Review

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Improvement in the diagnosis and treatment of T2 gallbladder carcinoma is pivotal to improvement in the overall prognosis for this disease

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Summary **Since the American Joint Committee on Cancer (AJCC) subdivided the T2 stage of gallbladder carcinoma (GBC) into T2a and T2b, the diagnosis and treatment of those stages have been a subject of heated discussion and controversy. T2 is a stage of GBC that might be treatable. Based on the extent of lymph node metastasis and distant metastasis, T2 GBC can be classified into various pathological stages such as IIA, IIB, IIIB, and IVB, leading to controversy in clinical settings. This review aims to discuss the effectiveness of and controversies concerning S4b+5 resection, the acceptable extent of lymph node dissection, the timing for treatment of incidental gallbladder cancer, and adjuvant therapy. This review also aims to suggest directions for and recommendations regarding clinical research in the future.**

Keywords: Gallbladder carcinoma, adjuvant therapy, chemotherapy, radiotherapy

1. Introduction

Stage T2 gallbladder carcinoma (GBC) is defined as cancer invading the connective tissue around the muscular layer without invasion of the serosa or liver. The TNM staging criteria for GBC (8th edition) of the American Joint Committee on Cancer (AJCC), which was issued on January 1, 2018, subdivided the original T2 stage in the 7th edition into T2a and T2b. T2a is cancer invading the peritoneal side of the gallbladder without invading the serosa while T2b is cancer invading the hepatic side of the gallbladder without invading the liver (*1*). This change is based on the fact that the location of a lesion may have a significant impact on the treatment regimen and patient outcome. In China, the most updated guidelines for GBC are the "Guidelines for Diagnosis and Treatment of Gallbladder Carcinoma" developed by the Group of Biliary Surgery of the Chinese Society of Surgery in 2015, but those guidelines did not mention the impact of the location of cancer on the treatment strategy and patient prognosis (*2*). T2 GBC is a highly unique entity. Based on the extent of lymph node metastasis and distant metastasis, T2 GBC can be classified into various pathological stages such as IIA, IIB, IIIB, and IVB, leading to controversy in clinical settings. For example, when is S4b+5 segmental hepatectomy needed? What is the acceptable extent of lymph node dissection? What is the timing for treatment of incidental GBC? What form of postoperative adjuvant therapy should be used? The data reported in the literature regarding the rate of lymph node metastasis and patient prognosis also vary substantially. While referring to the AJCC's redefinition of T2 GBC, this review will discuss topics that are the subject of heated discussion and controversy. This review will also suggest directions for and recommendations regarding clinical research in the future.

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2. The necessity of S4b+5 liver resection

2.1. *Surgical anatomical basis for S4b+5 segmental hepatectomy*

The 2015 guidelines refer to a study by Goetze *et al*.

(*3*) which found that the extent of cystic vein drainage from T2 GBC into the liver was about 2 to 5 cm from the gallbladder bed and was > 4 cm in at least one direction. Wedge resection alone does not guarantee an R0 resection, so an S4b+5 resection is considered essential.

2.2. *Current status of S4b+5 resection*

According to a statistical study by Sternby *et al*. (*4*) of 44 articles published between April 2015 and June 2016, S4b+5 segmental hepatectomy improved the prognosis for T2 GBC. However, Sternby *et al*. contended that those studies constituted a low level of evidence because they involved a limited number of cases, they were exclusively retrospective observational studies and case reports, and they did not discuss the impact that lesions on the peritoneal or hepatic side of the gallbladder had on prognosis. In March 2017, Kawahara *et al*. (*5*) published a retrospective study of 22 patients who underwent surgery for T2 GBC. The authors performed different surgical procedures based on the location of the lesion: full-thickness cholecystectomy (FC) + local lymph node dissection if a lesion of the gallbladder fundus or corpus is on the peritoneal side of the gallbladder (P-type) [author's note: this is T2a] ; gallbladder bed resection (GBR) + local lymph node dissection if the lesion is on the hepatic side of the gallbladder (H type) [author's note: this is T2b]; GBR + extrahepatic bile duct resection + local lymph node dissection if the lesion is on the cystic duct (N type). Of 7 patients with the P Type, only one developed bile duct recurrence 5 years after surgery. Of 6 patients with the H Type, one developed bile duct recurrence and another developed lymph node metastasis, but no patients developed liver metastasis; of 9 patients with the N type, 1 developed bile duct recurrence, 1 developed lymph node metastasis, and 2 developed liver metastasis. The 3-year survival rate was 50% for patients with the P Type, 100% for patients with the H Type, and 75% for patients with the N Type compared to patients undergoing S4b+5 liver resection during the same period. Therefore, the authors concluded that FC or GBR could be performed for T2 GBC involving the fundus or corpus of the gallbladder. However, the biggest limitation of that study was the number of cases it included. In 2017, a study with a larger sample size was reported (*6*). That study involved 6 centers (including 93 patients with T2b GBC and 99 patients with T2a), and it found that S4b+5 resection significantly improved the 5-year survival rate (80.3% *vs*. 30.0%, $p = 0.032$) for T2b GBC. However, hepatic resection was not associated with prognosis (70.5% *vs*. 54.8%, $p = 0.111$) for T2a. A couple of recent studies have reached similar conclusions (*7-9*), but none of them used T2 GBC located in the neck of the gallbladder as a single arm as the study by Kawahara *et al*. did. In addition, a cohort study of 232 patients with T2 GBC from 2002 to 2012 by the Ontario Cancer Registry in Canada indicated that S4b+5 resection did improve 5-year survival, but the prognosis still remained poor once vessels and lymph ducts were involved (*10*).

