

Gallbladder cancer: Clinical and pathological approach

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Abstract

Gallbladder cancer (GBC) shows a marked geographical variation in its incidence. Middle-aged and elderly women are more commonly affected. Risk factors for its development include the presence of gallstones, chronic infection and pancreaticobiliary maljunction. Controversy remains in regard to the theory of carcinogenesis from adenomyomatosis, porcelain gallbladder and adenoma of the gallbladder. The surgical strategy and prognosis after surgery for GBC differ strikingly according to T-stage. Discrimination of favorable cases, particularly T2 or T3 lesions, is useful for the selection of surgical strategies for individual patients. Although many candidate factors predicting disease progression, such as depth of subserosal invasion, horizontal tumor spread, tumor budding, dedifferentiation, Ki-67 labeling index, p53 nuclear expression, CD8+ tumor-infiltrating lymphocytes, mitotic counts, Laminin-5-gamma-2 chain, hypoxia-inducible factor-1a, cyclooxygenase-2 and the Hedgehog signaling pathway have been investigated, useful prognostic makers or factors have not been established. As GBC is often discovered incidentally after routine cholecystectomy and accurate preoperative diagnosis is difficult, close mutual cooperation between surgeons and pathologists is essential for developing a

rational surgical strategy for GBC.

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Key words: Gallbladder cancer; Surgical strategy; Pathology; Prognostic factors

Core tip: This review has documented the basic knowledge and surgical strategies for gallbladder cancer (GBC) based on the clinical and pathological data from previous studies. Discrimination of favorable cases, particularly T2 or T3 lesions, is useful for the selection of surgical strategies for individual patients. As GBC is often discovered incidentally after routine cholecystectomy and accurate preoperative diagnosis is difficult, close mutual cooperation between surgeons and pathologists is essential for developing a rational surgical strategy for GBC.

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EPIDEMIOLOGY

Gallbladder cancer (GBC) has a distinctly higher incidence in certain demographic groups and areas. Women are affected three times more often than men, and the vast majority of patients with GBC are older than 40 years of age. A high incidence has been reported in women in countries such as Chile, Poland, India, Israel, Pakistan, Ecuador, South Korea and Japan, whereas GBC is considered a rare neoplasm in most Western countries and the United States^[1-4].

RISK FACTORS

Gallstones are a well-known risk factor for GBC^[5,6]. It has been reported that a large stone size of more than 3

cm, a family history of GBC, and prolonged cholelithiasis are potential risk factors for GBC^[7-9]. These factors could be used in the decision making when performing a cholecystectomy for asymptomatic gallstones. However, no definite evidence of a direct causal relationship between gallstones and gallbladder cancer has been presented and biases of other risk factors remain unsolved problems^[10]. The composition and mutagenicity of gallstones have previously been studied with inconclusive results^[11]. A prospective study of 123 consecutive patients with asymptomatic gallstones who were followed-up for 10 years or longer revealed no cases of GBC^[12].

Historically, an association between calcified gallbladder (porcelain gallbladder) and GBC has been reported^[13,14], although there has also been a report suggesting that porcelain gallbladder is not associated with GBC^[15]. Therefore, the causal association of porcelain gallbladder and GBC remains controversial.

Pancreaticobiliary maljunction (PBM) is considered an established risk factor for biliary tract cancers involving GBC^[16,17], especially in relatively young female patients without gallbladder stones^[18,19]. It is generally accepted that pancreatic juice reflux into the biliary tract due to PBM plays a pathogenic role in biliary tract cancers. K-ras mutations are more common in biliary tract carcinomas associated with PBM^[20].

Adenomyomatosis of the gallbladder has not been considered to have malignant potential; however, several reports have suggested that gallbladder cancer may originate from adenomyomatosis^[21-24] or have insisted that segmental-type adenomyomatosis shows an increased risk of progression to gallbladder cancer^[25]. Recently, a study showed that gross features of adenomyomatosis were found in approximately a quarter of gallbladders resected under the diagnosis of GBC^[26]. Although the magnitude of risk for GBC in patients with adenomyomatosis remains unclear, studies suggesting a correlation between adenomyomatosis and GBC have been gradually accumulating.

In regard to the development of GBC, several theories have been proposed, including the adenoma-carcinoma sequence and dysplasia-carcinoma sequence theories^[27-30]. However, recently reported articles have suggested that the vast majority of adenomas and/or polypoid lesions do not become GBC^[31,32]. Therefore, the validity of the adenoma-carcinoma sequence theory remains controversial. Other risk factors recently receiving attention include bacterial infections. Although the supporting evidence for an association is weak, *Salmonella*^[33,34] and *Helicobacter* species^[35] would be prime candidates for a bacterial predisposition to GBC.

SURVIVAL AND GENERAL SURGICAL STRATEGIES ACCORDING TO T-STAGE

The surgical strategy for GBC depends on the extent of the disease, particularly the T-stage from the TNM classification^[36]. The prognosis after surgery for GBC differs

strikingly according to T-stage. Five-year survival rates after surgery for T1, T2, T3, and T4 stage tumors in 73 cases at our institution were 100%, 78.3%, 16.7%, and 25.0%, respectively^[37]. The survival rates of our series were consistent with the results of other previous reports^[38-41].

