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REVIEW ARTICLE

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Essential updates 2019/2020: Surgical treatment of gallbladder cancer

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Abstract

Gallbladder cancer is a biliary tract cancer that originates in the gallbladder and cystic ducts and is recognized worldwide as a refractory cancer with early involvement of the surrounding area because of its anatomical characteristics. Although the number of cases is increasing steadily worldwide, the frequency of this disease remains low, making it difficult to plan large-scale clinical studies, and there is still much discussion about the indications for surgical resection and the introduction of multidisciplinary treatment. Articles published between 2019 and 2020 were reviewed, focusing mainly on the indications for surgical resection for each tumor stage, the treatment of incidental gallbladder cancer, and current trends in minimally invasive surgery for gallbladder cancer.

KEYWORDS

gallbladder cancer, IGBC, minimally invasive surgery, neoadjuvant chemotherapy, surgical strategy

1 | INTRODUCTION

Gallbladder cancer (GBC) is the most common biliary malignancy and the fifth most common gastrointestinal malignancy in Western countries.[1] Complete surgical resection is the only modality that can provide a chance of cure. Due to the anatomical characteristics of the gallbladder itself, GBC can lead to early invasion of the liver parenchyma, the hepatoduodenal ligament, the duodenum, and other surrounding organs, and various types of surgical resections have been performed according to tumor stage. Therefore, there is still much discussion about the indications for each treatment. In this biannual review, essential updates to the treatment of GBC worldwide in the 2-year period between 2019 and 2020 are reviewed, based on 39 case-control studies and case-series studies of more than 50 cases on surgical strategies for GBC, treatment of incidental gallbladder cancer (IGBC), minimally invasive surgery for GBC, and the concept of borderline resectable disease in GBC.

2 | SURGICAL TREATMENT

There is broad agreement that only simple cholecystectomy (SC) should be performed for T1a GBC in which tumor depth remains within the gallbladder mucosa. However, there is still a lack of evidence on the optimal extent of hepatic resection, appropriate lymph node dissection, and indications for bile duct resection for T1b or higher GBC. In 2019-2020, there were 10 case-controlled studies and four case-series studies published on surgical resection for T1b or higher GBC.

2.1 | T1b GBC

The National Comprehensive Cancer Network guidelines recommend radical cholecystectomy including en bloc liver resection with regional lymphadenectomy (RL) for T1b or higher GBC.[2] However, Vo et al found that data from the National Cancer Database from 2004 to 2012 actually showed that extended cholecystectomy (EC) with RL according to this guideline was performed in only 217 cases of 464 T1b cases (46.7%).[3] Therefore, the appropriateness of EC, including gallbladder bed resection and wedge liver resection for T1b GBC, and lymph node dissection remains controversial.

The results of EC for T1b GBC were compared to those of SC in two papers.[4,5] Xu et al analyzed data from 2004 to 2013 from the Surveillance, Epidemiology, and End Results (SEER) database and found no difference in long-term outcomes between EC and SC and stated that EC is not automatically required for T1b.[4] Yuza et al also compared EC and SC in T1b GBC and found no difference in long-term outcomes ($P = .618$), with a median survival time of 182 and 154 months, respectively. However, considering the difficulty of preoperative diagnosis of T1b, they concluded that the validity of performing EC in cases with a preoperative diagnosis of T1b was not compromised.[5]