2.3. *Discussion*

According to most of the large studies cited here, S4b+5 resection improves the prognosis for T2b GBC without liver metastasis. However, there is no strong evidence to support hepatectomy as a way to improve outcomes once liver metastasis has occurred, even if it is S4b or S5 "local metastasis" (M1).

Therefore, the following issues are crucial in clinical practice:

i) Preoperative assessment. ① Preoperative diagnosis and staging: to date, the most commonly used technique for preoperative evaluation of GBC is enhanced CT, which has a diagnostic accuracy of 84-92%, a sensitivity of 73-87%, and a specificity of 88-100%; its sensitivity and accuracy in T2 GBC staging are 73% and 80%, respectively (*11-12*). In 2014, Bang *et al*. (*13*) found that high-resolution ultrasound and MRCP may have a higher sensitivity and accuracy than MDCT in the diagnosis of T2 GBC and the differential diagnosis of T2 GBC and gallbladder gland adenoma. A point worth noting is that the definitive diagnosis of T2 GBC among clinicians is only 33.9%, which differs highly from the rate of definitive diagnosis using imaging (*8*). ② Characterization of the distribution of the cystic veins and involvement of those structures: once the subserosa is invaded, theoretically there is a risk of metastasis through lymph nodes, vessels, or nerve plexus. Metastasis through a cystic vein is the primary method of hematogenous metastasis and liver metastasis. According to anatomical studies, there are two models of drainage of the cystic veins: the first type is from the fundus and corpus of the gallbladder through the liver bed, before merging into branches of the portal vein in S4b, S5 (primary) and S1, S6, and S8 (secondary). This constitutes the anatomical rationale for S4b+5 resection; the second type is the cystic duct draining into the main trunk of the portal vein and somewhere around left and right bifurcation through the triangle of Calot. Alternatively, it may drain, alongside the peribiliary vein, into the portal vein supplying the anterior right lobe of the liver or intra-haptic branches of the portal vein in S4 and S1. In conclusion, the cystic veins will completely and eventually drain into the portal vein system. However, it may drain into different part of the portal vein in the liver. This may explain the potential cause of recurrence or metastasis in other liver segments even after S4b+5 resection (*14*). Therefore, preoperative and intraoperative determination of the pattern of cystic vein drainage and the relationship between the lesion and adjacent veins as well as

venous involvement may be helpful in predicting the risk of metastasis and deciding a surgical strategy. In this regard, preoperative hepatic CT angiography, superior mesenteric vein venography CT (CTAP), and intraoperative fluorescein angiography of the cystic artery with indocyanine green (ICG) may provide certain corroboration. A study using ICG has found that about 2/3 of the cystic veins eventually drain into S4 and S5 (*15*).

ii) Intraoperative evaluation. ① Intraoperative exploration of the liver: Once preoperative imaging has excluded liver metastasis, the liver is often not carefully explored during cholecystectomy, and especially during laparoscopic cholecystectomy. Thus, the risk of micro-metastases of the liver may exist. Like treating liver metastasis of colon cancer (*16*), intraoperative ultrasound should be used in radical resection for GBC to carefully scan the entire liver, and especially high-risk areas such as S4 and S5. This technique may detect micro-metastatic lesions smaller than 0.5 cm missed before surgery. It is extremely important in terms of assessing the procedure and predicting patient outcome. ② Examination of frozen sections: During cholecystectomy, and especially in the case of incidental gallbladder cancer, frozen sections are usually used to make a "qualitative diagnosis" of the lesion intraoperatively. A gross or microscopic exam tends to ignore the distribution of features of veins and lymphatic ducts, tissue layers infiltrated by a lesion, and most importantly involvement of vessels and nerves in the gallbladder wall adjacent to the lesion.

