



REVIEW ARTICLE

Robot-assisted radical cholecystectomy for gallbladder cancer: A review

Weng Jiayi^{1*}, Vishal G. Shelat²

¹Yong Loo Lin School of Medicine, National University of Singapore, Singapore, ²Department of General Surgery, Tan Tock Seng Hospital, Singapore

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*Corresponding author:

Weng Jiayi
Yong Loo Lin School of Medicine, National
University of Singapore, 10 Medical Dr,
117597, Singapore.
Tel: +65 98592965
Email: wengjiayi28@gmail.com

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ABSTRACT

Background: Radical cholecystectomy (RC) is recommended for Gallbladder cancer (GbC) patients with resectable T1b or higher stage. Traditionally, open RC is preferred over minimally invasive approach. Robotic surgery is increasingly gaining popularity and there are reports of robotic RC (RRC) for GbC. RRC is still new and mostly performed in high-volume centers with access to robotic technology.

Aim: This study aims to review the current literature on the safety and feasibility of RRC for GbC.

Methods: We performed a systematic review of RRC for GbC using PubMed and Embase until December 2020. The primary endpoint was major complications, while the secondary endpoints were conversion to open, R0 resection, and early recurrence.

Results: Seven studies with 74 patients were included in the study. Overall, four patients (5.41%) required open conversion. Five out of 74 patients (6.76%) experienced post-operative complications. There was no post-operative mortality. Among the patients with surgical margins reported (n = 63), 61 patients had negative margins (96.8%) and only two patients had positive margins. Two-year survival outcomes were reported as 60.5–100%.

Relevance for Patients: This is the first review that summarizes the current evidence on RRC for GbC. The endpoints suggest that RRC is feasible and safe in selected patients and when done in experienced centers. Understanding the strengths and limitations of RRC compared to other established therapeutic options may potentially aid surgeons in formulating the optimal treatment plan for GbC patients.

1. Introduction

The gallbladder is the most common primary cancer site among the biliary tracts [1]. Globally, gallbladder cancer (GbC) accounts for 1.2% of all cancer diagnoses and 1.7% of all cancer deaths [2,3]. GbC has poor prognosis due to late presentation that often results in advanced stage at the time of diagnosis. In the US, only 20% of GbC are diagnosed early, 40% are diagnosed after spread to distant organs or lymph nodes and overall, 5-year survival rate of GbC is below 20% [4-7]. GbC is detected either incidentally (on histopathology) following cholecystectomy, or based on clinical findings and imaging before cholecystectomy. Incidental GbC following cholecystectomy is found in approximately 0.2–1.1% of all laparoscopic cholecystectomies [8], and has a better prognosis than non-incidentally-discovered GbC, provided the patient is staged and managed appropriately with R0 resection [9].

Simple cholecystectomy (laparoscopic or open) is curative in patients with Tis and T1a GbC. For patients with resectable T1b and above disease, radical cholecystectomy (RC) is advocated. RC consists of en bloc resection of the gallbladder, wedge resection of the liver, extrahepatic bile duct, and the regional lymph nodes including first-echelon (cystic duct and pericholedochal) and second-echelon lymph nodes (posterosuperior pancreaticoduodenal,

retroportal, right celiac, and hepatic artery groups) [10,11]. Traditionally, the open approach is preferred over minimally invasive approach due to the difficulty in achieving adequate lymphadenectomy, the complexity of liver resection, and the risk of gallbladder rupture leading to peritoneal metastases [12-17]. Recently, robotic surgery is increasingly popular [18]. The robotic approach has advantages such as filtration of hand tremor, seven degrees of freedom of wrist articulation, 3-dimensional (3D) stereoscopic images, and elimination of counterintuitive “fulcrum effect” of conventional laparoscopic surgery [19]. These advantages may facilitate precise dissection and intracorporeal suturing and thus make surgery safe. However, robotic RC (RRC) is still new and mostly performed in high volume centers but if safe and effective could potentially be replicated [20]. This study aims to review current literature on safety and feasibility of RRC for GbC.

2. Methods

2.1. Search strategy

We searched PubMed and Embase indexed human studies reporting on outcomes of RRC for GbC until December 2020. Search terms included “mini* invasive surg*”, “mini* access surg*”, “robotic surgery”, “robot assisted surgery”, “RC”, “extended cholecystectomy”, “port* lymphadenectomy”, “port* lymph node dissection”, “gallbladder adenocarcinoma”, “gallbladder carcinoma”, and “GbC”. There was no restriction on article type. The articles from both databases were combined and all duplicates were removed.

