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Practical Guidelines for the Surgical Treatment of Gallbladder Cancer

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At present, surgical treatment is the only curative option for gallbladder (GB) cancer. Many efforts therefore have been made to improve resectability and the survival rate. However, GB cancer has a low incidence, and no randomized, controlled trials have been conducted to establish the optimal treatment modalities. The present guidelines include recent recommendations based on current understanding and highlight controversial issues that require further research. For T1a GB cancer, the optimal treatment modality is simple cholecystectomy, which can be carried out as either a laparotomy or a laparoscopic surgery. For T1b GB cancer, either simple or an extended cholecystectomy is appropriate. An extended cholecystectomy is generally recommended for patients with GB cancer at stage T2 or above. In extended cholecystectomy, a wedge resection of the GB bed or a segmentectomy IVb/V can be performed and the optimal extent of lymph node dissection should include the cystic duct lymph node, the common bile duct lymph node, the lymph nodes around the hepatoduodenal ligament (the hepatic artery and portal vein lymph nodes), and the posterior superior pancreaticoduodenal lymph node. Depending on patient status and disease severity, surgeons may decide to perform palliative surgeries.

Keywords: Gallbladder; Neoplasm; General Surgery; Guideline

INTRODUCTION

According to the Korea Central Cancer Registry's annual report of 2011, as published by the Korean Ministry of Health and Welfare, gallbladder (GB) cancer accounts for 1.1% of all cancers in Korea, making it the 11th most prevalent cancer in the country (1). In patients aged 65 yr or older, it is the fifth most prevalent cancer. Its incidence continually increased between 1999 and 2002 and given that Korea is an aging society, this trend is expected to continue. It is therefore imperative to establish practical guidelines for the diagnosis and appropriate treatment of GB cancer.

GB cancer can be cured with radical surgery, and many efforts have been made in the attempt to improve resectability and the survival rate. However, GB cancer has a low incidence, and no randomized, controlled trials have been conducted to establish the optimal treatment modalities. Although a few retrospective studies have been conducted in large series of patients with GB cancer, these have been limited in scope. Treatment guidelines for GB cancer have been published in peer-reviewed journals in countries outside of Korea, but these have been limited in their provision of established, evidence-based rationales for the most optimum surgical treatment of GB cancer (2-4). The Korean Association of Hepato-Biliary and Pancreas Surgery conducted a systematic review of the Korean and English literature to establish standard treatment guidelines for GB cancer and to improve treatment outcomes. The treatment guidelines described herein present evidence-based rationales to assist our colleagues in establishing optimal treatment strategies for GB cancer patients in clinical settings. Recommendations for treatment are noted (the grades of these recommendations are defined in Table 1) and the levels of evidence are also given (in parentheses) in the reference citations (see the definitions of levels in Table 2).

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SURGICAL APPROACHES FOR PATIENTS WITH SUSPECTED GB CANCER

According to published treatment guidelines, it is recommended that patients undergo laparotomy if they are suspected of having GB cancer based on the preoperative work-up (2, 3). This is based on the rationale that GB cancer should be treated by surgical modalities, such as laparotomic cholecystectomy, hepatectomy for GB fossa, and lymph node dissection. However, several recent studies have recommended that a simple cholecystectomy should be the standard treatment modality for T1 GB cancer (5-11). Laparoscopic cholecystectomy has shown equivalent or better treatment outcomes compared to those for laparotomy (5-7). This has led to the sugggestion that patients should undergo laparoscopic cholecystectomy unless there is evidence of invasion to the GB fossa (Level of evidence 4, Level of recommendation B). Otherwise, a laparotomy would be advised (Level of evidence 3, Level of recommendation B). Table 3 summarizes the recommendation for suspected GB cancer.