On the other hand, the necessity of regional lymphadenectomy (RL) for T1b GBC was suggested in all papers reviewed here.[3,4,6] Vo et al showed in their review of data of 464 T1b patients in the National Cancer Database that the 5-year survival rate of 181 patients who had negative nodes after EC with RL was significantly better than that of patients who underwent only SC ($P < .001$). They also reported that the lymph node metastasis rate in T1b GBC patients was 14.8%, and information on lymph node metastasis by RL is useful in planning treatment strategies for adjuvant chemotherapy.[3] Xu et al also used the above-mentioned SEER database to compare 144 patients who underwent RL and 247 patients without RL who were diagnosed with T1b GBC and reported a median survival time of 69 and 37 months, respectively. Although there was no significant difference ($P = .051$), there was a trend toward improved survival with RL, and when the study was limited to SC patients, SC with RL patients had a significantly better overall survival than SC without RL patients ($P = .024$).[4] They also noted the optimal number of lymph node dissections, noting that patients who underwent SC with five or more lymph nodes removed had better overall and cancer-specific survival than those who did not undergo lymph node dissection, and that RL was required for patients with T1b GBC.[4]

Wang et al analyzed data from the SEER database from 2004-2015 to determine the importance of tumor size and RL in T1b GBC. In this study, 127 of 277 T1b GBCs underwent RL, and although 23 patients with tumors less than 1 cm in size had no lymph node involvement, 15 of 104 (14.4%) patients with tumors greater than 1 cm in size had lymph node involvement.[6] Further large-scale, observational studies are needed to determine a strategy for the treatment of T1b GBC. At least for now, EC including gallbladder bed resection is not necessary, but RL may be necessary for tumors larger than 1 cm.

2.2 | T2 GBC

The guidelines recommend EC with RL for T2 gallbladder cancer. In recent years, it has been reported that the prognosis of T2 gallbladder cancer after resection differs according to whether the tumor is localized on the peritoneal side (T2a) or hepatic side (T2b)[7]; therefore, there is still considerable debate about the different treatment strategies for T2 gallbladder cancer depending on the localization of the tumor, the extent of hepatic resection (whether anatomical hepatectomy or non-anatomical hepatectomy), the importance of lymph node dissection, and the indications for bile duct resection.

Kwon et al retrospectively reviewed the outcomes of 937 T2 GBC cases from 14 hospitals in Korea, Japan, Chile, and the United States, and they reported that the 5-year recurrence-free survival rate of 683 patients treated with EC with RL was 73.0%, which was significantly better than the 61.5% of 193 patients treated with SC alone ($P = .012$). With regard to tumor localization, they reported a significantly worse 5-year overall survival rate of 65.5% in 384 T2b patients compared to 74.5% in 492 T2a patients ($P = .028$), and they further stated that the outcome of EC with RL was better than that of SC in T2a and T2b patients, respectively.[8]

Toge et al reviewed 81 T2 GBC cases and found that T2b patients still had a worse surgical outcome than T2a patients (72% vs 96%, $P = .027$). They also reported a significantly higher rate of lymph node metastasis in T2b patients (46%) compared with T2a patients (20%) ($P = .028$) and noted that there was no difference in the distribution of lymph node metastases between T2a and T2b, so that there was no need to distinguish between them in terms of the extent of lymph node dissection.[9]

Cho et al also reviewed 81 T2 GBC patients and showed that the surgical outcome of T2b cases was worse than that of T2a cases (76.0% vs 96.6%, $P = .041$). Furthermore, they reported a significantly higher recurrence rate of 44.4% after resection in T2b compared to 8.3% in T2a cases ($P = .006$). They also examined the type of recurrence. Whereas T2a patients had only lymph node recurrence, T2b patients had intrahepatic (13.3%) and distant (4.4%) metastases, and 15.6% of patients had paraaortic lymph node recurrence. Therefore, they stated that aggressive systemic chemotherapy is necessary for T2b patients.[10] A significantly higher recurrence rate after resection in T2b cases was also shown by Kwon et al who stated that recurrence rates for T2b and T2a were 31.0% and 24.6%, respectively ($P = .035$).[8]

Maruyama et al evaluated the relationship between the localization of GBC and perineural invasion (PNI) and found that PNI tends to be more frequent in the hepatic and proximal sides and less frequent in the peritoneal and distal sides, suggesting that bile duct resection may not be necessary in peritoneal and distal side GBC.[11]