2.4. *Recommendations*

i) An S4b+5 liver resection may help to improve the prognosis for T2b GBC, but its long-term effects on T2 cystic duct lesions still need to be studied;

ii) Before surgery for GBC or diseases involving thickening of the gallbladder wall, an accurate differential diagnosis and imaging staging should be performed to the extent possible to reduce the incidence of incidental T2 gallbladder cancer;

iii) Before and during surgery, drainage of the cystic veins into the liver and tumor invasion of the vessel should be thoroughly understood;

iv) The liver should be carefully explored with ultrasound during surgery to avoid overlooking micro-metastases;

v) Frozen sections should be used intraoperatively to determine the exact location of a lesion in gross specimens, the layout of the cystic veins, the extent of invasion by the tumor according to microscopy, and invasion of vessels/nerves in the gallbladder wall around the lesion;

iv) Segmental hepatectomy should be performed for GBC preoperatively staged as T2a based on careful pre/intra-operative evaluation in steps 2 to 5.

3. Determination of the extent of lymphatic dissection

3.1. *Anatomical basis for lymph node dissection in stage T2 GBC*

Based on pathology, 60% of the patients with T2 GBC are ultimately diagnosed with lymph node metastasis. There are two layers of lymphatic vessels in the gallbladder wall located in the subserosa, mucosa, and muscular layer. The lymphatic metastasis of GBC starts in the gallbladder and pericholecystic lymph nodes located in the triangle of Calot. The lymphatic drainage pathway is mainly: *i*) from cystic and choledochal lymph nodes through hepatic artery and portal vein lymph nodes to the abdominal aorta and inferior vena cava lymph nodes; *ii*) from cystic and hepatoduodenal ligament lymph nodes to the pancreatic head and portal vein lymph nodes; and *iii*) from portal vein lymph nodes to the superior mesenteric vein lymph nodes. In the 7th edition of the AJCC's staging criteria, N1 is defined as metastasis in the lymph nodes of the cystic duct, common bile duct, and hepatoduodenal ligament; N2 is defined as metastasis in the post-pancreatic duodenum lymph nodes, lymph nodes around abdominal arteries, superior mesenteric lymph nodes, para-aortic lymph nodes, and para-inferior vein cava lymph nodes. The 5-year survival rate for T2N0M0(II) is 55.56%, that for T2N1M0(IIIB) is 13.89%, and that for T2N2M0(IVB) is 11.11%, while N2 lymph node involvement is equivalent to distant metastasis (M1). Thus, N2 dissection does not improve prognosis (*17-18*). In the 8th edition of the staging criteria, the number of metastatic lymph nodes is the basis for staging. At least 6 lymph nodes should be sampled, with ≥ 4 positive lymph nodes indicating the N2 stage. This change is mainly based on recognition of the fact that the number of metastatic lymph nodes, instead of affected sites, is a key factor affecting prognosis. However, this is just Level III evidence, which means that there are obvious flaws in the design of the relevant studies and their subject enrollment (*19-20*).

3.2. *Current status of lymph node dissection*

Classifications of the extent of lymph node dissection in the West and Japan differ significantly. The classification of the Japanese Society of Hepatobiliary and Pancreatic Surgery is more detailed than the classification of the AJCC. The former includes: D1: bile duct and cystic duct lymph nodes; D2: common hepatic artery lymph nodes anterior and posterior to the hepatic hilum, superior and inferior to the proper hepatic artery, and superior and posterior to the portal vein and pancreatic head; D3: lymph nodes beyond the range of D1 and D2, including lymph nodes of the abdominal cavity and around the aorta. A retrospective study of lymph node dissection pursuant to this classification indicated that: *i*) The extent

