Effect of preoperative jaundice on long-term prognosis of gallbladder carcinoma with radical resection

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Research

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Abstract

Purposes: This study was designed to evaluate the long-term prognostic value of preoperative jaundice and explore which clinicopathological factor significantly influencing the long-term prognosis of gallbladder carcinoma (GBC) after radical resection (R0).

Methods: A total of 267 GBC patients who underwent R0 resection between January 2004 and December 2014 were enrolled, including 54 patients with preoperative jaundice and 213 patients without jaundice. The clinicopathological parameters between the two groups were compared, and the correlation between preoperative jaundice and the long-term prognosis was furtherly analyzed.

Results: Unilateral and multivariate analyses of 267 GBC patients showed that the depth of tumor invasion (pT stage), lymphatic metastasis, and hepatic invasion were independent prognostic factors. In terms of the 54 GBC patients with preoperative jaundice, univariate and multivariate analysis showed that only pT stage was an independent factor for prognosis. Furthermore, the intraoperative blood transfusion and pT stage were significant different between long-term survival (survival for more than 3 years) and those who died within 3 years (P<0.05).

Conclusion: Preoperative jaundice was not the independent factor affecting the poor long-term prognosis of gallbladder carcinoma after R0 resection. The pT stage was the only long-term prognostic factor in all GBC patients with and without preoperative jaundice.

Introduction

Gallbladder carcinoma (GBC) that has invaded the submucosa without lymph node metastasis may have a favorable prognosis after surgical resection [1]. However, GBC has a tendency to invade the surrounding organs, especially to the hilar and hepatoduodenal ligaments. This usually leads to obstructive jaundice, which usually indicates that the disease is in advanced stage and cannot be surgically resected [2].

Previous report has suggested that GBC patients with preoperative jaundice were significantly associated with poor prognosis [3-7]. In addition, some recent studies also have found that preoperative jaundice or extrahepatic bile duct invasion were independent predictors of poor prognosis [8,9]. Even so, some scholars supported surgical resection in such advanced patients [10,11]. Our previous study [12] has found that the jaundiced patients have lower survival rates than the non-jaundiced patients. However, the multivariate analysis showed that preoperative jaundice was not a significant risk factor of poor outcome in GBC patients who underwent surgical resection with curative intent (R0 and R1 resection). However, the role of preoperative jaundice in the prognosis evaluation of GBC patients after R0 resection has never been reported. The aim of this study was to evaluate the long-term prognostic value of preoperative jaundice in GBC patients after R0 resection.

Materials And Methods
Patients

A prospectively maintained hepatobiliary surgery database at the Eastern Hepatobiliary Hospital was reviewed for all patients with a diagnosis of GBC who underwent surgical resection with curative intent between January 2004 and December 2014. Permission from Second Military Medical University’s Institutional Review Board was obtained prior to data review. Written informed consent was obtained from all patients for surgical treatment and pathological examinations according to the institutional guidelines.

Resection completeness was classified into R0 microscopically margin-negative resection, R1 microscopically positive margin, and R2 macroscopic residuals on surgical margins. R0 was considered to be radical resection. During the operation, 10 patients underwent rapid freezing to confirm the negative margin, which was confirmed by the final pathological results. All patients who had undergone either R1 or R2 surgery were excluded from the analysis. All surgeries were performed by a single treatment team. Stage grouping was performed according to the pTNM classification system of UICC, 8th edition [13].

Surgical procedures

All patients were given preoperative imaging to assess the accurate range of tumor invasion, before they were scheduled for surgery. In order to reduce the risk of postoperative liver failure, preoperative portal vein embolization (PVE) was performed in patients with more than 60% of hepatic parenchymal resection [14]. Hepatectomy was scheduled 2-3 weeks after PVE when liver hypertrophy had been confirmed by volumetry and the serum bilirubin level was lower than 6 mg/dl. Two patients underwent hemihepatic PVE prior to extended right hemihepatectomy.

