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***Retrospective Cohort Study***

**Prognostic factors and long-term outcomes of hilar cholangiocarcinoma:** **A single-institution experience in China**

Hu HJ *et al*.Prognostic factorsof HCCA

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**Abstract**

**AIM:** To evaluate the prognostic factors of hilar cholangiocarcinoma in a large series of patients in a single institution.

**METHODS:** Eight hundred and fourteen patients with a diagnosis of hilar cholangiocarcinoma, evaluated and treated between 1990 and 2014 were included, of which 381 patients underwent curative surgery. Potential factors associated with overall survival (OS) and disease free survival (DFS) were evaluated by univariate and multivariate analysis.

**RESULTS:** Curative surgery provided the best long-term survival with a median OS of 26.3 mo. The median DFS was 18.1 mo. Multivariate analysis showed that patients with tumor size > 3 cm (HR = 1.482, 95%CI: 1.127-1.949, *P* = 0.005), positive nodal disease (HR = 1.701, 95%CI 1.346-2.149, *P* < 0.001), poor differentiation (HR = 2.535, 95%CI: 1.839-3.493, *P* < 0.001), vascular invasion (HR = 1.542, 95%CI: 1.082-2.197, *P* = 0.017) and positive margins (HR = 1.798, 95%CI: 1.314-2.461, *P* < 0.001) had poor OS outcome. The independent factors for DFS were positive nodal disease (HR = 3.383, 95%CI: 2.633-4.348, *P* < 0.001), poor differentiation (HR = 2.774, 95%CI: 2.012-3.823, *P* < 0.001) vascular invasion (HR = 2.136, 95%CI: 1.658-3.236, *P* < 0.001) and positive margins (HR = 1.835, 95%CI: 1.256-2.679, *P* < 0.001). Multiple logistic regression analysis showed that caudate lobectomy (OR = 9.771, *P* < 0.001, 95%CI: 4.672-20.433), tumor diameter (OR = 3.772, *P* < 0.001, 95%CI: 1.914–7.434), surgical procedures (OR = 10.236, *P* < 0.001, 95%CI: 4.738–22.116), AJCC T stage (OR = 2.010, *P* = 0.037, 95%CI: 1.043–3.870) and vascular invasion (OR = 2.278, *P* = 0.051, 95%CI: 0.997–5.207) were independently associated with tumor-free margin, and surgical procedures could indirectly affect survival outcome by influencing the tumor resection margin.

**CONCLUSION:** Tumor margin, tumor differentiation, vascular invasion and lymph node status were independent factors for OS and DFS. Surgical procedures can indirectly affect survival outcome by influencing the tumor resection margin and was the most important factor that play a role in affecting tumor-free margin.

**Key words:** Hilar cholangiocarcinoma; Surgical outcome; Tumor-free margin; Survival; Prognosis

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**Core tip:** Hilar cholangiocarcinoma remains among the most difficult management problems faced by surgeons. Curative surgery is significant in prolonging the survival time of patients diagnosed with hilar cholangiocarcinoma. Due to the difference in study methods and small patient numbers in some studies, it may cause potential biases or even contradictory outcomes. Furthermore, some large cases of multi-center reports may induce biases due to the heterogeneity of clinical methods and surgical strategies. Thus, we retrospectively analyzed the prognostic factors of hilar cholangiocarcinoma and factors associated with tumor free margin in a large sample of hilar cholangiocarcinoma cases in a single institution.