Table 1. Definitions of evidence by level

Levels	Definition of evidence
1	Evidence obtained from systematic review (SR) of all the randomized controlled trials (RCTs)
2	Evidence obtained from more than one well-controlled RCT
3	Evidence obtained from well-controlled trials (CT), multi-center cohorts, or case-control studies or that were obtained from longitudinal studies without intervention
4	Evidence obtained from the clinical experiences of key opinion leaders or those obtained from study

SURGICAL TREATMENT FOR EARLY GB CANCER

T1a GB cancer

Based on a literature review, simple cholecystectomy is the optimal treatment for patients with T1a GB cancer confined to mucosa. Laparoscopic cholecystectomy is also an appropriate modality (5-8, 12, 13). The five-year survival rate for simple cholecystectomy is as high as 95%-100%. An extended cholecystectomy is not effective in prolonging long-term survival unless there are tumor invasions into the resection margin of the cystic duct (9). According to a systematic review of the T1a GB cancer literature, the recurrence rate is 1.1% in such cases. The most frequent site of recurrence was the common bile duct (6) (more than 50% of the total cases). Therefore, histopathologic examination should be performed to determine whether there are tumor invasions into the resection margin of the cystic duct. If this is the case, extrahepatic bile duct (EHBD) resection should be considered (6, 7) (Level of evidence 3, level of recommendation A). Lymph node metastasis has been reported in less than 2.5% of total cases; therefore, lymph node dissection is not recommended for patients with T1a GB cancer (6, 10). The five-year survival rate is estimated at 100% for T1a GB patients who undergo laparoscopic cholecystectomy (6, 7), but there are some reports that bile juice leakage during laparoscopic cholecystectomy is associated with peritoneal metastasis and tumor recurrence at trocar sites. As such the surgical procedure should be carefully performed so as to prevent intraoperative GB perforation, and the resected GB should be removed using a vinyl bag (6, 12) (Level of evidence 3, level of recommendation A). Table

Table 2. Recommendation levels

Level of recommendation	Conditions
A	There is a sufficient amount of clinical evidence to make convincing recommendations and agreement has been reached among the board members as to the appropriateness of recommendations.
B	There is an insufficient amount of clinical evidence. However, based on low-level clinical evidence, agreement has still been reached among the board members as to the appropriateness of these recommendations.
C	Recommendations have been made based on low-level clinical evidence. No agreement has been reached on whether such recommendations are appropriate, although there is no great disagreement among the board members.
D	There is great disagreement among the board members on the recommendations.

Table 3. Summary of recommendations for patients with suspicious GB cancer

Surgical intervention	Level of evidence	Level of recommendation
Patients may undergo laparoscopic cholecystectomy unless there is preoperative evidence of GB fossa invasion.	4	B
Laparotomy is recommended for definite preoperative evidence of GB fossa invasion.	3	B

Table 4. Summary of recommendations for patients with T1a GB cancer

Surgical intervention	Level of evidence	Level of recommendation
The optimal treatment modality for T1a GB cancer is simple cholecystectomy, which can be carried out as either a laparotomy or a laparoscopic surgery.	3	A
A histopathologic examination should be performed to evaluate whether there is invasion in the resection margin of the cystic duct.	3	A
Intraoperative perforation of the GB should be avoided, and the resected GB should be removed using a vinyl bag during laparoscopic surgery.	3	A

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Table 5. Summary of recommendations for patients with T1b GB cancer

Surgical intervention	Level of evidence	Level of recommendation
There is an insufficient amount of clinical evidence demonstrating that extended cholecystectomy increases T1b GB cancer patient survival. It can therefore be inferred that either simple or an extended cholecystectomy is appropriate.	3	B
There is no evidence demonstrating that a laparoscopic cholecystectomy is likely to lead to a poor prognosis. It can therefore be inferred that laparoscopic cholecystectomy may be performed.	3	B
Extended cholecystectomy can be carried out in patients who are not at increased risk for developing postoperative complications.	3	B
Histopathologic examination should be performed to evaluate whether there is invasion in the resection margin of the cystic duct.	3	A
To avoid intraoperative perforation of the GB, special attention should be paid to surgical procedures. During the laparoscopic surgery, the resected GB should be removed using a vinyl bag.	3	A