Regarding the extent of liver resection for T2 GBC, Horiguchi et al analyzed data from the Japanese Biliary Tract Cancer Registry in 2013 and showed that there was no advantage of S4bS5 resection as an anatomical hepatectomy over gallbladder bed resection as non-anatomical hepatectomy.[12] Kwon et al showed that there

was no difference in 5-year overall survival between wedge liver resection (non-anatomical hepatectomy) and S4bS5 resection (anatomical hepatectomy) (74.1% vs 71.5%, $P = .720$).[8] As mentioned above, it has become clear that the prognosis after resection differs greatly depending on the localization of the tumor on the liver or peritoneal side. Future work should focus on identifying which biological or genetic differences are responsible for these differences in tumors.

2.3 | T3/4 GBC

Locally advanced gallbladder cancer, such as T3/4 GBC, requires extended surgery for curative resection, including vascular resection and reconstruction, right extended-hemihepatectomy, and hepatopancreatoduodenectomy (HPD). On the other hand, the surgical treatment itself is still controversial because the prognosis after resection for such locally advanced GBC is extremely poor. Mizuno et al stated that, although HPD for T4 GBC is an excellent local treatment, its indications are questionable from an oncological standpoint because of the high risk of complications and in-hospital death and the low likelihood of receiving adjuvant chemotherapy.[13] Sahara et al also discussed the indications for T4 GBC surgery in terms of the importance of lymph node dissection, based on their proposed therapeutic index (lymph node metastasis rate multiplied by 3-year overall survival); they noted that lymph node dissection has limited value in patients with a T4 or CA19-9 of 200 or higher.[14] Many of these cases are likely to have micro-metastases and, therefore, should be considered systemic disease. For locally advanced cases, such as T4 GBC, a multidisciplinary approach should be chosen to avoid over-invasive surgery at this time.

2.4 | Resectability criteria for locally advanced GBC

As mentioned previously, locally advanced GBC, such as T3/4 GBC, has not been improved by resection alone. In addition, the introduction of adjuvant chemotherapy (AC) is also difficult after over-invasive surgery, so the introduction of neoadjuvant chemotherapy (NAC) has long been awaited. Evidence for NAC is already accumulating in pancreatic cancer with a poor prognosis, as well as biliary tract cancer,[15] and resectability criteria have been established for the effective introduction of NAC; the introduction of NAC in cases diagnosed as borderline resectable is currently being investigated.[16,17] Unfortunately, there are still only retrospective studies of NAC for GBC,[18] and a large prospective study will be conducted in the future.[19,20] In order to effectively introduce NAC into GBC, it is urgent to identify preoperative prognostic factors of a poor outcome and to establish resectability criteria.

Higuchi et al reviewed 157 cases of T3/4 GBC and identified poor prognostic factors that could be diagnosed preoperatively as liver invasion ≥ 5 mm, invasion of the left margin or the entire area of the hepatoduodenal ligament, and ≥4 regional lymph node metastases, and the 5-year survival rate was 5.87% in patients with two of the factors and 0% in patients with three of the factors, indicating the need for a new treatment strategy for patients with two or more of the factors.[21]

Yamamoto et al reported that the surgical outcome for patients with preoperative CA19-9 values of 250 U/mL or higher was similar to that of non-resected patients, and they stated that the indication for surgery in such patients should be carefully considered.[22]

Sahara et al developed the GBC recurrence risk (GBRR) score to predict early recurrence within 12 months using 309 cases from the US Extrahepatic Biliary Malignancy Consortium database. The risk of early recurrence can be evaluated from high to low by inputting preoperative CA19-9, with or without hemihepatectomy, T stage, and histological grade (12-month RFS; low risk: 88.4%, intermediate risk: 77.9%, high risk: 37.0%).[23] The above factors should be used to develop resectability criteria in the future.

