Research Article

EASL JOURNAL OF HEPATOLOGY

Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: A multicentre study

Alessandro Vitale[1], Patrizia Burra[1,*], Anna Chiara Frigo[2], Franco Trevisani[3], Fabio Farinati[1], Gaya Spolverato[1], Michael Volk[4], Edoardo G. Giannini[5], Francesca Ciccarese[6], Fabio Piscaglia[7], Gian Lodovico Rapaccini[8], Mariella Di Marco[9], Eugenio Caturelli[10], Marco Zoli[7], Franco Borzio[11], Giuseppe Cabibbo[12], Martina Felder[13], Antonio Gasbarrini[14], Rodolfo Sacco[15], Francesco Giuseppe Foschi[16], Gabriele Missale[17], Filomena Morisco[18], Gianluca Svegliati Baroni[19], Roberto Virdone[20], Umberto Cillo[1], for the Italian Liver Cancer (ITA.LI.CA) group

[1]*Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy;* [2]*Biostatistics Unit, University of Padua, Padua, Italy;* [3]*Department of Medical and Surgical Sciences, Division of Semeiotics, Alma Mater Studiorum – University of Bologna, Bologna, Italy;* [4]*Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, USA;* [5]*Department of Internal Medicine, Division of Gastroenterology, University of Genova, Genova, Italy;* [6]*Division of Surgery, San Marco Hospital, Zingonia, Italy;* [7]*Department of Gastroenterology and Internal Medicine, Division of Internal Medicine, Alma Mater Studiorum – University of Bologna, Bologna, Italy;* [8]*Division of Internal Medicine and Gastroenterology, Complesso Integrato Columbus, Università Cattolica del Sacro Cuore, Rome, Italy;* [9]*Division of Medicine, Bolognini Hospital, Seriate, Italy;* [10]*Division of Gastroenterology, Belcolle Hospital, Viterbo, Italy;* [11]*Department of Medicine, Division of Radiology, Fatebenefratelli Hospital, Milan, Italy;* [12]*Biomedical Department of Internal and Specialistic Medicine, Division of Gastroenterology, University of Palermo, Palermo, Italy;* [13]*Bolzano Regional Hospital, Division of Gastroenterology, Bolzano, Italy;* [14]*Division of Internal Medicine and Gastroenterology, Policlinico Gemelli, Università Cattolica del Sacro Cuore, Roma, Italy;* [15]*Division of Gastroenterology and Metabolic Diseases, University Hospital of Pisa, Pisa, Italy;* [16]*Department of Internal Medicine, Ospedale per gli Infermi di Faenza, Faenza, Italy;* [17]*Division of Infectious Diseases and Hepatology, University Hospital of Parma, Parma, Italy;* [18]*Department of Medicine and Surgery, Division of Gastroenterology, University of Naples, "Federico II", Naples, Italy;* [19]*Division of Gastroenterology, Polytechnic University of Marche, Ancona, Italy;* [20]*Biomedical Department of Internal and Specialistic Medicine, Division of Internal Medicine 2, Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy*

Background & Aims: The role of hepatic resection for hepatocellular carcinoma (HCC) in different Barcelona Clinic Liver Cancer (BCLC) stages is controversial. We aimed at measuring the survival benefit of resection *vs.* non-surgical-therapies in each BCLC stage.
Methods: Using the ITA.LI.CA database, we identified 2090 BCLC A, B, and C HCC patients observed between 2000 and 2012: 550 underwent resection, 1046 loco-regional therapy (LRT), and 494 best supportive care (BSC). A multivariate log-logistic model was chosen to predict median survival (MS) after resection *vs.* MS after LRT or BSC. The results were expressed as net survival benefit of resection: (MS resection – MS LRT)/MS BSC.
Results: After stratifying for BCLC stage, the median net survival benefit of resection over LRT was: BCLC 0 = 62% (40%, 82%), A = 45% (13%, 65%), B = 46% (9%, 76%), C = −16% (−55%, 33%). Model for end-stage liver disease (MELD) score >9, Child B class, and performance status (PST) = 2 were the main risk factors for liver resection. 1181 Child A patients (57%) with MELD ⩽9 and PST <2 had always a large positive net survival benefit of resection over LRT, independently of BCLC stage: BCLC 0 = 64% (44%, 85%), A = 59% (45%, 74%), B = 71% (52%, 90%), C = 56% (36%, 78%). Among the 909 (43%) patients with at least one risk factor (MELD >9 or PST = 2 or Child B class), resection did not prove any survival benefit over LRT.
Conclusions: Resection could result in survival benefit over LRT for HCC patients regardless of their BCLC stage, provided that liver dysfunction (Child B or MELD >9) and PST >1 are absent.