Table 6. Summary of recommendations for extent of hepatic resection or lymph node dissection in extended cholecystectomy

Surgical intervention	Level of evidence	Level of recommendation
A wedge resection of the GB bed or a segmentectomy IVb/V can be performed.	3	B
Regional lymph node dissection is routinely performed within an extended cholecystectomy. The optimal extent of lymph node dissection should include the cystic duct lymph node, the common bile duct lymph node, the lymph nodes around the hepatoduodenal ligament (the hepatic artery and portal vein lymph nodes), and the posterior superior pancreaticoduodenal lymph node.	3	C
For accurate the determination of the TNM stage, more than three lymph nodes should be collected for histopathologic examinations.	4	C

4 summarizes the recommendations for T1a GB cancer.

T1b GB cancer

There is no clear evidence that extended cholecystectomy increases survival compared to the results for simple cholecystectomy in patients with T1b GB cancer (5, 6, 12). Moreover, several studies have shown that there is no significant difference in five-year survival between patients who undergo laparoscopic cholecystectomy and those who undergo laparotomy. It can therefore be inferred that laparoscopic cholecystectomy is not associated with poor prognosis (8, 11, 12). According to a systematic review of the T1 GB cancer literature, lymph node metastasis is present in approximately 11% of all cases, and the recurrence rate is 9.3% (6). However, this rate is higher in patients with T1b GB cancer who have undergone simple cholecystectomy (5, 6). Although there is a lack of clear evidence demonstrating that extended cholecystectomy increases patient's survival as compared with a simple cholecystectomy, the former may nevertheless be recommended for patients who are not at increased risk of developing postoperative complications in that simple cholecystectomy has a relatively higher recurrence rate (6, 7, 9, 14) (Level of evidence 3, level of recommendation B). Table 5 summarizes the recommendations for T1b GB cancer.

SURGICAL TREATMENTS FOR OTHER GB CANCER STAGES

An extended cholecystectomy is generally recommended for patients with GB cancer at stage T2 or above (15-20) (Level of evidence 3, Level of recommendation B). In patients who are indicated for radical cholecystectomy, a combined approach can also be considered.

Extent of hepatic resection in extended cholecystectomy

A wedge resection of the GB bed or segmentectomy IVb/V can be performed (Level of evidence 3, Level of recommendation B). In a wedge resection, it is recommended that the hepatic resection margin width should be proposed to be approximately 2-3 cm; however, there is by no means universal consensus on this point. Table 6 summarizes the recommendations for the ideal extent of hepatic resection in extended cholecystectomy.

Extent of lymph node dissection in extended cholecystectomy

Lymph node metastasis is a well-known prognostic indicator, and its incidence varies depending on the depth of mural invasion as follows: pT1a, 0%-2.5%; pT1b, 5%-16%; pT2, 9%-30%; T3, 39%-72%; and T4, 67%-80% (6, 9, 21, 22). There is no consensus on the optimum extent of lymph node dissection in extended cholecystectomy for GB cancer patients. The seventh edition of the AJCC Cancer Staging Manual (23), defines, regional lymph node group 1 (N1) as comprising the cystic duct lymph node, common bile duct lymph node, and the lymph nodes around the hepatoduodenal ligament (i.e., the hepatic artery lymph node and portal vein lymph node). The posterior pancreaticoduodenal lymph node, celiac artery lymph node, superior mesenteric artery lymph node, para-aortic lymph node, and pericaval lymph node are classified as belonging to regional lymph node group 2 (N2). N2 metastasis would be interpreted as remote metastasis, and such patients would be classified as TNM IVB. In most cases, the long-term survival cannot be predicted for patients with N2 metastasis, and radical lymph node dissection is not routinely performed (17, 24-26). Regional lymph node dissection is recommended for the cystic duct lymph node, common bile duct lymph node, the lymph nodes