3 | INCIDENTAL GALLBLADDER CANCER (IGBC)

Incidental gallbladder cancer (IGBC), which is diagnosed as gallbladder cancer by pathological diagnosis after cholecystectomy, has been reported frequently in recent years, partly because the number of laparoscopic cholecystectomies is increasing due to the increasing prevalence of laparoscopic techniques. It has been reported that half of all cases of GBC resected today is IGBC.[24] The results of the AFC-GBC-2009 study by Fuks et al in 2011 reported that, for patients with T2 and T3 IGBC, re-resection with additional hepatectomy and lymph node dissection improved surgical outcomes, with a 5-year survival rate of 41% in patients with re-resection compared to 15% in patients who did not undergo re-resection.[25] The current expert consensus recommends re-resection within 4-8 weeks after index cholecystectomy for patients with T1b-3 IGBC[26,27]; however, there are still issues for which no consensus has been reached, such as the details of the re-resection, with or without bile duct resection, the extent of liver resection, and the indications for T1b.

3.1 | The epidemiology of IGBC

In 2019-2020, seven case-controlled studies (Table 1) and nine case-series studies were published on IGBC. In these studies, the frequency of IGBC was reported to be between 0.11% and 2.5%,[28–35] and Fujiwara et al reported that the incidence of IGBC in cholelithiasis was 0.054%, whereas in acute cholecystitis, the incidence was as high as 1.3%, with more advanced cases.[36] Figueiredo et al also reported that 49 (0.77%) of 6329 cholecystectomy cases had IGBC, and while 23 (0.38%) of 5931 were elective surgery cases, a higher rate of 26 (6.53%) of 398 were emergency surgery cases.[28] In recent years, EUS-guided gallbladder drainage (EUS-GBD) for acute cholecystitis has been performed in specialized centers, and the pooled proportion of perforations in a recent meta-analysis of EUS-GBD

TABLE 1 Case-control studies of IGBC published in 2-year period between 2019 and 2020

Publication	Year	Subject of the study	No. of patients	T stage	Descriptions
de Savornin Lohman et al[40]	2020	Re-resection Non re-resection	110 353	pT1b-T3	Median OS of patients without re-resection was 13.7, compared with 52.6 months in re-resected patients ($P < .001$). In patients who underwent re-resection, RD in the liver (HR 5.54; $P < .001$) and lymph nodes (HR 2.35; $P = .005$) were the only significant prognostic factors in multivariable analysis.
Figureiredo et al[28]	2020	Emergency cholecystectomy Elective cholecystectomy	398 5931	NA	IGBC was more frequent in emergency cholecystectomies (6.53%) compared to elective cholecystectomies (0.38%). The profile of patients with IGBC in both types of procedure was female, older than 60 years, and with histopathological diagnosis of adenocarcinoma.
Vega, et al[43]	2020	Open re-resection Lap re-resection	190 65	pT1-T3	Three-year survival rates for laparoscopic and open re-resection were 87% and 62%, respectively ($P = .502$). Independent predictors of worse OS were RD found at re-resection, blood loss of at least 500ml and at least four positive nodes. Laparoscopic re-resection for patients with IGBC is oncologically non-inferior to an open approach.
Kim et al[32]	2019	Simple cholecystectomy Extended cholecystectomy	27(T1a:13, T1b:14) 12(T1a:4, T1b:8)	pT1a, T1b	In T1b IGBC, extended cholecystectomy was not superior to simple cholecystectomy in terms of the 5-year DFS rate (72.5% vs 57.1%; $P = .332$). The 5-year OS rates were also similar in both groups (70.0% vs 100%, $P = .091$), even when lymphovascular invasion was identified after simple cholecystectomy.
Lundgren et al[34]	2019	Cholecystectomy alone Re-resection planned	128 121	pTis-T4	Re-resection of pT2 and pT3 IGBC was associated with improved survival (MST pT2 : 44.1 months vs 12.4 months, $P < .001$, pT3 : 23.0 months vs 9.7 months, $P = .001$) , but survival was impaired when residual disease was present.
Vega, et al[39]	2019	Non-IGBC IGBC with re-resection	45 151	pT2, T3	Patients with T2b IGBC and time interval between index cholecystectomy and oncologic extended resection > 60 days had a much lower 3-years DSS rate than patients with T2b non-IGBC (16% vs 85%; $P = .004$).
Vega, et al[44]	2019	Positive cystic duct margin (pCDM) Negative cystic duct margin (nCDM)	18 95	pT1-T3	Patients with a pCDM had a worse 5-year OS rate than those with a nCDM (49% vs78%; $P = .012$). Among patients with a pCDM, those who underwent BDR had a 5-year OS rate (75%) similar to that of patients with a nCDM (78%; $P = .964$), whereas those who did not undergo common BDR had a dismal 5-year DSS rate of only 26% $P = .034$.

