

Evaluation of the mass forming intrahepatic cholangiocarcinoma with viral hepatitis

Kei Horino, Toru Beppu, Hiroyuki Komori, Toshiro Masuda,
Hiromitsu Hayashi, Hirohisa Okabe, Hiroshi Takamori and Hideo Baba

Department of Gastroenterological Surgery, Graduate School of Medical
Sciences, Kumamoto University

1-1-1 Honjo, Kumamoto 860-8556, Japan

Telephone: 81-96-373-5213, Fax: 81-96-371-4378

E-mail address: horino@tamana-chp.jp

Address reprint requests to Prof. Hideo Baba, the Department of
Gastroenterological Surgery, Graduate School of Medical Sciences,
Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan

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Abstract

Aim: The correlation between the mass-forming type of intrahepatic cholangiocarcinoma (ICC) and the infection of the hepatitis B virus and hepatitis C virus are poorly understood. In this study, the clinical features of 34 patients with the mass-forming type ICC were reviewed to evaluate prognostic determinants.

Methodology: Between January 1997, and December 2007, 34 patients underwent surgical resection for the mass-forming type of ICC in Kumamoto University Hospital. The significance of 14 clinicopathological factors consisting of age, gender, CA19-9 levels, CEA levels, size, intrahepatic metastases, portal vein invasion, bile duct invasion, histological differentiation, lymph node involvement, type B or C hepatitis, lymph node dissection, Sirius Red score of the tumor and platelet count in peripheral blood were analyzed, with regard to prognostic aspect.

Results: Univariate analysis showed that significant risk factors for poor survival included age ≥ 65 years, CEA levels ≥ 1.6 ng/ml and pathological lymph node involvement. Multivariate analysis revealed that age, CEA levels and lymph node involvement were independent and significant poor prognostic factors.

Conclusions: It was concluded that age, CEA levels and lymph node involvement were significantly poor prognostic factors. However, the infection with type B or C hepatitis was not a prognostic factor of the mass forming type ICC.

Introduction

Intrahepatic cholangiocarcinoma (ICC) has been reported to rank second in the incidence of primary liver cancer accounting for approximately 5-10% [1] in Japan. Several risk factors of ICC have been identified, including primary sclerosing cholangitis, hepato-lithiasis, parasitic infection and cirrhosis by heavy alcohol intake or through infection with the hepatitis B virus (HBV) or hepatitis C virus (HCV) [1-3]. Although ICC was recognized being most highly prevalent in Southeast Asia including Japan, recently an increase in the incidence and mortality of ICC has been reported world-widely[4-6] . A curative resection is the only effective therapy, but the outcome of patients with ICC remains unsatisfactory because of late clinical presentation and tumor detection. [2, 7, 8].

In 1997, the Liver Cancer Study Group of Japan (LCSGJ) proposed a new classification of ICC based on the macroscopic appearance of the tumors: the mass-forming (MF) type, the periductal infiltrating (PI) type, the intraductal growth (IG) type, and the mixed type containing more than one of these three basic types [9, 10]. Among these categories, the mass-forming type is the most common. Some authors reported several clinicopathological prognostic factors [10-13]. But the inclusion of the infection with viral hepatitis by HBV or HCV as one of the prognostic factors is controversial, especially in the mass-forming type ICC. The purpose of this study was to evaluate a characteristic of the mass-forming type ICC with type B or C hepatitis by focused to fibrosis of tumor and background liver.

Methodology

Between January 1997 and December 2007, a total of 46 patients underwent initial surgical resection of ICC at the Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University Hospital, Kumamoto, Japan. The criteria for surgical resection of ICC were the absence of extensive lymph node metastases, peritoneal dissemination, advanced invasion to the hepatoduodenal ligament, intrahepatic metastases in the future liver remnant, and obvious metastases for other distant organs. Extrahepatic bile duct resection with lymph node resection, both in the hepatoduodenal ligament and around the head of the pancreas, was performed when the tumor extended into the hepatic hilum or the hepatocoduodenal ligament. All patients were followed up at our hospital or at a satellite hospital on a monthly or bimonthly basis including a measurement of the serum levels of carbohydrate antigen 19-9 (CA-19-9) and carcinoembryonic antigen (CEA), ultrasonography and/or enhanced computed tomography.

All of patients were categorized as MF type (n=34), PI type (n=6), IG type (n=1), or other (n=5). Thirty-four patients with the MF type ICC were enrolled in the present study.