Table 7. Summary of recommendations for extrahepatic bile duct (EHBD) resection in radical surgery, surgery in GB cancer patients with para-aortic lymph node metastasis, surgical treatments in patients with invasion of the hepatic artery, portal vein, and adjacent organs, and palliative surgery in patients who are not indicated for radical surgery

Surgical resection	Level of evidence	Level of recommendation
EHBD resection is not mandatory for radical resection of GB cancer, but can be performed in certain cases.	3	C
In patients with GB cancer with para-aortic lymph node metastasis, radical surgery can also be performed based on the surgeon's judgment.	3	C
Both combined resection and R0 one are essential for achieving a good prognosis. A combined resection of the adjacent organs cannot guarantee a good prognosis for all the patients. Selection of appropriate patients is therefore essential.	3	C
Depending on patient status and disease severity, surgeons may decide to perform palliative surgeries, such as non-radical cholecystectomy, biliary bypass surgery, or gastric bypass surgery.	3	C

around the hepatoduodenal ligament (hepatic artery and portal vein lymph nodes), and the posterior superior pancreaticoduodenal lymph node (Level of evidence 3, Level of recommendation C). There is no consensus on the minimum or optimal number of resected lymph nodes required to accurately determine the TNM stage. The sixth edition of the AJCC Staging Manual stated that more than three lymph nodes are required to accurately determine the N-stage. However, this point was deleted in the manual's seventh edition. Some surgeons are of the opinion that only 3-4 lymph nodes can be collected despite N1 regional lymph node dissection although 1-2 lymph nodes can be collected using a simple cholecystectomy. Based on this, we propose that more than three lymph nodes should be collected for histopathologic examinations (Level of evidence 4, Level of recommendation C). Table 7 summarizes the recommendations for extent of the optimal lymph node dissection in extended cholecystectomy.

Clinical significance of extrahepatic bile duct resection in radical surgery

Since the early 1990s, it has been maintained that EHBD resection should be performed for GB cancer irrespective of the TNM stage (27). This is based on the rationale that this procedure achieves complete lymph nodes resection around the hepatoduodenal ligament in early GB cancer and also helps achieve radical tumor mass resection with perineural invasion in advanced GB cancer. However, it has been subsequently found that EHBD resection is not associated with increased survival (28-32). There are also contradictory reports that the incidence of early and late-stage complications is increased by this procedure (28, 33). Therefore, EHBD resection should not be seen as mandatory in the radical resection of GB cancer but rather as an option to be selectively performed in specific types of cases, such as GB cancer with extrahepatic bile duct invasion (Level of evidence 3, Level of recommendation C). Table 7 summarizes the recommendations for EHBD resection in radical surgery.

Clinical significance of surgery in GB cancer patients with para-aortic lymph node metastasis

It is generally known that patients with advanced GB cancer with para-aortic lymph node metastasis are contraindicated in surgery. However, it has been reported that survival is significantly prolonged following radical resection that includes para-aortic lymph node dissection in patients with GB cancer with para-aortic lymph node metastasis, compared to results for patients with distant metastasis or advanced, unresectable GB cancer (34). Conversely, another study reported that patients with TNM stage III or IV GB cancer should undergo extended lymph node dissection involving the para-aortic lymph node (35). Currently, surgical treatment efficacy cannot be predicted in GB cancer patients with para-aortic lymph node metastasis. The decision to perform radical surgery should thus be based on the surgeon's judgment (Level of evidence 3, Level of recommendation C). Table 7 summarizes the recommendations for surgery in GB cancer patients with para-aortic lymph node metastasis.

