

Extent of resection for T2N0 gallbladder carcinoma regarding concurrent extrahepatic bile duct resection

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Backgrounds/Aims: Gallbladder carcinoma (GBCa) T2 lesions are considered to be advanced tumors showing diverse features in tumor extent. When this T2 lesion does not involve the cystic duct and there is no evidence of lymph node metastasis, we have to consider what is the most reasonable extent of resection - that is, whether to perform concurrent extra-hepatic bile duct resection (EHBD) resection or not. This study intends to evaluate the adequacy of EHBD resection in patients undergoing resection for T2N0 GBCa. **Methods:** From our institutional database of GBCa, 48 cases of T2N0 GBCa who underwent R0 resection during November 1995 and August 2008 were selected. Patients who underwent prior laparoscopic cholecystectomy were excluded. Their medical records were reviewed retrospectively. **Results:** Their mean age was 63.2±83.3 years and females were 25. The mean serum CA19-9 level was 37.3±89.3 ng/ml. The extents of liver resection were wedge resection (n=36) and segment 4a+5 resection (n=12). Concurrent EHBD resection was performed in 16 (33.3%) patients. No fatal surgical complication occurred. The majority of tumor pathology was adenocarcinoma (n=42), with additional unusual types as papillary (n=3), sarcomatoid (n=1), signet ring cell (n=1) and adenosquamous (n=1) cancers. The overall survival rate was 87.1% at 1 year, 69.5% at 3 years and 61.7% at 5 years. After exclusion of mortalities not related to cancer, the overall patient survival rate was 89.6% at 1 year, 72.9% at 3 years and 64.7% at 5 years, with 3-year survival rates of 72% in the EHBD resection group and 69.2% in the non-resection group ($p=0.661$). **Conclusions:** The results of this study indicate that concurrent EHBD resection did not improve patient survival when R0 resection was achieved in patients with T2N0 GBCa. Therefore, routine EHBD resection may not be indicated for T2N0 GBCa unless the tumor is close to the cystic duct. (Korean J Hepatobiliary Pancreat Surg 2012;16:142-146)

Key Words: Gallbladder carcinoma; Extrahepatic bile duct resection; Extended cholecystectomy; Recurrence

INTRODUCTION

Gallbladder carcinoma (GBCa) is a relatively rare tumor, however, its prognosis has been poor over the past few decades. There is no effective therapy for GBCa except for curative surgical resection. The prognosis for patients with early GBCa shows a 5-year survival rate of 82-100%.¹⁻³ Due to the anatomical proximity to important organs, surgery for advanced GBCa requires an aggressive approach. For T2 or more advanced tumors, it is advocated to perform radical resection with lymph node dissection. It was reported that a second radical resection was associated with a significantly better survival than simple cholecystectomy alone in T2 GBCa patients whose

cancers were incidentally found after cholecystectomy - whereas it was reported that 40.5% of patients with unapparent pT2 tumors survived for more than 5 years after cholecystectomy alone.⁴ Partial hepatectomy (extended cholecystectomy or segment 4a+5 hepatectomy) combined with extra-hepatic bile duct (EHBD) resection and lymph node dissection is a recommended operation for the treatment of T2 GBCa, although the surgical procedure remains controversial, and there is no standard operation.¹

It is difficult to propose reliable treatment guidelines for T2 GBCa, although some surgeons recommend a routine resection of EHBD. However, the possibility of post-EHBD resection complications and the lack of a survival advantage lead us to question its rationale. This

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Table 1. Operation profiles of 48 patients with pT2 no gallbladder cancer according to concurrent resection of extrahepatic bile duct (EHBD)

Group	EHBD resection (n=16)	EHBD non-resection (n=32)
Extended cholecystectomy	14	22
Segment 4a+5 resection	2	10
Surgical complications	2*	3*

*All were wound complications

study intended to evaluate the adequacy of EHBD resection in patients undergoing resection for T2N0 GBCa.

METHODS

Patient selection

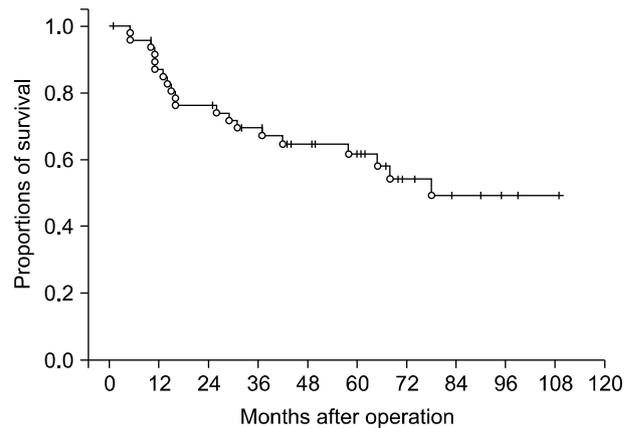
From our institutional database of GBCa having more than 600 cases having undergone surgical resection, 48 cases of T2N0 GBCa who underwent R0 resection during November 1995 and August 2008 were selected, all having had a follow-up period for more than 4 years. Patients who underwent prior laparoscopic cholecystectomy were excluded to avoid unnecessary bias. Their medical records were reviewed retrospectively after approval by the Institutional Review Board of our institution.