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**INTRODUCTION**

Hilar cholangiocarcinoma (HC) is a rare, devastating, and highly malignant disease of the bile duct[1-4]. On the basis of the Bismuth classification, hilar cholangiocarcinoma can be divided into 4 types: type I represents for tumors affecting the common hepatic duct, type II represents for tumors affecting the hilus, type III A/B represents for tumors invading the right or left hepatic duct, type IV with tumors infiltration of both right and left hepatic ducts and the sub-segments[1]. A variety of established risk factors are reported to increase the odds of hilar cholangiocarcinomas, which include the primary sclerosing cholangitis, the biliary duct cysts, the oriental cholangiohepatitis, the hepatolithiasis, the biliary parasitic disease and the toxins exposure, the specific etiology is still unclear[5,6]. HC is reported to be a slow-growing and late-metastasizing malignant disease[7-9], but it situated at a cabinet and pivotal space, encircled by the portal vein, hepatic artery, liver parenchyma and the bile duct, thus, having a strong tendency to extensively invade the portal vein, hepatic artery, perineural tissue and the surrounding liver parenchyma, including the caudate lobe[10-15]. Moreover, the caudate lobe lies in a deep and complex location and has an intimate relationship with the major vascular structures[16, 17], resulting in high operative risks and increased postoperative complications[18,19]. In addition, hilar cholangiocarcinoma always lies in the core part of the biliary system, causing malignant biliary obstruction and cholestatic hepatitis. Thus, major hepatic resection tends to associate with increased risk of postoperative hepatic insufficiency and postoperative hepatic failure is reported to be the most frequent cause of in-hospital death following major hepatectomy[14,20]. This is the reason why hilar cholangiocarcinoma is still recognized as the most difficult surgeries besides liver transplantation in hepatobiliary surgery. Nevertheless, surgical resection with extended hepatectomy, caudate lobectomy, lymphadenectomy, vascular resection and reconstruction remains the cornerstone of the treatment and represents the only potentially radical therapeutic modality to prolong the survival of patients with hilar cholangiocarcinoma[21-26].

Uni- and multivariate analysis have identified various prognostic factors for OS and DFS of hilar cholangiocarcinoma[7,27-29]. But only large-volume patient cases can provide more confidence to guide the treatment. Thus, the current study was planned to protrude the following points: (1) estimate prognostic factors associated with OS and DFS after successful resection of hilar cholangiocarcinoma in a large, single-center study; (2) evaluate which factors could contribute to the obtaining of R0 resection to help future surgical decision making; and (3) compare various surgical procedures in treating and prolonging the lifespan of hilar cholangiocarcinoma (HCCA) patients to guide the treatment of HCCA and forecast the postoperative prognosis.

**MATERIALS AND METHODS**

***Patients***

All patients with a diagnosis of hilar cholangiocarcinoma evaluated and treated at our institution since 1990 were identified from a hepatobiliary database. Patients were divided into 3 groups: patients who underwent curative surgery (381), those who only take palliative surgery (330) and those who did not take any surgery (103). Patients with intrahepatic bile duct carcinoma infringing the hilum, patients with gallbladder carcinomas, patients underwent liver transplantation were excluded. Clinical, radiologic, histopathologic, therapy and survival data were obtained and evaluated.

***Assessment of resectability***

Resectability was assessed both with preoperative imaging studies and intraoperative evaluation. Patients with any of the following were considered to be unresectable: poor conditions, Child-Pugh C, advanced biliary invasion that excludes complete tumor resection, encasement of major vessel structures that eliminate vascular reconstruction, lymph nodes metastases beyond the hepatoduodenal ligament, metastatic disease (lung and peritoneum metastases)[30,31]. Biliary drainage was performed in most of patients with obstructive jaundice. In patients with cholangitis, resection was performed after alleviation of inflammation. As for the patients who were considered to have potentially resectable tumors, portal vein embolization was performed when the future remnant liver volume (25%–30%) was deemed insufficient (53 patients). Surgical procedures were selected according to the preoperative and intraoperative evaluation.

***Follow-up protocol***

After treatment, patients were regularly followed-up at outpatient clinic with clinical examination, CA 19-9 serum level, liver function tests and hepatic ultrasonography. If recurrence was suspected in some specific patients, further assessments such as abdominal CT or MRCP were used to make a definitive diagnosis. The median follow-up period for resected patients was 21.7 mo (range, 3–85 mo) with a follow-up rate of 95.6%.

