

Single Centre Experience with Surgical Treatment of Hilar Cholangiocarcinoma

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Rezumat

Experiența unui centru în tratamentul chirurgical al colangiocarcinomului hilar

Premize/Scopuri: Rezecția chirurgicală este opțiunea terapeutică radicală pentru colangiocarcinoamele hilare. Cu toate acestea tratamentul curativ este dificil și prognosticul pacienților este prost. O evaluare a opțiunilor chirurgicale și a rezultatelor poate decela tratamentele eficiente.

Material și metodă: Am examinat retrospectiv caracteristicile demografice, protocoalele chirurgicale și rezultatele la 64 de pacienți cu colangiocarcinom hilar operați radical sau paliativ în perioada 2004-2012.

Rezultate: Pacienții au fost 43 de bărbați și 17 femei cu o vârstă medie de $61,4 \pm 10,4$ ani ($\pm$ SD, între 35-81 ani). Au fost efectuate 44 de rezecții: R0 – 22 cazuri (34,4%), R1 – 10 cazuri (15,6%), R2 – 12 cazuri (18,7%) și 20 operații paliative (31,3%). Rezecție R0 a căii biliare principale cu hepatectomie dreaptă extinsă la segmentul 1 a fost realizată în 8 cazuri, rezecția ductului hepatic comun cu hepatectomie stângă cu segment 1 în 9 cazuri și rezecția ductului hepatic comun în 5 cazuri. Procentul total de morbiditate postoperatorie este 51,5%. Complicațiile au fost următoarele: hemoragie intraabdominală 31,25%, fistula biliară temporară 26,56%, fistula anastomozei hepaticojejunale 7,81%, fistula biliară 7,81%, insuficiența

hepatică 17,18%, pleurezia 48,13%, abces intraabdominal 28,13%, infecția de plagă 48,3%. Supraviețuirea medie generală la 5 ani pentru rezecțiile R0 este 32%, pentru rezecțiile R1 și R2 de 12%, iar pentru operațiile paliative 0%. Supraviețuirea medie generală pentru rezecțiile R0 este de 37 de luni, pentru rezecțiile R1 și R2 este de 19 luni, iar pentru operațiile paliative de 7 luni.

Concluzie: Rezecția chirurgicală extinsă radicală pentru colangiocarcinom hilar este necesară pentru a obține o supraviețuire mai lungă a pacientului.

Cuvinte cheie: colangiocarcinom hilar, rezecție chirurgicală, hepatectomie extinsă

Abstract

Background/Aims: Surgical resection is a radical treatment option for hilar cholangiocarcinomas. However it is still difficult to cure and patient prognosis is poor. An evaluation of the surgical options and results may elucidate effective treatments.

Methodology: We retrospectively examined the demographic characteristics, surgical records and outcome in 64 patients with hilar cholangiocarcinoma undergoing surgical resections or palliative surgical procedures for the period of 2004-2012.

Results: The patients included 43 males and 17 females with a mean age of 61.4 ± 10.4 years ($\pm$ SD, range 35-81 years). Forty-four resections were done - R0 – 22 cases (34.4%), R1 – 10 (15.6 %) cases, R2 – 12 cases (18.7%) and 20 palliative (31.3%) operations were performed. R0 - resection of common bile ducts with right hepatectomy with Sg 1 was done in 8 cases, resection of common hepatic duct with left hepatectomy with Sg 1 – in 9 cases and resection of common hepatic duct – in 5

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cases. The total percentage of postoperative morbidity is 51.5 %. The types of complications are as follows: intra abdominal bleeding – 31.25 %, temporary biliary leakage - 26.56 %, leakage of hepatico-jejunostomy – 7.81 %, biliary fistula – 7.81 %, liver insufficiency – 17.18 %, pleural effusion – 48.13 %, intra-abdominal abscess – 28.13 %, surgical site infection – 48.3 %. The mean five-year overall survival for R0 - resection is 32%, for R1 - and R2 - resection is 12% and for the palliative operations - 0%. The mean overall survival for R0-resection is 37 months, for R1 - and R2 - resection is 19 months and for the palliative operations – 7 months.

