

# Impacts Of Tumor Location On Prognosis Of Patients With Gallbladder Carcinoma

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## Research

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# Abstract

**Objective:** To investigate the impacts of tumor location on the prognosis of patients with  $T_{1-3}N_{0-1}M_0$  gallbladder carcinoma(GBC) after radical surgery.

**Methods:** Totally, 136 patients with stage T1-3 gallbladder carcinoma after radical surgery from 2000 to 2018 were enrolled and divided into two groups according to anatomic location of GBC (neck /body and fundus). The clinicopathological features and survival time were compared between these two groups. At last, in combination with the difference between the liver side and the peritoneal side of the tumor, survival analysis and multivariable Cox-proportional hazards regression models were performed in GBC patients with survival differences between gallbladder neck and body/fundus tumors.

**Results:** The bile duct invasion, lymph node metastasis, tumor growth pattern, jaundice, albumin, and tumor markers were significantly related to the tumors in neck of gallbladder( $P<0.05$ ). Besides, patients with GBC in body and fundus of gallbladder had a higher rate of appearing microscopic liver metastasis( $P<0.05$ ). Survival analysis showed that there was significant difference on patients with stage T2 GBC in different tumor location (neck /body and fundus), but no significant difference on stage T1 and T3. Further combining the differences between the liver side and the peritoneal side of the tumor, tumor location, lymph node metastasis, bile duct invasion, microscopic liver metastasis, tumor differentiation, and jaundice were deemed as prognostic factors according to univariable survival analysis. Among these factors, multivariable Cox analysis showed that lymph node metastasis and tumor location were independent prognostic factors for survival of patients with T2 GBC ( $P <0.05$ ).

**Conclusions:** Tumor location is an important prognostic factor for GBC, especially for the patients with T2 stage. Besides the survival differences between the hepatic-side and peritoneal-side tumors, tumor in neck is also one of the factors predicting the poor prognosis at T2 stage. GBC in neck was more prone to cause bile duct invasion, lymph node metastasis and jaundice. However, tumors in body and fundus were more likely to appear microscopic liver metastasis. Further refinement of the surgery for T2 GBC according to the tumor location may improve their survival time.

## Introduction

Gallbladder carcinoma(GBC) is one of the most common biliary tract malignancy and has a rising trend of incidence year by year<sup>[1-2]</sup>. Globally, the incidence of GBC is about 2-3/100,000, but the mortality rate is extremely high, which is about only 5%<sup>[3-4]</sup>. Surgery is currently the only treatment that may offer a chance of cure<sup>[10]</sup>. R0 resection can improve the survival of patients with GBC greatly. However, the mechanism of the occurrence and development about GBC is not very clear. Just only 10% of patients can get curative resection<sup>[5-6]</sup>. Further exploring prognostic factors of GBC to guide clinical treatment may be needed.

Many factors will impact the overall survival of patients with GBC such as pathological stage, histological grade, and lymph node metastasis [7-8]. However, some factors remain controversial like its location. Due to the anatomically busy position and incomplete serosa of the gallbladder, whether tumor location has an impact also on the survival of GBC patients has attracted attention of researchers [7, 9]. Shindoh found in a recent study that the patients with GBC of hepatic-side location had a worse survival compared to patients with peritoneal-side tumor location in the T2 stage<sup>[10]</sup>. Subsequent research also proved the reliability of this view<sup>[11]</sup>. However, Besides hepatic-side and peritoneal-side tumors, whether the tumor in gallbladder neck could be deemed as an important prognostic value on the patients with GBC remains unknown.

Therefore, this study was designed to analyze the data of patients with T<sub>1-3</sub> GBC undergoing curative surgery in our hospital retrospectively, and to explore whether the anatomical location, which focuses on the location of gallbladder neck, had an impact on survival of these patients and to what extent did it impact when combined with differences between hepatic-side and peritoneal-side tumor locations.

## Patients And Methods

### Patients selection

A total of 136 cases of patients with stage T<sub>1-3</sub>N<sub>0-1</sub>M<sub>0</sub> GBC undergoing radical surgery from January 2000 to December 2018 at the 904th Hospital of Joint Logistic Support Force of PLA(China) were enrolled in this study. All patients underwent R0 resection (R0 resection is defined as a complete resection with no microscopic residual tumor). Some patients receiving chemotherapy use the well-tolerated oxaliplatin combined with gemcitabine regimen<sup>[12-13]</sup>. Inclusion criteria: a. All patients with GBC were confirmed by postoperative pathology and received radical surgery; b. The data of these patients was complete. Exclusion criteria: a. Preoperative examination has clearly indicated a loss of surgical opportunity, and those who undergo palliative surgery or had an unresectable tumor; b. Pathological data are incomplete, or the location of the tumor cannot be determined; c. Perioperative or non-tumor-related death; d. combined with tumors of other systems; e. Patients difficult to determine the location of the tumor (like perihilar cholangiocarcinoma extended to the gallbladder and a part of gallbladder carcinoma extended to the hilum)<sup>[10,14]</sup>.

