Review

JOURNAL OF HEPATOLOGY

Personalized treatment of patients with very early hepatocellular carcinoma

Alessandro Vitale[1,*], Markus Peck-Radosavljevic[2,3], Edoardo G. Giannini[4], Eric Vibert[5], Wolfgang Sieghart[2], Sven Van Poucke[6], Timothy M. Pawlik[7]

Keywords: Very early hepatocellular carcinoma; Evidence based treatment; Personalized approach; Ablation; Liver transplantation; Liver resection.

Received 17 May 2016; received in revised form 1 September 2016; accepted 16 September 2016

[1]*Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy*;
[2]*Department of Internal Medicine III, Division of Gastroenterology/Hepatology, Liver Cancer (HCC)-Study Group, Medical University, Vienna, Austria*;
[3]*Department of Gastroenterology, Hepatology, Endocrinology and Nephrology, Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria*;
[4]*Gastroenterology Unit, Department of Internal Medicine, IRCCS-Azienda Ospedaliera Universitaria San Martino-IST, University of Genoa, Genoa, Italy*;
[5]*AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, France*;
[6]*Department of Anesthesiology, Critical Care, Emergency Medicine and Pain Therapy, Ziekenhuis Oost-Limburg, Genk, Belgium*;
[7]*Department of Surgery, Wexner Medical Center at The Ohio State University, OH, USA*

Summary

Hepatocellular carcinoma (HCC), in its very early stage, is heterogeneous both in terms of liver function (i.e., presence or absence of portal hypertension, model for end-stage liver disease score, Child-Pugh score 5 or 6, bilirubin level) and tumor characteristics (i.e., location, alpha-fetoprotein values, pathological features such as microvascular invasion, tumor grade and satellitosis).
Existing evidence in comparing different curative options for patients with very early HCC is poor due to small sample sizes and lack of solid subgroup analyses. Large observational studies are available, with the potential to identify effective interventions in different subgroup of patients and to discover which treatments work "in a real world setting".
These studies suggest some important treatment selection strategies in very early HCC patients. According to extent of liver resection, and liver function, percutaneous ablation or liver resection are the recommended first line therapies in these patients. Laparoscopic surgery (resection or ablation) is the preferable strategy when the tumor is in the surface of the liver or close to extra-hepatic organs.
Due to scarce donor resources and competition with patients at high transplant benefit (HCC patients unsuitable for non-transplant radical therapies and non-HCC patients with decompensated cirrhosis), transplantation is recommended only as second line therapy in patients with very early stage HCC in case of tumor recurrence or liver failure after ablation or liver resection.

Key point

Different curative therapeutic options are potentially available for these patients, such as liver resection, liver transplantation, and ablation.

Introduction

Liver cancer is the sixth most frequent cancer and the second most frequent cause of cancer related death worldwide [1]. The incidence and mortality of hepatocellular carcinoma (HCC) in 2008 was 65,000 and 60,240, respectively, in Europe compared with 21,000 and 18,400, respectively, in the United States (US). Of particular concern is that both the incidence and mortality of HCC are increasing worldwide. In fact, it is estimated that by 2020 the number of cases in Europe and the US will reach 78,000 and 27,000, respectively [2]. The prognostic classification of patients with HCC is complex, since any prognostic scheme has to account for both the background liver disease and the tumor itself [3]. The management of HCC has significantly improved over the last decade related to a better knowledge of the natural history, improvements in staging systems and treatment algorithms, as well as emerging therapeutic options [4]. One of the most reliable and widely adopted methods for staging HCC is the Barcelona Clinic Liver Cancer (BCLC) system, which stratifies patients according to the characteristics of the tumor, underlying liver disease and performance status [3–5]. According to this system, the presence of an asymptomatic single nodule $\leqslant$2 cm, in the absence of vascular invasion or extra-hepatic disease, and in the presence of well-compensated cirrhosis (Child-Pugh A) is defined as very early stage HCC (BCLC stage 0). In recent years, largely due to improved surveillance programs in the cirrhotic population, more patients are being diagnosed with very early HCC [5]. Although some of these patients may benefit from alcohol injection or transarterial chemoembolization (TACE), here we focus on the three treatment modalities considered to represent

the best potential curative options for patients diagnosed with very early HCC [6]: liver resection (LR), liver transplantation (LT), and radiofrequency ablation (RFA). In general, patients with very early HCC who are treated with any of these strategies can have excellent recurrence-free and overall survival outcomes compared with patients who have more advanced tumors.