Abbreviations: OS, overall survival; RD, residual disease; HR, hazard ratio; IGBC, incidental gallbladder cancer; DFS, disease-free survival; MST, median survival time; DSS, disease-specific survival; pCDM, positive cystic duct margin; nCDM, negative cystic duct margin.

was 3.7%-6.7%.[37,38] Therefore, EUS-GBD may not be performed in the above-mentioned high-risk cases of IGBC.

3.2 | The efficacy of re-resection for IGBC

Three case-control studies have been published on the importance of re-resection for IGBC, and Lundgren et al performed re-resection in 92 of 249 IGBC cases, and although there was no advantage of re-resection in T1b cases, in T2 cases the median survival time of patients with re-resection was reported to be 44.1 months, compared to 12.4 months for patients without re-resection ($P < .001$). The median survival time of T3 patients with re-resection was 23.0 months, which was significantly better than the 9.7 months of patients without re-resection ($P = .001$), which led us to conclude that re-resection is necessary for T2 and T3 IGBC.[11] Vega et al also compared

TABLE 2A Clinical short outcome of minimally invasive surgery for gallbladder cancer

Publication	Year	Operation	No. of patients	T stage	Duration of operation (min)	*P* value
Hamad et al[51]	2020	MIS (Robot or Lap) GBR ± RL Open GBR ± RL	873 1141	pT1b-T4	NA	
Vega et al[43]	2020	Lap S4b + S5 + RL Open S4b + S5/Open Major Hx + RL	65 190	pT1-T3	240* 240*	0.336
Navaro et al[54]	2020	Lap SC/Lap GBR + RL Open SC/Open GBR/Open S4b + S5 + RL	43‡ 43‡	pT2	139.0 211.1	0.001
Dou et al[48]	2020	Lap GBR/Lap S4b + S5/Lap Major Hx + RL Open GBR/Open S4b + S5/Open Major Hx + RL	32 31	pTis-T4	252.4 281.9	0.295
Byun et al[47]	2020	Robot GBR + RL Open GBR + RL	13‡ 39‡	NA	187.7 187.4	0.984
Goel et al[50]	2019	Robot GBR + RL Open GBR + RL	27‡ 70‡	pTi-T3	295* 200*	<0.001
Jang et al[52]	2019	Lap SC/Lap GBR + RL Open SC/Open GBR + RL	55 44	pT2	231.0 252.5	0.226
Feng et al[49]	2019	Lap SC/Lap GBR + RL Open GBR + RL	41 61	pTis-T3	137 168	0.058
Nag et al[53]	2019	Lap S4b + S5 + RL Open S4b + S5 + RL	30 38	NA	286 274	0.565

Abbreviations: MIS, minimally invasive surgery; Robot, robotic; Lap, laparoscopic; RL, regional lymphadenectomy; Hx, hepatectomy; GBR, gallbladder bed resection; SC, simple cholecystectomy; NA, not applicable.

*Median.

‡Propensity score matching.