All patients underwent en bloc dissection of regional lymph nodes (lymph nodes along the hepatoduodenal ligament and common hepatic artery and behind the pancreatic head). Hepatectomies were carried out in all 276 patients. When the adjacent organ was found to be invaded, en bloc resection was performed simultaneously, such as pancreaticoduodenectomy, partial gastrectomy, partial duodenal resection and colon section. Vascular resection (hepatic artery and/or portal vein) was carried out when R0 resection was expected.

Statistical analysis

Overall survival was measured from the day of operation to death, including the death caused by cancer or other factors, or to the last day of follow-up. All patients were followed up for more than five years unless the patients died within five years. The average follow-up time was 76.7 months. The comparison between the two groups was done by Student’s t test for parametric data and the Mann-Whitney U test for non-parametric data. The Chi-square test was used for categorical data. Survival curves were estimated with the Kaplan-Meier method and compared by the log-rank test. Cox regression analysis was carried out to determine which factor was the best prognostic determinant. P value < 0.05 was considered
Results

Demographic data

In this 10-year study, 536 patients with gallbladder carcinoma underwent surgery, of which 267 patients underwent radical resection (R0 resection, 49.8%), 183 underwent R1 resection, and 86 underwent R2 resection. Among the 267 GBC patients who underwent R0 resection, 105 were male and 162 were female, including 54 patients with preoperative jaundice. The average age was 58.6 years (range 23-83 years).

Preoperative management

All 54 GBC patients with preoperative jaundice routinely underwent extrahepatic bile duct resection. The mean total bilirubin in 54 GBC patients with preoperative jaundice was 11.4 mg/dl (range: 2.89-33.01 mg/dl). Of the 54 patients, 34 patients (61.1%) were underwent preoperative biliary drainage according to liver function and the expected range of liver resection. 18 cases were treated with percutaneous transhepatic biliary puncture (PTBD) and 16 cases were treated with endoscopic biliary drainage (EBD). Among the 34 patients who underwent preoperative biliary drainage, the mean total bilirubin at admission was 15.6 mg/dl (range: 7.79-33.01 mg/dl), and decreased to 4.7 mg/dl (range: 3.2-5.8 mg/dl) before surgery. Four patients developed cholangitis and two patients developed hemorrhage associated with preoperative biliary drainage, who treated without sequela after conservative treatment.

Comparison between GBC patients with and without preoperative jaundice who underwent R0 resection (Table 1)

There were no significant differences in age, associated gallbladder disease, histoligical differention, and hepatic invasion between patients with and without preoperative jaundice. Male patients were more common in the preoperative jaundice group. A more advanced pT stage was associated with preoperative jaundice, which suggested a more seriously local tumor invasion. The extended hepatectomy was more common in the preoperative jaundice group. More intra-operative bleeding and operative time were found in the preoperative jaundice group (P<0.001 and P=0.001), which suggested a wider range of lesion resection performed. As a result, the average postoperative hospital stay of GBC patients with preoperative jaundice was 18.3 days (range: 4-85 days), which was longer than those without preoperative jaundice (P<0.001).

In terms of tumor location, gallbladder neck tumor was mostly occurred in the preoperative jaundice group. There was no significant difference in the incidence of hepatic invasion between the two groups, although the incidence of lymphatic metastasis was significantly higher in the preoperative jaundice group. There was no significant difference in mortality between GBC patients with and without
preoperative jaundice (P=0.105). Morbidity was significantly higher in patients with preoperative jaundice than without preoperative jaundice (27.8% vs. 6.1%, P<0.001).

Survival and Risk factors in all 267 GBC patients who underwent R0 resection (Tables 2 and 3)

The overall 3-year and 5-year survival rates of 267 patients were 35.2% and 23.7%, respectively. The mean survival time was 36 months. According to the presence or absence of preoperative jaundice, the prognosis of 267 patients were analyzed. The 3-year survival rate and mean survival time were 40.9% and 40.8 months in 213 patients without preoperative jaundice, and 13.0% and 18.0 months in 54 patients with preoperative jaundice, respectively. The survival rate of patients with preoperative jaundice group was significantly worse than those without jaundice group (P<0.001).

