Title Page

Title: Albumin-Bilirubin Grade Predicts The Outcomes Of Liver Resection Versus Radiofrequency Ablation For Very Early/Early Stage Of Hepatocellular Carcinoma

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Short title: **Albumin-Bilirubin Grade Predicts Outcomes of Liver Resection Versus**

Radiofrequency Ablation For Early Hepatocellular Carcinoma

Abstract

Background and Purpose

Whether liver resection or ablation should be the first-line treatment for very early/early hepatocellular carcinoma (HCC) in patients who are candidates for both remains controversial. The aim of this study was to determine if the newly-developed Albumin-Bilirubin (ALBI) grade might help in treatment selections and to evaluate the survival of patients treated with liver resection and radiofrequency ablation (RFA).

Methods

Patients with BCLC stage 0/A HCC who were treated with curative liver resection and RFA from 2003 to 2013 were included. Baseline clinical and laboratory parameters were retrieved and reviewed from the hospital database. Liver function and its impact on survival was assessed by the ALBI score. Overall and disease-free survivals were compared between the two groups.

Results

488 patients underwent liver resection (n = 318) and RFA (n=170) for BCLC stage 0/A HCC during the study period. Liver resection offered superior survival to RFA in patients with BCLC stage 0/A HCC in the whole cohort. After propensity score matching, liver resection offered superior overall survival and disease-free survival to RFA in patients with ALBI grade 1 (P=0.0002 and P<0.0001 respectively). In contrast, there were no significant differences in overall survival and disease-free survival between liver resection and RFA in patients with ALBI grade 2 (P=0.7119 and 0.3266, respectively).

Conclusions

Liver resection offered superior survival to RFA in patients with BCLC stage 0/A HCC. The

ALBI grade could identify those patients with worse liver function who did not gain any

survival advantage from curative liver resection.

Introduction

The clinical outcome of patients with hepatocellular carcinoma (HCC) depends on not only tumour burden but also hepatic function, performance status and treatment modality. Among more than 10 different staging systems for HCC, the Barcelona Clinic Liver Cancer (BCLC) system is currently the most widely accepted staging system to provide prognostic information and, simultaneously, guide therapeutic options.[1-3] It is the only staging system for HCC endorsed by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL).[4, 5] Curative treatments, including surgical resection, transplantation and ablation, are recommended for patients with very early/early stage (BCLC 0/A) disease.[5 6] Despite being an effective treatment which offers good long-term survival, the transplantation option is limited by organ shortage, especially in Asian-Pacific countries.[7] Liver resection and ablation are therefore the mainstay of curative therapeutic options in Asian-Pacific countries.[8]

Liver resection is recommended for patients with BCLC stage 0 disease (single tumour smaller than 2 cm and Child-Pugh grade A) and a subset of BCLC stage A disease (a single tumour without portal hypertension or hyperbilirubinemia). On the other hand, patients with another subset of BCLC stage A disease (portal hypertension, hyperbilirubinemia or multiple tumour nodules) are recommended for ablation.[5, 6] Recently, the BCLC group has suggested that ablation should be the first-line treatment for BCLC stage 0 disease because case-control and modeling studies show that ablation is comparably effective and more cost-effective than liver resection at this early stage HCC.[6, 9]

The aim of the present study was to evaluated the extent to which the newly developed Albumin-Bilirubin (ALBI) grade might help in patient selection for liver resection or ablation. We also evaluate the survival of patients who were treated with liver resection or radiofrequency ablation (RFA).

Methods and Materials

Patients

This retrospective cohort recruited patients who received potentially curative treatment (liver resection and RFA) for primary HCC from January 2003 to December 2013 at the Prince of Wales Hospital, Hong Kong.

The study was approved by the institutional review board. Baseline clinical and laboratory parameters were retrieved and reviewed from the hospital database. All parameters investigated were measured within 1 week before treatment. The ALBI score was computed by the formula, $-0.085\times$(albumin g/l) $+ 0.66\times$log(bilirubin µmol/l). Patients were stratified into 3 groups according to previously described cut-offs resulting in 3 grades: ALBI grade 1 (≤-2.60), grade 2 (>-2.60 to -1.39) and grade 3 (>-1.39). [10]

Portal hypertension was defined according to AASLD/EASL guidelines as the presence of esophageal varices or thrombocytopenia (platelet count $<100\times10^9$/l) associated with splenomegaly.[5] The blood tests, except viral serology, were taken within 1 week before treatment. All patients were staged according to the BCLC, CLIP and CUPI systems.[11-13] Only patients with BCLC stage 0/A disease were included. Among BCLC stage A, patients were further classified into A1 (a single tumour with Child-Pugh grade A, no portal hypertension and normal serum bilirubin), A2 (a single tumour with Child-Pugh grade A, portal hypertension and normal serum bilirubin), A3 (a single tumour with Child-Pugh grade A, portal hypertension and hyperbilirubinemia) and A4 (2 or 3 tumours less than 3 cm, Child-Pugh grade A or B).