151 IGBC patients with 45 non-IGBC patients and showed that re-resection in IGBC could achieve the same resection results as in non-IGBC by re-resection even in T3 patients.[39] On the other hand, de Savornin Lohman et al compared 110 patients with re-resection and 353 patients without re-resection of 463 IGBC patients, and they found that the median survival for patients with re-resection was 52.6 months, compared with 13.7 months for patients without re-resection. However, they noted that understaging of T stage and immortal time bias due to the lack of re-resection, especially in patients without re-resection, may lead to shorter survival estimates.[40]

3.3 | The efficacy of re-resection for T1b IGBC

As mentioned above, the efficacy of radical cholecystectomy for T1b GBC remains controversial, as does the importance of re-resection for pT1b IGBC with a diagnosis of pathological wall depth invasion after resection. There was only one case-control study for pT1b IGBC in the 2019-2020 literature. Kim et al compared SC and EC in T1b IGBC and found no advantage of EC. In this report, no lymph node metastasis was found. They also reported that the surgical outcome of patients with lymphatic invasion was poor, and EC in these patients did not improve the prognosis.[32] At present, no superiority of EC over SC has been shown in T1b GBC,[4,5] so that re-resection as an additional hepatic resection may not be necessary in T1b IGBC, but with regard to the need for RL, the reports of Vo et al and Wang et al suggest that re-resection with RL is necessary for T1b IGBC larger than 1 cm in diameter.[3,6]

3.4 | Prognostic factors after re-resection of IGBC

In terms of prognostic factors after re-resection of IGBC, many reports have described the presence or absence of residual disease (RD) in the resected liver and dissected lymph nodes.[34,40–43] Ramos et al reported a poor post-re-resection prognosis in the presence of RD, even if R0 resection could be achieved.[42] Vega et al evaluated the relationship between cystic duct margin status and RD at the time of index cholecystectomy and showed that patients with RD at the time of re-resection had a poor surgical outcome even after bile duct resection.[44] In addition, de Savornin Lohman et al reported that T3 or positive lymph node metastasis is a strong predictor of RD.[40] Cherkassky et al noted that systemic therapy, such as NAC, is necessary in addition to re-resection for patients at high risk of recurrence, such as those with positive lymph nodes, which has been widely accepted as a poor prognostic factor.[24]

Vega et al also compared 151 IGBC patients who underwent re-resection with 45 non-IGBC patients and found that there was no difference in surgical outcome for non-IGBC patients based on tumor location, but patients with tumor location on the liver side

Blood loss (ml)	*P* value	No. of retrived LNs	*P* value	Curative resection,%	*P* value	Morbidity rate, %	*P* value	Hospital stay, days	*P* value
NA		3* 3*	0.04	83.5 79.4	0.001	NA		2* 6*	<0.001
300* 200*	0.099	6* 6*	0.573	95.0 90.5	0.299	18.4 20.0	0.858	4* 6*	<0.001
71.6 208.1	0.004	6.1 11.9	0.004	93.0 95.3	1.000	4.6 11.6	0.050	NA	
267.2 502.6	0.007	7.5 8.2	0.412	100 96.7	0.492	12.5 16.1	0.732	11.0 14.4	0.028
209.2 311.9	0.079	7.2 7.8	0.650	NA		15.4 17.9	0.601	6.6 8.3	0.002
200* 600*	<0.001	10* 9*	0.408	100 95.7	0.558	3.7 21.4	0.035	4* 5*	0.046
225.1 310.5	0.163	7.6 9.9	0.095	NA		7.2 6.8	1.000	5.8 9.5	<0.001
358 368	0.732	5 5	0.973	80.5 77.0	0.679	7.3 9.8	0.933	5 11	<0.001
158 219	0.006	12 12	0.620	NA		NA		6.4 9.0	<0.001