Conclusions: Radically extended surgical resection for hilar cholangiocarcinoma is necessary to obtain improved patient survival.

Key words: hilar cholangiocarcinoma, surgical resection, extended hepatectomy

Introduction

Hilar cholangiocarcinomas are rare malignant tumors with a broad spectrum of treatment possibilities. They are known for their low percentage of resectability, high perioperative morbidity and mortality, as well as poor prognosis that makes surgical treatment still a challenge.

The first resection of extrahepatic biliary ducts for carcinoma was carried out by Brown in 1954. In 1965 Klatskin published 13 cases describing the clinical and pathological characteristics of this disease and since then hilar cholangiocarcinomas are known as tumors of Klatskin. The first surgical series with a satisfactory survival but accompanied with high postoperative mortality and morbidity are published in 1970-ies (1, 3). Tumor resection remains challenging because of the close location to major vascular structures and the liver parenchyma.

To estimate the present status regarding surgical treatment for hilar cholangiocarcinomas at our institute, we examined our series of hilar cholangiocarcinomas in 64 consecutive patients and discussed the results, clinical significance and limitations. The results of the surgical treatment of hilar cholangiocarcinoma, carried out in a Hepato-Biliary Surgery and Transplantation Centre in Bulgaria are presented in this article.

Patients and Methods

In the Department of Hepato-Biliary Surgery and Transplantation, Military Medical Hospital, Sofia 64 patients with hilar cholangiocarcinoma underwent surgical resection between 2004 and 2012 and preoperative characteristics, surgical methods and postoperative outcomes are analysed in present study. The study design was approved by the human ethics review board at our institution. Informed consent for data collection was obtained from each patient during this period. A standard diagnostic imaging algorithm defining

diagnosis and resectability of the tumor was strictly followed – ultrasonography, computer-tomography-angio-scan, magnetic-resonance imaging, endoscopic retrograde cholangiopancreatography. A resectional strategy according to the longitudinal growth of the tumor as described in Bismuth-Corlette classification (3) was followed.

Operative procedures and follow-up

Our surgical protocol strictly follows the well-known oncological standards of surgical treatment of hilar cholangiocarcinomas. The decision of whether right - or left hepatectomy is indicated is made according to the predominant site of the tumor lesion (taking into consideration longitudinal tumor extension). A radical R0-resection of biliary ducts and liver is carried out only if at least 30% of well-functioning residual liver parenchyma is guaranteed. Clear margins no less than 1 cm on proximal and distal biliary tract confirmed by frozen section should be achieved and resection of liver segment 1 – either isolated or associated with extended hepatectomy is done. Minimal volume of lymph node dissection is that of the hepatoduodenal ligament, posterior to the upper portion of the pancreatic head and around the common hepatic artery. “No-touch” surgical technique is applied in order to prevent tumor spillage, biliary contamination of surgical field in order to prevent infection or tumor spreading and if not indicated, intraoperative tumor biopsy is not performed. Resection of common hepatic duct is selected only in patients with type I hilar cholangiocarcinoma without any evidence of liver parenchyma infiltration or lymphnode metastases in the hepatoduodenal ligament. Resection of common bile ducts with right hemihepatectomy with Sg 1 was performed in patients with type II a cancer, resection of common hepatic duct with left hemihepatectomy with Sg 1 was performed in patients with type IIb cancer. In cases of contralateral portal vein involvement, combined vascular resection was carried on.

Statistical analysis program SPSS v14.0 was used for statistical analysis. Fisher-exact test and p-values were significant when lower than 0.05.

Results

The patients included were 43 males and 17 females with a mean age of 61.4 ± 10.4 years ($\pm$ SD, range 35-81 years). Preoperatively 84% of patients received biliary drainage – the proportion between endoscopically placing an endoprosthesis and percutaneous biliary drainage was 4:1.