of lymph node dissection had no effect on the prognosis for T2 GBC (T2N0M0) confirmed by postoperative pathology and without lymph node metastasis; this finding is consistent with the thinking of the AJCC; *ii*) D2 and even D3 dissection had more of an effect on the 5-year survival rate according to the Japanese Society of Hepatobiliary and Pancreatic Surgery (66.7%) in comparison to that in Europe and the US (53.8%) (*9*). Two notable issues are: *i*) There is little quality literature on how the location and number of lymph node metastases affect prognosis in D2 and D3 dissection (similar to N2 dissection in the 7th edition of the AJCC's staging criteria). Only one study analyzed pathological data from 9 cases of postoperative lymph node metastasis in patients with a long-term survival longer than 5 years after D2 or D3 dissection (*18*). In those cases, more than 2 post-pancreatic head and para-common hepatic artery lymph nodes and 9 para-abdominal aorta metastatic lymph nodes were dissected; *ii*) Studies have found that T2b GBC has a higher rate of lymph node metastasis as well as a higher probability of recurrence of distant lymph node metastasis compared to T2a (16% *vs*. 3%, $p = 0.019$). Thus, T2b GBC has a worse prognosis (*20-21*). However, few studies have examined the characteristics of lymph node metastasis in T2a and T2b and whether a different extent of dissection needs to be performed, whether it be in Europe, the US, Japan, South Korea, or China.

Another hot topic concerning lymphatic dissection is the need for excision of the extrahepatic bile duct. Theoretically, when dissecting lymph nodes around the extrahepatic bile duct, tissue around the blood vessels needs to be resected as much as possible, but connective tissue of a certain thickness around the extrahepatic bile duct must be preserved, thereby ensuring the blood supply of the biliary tract. If it is completely "skeletonized," this will lead to atrophy, hardening, stenosis, and even necrosis of the extrahepatic bile duct, thereby increasing the risk of bile leakage. Therefore, the hepatoduodenal ligament cannot be "completely dissected" at the histopathological level. In addition, cytological studies have found that there are hidden cancer cell clusters in the submucosal layer of the common bile duct in patients with T2 cancer (*22*). In a multi-center large-scale retrospective study in Japan, Onoe *et al*. (*23*) found that patients with T2 GBC with lymph node metastasis (T2N1M0) who underwent extrahepatic bile duct resection had a 5-year survival rate of 45% versus 55% for patients in whom the bile duct was preserved. Patients without lymph node metastasis (T2N0M0) who underwent extrahepatic bile duct resection had a 5-year survival rate of 72% versus 81% for patients in whom the bile duct was preserved; the 5-year survival rate did not differ significantly between the two groups. This indicates that lymph node metastasis is a key factor affecting prognosis, rather than the resection of the extrahepatic bile ducts. Now that T2 has been further divided into T2a and T2b, relevant studies have not yet been conducted. In addition, relevant studies on the prognosis for extrahepatic bile duct resection for GBC are mere case reports. In Japan, a total of 22 patients with T2 cancer underwent this procedure from 1975 to 2011, and 2 had no. 12 lymph node metastasis (*8*). Depending on the cut-off point for the date of follow-up in different studies, survival for patients with T2 cancer who underwent extrahepatic bile duct resection ranged from 12-136 months.

3.3. *Discussion*

The 7th edition of the AJCC's staging criteria focused on site of lymph node metastasis and contended that "extended lymph node dissection" did not improve patient outcomes. The 8th edition focuses on the number of metastatic lymph nodes. This change reflects the idea that "lymph node metastasis means a poor prognosis." However, T2 has now been divided into T2a and T2b, so neither sub-type is in fact sufficient to guide the determination of the extent of lymph node dissection during actual surgery given factors such as the lower level of evidence. Therefore, whether a different extent of lymph node dissection needs to be performed for T2a and T2b warrants more detailed and in-depth study.

3.4. *Suggestions*

i) The difference in lymph node metastasis between T2a and T2b GBC (T2a and T2b cystic duct carcinoma may be considered separately) probably needs to be studied with preoperative imaging and intraoperative exploration.

ii) Postoperative pathology needs to determine the location of lymph node metastasis and the corresponding number of positive lymph nodes at each site in order to provide a sufficient and persuasive rationale for performing dissection to a different extent with either type.

Controversies in the surgical treatment of stage T2 gallbladder cancer are shown in Figure 1.

4. Timing and precautions for treating incidental T2 GBC

4.1. *Current status of diagnosis and treatment of incidental T2 GBC*

One problem that cannot be ignored in the diagnosis and treatment of T2 GBC is the diagnosis and treatment of "incidental GBC." "Incidental GBC" refers to GBC as benign disease before cholecystectomy and determined to be GBC by pathology during or after surgery. "Incidental GBC" is found in 0.3-0.9% of all cholecystectomies. The vast majority of incidental GBCs are in the T1b, T2, or T3 stages, with T2 being the most common: up to 47% (*24*). In general, the rate of resection in incidental

