



Narrative review of controversies in the surgical treatment of gallbladder cancer

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Abstract: Gallbladder cancer (GBC), the most common malignancy of biliary tract with a poor prognosis, is a tricky problem for surgeons. It tends to disseminate via lymphatic pathway in the early stage without any symptoms. The past decades have seen increasingly rapid advances in the field of improvement of surgical practices. Radical operation is the only way to obtain long-term survival in GBC. Negative surgical margin and pathological stage are two most significance factors to determine the survival time of patients with GBC. However, there are many controversies about the surgical treatment of GBC in different countries and regions. Majority evident stems from retrospective studies of variable quality contradict each other and could not reach an authoritative conclusion. More valuable researches should be carried out. Simple cholecystectomy (SC) is adequate for T1a tumors. Whether T1b patients require radical surgery remains a subject of debate. Current method of extensive hepatic resection has proven to be ineffective in advanced stage. Questions have been raised about the best optimal extent of hepatic resection range and lymphadenectomy of T2 and T3 subsequently. With the rapid development of minimally invasive technique, the debate about port-site recurrence has gained fresh prominence with many arguing that laparoscopic surgery is safe and accurate. Literature has emerged that offers contradictory findings about ideal time interval to re-operation in unexpected GBC. This article will focus on these problems and attempt to provide direction for future prospective research.

Keywords: Gallbladder cancer (GBC); radical cholecystectomy (RC); lymphadenectomy; hepatectomy; laparoscopic cholecystectomy (LC)

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Introduction

Gallbladder cancer (GBC), the most common malignant tumor of the biliary tract cancer, with an overall global incidence of 0.02–0.03% (1). There are significant differences in an incidence rate among different races and regions, especially in Chile and India. As the tumor is asymptomatic in the early stage and relatively late in the first diagnosis, less than one-fourth of patients received radical

surgery, which directly leads to the overall 5-year survival rate of GBC less than 5% (2,3). The main risk factors were cholelithiasis and chronic cholecystitis. Other risk factors included chronic bacterial infection, primary sclerosing cholangitis, and abnormal pancreaticobiliary junction (4). Long-term stimulation leads to a variety of gene changes, eventually leads to carcinogenesis (5,6). In recent years, a large number of literatures have shown that radical surgery is the only way to reach long-term survival,

Table 1 AJCC 8th edition TNM classification and suggestion management according to the NCCN guidelines

T/N/M category	Descriptions	Suggestion according to the NCCN
Tumor invasion	Depth of invasion	Surgery
Tis	Carcinoma <i>in situ</i>	Cholecystectomy
T1a	Lamina propria	Cholecystectomy
T1b	Muscular layer	[§] RC
T2a	Perimuscular connective tissue on the peritoneal side	RC
T2b	Perimuscular connective tissue on the hepatic side	RC
T3	Perforates the serosa/liver/adjacent organ	[§] En bloc resection
T4	Main portal vein/hepatic artery/≥2 extrahepatic organs	Palliative care or neoadjuvant chemotherapy
Lymph nodes	Lymph node number	Lymphadenectomy extent
N0	None	[®] Lymphadenectomy
N1	1–3	Lymphadenectomy
N2	≥4	Lymphadenectomy
Metastasis	Distant metastasis	
M0	No	As mentioned above
M1	Yes	Palliation

[§], RC involves gallbladder resection, lymph node dissection, wedge hepatectomy (the gallbladder bed), extrahepatic bile duct resection (positive margin exists in the cystic duct), and port-site resection (gallbladder rupture during LC in unexpected GBC); [§], *en bloc* resection involves RC, 4b+5 segmental hepatectomy, and complete excision of invaded organ; [®], lymph node dissection involves the porta hepatis, gastrohepatic ligament, and retroduodenal regions without routine resection of the bile duct if possible. AJCC, American Joint Committee on Cancer; NCCN, National Comprehensive Cancer Network; RC, radical cholecystectomy; LC, laparoscopic cholecystectomy; GBC, gallbladder cancer.

