Analysis of the Relationships between Clinicopathologic Factors and Survival in Gallbladder Cancer following Surgical Resection with Curative Intent

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Abstract

Background: This study elucidated the relationships between various clinicopathologic factors and the outcome of patients with gallbladder cancer (GBC) treated by surgical resection with curative intent.

Methods: Between January 2003 and January 2011, 76 patients with GBC underwent surgical resection with curative intent at our department. We then conducted a retrospective analysis of clinicopathologic data. Fourteen clinicopathological variables were selected for univariate and multivariate analysis to evaluate their influence on the outcome.

Results: The actuarial 1-, 3-, and 5-year survival rates in the 76 resected cases were 56.6%, 32.7%, and 23.8%, respectively. The univariate analysis revealed that curative resection (P < 0.001), lymph node metastasis (P < 0.001), AJCC stage (P = 0.030), tumor location (P = 0.008), histologic differentiation (P = 0.028), intraoperative blood loss (P = 0.011), and preoperative jaundice (P = 0.012) were significant risk factors for survival. Multivariate analysis revealed that noncurative resection and tumor location on gallbladder neck were significant risk factors for poor outcome. Among jaundiced patients, we discovered that gallbladder carcinoma with tumor thrombus in common bile duct (CBD) was very rare but with relatively special clinical manifestation and characteristic radiography manifestation. The prognosis of gallbladder carcinoma with tumor thrombus in CBD after surgical procedure was apparently better than gallbladder carcinoma with invasion of hilar tissues.

Conclusions: Curative surgical resection remains the only effective approach to the treatment of GBC. This series confirm that jaundice is a poor prognostic factor. However, the presence of jaundice does not preclude resection, especially in highly selected patients (when R0 resection is achievable). Gallbladder carcinoma with tumor thrombus in CBD has special clinical characteristics, which need to be aware by radiologists and clinicians.

Introduction

Gallbladder carcinoma has geographic and ethnic variation throughout the world and is a highly fatal malignant tumor. The poor prognosis of this disease is due to the anatomic position of the gallbladder and the nonspecific symptoms and signs [1,2]. These characteristics of GBC result in advanced primary tumors and lymph node metastasis by the time of diagnosis. Because surgical resection is the only treatment that offers hope for cure, to elucidate the relationships between various clinicopathologic factors and the outcome of GBC patients treated by surgical resection with curative intent is very neccessary.

Several recent studies have shown that jaundice and extrahepatic bile duct involvement in gallbladder cancer are independent predictors of poor outcome [3–5]. Jaundice in gallbladder cancer usually results from cancer infiltration of the extrahepatic bile duct and indicates advanced disease [6,7]. Many surgeons, especially those in Western countries, consider jaundice to be a contraindication to resection, despite the consensus that surgical resection offers the only chance of long-term survival [8,9]. However, several experienced teams did not report such poor outcome and showed that some jaundiced patients obtained improved survival following resection of GBC [10–12]. A subgroup of jaundiced patients may therefore benefit from resection. This study was designed to re-assess the prognostic value of jaundice in GBC patients treated by surgical resection with curative intent.

Patients and Methods

Ethics

Written informed consent was obtained from all patients for surgical treatment and pathological examinations according to the institutional guidelines. All studies were approved by the Committee for the Ethical of Second Military Medical University.
General information
A total of 76 GBC patients were treated with curative intent in our treatment group at department of Biliary Surgery, Eastern Hepatobiliary Surgery Hospital, between January 2003 and January 2011. Their clinical characteristics, laboratory data, treatment including surgical procedure, operative findings, tumor pathological histology, operative outcome, and length of hospital stay were obtained from the database. Fourteen clinicopathological variables (age, sex, gallstones, preoperative jaundice, operative curability, location of tumors, AJCC [International Union Against Cancer, 7th edition] pT factor, lymph node metastasis, UICC stage, histologic differentiation, hepatic invasion, pathologic extrahepatic bile duct invasion, intraoperative blood loss and adjuvant therapy) were selected for univariate and multivariate analysis to evaluate their influence on the outcome.

