ORIGINAL ARTICLE

Risk factors and management for early and late intrahepatic recurrence of solitary hepatocellular carcinoma after curative resection

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Abstract

Background: Intrahepatic recurrence is a significant problem for patients who have undergone a hepatic resection for hepatocellular carcinoma (HCC). The objective of the present study was to identify risk factors and evaluate the management of early and late recurrence of solitary HCC after curative resection.

Methods: Included in this study were 816 patients with solitary HCC who underwent a curative partial hepatectomy. Intrahepatic recurrence in these patients was followed up retrospectively. Prognosis and therapy for the recurrence were investigated and analysed.

Results: Early and late intrahepatic recurrence occurred in 423 patients and 199 patients, respectively. Multivariate analysis showed that a tumour diameter >5 cm, the absence of a tumour capsule and the presence of microvascular invasion were correlated with early recurrence, whereas cirrhosis and alpha-fetal protein >400 μg/l were independent risk factors contributing to late recurrence. The 5-year survival of HCC patients with early recurrence was significantly lower than that of patients with late recurrence. Further curative treatment for intrahepatic recurrence offered a 5-year overall survival of 56.0%, which was better than alternative management.

Conclusion: Early and late recurrences of solitary HCC after curative resection are associated with different predictive factors. The time to recurrence and further curative treatment after recurrence were the best predictors of survival post recurrence.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most frequently diagnosed cancers and leading causes of cancer-related death worldwide.[1] Surgical treatment options for HCC include PH (partial hepatectomy) and LT (liver transplantation).[2] Theoretically, LT is the therapeutic gold standard in cirrhotic HCC patients who meet the Milan criteria because it can remove all the intrahepatic tumour foci together with the oncogenic cirrhotic liver.[3] Because of the shortage of donor organs and a long waiting time, primary PH remains the first-line treatment for HCC patients or serves as a bridge for future salvage LT.[4] Unfortunately, PH is associated with a high risk of post-operative intrahepatic recurrence that occurs in about 80% of HCC patients at 5 years and is the leading cause of post-operative death.[5–9] Therefore, it is essential that risk factors of recurrence be determined and a strict follow-up protocol as well as treatment strategies be established for early detection and intervention of recurrence.

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Previous studies reported that early recurrent tumours most likely originated from subclinical metastasis of primary tumours, whereas late recurrent tumours might be multicentric or *de novo* primary HCC in the remnant liver.[10–12] Different risk factors are considered to be involved in each type of recurrence. Increasing tumour stage, the presence of microsatellite and microvascular invasion (MVI) and an elevated alpha-fetoprotein (AFP) level have been reported to be associated with early recurrence, whereas cirrhosis, multinodularity and hepatitis activity have been shown to be predictors of late recurrence.[5,10,13] However, in most of these studies, the enrolled patients were heterogeneous in terms of clinicopathological characteristics and management-related factors. Various studies have produced conflicting results concerning factors predicting recurrence, and few previous studies have focused on risk factors for intrahepatic recurrence in an exclusive cohort of patients with solitary HCC after curative PH.

The aim of this study was to identify prognostic factors influencing post-operative recurrence and survival of patients undergoing curative PH for solitary HCC.

Materials and methods

Enrolled in this study were 918 consecutive patients who had undergone curative PH for solitary HCC at the Eastern Hepatobiliary Surgery Hospital (Shanghai, China) between March 2000 and September 2010. The pre-operative clinical diagnosis of HCC was consistent with the diagnostic criteria of the American Association for the Study of Liver Diseases (AASLD).[14] Patients who met the following criteria were included this study: pre-operative World Health Organization performance status of 0–1; Child–Pugh class A; only one hepatic lesion; no extrahepatic metastases; no image-visualizable tumour thrombus in the portal vein, hepatic vein or bile duct branches; and suitable for curative PH.

The surgical strategy for HCC was standardized for all patients. Curative resection of HCC was performed as described previously.[15] In brief, the whole tumour was resected with a negative surgical margin confirmed by histological examination; the pre-operative elevated AFP level decreased to the normal range within 2 months after surgery; and no new image-visualizable intra- and extrahepatic lesions within 2 months after surgery. Patients who underwent palliative resection and/or adjuvant therapy after a hepatectomy, or died owing to severe complications within 1 month after surgery were excluded from this study. This study was approved by the Institutional Review Board of the Eastern Hepatobiliary Surgery Hospital.

The diagnosis of HCC was confirmed in all patients by pathological evaluation of the surgically resected specimens. The histological grade of tumour differentiation was assigned by the Edmondson–Steiner's classification system.

Clinicopathological factors that were potentially related to recurrence included age, gender (male or female), serum hepatitis B surface antigen (HBsAg) status (positive or negative), hepatitis E surface antigen (HBeAg) status (positive or negative), cirrhosis (presence or absence), AFP level (≤400 or >400 μg/l), prothrombin time (PT) (≤13 or >13 s), platelet count (PLT) (≤100 or >100 × 10^9/l), total bilirubin (TBIL) (≤17.1 or >17.1 μmol/l), albumin (ALB) (≤35 or >35 g/l), alanine aminotransferase (ALT) (≤50 or >50 U/l), hepatitis B virus (HBV)-DNA (≤4 or >4 l g, IU/ml), intra-operative blood transfusion (yes or no), surgical margin (<2 or ≥2 cm), anatomical PH (yes or no), tumour diameter (≤5 or >5 cm), tumour capsule (yes or no), MVI (yes or no), and Edmondson–Steiner's classification (I/II or III/IV).

All patients were followed up regularly every 2 months during the first 2 years, and 3 months afterwards, and monitored by a standard protocol including serum AFP, immunological indexes of HBV, liver function, abdominal ultrasound or contrast-enhanced computerized tomography (CT)/magnetic resonance imaging (MRI) and chest X-ray. All patients were followed up until September 2013.

Once recurrence was suspected based on the combined results of these clinical examinations, patients were hospitalized and treated with curative treatments including re-resection, percutaneous ethanol injection (PEI) or radiofrequency ablation (RFA) when the recurrence was localized, or otherwise with transcatheter arterial chemoembolization (TACE) or conservative management with sorafenib when the recurrence was diffuse. Time to recurrence (TTR) was defined as the period between surgery and the diagnosis of recurrence by setting 2 years as the cut-off between the early and late recurrences.[5,13,16] The overall survival (OS) time was defined as the interval between PH and death or between PH and the last follow-up. Patients who died for reasons not related to HCC were censored at the time of death.

Statistical analysis

Continuous variables were reported as the median and range, The cut-off values of the continuous variables were based on those used commonly in previous studies or as determined by maximizing the Youden's index, i.e. sensitivity + specificity-1, as calculated from the receiver-operating characteristic curve (ROC).[17] The χ^2 test or Fisher's exact probability test was used for categorical variables. The cumulative survival time was calculated using the Kaplan–Meier method and compared by the log-rank test. The Cox proportional hazards model was used to determine independent factors of recurrence based on the variables selected by univariate analysis. All the significant predictors of recurrence in the univariate analysis were analysed in a logistic regression model to show an independent value at the multivariate analysis. Statistical analyses were performed by SAS 9.1.3 software (SAS Institute Inc., Cary, NC) and R 2.13.2 (http://www.r-project.org/). A two-tailed value of $P < 0.05$ was considered statistically significant.