### Surgical strategy

All 136 patients underwent different ways of radical surgery according to their Pathological stage<sup>[15]</sup>: a. T1a patients undergo simple cholecystectomy, and T1b-T3 patients undergo radical cholecystectomy (complete removal of the gallbladder and hepatectomy including wedge resection of at least 2cm away from the gallbladder bed); b. All patients with stage T1b-T3 undergo regional lymph node dissection within the hepatoduodenal ligament; c. Perform extrahepatic bile duct(EHBD) resection when frozen section diagnosis showed positive and residual lesion cannot be completely removed by additional bile duct resection during the operation; d. According to the specific situation during the operation, determine

whether to perform a larger range of resection, such as extended right hepatectomy, to ensure R0 resection.

## Grouping

Refer to the “General Rules for Clinical and Pathological Studies on Cancer of the Biliary Tract”<sup>[9]</sup>, the GBC was divided into three equal parts including neck, body and fundus. Meanwhile, according to the study of Shindoh et al<sup>[10]</sup>, the GBC was divided into hepatic-side (Gh) and peritoneal-side (Gp) tumors. Then, the 136 patients were grouped according to their tumor location: a. According to the macroscopic manifestations of surgical specimens and pathological sections, tumors that involved the neck or cystic duct of the gallbladder were classified as neck-side GBC (Gn), including tumors that expand from the neck to the body or fundus; Tumors in body and fundus were classified, according to the similar way, as body/fundus-side GBC(Gbf); b. Through the points system, record Gn and Gh as 1 point, Gp or Gbf as 0 points, and the final location score(LS) = Gn / Gbf + Gh / Gp. According to these points, divide GBC patients into 3 groups (LS = 0/1/2).

## Observation indicators

The data of the 136 patients collected through the medical record department of our hospital was included in this study (see Table 1-3 for details):

- (1) Preoperative indicators: age, gender, comorbidities, gallbladder stones, etc .;
- (2) Pathological features: pathological stage, histological grade, anatomical location, lymph node metastasis, etc .;
- (3) Postoperative evaluation: Overall survival (OS) was used as the evaluation standard of prognosis, of which the unit was month.

## Follow-up

Patients were followed up for survival by telephone, with a median follow-up time of 23.9 (1-97) months (as of January 2020). In addition, postoperative patients were strictly followed up every 3-6 months, to keep general examinations such as tumor markers and abdominal ultrasound after surgery. If they had a suspicious recurrence, further magnetic resonance imaging or enhanced CT was used to confirm the lesion.

## Statistical analysis

All the data were analyzed by IBM SPSS 23.0 statistical software. The continuous data between groups was compared by t test or Mann-Whitney’s U test, and the categorical data between them was compared by  $\chi^2$  or Fisher’s exact probability test. Kaplan-Meier method was used for survival analysis. Survival differences were examined by using log-rank test in univariate analysis. The Cox-proportional hazards

model was used for multivariate analysis to identify independent prognostic factors.  $P < 0.05$  was considered statistically significant.

## Results

### Basic characteristics

Among the 136 patients, 52 were male and 84 were female; And the median age was 64 years (range, 36-85 years). Their median survival time was 13 months (range, 1-95 months), and the average survival time was 20.32 months. The 1-, 3- and 5-year survival rates of them were 53.7%, 18.2%, and 9.2%.

Postoperative pathology revealed 134 cases of gallbladder adenocarcinoma and 2 cases of adenosquamous carcinoma. According to the 8th edition of AJCC staging, there were 21 patients in T1 stage, 64 in T2 stage, and 51 in T3 stage. According to the tumor location of GBC, 59 cases were located in the neck of the gallbladder, 77 cases in the body or fundus, 83 cases in the hepatic-side, and 53 cases in the peritoneal-side. All patients underwent radical resection according to their staging. Among them, 29 patients underwent extrahepatic bile duct resection due to the bile duct invasion confirmed during the operation and cannot be completely removed through more bile duct resection, including 23 cases of Gn and 6 cases of Gbf. 5 patients underwent right hepatectomy because of the extensive hepatic lobes invasion found during the operation. 2 patients underwent extended gastrointestinal resection/colectomy due to the invasion of adjacent gastrointestinal tract. And one patient underwent pancreaticoduodenectomy due to the invasion of the pancreatic head. 38 patients received oxaliplatin combined with gemcitabine chemotherapy after operation. All of them were well tolerated and no malignant chemotherapy events occurred (such as MODS or myelosuppression).