Criteria studied
R0 or R1 resections were considered to be resection with curative intent [12]. According to the UICC/AJCC TNM, 13 regional lymph nodes (gallbladder, pericholecodochal, hepatic pedicle, proper hepatic artery and periportal nodes) were considered to be N1. Involvement of the periaortic, pericaval, superior mesenteric artery and/or celiac artery lymph nodes were classified as N2. Routine sampling of inter-aortocaval lymph nodes was not performed in this study. Postoperative hepatic insufficiency was defined by elevation of serum total bilirubin level >2.9 mg/dL and prothrombin time<50% persisting for more than 5 postoperative days [14].

Surgical strategy
Our center’s surgical policy for GBC is as follows: radical surgery for GBC. For radical surgery, partial hepatectomy with en bloc resection of the GB and dissection of regional lymph nodes (lymph nodes along the hepatoduodenal ligament and common hepatic artery and behind the pancreatic head) were routinely conducted. Partial hepatectomy includes extended right/left hepatectomy, right trisectionectomy or wedge resection with a 2-cm margin (including segments IVb/V). Combined resection of the bile duct, pancreas and/or duodenum was performed whenever direct invasion to these organs was suspected. If jaundice (serum bilirubin level more than 3 mg/mL) was identified preoperatively and postoperative hepatic insufficiency was highly suspected, percutaneous transhepatic biliary drainage (PTBD) or endoscopic retrograde biliary drainage (ERBD) was performed to reduce the cholestatic liver damage. For reduction of serum bilirubin levels or preoperative workup, PTBD and ERBD were performed for 3 and 4 patients, respectively.

Demographic and clinical information
All 76 patients following surgical resection with curative intent were chosen as the subjects of the present study. The patients in whom hepatectomy and dissection of regional lymph nodes were expected to be curative on the basis of the preoperative imaging studies were candidates for surgery, and those in whom distant organ metastasis, cachexia, or extensive lymph node involvement was detected were considered not to have indications for hepatectomy. One patient underwent repeated hepatectomy for intrahepatic recurrence.

There were 26 men and 50 women, and their average age was 59 years (range 34 to 83). Sixty (78.9%) of the patients presented with some form of clinical manifestations, and the other 16 (21.1%) were asymptomatic. Fifty-five patients (72.4%) had associated liver disease: gallstones in 49, gallbladder polyp in 4 and chronic hepatitis (hepatitis B or C) in 2 (Table 1). Tumors diagnosed histologically after cholecystectomy are known as incidental GBC. In the study, among 76 patients with GBC referred to the hospital, in 19.7% of the patients (15 cases), the diagnosis of GBC has been missed at the time of routine cholecystectomy for gallstones in other hospital. In case of these incidental GBC, a radical second operation should also be offered to improve survival. The surgical procedures used to treat the patients are summarized in Table 2. In this study, “major hepatectomy” means right or left hepatectomy, extended right or left hepatectomy, or right or left trisegmentectomy; and “minor hepatectomy” means segmental resection or less. Of the total 77 hepatectomies in 76 patients, 4 (5.3%) were major, one of which was associated with combined celiac lymph node dissection, 1 with resection of the partial portal vein (PV) and one with hepatic artery resection. Combined resections of other organs were performed on 40 patients: bile duct resection (n = 32), pancreato-duodenectomy (n = 1), wedge resection of the duodenum (n = 1), segmental resection of the colon (n = 1) and partial gastrectomy (n = 5). Hepatoduodenal ligament lymph node dissection was performed routinely in all patients.