(T2b) had a poorer surgical outcome than those with tumor location on the peritoneal side (T2a) in the IGBC patients (5-year survival: 31% vs 58%, $P = .03$). In particular, they reported a remarkably poor 5-year survival rate of 16% in patients with IGBC who underwent re-resection after 60 days or more from index cholecystectomy.[39] When EC is performed for T2b tumors with the appropriate preoperative diagnosis, the prognosis after resection is similar to that of T2a tumors. Therefore, preoperative diagnosis is very important, and immediate referral to a dedicated center is recommended in the absence of a hepatobiliary surgeon. Aggressive re-resection within 60 days of the index cholecystectomy is advocated for patients unfortunately diagnosed with T2b GBC on postoperative pathology.[39]

3.5 | Bile spillage in index cholecystectomy

In cases of GBC, bile spillage is considered an adverse event associated with peritoneal dissemination, port site, and incisional recurrences. Horkoff et al found bile spillage in index cholecystectomy in 55 of 82 IGBC patients, with a significantly higher rate of peritoneal dissemination in patients with bile spillage (24% vs 4%, $P = .028$). In addition, patients with bile spillage were less likely to undergo radical re-resection (25% vs 56%; $P = .013$), and they were less likely to achieve an R0 resection margin. In a Cox regression model, bile spillage was an independent predictor of shorter disease-free survival (hazard ratio [HR]: 1.99, 95% CI: 1.07-3.67).[30] Therefore, in IGBC, early participation of a hepatobiliary specialist is necessary when there is a high probability of GBC, because bile spillage during index cholecystectomy has a negative impact on the surgical outcome of the patient.

4 | MINIMALLY INVASIVE SURGERY FOR GBC

Minimally invasive surgery, such as laparoscopic surgery or robotic surgery, has been introduced in many gastrointestinal cancer fields. Problems such as cancer dissemination and inappropriate lymph node dissection, which were initially concerns, have been gradually resolved with the innovative development of instruments and laparoscopic surgical techniques. On the other hand, the introduction of minimally invasive surgery for GBC is still controversial. The reasons for this are the risk of cancer exposure, residual cancer, bile spillage, port site recurrence, and inaccurate lymph node dissection. With the maturation of laparoscopic surgery techniques for malignant diseases in other fields, these problems have gradually been overcome. In recent years, several studies have shown that the laparoscopic approach did not adversely affect the prognosis of GBC patients when postoperative pathological examination confirmed complete oncological resection.[45,46]

The difficulty in selecting the appropriate surgery is due to the difficulty of differentiating between benign and malignant tumors and to the difficulty of determining wall depth invasion by preoperative imaging. It has been reported that the combination of staging laparoscopy, laparoscopic ultrasonography, and intraoperative pathological diagnosis, in addition to being less invasive, allows for the selection of the most appropriate technique for the treatment of suspected gallbladder cancer, thus avoiding unnecessarily invasive procedures.[45,46] In 2019-2020, nine case-control studies,[43,47–54] two case-series studies,[5556] and one systematic review[57] were published on minimally invasive surgery for GBC. In a case-control study, there were six studies of laparoscopic surgery vs open surgery,[43,48,49,52–54] two studies of robotic surgery vs open surgery,[47,50] and one study of minimally invasive surgery (laparoscopic plus robotic) vs open surgery[51] (Table 2a).

In all studies, laparoscopic surgery for GBC was associated with improved short-term outcomes compared to open surgery, including reduced blood loss, faster oral diet recovery, and shorter hospital stay. Furthermore, there was no difference in morbidity and mortality rates, R0 resection rates, number of retrieved lymph nodes, 5-year recurrence-free survival, and 5-year overall survival between laparoscopic surgery and open surgery, and the safety and accuracy of the surgery were also reportedly assured (Table 2b).

