



BRIEF ARTICLES

Addition of hepatectomy decreases liver recurrence and leads to long survival in hilar cholangiocarcinoma

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CONCLUSION: Hepatectomy, especially including the caudate lobe combined with bile duct resection should be considered standard treatment to cure hilar cholangiocarcinoma.

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Key words: Curative resection; Hepatectomy; Hilar cholangiocarcinoma; Recurrence; Survival

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Abstract

AIM: To evaluate hepatic recurrence and prognostic factors for survival in patients with surgically resected hilar cholangiocarcinoma in a single institution over the last 13 years.

METHODS: From 1994 to 2007, all patients with hilar cholangiocarcinoma referred to a surgical clinic were evaluated. Demographic data, tumor characteristics, and outcome were analyzed retrospectively. Outcome was compared in patients who underwent additional liver resection with resection of the tumor.

RESULTS: Of the 69 patients submitted to laparotomy for tumor resection, curative resection (R_0 resection) was performed in 40 patients, and palliative resection in 29. Thirty-one patients had only duct resection, and 38 patients had combined duct resection with liver resection including 34 total or part caudate lobes. Curative rates with the combined hepatectomy were significantly improved compared with those without additional hepatectomy (27/38 vs 13/31; $\chi^2 = 5.94$, $P < 0.05$). Concomitant liver resection was associated with a decreased incidence of initial recurrence in liver one year after surgery (11/38 vs 23/31; $\chi^2 = 13.98$, $P < 0.01$). The 3-year survival rate after R_0 resection was 30.7% and was 10.5% for palliative resection. R_0 resection improved the 3-year survival rate (30.7% vs 10.5%; $\chi^2 = 12.47$, $P < 0.01$).

INTRODUCTION

The surgical treatment of hilar cholangiocarcinoma has changed completely in recent decades, before 1980 the majority of patients were not resected, and in a few cases local excision of the tumor was performed with low radicality and poor long-term outcome. Since 1980, indications for resection have progressively improved and liver resection has been associated with bile duct resection in order to increase radicality and achieve better survival results^[1-5]. In contrast to reports from 2 or 3 decades ago, today most patients with hilar cholangiocarcinoma are diagnosed pre-mortem. The most important factor affecting prognosis is resectability of the tumor. Patients who undergo resection with curative intent have 3-year survival rates as high as 50% and 5-year survival rates between 10% and 44%. Significant determinants of improved prognosis in patients undergoing curative resection include well-differentiated tumors, absence of lymph node metastases, absence of direct tumor extension into the liver, papillary histology, serum bilirubin at presentation of less than 9 mg/dL, and a near-normal or normal performance status. Palliative resection, surgical bypass procedures, and various types of intubation and drainage procedures are associated with 3-year survival rates from 0% to 4%^[6-8].

The prognosis of patients with hilar cholangiocarcinoma is poor, and the survival rate reported so far describes a very limited life expectancy, < 3 mo if no treatment is offered. Although radical hilar tumor is a formidable challenge for surgeons, endoscopic transpapillary and/or percutaneous transhepatic biliary drainage offers the best survival^[9-11].

Local resection seems to have a very narrow role because of its poor results compared with those of hepatectomy associated with bile duct resection. We have tried to address the above-mentioned issues in this systematic retrospective analysis of the literature.

MATERIALS AND METHODS

Data selection

Long-term follow-up of patients with hilar cholangiocarcinoma undergoing surgical resection was performed by retrospective analysis. The study included 69 unselected consecutive patients whose tumor resection was attainable (46 males and 23 females with a mean age of 58 years) during treatment for hilar cholangiocarcinoma from 1994 to 2007 in the Department of General Surgery, at First Affiliated Hospital, Fujian Medical University. Data acquisition was based on hospital records. Furthermore, follow-up data were obtained by telephone contact with relatives of the patients. In order to evaluate the life expectancy of patients with hilar cholangiocarcinoma, follow-up analysis was performed from the time the patient received his or her first treatment until death. Negative margins of bile duct at final pathologic reports had R₀ resection, otherwise positive margins had palliative resection.

