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Observational Study

Evaluating the best treatment for multifocal hepatocellular carcinoma: a propensity score-matched analysis

Best treatment for multifocal HCC

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is a common tumor often diagnosed in a multifocal presentation. Patients with multifocal HCC represent a heterogeneous group. Although Trans-Arterial ChemoEmbolization (TACE) is the most frequently employed treatment for these patients, previous data suggested that liver resection (LR) could be a safe and effective procedure.

AIM

To compare LR and TACE in patients with multifocal HCC in terms of procedure-related morbidity and oncologic outcomes.

METHODS

All the consecutive patients with multifocal HCC who underwent the first procedure of LR or TACE between May 2011 and March 2021 were enrolled. The decision to perform surgery or TACE was made after multidisciplinary team evaluation. Only patients in Child-Pugh class A or B7 and stage B according to the Barcelona Clinic Liver Cancer staging system, without severe portal hypertension, vascular invasion, or extrahepatic spread were included in the final analysis. Propensity score matching was used to adjust the baseline differences between patients undergoing LR and the TACE group (number and diameter of lesions, presence of cirrhosis, AFP values, and MELD score). The Kaplan-Meier method was used to estimate overall and disease-free survival (OS and DFS). The outcomes of LR and TACE were compared using the log-rank test.

RESULTS

After matching, 30 patients were eligible for the final analysis, 15 for each group. Morbidity rates were 42.9% and 40% for LR and TACE, respectively ($p=0.876$). Median OS was not different comparing LR and TACE (53 vs. 18 mo, $P = 0.312$) while DFS was significantly longer with LR (19 vs. 0 mo, $p=0.0001$). Subgroup analysis

showed that patients in the ITA.LI.CA B2 stage, with AFP levels lower than 400 ng/mL, less than 3 Lesions, and lesions bigger than 41 mm benefited more from LR in terms of DFS. Patients classified as ITA.LI.CA B3, with AFP levels higher than 400 ng/mL, and more than 3 Lesions appeared to receive more benefit from TACE in terms of OS.

CONCLUSION

In a small cohort of patients with multifocal HCC, LR confers longer DFS compared with TACE, with similar OS and post-procedural morbidity.

Key Words: Hepatocellular carcinoma; Multifocal HCC; Liver resection; Trans-arterial chemoembolization; Guidelines; Liver tumor management

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Core Tip: Hepatocellular carcinoma (HCC) is a leading cause of death often presenting in a multifocal form. Trans-Arterial ChemoEmbolization (TACE) is the most frequently employed treatment in this category of patients. Since patients with multifocal HCC are a heterogeneous group, previous data suggested that liver resection (LR) could be a safe and effective procedure. A propensity score-matched analysis was performed to compare LR and TACE in terms of post-procedure morbidity and survival. Despite the limited number of patients, LR conferred longer disease-free survival with similar overall survival compared to TACE. Subgroup analyses identified the patients benefiting more from a specific treatment.

INTRODUCTION

³ Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer worldwide, accounting for approximately 90% of cases^[1]. HCC incidence has grown over the last two decades, with more than 900.000 new cases per year. Moreover, it ⁵ is expected to further increase in the next few years, due to the exponential growth in nonalcoholic fatty liver disease^[2]. Despite the improvements in diagnosis and management, HCC is detected in a multinodular form in 35-40% of cases^[3,4] with a reported 5-years survival rate of 19.5%^[5].

¹ Over the years, various staging systems have been proposed to overcome the limitations of the tumor-node-metastasis (TNM) system, which only considers tumor burden^[6]. Currently, the Barcelona Clinic Liver Classification (BCLC) is one of the most widely used staging systems for HCC, and ⁸ includes variables related to tumor status, liver function, and performance status, and recommends one or more specific treatment modalities for each disease stage ^[7].

Several efforts have been further made to deal with the heterogeneity of the BCLC-B or intermediate stage of this classification, and the Italian Liver Cancer (ITA.LI.CA) group recently proposed a new staging system and prognostic score, based on the BCLC staging system, which includes tumor burden, liver function, and other patient-related variables, providing a subclassification of this stage^[8].

Surgical treatments, including liver resection and liver transplantation, are considered the best choice in terms of survival and quality of life, whenever feasible. Conversely, Trans-Arterial ChemoEmbolization (TACE) is not a curative treatment and should be used for patients with well-defined, multifocal HCC, a preserved portal flow, and adequate liver function and performance status. TACE outcomes are poor and several lines of information about the safety and effectiveness of surgery in selected patients for whom TACE is usually recommended have been reported^[9-12]. Finally, liver transplantation could also have a central role for these patients, especially after successful downstaging^[7], but organ shortage is a problem difficult to overcome, and this could lead to high drop-out rates.