Performance of concurrent extrahepatic bile duct resection

In this study, EHBD resection was performed according to surgeons' preference and surgical findings, thus not being randomly assigned. The extent of liver resection, extended cholecystectomy or segment 4a+5 hepatectomy, was also determined by surgeons' preference. Tumor cell presence at the cystic duct resection margin upon intraoperative frozen-section biopsy was absolutely indicated for EHBD resection. To avoid reconstruction-related biliary complications, the proximal EHBD was transected at the hilar confluence portion and reconstructed with Roux-en-Y choledochojunostomy. No external biliary drainage was applied in this series.

Statistics

Numerical variables were presented as means with standard deviations or as medians with ranges. Survival and recurrence rates were determined by the Kaplan-

**Fig. 1.** The overall survival curve of 48 patients with pT2N0 gallbladder carcinoma.

Meier method and compared by the log-rank test. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

The mean age of 48 patients was 63.2 ± 83.3 years (range: 48-82) and females were 25. Mean serum CA19-9 level was 37.3 ± 89.3 ng/ml (range: 1.5-505).

The extents of liver resection were wedge resection (n=36) and segment 4a+5 resection (n=12). Concurrent EHBD resection was performed in 16 (33.3%) patients (Table 1). No significant surgical complications requiring surgical or radiological intervention occurred, except for wound complications requiring repair. All patients recovered from these types of surgery.

The majority of tumor pathology was adenocarcinoma (n=42), with additional types as papillary (n=3), saromatoid (n=1), signet ring cell (n=1) and adenosquamous (n=1) cancers.

The overall survival rate was 87.1% at 1 year, 69.5% at 3 years and 61.7% at 5 years (Fig. 1). Comparison of the overall patient survival curves depending on EHBD resection did not show a significant difference ($p=0.933$) (Fig. 2). After exclusion of mortalities not related to cancer recurrence, the patient survival rate was 89.6% at 1 year, 72.9% at 3 years and 64.7% at 5 years, with 3-year survival rates of 72% in the EBDR group and 69.2% in the non-EBDR group ($p=0.661$) (Fig. 3).

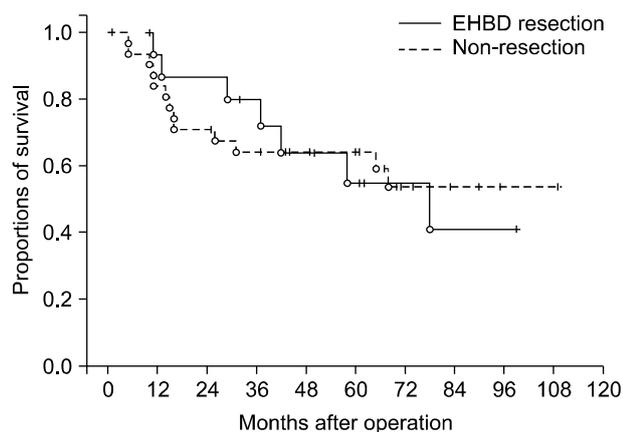


Fig. 2. Comparison of the overall patient survival curves according to the extrahepatic bile duct resection.

DISCUSSION

The presence of cancer in the EHBd in a GBCa patient can arise from various potential oncological features. GBCa due to causes such as gallstones, pre-existing porcelain gallbladder or gallbladder polyps following which the EHBd may be involved by three of the four patterns described by Shimizu et al.⁵ as follows: type I (direct spread from the primary tumor), type II (continuous intramural spread along the cystic duct to the EHBd), and type IV (permeation of tumor cells from metastatic lymph nodes in the hepatoduodenal ligament). In contrast, type III tumor (involvement of the EHBd non-contiguous with the gallbladder tumor) also can exist.

Involvement of the EHBd non-contiguous with GBCa (type III tumor) is based on the concept of field cancerization (the entire biliary tree is at a risk for developing a malignancy due to exposure to a potentially carcinogenic process or substance).⁶ In such cases, the method of EHBd involvement can be divided into retrograde (secondary to an anomalous pancreaticobiliary duct junction [APBDJ] with the consequent exposure of the biliary tree to the refluxing mixture of pancreatic and biliary juices^{7,8} or antegrade GBCa along with a synchronous/ metachronous malignancy in the EHBd distal to the attachment of the cystic duct), as seen in patients with gallstones but in the absence of APBDJ. Although there is a potential for the above-described pathways, the actual incidence of synchronous lesions in the EHBd in a GBCa patient is low. In a clinical series from Japan, where APBDJ as a cause for GBCa is more common, the incidence of syn-

