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Research Paper

Surgical treatment of intrahepatic cholangiocarcinoma: A retrospective cohort study

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ABSTRACT

Background: Intrahepatic cholangiocarcinoma (IHCC) is the second most frequently developed primary carcinoma of liver, after hepatocellular carcinoma (HCC). They are biologically aggressive and they are frequently discovered in late study. Surgical removal is the only curative therapeutic method for treatment of such tumors.

Patients and methods: From 1.1.2004 to 31.12.2014, at the Department of Surgery, University Hospital Martin and Jessenius Medical Faculty of Comenius University in Martin, we operated 411 patients with benign, primary, metastatic tumors of liver, where in 33 patients (8%) the histology confirmed the primary intrahepatic cholangiocarcinoma of liver. In the group, we evaluated the 1-year and 5-year survival of the patients according to radical resections, the degree of differentiation of tumor (grading), and according to positivity of lymph node. The results were statistically analyzed by the Student t-test and Kaplan–Meier curves of survival.

Results: The average age of the patients was 59.6 ± 11.4 years, the males represented 46.2%, the females represented 53.8%. The average age of males was 58 ± 13.2, and females 61 ± 9.8 years. Large anatomic resections of 3 and more segments of liver were performed in 24 patients, anatomic resections and metastasectomies were performed in 6 patients, two patients had radiofrequency ablation of tumor. R0 resection was achieved in 20 patients, R1 resection in 8 patients, and R2 resection in 5 patients. One-year survival in the R0 group was 65%, in the R1 group 62%, and in the R2 resections group it was only 20%; five-year survival after R0 resections was 52%, and in R1 and R2 it was zero, which proved to be statistically significant. The median of survival in R0 resections was 12 months (interval 1–87 months), in R1 resections it was 12 months (interval 1–36 months), and after R2 resections it was 7 months (interval 1–12 months). One-year and five-year survival, depending on the degree of differentiation, was statistically non-significant; however, the five-year survival of G1 tumors is on the level of being statistically significant – the 5-year survival expressed in percentage G1/G2/G3 was 50%/12%/0% respectively. Positive lymph nodes were found in 16 patients (48%) from the group of 33 patients. The one-year and five-year survival was not statistically significant; however, 5 years of survival was recorded in 30% patients with negative lymph node and 0% patients with positivity of lymph node.

Conclusion: Resection of tumor is the optional method; it should be attempted to achieve R0 resection and at the same time to preserve sufficient volume of residual functional parenchyma. Radical R0 resection is considered by us as the only possible method of surgical treatment for survival of patients with IHCC.

1. Introduction

1.1. Background

Intrahepatic cholangiocarcinoma (IHCC) is the second most frequently developed primary carcinoma of liver, after hepatocellular carcinoma (HCC). It is developed from the biliary epithelium cells of intrahepatic bile duct above the second branching of the right and left lobe. They are biologically aggressive, are frequently found in late study or are manifested only by distant metastases. Surgical removal is the only curative therapeutic method for such tumors. They represent approx. 10% of malign tumors of liver. The incidence and mortality for IHCC in the last years is growing, contrary to extrahepatic cholangiocarcinoma (EHCC), the occurrence of which has the tendency to fall down. However, it should be noted that both IHCC and EHCC may have almost the same microscopic morphology, and therefore, perihilar cholangiocarcinomas are frequently considered as IHCC. The incidence of IHCC in the U.S.A. is approx.

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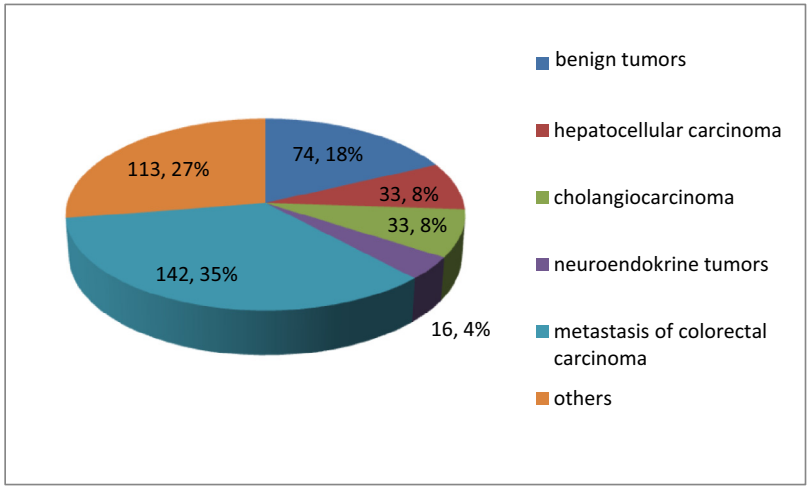

Fig. 1. Distribution of whole set by histology.