The surgeons assisted the pathologists to correctly identify complicated resection margins during preparation of sections of the fixed specimens. The surgical resection was considered curative, if all pathologic margins were free of tumor and there were no residual tumor. Well or moderately differentiated adenocarcinoma was diagnosed in 82.9% of the tumors and poorly differentiated adenocarcinoma in the other 17.1%. Stage grouping in the present study was performed according to the system of the pTNM classification of the International Union Against Cancer (UICC), 7th edition [13]. Most of the patients (82.9%) had UICC stage III or IV lesions at the time of diagnosis and treatment. Lymph node metastases (45 cases), hepatic invasion (40 cases), vascular invasion (2 cases) and involving the extrahepatic bile duct (31 cases) were recognized pathologically in 59.2%, 52.6%, 2.6%, and 40.8%, respectively, of the cases (Table 3). Twenty-three patients received adjuvant therapy: intraoperative and postoperative chemotherapy in 11 patients, postoperative radiotherapy in 9, and a combination of chemotherapy and radiotherapy in 3.

Table 1. Clinical characteristics of the 76 patients.

| Items                                      | Number (%) |
|--------------------------------------------|------------|
| Age (yr) average                           | 59 (range 34–83) |
| Sex (M:F)                                  | 26:50      |
| Body mass index(BMI)                       | 22.6 (range 14.8–29.8) |
| Clinical presentation                      |            |
| Asymptomatic                               | 16 (21.1%) |
| Symptomatic*                               | 60 (78.9%) |
| Associated gallbladder/liver disease       |            |
| Hepatitis B or C positive                  | 2(2.6%)    |
| gallstones                                 | 49(64.5%)  |
| gallbladder polyp                          | 4(5.3%)    |
| Nil                                        | 21(27.6%)  |
| Incidental GBC                             | 15(19.7%)  |

*Symptoms: jaundice, abdominal discomfort, general fatigue, abdominal mass.
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Statistical analysis

Non-parametric data was presented as median (range) and categorical data was presented as frequency and proportion (%). Variables were compared by the χ² test, Fisher’s exact test or Mann-Whitney’s U test, where appropriate. Overall survival was measured from the day of operation to death, including death due to cancer or to other causes, and to the last day of follow-up. Follow-up was continued until July 28, 2012, or until death, if earlier. Survival rates were estimated by the Kaplan-Meier method, and the differences between survival curves were tested by the log-rank test. A P value ≤ 0.05 was considered significant.

Results

Morbidity, mortality, and overall survival rates

The mean duration of the postoperative hospital stay was 14.6 days (range 8 to 85). The postoperative morbidity and mortality rates were low even after major hepatectomy with combined resection of adjacent organ or extrahepatic bile duct. There was only one hospital death, who died on postoperative day 19 due to multiple organ failure (including hepatic failure) secondary to intra-abdominal infections after major hepatectomy and choledochojunostomy. Morbidity occurred in 18 of the 76 ICC patients (23.7%), which was consisted of intra-abdominal infections in 2 patients, seroperitoneum needing to puncture in 9 patients, abdominal bleeding in 2 patients, bile leakage in 3 patients, liver abscess in 1 patient, and incision infection in 1 patient.

The median follow-up time was 23.9 months. There was no patient lost in follow-up. The median survival time of the entire 76 patients followed up was 14.0 months (range 1.0 to 88). The actuarial 1-, 3-, and 5-year survival rates of all 76 patients were 56.6%, 32.7%, and 23.8%, respectively (Fig. 1).

Univariate analysis

Univariate analysis revealed that neither age, sex, gallstones, pT factor, hepatic invasion, pEBI during which they initially examined, nor adjuvant therapy were significant factors for survival. By contrast, curative resection (P < 0.001), lymph node metastasis (P < 0.001), AJCC stage (P = 0.030), tumor location (P = 0.008), histologic differentiation (P = 0.028), intraoperative blood loss (P = 0.011), and preoperative jaundice (P = 0.012) were found to be significant risk factors for survival (Table 4).

Multivariate analysis

A multivariate analysis was performed to determine which univariate prognostic relationships were independent predictive
factors (Table 5). The results are shown in Table 5. Noncurative resection and tumor location on gallbladder neck were found to be significant risk factors for poor outcome.