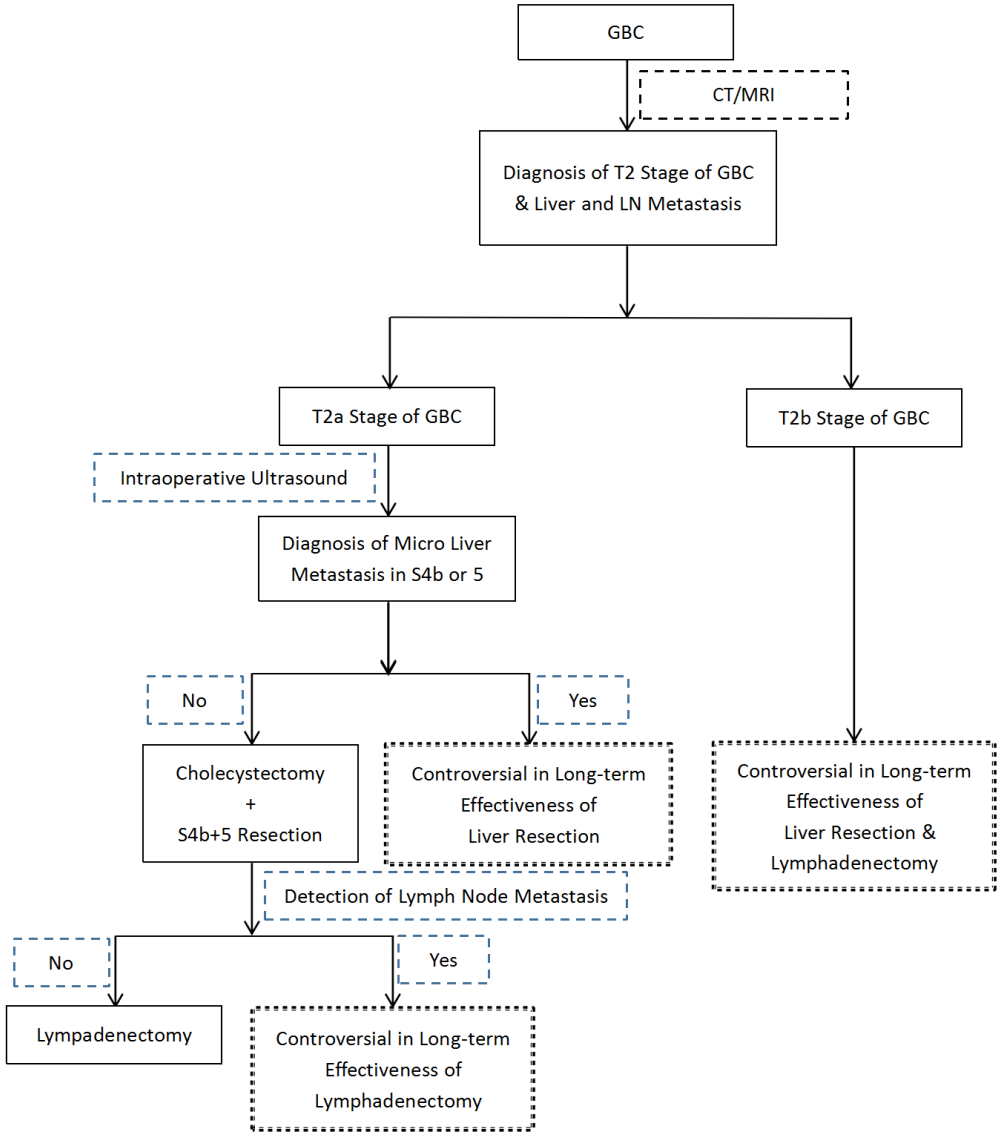

Figure 1. Controversies in the surgical treatment of stage T2 gallbladder cancer.

GBC may be higher than 85%. The rate of lymph node metastasis in T2 GBC is 19-62%, and the residual rate after initial surgery is about 10%. The 5-year survival rate for patients with stage T2 GBC who underwent radical surgery was 78%, which is comparable to that for patients undergoing routine radical surgery for T2 GBC and significantly higher than 38% for patients undergoing simple cholecystectomy (*25-26*). The rate of lymph node metastasis in patients with incidental T2 GBC and the residual rate of a tumor in primary surgery are significantly lower than those rates in patients with T3 GBC (45-70% and 36%, respectively), and the 5-year survival rate for patients with incidental T2 GBC is significantly higher than that for patients with T3 GBC (8-34%) (*24*). For patients with stage T3 or more advanced incidental GBC, there may be enough time before surgery and sufficient available resources to assist in diagnosis or early warning, except for a small number of patients who need urgent surgery for "acute severe cholecystitis, gallbladder perforation, or peritonitis." A question worth considering is whether such cases can be called "incidental gallbladder cancer." In order to reduce the incidence of "incidental gallbladder cancer" and improve the prognosis for those patients, sufficient attention must be paid to preoperative evaluation, primary surgery, and secondary radical surgery.