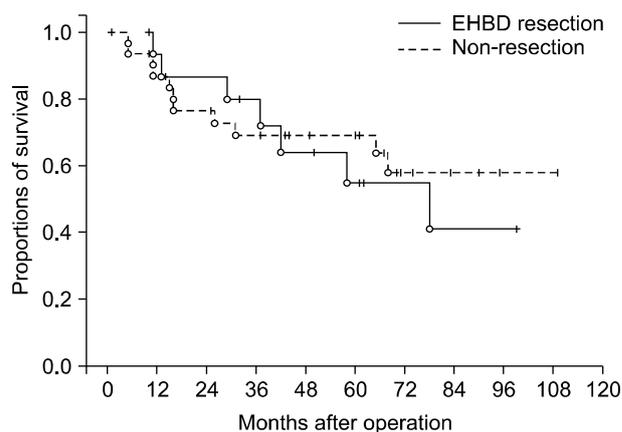


Fig. 3. Comparison of the overall patient survival curves according to the extrahepatic bile duct resection, with exclusion of mortalities not related to cancer recurrence.

chronous tumors in the EHBd and the gallbladder has been reported to be only 5-7.4%.⁹⁻¹¹

Literature on the role of EHBd resection for GBCa is confusing and also contradictory. EHBd resection was often proposed as a part of a radical resection for all stages of GBCa.^{5,12-14} In the early stages of GBCa, the reasons for EHBd resection are to facilitate clearance of the lymph nodes in the hepatoduodenal ligament and occult cancer cells in the connective tissue. In contrast, in the advanced stages, it also becomes a part of a radical resection with additional removal of the perineural invasion.¹⁵

Suzuki et al.¹⁶ suggested that a routine EHBd resection should be performed in patients with pT2 disease, based on their experience in treating 20 patients. However, in 8 of the 20 patients who had tumors in the fundus and body of the gallbladder, the EHBd was not resected and the median survival in this group was 64 months with no recurrence. Moreover, they also had two anastomotic leaks (16.7%). Shimada et al.¹⁷ supported the routine resection of the EHBd for T2 lesions, based on their experience with 41 patients for whom they performed a radical resection including excision of the EHBd for all patients with pT2 disease and above. They found that in patients with T2 disease there was a 3-year survival rate of 60%; and a 5-year survival rate of 49% in those who underwent a curative resection as opposed to a 0% 3-year survival rate in those who did not undergo a curative resection. Nagakura et al.¹⁸ found that nodal micrometastasis and perineural invasion were important determinants of

post-radical-resection survival in GBCa. However, they did find that perineural invasion was uncommon in T1b cancers, which tended to spread locally.⁴ They also found that extended resections were significantly associated with improved survival in the 54 patients with T2-4 disease. Based on these findings, they suggested that routine EHBD resection is essential in all patients with T2-4 disease.¹⁸ Chijiwa et al.¹⁹ suggested EHBD resection as part of radical resection for all patients with stages I to III GBCa, based on the perceived survival advantage. They performed EHBD resection (either alone or as part of a pancreatoduodenectomy) in 24 of the 52 patients studied, and encountered three anastomotic leaks.

Considerable data has accumulated over the last few years to substantiate the argument that routine EHBD resection is not warranted in GBCa. One of the reasons for this lies in the fact that it has not provided sufficient evidence to suggest a positive influence on survival.^{17,20-24} The other reason is that EHBD resection with its reconstruction is associated with an increased risk of early biliary anastomotic leak and late-onset stricture and subsequent cholangitis.^{17,23-25} At this time, we should not disaffirm the role of EHBD resection, because, in the presence of enlarged portocaval nodes encountered in T2 tumors, concurrent EHBD resection may be necessary to facilitate clearance of the hepatoduodenal ligament. Thus, for T2 cancers, in the absence of gross nodal disease, a resection that includes cholecystectomy with wedge resection of the gallbladder bed and segment 4a+5 resection, along with a regional lymph nodal dissection, has been shown to constitute a curative surgery.^{26,27}

While theoretically there is the possibility of involvement of the EHBD in GBCa, the synchronous existence of a malignancy in the EHBD and the gallbladder is uncommon. In the absence of convincing data to demonstrate a survival advantage for the routine EHBD resection in GBCa, the morbidity of the procedure needs to be taken into consideration. This is because the most important complication following EHBD resection and biliary reconstruction is the development of an anastomotic leak and subsequent stricture formation, leading to repeated attacks of cholangitis. Special attention is necessary to transect the proximal EHBD, especially when the common bile duct is not dilated. With these efforts, there was no biliary reconstruction-related complication in this

series.

As simply shown in the results of this study, concurrent EHBD resection did not improve patient survival when R0 resection was achieved in patients with T2N0 GBCa. Therefore, EHBD resection may not be indicated routinely for T2N0 GBCa unless the tumor is close to the cystic duct. However, it is clear that lymph node status should be evaluated during operation before deciding on preservation of the EHBD, because any lymph node metastasis can provide a rationale to support concurrent EHBD resection.

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