Bismuth classification and treatment strategies

The biliary stricture location was classified in relation to the confluence of hepatic ducts as described by Bismuth-Corlette. Bismuth stage was assessed by endoscopic retrograde cholangiography, endoscopic retrograde cholangioscopy, percutaneous transhepatic cholangiography and/or percutaneous transhepatic cholangioscopy. 3D images provided accurate information on the relationship between hilar cholangiocarcinoma and adjacent vessels. This technique is a powerful new tool for improving the proportion of potentially curative resections^[12]. In addition, selected patients underwent computed tomography (CT-scan), magnetic resonance imaging (MRI), or magnetic resonance cholangiopancreatography (MRCP). The final diagnosis was made by surgical specimens in addition to resection of the extrahepatic bile ducts with complete porta hepatis and lymphadenectomy. An en bloc resection of the right or left hepatic lobe and caudate lobe was performed in many patients. Biliary-enteric construction was completed with a single hepaticojejunostomy to the bile duct using a Roux-en-Y limb.

Statistical analysis

All data were analyzed with SPSS 15.0 statistical package.

Table 1 Pathologic characteristics and serum bilirubin level in patients

Number of patients	Lymph node metastases	Extension in liver parenchyma	Invasion of nervous tissue	Serum bilirubin (μmol/L)
Curative resection	11	17	20	267 ± 158
Palliative resection	8	13	19	280 ± 161

There were no significant differences between the data of the two groups (Curative resection *vs* palliative resection, $P > 0.05$).

Cumulative overall survival rate was calculated by the Kaplan-Meier method using the log rank test. Intergroup comparisons of hepatic recurrence rate and survival rate were analyzed using the χ^2 test. Significance was accepted with 95% confidence.

RESULTS

Characteristics of patients

A total of 69 consecutive patients underwent surgical resection for malignant hilar bile duct tumors during 1994-2007. The characteristics of the patients entered into this study included a mean age of 58 ± 10.5 years. Of the 69 patients at the time of final diagnosis, 10 were diagnosed as Bismuth stage I, 23 were diagnosed as Bismuth stage II, 35 as Bismuth stage III, and 1 as Bismuth stage IV. All the patients presented with jaundice and almost complete obstruction of the common and left or right hepatic duct. Pathologic characteristics and serum bilirubin levels of the patients are shown in Table 1.

Surgical treatment

We performed 31 local resections including the extrahepatic bile duct, gallbladder, and regional node-bearing tissue. From 2004, a resection usually included the caudate lobe and was performed in 8 cases for Bismuth stage I and II. In patients who did not have prior extensive abdominal surgery, and who demonstrated evidence of direct tumor extension into the right or left lobes of the liver Bismuth stage III, surgery was performed in addition to liver resection in 22 patients, which encompassed an en bloc extended left or right hepatectomy including 15 caudate lobes. In all, 40 patients with negative margins of the bile duct at final pathologic reports had radical resection with complete tumor removal. The other 29 patients had palliative resection. Radical resection rates combined with hepatectomy significantly improved curative rates compared with those without additional hepatectomy ($27/38$ *vs* $13/31$; $\chi^2 = 5.94$, $P < 0.05$). The surgical treatment of the patients is shown in Table 2.

Liver tumor recurrence and survival rate of patients

Two patients with additional liver resection died within 30 d of surgery, and only one patient without liver resection died. Three patients had liver recurrence one year after operation in the 12 patients who had resection

Table 2 Surgical treatment of Bismuth stage

Number of patients	Without hepatectomy	Addition of hepatectomy	
		Caudate lobe	Without caudate lobe
Bismuth I	7	2	1
Bismuth II	11	10	2
Bismuth III	13	15	7
Bismuth IV	0	1	0

Radical resection rates combined with hepatectomy significantly improved curative rates compared with those without additional hepatectomy (27/38 vs 13/31; $\chi^2 = 5.94$, $P < 0.05$).

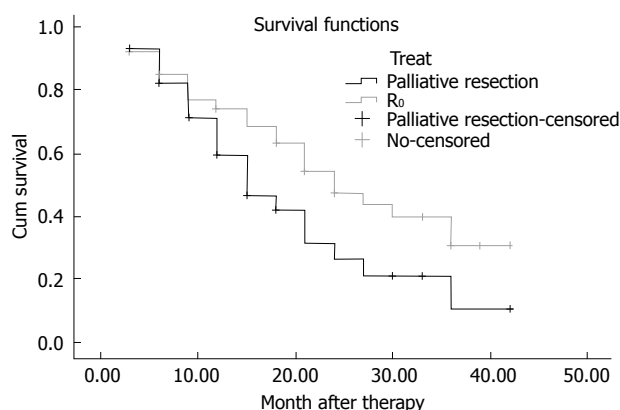


Figure 1 Kaplan-Meier estimate for survival depending on R₀/palliative resection. The three-year survival rate after R₀ resection was 30.7% and was 10.5% for palliative resection, R₀ resection improved the 3-year survival rate (30.7% vs 10.5%; $\chi^2 = 12.47$, $P < 0.01$).