### Comparison of patients' clinicopathological features between Gn and Gbf

Comparing the clinicopathological features of 136 patients with GBC, the results summarized in Table 1 showed that there were no significant differences between the two groups in terms of sex, age, tumor location (hepatic/peritoneal side), and the AJCC stage ( $P > 0.05$ ). However, they had some differences in their characteristic manifestations. First of all, more patients with Gn had bile duct invasion (57.6% vs. 10.4%,  $P < 0.05$ ) and lymph node metastasis (55.9% vs. 33.7%,  $P < 0.05$ ) than patients with Gbf. On the other hand, there were more patients with microscopic liver metastasis in the Gbf than those in the Gn (29.9% vs. 10.2%,  $P < 0.05$ ). Then, preoperative laboratory tests showed that patients with Gn had a higher TBIL levels than those with Gbf (24.4 vs. 13.6  $\mu\text{mol} / \text{L}$ ,  $P < 0.05$ ), and their albumin levels were lower than those with Gbf (38.1 vs. 42.2  $\text{g} / \text{L}$ ,  $P < 0.05$ ). In addition, Gn showed more invasive growth than Gbf (94.9% vs. 71.4%,  $P < 0.05$ ). Moreover, patients with Gn had a higher levels of preoperative tumor markers CEA (2.8 vs. 1.8  $\mu\text{g} / \text{L}$ ,  $P < 0.05$ ) and CA199 (20.7 vs. 12.8  $\text{U} / \text{ml}$ ,  $P < 0.05$ ) than those with Gbf.

### Survival differences between patients with Gn and Gbf

136 patients were divided into subgroups according to the depth of tumor invasion (T stage). The median survival time of patients in T1 stage was 37 months (range, 13-95 months), and the 1-, 3-, and 5-year

survival rates were 95.2%, 52.4%, and 33.3%; The median survival time of T2 patients was 16 months (range, 2-94 months), and the 1-, 3-, and 5-year survival rates were 60.9%, 18.0%, and 6.7%, respectively; The median survival time in T3 stage was 6 months (range, 1-41 months), and the 1-, 3-, and The 5-year survival rates were 25.5%, 5.9%, and 3.9%.

Comparing the survival differences between patients with Gn and Gbf, the results of survival analysis showed that the overall survival of patients with Gn was worse than those with Gbf (9 vs. 17 months,  $P < 0.05$ ). Furthermore, we compared these differences in different subgroups according to the depth of tumor invasion. The results showed that there was no significant difference in the survival of Gn and Gbf in the T1 and T3 stages ( $P > 0.05$ ). However, the survival of patients with Gn in the T2 stage was significantly worse than those with Gbf (12 vs. 22 Month,  $P < 0.05$ , Figure 1).

### **Impact of tumor location on the survival of patients with T2 GBC**

Among 64 patients with T2 GBC, 21 cases of Gbf on the peritoneal-side location (Gbf+p), 16 cases of Gbf on the hepatic-side location (Gbf+h), 11 cases of Gn on the peritoneal-side location (Gn+p), other 16 cases of Gn on the hepatic-side location (Gn+h). Survival analysis showed no significant difference in survival between Gbf+h and Gn+p (10 vs. 13 months,  $P = 0.056 > 0.05$ ). Based on the differences in the position of the hepatic-side, peritoneal-side, neck, body and fundus, Location score (LS) was adopted to further group T2 stage tumors. The results showed that the LS = 0 group had significantly better survival than the LS = 1 or 2 groups (35 vs. 11/10 months,  $P < 0.05$ ). While, there was no significant difference in survival between the LS = 1 and LS = 2 groups (11 vs. 10 months  $P > 0.05$ ). Further grouping patients with LS=1 or 2 and comparing their survival with the LS = 0 group, the results show that the difference is still statistically significant (35 vs. 11 months,  $P < 0.05$ ). Those patients with LS = 0 had better survival than overall T2 stage (35 vs. 16 months,  $P = 0.007 < 0.05$ ), while those with LS = 1/2 had worse survival than overall T2 stage patients (11 vs. 16 months,  $P = 0.017 < 0.05$ , Figure 2).

### **Prognostic factors of survival in T2 GBC**

14 clinicopathological factors that may have impact on the prognosis of GBC were included into univariate analysis. The results showed that location score (0 vs. 1/2), lymph node metastasis, bile duct invasion, microscopic liver metastasis, tumor differentiation and jaundice were prognostic factors for survival of patients with T2 GBC ( $P < 0.05$ ). However, gender, age, and tumor indicators (CEA and CA199) etc. had no significant predicting value for the prognosis of T2 GBC ( $P > 0.05$ , see Table 2 for details).

Eight factors with significant differences in univariate analysis were further included in the Cox model for multivariate analysis. The results showed lymph node metastases (N0 vs. N+) and location score (0 vs. 1/2) were independent risk factors that had impact on the survival of patients with T2 GBC ( $P < 0.05$ , see Table 3 for details).