### Table 4. Univariate analysis of 14 variables in relation to survival (76 cases).

| Variables                  | Cutoff levels | Number | 3 year | 5 year | P value |
|----------------------------|---------------|--------|--------|--------|---------|
| Age (yr)                   | 59            | 41     | 23.4   | 17.6   | 0.061   |
|                           | ≤59           | 35     | 42.9   | 31.4   |         |
| Sex                       | Male          | 26     | 30.3   | 22.7   | 0.976   |
|                           | Female        | 50     | 33.9   | 21.1   |         |
| Jaundice                   | Present       | 27     | 14.8   | 7.4    | 0.012   |
|                           | Absent        | 49     | 42.7   | 34.0   |         |
| Associated gallstone       | Present       | 48     | 32.8   | 21.5   | 0.639   |
|                           | Absent        | 28     | 32.1   | 27.6   |         |
| Curability                 | Curative      | 58     | 41.1   | 29.2   | <0.001  |
|                           | Noncurative   | 18     | 5.6    | 5.6    |         |
| Tumor location             | Gallbladder neck | 31   | 19.4   | 7.7    | 0.008   |
|                           | Gallbladder body/fundus | 45 | 42.0   | 36.0   |         |
| pT (UICC)                  | pT1 and 2     | 18     | 44.4   | 37.0   | 0.119   |
|                           | pT3 and 4     | 58     | 28.9   | 19.8   |         |
| Lymph node metastasis      | Negative      | 31     | 57.3   | 53.3   | <0.001  |
|                           | Positive      | 45     | 15.6   | 5.2    |         |
| Stage(UICC)                | I and II      | 13     | 53.8   | 35.9   | 0.030   |
|                           | III and IV    | 63     | 23.1   | 17.5   |         |
| Histologic differentiation | Well/Moderate | 63     | 34.6   | 28.1   | 0.028   |
|                           | Poor          | 13     | 23.1   | 0      |         |
| Hepatic invasion           | Present       | 40     | 27.3   | 18.2   | 0.126   |
|                           | Absent        | 36     | 38.7   | 29.5   |         |
| pEBI                       | Present       | 31     | 19.4   | 11.6   | 0.056   |
|                           | Absent        | 45     | 42.0   | 32.7   |         |
| Intraoperative blood loss  | ≤600ml        | 57     | 36.5   | 29.6   | 0.011   |
|                           | >600ml        | 19     | 21.1   | 7.0    |         |
| Adjuvant therapy           | Yes           | 23     | 39.1   | 33.5   | 0.151   |
|                           | No            | 53     | 27.4   | 19.6   |         |
| Overall                    | 76             | 32.7   | 23.8   |        |         |

*pEBI indicates pathologic extrahepatic bile duct invasion.

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### Table 5. Results of multivariate analysis.

| Variable                  | Regression coefficient | Standard error | P value | Relative risk | 95% Confidence interval |
|---------------------------|------------------------|----------------|---------|---------------|-------------------------|
| Jaundice                  | 0.25                   | 0.34           | 0.463   | 1.284         | 0.659–2.500             |
| Curability                | 1.189                  | 0.356          | 0.001   | 3.285         | 1.636–6.597             |
| Tumor location            | −0.733                 | 0.323          | 0.023   | 0.480         | 0.255–0.904             |
| Stage(UICC)               | 0.423                  | 0.553          | 0.444   | 1.527         | 0.516–4.519             |
| Lymph node metastasis     | 0.68                   | 0.440          | 0.122   | 1.974         | 0.833–4.674             |
| Histologic differentiation| 0.468                  | 0.372          | 0.209   | 1.597         | 0.770–3.313             |
| Intraoperative blood loss | 0.496                  | 0.314          | 0.114   | 1.642         | 0.887–3.038             |

Clinicopathologic Features of Nine 5-Year Survivors

Of the 76 patients, 9 survived more than 5 years. There were 2 male and 7 female survivors with an average age of 57.1 years. None presented with jaundice. All the patients had been treated by
removal of the GB, wedge resection of the GB bed (including segments IV and V) and portal lymphadenectomy. There was no combined resection of adjacent organs. Curative resection was obtained in all of them. Histologically, none of the patients had lymph node metastasis. Seven of the 9 patients were still alive without tumor recurrence. Of the other 2 patients, one died of tumor recurrence at 5 years 11 months, and the other died of cardiovascular disease disease at 5 years 0 months.