Keywords: Hepatocellular carcinoma; Cirrhosis; Liver resection; Loco-regional therapies; Best supportive care; Survival benefit.
Received 2 May 2014; received in revised form 14 October 2014; accepted 22 October 2014; available online 30 October 2014
* Corresponding author. Address: Multivisceral Transplant Unit, Padova University Hospital, via Giustiniani 2, 35128 Padova, Italy. Tel.: +39 3473464494; fax: +39 049/821 1816.
E-mail address: burra@unipd.it (P. Burra).
Abbreviations: HCC, hepatocellular carcinoma; BCLB, Barcelona Clinic Liver Cancer; LRT, loco-regional therapy; BCT, best supportive care; MS, median survival; PST, performance status; ECOG, Easter Cooperative Oncology Group; CRPH, clinically relevant portal hypertension; IQR, interquartile range; HCV, hepatitis C virus.

Introduction

Prognostic assessment and treatment strategy for patients with hepatocellular carcinoma (HCC) and liver cirrhosis are extremely

Cancer

complex due to the simultaneous presence of two distinct diseases [1].

The Barcelona Clinic Liver Cancer (BCLC) classification is the only HCC staging system accounting for tumor burden, liver function, general conditions (as expression of symptomatic tumor), and able to guide treatment decisions [1]. The main limit of BCLC is the great prognostic heterogeneity within each stage [2]. In the last years, some authors suggested a new model for prognostic prediction in HCC patients [3]: the model to estimate survival in ambulatory HCC patients score (MESIAH). The MESIAH score showed a significantly higher predictive power than BCLC [3], but its main limit is that it does not help clinicians in treatment decision.

Although the BCLC classification is directly translated into a strict treatment algorithm, assigning different therapies to different subgroups of patients [1], there is a great overlap between treatments and prognostic stages in daily clinical practice. Recent studies demonstrated that radical therapies, such as hepatic resection and liver transplantation, are commonly preferred and have a great benefit even for intermediate and advanced HCC [4,5], while locoregional therapies, such as radiofrequency (RF) percutaneous ablation and transarterial chemoembolization (TACE), are largely used as first-line therapy even for early HCC [6].

With the exception of liver transplantation, which is greatly limited by scarce donor resources [5], liver resection is considered the best oncological treatment for HCC [4].

Only few randomized control trials, comparing resection to percutaneous ablation, in very selected subgroups of patients, have been published until now [7]. These studies are often underpowered and propose percutaneous ablation as an alternative to resection in BCLC 0 HCC patients [1,8].

There is a lack of well-designed large studies comparing resection *vs.* the whole span of therapeutic alternatives for each BCLC stage. Moreover, while comparing resection and other therapies, the natural history of the disease should be taken into account, to determine the actual benefit/harm ratio of each therapy.

All this considered, we aimed at comparing the net survival benefit of resection over non-surgical loco-regional therapies (LRT) and best supportive care (BSC) in a large cohort of HCC patients with different BCLC stages.

Materials and methods

Patient demographic and clinical data

A total of 2686 patients, undergoing surgical or non-surgical treatment for HCC, were identified between 2000 and 2012 in institutions participating in the Italian Liver Cancer (ITA.LI.CA.) database. Patients with BCLC stage D (n = 385), presence of extrahepatic metastasis (n = 114) and treated with liver transplantation (n = 77) were excluded from the study. Since only 40 patients received sorafenib (<2% of the entire cohort), these patients were also excluded from the analysis. The study group finally consisted of 2090 patients.

We considered three main therapeutic subgroups. Firstly, we selected all patients undergoing liver resection (resection group, n = 550) and we followed them from the time of resection onwards. These patients were considered in the resection group even if they underwent other HCC non-surgical therapies. Then, we selected patients undergoing at least one LRT such as RF or TACE (LRT group, n = 1046) and we followed them from the time of first LRT onwards, independently of other non-surgical treatment received during their follow-up. The remnant patients were considered in the BSC group (n = 494).