To evaluate the amount of collagen in stroma of tumor tissue, the Sirius red (Polysciences Inc., Pennsylvania, USA) staining method was performed as described previously [14]. The tissue fraction containing collagen was stained red. The collagen content of the tumor stroma was also quantified by computer-assisted image analysis. The intensity of Sirius red expression was quantified as the relative percentage of the Sirius red area to the selected field area with an imaging processor, VH Analyzer (Keyence Co.,

Osaka, Japan).

The pathological features of ICC at the initial hepatectomy were evaluated according to the classification guidelines, proposed by the Liver Cancer Study Group in Japan[15]. In the patients who were categorized in the MF type, the significance of 14 clinicopathological factors potentially influencing the prognosis were analyzed using the log rank test. These included age, gender, CA19-9 levels, CEA levels, size, intrahepatic metastases, portal vein invasion, bile duct invasion, histological differentiation, lymph node involvement, type B or C hepatitis, lymph node dissection, Sirius Red score of the tumor and platelet count in peripheral blood. Cox's proportional hazard model was used in a stepwise multivariate analysis to identify factors independently associated with the prognosis after surgery. The relationships between Sirius Red score and possible prognostic factors, which include age, CEA levels and lymph node involvement, were examined. Trends and differences were tested by the Yates' chi-square test. Probability values <0.05 were considered significant.

Results

Among forty-six patients underwent surgical resection of ICC, surgical procedures included extended hemihepatectomy in 11 patients, hemihepatectomy in 13 patients, central bisegmentectomy in 3 patients, and partial resection of the liver less than segmentectomy in 7 patients.

These comprised 21 men and 13 women with a median age of 65 years (range, 26-81 years). The median follow-up time was 29 months (range, 3-126).

Clinicopathological features of 34 patients with the MF type are summarized in Table 1. The cumulative 5-year survival rate was 55.9% and median survival time after initial hepatectomy was 29 months. Univariate analysis showed that significant risk factors for poor survival included age ≥ 65 years old ($p = 0.0119$), CEA levels ≥ 1.6 ng/ml ($p = 0.0141$) and lymph node involvement ($p = 0.0284$). In contrast, gender, CA19-9 levels, size, intrahepatic metastases, portal vein invasion, bile duct invasion, histological differentiation, B or C hepatitis, lymph node dissection, Sirius Red score of the tumor tissue nor platelet count in peripheral blood were not correlated with patients' survival after initial hepatectomy (Table 1). Multivariate analysis revealed that age, CEA levels and lymph node involvement were independent and significant poor prognostic factors (Table 2).

A significant negative correlation was found in only Sirius Red score of the tumor tissue in the patients with type B or C hepatitis and a platelet count in the peripheral blood ($R = -0.6831$, $P = 0.0425$).

Discussion

Some reports have shown the clinicopathological prognostic factors of ICC among all categories [10-13]. These prognostic factors included periductal infiltration, perineural invasion, portal vein invasion, presence of intrahepatic metastases, two or more lymph node metastases, ascites, mixed type (mass-forming type plus periductal infiltrating type), multiple tumors, and high serum CA19-9 level. It is a well-known fact that HCC and the infection with HBV or HCV are closely related, and the relevance of the ICC and the

infection with HBV or HCV are recently reported (1-3). ICC has a quite malignant biological behavior, so its prognosis is still poor even after curative surgery. Although Fu showed HBs-antigen was significantly related to prognosis of mass forming ICC by multivariate analysis [12], the infection with type B or C hepatitis was not a prognostic factor of the MF type ICC in this study.

A significant negative correlation was recognized between Sirius Red score of the tumor with type B or C hepatitis and a platelet count in the peripheral blood. On the other hand, the Sirius Red score of the tumor without type B or C hepatitis bears no relation to a platelet count in the peripheral blood. In this study, the degree of the intratumoral fibrosis tended to reflect the degree of the fibrosis of the background liver ($R=0.8651$, $P=0.1349$). Recently, several close relations between the platelet itself or platelet-derived serotonin [16] and growth factors C [17], and the hepatic fibrosis in type B or C viral hepatitis [18] have been reported. The fibrosis of the liver parenchyma is known as one of the mother glands of cancer, and negative correlation between the degree of fibrosis of the liver parenchyma and the platelet counts was elucidated, also. Consequently, the fibrosis in the tumor tissue is reversely related to a platelet count in the peripheral blood for reasons of reflecting fibrosis of the background liver parenchyma.

We concluded that age, CEA levels and lymph node involvement were poor prognostic factors, but the infection with type B or C hepatitis was not a prognostic factor of the mass forming type ICC in this study.

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