including the caudate lobe for Bismuth stage I and II, otherwise, there were 11 liver recurrences within one year of surgery in 18 patients without resection of the liver lobe for Bismuth stage I and II. Concomitant liver resection was associated with a decreased incidence of initial recurrence in the liver one year after surgery (11/38 vs 23/31; $\chi^2 = 13.98$, $P < 0.01$) compared with those without liver resection. R₀ resection improved 3-year survival rates (30.7% vs 10.5%; $\chi^2 = 12.47$, $P < 0.01$). The Kaplan-Meier estimates for survival depending on R₀/palliative resection are shown in Figure 1.

DISCUSSION

Cholangiocarcinoma at the liver hilum, or Klatskin tumor, is the most common type of bile duct cancer. It is often unresectable owing to regional extension into the liver, surrounding lymphatics, and, most notably, hilar vascular structures^[13]. It can occur against the background of primary sclerosing cholangitis with its associated liver disease, and may elude detection until an advanced stage^[14]. Chemotherapy, as well as radiation or photodynamic therapy, yield negligible response rates, and do not favorably impact either local control or long-term survival. Effective adjuvant agents are still lacking. For unresectable cholangiocarcinoma, chemotherapy-impregnated biliary stents and photodynamic therapy have been used^[15,16].

The only effective treatment for hilar cholangio-

carcinoma is major surgery^[17]. Surgeons have pushed the technical envelope to achieve negative margins. In patients with hilar cholangiocarcinoma, concomitant hepatic resection is associated with improved median disease-specific and disease-free survival, and decreased hepatic recurrence^[18]. Today, extended biliary-hepatic resections together with vascular resections/reconstructions are being performed. Survival rates, however, have still not exceeded 40%^[19]. In our research the 3-year survival rates after R₀ resection were 30.7%, considerably more than the 10.5% achieved after palliative resection. After all, it is not uncommon to find skip lesions above and below the primary cancer. Despite negative frozen sections of margins at the time of index resection, surgeons will occasionally be left to deal with positive margins at final pathologic reports. This is an insidious cancer, prone to submucosal spread, and especially when it is well differentiated it can be difficult to realize^[20]. Frozen section analysis of the proximal bile duct margin is misleading in 9% of patients. Among patients who are determined to have negative duct margins intraoperatively, only 60% will have margins adequately wide enough to be associated with an improvement in disease-specific survival^[21]. Therefore in our research negative margins of bile duct at final pathologic reports had R₀ resection, otherwise positive margins had palliative resection, and then Bismuth stage II became Bismuth stage III for the final diagnosis. The resection must encompass the bile duct and areas of the liver at risk of involvement by direct tumor extension as well as the lymph nodes draining the region. Because cholangiocarcinoma is known to spread along the wall of the bile ducts and because the caudate lobe is a frequent site of tumor recurrence following extrahepatic duct resection, surgeons perform a resection that includes the caudate lobe. However, from 2004 in our research, a resection including the caudate lobe was carried out in 8 cases for Bismuth stage I and II, because of the small number of patients the results were not enough to show that liver recurrence within one year of surgery was related to resection of the liver lobe for Bismuth stage I and II. Major hepatectomy can improve the outcome of hilar cholangiocarcinoma. Compared with nonoperative treatment or R₀ hepatectomy, R₁ resection in patients with no other risk factors can offer long-term survival^[22]. If evidence of direct tumor extension into both the right and left lobes of the liver is demonstrated, no further surgery is performed. In contrast, tumor extension into only the right or the left lobe that can be encompassed by an en bloc extended left or right hepatectomy is not a contraindication to proceed with resection. In cases where the hilar cholangiocarcinoma extends directly into the right or left bile duct, we performed an en bloc extended right or left hepatectomy.

