

## RESEARCH COMMUNICATION

# Prognosis and Management for Gallbladder Cancer with Hepatic Invasion: Long-term Results of 139 Patients from a Single Center in China

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### Abstract

**Objective:** To improve the diagnosis of primary gallbladder carcinoma (GBC) with/without hepatic metastases by analyzing our experience of different GBC treatment in our patients. **Methods:** A retrospective study was carried out to analyze the clinical data of the 139 patients with GBC who underwent hepatic resection in our unit from January 2003 to December 2007. Patients were divided into two groups according to whether they demonstrated hepatic invasion. Tumor presentation, surgical modes, and prognosis of each patient were retrospectively reviewed. Kaplan-Meier curves and log-rank tests were employed to compare the survival rates of those patients undergoing different surgical procedures. **Results:** Of the 139 patients, 46 were men and 93 were women with the male to female ratio of 1:2.0. Their ages were ranged from 35 to 86 years with a mean age of  $62.8 \pm 10.4$  years. There were 73 patients complicated with hepatic invasion (group A), and no hepatic invasion occurred in the other 66 patients (group B). Compared with the group B, the patients with hepatic invasion suffered lower differentiation of tumor ( $p=0.000$ ), more advanced Nevin staging ( $p=0.008$ ) and poorer prognosis ( $p=0.013$ ). Radical resection were more frequently performed in group B (75.76%) than in group A (45.20%) with better outcomes ( $p=0.000$ ). **Conclusion:** GBC patients complicated with hepatic invasion had poorer prognosis than those without invasion in long-term follow-ups. Radical resection might result in a satisfied prognosis in patients without hepatic invasion, but appears less favorable than palliative resection in those who were complicated with hepatic invasion.

**Keywords:** Gallbladder cancer - hepatic invasion - long-term prognosis - surgical management

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### Introduction

Gallbladder carcinoma (GBC) is one of the most common lethal biliary tract malignancies with poor prognosis (Ishikawa et al., 2003), which is usually detected at an advanced stage due to its non-specific symptoms (Moore et al., 2010). The 5-year mortality rate of GBC patients varies from 35 to 100% in most large series (Fong et al., 2000; Lazcano-Ponce et al., 2001; Dixon et al., 2005). The spread modes of gallbladder carcinoma include direct invasion, lymphatic, vascular, neural, intraperitoneal, and intraductal metastasis. The liver is the most commonly suffered organ by direct invasion, followed by regional lymph node metastasis (Kokudo et al., 2003).

Previous studies demonstrated that there were two ways of hepatic metastasis in the GBC, namely the extensive pattern and the infiltrating pattern. Two ways of tumor invasion have been noted in the infiltrating pattern, of which one is located in hepatic parenchyma, which is

the most common site of the main tumor, where the front part of the tumor involving vascular infiltration invades the hepatic hilum along with the Glisson's sheath. The other is localized in the hepatic metastasis near the gallbladder bed. It was reported that the most important route of early hepatic metastasis from gallbladder carcinoma seemed to be the portal tracts (Lin et al., 2005).

It is still controversial in regards of the surgical procedures for gallbladder cancer, with surgeons recommending operations ranging from simple cholecystectomy to combined extended hepatectomy with common bile duct resection in the same stage. Radical surgery is advocated for patients in Stages II and III. However, considering the particularly poor prognosis of Stage IV patients, debate can be expected to continue as to the relative risk-benefits of such advanced stage patients with radical surgery (Meng et al., 2011). Given these facts, we here assessed the related surgical procedures and discuss the prognosis of patients undergoing different resections.

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## Materials and Methods

### Patients

Patients with the diagnosis of GBC who received surgical treatment at our center were collected in the First Affiliated Hospital of Medical College, Xi'an Jiaotong University from January 2003 to December 2007. Hepatic invasion lesions were found by radiological methods including CT scan and magnetic resonance imaging (MRI). All of these lesions were defined in surgical procedures and confirmed by pathological examination.