Whether selected patients with multinodular HCC may benefit from surgery rather than from TACE remains debated.

In this study, a propensity-score matching analysis was used to compare procedure-related morbidity and oncological outcomes in multifocal HCC patients classified as BCLC-B who underwent LR or TACE to determine if one treatment should be given priority over the other.

MATERIALS AND METHODS

Study Design and Patients

A retrospective analysis of all patients with multifocal HCC who have undergone surgical resection or TACE as first-line treatment between May 2011 and March 2021 was conducted. Exclusion criteria were age <18 years, Child-Pugh score >7, vascular invasion or extrahepatic spread, and a hepatic venous pressure gradient (HVPG) higher than 15 mmHg. HCC was diagnosed histologically or through imaging techniques (magnetic resonance imaging and/or triphasic computed tomography) according to the version of EASL guidelines available at the time of diagnosis. Age, comorbidities, blood chemistries, tumor number and size (major radiological diameter of the largest lesion from the last available imaging test), ITA.LI.CA. stage and Eastern Cooperative Oncology Group performance status (ECOG PS) were evaluated before LR or TACE.

The decision to perform surgery or TACE was taken by the local multidisciplinary team who considered patients and tumor features, including lesion location and relation with the pedicles, and the volume of the future liver remnant. Intraoperative ultrasound sonography (IOUS) was routinely performed during surgery to confirm preoperative planning. Whenever feasible, anatomic resections were preferred. Both conventional, lipiodol-based, TACE and TACE with drug-eluting beads were included. The patients' response was evaluated one month after the procedure with a Computed Tomography (CT) scan. For patients who did not achieve a complete response, data and the effectiveness of each subsequent TACE were also recorded.

Post-treatment morbidity was evaluated according to the Clavien-Dindo classification^[13].

All patients underwent a standardized follow-up program that included blood tests with alpha-fetoprotein (AFP), and a triple phase-contrast enhanced CT scan every three months for the first year, and then biannually for 5 years after surgery (starting 3 mo after surgery or 1 mo after TACE). Recurrence was diagnosed in the case of radiological evidence of HCC.

Statistical analysis

Quantitative data were expressed as mean \pm standard deviation (SD) or median and range, as appropriate. Qualitative data are reported as absolute and relative frequencies. To assess the difference in quantitative variables between treatment groups t-test, Satterthwait's test or Mann-Whitney test were used according to Shapiro-Wilk test and F-Test, respectively, for normality distribution and homoscedasticity. To verify the association between qualitative variables and treatment groups, the chi-square test or Fisher's test were used as appropriate.

To compare similar treatment groups for known prognostic factors (AFP values as a dichotomous variable with a cut-off set at 400 ng/dL, presence or not of cirrhosis, Child-Pugh and MELD score, number, and diameter of lesions) the PSM method was used. An AFP value $>400\text{ng/mL}$ was considered a prognostic factors of poor outcome, as suggested by recent guidelines^[14]. A diagnosis of cirrhosis was established based on the presence of one or more of the following: compatible histology, imaging showing compatible hepatic morphology, liver stiffness $>15\text{kPa}$ by vibration-controlled transient elastography, clinical or endoscopic or imaging signs of portal hypertension. The propensity score was calculated by a multiple logistic regression model with a backward selection method. The nearest neighbor method was used to match the two groups with a 1:1 ratio.

Overall survival (OS) was calculated from the date of the first treatment to death of any cause or the last follow-up. Since TACE patients could need more than one treatment to

achieve a complete response, disease-free survival (DFS) was calculated from the date of the effective treatment to the date of first radiological recurrence. Survival was expressed as median and 95% Confidence Interval (95%CI).

To evaluate the difference in OS and DFS between groups, the Kaplan-Meier curve method and the Log-rank test were used.

Subgroup survival analyses were performed comparing the results of the different treatment modalities and stratifying patients by the different grades of the ITA.LI.CA classification, the AFP levels (using 400 ng/mL as cut-off), and by the different number and size of HCC (dividing them into two groups using the median value as a cut-off). A p-value <0.05 was considered statistically significant.

All the analyses were conducted using SAS, version 9.2 (SAS Corporation, Cary, NC), and revised by a biomedical statistician.