and negative margin and lymph node status are associated with long-term survival of GBC (7-9). With the American Joint Committee on Cancer (AJCC) TNM of GBC was updated to the 8th edition (*Table 1*) (10), the treatment of GBC is also constantly updated. In the 8th edition of AJCC Cancer Staging Manual, T2 was further divided into T2a and T2b. The literature shows that when the tumor is located on the liver side, it is more likely to cause lymph node, nerve and liver metastasis, resulting in worse prognosis compared with those on the peritoneal side tumor (11). The N category changed fundamentally, according to the number instead of the site. The location of lymph nodes does not show more value in prognostic gratification (8). It is not recommended extensive hepatectomy and lymph node dissection for those stage IV patients any longer. Although lacking of exact data support, experts generally support neoadjuvant chemotherapy for advanced gallbladder patients with jaundice. Neoadjuvant treatment based on gemcitabine and platinum chemotherapy may be a better

option for those patients (12). Radical *en bloc* resection remains the cornerstones of curative treatment in the progressive tumor. However, many controversies remain in the area of surgery. Currently, all the guidelines are based on researches in the last 20 years, disturbingly, majority of these were retrospective studies that always could not reach an authoritative conclusion in many points in the surgery treatment. Levels of these evidences were not strength enough to eliminate controversies. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/dmr-20-130>).

Method

A literature search of English language publications from 1995 to 2020 was used to identify data on surgery as the treatment for GBC. Databases were searched in PubMed. Terms used in the search were “gallbladder carcinoma

surgical treatment”, “hepatic resection AND gallbladder cancer”, “lymphadenectomy AND gallbladder carcinoma”, “port-site excision AND incidental gallbladder carcinoma”, “salvage radical cholecystectomy OR secondary radical cholecystectomy”. No randomized controlled trials were identified.

Discussion

Controversies of surgery in patients with T1 gallbladder carcinoma

It is well known that stage T1a gallbladder carcinoma is confined to the lamina propria of the mucosa and T1b invades the muscularis. T1 stage gallbladder carcinoma is difficult to diagnosed by imaging before operation since most lesions are small and asymptomatic, which are often detected by intraoperative or postoperative pathological examination. For patients with T1a, it is lucky that the lymph node metastasis rate was only 1.8%, cholecystectomy is adequate and safe (13-15). However, the lymph node metastasis rate of T1b could up to 10.9% (14). Many experts support radical surgery, which include lymphadenectomy or lymphadenectomy with wedge hepatectomy, instead of simple cholecystectomy (SC) for T1b patients (13,15-17). On the other hand, some authors hold the opinion that laparoscopic cholecystectomy (LC) is enough (18,19). As Downing *et al.* reported in a retrospective research, 462 patients with T1b GBC showed no adjusted survival difference by extent of surgical resection. But writers also acknowledged the original data listed only initial surgical treatment and believed a type II error was in play for T1b tumor (20). Part of scholars grasped neutral point of view and tried to further analyze data to tell the different between subgroups. Wang *et al.* using the Surveillance, Epidemiology, and End Results (SEER) database analyzed 277 T1b GBC patients, concluded that SC was adequate for treatment of T1b GBC diameter less than 1 cm (21). But these studies, limited by its retrospective nature, may be insufficient to examine the difference of surgical procedures on survival. At present, except the Japanese and Korean guidelines (22,23). Other guidelines including National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), Chinese and other national guidelines recommend lymphadenectomy and hepatic resection with or without bile duct excision for T1b GBC (9,24-27). Another larger SEER database study including 891 patients with T1b GBC explored prognosis

of underwent different surgical procedure. The overall survival (OS) of patients with radical cholecystectomy (RC) (101.7±9.3 months) were more than SC (71.3±4.4 months) ($P<0.05$), which supported RC to be the standard surgical procedure for T1b GBC (28). RC could remove the residual lesions in the liver and lymph nodes, reduce the recurrence rate and improve survival rate. However, majority of current studies are retrospective series (*Table 2*), the quality of the evidence is not strength enough to provide a convincing proposal. To settle the dispute, more randomized controlled trial is needed to determine whether RC could benefit T1b patients.

Controversies of Hepatic resection range of T2/T3

Hepatic resection for T2/T3 GBC has become a consensus if condition permit, which have been proven to improve patient survival (9). An important anatomic reason is that the serosa along the liver edge is absent and perimuscular connective tissue is densely adherence to the liver. But the resection scope of hepatectomy is controversial. According to the German S3 guideline, bisegmentectomy of liver segments 4b and 5 is recommended in the case of T2 or T3 (30). And the Chinese latest guidelines recommend wedge hepatectomy for T1b/T2a patients, wedge hepatectomy or segmentectomy 4b+5 can be used for T2b and a part of T3, and right hepatectomy is required for T3 tumor that involved gallbladder-bed with a size of more than 2 cm (27). However, a retrospective study involving 485 T2/3N0 GBC patients suggested that there is no significant difference in survival rate or recurrence rates among different hepatic resection groups (resection of the gallbladder bed/segmentectomy 4a+5/right hepatectomy) (31). Extensive hepatectomy for advanced disease does not appear to improve outcome, but increases complications and perioperative mortality (32). When the tumor invades the neck of gallbladder, the right portal pedicle may be involved, right hepatectomy is necessary. The ultimate goal of hepatectomy is to reach a negative margin under the microscope.

