



Early intrahepatic recurrence of hepatocellular carcinoma after hepatectomy treated with re-hepatectomy, ablation or chemoembolization: A prospective cohort study

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Abstract

Aims: To observe the outcomes of various treatments for patients with early intrahepatic recurrent hepatocellular carcinoma (HCC) after partial hepatectomy.

Methods: A total of 629 patients with intrahepatic recurrent HCC within Milan criteria following hepatectomy were prospectively collected between November 2004 and May 2010. Overall survival (OS) and recurrence to death survival (RTDS) were analyzed by the Kaplan–Meier method and log-rank test. Cox regression analysis was used for multivariate analyses.

Results: The 5-year OS and RTDS rates were 64.5%, 43.0%; 37.0%, 26.7%; 27.7% and 8.3% for patients who received re-hepatectomy ($n = 128$), percutaneous radiofrequency ablation (PRFA, $n = 162$) and transarterial chemoembolization (TACE, $n = 339$) (re-hepatectomy vs. TACE, $P < 0.001$, <0.001 ; vs. PRFA, $P = 0.005$, 0.008 ; PRFA vs. TACE, $P < 0.001$, <0.001). The independent predictors of OS and RTDS were tumor number (hazard ratio: 1.54, 95% confidence interval: 1.18–2.00; 1.57, 1.21–2.04), alpha fetoprotein >20 ng/mL (1.64, 1.24–2.17; 1.66, 1.26–2.20), presence of varices (1.69, 1.28–2.22; 1.61, 1.23–2.10) and Edmondson–Steiner grade III–IV (1.66, 1.17–2.35; 1.70, 1.20–2.40) at the initial stage; and tumor number (1.34, 1.04–1.73; 1.32, 1.03–1.70), time to recurrence (TTR) (3.46, 2.58–4.65; 1.59, 1.19–2.14) and treatment for recurrence (TACE: 3.18, 2.16–4.66; 2.95, 2.02–4.31; PRFA: 1.49, 0.97–2.29; 1.44, 0.94–2.19).

Conclusions: For early intrahepatic recurrent HCC, re-hepatectomy achieved best outcome. It produced similar result as PRFA for patients with more invasive primary tumors and underlying cirrhosis/varices. TACE had worst prognosis which was only suitable for multifocal recurrence and TTR ≤ 1 year.

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Keywords: Hepatocellular carcinoma; Intrahepatic recurrence; Hepatectomy; Ablation; Chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) is a common malignancy with the third highest cancer-related mortality in the world.¹ Partial hepatectomy is still an effective and commonly used treatment for HCC, but the long-term prognosis is far from satisfactory due to a high recurrence rate which was up to 70% at 5 year after surgery.² It is important to find an effective way to improve the survival of patients with recurrent HCC after hepatectomy.

Improvement in recurrence surveillance and medical imaging has led to the diagnosis of recurrent HCC at an early stage. Re-hepatectomy,^{2–7} ablative therapies,^{8–10} and transarterial chemoembolization (TACE)^{2,11,12} were commonly used in the treatment of early intrahepatic recurrence. The appropriate selection of treatment is the key to improve the therapeutic outcome. The validity of previous reports comparing re-hepatectomy, percutaneous radiofrequency ablation (PRFA) and TACE for HCC recurrence were affected by selection bias in the inclusion of patients to receive the different therapeutic methods.^{13–15} Salvage liver transplantation is also an option but it is of limited use in regions with liver donor shortage and high incidence of HCC.^{16,17}

In this study, we prospectively collected the data of 629 patients with early intrahepatic recurrence after curative hepatectomy. We confined study object to the patients with recurrent HCC within the Milan criteria, as these recurrent tumors are commonly treated by re-hepatectomy, PRFA or TACE. The study aimed to compare the efficacy of these three treatments.

Patients and methods

Patients

Prospectively collected data from the Department of Hepatic Surgery IV of the Eastern Hepatobiliary Surgery Hospital (EHBH) from November 2004 and May 2010 were reviewed retrospectively. Patients who developed intrahepatic tumor recurrence after partial hepatectomy for pathologically proven HCC were studied. The inclusion criteria were: (1) patients underwent R0 resection for primary HCC as described in our previous study¹⁸; (2) the recurrent tumors met the Milan criteria; (3) no evidence of extrahepatic metastasis; (4) liver function of Child-Pugh class score ≤ 8 , without severe esophageal varices; (5) underwent re-hepatectomy, PRFA or TACE as the first-line treatment for recurrence. Patients who had incomplete clinical data, and who were in-hospital death and lost to follow-up were excluded from this study.

The study was approved by the institutional ethics committee. Informed consent was obtained from all patients for use of their data in the research.

Diagnosis and treatment of recurrent HCC

The clinical diagnosis of HCC at both its initial and recurrent stages was based on the criteria of American

Association for the Study of Liver Diseases (AASLD).^{11,19} Histopathological examination of surgical specimens after the initial and re-hepatectomy was carried out independently by three pathologists who came to a consensus by discussion if there was any controversy. Tumor cell differentiation was histologically classified using the Edmondson-Steiner classification.²⁰

Once HCC recurrence was diagnosed, the selection of treatment depended on the general condition of the patient, tumor stage, liver functional reserve, and estimated volume of future liver remnant.⁷ Of course, the doctor's conception and experience and the patient's decision were also be considered. Re-hepatectomy was the first choice, which was used mainly for patients who had single tumor or multiple tumors limited in the semi-liver with liver function of Child-Pugh A and time to recurrence (TTR) ≥ 12 months.⁷ The resectability and safety was judged by the experienced hepatic surgeon. PRFA was used for those who were unsuitable for re-hepatectomy, especially for solitary tumor ≤ 3 cm located deeply in the parenchyma of liver or multiple tumors located in both of lobes with TTR ≥ 12 months.¹⁵ TACE was given to patients who were not candidates for or unwilling to receive the above 2 treatments.^{14,16} Sorafinib was not used as a first line treatment for these patients with early recurrent HCC. Although liver transplantation is also an option for HCC recurrence, it was not used in this series.^{16,17}

Anatomical hepatectomy was the preferred method unless the lesion was situated peripherally when a non-anatomical resection was carried out. TACE and PRFA for recurrent HCC were performed as previously reported.^{21,22}

Follow-up

The follow-up for patients after primary resection for HCC has been reported.¹⁸ After re-hepatectomy, the patients were followed-up once every 2 months within the first 2 years, and then once every 3 months thereafter. Patients who received PRFA and TACE for HCC recurrence underwent a similar follow-up regimen as those who received re-hepatectomy. However, these patients were more closely examined with contrast-enhanced CT and MRI once every 3 months to investigate the status of local tumor control, tumor progression and metastasis.

Statistical analysis

The study endpoints were overall survival (OS) and recurrence to death survival (RTDS). OS was defined as the interval between the date of the initial hepatectomy and the date of death or last follow-up; RTDS was defined as the interval between the date of diagnosis of HCC recurrence and the date of death or last follow-up.

Statistical analyses were performed using SPSS 15.0 (SPSS Inc). Categorical variables were compared using

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