***Statistical analysis***

Data analysis was performed using SPSS version16.0 (SPSS Inc., Chicago, IL, United States). Frequency and descriptive analysis were used to depict patient characteristics. Parametric statistical analysis was conducted using Student *t* test, while nonparametric analysis was calculated using *χ*2. Survival (calculated from the time of surgery) was estimated using Kaplan-Meier methods, differences in survival were reviewed using the log-rank test. Multivariate analysis was performed on all factors with a P value of less than 0.10 in univariate analysis. Univariate and bivariate analysis were used to check the association of several tumor variables with tumor resection margin. Multiple logistic regression analysis was used in the final analysis to adjust for independent variables for tumor-free margin. The hazard ratio and the 95%CI were estimated and a *P* value less than 0.05 were considered significant.

**RESULTS**

***Patients and tumors***

The clinical characteristics of the study population are summarized in Table 1. The specific surgical procedures for patients underwent curative and palliative surgery are presented in Table 2.

***Morbidity and mortality***

**Curative intent surgery:** The perioperative complication rate after major surgical treatment was 29.4% (*n* = 112), which includes, hemorrhage (15 cases), bile leakage (40 cases), peritoneal cavity infection (16 cases), lung infection (23 cases), sepsis (3 cases), acute cardiac failure (3 cases), hepatic failure (20 cases), renal failure (5 cases), stress ulcer (10 cases), wound dehiscence (4 cases) and hydrothorax or ascites (6 cases). Perioperative mortality rate was 3.8% (*n* = 10). And both postoperative morbidity and operative mortality were deemed as those occurring within 60 d of the major surgery, or occurred at any time of the postoperative hospital stay. Then we examined the relationship between postoperative complications and risk factors, we found that patients undergoing hepatectomy had more complications when compared with those who underwent bile duct resection alone (*P* < 0.001). In patients with postoperative hyperbilirubinemia, the incidence of postoperative complication rate was also higher (*P* = 0.004).

**Palliative intent surgery:** The perioperative complication rate after palliative treatment was 11.2% (*n* = 37), of which the most frequent was lung infection (16 cases), others include hemorrhage (4 cases), bile leakage (7 cases), peritoneal cavity infection (13 cases), sepsis (2 cases), wound infection (2 cases), hepatic failure (3 cases), renal failure (1 cases), wound dehiscence (1 cases), and others (3 cases). And the perioperative mortality rate was 4.5% (15 case), of which the most common cause was multiple organ failure because of liver failure (8 cases) followed by renal failure (3 case), infective complications (3 cases) and heart failure (1 cases).

***Survival analysis of curative and palliative surgery***

As expected, the radical resection provided the best opportunity of OS with a median survival time of 26.3 mo, and the 1-, 3-, 5-year survival rate was 80%, 43%, and 28% respectively. This contrasted to the patients who underwent palliative surgery with a median OS of about 7.3 months and the 1-, 3-, 5-year survival rate was 10%, 2%, and 0% (Figure 1, log-rank test, *P* < 0.001). As for patients who did not take any surgical treatment, the median OS and the 1-, 3-year survival rate was 2.6 mo and 1% and 0%, respectively (Figure 1, log-rank test, *P* < 0.001). The median DFS of radically resection group was 18.1 months, and the 1-, 3-, 5-year DFS was 78%, 18%, and 10% respectively. Furthermore, we compared the survival rate of those underwent surgical palliation and nonsurgical palliation, the former had a median survival time and 6-month survival rate of 7.4 mo and 27% respectively, while the latter had a median survival time of 5.5 mo and 6-mo survival rate of 9% respectively (*P* < 0.001).

***Factors associated with OS and DFS after curative resection***

As was shown in Table 3, OS was significantly longer in patients with no lymph node metastasis (*P* < 0.001), well histological differentiation (*P* < 0.001), negative resection margin (*P* < 0.001), tumor size ≤ 3 cm (*P* < 0.001), caudate lobectomy (*P* = 0.04), lower CA 19-9 level (*P* = 0.039) and no vascular invasion (*P* = 0.009). Hepatectomy and the lack of perineural infiltration were approaching statistical differences as positive prognostic factors for OS in univariate analysis (*P* = 0.072 and 0.084 respectively). Then we further examined factors associated with disease-free survival, it showed that resection margins (*P* < 0.001), tumor differentiation (*P* < 0.001), lymph nodes metastases (*P* < 0.001), tumor size (*P* < 0.001), caudate lobectomy (*P* < 0.001), CA 19-9 level (*P* = 0.018), T stage of AJCC (*P* = 0.028), and vascular invasion (*P* < 0.001) were associated with DFS (Table 3).

