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Review Article

Update on Surgical Management of Gallbladder Cancer

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ABSTRACT

Gallbladder cancer is the most common biliary tract malignancy and has poor 5-year survival. Incidental gallbladder cancers have good survival after cholecystectomy because most are diagnosed at an early stage. The latest The American Joint Committee on Cancer guideline (8th edition, 2017) has changes in the criteria for T and N staging, leading to new surgical approaches for gallbladder cancer. In the new guideline, negative resection margins with adequate clearance for regional lymph nodes is the main principle of curative treatment.

Keywords: gallbladder carcinoma; incidental gallbladder cancer; surgical management

INTRODUCTION

Gallbladder cancer (GBC) is the most common biliary tract malignancy with a variety of incidences reported worldwide[1,2]. It is a relatively rare adenocarcinoma but ranks fifth to sixth among gastrointestinal cancers[3,4]. The major risk factors for gallbladder cancer are chronic cholecystitis, gallbladder polyps and porcelain gallbladder. The poor overall outcome of gallbladder carcinoma is caused by delays in diagnosis and treatment arising from non-specific and silent symptoms, with retrospective reviews reporting that 80% of gallbladder cancers have already spread to the lymph nodes when diagnosed. Most GBC patients are female and the median survival for stage IV cancer is 4-6 months[5-7]. The overall 5-year survival rate is less than 5%, and until the latest guidelines update, complete surgical resection was the main curative treatment for early stage gallbladder cancer, which can significantly prolong survival outcomes[8-13].

The recently updated edition of the American Joint Committee on Cancer (AJCC) staging (8th edition, 2017) has revised the criteria for the tumor (T) and lymph nodal (N) categories for staging gallbladder cancer. This version reports differences in overall survival based on the location of the tumor and number of metastasized lymph nodes[14]. The recommendations for surgical management of gallbladder cancer have also been revised, especially for management of T2 lesions. This review focuses on the surgical management of gallbladder cancer using the new TMN staging criteria.

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Important anatomy

The gallbladder (GB), part of the biliary system, is attached to the liver segments IVb and V. The gallbladder surface can be divided into 2 parts, the hepatic side without peritoneal lining and the peritoneal side (covered by the visceral peritoneum). Most of the venous drainage from the GB returns to the cystic vein and drains into the right portal vein, while the small venous drainage is directly into the liver parenchyma. The gallbladder wall consists of the mucosa, lamina propria, muscular layer, peri-muscular connective tissue, and serosa (visceral peritoneum). Because of the lack of a submucosal layer, cancer cells can easily penetrate through the gallbladder wall, resulting in liver invasion or lymph node metastasis[15].

Updated staging

The 8th edition of the AJCC came into an official use on January 1, 2018 (Table 1). This version differentiates T2 lesions into 2 groups, T2a for tumors on the peritoneal side and T2b for tumors on the hepatic side, and re-defines the N category by the number of metastatic lymph nodes to N0 (no metastasis), N1 (1-3 metastatic nodes), and N2 (more than 3 metastatic nodes), instead of the anatomical lymph node locations as in the previous version (Figure 1).

Surgical management

Based on the AJCC Staging of Gallbladder Cancer 8th edition, the plan of surgical management for gallbladder cancer can be decided by T staging.

Gallbladder cancer diagnosed before definitive operation

T1a: Limited invasion of the tumor to the lamina propria, with very low chance of lymph node metastasis. Many guidelines such as those of the American Joint Committee on Cancer, the American Hepato-Pancreato-Biliary Association (AHPBA), or the National Comprehensive Cancer Network (NCCN) agree that a simple cholecystectomy with removal of the cystic plate without lymph node dissection is sufficient for curative treatment of T1a gallbladder carcinomas. The long term survival after such a cholecystectomy is 73-100[16-20].

T1b: The tumor has invaded the muscular layer. The T1b lesion has a greater chance of lymphatic metastasis than the T1a lesion, at 15% and 2.5%, respectively[16,18,20-23]. The NCCN guidelines recommend a radical cholecystectomy for these lesions, including *en bloc* liver resection with regional lymphadenectomy (RL) for T1b or greater GBCs[24].