Standard patient demographic and clinicopathological data were collected, including age, sex, co-morbidities, Easter Cooperative Oncology Group (ECOG) performance status (PST), general symptoms, modality of HCC and cirrhosis diagnosis (biopsy/surgical specimen or unequivocal clinical and radiological findings), serological parameters (sodium, bilirubin, albumin, INR, creatinine, platelet count, alfa-fetoprotein (AFP) levels), Child Pugh class, clinically relevant portal hypertension (CRPH) and BCLC stage. Tumor characteristics were also collected, including tumor location, size, number, and vascular invasion.

CRPH diagnosis was based on unequivocal clinical signs (gastroesophageal varices, ascites, splenomegaly with a platelet count of less than 100,000/ml), since hepatic venous pressure gradients were not determined [1].

The BCLC classification was used to stratify the study population in different prognostic stages, after the adoption of the following changes: since recent evidence has reassessed the role of PST in the BCLC classification [9], patients with PST = 1 and without macroscopic vascular invasion were included in BCLC stage B. The definition of early HCC according to the BCLC classification is still debated (i.e. early HCC is single nodule of any size when the tumor is considered resectable, while it is a single nodule smaller than 5 cm when the tumor is considered unresectable); therefore, we added a separate subgroup of patients (named stage AB) that included patients with a single nodule larger than 5 cm without vascular invasion, Child Pugh A-B cirrhosis, and PST 0 or 1 [1].

According to tumor characteristics, liver functional status, and patient will, several therapeutic strategies were used, such as resection, percutaneous tumor ablation, transarterial LRT, systemic therapy and BSC.

Statistical analysis

Qualitative data were described by frequency and percentage. Quantitative data were described by median (interquartile range (IQR)). In the comparison among different subgroups, quantitative variables were compared using Student's *t* or Wilcoxon Rank Sums tests, and categorical variables using χ^2 or Fisher's exact tests, as appropriate. Length of follow-up and survival are expressed as medians (IQR). Overall survival was calculated from the baseline visit until death from any cause or latest follow-up. Survival curves were estimated using the Kaplan-Meier method, whereas the statistical significance between survival curves was tested by the Log-Rank test.

We tested several multivariate survival models (the semi-parametric Cox model, and parametric exponential, log-normal, Weibull, and log-logistic models) including the following variables: patient-related covariates (age, and PST), liver function-related (MELD score, Child Pugh class, CRPH), and tumor-related (diameter, number of nodules, AFP values, and macroscopic vascular invasion). The selection of these variables was based on recent literature reports [1,2,4,5,8]. Treatment (resection *vs.* LRT *vs.* BSC) was used as stratifying covariate.

The log-logistic model was finally chosen among semi-parametric and parametric ones since it showed the lowest Akaike Information Criterion (AIC) and the highest Harrell C-index values [10].

This multivariate survival model was used to investigate the impact of patient-, liver-, and tumor-related variables on survival after each treatment. To overcome biases, owing to the different distribution of covariates among patients undergoing resection and those undergoing LRT or BSC, we calculated three individual median survival predictions – after resection, after LRT therapies or after BSC – independently of the therapy received. Subgroup analyses were then performed based on BCLC staging, Child Pugh class, MELD score, and presence of CRPH. Since MELD score in HCC patients undergoing loco-regional therapies is mainly used as dichotomous variable, MELD >9 was used in the subgroup analysis [11]. To weight the benefit/harm ratio of therapy in each patient, we calculated the net benefit of resection over LRT with the following formula: (median survival with resection – median survival with LRT)/median survival with BSC. The net benefit of resection over LRT represents a simple novel endpoint based on the commonly used concept of survival benefit (expressed as gain in survived months) adjusted for the median survival of patients not receiving any anti-cancer therapy (natural history of the disease). This measure gives an estimation of the net proportion (%) of survival in months gained or lost using resection instead of LRT in each patient. Net benefit results were presented as medians (interquartile range).

A boosting forest tree method (partition modelling) was finally used to measure the contribution of each covariate to resection net benefit over LRT [12]. Partition trees were constructed using a training set (corresponding to 70% of the entire cohort) and a validation set (corresponding to 30% of the entire cohort) and the final model was that with the highest R square, in both training and validation sets. Cox model results were reported as hazard ratios (95% confidence interval (95% CI)) estimates together with corresponding *p* values.

A further log-logistic multivariate model was performed including the abovementioned covariates, but splitting the LRT group in those undergoing RFA ± TACE and those undergoing TACE alone. In this way, we were able to calculate individual survival predictions for each of the 2090 patients enrolled after four treatment procedures (resection *vs.* RFA *vs.* TACE *vs.* BSC).