Forty-four resections were done - R0 – 22 cases (34.4%), R1 – 10 (15.6 %) cases, R2 – 12 cases (18.7%) and 20 palliative (31.3%) operations were performed. Three cases of R0-resections were accompanied with a resection of the contralateral portal branch. Resection of common bile ducts with right hepatectomy with Sg 1 was done in 8 cases (Fig. 1A), resection of common hepatic duct with left hepatectomy with Sg 1 – in 9 cases (Fig. 1B) and resection of common hepatic duct – in 5 cases. (Fig. 1)

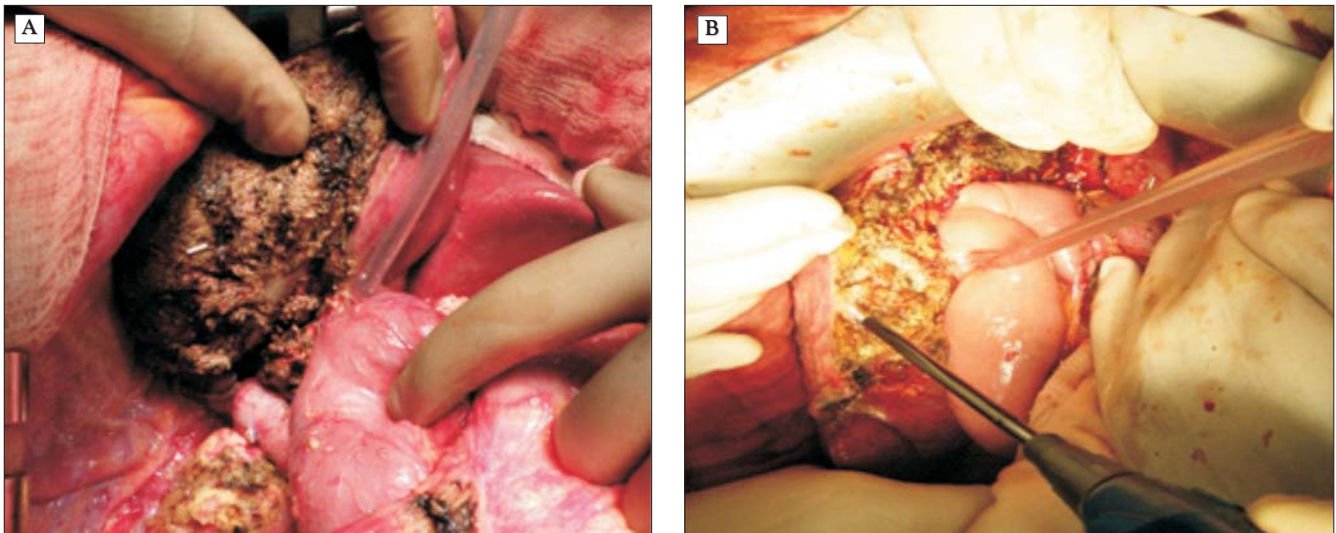


Figure 1. (A) Extended right hepatectomy + SgI in a hilar cholangiocarcinoma type III a; (B) Extended left hepatectomy + SgI for hilar cholangiocarcinoma type III b

The total percentage of postoperative morbidity is 51.5 %. The types of complications are as follows: intraabdominal bleeding – 31.25 %, temporary biliary leakage - 26.56 %, leakage of hepatico-jejunoanastomosis – 7.81 %, biliary fistula – 7.81%, liver insufficiency – 17.18 %, pleural effusion – 48.13 %, intraabdominal abscess – 28.13 %, surgical site infection – 48.3 %.

Complication rate for patients with preoperative biliary drainage is slightly higher – 55.6 % to 47.4 % without statistically remarkable significance ($p=0.634$).

The perioperative mortality of the series discussed is 7.8 % (5 cases).

Tumor stage was T1 in 4 patients (6.25%), T2 in 12 (18.75%), T3 in 16 (25%) and T4 in 32 patients (50%).

