ORIGINAL ARTICLE

Impact of pathological features of primary hepatocellular carcinoma on the outcomes of intrahepatic recurrence management: single center experience from Southern Taiwan

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Abstract

Background: Currently, there is no definitive management for hepatocellular carcinoma (HCC) intrahepatic recurrence (IHR) after primary resection (PR). The aim of this study was to analyze the outcomes of three modalities for patients who received curative PR and had IHR within the University of California San Francisco (UCSF) criteria.

Methods: Between 2003 and 2010, patients with IHR after PR were treated with salvage liver transplantation (SLT), re-resection (RR) or local ablation (LA). Clinico-pathological features of primary tumor and recurrent HCC were analyzed to determine the risk factors that adversely affected overall survival (OS) and disease free survival (DFS).

Results: The study included 130 patients with subgroups of SLT (n = 25), RR (n = 31) and LA (n = 74). The 5-year DFS and OS were 75%, 31% and 17% and 80%, 60% and 58% respectively for each subgroup. SLT had a significantly better DFS than other modalities ($p < 0.001$). There was no difference in OS. In multivariate analysis, two variables adversely affected DFS: microvascular invasion in PR and not treating patients with SLT.

Conclusions: SLT provides better DFS for patients with IHR within the UCSF criteria. However, SLT failed to show the same advantage in OS.

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Introduction

Hepatic resection is considered to be a potentially curative treatment for hepatocellular carcinoma (HCC), especially in patients with preserved liver function. However, a high incidence of recurrence remains the main challenge after curative resection of HCC with a 5-year disease-free survival rate (DFS) of 27–42%; with more than 70% of recurrences occurring within the hepatic remnant.[1–5] Successful subsequent management with curative intent has been shown to prolong survival in patients with intrahepatic recurrence (IHR).[6,7] Different modalities have been used for IHR management, including salvage liver transplantation (SLT), re-resection (RR), local ablation (LA) using radiofrequency ablation (RFA) and/or percutaneous ethanol

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injection (PEI) and trans-arterial embolization/chemo-embolization (TAE/TACE).[7–14] Currently, there are no definitive selection criteria for IHR management other than those applied to the management of primary HCC.[13,15]

The pathological features of HCC and non-tumor liver parenchyma (NTLP) are strongly related to recurrence.[2–4,16] When deciding on therapeutic management options for patients with IHR the pathological features of the primary HCC can also be taken into account. This concept has previously been applied to identify patients at high risk of recurrence and whom would benefit from SLT prior to the diagnosis of recurrence.[17]

The aim of this study was to analyze the outcomes of three modalities (SLT, RR and LA) used for management of patients who underwent curative primary resection (PR) complicated by IHR that fell within the University of California San Francisco (UCSF) criteria.[18] Prognostic factors affecting DFS and overall survival (OS) after IHR management were identified.

Patients and methods

From January 2003 to December 2010, all patients who underwent curative PR complicated by IHR that fell within the UCSF criteria were included for further study. All patients with possible diagnosis of HCC were discussed in a weekly multidisciplinary tumor conference prior to initiating treatment. The BCLC treatment guidelines were used with minor adjustment. The AJCC staging system was used to determine adjuvant treatment. Patients who underwent palliative PR, patients with associated malignancies and patients with recurrence beyond the UCSF criteria were excluded. The UCSF criteria (solitary tumor < or = 6.5 cm, or three or fewer nodules with the largest lesion < or = 4.5 cm and total tumor diameter < or = 8 cm, without gross vascular invasion) was applied because patients listed for liver transplantation (LT) are required to fall within the criteria as determined by the National Health Insurance Administration (NHI), Ministry of Health and Welfare, Taiwan. Histopathological features of PR and clinical data of recurrence were collected from a prospectively maintained database. The study protocol was approved by the hospital's ethics committee (IRB No. 101-2817B).

Primary resection, follow-up and diagnosis of recurrence

Preoperative assessments and the PR operative procedures have been described previously.[3] A major resection was defined as a resection of at least three hepatic segments. The features of HCC and NTLP in PR were histopathologically examined. The degree of fibrosis in the NTLP was graded according to an Ishak score.[19] Microvascular invasion was defined as tumor emboli within the central vein, a lobar or segmental portal or hepatic vein and large capsular vessels. Patients were followed up regularly at the first month, then every 3 months for 5 years and then every 6 months thereafter. Follow-up comprised serum alpha fetoprotein level (AFP) analysis and abdominal ultrasonography. Patients suspected of having recurrence underwent computed tomography (CT) for confirmation. Diagnosis of primary and recurrent HCC was based on the criteria of practice guidelines of the European Association for the Study of the Liver (EASL) or the American Association for the Study of Liver Disease (AASLD).[20,21]

Management of recurrence

The BCLC treatment guidelines were used with minor adjustment. The AJCC staging system was used for possible adjuvant treatment. In general, RR was performed in Child–Pugh score A patients whose future remnant liver volume was >30–40% of the standard liver volume (Appendix Fig. A1). For patients to be eligible for SLT, the UCSF criteria had to be met. Local ablation therapy was considered in Child–Pugh score A patients and selected B patients. Neither number nor size of primary HCC was considered in the UCSF categorization of recurrent HCC, but major vascular invasion and extrahepatic metastasis in PR precluded the patients from the study. Techniques of hepatectomy, SLT and LA have been described elsewhere.[3,22,23]

Follow-up after management of recurrence

Perioperative mortality was defined as a patient's death within 90 days of the procedure. The follow-up protocol after management

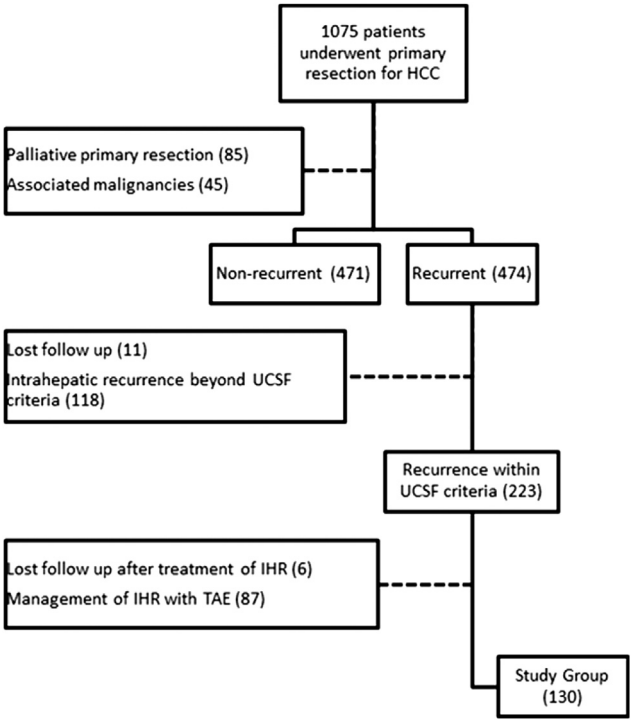

Figure 1 Inclusion and exclusion criteria