In multivariate analysis, tumor size > 3 cm (HR = 1.482, 95%CI: 1.127-1.949, *P* = 0.005), positive nodal disease (HR = 1.701, 95%CI 1.346-2.149, *P* < 0.001), poor differentiation (HR = 2.535, 95%CI: 1.839-3.493, *P* < 0.001) vascular invasion (HR = 1.542, 95%CI: 1.082-2.197, *P* = 0.017) and positive margins (HR = 1.798, 95%CI: 1.314-2.461, *P* < 0.001) remained associated with OS (Table 4). For DFS, positive nodal disease (HR = 3.383, 95%CI: 2.633-4.348, *P* < 0.001), poor differentiation (HR = 2.774, 95%CI: 2.012-3.823, *P* < 0.001), vascular invasion (HR = 2.136, 95%CI: 1.658-3.236, *P* < 0.001) and positive margins (HR = 1.835, 95%CI: 1.256-2.679, *P* < 0.001) were correlated with DFS in multivariate analysis (Table 4).

***Factors associated R0 resection***

Now that R0 resection was important as R0 resection conferred to a median survival time of 35.2 mo while patients with R1 and R2 resection had a median survival time of 12.4 mo, and the palliative surgery only granted a median survival time of 7.3 mo. Thus, further studies emphasized on the factors that could affect the tumor-free margin. Univariate analysis showed that tumor differentiation (*P* = 0.001), tumor diameter (*P* < 0.001), hepatectomy (*P* = 0.012), lymph node metastasis (P = 0.001), T stage (AJCC, *P* = 0.001) caudate lobectomy (*P* = 0.001), Bismuth-Corlette classification (*P* = 0.038), and vascular invasion (*P* = 0.01) were associated with tumor-free margin. Multiple logistic regression analysis (Table 5) showed that caudate lobectomy (OR = 9.771, *P* < 0.001, 95%CI: 4.672-20.433), tumor diameter (OR = 3.772, *P* < 0.001, 95%CI: 1.914–7.434), surgical procedures (OR = 10.236, *P* < 0.001, 95%CI: 4.738–22.116), AJCC T stage (OR = 2.010, *P* = 0.037, 95%CI: 1.043–3.870) and vascular invasion (OR = 2.278, *P* = 0.051, 95%CI: 0.997–5.207) were independently associated with tumor-free margin after adjusting for other factors.

**DISCUSSION**

Hilar cholangiocarcinoma remains among the most difficult management problems faced by surgeons. The accumulated outcomes from many institutions show firmly that only an excision with negative resection margin can be regarded as radically therapeutic and in this condition hepatic resection is often demanded[28,30]. Many authorities have reported various prognostic factors of HCCA; however, due to the difference in study methods and small patient numbers in other studies, it may cause potential biases or even contradictory outcomes. Furthermore, some large cases of multi-center reports may induce biases due to the heterogeneity of clinical methods and surgical strategies. Thus a large number of HCCA cases of single center experience are urgently needed to standardize the prognostic factors and to supply better guidance and treatment for HCCA.

