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ScienceDirect

Journal of the Chinese Medical Association xx (2017) 1−9

www.jcma-online.com

Original Article

Impact of tumor size on the prognosis of hepatocellular carcinoma in patients who underwent liver resection

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Received January 16, 2017; accepted June 4, 2017

Abstract

Background: Health burdens of hepatocellular carcinoma (HCC) are emerging quickly in the world, including in Taiwan. Surgical resection has been recognized as the first-line treatment for early tumors. This study aimed to investigate the prognostic risk factors for mortality and recurrence rate in Taiwan, which has a high prevalence of chronic viral hepatitis.
Methods: A total of 397 HCC patients receiving tumor resection were consecutively examined in central Taiwan from 2008 to 2014. A hospital-based patient cohort was designed to collect serological markers to further assess liver function. We modified the Kaplan−Meier method according to the competing death risks for comparing recurrence and used multivariate Cox proportional hazard regression to adjust for significant risk factors.
Results: In addition to advanced fibrosis, tumor size ≥5 cm was significantly associated with higher mortality within the 5-year period when compared with <5 cm (43.3% vs. 13.2%, $p < 0.0001$). Patients with tumor size ≥5 cm also easily progressed to early recurrence within two years when accounting for death as a competing risk (20.1% vs. 10.1%, $p = 0.01$). Higher AFP levels played a major role in further predicting higher mortality in those patients. We determined that there were a 4.5-fold and 2.2-fold higher mortalities in patients with size ≥5 cm/AFP ≥20 ng/mL and with size ≥5 cm/AFP< 20 ng/mL, respectively, when compared to patients with small tumors.
Conclusion: Tumor size ≥5 cm might be a good predicting factor for death and early recurrence when considering death as a competing risk.

Keywords: Alpha-fetoprotein; Hepatitis B virus; Hepatitis C virus; Hepatocellular carcinoma; Tumor size

1. Introduction

With a rapidly increasing incidence rate, hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer mortality in the world.[1] Most HCCs progress from chronic viral hepatitis (chronic hepatitis B, CHB; chronic hepatitis C, CHC), alcohol intake,

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, alpha-fetoprotein.

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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https://doi.org/10.1016/j.jcma.2017.06.018

aflatoxin exposure, older age and male gender.[1−5] The etiologies appear to differ in an ethnicity-specific manner.[6] All etiologic forms of advanced liver fibrosis may be complicated by tumor formation.[7,8] One-third of cirrhotic patients will develop HCC[9] by gradually (with 1−8% growth per year).[10]

After a diagnosis of HCC, surgical resection, liver transplantation, radiofrequency ablation, transarterial chemoembolization, and targeted molecular therapy are used to treat HCC according to clinical profiles.[1] Resection is the first-line treatment option for patients with early tumors (solitary tumor or very well-preserved liver function), with a 5-year survival rate of 60−80%.[11,12] However, standard HCC resection in cirrhotic patients leads to a higher mortality rate, contributing to a lower 5-year survival rate of approximately 50−60%.[2,13]

Two major prognostic factors, liver function and tumor characteristics, have been associated with all-cause mortality or recurrence rate after resection. Child-Pugh class has often been used to assess liver function that might be related to late recurrence (>2 years), but not with early recurrence.[14] Regarding tumor characteristics, the main predictors of survival are tumor size,[15−19] tumor number and vascular invasion.[14,20−24] In addition, combined with liver function and other risk factors, poorer differentiation grades at Ishak stage 6[25] and surgical resection margin ≤1 cm in small tumors[26] have been associated with higher recurrence or mortality or rate.

Despite the known factors related to tumor and liver function that are associated with long-term survival in ethnic and etiologic groups, death occurring before HCC recurrence leads to information censoring and often to overestimation of the recurrence probability. Recently, several studies have reported that death should be regarded as a competing risk event in estimating the recurrence of HCC.[27] The aim of the present study was to investigate the prognostic risk factors for mortality and HCC recurrence rate with consideration of the competing risk in Taiwan.

2. Methods

2.1. Patient eligibility

Between November 2008 and December 2014, a total of 477 patients diagnosed with liver cancer who received surgical resection as first-line therapy in a medical center in central Taiwan were consecutively examined for eligibility. Thirty-eight patients were ineligible to enroll in this study for the following reasons: 5 had cholangiocarcinoma, 17 had combined cholangiocarcinoma and HCC, and 16 had adenocarcinoma or other cancer. Fourteen HCC patients who were not suitable for resection were also excluded. Seventeen surgical deaths within 60 days and 11 patients with HCC occurrence within 90 days were excluded among these remaining 425 patients since it was not appropriate to enroll the patients who died early and had HCC recurrence soon after the operation possibly due to misdiagnosis caused by current medical limitation. Finally, 397 HCC patients with Barcelona Clinic Liver Cancer (BCLC) stage 0 to B receiving tumor resection were enrolled in the study. The flow of participants through the hospital-based study is presented in Fig. 1.

All patients provided written informed consent. The institutional review board of the Kaohsiung Medical University Hospital approved the protocols, which conformed to the guidelines of the International Conference on Harmonization for Good Clinical Practice. All procedures followed were by the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Assessment of serological markers and liver function

After enrollment, serum biochemistries (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alpha-fetoprotein (AFP), total bilirubin, albumin, creatinine, prothrombin time (PT)/International Normalized Ratio (INR), and complete blood counts (white blood cells, platelets, hemoglobin)) were measured using a systemic multi-autoanalyzer (Technicon SMAC, Technicon Instruments Corp., Tarrytown, NY, USA). Hepatitis B surface antigen (HBsAg) and anti-HCV antibodies were detected using a third-generation, commercially available enzyme-linked immunosorbent assay kit (AxSYM 3.0; Abbott Laboratories, Chicago, IL, USA). Liver function was cautiously evaluated with biochemistry tests and the Child-Pugh classification.

2.3. Diagnosis of HCC

The diagnosis of HCC in all patients was assessed using axial imaging [computed tomography (CT) scan with intravenous contrast or magnetic resonance imaging (MRI) with intravenous contrast]. All patients were retrospectively assigned to the various stages according to the classification criteria of the BCLC[28] and the American Joint Committee on Cancer (AJCC), 7th edition TNM staging systems.[29] Liver resection was performed in patients with normal synthetic liver function as assessed by normal serum total bilirubin, albumin and PT (INR).

2.4. Assessment of liver histopathology and tumor characteristics

After the operation, specimens were fixed and assessed for tumor characteristics and liver fibrosis by a pathologist. Neoplastic liver tissue, tumor number, largest tumor diameter, differentiated grades and surgical margins were determined. A free surgical margin was defined as a distance of 1 cm between the cut surface and the tumor edge in the resected specimen. In non-neoplastic liver tissue, the degree of hepatic inflammation and fibrosis was assessed with the Ishak fibrosis score as follows: stage 0 (normal liver); stage 1 (fibrosis expansion of a few portal tracts); stage 2 (fibrosis of all portal tracts); stage 3 (fibrosis expansion of most portal areas with occasional portal-to-portal bridging); stage 4 (fibrosis expansion of portal areas with marked bridging);

Please cite this article in press as: Dai C-Y, et al., Impact of tumor size on the prognosis of hepatocellular carcinoma in patients who underwent liver resection, Journal of the Chinese Medical Association (2017), https://doi.org/10.1016/j.jcma.2017.06.018