0.85 cases per 100,000 inhabitants, but for example in Thailand it is 96 cases per 100,000 inhabitants, which represents 100 multiply. Obligatory precancerosis is primary sclerosing cholangitis (PSC) and IHCC develops in 8%–40% cases during 10–20 years. The other precanceroses include congenital biliary cystic disease, parasitical and bacterial infections, cirrhosis, HBV, HCV infections, and benign tumors of bile duct, as cystadenoma and papilloma.

From the pathogenic aspect, chronic inflammation represents an important component of many risk factors and is also connected with malign transformation of biliary epithelium. Chronic inflammation damages the DNA cholangiocytes with simultaneous stimulation of the cell proliferation, which may lead to malign transformation. That process leads to increased expression of oncogenes and reduced expression of the genes suppressing tumor.

In addition to the history and complete clinical examination, the diagnostics should include mainly biochemical examinations – bilirubin, hepatal ensymes, oncomarkers, and radiologic imaging methods. In addition to the scope of the tumor disease, we must determine the function of liver and functional reserve thereof. Metastatic intervention to liver by other tumors should also be excluded. Pre-operation biopsy is recommended as routine only for non-resectable tumors, otherwise it is not recommended due to tumor dissemination before resection. Some authors recommend staging laparoscopy in order to exclude extrahepatic dissemination of tumor. From oncomarkers, CA19-9 are used in the diagnostics. However, the serum level of CA19-9 is increased not only in case of cholangiocarcinoma, but also in case of carcinomas of the upper gastrointestinal tract, in smokers, in case of cholangoitis and cholestasis. The level of CA19-9 above 150 U/ml is considered as an independent negative prognostic factor for perihilar cholangiocarcinoma [1]. From the other oncomarkers, determination of serum levels of CEA, IL 6, Trypsinogen II and others is applied, but their sensitivity and specificity is lower. From the imaging method, spiralCT5 with three-stage contrast, MR, MRCP and PET-CT are appropriate. PET-CT is useful mainly in detection of recurrence, detection of affected lymph node (LG), and distant metastases. In classification of IHCC and staging of the system, TNM classification or Yamasaki classification (Liver Cancer Study Group of Japan) is applied. The evaluation includes the number of lesions, the size thereof, infiltration of the portal and hepatic vein, and growing into capsule. It is important to determine the level of differentiation of the tumor, which is divided, from the pathologic aspect, to G1 (well differentiated cholangiocarcinoma, G2 (medium differentiated cholangiocarcinoma), and G3 (low differentiated cholangiocarcinoma).

1.2. Objectives

First objective of this work is to determine the benefits of surgical treatment of cholangiocarcinoma in our set of patients. The second objective is to determine the survival of patients with cholangiocarcinoma according to type of resection and differentiation of the tumor.

2. Material and methods

2.1. Study design

This is a retrospective analysis of patients who underwent surgical treatment of cholangiocarcinoma at Department of Surgery and Transplantation Center, University Hospital Martin.

2.2. Setting

From 1.1.2004 to 31.12.2014, at the Department of Surgery and Transplantation Center, University Hospital Martin, we operated 411 patients with benign, primary, metastatic tumors of liver, where in 33 patients (8%) the histology confirmed the primary intrahepatic cholangiocarcinoma of liver (Fig. 1).

We evaluated the 1-year and 5-year survival of the patients according to radicality of resections, the level of differentiation of tumor (grading), and according to positivity of lymph node.

In the statistical analysis, we applied the certified statistic program MedCalc version 13.1.2. and the following statistical analyses: Student t-test, Kaplan–Meier curves of survival. The value of $P < 0.05$ is considered statistically significant.

3. Results

The average age of the patients was 59.6 ± 11.4 years; the males represented 46.2%, the females represented 53.8%. The average age of males was 58 ± 13.2, and females 61 ± 9.8 years.

Large anatomic resections of 3 segments of liver and more were performed in 24 patients, anatomic resections and metastasectomies were performed in 6 patients, 2 patients had radiofrequency ablation of tumor.