4.2. *Suggestions*

4.2.1. *Preoperative evaluation: Screening for high-risk patients with "incidental GBC"*

As the concept of laparoscopic cholecystectomy (LC) and day surgery gains traction in hospitals of different levels across the country, preoperative differential diagnosis and treatment for benign gallbladder diseases has become less standardized to some extent. Most surgeons perform LC only after a simple ultrasound and tend to

neglect taking a detailed medical history or performing high-risk screening. Incidental GBC must be kept in mind before the following 13 types of patients undergo a cholecystectomy: (1) elderly patients with gallstones, and especially women. Eight to 10% of patients over 70 years of age with gallstones have associated with gallbladder carcinogenesis; (2) patients with a history of gallstones or cholecystitis for 10 to 15 years or longer; (3) stones larger than 2 cm; (4) fully filled stones; (5) gallbladder wall calcification, porcelain gallbladder, with a malignancy rate as high as 50%; (6) thickening of the gallbladder wall; (7) atrophic gallbladder; (8) gallbladder adenoma or stones with gallbladder polypoid lesions; (9) gallbladder polyps larger than 1 cm; (10) preoperative MRCP suggesting an abnormality in the juncture of the bile and pancreatic ducts; (11) Mirizzi syndrome; (12) previous gallbladder ostomy (*27*); and (13) in China, patients who have undergone gallbladder-preserving micro-blasting lithotripsy should also be included.

For the above patients, imaging and biochemistry results should be carefully reviewed before surgery, and precancerous lesions such as chronic inflammation, gallbladder mucosal hyperplasia, gallbladder adenomyosis, and yellow granulomatous cholecystitis should be carefully excluded. When the lesion is on the hepatic side of the gallbladder and differential diagnosis is particularly difficult, conventional open surgery should be performed instead of laparoscopic surgery, and pathology of frozen sections should be performed.

4.2.2. *Primary surgery: Timely examination of frozen sections*

Multi-center studies by Lundgren *et al*. (*28*) in 2017 and Emmett *et al*. (*29*) in 2015 indicated that timely examination of frozen gallbladder specimens with gallbladder wall thickening and an abnormal morphology helps to improve the "timely confirmed diagnosis" of incidental GBC and improve prognosis. This is particularly true in elderly patients and patients undergoing emergency cholecystectomy. If laparoscopic exploration reveals a thick gallbladder wall, severe adhesions, or suspected invasion in high-risk patients, then open surgery needs to be performed to avoid cutting through the gallbladder and causing bile to leak. After the resection is complete, frozen sections must be prepared. Even if there is no obvious abnormality, the specimens should be carefully examined after the gallbladder is resected, and the mucosa should be carefully observed for any suspicious lesions before preparing frozen sections. If there is a suspected abnormality, the location should be marked and the pathologist should be informed. Surgery should not conclude until a malignancy-free diagnosis is made. A trocar should be carefully removed to avoid potential implantation.

4.2.3. *Secondary cure: Indications and timing*

Incidental GBC diagnosed after cholecystectomy should be treated as follows: *i*) TNM staging should be performed as early as possible before the second surgery. ① T staging: to confirm whether the initial surgery is a full-thickness cholecystectomy (FC) and pathological T staging. If the gallbladder is completely resected and the stage is Tis or T1a, no further surgery is needed. If there is residual gallbladder tissue or the pathology is T1b or T2 or more advanced during the first surgery, further surgery may be required. ② N and M staging: to confirm the presence or absence of systemic and lymph node metastasis and to assess the feasibility of further surgery with imaging techniques such as thin-layer dual-source CT or PET-CT. *ii*) The timing of radical surgery is still controversial. The general belief is that immediate radical surgery is necessary when: frozen sections from initial surgery indicate a malignancy; gallbladder inflammation is mild and the anatomical structure of the area to be radically treated is clear; or gallbladder rupture or bile leakage could during LC, leading to implantation. Indications for second-stage radical surgery: frozen sections from the primary surgery do not indicate a malignancy; tissue inflammation and adhesions in the area to be radically treated are so severe that its anatomical structure cannot be identified; assessment of tumor resectability and accurate preoperative staging is not feasible in the short term. Currently, there are no prospective, large-sample randomized controlled trials indicating an acceptable interval between primary surgery and secondary radical surgery. In a large-sample retrospective study in 2017, Ethun *et al*. (*30*) suggested that secondary radical surgery for incidental T1b and T2 GBC should be performed within 4-8 weeks after primary surgery to improve prognosis. Prior to 4 weeks, inflammation, edema, and adhesions caused by the primary surgery will affect radical surgery, while the rate of an R1 or R2 resection increases significantly (p = 0.05 and < 0.001). Eight weeks after the primary surgery is long enough to significantly increase the probability of recurrence and metastasis. However, a study has reported that an interval of 3 months is more helpful in eliminating distant metastases, avoiding an unnecessary laparotomy, improving the rate of a radical resection, and improving the long-term survival rate (*31*) A national multicenter, prospective, randomized, controlled trial should be conducted to determine the optimal timing for radical surgery to treat incidental T2a and T2b GBC in the future.