Univariate and multivariate analysis were given to determine the significant factors that affected long-term survival in 267 GBC patients who underwent R0 resection. In the univariate analysis, the significant prognostic factors include the depth of tumor invasion (pT stage), age, preoperative jaundice, tumor location, lymph node metastasis, hepatic invasion, combined resection of adjacent organs (CRAO), portal vein/hepatic artery (HA/PV) resection, intraoperative blood transfusion, extrahepatic bile duct resection, treatment of complications, and histologic differentiation (Table 2). In the multivariate analysis, only pT stage, lymph node metastasis, and hepatic invasion were independent factors (Table 3).

Risk factors in 54 GBC patients with preoperative jaundice who underwent R0 resection (Table 4)

Univariate and multivariate analysis were given to identify risk factors in 54 GBC patients with preoperative jaundice who underwent R0 resection. In the univariate analysis, pT stage, tumor location, hepatic invasion and histologic differentiation were identified as significant prognostic factors. In the multivariate analysis, only advanced pT stage was an independent risk factor for poor prognosis.

Clinicopathologic Features of Seven 3-Year Survivors (Table 5)

Of the 54 GBC patients with preoperative jaundice, 7 survived for more than three years. They were 2 males and 5 females, with an average age of 57.4 years. Comparing the 7 jaundiced patients who survived for more than three years with those who didn't, a significant difference of intraoperative blood transfusion and pT stage was observed.

Discussion

This was a large sample study and confirmed that jaundice was a predictor of advanced gallbladder cancer. The three-year survival rate and median survival time were 13.0% and 18.0 months for the 54 jaundiced patients, respectively, and 40.9% and 40.8 months for the 213 non-jaundiced ones, respectively (p < 0.001). The jaundiced patients had significantly lower survival rates than the non-jaundiced patients. In this study, the impact of preoperative jaundice on the prognosis of GBC patients after R0 resection was thoroughly evaluated. So far, no other report is known to be published. This study provided a basis and data support for clinical prognostic evaluation of GBC patients after R0 resection.
In previous reports, preoperative jaundice was an important predictor of advanced gallbladder carcinoma, and the median survival in the presence of jaundice was poorer than that of non-jaundiced patients (11 vs. 36 months; \( p < 0.0001 \)) [11]. In the first report on the prognostic impact of jaundice in gallbladder carcinoma [2], the rate of R0 resection was only 5%, and the prognosis was very poor. However, the result of the low R0 resection rate was calculated by taking all 82 GBC patients as base number, rather than the patients who went through surgical resection. Previous studies have found that the rate of surgical resection was higher in non-jaundice patients (64% vs 45%), although there was no significant difference of R0 resection between the jaundice group and the non-jaundice group [11]. In contrast, Agarwal et al found no significant difference in surgical resection rates between the jaundice group and the non-jaundice group (27% vs 36%, \( P > 0.05 \)) [15]. At present, with the advancement of imaging technology, especially the extensive application of laparoscopic exploration, the rate of surgical resection (R0 resection) was expected to be significantly improved, especially in GBC patients with preoperative jaundice [16,17].

However, jaundice can cause a series of pathophysiological changes, including hyperbilirubinemia, endotoxemia, bleeding tendency, and immune dysfunction [18]. Effective and rapid biliary drainage before surgery was very important [19]. The routine biliary drainage includes PTBD (percutaneous transhepatic biliary drainage) and endoscopic biliary drainage (EBD). Although both methods were effective for biliary decompression, there were significant differences in pathophysiology between internal drainage and external drainage. There was still some controversy about which drainage method should be preferentially used [19,20]. According to our previous research [12], compared with factors such as intestinal bacterial translocation and pancreatitis associated with EBD, PTBD was simpler and less expensive. However, there were many problems such as nutritional status and decreased immune function after bile wastage in PTBD. To our experience, we recommend that PTBD combined with oral bile before surgery was an effective method. Furthermore, this treatment did not increase the incidence of postoperative abdominal infection [12]. In the present study, the decrease in the bilirubin level after preoperative biliary drainage was statistically relevant (\( p < 0.001 \)). However, this benefit was not associated with a longer survival time (\( p = 0.151 \)).