2.2. Selection criteria

Search did not yield any prospective randomized control trial. Retrospective single-arm case series or case-control studies were included. Elective RRC (performed when GbC was suspected before cholecystectomy) and completion RRC (performed as a completion treatment after a GbC was diagnosed following a simple cholecystectomy) were both included. We excluded articles that reported outcomes of robotic-assisted surgery for benign gallbladder diseases, metastases to gallbladder, or cholangiocarcinoma. We also excluded studies reporting on liver resection, isolated lymphadenectomy, or staging laparoscopy. Case reports, review articles, and guideline publications were excluded from the study. Case series that reported on robotic-assisted surgeries for GbC, but did not report the individual outcomes of RRC for GbC separately were excluded from the analysis [21,22]. We performed manual search of the citations of the selected publications to include additional study. Abstracts of International HepatoPancreaticoBiliary Association (IHPBA) meetings (11th [Korea, 2014], 12th [Brazil, 2016] and 13th [Switzerland, 2018]) were browsed to identify additional study. If duplicate publications were reported from same institution, the most recent publication was included in the study.

2.3. Screening and data extraction

Of 227 potentially relevant publications identified through database and manual search, 206 publications were excluded by title and abstract screening, resulting in 21 articles which then

underwent full-text screening. Any conflicts with regards to inclusion of the study was internally discussed between the two authors and consensus was achieved. Seven studies reporting 74 RRC were eligible for inclusion in this review (Figure 1).

3. Results

Seventy-four patients underwent RRC. Table 1 reports the demographic and clinical profile of patients included in this study. Table includes study period, number of patients, age and gender of patients, body mass index (BMI), conversion rate to open surgery, and number of completion and elective RRC. RRC was attempted as an elective procedure for a suspicion of GbC in 42 out of 54 (77.8%) patients and as a completion procedure for incidental GbC discovered after cholecystectomy in 12 out of 54 (22.2%) patients. The report of Pickens *et al.* (n = 20) did not mention if RRC was performed as index procedure or as completion following incidentally diagnosed GbC following simple cholecystectomy [20]. Overall, 4 patients (5.41%) required open conversion. Reasons for conversion include bile spillage (intraoperative gallbladder perforation) in one patient, frozen porta (nodes being adherent to the anterior surface of the portal vein) in one patient and elective conversion for excision of the extrahepatic biliary tree in two patients.

3.1. Operative outcomes

Table 2 shows the operative outcomes of RRC procedure. Table includes total blood loss, operation time, length of stay

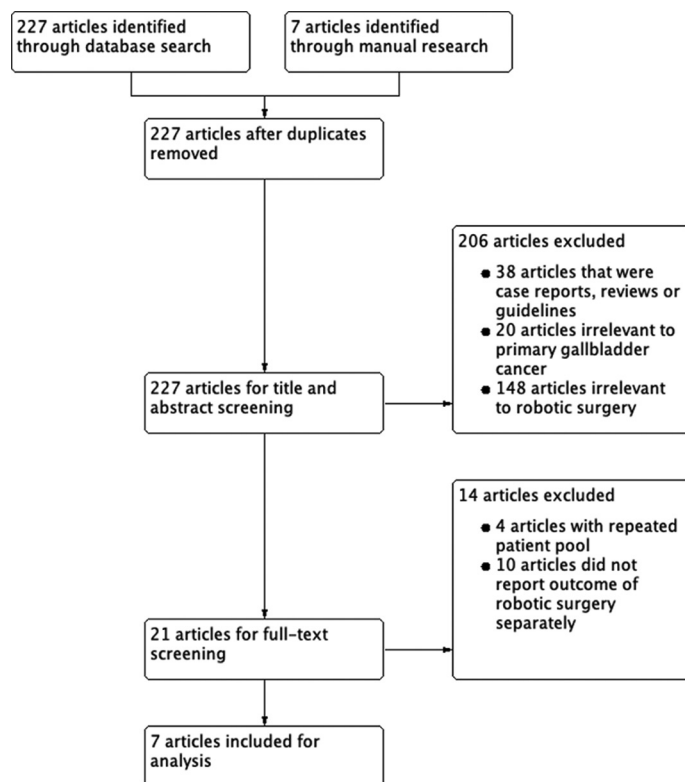


Figure 1. Flow chart for study inclusion. Figure created with Review Manager 5.3.