RESULTS

Patient clinical characteristics

A total of 50 patients with multifocal HCC were included in the study, 25 underwent LR while 25 underwent TACE. The distribution of the factors used for the PSM in the general population is reported in **Table 1**. All patients belonging to the TACE group had cirrhosis, whereas, among those who underwent LR, cirrhosis was absent in 36% of cases ($P = 0.002$). The number of lesions was higher among patients who underwent TACE, whereas resected patients had usually bigger tumors. No significant differences were found between the two groups regarding Child-Pugh score and alpha-fetoprotein values. In contrast, MELD tended to be higher in patients who underwent TACE compared with the resected ones. After the PSM, only 30 patients were eligible for the final analysis, 15 for each subgroup.

The general baseline clinical characteristics are shown in **Table 2** while data about liver function aspects, tumor characteristics, and patient distribution according to the Up-to-7 criteria^[15] and ITA.LI.CA classification are reported in **Table 3**. No statistical differences were found in baseline characteristics. The median age was 69 years, and

more than two-thirds of patients were male. The most common cause of the liver disease was viral hepatitis, followed by NASH and alcohol use disorder. Lower platelet counts and higher bilirubin levels were present in the TACE group. There was also a trend towards a higher presence of varices in the TACE group. No significant differences across the Up-to-7 criteria in or out and ITA.LI.CA. staging distribution was found.

Postoperative short-term outcomes and survival analysis

Patients of the TACE group received a significantly higher number of treatments (**Table 5**, $P = 0.001$). Post-procedure complications were not significantly different between patients who underwent LR and TACE (**Table 4**). In the surgery group, complications classified as grade 1 and 2 of Clavien-Dindo included fever, pneumonia, or need for blood transfusion. Only one patient developed a bile leak classified as grade 3 according to Clavien-Dindo and was treated with percutaneous drainage.

In the TACE group, complications classified as grade 1 and 2 of Clavien-Dindo included mostly transient alterations of liver biochemistries and/or fever. Only one patient developed transient liver failure and required percutaneous drainage because of an abdominal effusion.

The median follow-up was 19 mo (range 3-62). The estimated global median OS and DFS were 31 and 5 mo, respectively (**Figure 1**). There were no significant differences in terms of OS and DFS for the global population stratified by the ITA.LI.CA classification. Median OS for B1, B2, and B3 groups were 31, 31, and 14 mo, respectively ($P = 0.803$), while median DFS for B1, B2, and B3 groups were 5, 14.5, and 1.5 mo, respectively ($P = 0.516$).

No differences in OS were observed comparing the two treatment groups. A significantly longer DFS was found in resected patients compared with those undergoing TACE (19 vs. 0 mo respectively, $P = 0.0001$) (**Figure 2**).

Subgroup analyses were also performed to evaluate the possible differences in OS or DFS according to alpha-fetoprotein values, size, and lesion number, Up-to-7 criteria, and ITA.LI.CA staging between each treatment group.

A significant difference was found in both OS and DFS ($p < 0.0001$ and $P = 0.0001$, respectively, **Figure 3A**) with patients presenting with lower levels of AFP showing the best prognosis, in both treatment groups. Furthermore, patients with AFP levels higher than 400 ng/mL and receiving surgery showed a poor OS compared to the TACE group.

No difference in OS were found comparing treatment modalities in patients stratified according to the Up-to-7 criteria. On the contrary, DFS was higher for LR group ($P = 0.002$) (**Figure 3B**).

Results of different treatment modalities for patients stratified by the ITA.LI.CA classification are reported in **Figure 3C**. Similar to the previous analysis, a significant difference was found in both OS and DFS ($P = 0.047$ and $P = 0.001$, respectively) with patients classified as B2 and receiving resection, showing the best prognosis, while those classified as B3 and receiving resection had the worst prognosis.

Although no significant differences were found in OS, the 4 patients with more than 3 Lesions receiving TACE showed a 1, 3, and 5-year OS of 75%, 25%, and 25%, respectively. Among the surgery group, patients with less than three lesions had a significantly higher DFS compared with those with three or more lesions ($P = 0.001$). Conversely, no differences in terms of OS and DFS were found in the TACE group stratifying for the number of lesions (**Figure 3D**). Similar results were obtained when the treatment groups were stratified according to the size of the bigger lesion (**Figure 3E**). Patients with smaller lesions obtained a better DFS among the surgery group.

DISCUSSION

HCC is the most common primary liver tumor. Despite recent advantages in terms of follow-up, early diagnosis, and treatment, a considerable percentage of patients are still

diagnosed in multiple or advanced forms and global mortality remains high with poor long-term prognosis^[16]. The term multifocal HCC comprises patients presenting with a broad disease spectrum, ranging from small, oligonodular tumors to diffuse disease. The accompanying liver cirrhosis, portal hypertension, and liver function impairment should be considered since they are related to high post-procedure morbidity and mortality. Therefore, a tailored approach is mandatory for each patient, and the decisional role of a specialized multidisciplinary team has been highlighted and encouraged in the last version of the BCLC classification^[7].