### Surgical procedures

Surgical procedures were divided into palliative surgery and radical surgery. The palliative surgery included exploratory laparotomy, simply cholecystectomy, bile drainage of tumor-induced obstruction or biopsy. Palliative procedures were performed in 56 patients (40.29%). Forty-four patients underwent simple cholecystectomy and twelve underwent cholecystectomy and hepatic wedge resection of segments IVb and V.

The radical surgery were referred to as the extensive resection of primary the tumor and the peripheral hepatic tissues and metastatic lymph nodes. Totally, 83 patients underwent radical resection in this study, in which 33 patients underwent hepatic wedge resection of segments IVb and V, 35 patients underwent dissection of lymph nodes in the hepatoduodenal ligament and the posterosuperior pancreaticoduodenal nodes and 15 patients underwent extended radical surgery (including partial gastrectomy or colectomy), because of tumor adherence or invasion. None of the patients who underwent radical cholecystectomy had grossly positive resection margins.

### Data extraction and follow-up

Data collected from chart review, office visits, and a telephone questionnaire included patient demographics, laboratory data, operative management, surgical morbidity, length of hospital stay, pathologic findings, and long-term follow-up. The collected cases were individually evaluated for necessary information, and details were extracted and computerized for further analysis. Potential prognostic determinants that were coded included patient demographics, clinical and histologic findings. The data were pooled to determine the risk factors of prognosis in GBC patients with or without hepatic invasion.

### Statistical analysis

The descriptive variables were expressed as median value (inter-quartile range), and the overall survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. SPSS version 15.0 statistic software (SPSS Inc, Chicago, IL) was used for data analysis and a *p* value less than 0.05 was considered statistically significant.

## Results

### Characteristics of GBC patients

Of the 139 patients with the diagnosis of gallbladder cancer, 73 were complicated with hepatic invasion

(Group A), while the other 66 patients suffered no hepatic invasion (Group B). The average age of the patients was  $62.83 \pm 10.36$  years (range from 35 to 86 years). A male-to-female ratio of 0.5 (46/93) was calculated for the overall series and for patients in different groups (25/48 and 21/45, respectively). There were no significant difference in average age or gender between the groups with or without hepatic invasion ( $p=0.863$ ,  $p=0.857$ , respectively). The positive rate of cholelithiasis in the Group A was higher than in the Group B ( $p=0.010$ ) (Table 1).

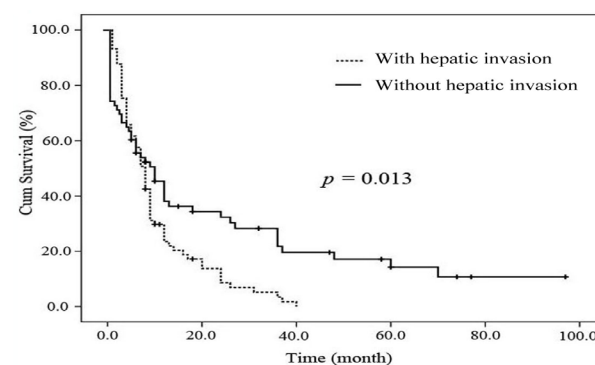
### Tumor characteristics of GBC patients with or without hepatic invasion

In the 139 patients with histologically proven gallbladder cancer, 87.77% patients (122/139) were adenocarcinomas and 12.23% (17/139) were adenosquamous cell carcinomas. Tumor grading in the 139 patients was as follows: high degree, 24 patients (17.27%); moderate degree, 27 patients (19.42%); low degree, 88 patients (63.31%). Eight out of ten (81.29%) patients' tumor were located at fundus and body of gallbladder, followed by neck (12.95%) and other locations (5.76%) (Table 1).

