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 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 9 months (interval 1–36 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.

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http://dx.doi.org/10.1016/j.ijso.2016.05.003

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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 enzymes, 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 (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.
R0 resection was achieved in 20 patients, R1 resection in 8 patients, and R2 resection in 5 patients (Fig. 2).

One-year survival and five-year survival of the patients depending on the radicality of resection are shown in Figs. 3 and 4. 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).

Grading of G1 tumors was in 8 patients, G2 in 8 patients, and G3 in 17 patients. The one-year and five-year survival depending on the level of differentiation of tumor is shown in Figs. 5 and 6. Although the survival of the individual groups of patients is statistically not significant, the five-year survival of G1 tumors is on the limit of statistical significance. The 5-year survival expressed in percentage of G1/G2/G3 was 50%/12%/0% respectively.

Positive lymph nodes were detected in 16 patients (48%) in the group of 33 patients. The one-year and five-year survival are shown in Figs. 7 and 8. Although the survival of the individual groups of patients is statistically not significant, 30% of patients with negative lymph node and 0% of patients with positivity of lymph node survive for 5 years.

4. Discussion

Treatment of IHCC is primarily surgical. Resection of tumor is an elected method; the doctors should try to achieve R0 resection and at the same time to preserve sufficient volume of the residual functional parenchyma. In case of extensive tumors, we may apply embolization of vena portae or ALPPS (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy – double resection of liver with ligature of v. portae on side of tumor). In order to achieve R0 resection, extensive hepatectomy is frequently made, which in case of correct indication and non-complicated surgery do not shorten the survival in spite of higher risk of post-operation complications [2]. In our group of patients, radical extensive resections of tumors were dominating – they were performed in more than one half of the patients. Radical R0 resection is considered by us as the only possible method of surgical effect on survival of patients with IHCC. Survival of non-treated patients is less than 5
One-year survival of patients according to lymph node positivity.

Five-year survival of patients according to lymph node positivity.

Generally, it may be said that the negative prognostic factors of survival include the affected lymph node, which leads to shortening thereof [3]. Although in our group it was statistically non-significant, the 5-year survival of patients was lower when expressed in percentage. The discussed issue is whether the routine lymphadenectomy prolongs the survival of patients with IHCC or has no effect on survival. For many departments, the affected lymph node represents a contraindication for resection [4]. Generally, it may be said that the negative prognostic factors of survival of patients with IHCC after resection are considered to be the positive resection edge, the growth type of tumor, vascular invasion, metastases in lymph node, and increased levels of CA19-9 oncomarker [5,6]. The R1 resection and the positive resection edge are the terms which should be explained and more precisely defined. Positivity of the resection edge in the literature is said to be between 15% and 68% of patients with IHCC [7]. In our group, the microscopic positive edge after resection was in 8 patients (24%). The sufficient resection edge is the only prognostically negative risk factor which may be directly affected by surgeons. In respect of the peripheral types of IHCC, it is possible to more precisely define the resection edge in the tumors placed centrally and infiltrating hilus of liver, where radicality of resection is more limited by the hilar structures with more frequent presence of microscopic positivity of the resection edge in the given site. Very frequently, it is combined with positivity of hilar lymph node. For R0 resection, the distance of the edge of tumor from the resection line of 10 mm is considered as sufficient; however, this cannot be precisely applied for tumors infiltrating the hilus of liver. The analyses of our group of patients show that the centrally placed IHCC had positive resection edges and positivity of lymph node.

Transplantation of liver is not a routine therapeutic method, although the latest studies refer to significantly improved survival after orthotopic transplantations: 5-year survival is even 23%. However, the condition is absence of extrahepatic dissemination. The continuing problem is the lack of more effective neoadjuvant and adjuvant chemotherapy before and after the surgery. In spite of that, in the patients with R1 resection and positive lymph node, the adjuvant chemotherapy improves the survival and reduces recurrence of the disease [8].

Recurrence of tumor disease is high also after radical resections and is between 40% and 80% within 5 years after resection [9]. The risk factors include occurrence of satellite metastases, perihilar affection of lymph node, and perineural dissemination [10,11].

The ablation methods are rarely applied in case of IHCC. This is due to the firm consistence of tumor and the size of tumor, which is often beyond the possibilities of ablation. The same applies for TACE (Transarterial Chemo Embolization) with use of gemicitabine, cisplatin, oxaliplatin or mitomycin C which are used solely for certain selected groups of patients with median of survival of 12–21 months [12,13].

The patients with cholangiocarcinoma must be examined by a multidisciplinary team and treated according to the individually prepared protocol. As the first step, assessing the potential resectability of tumor is required, because the surgical treatment represents the optional method for such patients. Cholangiocarcinomas have very bad prognosis, the 5-year survival is 5%–10%; however, in potentially curative R0 resections, the literature states the survival is 25%–50%. Therefore, increasing the number of curative resections with application of adjuvant chemotherapy is required. The most relevant studies on adjuvant chemotheraphy of cholangiocarcinomas are from Japan (ESPAC-3 study) and from Great Britain (BILCAP study). Adjuvant chemotherapy is recommended for all patients with IHCC and EHCC, with microscopically positive resection edges and for the patients after R0 resection with positive lymph node [14].

Although no highly effective adjuvant chemotherapy exists, gemcitabine is recommended after resection, and according to the latest studies, it improves the survival. Likewise, the post-operative radiotherapy improves the survival after R0 and even after R1 resections [15]. In the patients with locally advanced IHCC after R2 resection or primary non-resectable tumor, the surgical treatment is not indicated, but the patients may benefit from application of chemoradiation therapy which may prolong the survival and improve the quality of life. Duodenobiliary stents or PTD (percutaneous tranhepatic drainage) are applied as palliative treatment in case of centrally placed tumors.

**5. Conclusion**

IHCC represents rare primary tumors of liver, outgrowing from epithelium of bile ducts. In the CT or MR examination are shown the image of hypovascular lesion. R0 resection is the optional method and 5-year survival is between 20% and 60%. Adjuvant chemotherapy is currently not very effective, but it prolongs the survival mainly of the patients with R1 resection and positivity of hilar lymph node. From the surgeon’s aspect, it is important to perform as much R0 resections as possible, because it is currently the most important factor of improved survival of the patients with IHCC. The patients with cholangiocarcinoma must be examined by a multidisciplinary team and treated according to the individually prepared protocol.
The Ethical Approval

None.

Funding

None.

Author Contribution

Prof. MUDr. L’udovít Laca, Ph.D.: Participated in research design and in writing of the paper.
MUDr. Ivana Dedinská, Ph.D.: Participated in research design, in the performance of research and in data analysis.
MUDr. Blažej Palkoci: Participated in data analysis.
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Conflict of interest

The authors declare no conflicts of interest.

Guarantor

Grant of Organisation “Donated life”.

Research registration UIN

N/A.

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