## **Discussion**

The question about the impact of GBC location on its postoperative survival has been around for a long time. Recently, Shindoh identified that the prognosis of hepatic-side tumors at T2 stage was significantly worse than that of the peritoneal-side tumors<sup>[10]</sup>. However, besides the survival differences between the hepatic-side and the peritoneal-side, the impact of differences between gallbladder neck and body/fundus on GBC is still controversial. Yamaguchi K et al. first reported in an anatomic experiment that compared with GBC in body and fundus, GBC in neck was closer to the hepatic hilum, including the right hepatic duct and portal vein, and then suggested that GBC in neck may require a wider range of surgical resection for R0 margin<sup>[16]</sup>. Xin-Wei Y et al. also found in a subsequent study<sup>[17]</sup> that GBC in neck is also an independent risk factor for poor prognosis. Maybe the reason was that gallbladder neck tumors had an anatomically busy location, which is prone to cause invasion on adjacent organs such as biliary tracts, portal veins, liver, duodenum, colon. Moreover, in gallbladder neck, a small tumor may have the ability to cause jaundice. In addition, Kurahara H suggested in recent research that GBC located in the neck and cyst duct of gallbladder is more prone to bile duct invasion and lymph node metastasis, which in turn affects patient survival<sup>[9]</sup>. However, Wang Jun-Ke found in a recent study that the anatomical location (neck vs. body and fundus) in advanced GBC did not significantly affect its postoperative survival<sup>[14]</sup>. Although the debate has been around for a long time, there were few exhaustive studies on it, and the specific impact of differences between neck and body/fundus on the prognosis of gallbladder cancer has not been studied combined with differences between the hepatic-side and peritoneal-side tumors. This study found that, similar to the impact of the hepatic-side and peritoneal-side location, the survival difference between the position of neck and body/fundus on patients with GBC after surgery also mainly exists in T2 stage. For T1 and T3 tumors, the overall prognosis of T1 tumors was mostly good, and the overall prognosis of T3 tumors was often poor. The tumor location had no significant impact on their survival. Further, in this study, via the form of points system (LS), the location difference among hepatic-side, peritoneal-side, neck, body and fundus were all analyzed in patients with T2 GBC. The results showed that the gallbladder neck tumors in the peritoneal-side location (LS = 0) had a better prognosis, but patients with GBC in neck/hepatic-side location (LS = 1) or both (LS = 2) have significantly worse prognosis ( $P < 0.05$ ). However, there was no sufficient evidence showing a survival difference between the single neck/hepatic-side tumors (LS = 1) and gallbladder neck tumors in hepatic-side location (LS = 2) ( $P > 0.05$ ).

Gallbladder has a special anatomical location and structure, which is close to adjacent organs and has an incomplete serosa. Therefore, different locations of GBC may cause differences in their features during tumor progression<sup>[10]</sup>. Mostly, GBC occurred in the gallbladder body and fundus, because of biological factors such as bacteria  $\beta$ -glucuronidase degradation, toxic substances deposition and cholestasis<sup>[7]</sup>. On the other hand, it also suggested that the occurrence of gallbladder neck tumors may have differences also with tumors in body and fundus. In this study, when comparing the characteristics of patients with Gn and Gbf, it was found that GBC in neck is more prone to bile duct invasion and lymph node metastasis. However, patients with Gbf were more likely to have microscopic liver metastasis. In addition, patients with Gn had a higher level of TBIL than those with Gbf, which supports the view that gallbladder neck tumors are more prone to jaundice. Meanwhile, patients with Gn had a lower level of

albumin. The cause of this phenomenon may be the impact of cholestasis on the protein synthesis ability of liver.

Inflammation plays an important role in the occurrence and progression of GBC. It is closely related to tumor invasion and migration and is known as the "seventh characteristic" of cancer<sup>[18-20]</sup>. Hao Haiping found that bile acids during cholestasis can control the inflammasome, revealing that jaundice may be associated with inflammation and further affect tumor progression<sup>[21]</sup>. Although the results of this study showed that there was no significant difference in CRP between two groups of Gn and Gbf, the reason of it may be that CRP were affected by any other factors besides jaundice. But, the gallbladder neck tumors had more cases of Infiltrative growth type in tumor growth pattern, and a higher level of CEA and CA199 compared with tumors in body and fundus, suggesting that Gn may be more aggressive than Gbf. The tumor microenvironment of cholestasis may be one of the main reasons.

GBC is hidden and highly aggressive. Most patients have advanced disease at presentation, and the mortality rate is extremely high. Surgery is still the only chance of cure<sup>[10]</sup>. 47% of patients have an opportunity for surgery at the consultation, and R0 resection can greatly improve the prognosis of these patients<sup>[6]</sup>. Patients with T2 GBC account for a significant portion of patients who have a chance of resection, and is the key to improving the overall survival of GBC because of its potential chance for curative resection. Therefore, T2 GBC should be taken as the focus of surgical treatment in GBC<sup>[19, 22]</sup>. This study analyzed the factors that may affect the survival of patients with T2 GBC. The results showed that location score (0 vs. 1/2), lymph node metastasis, bile duct invasion, microscopic liver metastasis, tumor differentiation and jaundice had impact on the survival of patients with T2 GBC ( $P < 0.05$ ). However, this study did not show that extra-serous fat/nerve infiltration is a risk factor for T2 GBC ( $P > 0.05$ ), which may be the reason for the limited depth of infiltration in T2 tumors and the thorough dissection of the fat and nerve tissue during the surgery. In addition, the positive rate of tumor markers CEA and CA199 was not high for T2 GBC in this study. The results of analysis did not show that it has an effective predictive factor on the prognosis of T2 GBC. The study of more sensitive tumor detection methods may be conducive to improving its prognosis via increasing the number of resectable GBC. Moreover, previous studies on chemotherapy in GBC generally believe that postoperative chemotherapy has an effective role in patients with regionally advanced disease, lymph node metastasis, or patients who have not received R0 resection<sup>[23-25]</sup>. But its role in GBC at T1b-T2 stage is still questionable. The first-line recommended chemotherapy regimen of gemcitabine combined with platinum (oxaliplatin) drugs was used in this study. All patients were well tolerated and no malignant adverse events occurred, but the results showed that postoperative chemotherapy could not effectively make the survival of T2 GBC better. Further effective chemotherapy and drugs may be needed for T2 hepatic-side/neck tumors with poor prognosis.