The mean and five-year overall survival rates are presented in Table 1. The mean five-year overall survival for R0-resection is 32%, for R1- and R2-resection is 12% and for the palliative operations - 0%. The mean overall survival for R0-resection is 37 months, for R1- and R2-resection is 19 months and for the palliative operations – 7 months ($p < 0.01$).

Discussion

Surgical treatment of hilar cholangiocarcinomas has

Table 1. Mean survival rate in surgical treatment of hilar cholangiocarcinoma

	R0 (n=22)	R1+R2 (n=22)	Palliative operations (n=20)
Five-year overall survival, %	32	12	0
Mean overall survival rate, months	37	19	7

accomplished a great headway in the last two decades due to the advance in the preoperative diagnostic work-up allowing more precise staging and preoperative preparation. Operative procedures for cholangiocarcinoma are associated with significant morbidity, therefore accurate noninvasive preoperative staging of these patients is critical. The goal of diagnostic staging of cholangiocarcinoma is to evaluate resectability and the extent of surgery. Multidetector computer-tomography scan has made the disease spread adequately determinable. Portal vein embolisation has definitely improved the results after extended hepatic resections and contributed to confirming the need of such hepatic resections to cover both the direct hepatic spread, as well as the vertical intraductal spread characteristic of hilar cholangiocarcinomas (2,10). The principal goal of the surgical treatment is the achievement of clear margins, i.e. R0-resection. An adequate diagnostic work up is mandatory in order for an acceptable selection of patients to be resected to be fulfilled. Our diagnostic standards are set up to denote the well-known criteria for unresectability (4,5,11, 13,18) - signs of local tumor invasion such as bilateral intrahepatic spread to secondary or segmental biliary radicles, bilobar involvement of hepatic arterial and/or portal venous branches, encasement or occlusion of the main portal vein proximal to its bifurcation, unilateral segmental duct extension with contralateral vascular involvement, lobar atrophy with contralateral segmental duct extension or vascular involvement, lymph node metastases outside the hepatoduodenal ligament and distant metastases. At this stage however, at our center the precise evaluation of cancer extension and lymph node metastasis is still difficult before operation. We lack the opportunity of applying portal embolisation as well. Recently, we introduced diagnostic laparoscopy in order to exclude peritoneal and small liver metastases for which other noninvasive tests lack specificity as a final step prior to converting to major surgery or avoiding an unnecessary laparotomy.

The efficacy of preoperative biliary drainage in the

treatment of patients with obstructive jaundice and hilar cholangiocarcinoma is still controversial. Its routine use in patients with obstructive jaundice and namely those with carcinoma of the distal biliary ducts without actual complications is not recommended, having in mind reports of negative effects such as acute pancreatitis, cholangitis, as well as tumor dissemination along the interventional route and a meta-analysis comparing both operative interventions, concluding lack of advantages of this intervention (21).

Our results denote increased rate of perioperative complications although not statistically significant. Leading cause of shortcoming is surgical infection. Our opinion is that if radical surgical treatment is intended at an early diagnosed hilar carcinoma an uncomplicated field of operation should be essential if not mandatory and invasive cholangiography should be reserved for therapeutic decompression where there is cholangitis or stent insertion in unresectable cases.

Despite the achievements in hilar carcinoma treatment there are still controversial issues to be discussed. These include – the type and the volume of the resection, the resection of caudate lobe and portal vein as well as the need and volume of lymph node dissection.

The surgical protocol strictly observed at our clinic follows the well-known standards of surgical treatment of hilar cholangiocarcinomas and most cases follow the resectional strategy described in Bismuth-Corlette classification (3,4,5, 14,15): types I and II can be resected with excision of the extrahepatic bile duct with or without the hilar plate and caudate lobe, types IIIA and IIIB can be resected with the addition of an “en bloc” right or left hepatic hepatectomy, respectively and type IV is by definition unresectable and the most applied method in this case is percutaneous biliary drainage. The most economical alternatives are the local or hilar resections of the extrahepatic biliary ducts. Our results show the importance of partial hepatectomy in achieving a complete resection and further suggest that only a concomitant hepatic resection effectively clears all disease and offers the possibility of prolonged survival.