The BCLC algorithm recommends TACE as the main treatment modality for multinodular HCC, but whether a subset of patients may benefit from a surgical approach remains to be established. We conducted a retrospective analysis using the PSM, a method that may provide high-quality evidence in conditions when randomized clinical trials are unethical or unfeasible. For the PSM analysis, both indicators of liver function and tumor burden and aggressiveness were used. Although the Child-Pugh and MELD scores could be considered outdated after the last published version of the BCLC staging system^[7], these data are still commonly used in clinical practice. Wang *et al* showed that patients with gradual deterioration of CP score had shorter survival times and worse prognosis (5-years OS rates of 31.1%, 2.4%, and 0.9% for CP A, B, and C respectively). AFP is a well-established independent risk factor for survival in HCC patients and values greater than 400 ng/mL are generally considered diagnostic for HCC, in the presence of appropriate radiologic findings^[5,17]. Finally, the number and dimension of the nodules are two of the major prognostic factors, and the most used guidelines underscore their importance in treatment allocation^[7,8,14,18].

TACE is considered the standard treatment for BCLC-B patients, as evidence from randomized clinical trials and meta-analyses indicates that TACE provides better survival outcomes compared to the best supportive care with a 1-year mortality rate of 34.1%^[19–21]. On the other hand, guidelines do not recommend LR for BCLC-B patients, because of the unfavorable prognostic impact of multinodular presentation and high postoperative morbidity^[18]. Moreover, LR for multifocal HCC is a challenging surgery,

since wide and/or multiple resections are needed, possibly leading to bile leaks and/or postoperative liver failure (PHLF).

Advances in surgical techniques, including extensive use of IIOUS, better coagulation devices, and wider application of minimally invasive surgery, together with better perioperative management, have contributed to improving the results of liver resection in this difficult-to-treat population. Remarkably, the comparison among different studies is hurdled by the different modalities of detection and reporting of post-procedural complications.

In the present series, we did not find any differences in post-procedure morbidity comparing resection and TACE. According to the CD classification, only three patients undergoing LR and one patient in the TACE group had a clinically relevant event. However, it should be documented that TACE patients often required more than one treatment to achieve the best response, thus partially explaining the lower morbidity rate of the procedure. Conflicting results about morbidity were previously reported. Zhong *et al* showed a complication rate of 35% and 21% for resection and TACE, respectively^[22]. On the contrary, a metanalysis did not find any difference in post-procedure morbidity between these two treatment modalities^[23].

While only a nonsignificant trend towards better OS was observed with surgery, we found that DFS was significantly longer in resected patients. These results confirm and extend previous studies conducted in patients with multinodular HCC. Favorable results with surgery were originally reported by uncontrolled studies^[10,24]. In a multicentric study including 736 BCLC-B patients, Torzilli *et al* reported a 5-years survival rate of 57% and a DFS of 27%. The survival benefit of LR compared with TACE in BCLC-B patients has been previously reported in the meta-analysis by Liu *et al*^[23], and similar conclusions were reached in an RCT enrolling 173 patients^[25].

Considering the marked population heterogeneity of patients with multinodular HCC, subgroup analyses may provide additional clues for a better selection of the treatment modality. Not surprisingly, patients with lower AFP levels had the best prognosis. An exciting result was the observation that patients with high AFP levels

benefit more from TACE in terms of OS, and further studies are needed to confirm these data and investigate the possible mechanisms thereof. Another aspect which deserves further investigation is to what extent some of these patients with multinodular HCC could benefit from new systemic combination treatments which include the use of immunotherapy with excellent results^[26].

Interesting results were also provided by patient stratification according to the ITA.LI.CA classification. Patients in the B2 subgroup, characterized by nodules of smaller size or lower number showed the best prognosis when receiving LR. In contrast, those classified as B3, i.e., with larger nodules and higher numbers had the worst prognosis when resected. Coherently, patients with two HCC nodules had a greater benefit from LR compared with TACE in terms of DFS. This data emphasizes the relevance of the number of nodules, which is considered a poor prognostic factor and a predictor of early recurrence. Nonetheless, a clear cut-off value for the number of nodules beyond which resection is contraindicated has not been determined^[10,12,25,27]. Furthermore, although using the same parameters of the Up-to-7 criteria (number of lesions and maximum diameter of the bigger lesions), the ITA.LI.CA. classification showed a better ability in patients' stratification.