Further multivariate analysis showed that lymph node metastasis and tumor location were independent prognostic factors for GBC. Combined with the previous comparison of clinicopathological features for GBC at different anatomical positions, in order to ensure R0 resection, resection of liver tissue above 2 cm

from the gallbladder bed of the liver may be necessary for hepatic-side tumors to prevent the accident of local residual. However, for neck tumors, extrahepatic bile duct resection and thorough lymph node dissection may effectively extend patient survival.

The debate of extrahepatic bile duct resection has been around for a long time. The previous view was that extrahepatic bile duct resection should be recommended when bile duct invasion was found during surgery according to the frozen section diagnosis<sup>[26]</sup>. Onoe S held that it is difficult to evaluate the bile duct invasion of T2 GBC before surgery, and extrahepatic bile duct resection can effectively prolong the survival of these patients<sup>[27]</sup>. Kurahara H believed that extrahepatic bile duct resection in patients with gallbladder neck tumors could effectively reduce the events of residual lesion or regional lymph node recurrence after surgery and improve patient survival<sup>[9]</sup>. Wang Jun-Ke found that patients with GBC at T3/T4 stage with N+ who performed extrahepatic bile duct resection without regard to the frozen section diagnosis were effective in extending postoperative survival of them<sup>[14]</sup>. However, Igami T also proposed that extrahepatic bile duct resection is not reasonable for patients with limited advanced GBC without bile duct invasion, and the resection should be determined in combination with the frozen section diagnosis<sup>[28]</sup>. In this study, although bile duct invasion was difficult to determine before surgery, nearly 60% of patients with Gn had bile duct invasion according to postoperative pathology examination, and the survival difference was mainly reflected in the T2 stage. Therefore, for patients with Gn, direct extrahepatic bile duct resection may discover hidden lymph node metastases and increase the chance of R0 resection. However, in this study, there were few patients undergoing extrahepatic bile duct resection at T2 stage (4 cases), and most of them were advanced patients with lymph node metastasis. The samples were less random, so the effect of extrahepatic bile duct resection was not studied here. Further multicenter, large-sample studies may be needed to clarify the impact of extrahepatic bile duct resection on gallbladder neck tumors.

Microscopic liver metastasis means metastases smaller than 5 mm in the liver, mostly occurred in advanced tumors at stage T3-4<sup>[29]</sup>. Endo found in a study that T2 GBC also had microscopic liver metastasis, mostly in hepatic-side tumors, and most of them existed within 1-2 cm of the hepatic gallbladder bed tissue, not exceeding 3 cm of the liver<sup>[29]</sup>. Meanwhile, further survival analysis in the study suggested that microscopic liver metastasis is an independent risk factor for the prognosis of T2 GBC, and simple partial hepatectomy cannot effectively prevent hepatic recurrence for these patients<sup>[29]</sup>. In this study, there were 5 cases of microscopic liver metastasis in 64 patients with T2 GBC, and the prognosis for them was poor ( $P < 0.05$ ). But further Cox multivariate analysis did not show that it was an independent risk factor affecting the prognosis of patients. After resection, patients could still have a better survival. However, for patients with microscopic liver metastasis, compared with further extent of liver resection, the need for effective chemotherapy seems to be more urgent.

The impact of jaundice on the prognosis of patients with GBC is keeping controversial. Some researchers considered that jaundice is a predicting sign of unresectable carcinoma, and palliative treatment should be recommended for these people instead of radical surgery<sup>[30]</sup>. However, some researchers believed that

although preoperative jaundice has an impact on the prognosis of patients with GBC, it is not a major risk factor affecting prognosis, and the degree of bile duct invasion should also be considered as one of the considerations<sup>[17,31]</sup>. In this study, the univariate survival analysis suggests that jaundice does have an impact on the survival of patients with T2 GBC, but it is not an independent risk factor that affects the prognosis of these patients. It indicates that the cause and extent of jaundice should be considered for them. Radical resection should be performed, when there was a chance of R0 resection, to improve overall survival for these people.