Combining extended right or left hepatectomy is recommended when preoperative imaging suggests extension above the hilum to either side. Furthermore, CT liver volume estimates can guide resection strategy, even to include preoperative selective portal vein embolization to induce remnant hypertrophy. Others describe how

radical vascular resections can be attempted to achieve wide tumor clearance. Resection increases survival, but carries the risk of significant morbidity and mortality^[23-26]. In our research of 69 patients submitted to laparotomy for tumor resection, R₀ resection was performed in 40 patients, and palliative resection in 29. 31 patients had only duct resection, 38 patients had combined duct resection with liver resection including 28 total or part caudate lobes. R₀ resection rates combined with hepatectomy significantly improved the recurrence rate compared with those without additional hepatectomy. Concomitant liver resection was associated with a decreased incidence of initial recurrence in the liver one year after surgery. The 3-year survival rate after R₀ resection was 30.7% and was 10.5% after palliative resection. R₀ resection, thus, improved the 3-year survival rate.

A transhepatic approach may be useful when performing extensive hilar bile duct resection for bile duct stricture of biliary disease at the hepatic hilus, especially in high-risk patients who are unfit for major hepatectomy as well as in those with benign bile duct stricture and low-grade malignancy^[27]. In highly selected patients with advanced hilar cholangiocellular carcinoma, a high hilar resection is technically safe and oncologically justifiable. In combination with our new technique of sheath-to-enteric anastomosis, patients benefit considerably from the preservation of liver parenchyma with low postoperative morbidity and very short in-hospital stay^[28]. Excellent survival rates without any in-hospital deaths have been demonstrated following right trisectionectomy with caudate lobectomy. This procedure may be an effective surgical technique which can be executed to achieve low mortality rate and high pathological curability for hilar cholangiocarcinomas, with the exception of Bismuth type III (b)^[29].

In patients with hilar cholangiocarcinoma, local resection is not an adequate treatment for hilar cholangiocarcinoma involving the bile duct confluence; associated liver resection should be recommended. In Bismuth-Corlette type I and II hilar cholangiocarcinoma, survival benefits with the association of biliary and liver resection have been reported. Concomitant hepatic resection is associated with improved rates of radical resection, decreased hepatic recurrence, and longer survival. Therefore, hepatectomy especially including the caudate lobe combined with bile duct resection should be considered standard treatment to cure hilar cholangiocarcinoma. The surgical approach to Bismuth type I and II hilar cholangiocarcinomas should be determined according to cholangiographic tumor type. For nodular and infiltrating tumors, right hepatectomy is essential; for papillary tumors, bile duct resection with or without limited hepatectomy is adequate^[30].

resection is good and has a high 5-year survival rate. In contrast to reports from 2 or 3 decades ago, today most patients with hilar cholangiocarcinoma are diagnosed pre-mortem. The most important factor affecting prognosis is resectability of the tumor; however, the surgical prognosis is poor even when local tumor resection is performed. Local resection seems to have a very narrow role. Thus, finding a surgical approach for the treatment of hilar cholangiocarcinoma is essential.

Research frontiers

In patients with hilar cholangiocarcinoma, local resection is not an adequate treatment for hilar cholangiocarcinoma involving the bile duct confluence; associated liver resection should be recommended. In Bismuth-Corlette type I and II hilar cholangiocarcinoma, survival benefits with the association of biliary and liver resection have been reported. Concomitant hepatic resection is associated with improved rates of radical resection, and decreased hepatic recurrence. Therefore, the surgical approach to hilar cholangiocarcinomas should be determined according to cholangiographic tumor type.

Innovations and breakthroughs

Of the 69 patients submitted to laparotomy for tumor resection, curative resection was performed in 40 patients, and palliative resection in 29. Thirty-one patients had only duct resection, and 38 patients had duct resection combined with liver resection including 34 total or part caudate lobes. Curative rates with the combined hepatectomy significantly improved compared with those without additional hepatectomy. Concomitant liver resection was associated with a decreased incidence of initial recurrence in the liver one year after surgery, and curative resection improved 3-year survival rates.

Applications

The study results suggest that hepatectomy, especially including the caudate lobe combined with bile duct resection should be considered standard treatment to cure hilar cholangiocarcinoma.

Peer review

Concomitant liver resection was associated with improved curative and survival rates and decreased hepatic recurrence. The content of the paper has merit since this cancer has a poor prognosis and is still a challenge for surgeons and clinicians.

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COMMENTS

Background

Hilar cholangiocarcinoma was first reported by Gerald Klatskin in 1965. Many therapeutic methods have been established to treat this type of tumor, surgical

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