Table 1. Demographic and clinical profile of patients treated by RRC

Author, publication year	Country	Study period	Number	Age	Gender	BMI, kg/m ²	Conversion to open RC (%)	Elective surgery/ Completion surgery
Byun <i>et al.</i> , 2020 [19]	South Korea	February 2018–April 2019	13	63.5±10.5 ^a	8 male, 5 female	24.4±2.6 ^a	Nil	13 elective
Pickens <i>et al.</i> , 2019 [20]	USA	January 2006–August 2018	20	NR	NR	NR	Nil	NR
Goel <i>et al.</i> , 2018 [24]	India	July 2015–August 2018	27	54 ^b (28–75) ^c	9 male, 18 female	24.4 ^a (18.09–33.2) ^c	4 (14.8%)	2 completion, 25 elective
Shen <i>et al.</i> , 2012 [25]	China	March 2010–July 2011	5	57.4 ^a (46–63) ^c	2 male, 3 female	NR	Nil	2 completion, 3 elective
Sinagra <i>et al.</i> , 2017 [23]	Italy	April 2012–June 2014	3	NR	NR	NR	Nil	3 completion
Zeng <i>et al.</i> , 2018 [26]	Singapore	September 2015–June 2017	3	NR	1 male, 2 female	NR	Nil	1 elective, 2 completion
Araujo <i>et al.</i> , 2019 [27]	Brazil	NR	3	45 ^a (33–53) ^c	1 male, 2 female	30.9 ^a (29.9–31.8) ^c	Nil	3 completion

a: mean, b: median, c: range, BMI: body mass index, RC: Radical cholecystectomy, RRC: Robotic radical cholecystectomy, NR: not reported

Table 2. Operative outcomes of patients operated by RRC

Author, publication year	Total blood loss, ml	Operation time, min	LOS, days	Morbidity (%)	Mortality	F/u duration, months
Byun <i>et al.</i> , 2020	270.8±297.9 ^a	187.7±34.6 ^a	6.6±1.7 ^a	2 (15.4%)	90 day: Nil	NR
Pickens <i>et al.</i> , 2019	150 ^b (5–1200) ^c	193 ^b (112–447) ^c	2.5 ^b (0–6) ^c	2 (10%)	30 day: Nil	12.8 ^b (1–62) ^c
Goel <i>et al.</i> , 2018	200 ^b (20–700) ^c	295 ^b (200–710) ^c	4 ^b (2–12) ^c	1 (3.7%)	90 day: Nil	9 ^b (1–46) ^c
Shen <i>et al.</i> , 2011	210 ^a (50–400) ^c	200 ^a (120–300)	7.4 ^a (7–8) ^c	Nil	Nil in-hospital mortality	11 ^a (1–17) ^c
Sinagra <i>et al.</i> , 2017	150 ^b (100–350) ^c	300 ^b (240–310) ^c	6 ^b (5–7) ^c	Nil	Nil in-hospital mortality	24 ^b (18–32) ^c
Zeng <i>et al.</i> , 2018	200 ^b (50–700) ^c	360 ^b (220–530) ^c	3 ^b (3–4) ^c	Nil	Nil in-hospital mortality	NR
Araujo <i>et al.</i> , 2019	183 ^a (50–300) ^c	392 ^a (380–410) ^c	3 ^a	Nil	90 day: Nil	3 ^a

a: mean, b: median, c: range, BMI: body mass index, LOS: Length of stay, F/u: Follow-up, NR: not reported, RRC: Robotic radical cholecystectomy

(LOS), morbidity, mortality, and follow-up duration. Mean total blood loss was 194.8ml (range: 5-1200 ml), mean operation duration was 275 min (range: 112-710 min), and mean LOS was 4.65 days (range: 0-12 days). Overall, 5 out of 74 patients (6.76%) experienced post-operative morbidity. There was no post-operative mortality. The mean follow-up duration was 12.0 months (range: 1-62 months).

3.2. Oncologic outcomes

Table 3 shows the oncologic outcomes of GbC patients operated by RRC. Table includes survival outcomes, cancer staging, number of lymph nodes harvested, rate of R0 resection, and recurrence during follow-up. Long-term survival outcomes were reported in four studies [20,23-25]. As for cancer staging, T stage was reported for 54 patients. 15 patients (27.8%) had T1b or less advanced stage, 38 patients (70.4%) had T2 or more advanced

stage, while the remaining 1 patient had Tx stage. N stage was reported for 41 patients, out of which 2 patients had N1 stage (4.88%). M stage was reported for 54 patients, out of which 1 patient had metastatic GbC (1.85%). Mean number of lymph nodes resected was 9.07 (range: 1–22). Across the seven studies, surgical margins were reported in 63 patients, out of which R0 resection was achieved in 61 patients (96.8%). Out of the three studies that reported recurrence during follow-up, two patients developed bilobar liver metastases [24], and one patient had tumor occurrence that resulted in mortality [25].