**Table 1. Clinical Characterization of Gallbladder Cancer with or Without Hepatic Invasion**

Subject	Group A With hepatic invasion (n = 73)	Group B Without hepatic invasion (n = 66)	p Value
Age (year)	62.97±10.47	62.67±10.32	0.863
Sex			0.857
Male	25 (34.25%)	21 (31.82%)	
Female	48 (65.75%)	45 (68.18%)	
Cholelithiasis*			0.01
No	34 (46.58%)	45 (68.18%)	
Yes	39 (53.42%)	21 (31.82%)	
Tumor localization			0.535
Fundus and Body	58 (79.45%)	55 (83.33%)	
Neck	10 (13.70%)	8 (12.12%)	
Others	5 (6.85%)	3 (4.55%)	
Histologic type			0.196
Adenocarcinoma	67 (91.78%)	55 (83.33%)	
Squamous carcinoma	6 (8.22%)	11 (16.67%)	
Differentiation**			0
High degree	4 (5.48%)	20 (30.30%)	
Moderate degree	13 (17.81%)	14 (21.21%)	
Low degree	56 (76.71%)	32 (48.48%)	

\* $p<0.05$ ; \*\* $p<0.01$

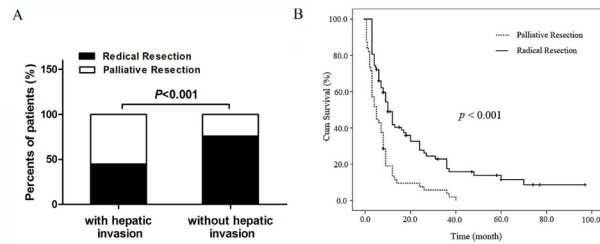


**Figure 1. Overall Survival of GBC Patients with/Without Hepatic Invasion.** There was significant difference between two groups of GBC patients ( $p=0.013$ )

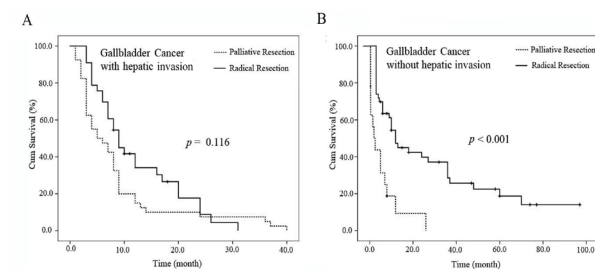
**Table 2. Survival of Gallbladder Cancer with or Without Hepatic Invasion**

Survival	Group A With hepatic invasion (n = 73)	Group B Without hepatic invasion (n = 66)	p Value
> 6 months	45 (61.64%)	38 (57.58%)	0.625
> 1 years	19 (26.03%)	25 (37.88%)	0.134
> 2 years*	8 (10.96%)	17 (25.76%)	0.023
> 3 years**	3 (4.11%)	13 (19.70%)	0.006
> 5 years**	0 (0)	7 (10.61%)	0.005

\*p<0.05; \*\*p<0.01



**Figure 2. Different Outcomes of Surgical Management Performed in GBC Patients.** A. Overall survival of different surgical managements for GBC patients; B. Radical resections were performed lesser in GBC patients with hepatic invasion than those without



**Figure 3. Outcomes of Different Surgical Management Performed in GBC Patients with or Without Hepatic Invasion.** A. There was no difference in outcomes between different surgical managements for GBC patients with hepatic invasion ( $p>0.05$ ); B. There was significant difference in outcomes between different surgical managements for GBC patients without hepatic invasion ( $p<0.001$ )

#### Overall Survival of GBC patients with or without hepatic invasion

The overall outcome of GBC patients without hepatic invasion were better than those with hepatic invasion (Figure 1). The 0.5-, 1-year survival rates in Group A and Group B were 61.64%, 26.03%, and 57.58%, 37.88%, respectively. However, there was no significant difference in the short-term survival between the two groups. In contrast, the postoperative 2-, 3- and 5-year survival rates of the patients without hepatic invasion were 25.76%, 19.70% and 10.61%, respectively, which were significantly better than those with hepatic invasion (Table 2).