Clinical significance of surgical treatments in patients with invasion of the hepatic artery, portal vein, and adjacent organs

Very poor prognoses are expected in advanced GB cancer cases, and most patients refuse to undergo surgery when invasion of the hepatic artery and portal vein are suspected. Kobayashi et al. (36) performed analysis in 71 patients with GB cancer and found that the prognosis was poorer if surgeons performed a combined resection of the hepatic artery and portal vein for patients with invasion of both vessels as compared with results for those patients who had no invasion. Moreover, the authors reported that invasion of the hepatic artery and portal vein is a key prognostic indicator (36, 37). There are no effective treatment modalities other than surgery for patients with GB cancer. Surgical treatments are recommended for GB cancer patients if complete tumor removal (R0 resection) can be achieved through a combined resection of the hepatic artery and portal vein (Level of evidence 3, Level of recommendation C).

Combined resection is routinely recommended for advanced GB cancer cases in which there is invasion of adjacent organs (colon and duodenum). As this requires both a combined resection and R0 resection, favorable prognoses are not guaranteed. The selection of appropriate patients is essential (38) (Level of evidence 3, Level of recommendation C). Table 7 summarizes the recommendations for surgical treatment in patients with invasion of the hepatic artery, portal vein, and adjacent organs.

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Table 8. Summary of recommendations for GB cancer found incidentally on postoperative histopathology

Postoperative situations	Level of evidence	Level of recommendation
The optimal treatment modality for T1a GB cancer is a simple cholecystectomy.	3	A
There is no clear evidence demonstrating that extended cholecystectomy prolongs survival in patients with T1b GB cancer. The additional use of extended cholecystectomy is thus subject to the surgeon's judgment.	3	B
Patients with GB cancer at T2 or higher should additionally undergo extended cholecystectomy.	3	B
If surgeons determine that additional surgeries are needed, they should be performed without delay.	3	C

Table 9. Summary of recommendations for GB cancer found incidentally during surgery

Clinical conditions	Level of evidence	Level of recommendation
In patients suspected of having T1 GB cancer during surgery, it is difficult to differentiate between T1a and T1b cancers. Therefore, cholecystectomy should be performed as the first-choice treatment, and any additional surgeries should be carried out based on postoperative histopathologic findings.	4	C
In T2 or higher GB cancers, extended cholecystectomy should be performed based on a tentative or revised diagnosis.	4	C

Clinical significance of palliative surgery in patients who are not indicated for radical surgery

The median and one-year survival rates in patients with unresectable GB cancer are reported to be approximately 2-4 months and less than 5%, respectively. It is also known that cytoreductive surgery is not useful in patients with GB cancer (39-42). However, palliative surgery will most likely be able to prolong the short-term survival period and improve the quality of life of patients with unresectable GB cancer. Palliative surgery options here include non-radical, simple cholecystectomy. If biliary atresia or gastric outlet obstruction are concurrently present, bypass surgery would also improve patient quality of life. Surgeons should therefore decide the optimal treatment modality in view of the patient status involved (43, 44) (Level of evidence 3, Level of recommendation C). Table 7 summarizes the recommendations for palliative surgery in patients who are not indicated for radical surgery.

TREATMENT OF INCIDENTALLY FOUND GB CANCER AFTER CHOLECYSTECTOMY

GB cancer incidentally found on postoperative histopathology

The core principles for the surgical treatment of GB cancer incidentally found on postoperative histopathology are identical to those described earlier. That is, no additional surgeries should be considered for histologically-proven T1a GB cancer if the GB was completely resected during surgery (5-8, 12, 13) (Level of evidence 3, Level of recommendation A). However, in cases of histologically-proven T1b GB cancer, there is still controversy regarding whether extended cholecystectomy or follow-up without additional surgeries should be performed (5, 6, 8, 11, 12) (Level of evidence 3, Level of recommendation B). In cases of GB cancer at T2 or above, the additional use of extended cholecystectomy is recommended (Level of evidence 3, Level of recommendation B). There are no established reports regarding the timing of additional surgeries; however, some studies have been performed immediately after GB cancer diagnosis (45, 46) (Level of evidence 3, Level of recommendation C). Table 8 summarizes the recommendations for GB cancer incidentally found on postoperative histopathology.