There are many retrospective studies which have provided evidence supporting the use of radical cholecystectomy with regional lymphadenectomy in T1b GBC. For example, a review of 464 patients from 2004 to 2014, diagnosed with gallbladder cancer in the National Cancer Database found that 46.7% of the T1b patients underwent extended cholecystectomy with RL and around 15% of this group had lymph node metastasis, but there was no lymph node involvement in tumors less than 1 cm[25,26]. Another retrospective study reported that the extended cholecystectomy group had a better 5-year survival than the simple cholecystectomy group (87.5% vs 61.3%, respectively), and also better life-expectancy, 6.42 vs 9.85 years, respectively[27]. Other studies have reported that regional lymphadenectomy in T1b lesions showed better overall survival than patients without regional lymphadenectomy[24-26]. Recent retrospective studies did not support the principle of radical cholecystectomy in T1b lesions because they found no significant differences in long-term outcomes between extended cholecystectomy and simple cholecystectomy[28,29].

Based on our review, we recommend a simple cholecystectomy should only be done in T1b <1 cm with negative malignancy in the cystic duct lymph node. Otherwise, a formal extended cholecystectomy with regional lymphadenectomy should be done.

T2: In this type of cancer, the tumor invades the peri-muscular connective tissue, and has a high incidence

Table 1 The American Joint Committee on Cancer (AJCC) staging, comparing between the 7th and 8th editions

	7th edition AJCC	8th edition AJCC
T category		
Tis	Carcinoma in situ	Carcinoma in situ
T1a	Limited to the lamina propria	Limited to the lamina propria
T1b	Invades the muscle layer	Invades the muscle layer
T2	Invades the peri-muscular connective tissue	Invades the peri-muscular connective tissue
T2a	-	Invades the peri-muscular connective tissue on the peritoneal side
T2b	-	Invades the peri-muscular connective tissue on the hepatic side
T3	Perforates the serosa and/or directly invades the liver and/or other adjacent organs or structures (stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts)	
T4	Invades the main portal vein or hepatic artery or two or more extrahepatic organs or structures	
N category		
N0	No regional metastasis	No regional metastasis
N1	Metastasis to the nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein	Metastasis in 1-3 regional lymph nodes
N2	Metastasis to the periaortic, pericaval, superior mesentery artery, and/or celiac artery lymph nodes	Metastasis in 4 or more regional lymph nodes
M category		
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis
Stage group		
0	TisN0M0	TisN0M0
I	T1N0M0	T1N0M0
II	T2N0M0	T2N0M0
IIA	-	T2aN0M0
IIB	-	T2bN0M0
IIIA	T3N0M0	T3N0M0
IIIB	T1N1M0, T2N1M0, T3N1M0	T1N1M0, T2N1M0, T3N1M0
IVA	T4N0M0, T4N1M0	T4N0M0, T4N1M0
IVB	Any T, N2M0 Any T, Any N, M1	Any T, N2M0 Any T, Any N, M1

AJCC = The American Joint Committee on Cancer; T = primary tumor extent; N = lymph node status; M = metastatic status