Clinicopathologic Features of the 27 Jaundiced Patients

The clinicopathologic features of the 76 patients, grouped according to presence or absence of preoperative jaundice, were summarized in Table 6. All patients with preoperative jaundice underwent extrahepatic bile duct resection and reconstruction with curative intent. Combined resection of adjacent organs was necessary in more patients with preoperative jaundice. A longer postoperative hospital stay and more lymph node metastasis were associated with preoperative jaundice. As a result, R0 resection was more difficult to obtain in patients with preoperative jaundice than those without preoperative jaundice. Five-year survival rate and median survival time for the 49 patients without preoperative jaundice was 34% and 20.0 months, and for the 27 patients with preoperative jaundice were 7.4% and 12.0 months. Survival for patients with preoperative jaundice was significantly worse than for patients without preoperative jaundice (P = 0.012) (Fig. 2), though was not significant risk factor in multivariate analysis (P = 0.463).

An unusual way of growing invasion in GBC

In this period, three patients with gallbladder carcinoma who were identified of tumor thrombus in common bile duct in surgical procedure were analyzed. Abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP) were used for preoperative diagnosis (Fig. 3). All 3 patients were given radical operations, which were composed of cholecystectomy, resection of the extrahepatic biliary duct, cuniform hepatectomy of gallbladder bed, skeletonization of the hepatoduodenal ligament, hilar cholecystectomy, and clearance of tumor thrombus from bile duct. All three patients were recovered well after surgery, which were respectively alive for 30 months, 17 months and 23 months without tumor recurrence, and 58 months, 41 months and 40 months for survival time after operation. Gallbladder carcinoma with tumor thrombus in common bile duct was very rare but with relatively special clinical manifestation and characteristic radiography manifestation. MRCP was one of the most potent diagnostic method. The prognosis of gallbladder carcinoma with tumor thrombus in common bile duct after surgical procedure was apparently better than gallbladder carcinoma with invasion of hilar tissues. Radical operation was feasible and safe for obtaining longer survival.

Discussion

The majority of the patients with GBC remain asymptomatic or have vague complaints in the early stage of the disease, and by the time they become symptomatic, the tumor is in the advanced stage.

Table 6. Demographic data of jaundiced (n = 27) and non-jaundiced patients (n = 49) with gallbladder cancer.

| Variables                          | Jaundiced, n | Non-jaundiced, n | p-Value |
|------------------------------------|--------------|------------------|---------|
| Male gender                        | 12           | 14               | 0.166   |
| Mean age (range)                   | 58.3(35–78)  | 59.4(34–83)      | 0.858   |
| Postoperative hospital stay        | 19.6(8–85)   | 11.9(8–33)       | 0.001   |
| Extent of liver resection          |              |                  | 0.330   |
| Major hepatectomy (>3 segments)    | 1            | 3                |         |
| Anatomical segments IV-V           | 7            | 17               |         |
| Gallbladder bed                    | 19           | 29               |         |
| Combined resection of adjacent organs | 7 (25.9%) | 2 (4.1%)         | 0.005   |
| Microscopic invasion of the liver parenchyma | 18 (66.7%) | 22 (44.9%)      | 0.071   |
| Lymph node metastasis              | 22 (81.5%)   | 23 (46.9%)       | 0.004   |
| pT                                 |              |                  | 0.091   |
| pT4                                | 9 (33.3%)    | 9 (18.4%)        |         |
| R0                                | 17 (63.0%)   | 41 (83.7%)       | 0.043   |
| Mortality (number of patients)     | 9(33.3%)     | 9(18.4%)         | 0.145   |

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

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We state that the subject of the photograph has given written informed consent by the patient to publication of the photograph.