## Conclusion

Tumor location is an important prognostic factor of patients with T2 GBC. Neck-side tumors also have an impact on the survival of patients in stage T2, and jaundice may be one of the reasons. However, there is no sufficient evidence currently that the prognosis for tumors in the neck and hepatic side are better than that in the neck or hepatic side alone. Neck-side tumors are more prone to arise bile duct invasion and lymph node metastasis. Therefore, extrahepatic bile duct resection and thorough lymph node dissection may be effective in prolonging their survival. While, tumors in the body and fundus are more prone to microscopic liver metastasis. So partial liver resection may be necessary for this group of patients, especially for hepatic-side GBC. Postoperative chemotherapy (oxaliplatin combined with gemcitabine) has no significant effect on prolonging the survival of patients with T2 GBC. For T2 GBC, preoperative CEA and CA199 cannot effectively predict patient survival. New detection methods for early stage of GBC may help increase the chance of surgery. Jaundice is not an absolute contraindication for surgical treatment. Active radical surgery can also effectively prolong the survival of these patients.

## Abbreviations

GBC Gallbladder carcinoma

Gn GBC occurring in gallbladder neck

Gbf GBC occurring in gallbladder body or fundus

LS Location score

## Declarations

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None.

### Authors' contributions:

Article topic design was contributed by Kunlun Luo. Manuscript preparation and data analysis were contributed by Zhencheng Zhu. Qingzhou Zhu contributed to the data collection. Weixuan Xie contributed

to the manuscript editing. Kunlun Luo is the corresponding authors. All authors read and approved the final manuscript.

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### **Availability of data and materials:**

The data came from our hospital( the 904th Hospital of Joint Logistic Support Force of PLA, Wuxi, Jiangsu 214044, China)'s data system.

### **Ethics approval and consent to participate:**

The name of the ethics committee: Ethics Committee of the 904th Hospital of Joint Logistic Support Force of PLA.

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### **Consent for publication:**

We simply extracted data and did not involve the private information of patients.

### **Competing interests:**

The authors declare that they have no competing interests.

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## Tables

Table 1  
Clinicopathological features of 136 GBC patients grouped by tumor location(Gn/Gbf)

Variable	Gn (n = 59,43.4%)	Gbf (n = 77,56.6%)	$\chi^2$ /t(U)	P value
Sex			0.830	0.362
male	20(33.9)	32(41.6)		
female	39(66.1)	45(58.4)		
Associated hypertension	21(35.6)	29(37.7)	0.062	0.804
Associated gallstone	47(79.7)	64(83.1)	0.266	0.606
Bile duct invasion	34(57.6)	8(10.4)	34.920	<b>0.001</b>
Microscopic liver metastasis	6(10.2)	23(29.9)	7.728	<b>0.005</b>
Extra-serous fat/nerve infiltration	18(30.5)	17(22.1)	1.242	0.265
Depth of tumor invasion			0.101	0.951
T1	9(15.3)	12(15.6)		
T2	27(45.8)	37(48.1)		
T3	23(39.0)	28(36.4)		
Lymph node metastasis			4.495	<b>0.034</b>
N0	26(44.1)	48(62.3)		
N+	33(55.9)	29(37.7)		
8th AJCC stage			1.118	0.572
I	7(11.9)	11(14.3)		
II	16(27.1)	26(33.8)		
III	36(61.0)	40(51.9)		
Tumor differentiation			0.654	0.419
Poor	25(42.4)	38(49.4)		
Well/moderately	34(57.6)	39(50.6)		
Tumor growth pattern			10.766	<b>0.001</b>

GBC, gallbladder carcinoma; Gn, GBC in gallbladder neck; Gbf, GBC in gallbladder body and fundus; Gh, GBC in hepatic-side; Gp, GBC in peritoneal-side; TBIL, total bilirubin; ALB, albumin; CRP, C-reactive protein; Categorical data was presented as numbers (percentages); Continuous data in normal distribution was presented as mean  $\pm$  SD; Continuous data in skewed distribution was presented as median (range).

Variable	Gn (n = 59,43.4%)	Gbf (n = 77,56.6%)	$\chi^2$ /t(U)	P value
Infiltrative growth type	56(94.9)	55(71.4)		
Expansive growth type	3(5.1)	22(28.6)		
Tumor location(Gh/Gp)			3.137	0.077
Hepatic-side	41(69.5)	42(54.5)		
Peritoneal-side	18(30.5)	35(45.5)		
Postoperative chemotherapy	12(20.3)	26(33.8)	2.991	0.084
Age(years)	64.61 ± 9.50	62.17 ± 9.85	1.454	0.148
Tumor size(major axis,cm)	2.5(0.5-8.0)	2(0.5–13.0)	1314.000	0.961
TBIL( $\mu$ mol/L)	24.4(4.8-392.1)	13.6(4.3-400.1)	3280.500	<b>0.001</b>
ALB(g/L)	38.1(23.7–48.2)	42.2(26.3–48.3)	1764.000	<b>0.026</b>
CRP(g/L)	5.9(0.1-225.4)	4.1(0.4–110.0)	2451.000	0.431
Leukocyte(x 10 <sup>9</sup> /L)	5.8(2.9–15.0)	6.3(2.5–28.2)	2084.500	0.411
CEA( $\mu$ g/L)	2.8(0.7-150.8)	1.8(0.2-145.5)	2847.000	<b>0.012</b>
CA199(U/ml)	40.7(1.2-10000.0)	12.8(0.5–1164.0)	3247.000	<b>0.001</b>
GBC, gallbladder carcinoma; Gn, GBC in gallbladder neck; Gbf, GBC in gallbladder body and fundus; Gh, GBC in hepatic-side; Gp, GBC in peritoneal-side; TBIL, total bilirubin; ALB, albumin; CRP, C-reactive protein; Categorical data was presented as numbers (percentages); Continuous data in normal distribution was presented as mean ± SD; Continuous data in skewed distribution was presented as median (range).				