We also evaluated the impact of nodule size on survival in our series. Interestingly, patients with lesions larger than 41 mm had an even greater benefit from LR in terms of DFS. Previously published studies reported that large solitary HCC had better survival rates when treated with resection than with TACE^[28,29]. Furthermore, conflicting results have been reported about the potential role of tumor diameter as a prognostic factor. While some studies indicated that tumor size alone was not a predictor of poor prognosis^[24,30,31], other reports mentioned tumor dimension as a predictor of survival^[32-34]. In particular, in the analysis of 2887 HCC patients, tumor size was an independent prognostic factor of poor survival at multivariate analysis^[5], and Wada *et al* concluded that while size alone was not a contraindication for resection, a diameter lower than 5 cm was a favorable factor^[12].

Several limitations of this study must be acknowledged, including its retrospective nature with the inherent selection bias. Moreover, the fact that a limited number of patients from a single center were enrolled should lead to caution in the general applicability of the results. In addition, the relatively long period of enrollment could have been associated with differences due to modification in the HCC management. On the other hand, we performed a rigorous matching using a powerful statistical tool such as the propensity score, although some additional variables not included in the score could have influenced the outcomes.

CONCLUSION

Although the small sample analyzed should lead to careful interpretations of the results, after a propensity score matching analysis, patients with multinodular HCC appear to significantly benefit from a surgical approach over TACE in terms of DFS. These results are more evident in the sub-population belonging to the less advanced, B2 subgroup according to the ITA.LI.CA. classification, with AFP levels lower than 400 ng/mL, 2 lesions, and with lesions bigger than 41 mm. Patients classified as ITA.LI.CA B3, with AFP levels higher than 400 ng/mL, and more than 3 Lesions had higher benefit from TACE in terms of OS. Future studies are needed to confirm these results in a larger population and to identify other HCC subgroups of patients who can assist the clinician in directing the patients to personalized treatment.

ARTICLE HIGHLIGHTS

Research background

⁴ Hepatocellular carcinoma (HCC) is the most frequent primary liver tumor and a leading cause of death. Despite follow-up programs for cirrhotic patients, HCC is diagnosed in a multifocal form in up to 40% of the patients. Although being a heterogeneous group, the existing classifications consider together the patients with multifocal HCC and generally recommend a Trans-Arterial ChemoEmbolization (TACE) as the main treatment. Considering the progress in perioperative care, a

growing body of literature has started to propose liver resection (LR) in selected cases showing best long-term oncological results.

Research motivation

A consensus and detailed guidelines that consider also LR for these patients have not been proposed yet. Moreover, the characteristics of the patients that could benefit more from LR have still to be stated. Defining these aspects could help clinicians in patient management potentially improving their prognosis.

Research objectives

A comparison between LR and TACE as the first main treatment in terms of post-procedural results and long-term oncological outcomes has been performed in patients with multifocal HCC.

Research methods

To reduce the influence of the well-known prognostic factors (i.e., AFP values as a dichotomous variable with a cut-off set at 400 ng/dL, presence or not of cirrhosis, Child-Pugh and MELD score, number, and diameter of lesions), a propensity score-matched analysis was performed. So, two homogeneous groups (with a 1:1 ratio) were compared to assess the difference in short and long-term post-procedural results.

Research results

After matching, 30 patients were eligible for the final analysis. Morbidity rates were 42.9% and 40% for LR and TACE, respectively ($P = 0.876$). Median OS was not different comparing LR and TACE (53 vs. 18 mo, $P = 0.312$) while DFS was significantly longer with LR (19 vs. 0 mo, $P = 0.0001$). Subgroup analysis showed that patients in the ITA.LI.CA B2 stage, with AFP levels lower than 400 ng/mL, 2 Lesions, and lesions bigger than 41 mm benefited more from LR in terms of DFS. Patients classified as

ITA.LI.CA B3, with AFP levels higher than 400 ng/mL, and more than 3 Lesions appeared to receive more benefit from TACE in terms of OS.

However, not all the patients with multifocal HCC are amenable to be treated with LR or TACE. Consequently, only a small sample of patients resulted in being eligible for the analysis. Therefore, these results should be considered with caution and further studies are needed.

Research conclusions

There are subgroups of patients with multifocal HCC that seem to benefit more from LR than TACE.

Research perspectives

Further studies are needed to include in the guidelines LR as a potential treatment to be offered to specific subgroups of patients with multifocal HCC.

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