5. Adjuvant therapy

Postoperative adjuvant therapy is the least valued part of the comprehensive treatment of GBC worldwide. This is explained by the fact that there is no widely accepted or effective adjuvant therapy regimen. Surgeons typically emphasize surgery, the concept of multi-disciplinary treatment (MDT) is seldom adopted, and GBC is

known to be extremely resistant to radiotherapy and chemotherapy. In fact, insightful studies of various agents and new radiotherapy techniques have increasingly reported forms of adjuvant therapy that could improve the prognosis for GBC.

5.1. *The significance of adjuvant therapy for T2 GBC*

The extent of organ resection and lymphadenectomy in radical surgery for T2 or more advanced GBC has not been determined. Postoperatively, the rate of residual cancer, recurrence, and metastasis is high, so adjuvant therapy is of great significance. In 2017, Mitin *et al*. (*32*) published statistics on the diagnosis and treatment of 5029 patients with T1-3 N0-1 GBC between 2005 and 2013, and they found that postoperative adjuvant therapy was under-performed for GBC. The proportion of patients receiving adjuvant chemotherapy decreased from 4.2% to 1.7%, the proportion of patients receiving radiotherapy increased from 8.3% to 13.8%, and the proportion of patients receiving a combination of radiotherapy and chemotherapy remained the same at 15.9%. At the same time, adjuvant therapy has been found to significantly improve the 3-year survival rate for patients with GBC except for T1N0. In patients with T2N0 cancer, the 3-year survival rate was 46.8% for surgery alone, 63.0% for adjuvant chemotherapy (AC), and 61.2% for adjuvant chemotherapy and radiation therapy (ACR). The 3-year survival rate differed significantly between surgery alone and AC or ACR, but the results of adjuvant radiotherapy are uncertain. In 2015, Hoehn *et al*. (*33*) examined clinical data from 6,690 patients with GBC in the National Cancer Database of the American College of Surgeons from 1998 to 2006, and they found that ACR significantly improved the prognosis for patients with T2/3 cancer, and especially lymph node metastasis (T2-3/N1-2) or with an unknown status of lymph node metastasis (T2-3/Nx). Kasumova *et al*. (*34*) found that patients receiving extended radical + postoperative adjuvant therapy had a significantly longer median survival (23.3 months) than that of patients receiving cholecystectomy + postoperative adjuvant therapy (16.4 months), simple cholecystectomy (12.4 months), or extended GBC surgery (10.7 months). This suggests that adjuvant therapy can benefit patients with T2/3 GBC. Therefore, the short-term effect of cholecystectomy plus postoperative adjuvant therapy is superior to extended resection, which can serve as a potential alternative treatment for high-risk patients who cannot undergo extended radical resection.

5.2. *Adjuvant chemotherapy*

According to current National Comprehensive Cancer Network (NCCN) guidelines, chemotherapy for GBC involves a 5-fluorouracil (5-FU)-based chemotherapy regimen. Regular options for drugs include 5-FU, capecitabine, gemcitabine, and oxaliplatin. Most phase II clinical trials support multi-drug combined chemotherapy. To date, numerous clinical trials of adjuvant chemotherapy have been conducted worldwide (Table 1), but only one phase III clinical trial had positive outcomes: gemcitabine plus cisplatin (GP) was superior to gemcitabine alone and significantly prolonged median progression-free survival (PFS) in patients with GBC (*35*).

