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ORIGINAL ARTICLE

A systemic review and meta-analysis comparing the prognosis of multicentric occurrence and vs. intrahepatic metastasis in patients with recurrent hepatocellular carcinoma after hepatectomy

Sheng-lan Yang[1], Ying-ying Luo[1], Min Chen[2], Yan-ping Zhou[1], Fu-rong Lu[1], Dan-fang Deng[1] & Yan-ran Wu[1]

[1]Department of Traditional Chinese Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, and [2]Department of Geriatric, Zhongnan Hospital of Wuhan University, Wuhan, 430071, Hubei, PR China

Abstract

Background: The aim of this meta-analysis was to evaluate the prognosis of patients with different types of hepatocellular cancer (HCC) recurrence following hepatectomy. Specifically, it evaluated overall survival and disease-free survival in HCC patients with multicentric occurrence (MO) or intrahepatic metastasis (IM).

Methods: Medline, Cochrane, EMBASE, and Google Scholar were searched until August 22, 2016 using the following search terms: hepatocellular carcinoma, multicentric occurrence, intrahepatic metastasis, early recurrence, and late recurrence. Prospective, retrospective, and case control studies were included.

Results: The pooled results showed that patients in the MO group had lower risk of death than the IM group (pooled HR = 0.495, 95% CI = 0.378 to 0.648, P < 0.001). The MO group also had significantly longer disease-free survival than the IM group (pooled HR = 0.774, 95% CI = 0.663 to 0.903, P = 0.001). Sensitivity analysis indicated that no one study dominated the findings and that the data are robust. Overall the included studies were of good quality.

Conclusion: This study found that MO patients have greater survival following surgery than IM patients, indicating the prognosis of MO patients is significantly better than that for IM patients.

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Correspondence

Min Chen, Department of Geriatric, Zhongnan Hospital of Wuhan University, #169, Donghu Road, Wuchang District, Wuhan, Hubei 430071, PR China. E-mail: 1307325063@qq.com

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common leading cause of cancer death worldwide.[1] It is estimated that the annual number of patients with a new diagnosis of HCC exceeds 600,000, with half of those residing within China.[2] The high incidence of HCC in China and other East Asia countries reflects the high hepatitis B virus infection rate.[3] The guidelines recommend a number of treatments options for HCC including surgical resection.[4–6] Compared with other cancers that can be treated with surgery, the prognosis for patients with HCC is poor; the five-year survival rate for HCC following surgery is about 47%.[7]

Recurrence is an important challenge in treating HCC and is the main cause of death following surgery.[8–10] Recurrence can occur following all treatments.[8,9] Recurrent intrahepatic HCCs are caused by two different mechanisms: intrahepatic metastasis (IMs) originating from the primary cancer, or independent carcinogenesis resulting in multicentric occurrence (MO).[11–14] It is crucial to discriminate between the two different mechanisms for recurrence, not only for understanding the cause of recurrence but also for treatment decisions.[11,15,16] Lesions are regarded as MO when the tumor meets the following criteria: consisting of multiple nodules of well differentiated carcinoma, nodules of well differentiated carcinoma surrounding less differentiated carcinoma ("nodule-in-nodule" form), have higher differentiation than the primary resected tumors, and the absence of vascular involvement.[12–14] Tumors not corresponding to these criteria and show either the same level of or less

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differentiation than the primary resected tumor are diagnosed as IMs.[14] IMs are usually distributed in a gradient-like pattern or have separate tumors located near the largest lesion that are clearly smaller than the largest lesion, and histologically are similar to or less differentiated than the largest lesion.[12]

Prior studies have indicated that patients with MO may have better outcomes following repeat hepatic resection compared with those with IM n.[13,14] However, many of these studies had small populations and differed in design. The purpose of this systematic review and meta-analysis was to compare the prognosis of patients with IM or MO following repeat hepatic resection.

Methods

Search strategy

The study was performed according to the PRISMA guidelines. Medline, Cochrane, EMBASE, and Google Scholar databases were searched until August 22, 2016 using the following search terms: hepatocellular carcinoma, multicentric occurrence, intrahepatic metastasis, early recurrence, and late recurrence. Prospective, retrospective, and case control studies were included. All eligible studies evaluated patients with recurrent HCC following hepatectomy and who had a history of MO or IM at the time of surgical resection or pre-operative assessment. Studies had to report quantitatively outcomes of interest. Letters, comments, editorials, case reports, proceedings, and personal communications were excluded. The list of potential studies was reviewed by two independent reviewers, and in cases of uncertainty regarding eligibility, a third reviewer was consulted.

Data extraction

The following information/data was extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants' age and gender, Child-Pugh score, hepatitis profile, characteristics of HCC, length of follow-up time, and major outcomes.

Quality assessment

The quality of the included studies was assessed using Quality in Prognostic Studies (QUIPS), which consists of six domains (study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, analysis).[17]

Statistical analysis

The primary outcomes for the prognostic study were overall survival and disease-free survival. Hazard ratio (HR) and 95% confidence interval (95% CI) were used as the measure of effect size. If individual studies did not provide results of HR, the HR value was obtained from summary statistics of time-to-event analyses with the methods proposed by Tierney *et al.* (2007).[18] HR < 1 indicated patients in the MO group had lower risk of death and greater disease-free survival than those with IM group.

Study heterogeneity was examined using the χ^2-based Cochran Q statistic and I^2. For the Q statistic, P values < 0.1 were considered to indicate statistically significant heterogeneity. For the I^2 statistic, I^2 < 25% indicated low heterogeneity, while I^2 > 50% indicated moderate to high heterogeneity. Random-effects models (DerSimonian-Laird method) of analysis were used to calculate pooled hazard ratio across studies for each outcome measure. To examine whether any single study overly impacted the pooled study, sensitivity analysis was conducted using a leave-one-out approach. In this analysis, the pooled results were calculated with each study removed in turn. All statistical analyses were performed using the statistical software Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Of the 192 studies identified in the database searches, 181 were eliminated following the initial screening for not being relevant. Eleven studies underwent full-text review and five were eliminated for not reporting outcomes of interest or included patients who did not have surgery (Fig. 1).

A total of seven studies were included with a total of 704 patients (232 [33%] in the MO group and 472 [67%] in the IM group) (Table 1).[15,16,19–23] Four studies were prospective, two retrospective, and one was a case control study. The clinical characteristics and outcomes of survival analysis are presented in Table 2. The length of follow-up for survival analysis after repeat resection were inconsistent among the included articles. Five-year overall survival (OS) was shown in most of the study. Li *et al.* (2013)[19] and Wang *et al.* (2009)[20] showed 4-year OS. The length of follow-up for disease-free survival (DFS) ranged from 3 years to 5 years.

Meta-analyses

Six studies were included in the evaluation of overall survival.[15,19–23] All six studies reported a lower risk of death in the MO group compared with the IM group, with this difference being significant in all studies.[15,19–23] There was low heterogeneity across studies (Q = 8.0, P = 0.155, I^2 = 37.7%). The pooled results showed that patients in the MO group had lower risk of death than those in the IM group (pooled HR = 0.495, 95% CI = 0.378 to 0.648, P < 0.001) (Fig. 2a).

Six studies reported information on DFS.[15,16,19,21–23] In three of the studies, the MO group was associated with a significant higher DFS rate compare with the IM group.[16,19,22] No heterogeneity among the six studies for DFS was observed (Q = 3.8, P = 0.581, I^2 = 0%). The risk of death due to disease (or by tumor) was significantly lower in the MO group than the IM group (pooled HR = 0.774, 95% CI = 0.663 to 0.903, P = 0.001) (Fig. 2b).

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