



Review

The role of liver resection in the management of intermediate and advanced stage hepatocellular carcinoma. A systematic review

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Abstract

Background: The ideal management for patients with intermediate and advanced stage hepatocellular carcinoma (HCC) is controversial. The main purpose of this systematic review is to examine the role of liver resection in patients with intermediate stage HCC (multinodular HCCs) and in advanced stage HCC [mainly patients with portal vein tumor thrombosis (PVTT)].

Methods: A systematic search of the literature was performed in Pub Med and the Cochrane Library from 01.01.2000 to 30.06.2016.

Results: Twenty-three articles with 2412 patients with multinodular HCCs were selected. Also, 29 studies with 3659 patients with HCCs with macrovascular invasion were selected. In patients with multinodular HCCs the median post-operative morbidity was 25% and the 90-day mortality was 2.7%. The median survival was 37 months and the 5-year survival 35%. The 5-year survival was much better for patients with a number of HCCs ≤ 3 vs. HCCs > 3 (49% vs. 23%).

In patients with macrovascular invasion, who underwent hepatic resection, the median post-operative morbidity was 33% and the in-hospital mortality 2.7%. The median survival was 15 months. The 3 and 5 year survival was 33% and 20% respectively. Moreover a significant difference in survival was noted according to PVTT stage: 5- year survival for distal PVTT, PVTT of the main intrahepatic PV branch and PVTT extending to the main PV was 45%, 19% and 14.5% respectively.

Conclusions: Liver resection in patients with multinodular HCCs and HCCs with PVTT offers satisfactory long-term survival and should be considered in selected patients.

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Keywords: Hepatocellular carcinoma; Liver resection; Hepatectomy; Multinodular; Portal vein tumor thrombosis; Survival

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and the 3rd leading cause of cancer-

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related deaths worldwide [1,2]. The incidence of HCC is increasing in the West, mainly due to the effects of the non-alcoholic fatty liver disease [3]. The majority of patients are diagnosed in advanced stage, and if left untreated, life expectancy is less than a year [4,5].

Surgical treatment including liver resection and liver transplantation is the treatment of choice for patients with HCC as they offer long term survival and quality of life. Liver transplantation might be considered the ‘definitive’ treatment as it treats both the tumors and the liver cirrhosis and minimizes the recurrence but it has also limitations. It is applied in a small group of patients, mainly satisfying the Milan criteria, and the availability of liver grafts is limited. On the other hand, liver resection can be applied more easily. Nonetheless, hepatectomy is usually performed on an unhealthy liver, with high post-operative morbidity and mortality, while the recurrence rate of HCC remains high. It is recommended that the future liver remnant should be at least 40%, while the application of pre-operative portal vein embolization can increase the resectability rate [6]. The estimation of the liver functional reserve is also important. For this reason Indocyanin-green retention rate at 15 min, ¹³C-Methacetin Breath test (Limax test) and imaging based liver function tests are used [7].

Barcelona clinic liver cancer (BCLC) staging system has been adopted and approved for guidance for HCC management by the European Association for the Study of Liver (EASL) [8] and the American Association for the Study of Liver Disease (AASLD) [9]. It is a reliable system taking into account different factors such as patient’s general condition (performance status), liver function, tumor characteristics and its extension. It has been proved reliable to classify patients according to stages with different prognosis [5]. According to BCLC recommendations, curative treatments (liver resection, liver transplantation and ablation) should be applied to patients with very early (stage 0: single HCC < 2 cm), or early stage disease (A: single or 3 nodules < 3 cm each). Single tumors greater than 5 cm used to be classified as intermediate stage (B). However, recent proposals classify this category as early stage (A) [10,11], but the issue remains controversial in the literature [12].

For patients in intermediate stage [B: multiple (>2) HCCs with diameter > 3 cm each], trans-arterial chemoembolization (TACE) is recommended which is a palliative treatment with a mean life expectancy of 18–27 months [11]. For patients with macrovascular invasion (MVI), in advanced stage C, Sorafenib administration, a Tyrosine kinase inhibitor, is recommended which provides a median survival of 9 months [11].

BCLC recommendations have been questioned by the liver surgical society as they exclude many patients from liver resection. Many hepatobiliary centers in the world manage patients with intermediate and advanced stage HCC with liver resection, achieving satisfactory long-term survival [13].

In a recent systematic review from China, by Zhong et al. [14], the role of liver resection in large (>5 cm), multinodular HCCs and in HCCs with macrovascular invasion was studied. The authors state that liver resection in patients with large or multinodular HCCs provides satisfactory 5-year survival (42% in Asian studies vs. 32% in non-Asian studies) and acceptable 5-year survival in patients with macrovascular invasion (18% in Asian studies and 14% in Western studies). These findings argue for the expansion of the indications for hepatic resection in official treatment guidelines.

However, it should be considered that large (>5 cm) and multinodular HCCs were studied together in this review [14]. Patients with single large HCC >5 cm, as mentioned above, represent a group of patients in the ‘gray area’ which was initially classified as intermediate stage but now many authors suggest it should be regarded as early stage [11]. Furthermore, the search included studies up to the end of March 2014, and number of important studies have been published since then.

The aim of our review is to present the evidence for the role of liver resection in patients with multinodular intermediate stage HCCs and in patients with HCC with macrovascular invasion with an emphasis on portal vein tumor thrombosis (PVTT).

Materials and methods

Search strategy and information sources

A systematic search of the published literature was performed in PubMed and the Cochrane Library from 01.01.2000 to 30.06.2016 using a predefined, pilot-tested search algorithm as follows: “Hepatocellular Carcinoma” OR HCC OR liver cancer OR hepatoma AND (Intermediate OR Advanced OR Multinodular OR Portal Vein Thrombosis OR BCLC B OR BCLC C OR macrovascular invasion) AND “Liver and (Surgery or resection)” OR Hepatectomy or resection). Two investigators independently screened (AT, MCS) the retrieved citations at the title and abstract level. The final selection of the articles was made in consensus by all authors (Fig. 1).

Eligibility criteria

Eligible studies included clinical studies assessing the effect of liver resection on patients with multinodular HCCs and HCCs with macrovascular invasion and reporting data on overall survival and or disease free survival and median survival.

Case-reports and case-series involving less than 10 patients, animal studies, reviews, and non-English publications were excluded. Whenever we identified studies pertaining to the same patient population and the same outcome(s), we retained the one with the larger sample size or, for studies with the same sample size, the longer follow-up.

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