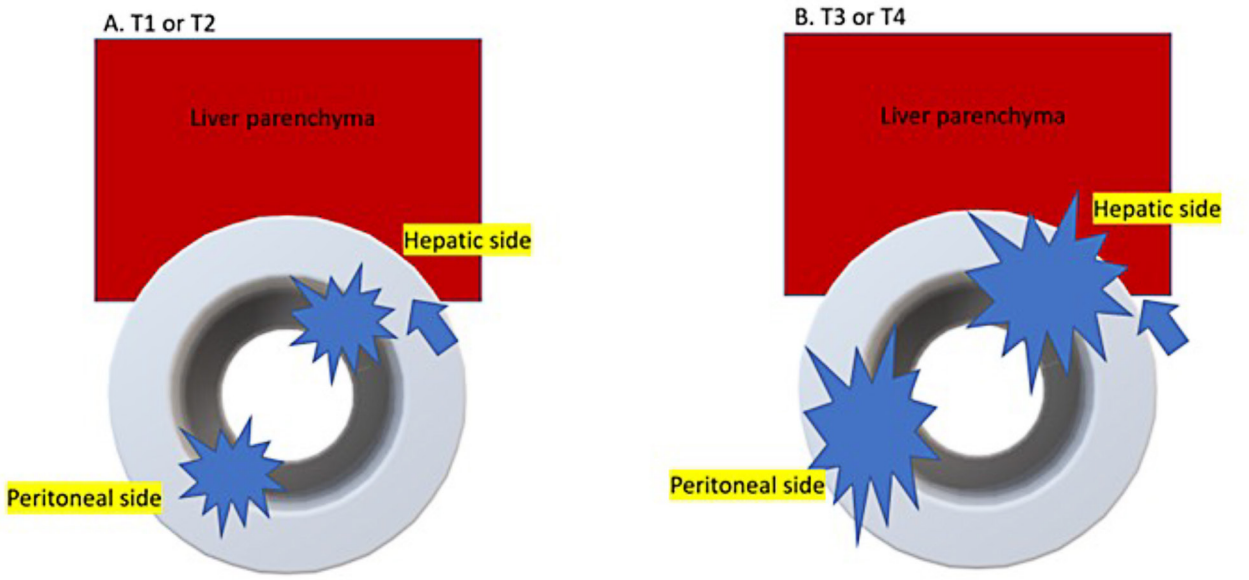

Figure 1 Pattern of gallbladder cancer infiltration. A. For T1–2 lesions: A peritoneal side tumor is defined as a tumor located only on the serosal side of the gallbladder, and a hepatic side tumor is defined as a tumor invading the liver part of the gallbladder (arrow). B. For T3–T4 lesions: A peritoneal side tumor is defined as a tumor which has spread through the gallbladder wall but not involving the liver parenchyma and a hepatic side tumor is defined as a tumor at the peritoneal side of the gallbladder invading the hepatic parenchyma (arrow)

of lymph node metastasis. All guidelines recommend extended cholecystectomy with regional lymphadenectomy for T2 GBC.

The latest AJCC guideline separates T2 GBC into 2 groups, T2a on the peritoneal side and T2b on the hepatic side, based on the prognostic data. The T2b lesion has significantly higher rates of vascular invasion, neural invasion, and nodal metastasis than the T2a (51% vs 19%, 33% vs 8%, and 40% vs 17%, respectively). One study reported that the predicted recurrence rates in the liver after radical resection and distant lymph nodes metastasis were 23% vs 3% and 16% vs 3%, respectively[30]. In another study the 5-year survival rate of T2a was 64.7% compared to T2b which was 42.6%, P=0.0006[31]. In the same study, the 5-year disease-free survival rate was 73.0% in extended cholecystectomy and 61.5% in simple cholecystectomy, and there were significant differences in subgroup analysis both in T2a (76.5% vs 66.1%) and T2b (68.2% vs 56.2%) lesions. Other studies found that the recurrence rates were significantly higher in T2b cancers than in T2a cancers (31.0% vs 24.6%), but were not significantly different in the 5-year disease-free survival rates of patients who underwent wedge liver bed resection compared to segment IVb/V resection[32,33]. In another study, the overall survival rate after resection of T2b cancers was significantly worse than in T2a cancers because of a significantly higher rate of lymph node metastasis, 46% vs 20%[34]. Another study reported that the most common lymph node metastasis in T2a was a para-aortic lymph node, but in T2b were the para-aortic lymph nodes and intra-hepatic metastasis[35].

Based on our review, we recommend radical cholecystectomy with regional lymphadenectomy for all T2 GBC, and adequate liver bed resection for T2a lesions and segment IVb/V resection for T2b GBC.

T3/T4: This tumor invades beyond the gallbladder wall. All guidelines recommend radical cholecystectomy with regional lymphadenectomy for T3/T4 GBC, but resections of aggressive organs such as an extended right hemi-hepatectomy, hepato-pancreatoduodenectomy (HPD), or vascular reconstruction are still controversial as the prognosis after surgery is very poor.