#### Operative procedures in different groups

The tumor localization significantly determined the necessity of macroscopically complete resection. There were 33 patients (45.20%) and 50 patients (75.76%) underwent radical resection in group A and group B, respectively. The overall survival rates of different surgical procedures were different. The outcomes of GBC

patients underwent radical surgery were better than those underwent palliative surgery in integrity level ( $p<0.001$ ).

#### Outcomes of surgical management performed in different groups

In different groups, different results were obtained in the radical and palliative surgery in long-term follow-up. In group A, there was no significant difference between radical and palliative surgery ( $p>0.05$ ), however, radical surgery achieved better outcomes than palliative surgery in group B ( $p<0.001$ ).

## Discussion

The prognosis of patients with gallbladder carcinoma remains dismal especially in advanced cases. Even with the increasing safety of hepatic and pancreatic surgery, the morbidity and mortality of major surgery procedures hasn't been reduced in recent reports, which is probably due to its non-specific symptoms, delay in detection at an advanced stage and early metastasis. Moreover, the outcome of different surgical procedures was still controversial. Some surgeons supported that radical resection were associated with a high morbidity (53%) and mortality (5%) (D' Angelica et al., 2009). However, others believed that various radical procedures should be advocated to improve the curative outcome for advanced gallbladder cancer (Meng et al., 2011).

As the most common site of metastasis of gallbladder carcinoma, the patterns of direct hepatic invasion had been reported before (Shirai et al., 1995). Some authors indicated that venous blood from the gallbladder is drained into segments IV and V by short direct communicating veins or by veins accompanying the extrahepatic ducts into the liver (Boerma et al., 1994). This observation explained the reason why the initial location of liver metastasis was adjacent to the gallbladder, mostly in segments IV and V, rather than the distant sites of the liver. Additionally, there were two patterns of hepatic infiltration reported by Ogura Y et al. (1998). The most common site of the main tumor was located in hepatic parenchyma (Ogura et al., 1998), localized hepatic metastases from gallbladder carcinoma near the gallbladder bed were also reported. The most important route of early hepatic metastasis from gallbladder carcinoma seemed to be the portal tracts (Lin et al., 2005).

Decision of hepatic resection for advanced carcinoma of the gallbladder should be based on the way of liver metastasis. Most surgeons agreed that disease of the early stage did not require any operation other than simple cholecystectomy. It was reported that the prognosis was good, although the morbidity of radical surgery was not justified (Suzuki et al., 2004). However, there are still many questions unresolved. Firstly, whether such radical resections are warranted for GBC with hepatic invasion is still unknown. Furthermore, among the many tumor staging systems, which is the most useful criteria for prediction of prognosis for gallbladder cancer, for selection of patients for adjuvant therapy, and for stratification of patients in clinical trials? In addition, are radical resections warranted after noncurative cholecystectomy of the many

GBC patients who were supposed as gallstone previously?

As far as we know, advanced GBC is one of the most biologically virulent malignancies and is notoriously difficult to cure, especially when it is associated with lymph node metastasis and/or liver metastasis (Lin et al., 2005). Chemotherapy and radiation therapy are not effective in the treatment of gallbladder cancer, and adjuvant therapy after cholecystectomy or complete resection is not encouraged. Only a few recent reports demonstrated the long-term survival after radical resection for advanced GBC (Nishio et al., 2007).

Why the prognosis of patients with GBC in advanced stage is dismal even with extensive radical surgery and other nonsurgical therapies? We speculate that factors contributing to these dismal outcomes include the anatomic proximity of the gallbladder to the porta hepatis and the aggressive biologic nature of this cancer. Furthermore, GBC is usually detected at an advanced stage due to no specific symptoms (Gourgiotis et al., 2008). Organs in proximity such as the duodenum, the hepatic flexure of the colon, and the pancreas, bring up with technical challenges in achieving a margin negative, potentially curative resection (Dixon et al., 2005).

In summary, there is still much work to do to evaluate the value of various types of resection for gallbladder carcinoma. To achieve this goal, further analysis of the GBC's surgical procedures will be definitely necessary in the subsequent process.

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