Although the surgical prognosis of advanced gallbladder cancer was not satisfactory, it was the only expected treatment to be cured [6,8]. Advanced gallbladder carcinoma was usually accompanied with adjacent organ invasion, such as the liver, transverse colon, duodenum, extrahepatic bile duct, hepatic artery, and portal vein. Enlarged surgical resection was required for radical resection. The morbidity and mortality of this operation were still high. It was reported that the postoperative complication rate was as high as 53% and the mortality was 4%-27% in extended hepatectomy [21]. With the advent of preoperative biliary drainage and portal vein embolization (PVE), extended hemihepatectomy, mainly extended right hepatectomy, was safer and more feasible. Although extended hemihepatectomy was expected to remove tumor lesions radically, the postoperative mortality was higher and survival benefits remained controversial [22]. In addition, the local radical resection with more liver parenchyma reservation was expected to achieve similar prognosis [15]. In short, the advantages and disadvantages of extended surgery should be carefully weighed. This study has found that the jaundiced group had a worse prognosis than the non-jaundiced group, suggesting that preoperative jaundice was identified as
advanced stage. However, there was no specific correlation between preoperative jaundice and long-term survival. The mechanism between preoperative jaundice and prognosis remained unclear. In conclusion, advanced GBC with extrahepatic bile duct invasion and/or jaundice was a candidate for resection when R0 resection was achievable. However, the radical resection of advanced gallbladder carcinoma was still challenging with high postoperative morbidity and poor prognosis. In our opinion, the scope of surgical resection should not be blindly expanded. Patient benefit was the most important evaluation index.

In previous reports, hilar invasion was identified as an important prognostic factor [10,23]. The clinical manifestation of hilar invasion was jaundice, which was an independent factor for poor prognosis [10,23]. In our previous study, the jaundiced patients had lower survival rates than the non-jaundiced patients (p < 0.001). The lymph node metastasis and gallbladder neck tumors were the only significant risk factors of poor prognosis in GBC patients who underwent surgical resection with curative intent (R0 and R1 resection). However, in this study, preoperative jaundice and gallbladder neck tumors were not the independent factors associated with poor prognosis after R0 resection, which suggested that GBC patients with preoperative jaundice and gallbladder neck tumors should be actively given surgery, if R0 resection was expected. This was different from previous research results. This again emphasized the clinical importance of radical resection.

In addition, another important predictor of poor prognosis in gallbladder cancer was lymph node metastasis [23,24,25]. In a report, the authors insisted that radical resection can be only acquired in GBC patients with regional lymph node metastasis [26]. In contrast, reports from the Japanese Society of Biliary Surgery, have found that GBC patients with extensive lymph node metastasis were also benefit from lymphadenectomy [10,25]. The univariate analysis of this study has found that lymph node metastasis was closely associated with survival (P < 0.001). At the same time, the para-aortic lymph nodes are considered to be distant metastasis [13]. Kondo et al [26] insisted that surgery can not improve the prognosis of gallbladder cancer patients with lymph node metastasis around the abdominal aorta. The multivariate analysis of this study has found that regional lymph node involvement was not an independent prognostic factor for long-term survival, and only pT stage was a key prognostic factor. With the continuous advancement of imaging technologies such as CT, MRI, and PET-CT [27], the pT stage can be more accurately evaluated before surgery. Therefore, once more advanced pT stage (pT4) was suggested by preoperative imaging, the choice of surgical indications and multidisciplinary treatment should be more cautious. The pT stage was the most important long-term prognostic factor of gallbladder cancer, which should be paid attention to clinical assessment.

This was a study from a famous hepatobiliary surgery center in China. The univariate and multivariate analysis of GBC patients showed that preoperative jaundice did not affect long-term survival after R0 resection. The independent prognostic factor was precisely the pT stage in TNM staging. This study confirmed the absolute authority of TNM staging in the evaluation of tumor prognosis.