The aim of *en bloc* surgery is an R0 resection with negative margins. Some surgeons do an aggressive procedure to improve overall survival, but the survival outcome is related to tumor biology and stage rather than the extent of resection. Retrospective studies have reported that locally advanced GBC patients who underwent major hepatectomy and bile duct excision had significantly worse median and 5-year survival than patients without *en bloc* resection (22 vs 40 months and 20% vs 43%, respectively[36,37]. The result of aggressive organ resection is significantly worse than simple *en bloc* resection because the primary tumor is more locally advanced. One study reported that the overall survival of T3/T4 GBC patients who underwent major hepatectomy alone was significantly longer than in HPD (median survival times 32 vs 10 months)[38]. HPD is appropriate when necessary to clear disease but is not advised in all cases[38]. The T4 GBC has less benefit from lymph node dissection[39]. In another study the overall survival of patients who had CA19-9 more than 250 U/ml and underwent either major hepatectomy or PD had similar outcomes to the unresectable group[40]. The poor prognostic factors of T3/T4 GBD are liver invasion ≥5 mm, invasion of the left margin or the entire area of the hepatoduodenal ligament, and ≥4 regional lymph node metastases. Another study found that the 5-year survival rates were 5.87% and 0% in patients who had two and three of the risk factors, respectively[41]. The GBC recurrence risk (GBRR) score is used to predict early recurrence within 12 months after resection of GBC. This score is available online at https://ktsahara.shinyapps.io/GBC_earlyrec/[42].

Based on our review, we recommend radical *en bloc* surgery (including major hepatectomy or bile duct excision) with regional lymphadenectomy for R0 resection in T3/T4 GBC. HPD with aggressive lymphadenectomy should be reserved for experienced hepato-pancreatic-biliary (HPB) surgeons.

Lymph node dissection

Lymph node status is the most important prognostic and predictive factor for GBC. Positive lymph node metastasis is associated with T stage (T2 16%, T3 42%, T4 79%), leading to adjuvant chemotherapy, and worse long-term survival[43]. All guidelines recommend portal lymph node dissection of ≥6 nodes for accurate staging in T1b or greater GBC[44]. The extension of regional (portal) lymphadenectomy includes the first-echelon nodes (cystic duct or pericholedochal nodes) and second-echelon nodes (posterosuperior to the head of the pancreas and around the portal vein/hepatic arteries). Some surgeons routinely biopsy 16b1 lymph nodes in locally advanced GBC to prevent non-curative surgery and morbidity associated with radical resection, especially in patients with jaundice and high preoperative CA 19-9 levels[45].

Gallbladder cancer diagnosed intra-operatively during a cholecystectomy

The widespread use of laparoscopic cholecystectomy has led to an increased number of incidentally found gallbladder carcinomas. The management of intraoperatively suspected GBC is unsettled. The NCCN guideline version 5, 2021 recommends intraoperative staging and sending the gallbladder for frozen section. If a frozen pathology examination cannot be done and post-operative diagnosis is required, the incidental gallbladder cancer (IGBC) guidelines below are used.

Intra-operative decision making depends on the individual surgeon's experience and skill. A well-experienced HPB surgeon may go on to complete the

cholecystectomy or biopsy the tumor for frozen pathology. If positive for malignancy, an extended cholecystectomy with lymphadenectomy should be performed. For a less-experienced surgeon, the operation should be terminated without cholecystectomy and referral to a high-volume center is recommended. One study reported that immediate conversion to open surgery or delayed radical surgery by an experienced surgeon had no significant differences in overall survival rates[46].

Gallbladder cancer diagnosed post-operative cholecystectomy (IGBC)

Incidental gallbladder cancer (IGBC) is a malignancy identified in a gallbladder specimen after a cholecystectomy[11]. Half of gallbladder cancers are IGBCs, and one study reported that 6.53% were found during an emergency cholecystectomy[47].

T1a: A simple cholecystectomy with removal of the cystic plate without lymph node dissection is the curative treatment for T1a gallbladder carcinoma.

T1b or greater: There are various resection options in T1b GBC. The authors recommend a simple cholecystectomy in T1b lesions less than 1 cm with negative malignancy in a cystic duct lymph node. Otherwise, a formal extended cholecystectomy with regional lymphadenectomy should be done.