We reported a median OS of 26.3 months with the 1-, 3-, 5-year survival rate of about 80%, 43%, and 28%, which was comparable to some published articles from high-volume hepatobiliary centers that recorded a median OS between 16 and 40 mo and a 5-year survival rate of 11% to 40%[4, 32-34]. We also reported a median DFS of 18.1 mo for radically resection group, which was commendably within the range from 12 to 20 mo covered by other literatures[1,4,31,35]. The data in our series has also verified the common notion that curative surgery provided the best opportunity in increasing the median and long term survival rate of patients diagnosed as HCCA, as the failure of conducting curative surgery resulted in a sharp decrease in the overall survival (Figure 1; *P* < 0.001). And compared with patients who did not accept any treatment, palliative surgery resulted in a relatively better outcome, which might explained as follows: Palliative surgery can roughly remove the root of obstructive jaundice and adequately open biliary tract and then the liver function can be improved and relatively better survival outcomes can be expected to some extent. We also identified that intraoperative palliation conferred to a relatively longer survival than nonsurgical palliation when compared with nonsurgical palliation, intraoperative palliation can directly lessen the odds of bile duct obstruction by completely opening bile duct as much as possible, facilitating whole biliary decompression and finally enhancing liver function and survival outcomes. Therefore, we believe that intra-operative palliation is superior to nonsurgical palliation in patients who lost the chance of undergoing curative resection. However, further studies with more number of cases are needed in future to testify the reasonability of whether surgical palliation is superior to nonsurgical palliation. In the long run, compared with the curative surgery, we convincingly believe that curative surgery is the best way in prolonging the survival outcome.

Many clinical, surgical, and pathological factors have been shown to influence OS and DFS after major resection in recent literature[28, 29,31,36]. In our retrospective study, multivariate analysis showed surgical margin, lymph node, tumor differentiation, vascular invasion were independent factors for OS and DFS. In addition, tumor size was also an independent factor for OS but not for DSF.

It is broadly recognized that among a large succession of prognostic factors of HCCA, tumor-free margin is the most powerful predictor for both OS and DFS[35,37,38]. In our present study, R0 resection emerged as an independent prognostic factor for both disease-free (Figure 2A) and overall survival (Figure 3A), patients with negative margins had markedly better OS and DFS than those with positive ones. The fact that patients undergoing R1 or R2 resection have better outcomes than patients undergoing palliative surgery has also been reconfirmed in current research. And we further examined factors associated with R0 resection, finding that patients with smaller tumor size, concomitant hepatic resection, caudate lobectomy, T1 and T2 stage (AJCC) and the lack of vascular invasion had a higher tendency of obtaining tumor-free margin.

In our study, survival was hazarded by the existence of lymph node metastasis as testified by univariate and multivariate analysis, with a decrease in the median OS from 39.9 mo to 15.7 mo, and a decrease in the median DFS from 25.4 mo to 12.3 mo. This corresponded with those reported by other previous studies that lymph node metastasis is an important independent prognostic factor for both disease-free[31,39,40] and overall[26,28,39,41,42] survival. The prognostic significance of node status stressed the necessity for a radical lymphadenectomy. In this respect, thoroughly lymph nodes dissection may be significant and should be prospectively evaluated and studied in the future.

Tumor differentiation is a disputable factor in many retrospective studies, Hasegawa *et al*[42] did not find a survival disadvantage in case of tumor differentiation, while Saxena *et al*[4] have shown that tumor differentiation is a biological marker for measuring tumor invasion and metastasis and predicting long-term survival, which was comparable to our results, as the median OS decreased sharply from 54.1 mo to 13.5 mo when the patients had a poor differentiation. And the median DFS of well-differentiated patients was two folders greater as compared with poor-differentiated patients. Thus in view of the fact that histologic differentiation is an independent prognostic factor both in OS and DFS, we were tempted to conclude that poorly differentiated cancers have poor prognosis and higher recurrence rate.

Vascular invasion is no longer a contraindication for the excision of HCCA. With the reason that this procedure has high mortality and risk, we performed vascular resection and reconstruction only when the patients were clinical suspicious of vascular infiltration. Our report demonstrated that patients with vascular invasion were more likely to have a poor OS and DFS (Figures 2B and 3B); similarly, vascular invasion was also associated with a higher tendency of R1 and R2 status although it was only approaching statistical difference in the multivariate logistic regression (OR = 2.278, 95%CI: 0.997-5.207, *P* = 0.051). Thus in those highly suspected patients, vascular resection is recommended.

Perhaps more importantly, we found that tumor size was a significant prognostic parameter for OS and DFS in univariate analysis. It was also an independent factor that was associated with OS in multivariate analysis (Figure 2C). So far, no other reports have shown this association as clear as us in the current study. And our reports also confirmed the T stage of DeOliveira staging system was important in which the 3 cm cut-off was regarded as T3. Moreover, tumor size could influence R0 resection in multivariate logistic regression. Thus, from this point of view, this factor is needed to be taken into consideration when we evaluate the long term survival of HCCA patients.