4.1 | Laparoscopic surgery

Dou et al also performed S4bS5 resection and major hepatectomy for locally advanced GBC, such as T3 and T4, which showed reduced blood loss and shorter hospital stay compared to the open surgery group. They also reported good short- and long-term results, with no difference in the number of retrieved lymph nodes between the two groups.[48] Nag et al also performed laparoscopic S4bS5 resection in 30 GBC patients compared to 38 open S4bS5 patients and showed a reduction in blood loss and shorter hospital stay.[53] In a multicenter study by Vega et al, the operative time, blood loss, number of retrieved lymph nodes, surgical margin status, and postoperative complications of laparoscopic S4bS5 re-resection in patients with IGBC were comparable to those of open S4bS5, and the 5-year overall survival and 5-year recurrence-free survival were also comparable to those of open S4bS5.[43] It has been shown that, even in advanced cases of liver resection, the safety of laparoscopic surgery is comparable to that of open surgery, and the accuracy of lymph node dissection is comparable to that of open surgery. Minimally invasive laparoscopic surgery is particularly useful in cases of GBC, in which preoperative diagnosis is difficult to achieve because it provides both diagnosis and treatment. It is also possible to reduce the risk of bile spillage by performing a gallbladder bed wedge resection without grasping the gallbladder wall with forceps.

4.2 | Robotic surgery

Robotic surgery is expected to be useful in hepatobiliary surgery as well because of its multi-joint and anti-shake functions, which enable more delicate surgery. Byun et al performed robotic EC and RL in 13 patients with GBC and reported the usefulness of robotic

TABLE 2B Clinical long-term outcome of minimally invasive surgery for gallbladder cancer

Publication	Year	Operation	No. of patients	T stage	Overall survival, (%)	*P* value	Disease-free survival, (%)	*P* value
Vega et al[43]	2020	Lap S4b + S5 + RL Open S4b + S5/Open Major Hx + RL	65 190	pT1 - T3	5Y 74.0 5Y 54.3	0.502	5Y 76.0 5Y 63.3	0.038
Navaro et al[54]	2020	Lap SC/Lap GBR + RL Open SC/Open GBR/ Open S4b + S5 + RL	43 43	pT2	5Y 64.0 5Y 80.4	0.214	5Y 77.1 5Y 82.2	0.641
Dou et al[48]	2019	Lap GBR/Lap S4b + S5/Lap Major Hx + RL Open GBR/Open S4b + S5/Open Major Hx + RL	32 31	pTis-T4	1Y 72.9 1Y 47.8	0.086	NA	
Jang et al[52]	2019	Lap SC/Lap GBR + RL Open SC/Open GBR + RL	55 44	pT2	5Y 73.1 5Y 65.7	0.116	5Y 78.0 5Y 62.4	0.017
Feng et al[49]	2019	Lap SC/Lap GBR + RL Open GBR + RL	41 61	pTis - T3	5Y 51.9 5Y 55.7	0.453	NA	
Nag et al[53]	2019	Lap S4b + S5 + RL Open S4b + S5 + RL	30 38	NA	5Y 79 5Y 62	0.450	NA	

Abbreviations: Lap, laparoscopic; RL, regional lymphadenectomy; Hx, hepatectomy; GBR, gallbladder bed resection; SC, simple cholecystectomy; NA, not applicable.

surgery by comparing the surgical outcomes with those of 39 open surgery patients.[47] Goel et al also compared robotic surgery to open surgery for GBC and concluded that robotic surgery is safe and feasible.[50] Despite the growing demand for robotic-assisted surgery, there are still only a few reports, and the patients' long-term outcomes are unknown, so more cases are needed to evaluate its usefulness.

5 | CONCLUSION

Current trends in surgical treatment of GBC were reviewed. GBC is still a highly lethal and aggressive disease with a dismal prognosis in advanced stages and requires a multidisciplinary approach. On the other hand, minimally invasive surgery has been attempted for GBC that is localized and has a mild tendency to invade. There are many problems that need to be investigated further, including surgical indication for IGBC and T3/4 GBC, NAC and AC for borderline resectable GBC, and the safety and role of minimally invasive surgery for advanced GBC. Future research likely offers the best hope for improving the clinical outcomes of patients with GBC.

DISCLOSURE

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