Table 2  
Univariate analysis of prognosis in T2 GBC

Variable	Number	OS*(months)	Survival rates(%)			P value
			1 year	3 year	5 year	
Sex						0.368
male	26	13	57.7	15.9	7.9	
female	38	18	63.2	19.7	7.5	
Age						0.482
≤64 years	31	17	67.7	18.9	11.4	
>64 years	33	16	54.5	17.3	0	
Associated hypertension						0.223
Yes	25	22	68.0	24.1	12.1	
No	39	13	56.4	14.2	4.3	
Associated gallstone						0.651
Yes	51	16	58.8	18.7	10.7	
No	13	19	69.2	15.4	0	
Location score						<b>0.001</b>
0	21	35	90.5	43.2	14.4	
1/2	43	11	44.2	9.3	6.2	
LN metastasis						<b>0.001</b>
N0	42	23	71.4	27.7	10.3	
N+	22	10	40.9	4.5	0	
Bile duct invasion						<b>0.019</b>
Yes	13	11	38.5	15.4	0	
No	51	20	78.4	21.5	8.0	
Microscopic liver metastasis						<b>0.028</b>
Yes	5	7	40.0	20.0	0	
No	59	18	62.7	19.6	7.3	
Extra-serous fat/nerve infiltration						0.767
OS*, overall survival was presented as median; LN, lymph node.						

Variable	Number	OS*(months)	Survival rates(%)			P value
			1 year	3 year	5 year	
Yes	6	11	50.0	25.0	0	
No	58	16	62.1	19.0	7.0	
Tumor differentiation						<b>0.011</b>
Poor	27	13	51.9	7.4	0	
Well/moderately	37	21	67.6	26.6	12.7	
Jaundice						<b>0.016</b>
Yes	46	19	69.6	24.1	8.9	
No	18	11	38.9	11.1	0	
CEA						0.712
≤5 µg/L	57	17	61.4	19.2	7.1	
≥5 µg/L	7	16	57.1	28.6	0	
CA199						0.439
≤37.0 U/ml	50	18	64.0	17.7	10.1	
≥37.0 U/ml	14	12	50.0	9.5	0	
Postoperative chemotherapy						0.532
Yes	16	22	68.8	18.8	6.3	
No	48	13	58.3	18.4	9.2	
OS*, overall survival was presented as median; LN, lymph node.						

Table 3  
Cox multivariate analysis of prognosis in T2 GBC

Variable	Regression coefficient	Standard error	Wald	df	P value	Relative risk	95%CI
Location score(0 vs. 1/2)	1.180	0.349	11.447	1	0.001	3.253	1.643 ~ 6.444
LN metastasis(N0 vs. N+)	0.897	0.331	7.332	1	0.007	2.453	1.281 ~ 4.698
LN, lymph node.							