Figure 3. A jaundiced gallbladder carcinoma with tumor thrombus in common bile duct. (A: MRCP photography shows filling defect in CBD and gallbladder; B: In surgery specimen arrows 1–3 point at tumor tissues in gallbladder, cystic duct and CBD respectively.)

We have not considered jaundice alone to be a contraindication. Some jaundiced patients appeared to benefit from surgery in terms of survival following resection. Moreover, the extent of bile duct invasion, rather than jaundice, is a determinant of resectability due to anatomical reasons. In this study, preoperative jaundice was not a significant risk factor for poor outcome in multivariate analysis.

Therefore, we have not considered jaundice alone to be a contraindication to resection. Some jaundiced patients appeared to benefit from surgery in terms of survival following resection. Moreover, the extent of bile duct invasion, rather than jaundice, is a determinant of resectability due to anatomical reasons. In this study, preoperative jaundice was not a significant risk factor for poor outcome in multivariate analysis.

Jaundice should not be considered as an absolute contraindication

Most studies have reported that jaundice is an indicator of advanced disease with a dismal prognosis in GBC [1,3,7,10–12]. In the present study, we confirmed that jaundiced patients had longer postoperative hospital stay and poorer 5-year survival than non-jaundiced patients (7.4% and 34%, respectively), even though preoperative jaundice was not a significant risk factor for poor outcome in multivariate analysis.

Therefore, we have not considered jaundice alone to be a contraindication to resection. Some jaundiced patients appeared to benefit from surgery in terms of survival following resection. Moreover, the extent of bile duct invasion, rather than jaundice, is a determinant of resectability due to anatomical reasons. In this study, preoperative jaundice was not a significant risk factor for poor outcome in multivariate analysis.

A special infiltration manner in jaundiced patients with GBC

To date, only Midorikawa et al. [29] described one case of tumor embolus in the CBD from gallbladder carcinoma; however,
the tumor embolus he described was separated from the tumor. According to our own cases and literature review, gallbladder carcinoma with tumor thrombus in the CBD has the special clinicopathologic characteristics and better prognosis. GBC with cancer embolus extending into the CBD has different imaging manifestations on MRCP from GBC infiltrating the hilar bile duct. The latter usually displays abrupt truncation of the extrahepatic bile duct, whereas the former tends to develop an expansive mass. It has been reported that advanced gallbladder carcinoma with obstructive jaundice has a poor prognosis, and the advantages of radical surgery for these patients are still controversial [3,7,10–12,22]. Observing our own patients and the patient reported by Midorikawa [29], since obstructive jaundice caused by tumor thrombus is not always associated with advanced staging, radical surgery should be performed. The prognosis of gallbladder carcinoma with tumor thrombus in the CBD after radical surgery may be apparently better than that of gallbladder carcinoma with invasion of hilar tissues.

In conclusion, curative surgical resection remains the only effective approach to the treatment of GBC. Extensive resection is indicated if lymph node metastasis cannot be identified preoperatively or intraoperatively. This series confirms that jaundice is a poor prognostic factor. However, the presence of jaundice does not preclude resection, especially in highly selected patients. Among jaundiced patients, gallbladder carcinoma with tumor thrombus in the CBD had the different clinical, radiologic, and prognosis characteristics, which need to be aware by radiologists and clinicians as a special type of gallbladder carcinoma.

However, the limitations of this study are its retrospective design and the small number of patients studied. Further studies on larger numbers of patients, including prospective studies, are required to confirm the results of this study.

Author Contributions
Conceived and designed the experiments: BHZ FS MW. Performed the experiments: XY JY LL. Analyzed the data: XM XY. Contributed reagents/materials/analysis tools: XY JY LL. Wrote the paper: XY BHZ.

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