging purpose before definitive resection. On the other hand, there are clinical practice and several articles of the last two decades in which laparoscopy acquires an increasingly important role. There are two major concerns over the application of laparoscopy in GBC. Port-site recurrence or peritoneal dissemination due to intraoperative gallbladder perforation and the potential difficulty in achieving clear resection margins and proper lymphadenectomy. However, the studies supporting the inadequacy of laparoscopy are often old and questionable. In the Z'graggen *et al.* paper (13), in 1998, laparoscopic cholecystectomy was associated with a high rate of port-site metastasis in patients with preoperative undetected GBC. Although the study was conducted prospectively by the Swiss Association of Laparoscopic and Thoracoscopic Surgery on 10,925 patients who underwent laparoscopic cholecystectomy, only 37 had a GBC cancer diagnosis after the operation. Of these, 5 had port-site metastasis. In 2 out of 5 (40%) there was an intraoperative macroscopic gallbladder perforation whereas in 2 out of 32 (9%) the organ was intact. The use of the retrieval bag was not specified. Paolucci *et al.* (12) in 1999 published an article discouraging the use of laparoscopy for the surgical management of gallbladder and colorectal cancer based on a survey on 117,840 laparoscopic cholecystectomies (409 iGBC) and 412 colorectal resections. 70 out of 409 patients with iGBC (17.1%) developed port-site recurrence. Only in 8 out of 70 cases (11.5%) a protective plastic bag was used for gallbladder retrieval. Despite the evident biases, represented by the small number of events in the first study and the fact that technology available 25 years ago was completely different in terms of quality of images and the current routinely use of the plastic bag in the second one, these two papers have more than 200 citations each and they are still cited in the more recent international guidelines. Besides, although the Paolucci's study, the laparoscopic approach is currently the gold standard in colorectal cancer. Drafting this review, we found 20 relatively recent articles focused specifically on the laparoscopic treatment of GBC. Basically, all these studies draw the same conclusions: laparoscopic surgery for GBC treatment is feasible and safe in both short- and long-term outcomes. In all studies 1-3-5 OS and DFS are comparable or even better in the laparoscopic group. Nevertheless, laparoscopy confirms its known advantages: less bleeding and blood transfusion, less postoperative morbidity and shorter length of hospital stay. While it is true that currently there are no RCTs in medical literature, among the 20 studies retrieved, 4 were systematic review and meta-analysis (2,31-33) and 4 were propensity score matched analysis (6,21,25,26), therefore less biased than case series. Moreover, case reports and non-comparative case series were voluntarily excluded from the review. Furthermore, 2 analyses of the US (24) and German (16) registry on large cohorts of patients were collected. Both the European and the US articles confirm that the primary access technique (open or laparoscopic) has no impact on patients' long-term prognosis. Evidence coming from registries is not comparable to the RCT, however this kind of study provides a good snapshot about the current clinical practice "in real life" which must not be neglected. Lastly, from an expert meeting held in 2016 in Seoul, an international survey with several statements was produced (29). The scholars agreed that laparoscopic surgery, in expert hands and with careful manipulation to avoid bile spillage does not worsen the patient's prognosis. Besides, this survey, like most of the other studies included in this review, concluded also advocating the necessity of large and prospective studies in order to obtain stronger evidence. However, although RCT would probably provide a definitive response, this might not be feasible owing to the rarity and the clinical presentation of the disease.

A gradual modification of clinical practice with an increased role of laparoscopy in the surgical management of GBC is already taking place and will probably take place despite the absence of randomized clinical trials. Therefore, articles like the present review, that make the effort to collect, review and summarize what is present in the scientific literature are still useful to strengthen the growing evidence of the important role of laparoscopy and push towards a transition that can eventually translate into a

modification of the current guidelines in the future.

Conclusions

The results of the articles considered in the present review seem to suggest that laparoscopy is feasible and safe in surgical management of GBC. Long-term outcomes appear to be comparable to open approach, at least in early stages of the disease and if surgery performed in referral centers. Moreover, laparoscopy confirms its well-known short-term benefits with less intraoperative bleeding, less morbidity and shorter length of hospital stay.

Therefore, it could play an increasingly important role in the future.

Although difficult to carry out, high-quality studies that can more solidly confirm these results are desirable.

Stage adjusted therapy, pathologic factors, proper lymphadenectomy and avoiding bile spillage rather than the primary access technique, appear to be the key factors determining the long-term patient prognosis.

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