## Figures

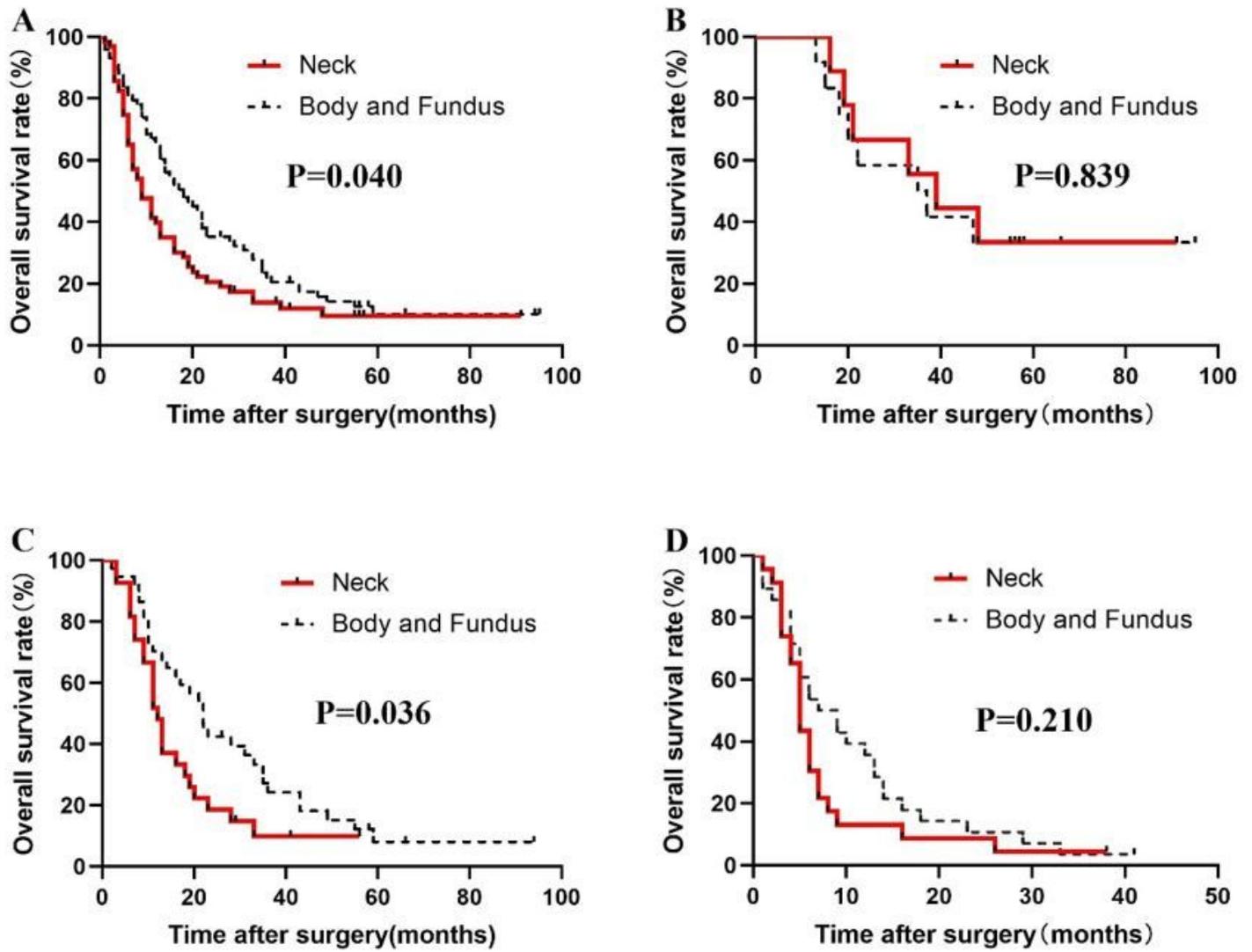
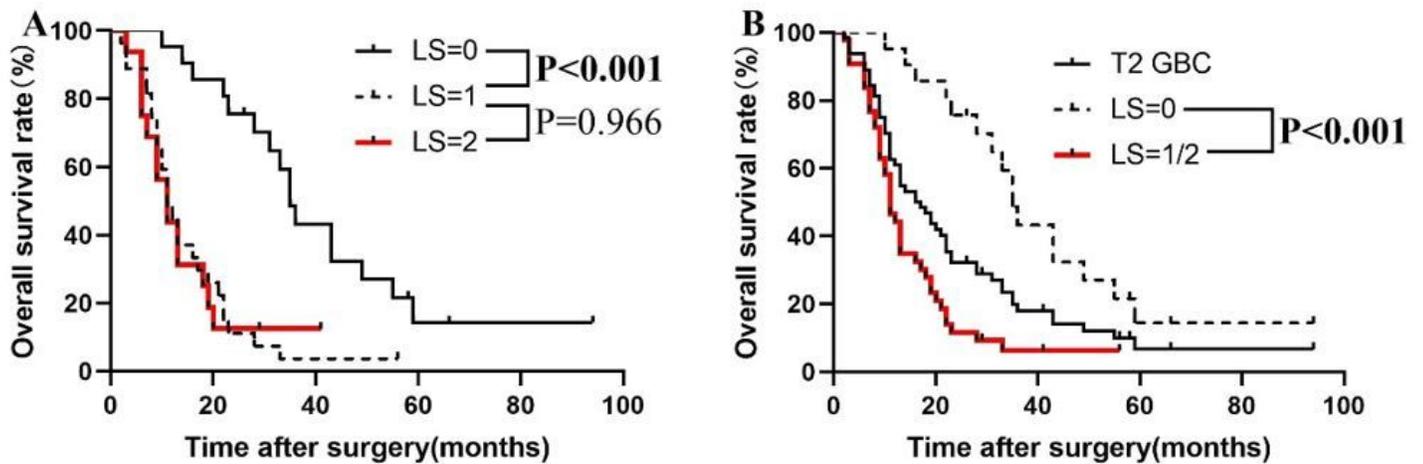


Figure 1

K-M analysis of survival differences between patients with Gn and Gbf. (A) The entire cohort; (B) Patients with T1 lesion; (C) Patients with T2 lesion; (D) Patients with T3 lesion.



## Figure 2

K-M analysis of survival differences in T2 GBC between groups according to location score (LS). (A) Survival difference among three groups (LS = 0/1/2); (B) Survival difference between patients with LS = 0 and 1/2, along with T2 GBC patients overall survival.