Many studies have shown that caudate lobectomy appears to have a positive effect on tumor-free margin and survival after the resection of Klatskin tumors[26,43,44]. In our study, caudate lobe was routinely removed, and it was not associated with postoperative complications, the OS and DFS were found to be significantly longer in patients with caudate lobectomy as compared with those without caudate lobectomy in the univariate analysis (median OS 35.7 : 21.4 mo, median DSF 21.3 : 15.0 mo; *P* = 0.04 and *P* < 0.001 respectively). At the same time, caudate lobectomy was approaching statistical significance as a positive prognostic factor for OS on multivariate analysis (HR = 1.257, 95%CI: 0.981-1.612, *P* = 0.071). Furthermore, it was also an independent factor for tumor-free margin in our current series (OR = 10.236, 95%CI: 4.738-22.116, *P* < 0.001). Thus, we firmly believe that this procedure should be considered as a part of the standard surgical resection.

In contrast to previous researches, our study did not find a survival advantage in case of hepatectomy. We only found curative surgery accompanied with hepatectomy could easily achieve more complete tumor-free margins, this was consistent with many previous studies[27,29,43,45]. Tumor- free margin in turn could promote the overall survival outcome and is the powerful predictor of survival both reported in our series and in other literature. In our research, hepatectomy was the most important factor that could affect the tumor-free margin. Thus hepatectomy is an indirect prognostic factor that can promote the overall survival, it can indirectly affect survival outcome by influencing the tumor resection margin.

In conclusion,radical surgical resection is the best treatment option for HCCA. R0 resection along with negative lymph nodes metastases, well-differentiation and lack of vascular invasion indicate better OS and DFS. Smaller tumor size also predicts better OS but not DFS. Multivariate logistic regression analysis shows that hepatectomy, tumor diameter, T stage, caudate lobectomy and vascular invasion are independently associated with tumor-free margin. Hepatectomy can help achieve more tumor-free resection margins and then indirectly affect OS; it is an indirect prognostic factor on survival.

**COMMENTS**

***Background***

Many authorities have reported various prognostic factors of hilar cholangiocarcinoma (HCCA); however, due to the difference in study methods and small patient numbers in other studies, it might cause potential biases or even contradictory outcomes. Furthermore, some large cases of multi-center reports might induce biases due to the heterogeneity of clinical methods and surgical strategies.

***Research frontiers***

To estimate prognostic factors associated with overall survival (OS) and disease free survival (DFS) after successful resection of hilar cholangiocarcinoma in a large, single-center study and to evaluate which factors could contribute to the R0 resection to help future surgical decision making and then guide the treatment of HCCA.

***Innovations and breakthroughs***

Based on our study, R0 resection along with negative lymph nodes metastases, well-differentiation and lack of vascular invasion indicated better OS and DFS. Smaller tumor size also predicts better OS but not DFS. Hepatectomy, tumor diameter, T stage, caudate lobectomy and vascular invasion were independently associated with tumor-free margin. Hepatectomy can help achieve more tumor-free resection margins and then indirectly affect OS; it was an indirect prognostic factor on survival.

***Applications***

Hilar cholangiocarcinoma remains among the most difficult management problems faced by surgeons. Our results may help future surgical decision making and then better guide the treatment of HCCA.

***Terminology***

Curative resection is important for the prognosis of hilar cholagiocarcinoma, and R0 resection plays a significant role in prolonging the survival time of patients, R0 resection refers to those with microscopically negative tumor resection margin.

***Peer-review***

The authors examined the potential risk factors correlated with HCCA and factors that could affect tumor free margin in a large, single-center study. The study was well performed and its findings are interesting and informative.