Controversy of lymphadenectomy extent

At present, there is no randomized controlled trials comparing the effectiveness of lymphadenectomy for this disease and the optimal range of lymph node dissection is still unclear. Most of the evidence comes from retrospective studies. With the development of T stage of gallbladder

Table 2 Summary of studies evaluating the surgical procedure of GBC

Author [year]	N	Patients	Intervention	Control	Outcome	Study type (quality of evidence)
Yuza [2020], (18)	47	T1b GBC	18 (38%) RC	29 (62%) SC	Ten-year OS rate 66% (SC) vs. 64% (RC) (P=0.618)	Retrospective cohort (low)
You [2008], (16)	52	T1a [27], T1b [25]	17 (32.7%) RC	6 (11.5%) C + L	T1b: no difference between two groups	Retrospective cohort (low)
Zhang [2017], (29)	25	T1b GBC	14 (56%) radical resections	11 (44%) SC	No difference between two groups	Retrospective cohort (low)
Wang [2019], (21)	277	T1b GBC (SEER data)	127 (45.8%) EC	150 (54.2%) SC	T1b <1 cm OS ES vs. OS (P=0.649); T1b ≥1 cm OS EC vs. SC (P=0.012)	Retrospective cohort (low-moderate)
Goetz [2014], (15)	84	T1b GBC	28 (33.3%) radical RR	56 (66.7%) SC	Five-year survival rates T1b: 75% (RR) vs. 34% (SC), P=0.01	Retrospective cohort (low)
Hari [2013], (17)	1,115	T1 GBC (SEER data)	RC	SC	Five-year survival rates T1: 79% (RC) vs. 50% (SC), P<0.01	Retrospective cohort (moderate)
Liu [2018], (28)	891	T1b GBC (SEER data)	98 (11%) RC; 231 (26%) C + L	562 (63.1%) SC	OS SC (71.3±4.4 months); C + L (87.6±5.8 months); RC (101.7±9.3 months); (P<0.05)	Retrospective cohort (moderate)
Downing [2011], (20)	2,495	T1s [279], T1 [683], T2 [1,533] GBC (SEER data)	EC	Simple cholecystectomy	T1b [HR, 1.51 (95% CI, 0.78–2.90), P=0.22]; T2 [HR, 0.64 (95% CI, 0.46–0.9), P=0.01]	Retrospective cohort (moderate)
Steffen [2020]	2,112	T1a [241], T1b [390], T2 [1,481] GBC (SEER data)	LNE	SC	T1a [HR, 1.80 (95% CI, 0.76–4.26), P=0.185]; T1b [HR, 0.95 (95% CI, 0.57–1.58), P=0.844]; T2 [HR, 0.68 (95% CI, 0.55–0.83), P<0.001]	Retrospective cohort (moderate)

GBC, gallbladder cancer; RC, radical cholecystectomy; SC, simple cholecystectomy; OS, overall survival; C + L, cholecystectomy + lymphadenectomy; SEER, Surveillance, Epidemiology, and End Results; EC, extended cholecystectomy; RR, re-resection; LNE, lymph node excision.

carcinoma, the incidence of lymph node metastasis gradually increased, T1, T2, T3 were 12%, 31%, 45% respectively (14,33). Lymph node dissection is proper to T1b and higher-stage tumors (34). When the tumor invaded the para-aortic, coeliac or superior mesenteric artery (SMA) lymph nodes, the patients died within 1 year, whether underwent surgery or not. Most researches believe that lymph node metastasis beyond the hepatoduodenal lymph nodes means poor prognosis, and radical surgery cannot remove all metastatic lymph nodes (35,36). However, the 5-year disease-specific survival rate was comparable between patients with nodal metastases to the hepatoduodenal ligament or common hepatic artery and those with

extending to the posterosuperior pancreatic head lymph nodes in a Japanese study (36% vs. 34%; P=0.950). They insisted that pancreaticoduodenal and common hepatic artery lymph nodes metastasis could also be removed (35,37). In order to obtain accurate staging, it is better to get at least six lymph nodes (38). The median number of lymph nodes harvested was only two (39). Conventional extrahepatic bile duct resection does not increase the output of lymph nodes, besides, the AFC-GBC-2009 Study Group producing a retrospective registry of operated GBC patients found that resection of the common bile duct (43%) was the only risk factor for morbidity in a univariate analysis (60% vs. 23%, P=0.0001) (40). Therefore, in order to obtain enough

lymph nodes, dissection beyond the immediate portal nodes is frequently required (9). Compared with the location of lymph nodes, the lymph node ratio could reflect the prognosis properly. An LN ratio of 0.15 is a better method of stratifying prognoses in N+ patient (7,41).