The survival of patients with T1a lesions (invasion restricted to the lamina propria) is particularly good, and lymph node metastasis is extremely rare in such cases. Simple cholecystectomy with or without lymphadenectomy is thus widely accepted as sufficient for T1a lesions^[38,42,43]. Intraoperative perforation of the gallbladder and positive surgical margins around the cystic duct are important prognostic factors in surgery for T1a lesions^[44].

Survival rates and strategies for T1b (invasion to the muscle layer) remain somewhat controversial. Several studies have reported LN metastasis in up to 20% of cases, with recurrence rates of 30%-60% following simple cholecystectomy^[45-51]. In addition, distinguishing T1b lesions from T2 lesions pre- or intraoperatively is usually difficult. Therefore, it seems reasonable to perform cholecystectomy combined with lymphadenectomy with or without liver resection in patients with pre- or intraoperative presumption of T1b GBC. However, T1b GBC is often discovered after laparoscopic cholecystectomy for presumed benign disease. In our T1b series ($n = 8$), lymph vessel invasion was found only one case and no LN metastases or recurrences were observed, and thus additional operation of lymphadenectomy was not always needed in patients with T1b lesions diagnosed after routine cholecystectomy. However, caution is required in that the pathological work for resected specimens must be performed intensively with sections from the whole specimen, in order to minimize the possibility that a more invasive site or findings of residual lesion remain present in the resected specimen.

The prognosis for T2 (invasion to the subserosal layer) lesions varies widely, with the 5-year survival rates being approximately 20%-70% after simple cholecystectomy, compared to 60%-100% after radical surgery^[37,43,52-55]. The surgical strategy for T2 lesions thus remains unclear. The conventional opinion is that patients with T2 lesions should be treated using radical cholecystectomy, including en bloc resection of the adjacent liver as well as regional lymphadenectomy with or without extrahepatic bile duct resection (BDR)^[38,56]. Pathologists should pay close attention in order not to misdiagnose a T1a tumor with spreading into the Rokitansky-Aschoff sinuses (RAS) as a T2 tumor with invasion of the subserosal layer.

The prognosis is poor for most patients with T3 tumor, which shows perforation of the serosa and/or direct invasion of the liver and/or one other adjacent organ or structure. Surgery for T3 lesions is only appropriate if there is potential to achieve a curative resection. T3 lesions require hepatic resection with regional lymphadenectomy at a minimum. This can include major hepatectomy if there is extensive spreading into the liver or major vascular structures. In addition, if direct invasion

into an adjacent organ (duodenum, pancreas, stomach or colon) is suspected, *en bloc* resection would be required for curative resection^[56]. Because of the high degree of surgical stress involved, the utility of aggressive surgery with extended resection for T3 lesions is often debated in clinical practice, and case-by-case selection is required with due consideration for the patient's performance status, complications, and age.

Chemotherapy or palliation is typically appropriate for T4 disease (tumor invading into the main portal vein or two or more extrahepatic organs or structures), except in rare cases where *en bloc* resection of multiple organs is possible. This is because of the unfortunate prognosis and difficulty of achieving curative resection. Unresectability discovered at the time of laparotomy may be treated with bypass surgery to relieve symptoms related to biliary obstruction. Cases identified preoperatively as unresectable may be considered for percutaneous biliary drainage or endoscopic stenting to address biliary obstruction^[38].

CLINICAL CHALLENGES FOR T2 AND T3 TUMORS

As mentioned above, T2 and T3 tumors are indications for radical surgery. However, which type of radical surgery is most appropriate remains unclear. Although regional lymphadenectomy is widely accepted as necessary at a minimum, the efficacy of extended resection, such as hepatectomy, BDR or pancreatoduodenectomy (PD), remains controversial. BDR is usually necessary in cases with biliary infiltration associated with perineural invasion and complete lymphadenectomy and eradication of the connective tissue around the common bile duct^[57-60]. In terms of hepatectomy for GBC, the resection may vary from a small wedge resection near the gallbladder fossa to an extended right hepatectomy. The appropriateness of segment 4a+5 (S4a+5) hepatectomy for advanced GBC is supported by the drainage of the cystic vein into anatomic Couinaud's segments IVa and V and the frequency of liver metastases in this anatomical area^[61]. The results of our previous study support the use of S4a+5 hepatectomy combined with BDR and regional lymphadenectomy for the treatment of T2 or T3 GBC^[37]. However, additional PD achieved no significant difference in survival in patients with T2 or T3 GBC. Indications for PD in these cases were obvious duodenal or pancreatic invasion, or infiltrating LN metastases at the retro-pancreatic head portion^[37].