Major liver resections for hilar cholangiocarcinomas are potentially accompanied by developing liver failure as described in up to 32 % of patients with combined resections (11) as well as increased risk of postoperative complications (15,16,17). In this concern portal vein embolisation is a strategy of inducing hypertrophy in the anticipated remaining hepatic remnant for prevention of liver failure (19, 20). The effectiveness and safeness of this procedure have been proved and it should be discussed in patients with anticipated liver remnant volume of under 20 % from the total one (20).

Although there are no prospective randomized trials comparing the results between common bile duct resection to major hepatic and biliary resections some retrospective studies point out advantages in resection margins and increasing the overall survival in major interventions despite higher percentage of overall morbidity and mortality (11). The major sources of morbidity remain infectious complications and

biliary complications (anastomotic or hepatic parenchymal leak), with mortality rates generally around or slightly less than 10% (23). The complication rate in major hepatic resections seems to have decreased considerably in recent years (12,13,17). Our complication rate is still high but there is a tendency of a steady decrease over the past years along with increasing the relative volume of major hepatic resections at our center carried out both for primary and secondary biliary and hepatic malignancies, as well as with better preoperative selection and improved anesthesiological and intensive care. We advocate the statement that nowadays extended right - or left hepatectomy are to be regarded as standard radical operation for hilar cholangiocarcinoma.

One of the major problems of hilar cholangiocarcinoma resection technique is the development of local recurrence. Many studies reveal caudate lobe involvement and it being the main liver recurrence location (8,11). Some authors recommend routine resection of the caudate lobe in order to decrease its incidence (14). If the hepatic duct confluence is involved, we resect the first liver segment whatever hepatic procedure is planned. The reason for this is the high incidence of bile duct involvement as the tumor spread follows three main routes – infiltration along the bile duct epithelium, direct infiltration of the first liver segment parenchyma, periductal infiltration of the interstitium of the lobus caudatus (9,18). The caudate lobe and the connecting liver parenchyma are usually localized behind the biliary duct and portal bifurcation. There are many tiny biliary ducts draining towards the main biliary tree in vicinity to its bifurcation (9). The caudate lobe resection recommenders point out the fact that this improves the margin status at a minimally increased complication rate optional by other authors, when there is suggested tumor extension into the caudate lobe (2,14,15). Nowadays all liver resections for hilar cholangiocarcinoma should be accompanied by caudate lobe resection (14).

The portal vein resection and reconstruction is considered a routine procedure that is to be conducted in highly specialized centers. It is to be performed only in selected patients if venous infiltration is detected preoperatively or intraoperatively during the course of the operation (13,22). Our experience is limited to three cases with portal resection for surgical treatment of hilar cholangiocarcinoma without increasing the rate of post-operative complications ($p=0.761$).

Numerous clinico-pathological factors have been proven to have positive effects on the long-term survival such as negative surgical margins, liver resection done, negative nodal status, lower T-status, well differentiated tumor, lack of perineural invasion (6,7,12,18). Despite the achievements in the surgical treatment of hilar cholangiocarcinomas the five-year survival varies from 25% to 40% in recently published series. In our series aggressive surgical resection was performed in 44 patients with hilar cholangiocarcinoma over the past 8 years and radical operations were safely performed in many cases. While palliative operations showed no survival at 5 years, R0 and R1-2 resections' survival proves the efficacy of extended surgical resection.

Conclusion

Radical surgical treatment performed by a highly specialized team in a high volume hepato-biliary centre remains the most effective and the only potentially curative treatment of hilar cholangiocarcinomas. The modern surgical tactics requires "en bloc" resection of extrahepatic biliary duct and unilateral hepatic lobe extended in most cases to Sg1. Clear margins and adequate sufficient function of the liver remnant along with assured biliary drainage are prerequisites of acquiring a long-term good survival.

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