The limitation of this study is the limited amount of cases. Further multi-center studies are needed to confirm this conclusion. In addition, there are limitations in retrospective research itself. However, this
study suggested that there was no absolute relation between preoperative jaundice and poor long-term prognosis. The pT staging was a key long-term prognostic factor for gallbladder carcinoma after R0 resection.

In conclusion, unilateral and multivariate analyses of 267 GBC patients showed that the depth of tumor invasion (pT stage), lymphatic metastasis, and hepatic invasion were independent prognostic factors. The univariate and multivariate analysis of 54 GBC patients with preoperative jaundice showed that only pT staging was an independent factor for prognosis. In the 54 GBC patients with preoperative jaundice, intraoperative blood transfusion and pT stage were significantly different between long-term survival (survival for more than 3 years) and those who died within 3 years. Preoperative jaundice and gallbladder neck tumors were not the independent factors affecting the long-term prognosis of gallbladder carcinoma after R0 resection. The pT staging was the only long-term prognostic factor for both GBC patients with and without preoperative jaundice. Once advanced pT staging was suspected preoperatively, we should be prudent in deciding whether surgery is indicated so as to avoid unnecessary surgery. This study confirmed the absolute authority of TNM staging in the evaluation of long-term prognosis.

Declarations

Ethics approval and consent to participate

All studies were approved by the Committee on Ethics of Second Military Medical University. Permission from Second Military Medical University’s Institutional Review Board was obtained prior to data review.

Consent for publication

Written informed consent was obtained from all patients for surgical treatment, pathological examinations and further analysis according to the institutional guidelines.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interest.

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Authors’ contributions

YXW, WZJ, WFY, and CJY performed the majority of the research and collected all the clinicopathological data. YXW wrote the manuscript. CJY, YJ, and LL provided analytical tools and edited the manuscript. ZBH and SF designed the study. YXW, WZJ, CJY, LYL, and WFY equally contributed to the present study. All authors read and approved the final manuscript. Wen Zhi-jian, Li Yu-long and Chen Jun-yi are the co-first author.

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Abbreviations

GBC: gallbladder cancer; R0: radical resection; pT: the depth of tumor invasion; PVE: portal vein embolization; PTBD: percutaneous transhepatic biliary puncture; EBD: endoscopic biliary drainage; CRAO: combined resection of adjacent organs; PV: portal vein; HA: hepatic artery; OS: overall survival; DFS: disease-free survival.