After treatment, all patients were followed up according to institutional practice including serum alpha-fetoprotein (AFP) measurement at every visit and ultrasound or contrast

computed tomography every 6 to 12 months. The duration of follow-up was measured from the date of operation to the date of the last follow-up before we analyzed the data or the date of death. Overall survival was measured from the time of liver resection to the time of HCC-related death or last follow-up if death had not occurred. Disease-free survival was measured from the time of liver resection to the time of radiological evidence of tumour relapse.

Statistical analyses

Continuous variables were expressed in mean ± standard deviation (SD) or median with interquartile range (IQR). Comparison between groups was analyzed by chi-square test or Fisher's exact test for categorical variables, and Student's t test or Mann-Whitney test for continuous variables as appropriate. Correlation was evaluated by the Spearman correlation test. The Kaplan-Meier method was used to estimate the survival rates for different groups. The equivalences of the survival curves were tested by log-rank statistics. The Cox proportional hazards model was employed for univariate and multivariate survival analyses. Propensity score matching analysis in a 1:1 ratio was employed to minimize the confounding prognostic factors affecting the effectiveness of liver resection and RFA. All statistical analyses were performed in R version 3.02 (R Foundation for Statistical Computing, Vienna, Austria). R package (MatchIt 3.01) was used for propensity score matching. A 2-tailed *P*-value <0.05 was regarded as statistically significant.

Results

Comparison of clinical characteristics between liver resection and RFA

A total of 768 patients underwent liver resection or RFA for hepatic tumour during the study period. Two hundred and eighty patients were excluded because the HCC was recurrent (n=85), cholangiocarcinoma/combined HCC-cholangiocarcinoma (n=13), metastatic tumour

(n=25), HCC with stage beyond BCLC 0/A (n=140) and incomplete clinical/laboratory data (n=17). The remaining 488 patients were all eligible for the study: 318 and 170 patients received liver resection and RFA, respectively. The majority of patients (80.3%) had chronic hepatitis B virus (HBV) infection. Seventy-five (15.4%) were graded as having BCLC 0 disease, whereas 330 (67.6%) and 83 (17.0%) had BCLC A1 and A2-4 disease, respectively. Patients undergoing liver resection were more often male (88.1% vs. 78.8%), of younger age, had higher frequency of HBV infection (83.6% vs. 74.1%), a non-cirrhotic background (58.8% vs. 88.2%), larger tumour size, spontaneous rupture (6.6% vs. 0.6%) and BCLC stage A1 (76.1% vs. 51.8%). These surgically treated patients had better liver function as reflected by liver biochemistries, platelet count, INR, Child-Pugh grade, ALBI grade and MELD score. Table 1 summarizes the clinical characteristics of the patients.

Comparison of clinical outcomes between liver resection and RFA
The median duration of follow-up was 48.4 (IQR 32.6-80.8) months. The 1-, 3- and 5- year overall survival rates were 97%, 88% and 80% versus 93%, 75% and 55% for patients receiving liver resection and RFA, respectively. The 1-, 3- and 5- year disease-free survival rates were 83%, 66% and 56% versus 66%, 29% and 19% for patient undergoing liver resection and RFA, respectively. Liver resection provided better overall and disease-free survival than RFA (both P<0.001) (Fig. 1A, B). In subgroup analyses, liver resection achieved more favourable overall and disease-free survival than RFA among patients with BCLC stage 0, A1 and A2-4 diseases (all P<0.001).

Propensity score matching analysis was used to minimize bias and confounding factors in patient selection and generate 1:1 matched pairs of patients for comparison of efficacy between liver resection and RFA. Patients with multifocal tumours were excluded. After

propensity score matching, a subset of 242 patients (121 patients in each treatment group) was selected. Baseline characteristics of these patients were well matched except serum albumin and bilirubin levels, INR and ALBI grade (Table 2). The 1-, 3- and 5- year overall survival rates were 98%, 90% and 81% versus 94%, 76% and 60% for patients receiving liver resection and RFA, respectively. The 1-, 3- and 5- year disease-free survival rates were 85%, 63% and 51% versus 66%, 30% and 19% for patients undergoing liver resection and RFA, respectively. Liver resection still offered superior overall and disease-free survival to RFA (P=0.0002 and P<0.0001 respectively). (Fig. 2 A,B)

Impact of ALBI grade on the selection of patients for liver resection or RFA

In subgroup analyses of patients after propensity score matching (supplementary table 1 and 2), insignificant differences in overall and disease-free survival between liver resection and RFA were observed among patients with ALBI grade 2, whereas liver resection still provided superior survival benefit than RFA in patients with ALBI grade 1 (Fig. 3). The ALBI grade 2 would thus appear to identify those patients with worse liver function who did not gain any survival advantage from curative liver resection.

Discussion

We analyzed a retrospective cohort of 488 patients receiving potentially curative liver resection or RFA for HCC with a median follow-up time of more than 4 years. In the initial analysis of unselected patients and the subsequent analysis after propensity score matching, liver resection was associated with better overall and disease-free survival than RFA. Even among patients with BCLC stage 0 and A2-4 diseases, liver resection still offered survival benefit compared with RFA. However, in those patients with poorer liver function (ALBI grade 2/3), survival advantage of liver resection diminished. The ALBI grade was a potential

decision tool for clinicians to choose between liver resection and RFA in patients with very early/early stage HCC.