ATTEMPTS TO DISCRIMINATE FAVORABLE CASES IN T2 GBC

T2 GBC shows a wide variety of tumor spread. Some T2 tumors show none of the histological invasive factors of LN metastasis, lymphatic or venous invasion, but others show prominent LN metastases, along with venous,

lymphatic, or perineural invasion, resulting in poor prognosis. This issue indicates that patients with T2 GBC can be allocated to a favorable prognosis group or a poor prognosis group. If discrimination of favorable cases is appropriately performed, patients with favorable prognosis could be spared excessive extended radical surgery. To identify cases with a favorable prognosis, subset analyses of patients with T2 tumor according to certain pathological criteria have been performed. Several studies, including one from our institution, reported the usefulness of discrimination of T2 GBC according to the depth of subserosal invasion and horizontal tumor spread in the subserosal layer with or without a scoring system^[62-65]. Our study focused on the phenomena of dedifferentiation (DD) and tumor budding (BD) demonstrated a significant prognostic impact of both BD and DD in patients with T2 tumor^[66].

INVESTIGATION OF USEFUL PROGNOSTIC MARKERS AND FACTORS

Although prognostic markers of GBC have been widely investigated, promising prognostic markers or factors have not yet been established. Ki-67 labeling index (LI), p53 nuclear expression, CD8+ tumor-infiltrating lymphocytes (TIL) and mitotic count (MC) have classically been considered as candidates for prognostic markers. However, several previous studies have reported no prognostic impact of p53 overexpression in GBC^[67-71], although reports of poor prognosis in cases with p53 overexpression are also available in the literature^[72,73]. A previous study showed that patients with GBC and high Ki-67 exhibited worse postoperative prognosis than those with low Ki-67^[40], although here again, several previous studies also reported that Ki-67 LI of cancer cells was not correlated with patient survival^[68,70,71]. Therefore, the prognostic impact of p53 overexpression and Ki-67 LI in GBC remains controversial. In regard to CD8+ TIL, there is little evidence that this is a prognostic indicator. Only one study has reported that CD8+ TIL was correlated with prolonged survival in a univariate analysis^[74]. A study from our institution concerning Ki-67 LI, p53 nuclear expression, CD8+ TIL and MC status in a series of 101 GBC patients indicated that only MC reflected the prognosis of GBC. In that study, MC showed a particularly strong prognostic impact in patients with T3 tumor and was identified as an independent prognostic factor in multivariate analyses that included the N and M factors of the TNM system of classification^[75]. It is difficult to distinguish the extension of carcinoma in situ (CIS) from invasive carcinoma along the RAS. Laminin-5-gamma-2 chain, which is expressed in various types of invasive carcinoma, can be detected in the invasive fronts of invasive GBC, but is not expressed in CIS with extension along the RAS^[76]. The results indicate that laminin-5-gamma-2 chain is a useful marker of determining the T factor. Heparanase and its transcriptional factor, hypoxia-inducible factor-1a, contribute to the invasion and meta-

static potentials, and are correlated with poor survival in GBC^[77]. Cyclooxygenase-2, a well-known oxidative stress factor expressed in invasive fronts, is also related with poor prognosis of GBC^[78]. The Hedgehog signaling pathway is considered to be a potential therapeutic target for various cancers, and hedgehog signaling factor Gli1 may be involved in the invasive phenotype through the matrix metalloproteinases^[79]. Other, more recently reported factors that may have a prognostic impact in GBC based on multivariate analyses include transmembrane protease/serine 4^[80], loss of microRNA-335^[81], aldehyde dehydrogenase-1A3 overexpression, and decreased glutathione peroxidase-3 expression^[82].

PATHOLOGICAL EXAMINATION FOR OPTIMAL SURGERY

Preoperative diagnosis using an imaging study is very important for selecting the optimal surgery according to T-stage. However, preoperative diagnosis of the T-stage in T1 or T2 GBC is not easy, and it is especially difficult in GBC arising in the gallbladder concomitant with adenomyomatosis, despite advances in medical imaging^[83]. As a result, stage T1 or T2 GBC is often discovered incidentally after routine cholecystectomy. In such cases, pathological evaluations of prognostic factors using entire tumor sections can be used to determine the need for additional extended radical surgery. Intraoperative histological examination is usually performed during surgery for lesions preoperatively diagnosed as “suspected GBC” or “possible T1 or T2 GBC”. In such cases, the resected specimen from cholecystectomy with or without en bloc liver resection (S4a+5 or liver bed) is submitted for intraoperative histological examination. However, diagnosis of the depth of invasion from frozen sections of GBC is a difficult task, and care must be taken to avoid obstructing the pathological diagnosis of formalin-fixed specimens when the tumor lesion is small.

CONCLUSION

This review has documented the basic knowledge and surgical strategies for GBC based on clinical and pathological data from previous studies. Discrimination of favorable cases, particularly T2 or T3 lesions, is useful for the selection of surgical strategies for individual patients. To establish useful prognostic markers or factors, further accumulation of studies is needed. As GBC is often discovered incidentally after routine cholecystectomy and definite preoperative diagnosis is often difficult, close cooperation between surgeons and pathologists is essential for developing a rational surgical strategy for GBC.

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