4. Discussion

GbC has dismal survival outcomes due to delayed presentation, aggressive tumor biology, and lack of effective chemotherapy. RC is the only curative option, and it is advocated either as a completion surgery after GbC was diagnosed following a

Table 3. Oncologic outcomes of patients operated by RRC

Author, publication year	Survival	T stage	N stage	M stage	Number of LN harvested	R0 resection	Recurrence
Byun <i>et al.</i> , 2020	NR	T0-T1: 5 T2/T3: 8	NR	M0:13	7.2±3.1 ^a	13 (100%)	NR
Pickens <i>et al.</i> , 2019	1 year survival – 70.6% 2 year survival – 60.5%	NR	NR	NR	5 ^b (2–15) ^c	12 out of 14 (85.7%)	NR
Goel <i>et al.</i> , 2018	DFS at 9 months –92.6%	Tx: 1 Tcis: 1 T1a: 2 T1b: 1 T2: 18 T3: 4	N0: 27	M0: 27	10 ^b (2–21) ^c	27 (100%)	2 (7.41%)
Shen <i>et al.</i> , 2011	1 year survival – 80%	T2: 2 T3: 3	N0: 5	M0: 5	9 ^a (3–11) ^c	NR	1 (20%)
Sinagra <i>et al.</i> , 2017	2 year survival – 100%	T1b: 3	N0: 2 N1: 1	M0: 3	21 ^b (20–22) ^c	3 (100%)	Nil
Zeng <i>et al.</i> , 2018	NR	T2: 1 T3: 2	N0: 2 N1: 1	M0: 2 M1: 1	7 ^b (1–11) ^c	3 (100%)	NR
Araujo <i>et al.</i> , 2019	NR	T1b: 3	N0: 3	M0: 3	4.3 ^a (3–6) ^c	3 (100%)	NR

a: mean, b: median, c: range, LOS: length of stay, F/u: follow-up, DFS: disease-free survival, OS: overall survival, LN: lymph nodes, NR: not reported, RRC: Robotic radical cholecystectomy

simple cholecystectomy or as an elective surgery when GbC was diagnosed or suspected before cholecystectomy. With advances in robotic technology, RRC is reported by high-volume centers with access to robotic technology. This review confirms that in patients with GbC, RRC is safe and feasible with acceptable peri-operative outcomes.

The optimal surgical management of GbC is guided by TNM classification system [1,2]. Simple cholecystectomy by either open or laparoscopic technique [3,4] is adequate for T0 or T1a GbC with 5-year survival rate 95%–100% [7]. Open RC is considered the gold standard for stage T1b and beyond operable patients with GbC. The open approach is preferred over the laparoscopic approach due to concerns for port-site metastases, the difficulty in achieving adequate lymphadenectomy, the complexity of liver resection, and the risk of gallbladder rupture leading to disseminated peritoneal metastases [12–17]. Minimal access surgery is proven to improve peri-operative outcomes by reducing post-operative pain, wound complications and facilitates early recovery. With advances in technology and surgical instrumentation, minimal access surgery is increasingly adopted in gastrointestinal oncology including major hepatobiliary and pancreatic surgery. Due to the paucity of GbC in Western world, lack of screening programs for early diagnosis of GbC, and relatively slow adoption of minimal access surgery for complex biliary procedures, there is a lack of evidence supporting safety and feasibility of minimal access RC. Increased prevalence of GbC in developing economies like Bolivia, Chile, India, and Thailand where accessibility and affordability of robotic surgery is limited is contributory to the paucity of high-quality clinical data showing benefits of RRC. Despite such sporadic disparities, increased availability, accessibility, and adoption of robotic technology have fuelled the enthusiasm in minimal access

complex biliary surgery as robotic platform reduces technical challenges associated with laparoscopic surgery. Thus, the past decade has witnessed reports of GbC treated by RRC. At the present time, affordability remains the main challenge for many surgical units to embrace robotic surgery. Healthcare systems largely follow utilitarian ethics, and thus without strong evidence of benefit, it is not rational to justify the extra cost incurred for using robotic platform for the procedures that can be performed by laparoscopic techniques. As for example in Singapore, an estimated additional cost of SGD 5000 is billed to patient for using robotic platform.