GB cancer incidentally found during surgery

The surgical treatment principles for histologically-proven GB cancer found during surgery are identical to those for GB cancer incidentally found on postoperative histopathology. However, in patients who are suspected of having T1 GB cancer during surgery, it is difficult to differentiate between T1a and T1b GB cancers. Therefore, cholecystectomy should be the first-choice treatment. It is recommended that additional surgeries should be determined based on the postoperative histopathology (Level of evidence 4, Level of recommendation C). In GB cancer at T2 or above, extended cholecystectomy should be performed based on a tentative or revised diagnosis (Level of evidence 4, Level of recommendation C). Table 9 summarizes the recommendations for GB cancer incidentally found during surgery.

SURGICAL TREATMENT OF GB CANCER ACCOMPANIED BY ACUTE CHOLECYSTITIS

GB cancer is often accompanied by bile stones, leading to acute cholecystitis symptoms in many cases. There are no accurate reports on the incidence of acute cholecystitis, although it has been reported to range from 8.8% to 20% (47-49). A preoperative differential diagnosis of acute cholecystitis accompanied by GB cancer is essential for determining surgical plans, but there are some situations in which such a differential diagnosis is difficult. Indeed, surgery should possibly be delayed in patients with GB cancer who have concurrent acute cholecystitis. In addition, the appropriate extent of surgery cannot be intraoperatively determined, leading to poor prognoses (50). Surgeons are recommended to consider the possibility of GB can-

Table 10. Summary of recommendations for postoperative adjuvant therapy for GB cancer

Adjuvant therapy	Level of evidence	Level of recommendation
Anti-cancer chemotherapy regimens involving fluoropyrimidine or gemcitabine or their combinations with local radiotherapy i.e., CCRT, can be used.	3	C
Postoperative adjuvant chemotherapy and CCRT are not recommended for T1 GB cancer patients who have undergone radical resection.	3	C

cer in patients who are suspected of having acute cholecystitis if they are older and exhibit focal GB wall thickening, a mass within the internal GB lumen, overall GB wall thickening with decreased GB size, or lymphadenopathy around the GB (51) (Level of evidence 4, Level of recommendation C).

POSTOPERATIVE ADJUVANT THERAPY

Complete surgical excision of GB cancer is the only radical treatment modality at present, but the rate of resection is at most 25%-30%. Nearly half of patients are at increased risk for recurrent GB cancer despite having undergone complete resection (52, 53). Recurrent GB cancer may be the result of distant metastasis, but it may also be characterized by local recurrence (54-56). Patients with recurrent GB cancer are therefore required to undergo local treatment modalities, such as postoperative adjuvant chemotherapy or concurrent chemoradiation therapy (CCRT). For postoperative adjuvant chemotherapy, fluoropyrimidine drugs such as 5-fluorouracil or capecitabine are the preferred choice. CCRT is also recommended to be carried out in conjunction with these drugs. Depending on patient status or surgeon preference, monotherapy or combination treatment regimens using gemcitabine or fluoropyrimidine may also be considered (6). However, postoperative adjuvant chemotherapy or CCRT are not recommended in patients with T1 GB cancer who have undergone radical resection (58-60) (Level of evidence 3, Level of recommendation C). Table 10 summarizes the recommendations for the optimum postoperative adjuvant therapy for GB cancer.

CONCLUSIONS

There are no randomized, prospective studies assessing the surgical treatments for GB cancer. Moreover, there are only a few systematic reviews of the GB cancer surgical literature. There are many retrospective studies in this series, but when taken as a whole, these have the following limitations: 1) small numbers of enrolled patients; 2) heterogeneity of patient populations across studies, and 3) inconsistent surgical procedures across studies. Therefore, we experienced considerable difficulty in drawing conclusions and developing recommendations based on the existing clinical evidence. Nevertheless, the current report is based on a systematic review of the literature and in-depth discussion among board members. We believe that these treatment guidelines are of value for selecting the optimal surgical modalities in GB cancer patients.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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