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**Figure 1 Comparing overall survival of patients who underwent curative intent surgery, palliative surgery and those who did not take any treatment for Hilar Cholangiocarcinoma (*P* < 0.001).**



**A B**



**C**

**Figure 2 Overall survival of patients who underwent curative surgery for hilar Cholangiocarcinoma stratified by (A) resection margin, vascular invasion (B), tumor size (C).**

 

A B

**Figure 3 Disease free survival of patients who underwent curative surgery for hilar Cholangiocarcinoma stratified by resection margin (A), vascular invasion (B).**

**Table 1 Patient characters: comparison between resected and palliative patients**

|  |  |
| --- | --- |
|  | **Number (%) or median [range]** |
| **Variable** | **Curative surgery****(*n* = 381)** | **Palliative surgery****(*n* = 330)** |
| Age (median [range]) | 60 [26-82] | 58 [19-80] |
| Gender, male (%) | 231 (60.6) | 178 (53.9) |
| Presenting symptoms, *n* (%) |  |  |
| Jaundice | 267 (70.1) | 240 (72.7) |
| Weight loss | 26 (6.8) | 22 (6.7) |
| Abdominal pain | 24 (6.3) | 28 (8.5) |
| Nausea and vomiting | 20 (5.2) | 17 (5.1) |
| General fatigue | 44 (11.6) | 23 (7.0) |
| Tumor markers (median [range]) |  |  |
| Pre-operative CA 199 level, U/mL  | 348 [0.6-1000] | 539.9 [0.6-3015.17] |
| Pre-operative CA 125 level, U/mL  | 19.84 [1.23-257.7] | 33.94 [1.54-1598] |
| Pre-operative CEA level, ng/mL | 3.23 [0.2-65.51] | 4.44 [0.47-1000] |
| Liver functions (median [range]) |  |  |
| Pre-operative TB level, mg/dL  | 209.4 [7.1-586.3] | 239.65 [1.9-805.7] |
| Pre-operative ALT level, U/L  | 95 [10-967] | 78.5 [6-1212] |
| Pre-operative AST level, U/L  | 86 [14-1016] | 87 [11-927] |
| Pre-operative Albumin level, g/L  | 36.7 [18.7-51.8] | 35.95 [21.3-72.5] |
| Preoperative hospital stay (median [range]) | 7 [2-44] | 7 [3-48] |
| Total hospital stay (median [range]) | 19 [9-113] | 16 [4-102] |
| Portal vein embolization, *n* (%) | 53 (13.9) |  |
| Biliary drainage, *n* (%) | 201 (52.8) |  |
| Estimated blood loss ( median [range]) | 600 [50-2000] | 348 [0.6-1000] |
| Bismuth-Corlette classification, *n* (%) |  |  |
| Type I  | 95 (25.2) | 16 (4.8) |
| Type II  | 92 (24.2) | 59 (17.9) |
| Type IIIa or IIIb | 102 (26.8) | 102 (30.9) |
| Type IV  | 92 (24.2) | 153 (46.4) |
| CA-19-9: carbohydrate antigenic determinant 19-9; CA125: carbohydrate antigen 125; TB: total bilirubin; ALT: alanine aminotransferase; AST: aspartate transaminase; CEA: Carcino Embryonie Antigen. |

**Table 2 Type of surgical procedures**

|  |  |
| --- | --- |
| **Surgical procedures** | ***n* (%)** |
| Curative intent surgery | 381 (53.6) |
| Hilar bile duct resection alone | 50 (13.1) |
| Left hemihepatectomy | 142 (37.3) |
| Right hemihepatectomy | 101(26.5) |
| Left trisegmentectomy | 46 (12.1) |
| Right trisegmentectomy | 20(5.2) |
| Mesohepatetctomy | 22 (5.8) |
| Additional procedures |  |
| Caudate lobectomy | 300 (78.7) |
| Portal vein resection | 51 (13.4) |
| Pancreatoduodenectomy | 8 (2.1) |
| Palliative intent surgery | 330 (46.4) |
| Surgical palliation | 266 (80.6) |
| Nonsurgical palliation | 64 (19.4) |
| ERCP | 35 (10.6) |
| PTCD | 29 (8.8) |
| ERCP: Endoscopic retrograde cholangiopancreatography; PTCD: Percutaneous transhepaticcholangial drainage. |