In the last decade, the concept of "evidence based management" of patients with HCC has been introduced to define therapeutic strategies or algorithms derived from comparative studies evaluating treatment efficacy [6]. Following the traditional pyramid of evidence based medicine (EBM), the best evidence is based on data obtained from randomized clinical trials (RCTs) or meta-analyses of RCTs [7]. However, in the absence of RCTs, some treatment protocols have also been established based on the results of observational and cost-effectiveness studies [6]. The concept of EBM continues to change over recent years, however, and the quality of data should be considered only in light of a more dynamic EBM paradigm [7,8]. For example, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group has now replaced the traditional EBM pyramid and allows observational studies to be upgraded (or RCTs downgraded) along the evidence pyramid [7]. Moreover, systematic reviews are omitted from the pyramid (i.e., in the revised pyramid, systematic reviews are a lens through which evidence is viewed/applied) [7]. Along with these changes, many experts worldwide now strongly support the use of observational studies and evidence derived from "big data" [8,9] to develop and validate individual prognostic prediction and treatment decision tools at the individual patient level.

In this era of "precision medicine", therefore, a "personalized approach" to very early HCC should be based on not only the traditional EBM model, but also all the data from the literature that could be extracted for the individual patient setting. This way, the therapeutic decision could be made in the context of individual, patient-specific cases [8,9]. In light of this, we herein review data on the management of early HCC. Specifically, data derived from randomized and non-randomized comparative studies, prognostic studies, as well as simulation effectiveness studies were examined with the aim to define the optimal personalized treatment strategy for patients with very early HCC.

Comparative efficacy studies of patients with very early HCC undergoing curative therapies

Randomized clinical trials

There are only a few randomised control trials that investigate curative options for patients with HCC [10–15], and all focus solely on the comparison of LR *vs.* RFA. Among the six RCTs (Table 1), three studies demonstrated a superiority of LR over RFA in terms of overall survival, while the other three reported comparable results with either therapy. Of note, these trials were designed to detect relatively large differences in survival among patients with early HCC being treated by resection *vs.* ablation. In turn, these RCTs were likely underpowered and suffered from a small sample size to detect smaller differences in survival among the treatment groups. Moreover, enrolment criteria for these trials were heterogeneous in terms of tumor characteristics, liver function, and treatment procedures (i.e., RFA or microwave ablation were used in one trial, RFA plus TACE were used in another trial), thus making it difficult to interpret the data. The small sample size also made it difficult to examine subgroups to identify potential prognostic factors or identify whether one treatment might be superior to another (e.g., microwave *vs.* radiofrequency).

Another important limit was that all of these RCT studies were solely conducted in Asia/China, thereby limiting the generalization of the results to the rest of the world.

To mitigate some of the problems associated with these studies due to small sample size, meta-analyses of the RCT data have been performed [16]. In one such meta-analysis, Qi *et al.* reported that LR was superior to RFA in terms of recurrence-free and overall survival [16]. In contrast, LR had a higher incidence of post-operative complications compared with RFA [16]. A separate study by Wang *et al.* similarly noted that LR was superior to RFA among patients with very early HCC, however LR was associated with a higher morbidity [17]. Unfortunately, to date, there are no RCTs that directly compare LT with LR or RFA.

Retrospective matched comparisons

In addition to the handful of prospective trials, numerous retrospective studies that compared LR *vs.* RFA or *vs.* LT for HCC have been published [18–32]. Comparing the efficacy of different therapeutic modalities such as LT, LR, and RFA for HCC using retrospective data can be problematic. In particular, many of these studies suffer from selection bias and confounding by indication. Patients treated with RFA are usually older, have slightly worse liver function and most importantly, an increase in associated comorbidities (which contraindicate LR). In an attempt to simulate RCTs (i.e., comparative efficacy studies) and mitigate the inherent selection bias characteristic of retrospective studies, many investigators have adopted specific statistical techniques (i.e., case-matching, propensity score analysis, etc.) in an attempt to compare more homogeneous groups of patients [18–23]. Matching of cases can lead, however, to decreased sample size needed to create comparable groups of patients. In turn, this

Key point

A personalized approach to very early HCC incorporating the strong evidence derived from various data sources including comparative effectiveness studies (i.e., randomized clinical trials, retrospective matched comparisons, large observational studies, big data, etc.) is required to optimize the care of the patient with early stage HCC.
An example of a personalized approach to very early HCC based on the whole available evidence (not only randomized clinical trials) was provided at the end of this study.

* Corresponding author. Address: Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy, or Via Giustiniani, 2, 35128 Padova, Italy. Tel.: +39 3358247099.
E-mail address: alessandro.vitale@unipd.it (A. Vitale).