Apart from tumour-related factors, the overall survival of patients with HCC was also determined by the underlying liver function. It is generally accepted that patients with good liver function should undergo liver resection while patients with poor liver function should receive RFA.[8] However, there is no ideal classification to define the liver function. Even the presence of portal hypertension is not regarded as an absolute contraindication for liver resection in patients with compensated cirrhosis. Liver function assessment in subgroups of BCLC stage A includes portal hypertension, hyperbilirubinemia and Child-Pugh grade.[6] However, all these parameters (portal hypertension, hyperbilirubinemia and Child-Pugh grade) have failed to identify those patients who would not benefit from curative liver resection.

In the present study, we evaluated the use of ALBI grade to select patients for liver resection or RFA. At the initial analysis of the whole cohort, we found that liver resection was associated with a better overall survival when compared with RFA. This is most likely because the liver resection group was associated with larger tumour, more BCLC stage A tumour, and younger patients with better liver function. As this may introduce potential bias in the subsequent analysis, we therefore conducted a propensity score matching analysis to minimize the potential inherent confounding bias. In the propensity model, the two groups were balanced in terms of tumour factors, as well as Child-Pugh and MELD score. Liver resection still offered superior overall and disease-free survival to RFA (both P<0.001). Despite the propensity score matching and comparable Child-Pugh grade and MELD score there remained statistically significant differences in the INR, serum albumin and bilirubin levels as well as the ALBI grade. However, these differences were all very small and unlikely to be of *clinical* significance.

Nevertheless, our results support the contention that there exists distinct subgroups of patients with different liver function within the so-called "good liver function" group, as categorized by the commonly used grading system for liver function. Recently, Johnson et al reported a new model, the albumin-bilirubin (ALBI) score, for assessing liver function in patients with HCC.[10, 14] Subsequently, we showed that the ALBI score can identify two distinct groups among Child's A patients undergoing liver resection or ablative therapies with curative intent and the ALBI score can significantly affect the long term survival. Here we have performed subgroup analysis according to the ALBI grade and have found that liver resection still provides better overall survival in the group with better liver function i.e. ALBI grade 1. In contrast, for patients with ALBI grade 2 or 3, there was no significant difference in terms of overall and disease free survival between liver resection and RFA group. The ALBI grade can therefore be used to identify those patients with worse liver function who may not gain survival advantage from curative liver resection.

Whether liver resection or ablation should be the first-line treatment for very early/early HCC remains hotly debated. Recently, the BCLC group proposed a refinement of the decision-making strategy, especially for patients with very early stage HCC [6, 15] in which liver resection is no longer the only first-line treatment. Ablation is suggested to be non-inferior and more cost-effective for patients with very early stage HCC.[9, 16-18] Our current study has shown that liver resection provides survival benefit to those patients with BCLC stage 0 HCC compared to RFA, thereby questioning the current opinion that RFA should be the first-line treatment for very early HCC. In a Japanese nationwide survey of 28,510 patients with HCC, Hasegawa et al showed that liver resection offered better overall and recurrence-free survivals than RFA in a subgroup of 2,026 patients with a single HCC of <2 cm and good liver function.[19] Regarding BCLC stage A, Kao et al analyzed 635 patients with BCLC A2-4 HCC and showed that liver resection offered a better survival than RFA.[20] These findings were

similar to our current study. In fact, more stress should be put on the background liver function when determining the the first-line treatment for early HCC and a more thoroughgoing classification of liver function is needed. Our study showed that the application of ALBI grade can help determining the outcome of RFA vs liver resection in early HCC.

The limitations of this study include retrospective nature, lack of pre-ablation biopsy in the RFA group, long study period and the difference in background demographics between liver resection and RFA groups. We tried to minimize the potential confounders by using the propensity score-matching method. Unfortunately, the two treatment groups still had a significant difference in background liver function factors. We therefore performed subgroup analysis on patients with different liver function subgroups in order to make the two groups more comparable. A prospective randomized study on patients with borderline liver function will be needed to eliminate the selection bias.

Conclusion:

In patients with early BCLC stage HCC, the ALBI grade could identify those patients with worse liver function who did not gain any survival advantage from curative liver resection compared to ablation. Liver resection still offered superior overall and disease-free survival to RFA, except for patients with ALBI grade 2.

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Figure legends

Figure 1: Kaplan-Meier survival plots comparing (A) overall survival and (B) disease-free survival among patients undergoing liver resection and RFA.

Figure 2: Kaplan-Meier survival plots comparing (A) overall survival and (B) disease-free survival among patients undergoing liver resection and RFA after propensity score matching.

Figure 3: Kaplan-Meier survival plots comparing overall survival and disease-free survival of patients undergoing liver resection and RFA after propensity score matching in subgroups of (A, B) ALBI grade 1, and (C, D) ALBI grade 2.