**Table 3 Univariate analysis of prognostic factors on overall survival and disease free survival**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables**  | **Median OS (mo)** | ***P* value** | **Median DFS (mo)** | ***P* value** |
| Tumor size |  |
| ≤ 3 cm | 35.2 | < 0.001 | 19.8 | < 0.001 |
| > 3 cm | 14.7 |  | 13.0 |  |
| Surgical procedures |  |
| BDR | 20.8 | 0.072 | 15.0 | 0.065 |
| BDR+hepatectomy | 27.6 |  | 18.7 |  |
| Lymph node metastasis |  |
| N0 | 39.9 | < 0.001 | 25.4 | < 0.001 |
| N1-2 | 15.7 |  | 12.3 |  |
| Tumor differentiation |  |
| well | 54.1 | < 0.001 | 25.3 | < 0.001 |
| moderate | 27.6 |  | 17.8 |  |
| poor | 13.5 |  | 12.1 |  |
| Resection margin |  |
| R0 | 35.2 | < 0.001 | 20.6 | < 0.001 |
| R1 and R2 | 12.4 |  | 9.6 |  |
| Presence of vascular invasion |  |
| No | 26.3 | 0.009 | 19 | < 0.001 |
| Yes | 20.9 |  | 10.6 |  |
| Caudate lobe resection |
| Yes | 35.7 | 0.04 | 21.3 | < 0.001 |
| No | 21.4 |  | 15.0 |  |
| CA 19-9 >100 U/L |  |  |  |  |
| No | 39.7 | 0.039 | 23.6 | 0.018 |
| Yes | 23.0 |  | 16.7 |  |
| Perineural infiltration |  |  |  |  |
| No | 27.3 | 0.084 | 22.7 | 0.09 |
| Yes | 20.8 |  | 15.9 |  |
| T stage (AJCC) |  |
| T1 and T2 | 27.6 | NS | 19.2 | 0.028 |
| T3 and T4 | 25.7 |  | 16.9 |  |
| Additional factors not significant in univariate analysis included age, gender, gross feature, operative time, total hospital stay, preoperative biliary drainage, Bismuth-Corlett classification *et al.* NS: Not significant; OS: Overall survival; DFS: Disease free survival; BDR: Hilar bile duct resection; CA-19-9: Carbohydrate antigenic determinant 19-9; AJCC: American Joint Committee On Cancer. |

**Table 4 Multivariate analysis of prognostic factors on overall survival and disease free survival**

|  |  |  |
| --- | --- | --- |
| **Variables**  | **For OS** | **For DFS** |
| **Hazard ratio** | **95% CI** | **P value** | **Hazard ratio** | **95% CI** | ***P* value** |
| Tumor size > 3 cm | 1.482 | 1.127-1.949 | 0.005 | - | - | - |
| Poor tumor differentiation | 2.535 | 1.839-3.493 | < 0.001 | 2.774 | 2.012-3.823 | < 0.001 |
| Positive resection margin | 1.798 | 1.314-2.461 | < 0.001 | 1.835 | 1.256-2.679 | < 0.001 |
| Positive nodal status | 1.701 | 1.346-2.149 | < 0.001 | 3.383 | 2.633-4.348 | < 0.001 |
| Vascular invasion | 1.542 | 1.082-2.197 | 0.017 | 2.136 | 1.658-3.236 | < 0.001 |

 OS: Overall survival; DFS: Disease free survival.

**Table 5 Multivariate analysis of risk factors for tumor free resection margin**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables**  | **Hazard ratio** | **95% CI** | ***P* value** |
| Tumor size | 3.772 | 1.914–7.434 | < 0.001 |
| AJCC T stage | 2.010 | 1.043–3.870 | 0.037 |
| Surgical procedures | 10.236 | 4.738–22.116 | < 0.001 |
| Caudate lobectomy | 9.771 | 4.672-20.433 | < 0.001 |
| Vascular invasion | 2.278 | 0.997–5.207 | 0.051 |

AJCC: American Joint Committee on Cancer.