Robotic surgery is increasingly used in a number of surgical procedures in recent years, notably complex hepato-pancreato-biliary surgeries such as major hepatectomy [28] and pancreatoduodenectomies [29–31]. Advancements in the field of robotic technology have overcome many limitations associated with laparoscopy, prompting more surgeons to consider using robotic surgery in treatment of GbC [26]. Although there are several reports of good outcomes for laparoscopic RC, these are limited to a few highly specialized centers [32–35]. GbC is typically diagnosed at advanced stage and has a high possibility of lymphatic metastasis [2,36]. Adequate lymphadenectomy is essential to improve survival outcomes [37–39]. Studies have shown that the resection and histologic evaluation of at least six lymph nodes are required to improve the risk stratification of GbC [15,38–40] and the range of lymphadenectomy should include the posterosuperior pancreatic head lymph nodes along the hepatoduodenal ligament and the hepatic artery [41–43]. Studies included in this review [20] showed that RRC had significantly greater lymph node harvest compared to laparoscopic RC. Mean number of lymph nodes resected was 10, which exceeded the criteria of at least six lymph nodes

and demonstrated that adequate and safe lymphadenectomy can be performed through the robotic approach. To achieve sufficient lymphadenectomy in hepatoduodenal ligament territory, critical structures such as the hepatic artery, portal vein, and common bile duct must be fully skeletonized. This is often technically challenging to perform with conventional straight and rigid laparoscopic instruments and risks rupturing the gallbladder causing peritoneal metastases [44]. Compared to the traditional rigid laparoscopic instruments [26], the flexibility of the robotic arms offers better access to the operative field and improved dexterity, allowing surgeons to perform the hilar dissection more easily. Robotic technology allows precise dissection, stable retraction, stereoscopic image with depth perception as well as facilitates intracorporeal suturing and this makes dissection safe and elegant. It is important to note that despite these promising outcomes, one of the non-elective conversion to open RC reported by Goel *et al.* was due to lymph nodes being adherent to the anterior surface of the portal vein. This shows that achieving lymphadenectomy still proves challenging in robotic surgery and endorses that despite using robotic platform, in some patients, surgery will remain challenging. In addition, our review reports two open conversions for hepaticojejunostomy reconstruction. It is not entirely clear if there were competing reasons for open conversion, as we would assume that robotic platform facilitates bilio-enteric reconstruction. In our opinion learning curve and considerations of patient safety probably contributed to open conversions.

Current studies on the use of robotic surgery for GbC, although limited, show promising perioperative outcomes. This is well supported by evidence presented in this review. Compared to open RC, RRC was associated with shorter LOS, lesser intraoperative blood loss, and post-operative morbidity [20,24]. The poorer perioperative outcomes of conventional open RC can be attributed to the inverted L-incision or the right subcostal incision transecting the rectus abdominis muscle. These incisions lead to post-operative pain, pulmonary complications related to pain and splinting of the diaphragm, and longer time to recovery [19]. Intuitively it is possible that RRC benefits patients from reduced pleuropulmonary and wound morbidity; and thus, adjuvant chemotherapy can be started early, with potential oncologic benefits. Studies in this review also demonstrated that RRC has high lymph node yield with comparable overall survival and R0 resection to that of open RC [20,24]. Goel *et al.* showed that the recurrence rate was much lower after RRC (7.41%) than after open RC (17.1%) [24]. This could be due to selection bias inherent to retrospective studies. This review is unable to conclude if RRC has oncologic advantage over open RC and more evidence is needed, preferably by prospective studies including more patients. In addition, port-site metastases are an important complication of GbC surgery. There is insufficient data if RRC has an equal or reduced risk of port-site metastases.

This is the first review that summarizes the current evidence on RRC. However, a small number of GbC patients treated by

RRC and heterogeneity in reporting outcomes is evident, and thus, generalizations cannot be made. Majority of studies did not report long-term oncologic outcomes, and thus benefits of robotic platform to enhance survival outcomes remain to be shown. We foresee that with more accessibility and affordability of robotic technology, more evidence will follow. In conclusion, RRC is safe and feasible, and more evidence is needed with regard to oncologic outcomes of RRC.

Conflict of interest

The authors declare no conflicts of interest.

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