5.3. *Adjuvant radiotherapy*

Adjuvant radiotherapy for GBC includes external, intraoperative, and intra-biliary radiotherapy. Of the three, external radiotherapy is most commonly used. A study has indicated that GBC beyond the T2 stage, and especially that with lymph node metastasis or an R1/2 resection, should be treated with radiotherapy with an intensity of > 40 Gy. The main goal is to reduce the rate of local recurrence (*36*). However, the preferred dose, timing, and form of radiotherapy have yet to be determined. In addition, new radiotherapy techniques such as stereotactic body radiotherapy (SBRT) are beginning to be used in the clinical treatment of advanced GBC.

5.4. *Adjuvant chemo/radiotherapy and neoadjuvant chemo/radiotherapy*

Adjuvant chemo-radiation for GBC is mainly a fluorouracil-based regimen combined with external radiotherapy. The main goal is to reduce the rate of local recurrence and thus prolong survival to a certain extent. Recent studies are mostly phase II clinical trials. For example, the SWOG S0809 Phase II trial (*37*) in 2015 involved patients with T2 or more advanced or lymph node-positive GBC. After the first stage of adjuvant chemotherapy with 4 cycles of gemcitabine (1,000 mg/m^2 daily, day 1, 8) + capecitabine (1,500 mg/m^2 daily, day 1-14), the second stage was capecitabine (1,330 mg/m^2 daily) + concurrent radiotherapy (tumor bed area 54.0-59.4 Gy+ the area of lymphatic drainage 45 Gy). Results indicated that the 2-year overall survival rate was 56% and the 2-year disease-free survival rate was 48%, which are acceptable rates.

Neoadjuvant chemoradiotherapy for GBC is currently in its infancy. That treatment is mainly used to treat patients with unresectable GBC that is beyond the T2 stage. In 2015, Sirohi *et al*. (*38*) used gemcitabine plus cisplatin as a regimen for the treatment of 37 patients with advanced GBC in India. The treatment achieved a total response rate of 67.5%, and cancer was down-staged in 48.6% of patients. In 17 (46%) the cancer was resectable. In general, the literature indicates that adjuvant chemoradiotherapy and neoadjuvant chemoradiotherapy are indicated for patients with T2 or more advanced GBC, patients with lymph node

Table 1. Clinical trials of adjuvant chemotherapy worldwide

Study Topic	Country
--	China
Efficacy of somatostatin + epirubicin +5-Fu in the treatment of advanced GBC	Australia
The efficacy of postoperative adjuvant chemotherapy for GBC	India
Efficacy of gemcitabine combined with pazopanib in the treatment of GBC	Greece
Selumetinib combined with cisplatin/gemcitabine (CIS/GEM) vs. CIS/GEM alone	Canada
Efficacy of adjuvant chemotherapy followed by adjuvant chemotherapy in patients with GBC	China
Effect of DKN-01 combined with gemcitabine/cisplatin on gallbladder cancer	USA
Efficacy of Acelarin combined with cisplatin in the treatment of locally advanced/metastatic stage Ib GBC	UK
Effect of conservative symptomatic treatment vs. combined with mFOLFOX chemotherapy regimen on locally advanced/metastatic GBC	UK
Efficacy of recombinant EphB4 fusion protein combined with standard chemotherapy regimen in the treatment of advanced/metastatic solid tumors	USA
Genetic analysis of different FOLFIRABRAX doses for the treatment of advanced gastrointestinal tumors	USA
Effect of ADH-1, gemcitabine combined with cisplatin on advanced metastatic GBC	USA
Effect of TAS-102 on advanced biliary tract tumors	USA
Effect of Merestinib (LY2801653) on advanced or advanced GBC in Japanese	Japan
Regorafenib alone for treatment of local progression and metastatic GBC with first-line treatment failure	USA
Effect of T cell-mediated adaptive immune response therapy on Her-2 positive digestive system tumors	China
Regorafenib alone for the treatment of refractory advanced biliary tract tumors	USA
Efficacy of gemcitabine and cisplatin combined with nab- paclitaxel in the treatment of advanced biliary tract tumors	USA
Effect of GEMOX regimen (gemcitabine, cisplatin) vs. XELOX (Xeloda, cisplatin) on advanced biliary tract tumors	South Korea
Ramucirumab for the treatment of advanced GBC	USA

metastasis, patients in whom an R0 resection has not been achieved, or patients with unresectable GBC.

6. Conclusion

Since the AJCC subdivided the T2 stage of GBC into T2a and T2b, the diagnosis and treatment of those stages have been a subject of heated discussion and controversy. T2 is a stage of GBC that might be treatable. Large-scale clinical studies adopting the concepts of comprehensive treatment and multidisciplinary collaboration might make progress in diagnosis, surgery, and adjuvant therapy. Those findings would contribute significantly overall improvement in the prognosis for GBC.

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