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Tables

Table 1 Demographic data of jaundiced (n = 54) and non-jaundiced GBC patients (n = 213)
|                                      | Jaundiced, n | Non-jaundiced, n | p-value |
|--------------------------------------|--------------|------------------|---------|
| Male gender                          | 30           | 75               | 0.006   |
| Mean age (range)                     | 58.04 ± 10.87 (35–80) | 59.21 ± 10.60 (23–83) | 0.478   |
| Postoperative hospital stay          | 18.31 ± 12.91 (4–85) | 10.92 ± 5.66 (5–51) | < 0.001 |
| Associated gallbladder disease       |              |                  | 0.285   |
| Gallstones                           | 24 (44.4%)   | 116 (54.5%)      |         |
| Gallbladder polyp                    | 1 (1.9%)     | 2 (0.9%)         |         |
| Nil                                  | 29 (53.7%)   | 95 (44.6%)       |         |
| Tumor location                       |              |                  | < 0.001 |
| Gallbladder neck                     | 38 (70.4%)   | 29 (13.6%)       |         |
| Gallbladder body + fundus            | 16 (29.6%)   | 184 (86.4%)      |         |
| Histologic type                      |              |                  | 0.107   |
| Moderately + well differentiated      | 51 (94.4%)   | 182 (85.4%)      |         |
| Poorly differentiated                | 3 (5.6%)     | 31 (14.6%)       |         |
| Extent of liver resection            |              |                  | < 0.001 |
| Major hepatectomy (>3 4–7.4% segments) | 20 (4.2%)  | 100 (61%)        |         |
| Anatomical segments IV–V             |              |                  |         |
| Gallbladder bed                      | 30 (55.6%)   | 66 (30.9%)       |         |
| Extrahepatic bile duct resection     | 54 (100.0%)  | 20 (9.4%)        | < 0.001 |
| Combined resection of adjacent organs| 9 (16.7%)    | 4 (2.1%)         | 0.003   |
| Hepatic invasion                     | 29 (53.7%)   | 100 (46.9%)      | 0.446   |
| Lymph node metastasis                | 39 (72.2%)   | 94 (44.1%)       | < 0.001 |
| Vascular invasion                    | 5 (9.3%)     | 0 (0%)           | < 0.001 |
| pT                                    |              |                  | 0.004   |
| pT2                                  | 0 (0%)       | 25 (11.7%)       |         |
| pT3                                  | 45 (83.3%)   | 174 (81.7%)      |         |
| pT4                                  | 9 (16.7%)    | 14 (6.6%)        |         |
| Intra-operative bleeding (mL)        | 656.48 ± 532.97 (200–329.67) | 257.13 (200–1800) | < 0.001 |
| Operative time (min)                 | 296.02 ± 76.91 (100–211.88) | 80.10 (100–400) | < 0.001 |
| Mortality (number of patients)       | 2 (3.7%)     | 1 (0.5%)         | 0.105   |
| Morbidity (need invasive treatment)  | 15 (27.8%)   | 13 (6.1%)        | < 0.001 |

Note that adjacent organs include the pancreas, duodenum, stomach, and/or colon other than the liver and extrahepatic bile duct.

Table 2 Univariate analysis of 14 variables related to survival of GBC patients who underwent curative resection (n = 267)
| Variable                        | Cutoff level | Number | Survival rates (%) | p-value |
|--------------------------------|--------------|--------|--------------------|---------|
|                                |              |        | 3 year | 5 year |
| Age (year)                     | < 60         | 133    | 42.2 | 32.0 | 0.019 |
|                                | ≥ 60         | 134    | 28.2 | 15.3 |
| Sex                            | Male         | 105    | 29.8 | 20.2 | 0.158 |
|                                | Female       | 162    | 38.7 | 25.7 |
| Jaundice                       | Present      | 54     | 13.0 | 1.9  | < 0.001 |
|                                | Absent       | 213    | 40.9 | 29.8 |
| Associated disease             | Present      | 143    | 36.0 | 25.2 | 0.654 |
|                                | Absent       | 124    | 34.5 | 22.3 |
| Tumor location                 | Gallbladder neck | 67  | 20.3 | 9.4  | 0.002 |
|                                | Gallbladder body / fundus | 200 | 40.2 | 28.9 |
| pT (TNM)                       | pT1 and 2    | 25     | 83.8 | 78.6 |
|                                | pT3 and 4    | 242    | 30.2 | 18.0 |
| Lymph node metastasis          | Negative     | 134    | 52.2 | 38.9 |
|                                | Positive     | 133    | 18.1 | 9.3  |
| Histologic differentiation     | Well / Moderate | 224 | 27.4 | 17.4 | 0.049 |
|                                | Poor         | 43     | 36.7 | 24.9 |
| Hepatic invasion               | Present      | 129    | 20.6 | 11.1 |
|                                | Absent       | 138    | 48.8 | 35.6 |
| CRAO                           | Present      | 18     | 5.6  | 0.0  | < 0.001 |
|                                | Absent       | 249    | 36.9 | 25.0 |
| Combined portal vein/hepatic artery resection | Present | 5 | 0.0 | 0.0 | 0.027 |
|                                | Absent       | 262    | 35.8 | 24.1 |
| Intraoperative blood infusion   | Present      | 44     | 25.0 | 10.9 |
|                                | Absent       | 223    | 37.1 | 26.5 |
| Morbidity                      | Conservative treatment | 239 | 37.6 | 25.1 | 0.004 |
|                                | need invasive treatment | | 14.3 | 5.4 |
| Extrahepatic bile duct resection | Present | 74 | 18.3 | 8.4  | < 0.001 |
|                                | Absent       | 193    | 41.7 | 30.0 |