Controversy of laparoscopic surgery for GBC

For a long time, once patients were suspected of GBC, laparoscopy was not considered. Although some guidelines prohibit laparoscopic surgery for GBC, a laparoscopic approach for GBC has been controversial. However, a 10-year prospective cohort study for GBC (T2) confined to the serosa showed outcome achieved by laparoscopic surgery was similar to that by laparotomy (42). More retrospective studies have confirmed this result (43-45). Laparoscopic surgery is safe for early GBC. However, intraperitoneal metastasis would be occurred once broken the gallbladder during the LC because of artificial pneumoperitoneum. Based on these facts, it is better to referred to an experienced laparoscopic center. Laparoscopic surgery for T3 GBC is rarely reported and is still in the exploratory stage, some scholars argue that the T3 stage with only liver involvement was not a contraindication (46). The prognosis of GBC with acute cholecystitis is dismal (47), which might be related to intraoperative gallbladder emptying with bile spillage and cancer dissemination. These patients may have to avoid laparoscopic surgery (48).

Controversy of port-site excision

In the early literature, many cases of retroperitoneal or port site metastasis after laparoscopy were reported, which led to the prohibition of laparoscopy in GBC (49,50). However, looking back at the previous literature, there may be publication bias. Port site recurrence occurred in about 14% of patients and all of them died within 35 months (51). However, this is not a unique complication of laparoscopy, and there is a similar situation in open surgery, which may be related to biological characteristics of tumor (52). As for whether port site resection is necessary, a 15-year multicenter study in the United States gave the answer. Port site excision did not reduce recurrence or improve survival (53). Another national database research of France also approved that prophylactic resection did not reduce port site recurrence, but trigger development of incisional hernia in 8% (54). The concerns about port site or peritoneal metastasis have gradually subsidized with the development of laparoscopic

technology, the awareness of GBC and the using of plastic bags to remove specimens during operation (55). Routine port site excision is not recommended. But an except exists and it may be considered according to ESMO guidelines if gallbladder rupture occurs during operation (25).

Controversy of choice of timing for re-operation

Incidental GBC (IGB), accounts for 0.7% of LC surgery, is a headache for all surgeons. Unfortunately, 50–70% of GBC is found during or after LC (56,57). Patients with IGB tend to be relatively early stage, which have a better median survival (26.5 months) compared with non-incidental primary GBC (9.2 months). Once IGB happened, RC is often required except for Tis/T1a. During reoperation, about 23% of patients had distant metastasis and could not be performed. This may be due to the rapid progress of the tumor and the best opportunity for a second operation is missed (56). So far, there is no randomized controlled study to provide a strong evidence of ideal time interval for re-operation. In a cohort study, 207 IGB patients were divided into three groups according to the time interval to re-operation, which were less than 4 weeks, 4 to 8 weeks and more than 8 weeks, respectively. It was found that the prognosis of patients underwent surgery at an interval of 4–8 weeks was the best in the three groups (58). On the contrary, according to the result of Japanese research, there is no difference in the prognosis between patients who underwent surgery within 30 days and those who underwent an additional resection simultaneously (59). In this paper, the authors also believe that the weight of interval time on prognosis is limited (60). While these literature data is further analyzed, the relatively small number of patients included and the heterogeneity between groups may limit its ability to discover potential differences (61). The authors of this paper share pragmatic views that radical surgery should be performed after partial remission of postoperative inflammation (62). In Brazil's latest evidence-based IGB consensus, similar suggestions also support reoperation within 2–4 weeks as soon as possible (63). Of course, more prospective studies are needed to support this proposal.

Conclusions

Radical operation is still the only way to obtain long-term survival for GBC. It is a wise measure to adjust the operation by stages. However, there are still many controversies about the details of the operation, such as

the scope of hepatectomy, lymph node dissection, surgical approach, choice of timing for re-operation and so on. At present, most of the evidence comes from retrospective studies, and the quality of evidence is not high. More prospective studies are needed to address these problems.

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Footnote

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