A simple cholecystectomy may be recommended as curative surgical management for T1b GBC. Retrospective studies with small numbers of patients found no significant differences in the 5-year disease free survival and overall survival rates between simple and extended cholecystectomies[48,49].

All guidelines recommend re-resection for T2 or greater GBC because of the high incidence rate of residual disease and lymph node metastasis. Some studies have reported that an extended cholecystectomy with hepatectomy and portal lymph node dissection had significantly better 5-year survival rates (41% vs 15%) and overall survival when compared to non-re-resection[50-52]. Some studies recommend a re-resection within 4-8 weeks after a primary surgery[53,54]. One study reported that the overall survival was poor with the presence of residual tumor or positive cystic duct margin[55].

Laparoscopic surgery

In the past, laparoscopic surgery for GBC was controversial due to the high risk of cancer exposure, residual tumor, bile spillage, port site recurrence or inadequate harvesting of lymph nodes. Nowadays, however, laparoscopic surgery is widely accepted for standard surgical treatment in GBC with confirmed good oncological outcomes[56,57].

A recent systematic review and meta-analysis reported that the short term outcomes in laparoscopic surgery were better than in open surgery in T2 GBC[58]. Other studies have reported that the benefits of laparoscopic surgery over open surgery were reduced blood loss, early oral diet, decreased length of hospital stay, and improved short term survival, but there were no differences in morbidity and mortality rates, R0 resection rates, number of harvested lymph nodes, 5-year recurrence-free survival, and 5-year overall survival[59-64].

Robotic-assisted laparoscopic extended cholecystectomy and lymphadenectomy is the newest technology for surgical management of GBC. Recent retrospective studies have shown that robotic radical cholecystectomy is feasible and safe, with short-term results comparable with open radical cholecystectomy[65,66].

Port site resection

The incidence of peritoneal metastasis at a port site was reported in one study to be less than 20% in laparoscopic cholecystectomy[67]. One study reported that routine port site resection did not improve survival or significantly reduce recurrence[68].

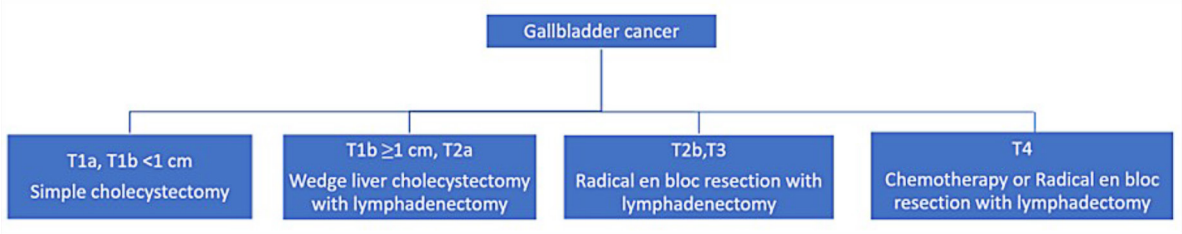

Figure 2 Surgical management of gallbladder cancer. The surgical procedure is decided by the tumor biology. For T1a and T1b tumors <1 cm, a simple cholecystectomy is recommended. For T1b ≥1 cm or T2a tumors, an extended cholecystectomy (wedge liver at gallbladder bed and portal lymphadenectomy) should be performed. For T2b or T3 tumors, a radical en bloc cholecystectomy (resection of liver IVb/V or with nearby organ invasion and portal lymphadenectomy) should be performed by an experienced HPB surgeon. For T4 tumors, an extensive radical en bloc resection (major hepatectomy, bile duct resection, HPD, or major vascular resection with lymphadenectomy) in selected cases performed by an experienced HPB surgeon is recommended. For patients at high risk from surgery, chemotherapy is recommended

CONCLUSION

Gallbladder cancer is a rare tumor with poor overall survival. Surgery is the main curative treatment for GBC (Figure 2). The goal of surgery is a total removal of the tumor with negative margins, and adequate regional lymph nodes dissection for accurate staging. Laparoscopic surgery is safe and overall survival is comparable with open surgery.

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