**Table 3 Results of multivariate analysis**
| Variable                                      | Regression coefficient | Standard error | p-value | Relative risk | 95% CI       |
|----------------------------------------------|------------------------|----------------|---------|---------------|--------------|
| Age                                          | 0.227                  | 0.148          | 0.125   | 1.255         | 0.939-1.679  |
| Jaundice                                     | 0.375                  | 0.321          | 0.243   | 1.455         | 0.776-2.731  |
| Tumor location                               | -0.390                 | 0.207          | 0.060   | 0.677         | 0.451-1.016  |
| pT                                           | 0.796                  | 0.360          | 0.027   | 2.217         | 1.095-4.491  |
| Lymph node metastasis                        | 0.537                  | 0.158          | 0.001   | 1.711         | 1.255-2.331  |
| Hepatic invasion                             | 0.677                  | 0.157          | 0.000   | 1.968         | 1.446-2.678  |
| CRAO                                         | 0.160                  | 0.296          | 0.588   | 1.174         | 0.657-2.096  |
| Combined PV/HA resection                     | 0.536                  | 0.497          | 0.280   | 1.710         | 0.646-4.528  |
| Intraoperative blood infusion                | -0.194                 | 0.212          | 0.360   | 0.824         | 0.543-1.248  |
| Extrahepatic bile duct resection             | -0.147                 | 0.275          | 0.592   | 0.863         | 0.503-1.480  |
| Histologic differentiation                   | -0.360                 | 0.200          | 0.071   | 0.697         | 0.472-1.031  |
| Morbidity (invasive treatment)               | 0.078                  | 0.253          | 0.759   | 1.081         | 0.658-1.775  |

Table 4 Univariate and multivariate analyses of 12 variables related to survival of GBC patients with preoperative jaundice (n = 54)
| Variable                     | Cutoff level | Number | Survival rates (%) | Univariate p-value | RR (95% CI) | Multivariate p-value |
|------------------------------|--------------|--------|--------------------|--------------------|-------------|----------------------|
|                              |              |        | 1 year  | 3 year  |              |                      |
| Age (year)                   |              |        |         |         | 0.334       |                      |
| < 60                         | 26           |        | 50.0    | 11.5    |             |                      |
| ≥ 60                         | 28           |        | 25.5    | 15.3    |             |                      |
| Sex                          |              |        | 0.391   |         |             |                      |
| Male                         | 30           |        | 53.3    | 6.7     |             |                      |
| Female                       | 24           |        | 54.2    | 20.8    |             |                      |
| Preoperative Biliary Drainage|              |        | 0.151   |         |             |                      |
| Present                      | 34           |        | 51.5    | 6.1     |             |                      |
| Absent                       | 20           |        | 57.1    | 23.8    |             |                      |
| Associated disease           |              |        | 0.672   |         |             |                      |
| Present                      | 25           |        | 44.0    | 16.0    |             |                      |
| Absent                       | 29           |        | 62.1    | 10.3    |             |                      |
| Tumor location               |              |        | 0.050   |         | 1.288       | 2.650                |
| Gallbladder neck             | 38           |        | 63.2    | 15.8    |             |                      |
| Gallbladder body / fundus    | 16           |        | 31.3    | 6.3     |             |                      |
| pT (TNM)                     |              |        | 0.010   |         | 2.221       | 4.631                |
| pT3                          | 14           |        | 64.3    | 35.7    |             |                      |
| pT4                          | 40           |        | 50.0    | 5.0     |             |                      |
| Lymph node metastasis        |              |        | 0.136   |         |             |                      |
| Negative                     | 15           |        | 66.7    | 13.3    |             |                      |
| Positive                     | 39           |        | 48.7    | 12.8    |             |                      |
| Histologic differentiation   |              |        | 0.025   |         | 0.521       | 1.253                |
| Well / Moderate              | 47           |        | 59.6    | 14.9    |             |                      |
| Poor                         | 7            |        | 14.3    | 0.0     |             |                      |
| Hepatic invasion             |              |        | 0.038   |         | 1.392       | 2.644                |
| Present                      | 29           |        | 41.4    | 13.8    |             |                      |
| Absent                       | 25           |        | 68.0    | 12.0    |             |                      |
| CRAO                         |              |        | 0.545   |         |             |                      |
| Present                      | 9            |        | 44.4    | 11.1    |             |                      |
| Absent                       | 45           |        | 55.6    | 13.3    |             |                      |
| Intraoperative blood infusion|              |        | 0.137   |         |             |                      |
| Present                      | 23           |        | 56.5    | 26.1    |             |                      |
| Absent                       | 31           |        | 51.6    | 3.2     |             |                      |
| Morbidity                    |              |        | 0.301   |         |             |                      |
| Present                      | 15           |        | 53.3    | 6.7     |             |                      |
| Absent                       | 39           |        | 53.8    | 15.4    |             |                      |

Table 5 Compared analyses for jaundiced patients with and without long survival (n = 54)
| Variables                                      | Survived more than 3 years, n = 7 | Died within 3 years, n = 47 | p-value |
|------------------------------------------------|-----------------------------------|-----------------------------|---------|
| Male gender                                   | 2                                 | 28                          | 0.221   |
| Mean age                                      | 57.43 ± 10.96                     | 62.14 ± 10.06               | 0.288   |
| Associated gallbladder stone                  | 4                                 | 21                          | 0.692   |
| Preoperative Biliary Drainage                 |                                   | 31                          | 0.096   |
| Tumor location                                |                                   |                             | 0.660   |
| Neck                                          | 6085.7%                           | 32068.1%                    |         |
| Body/fundus                                    | 1014.3%                           | 15131.9%                    |         |
| Postoperative hospital stay                   | 12.29± 3.82                       | 19.21 ± 13.56               | 0.188   |
| Bilirubin level at presentation               | 183.06 ± 103.79                   | 251.93 ± 133.50             | 0.149   |
| Intra-operative bleeding (mL)                 | 785.71 ± 371.61                   | 637.23 ± 553.49             | 0.380   |
| Intraoperative blood infusion                 | 6085.7%                           | 1736.2%                     | 0.034   |
| Operative time (min)                          | 320.00 ± 80.83                    | 292.45 ± 76.57              | 0.423   |
| Combined resection of 1 (14.3%)                | 8 (17%)                           |                             | 0.670   |
| Hepatic invasion                              | 4 (57.1%)                         | 25 (53.2%)                  | 0.585   |
| pT (TNM)                                      |                                     |                             |         |
| pT3                                           | 5071.4%                           | 919.1%                      | 0.010   |
| pT4                                           | 2028.6%                           | 3880.9%                     |         |
| Lymph node metastasis                         | 5 (71.4%)                         | 34 (72.3%)                  | 0.637   |
| Histologic type                               |                                     |                             | 0.576   |
| +Moderately differentiated                    | 14.3%                             |                             |         |
| Poorly differentiated                         | 0%                                | 714.9%                      |         |
| Extent of liver resection                     |                                   |                             | 0.219   |
| Major hepatectomy (>3 segments)               | 0%                                | 408.5%                      |         |
| Anatomical segments IV-V                      | 1014.3%                           | 1940.4%                     |         |
| Galbladder bed                                | 6085.7%                           | 2451.1%                     |         |
| CRAO                                          |                                     |                             | 0.670   |
| Yes                                           | 1014.3%                           | 817.0%                      |         |
| No                                            | 6085.7%                           | 3983.0%                     |         |
| Combined portal vein/hepatic artery resection | 0%                                | 5010.6%                     | 0.485   |
| Incidence of incidental gallbladder cancer (IGC)| 14.3%                             | 12.13%                      | 0.2445  |

**Figures**
Figure 1

Overall survival of GBC patients with (green) and without jaundice (blue).