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ORIGINAL ARTICLE

Transarterial radioembolization in patients with hepatocellular carcinoma of intermediate B2 substage

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Abstract

Purpose Patients with hepatocellular carcinoma (HCC) of intermediate stage (BCLC-B according to the Barcelona Clinic Liver Cancer classification) are a heterogeneous group with different degrees of liver function impairment and tumour burden. The recommended treatment is transarterial chemoembolization (TACE). However, patients in this group may be judged as poor candidates for TACE because the risk-benefit ratio is low. Such patients may receive transarterial radioembolization (TARE) only by entering a clinical trial. Experts have proposed that the stage could be further divided into four substages based on available evidence of treatment benefit. We report here, for the first time, the outcome in patients with BCLC-B2 substage HCC treated with TARE.

Methods A retrospective analysis of the survival of 126 patients with BCLC-B2 substage HCC treated with TARE in three European hospitals was performed.

Results Overall median survival in patients with BCLC-B2 substage was not significantly different in relation to tumour characteristics; 19.35 months (95% CI 8.27–30.42 months) in patients with a single large (>7 cm) HCC, and 18.43 months (95% CI 15.08–21.77 months) in patients with multinodular HCC ($p = 0.27$). However, there was a higher proportion of long-term survivors at 36 months among those with a single large tumour (29%) than among those with multiple tumours (16.8%).

Alberta Cappelli and Paloma Sangro were joint lead authors.

Key points

1. Intermediate stage BCLC-B HCC includes a heterogeneous group of patients with different degrees of liver function impairment and tumour burden in whom the recommended treatment is transarterial chemoembolization (TACE).
2. Patients with BCLC-B stage HCC are sometimes poor candidates for TACE, and transarterial radioembolization (TARE) is then an option in multidisciplinary team discussions.
3. Experts have proposed a subclassification of stage BCLC-B into four substages on the basis of the degree of liver function impairment, tumour burden and performance status.
4. Patients with BCLC-B2 substage HCC with a large tumour could benefit more from TARE treatment.

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Conclusion Given the poor efficacy of TACE in treating patients with BCLC-B2 substage HCC, TARE treatment could be a better choice, especially in those with a large tumour.

Keywords Hepatocellular carcinoma · Transarterial chemoembolization · Transarterial radioembolization · BCLC-B subclassification

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third leading cause of cancer-related death [1]. The Barcelona Clinic Liver Cancer (BCLC) staging system has been externally validated in different clinical settings and is endorsed by the American Association for the Study of Liver Diseases (AASLD) [2–4], the American Gastroenterology Association (AGA) and the European Association for the Study of the Liver (EASL) [5]. Stage BCLC-B includes patients with intermediate-stage disease and it lies between early and advanced HCC. This stage represents roughly 30% of patients with HCC, and includes a heterogeneous group of patients with Child–Pugh (CP) class A or B, multifocal tumours (defined as more than three tumours regardless of size, or two or three tumours >3 cm in maximum diameter), in the absence of cancer-related symptoms, macrovascular invasion or extrahepatic spread. Guidelines recommend that single "large" tumours be considered as early stage BCLC-A. In clinical practice, because of the heterogeneity of the intermediate stage, different therapeutic approaches are often used due the lack of evidence that a single therapeutic option fits all patients with intermediate stage, and are associated with different rates of survival [4–9].

Recently, a panel of experts has proposed the subclassification of patients with intermediate stage HCC so that different therapeutic options can be suggested for each substage to facilitate treatment decisions in clinical practice [10, 11]. Patients with stage BCLC-B were reclassified into four substages on the basis of impairment in liver function assessed in terms of CP class, tumour burden staged according to the Milan and 'up-to-seven' criteria, and performance status (Table 1) [10]. The B2 substage includes those patients with CP class A status, tumour burden exceeding the up-to-seven criterion (single or multiple tumours), no clinical ascites or jaundice, and ECOG performance status 0.

Treatments recommended for patients with the B2 substage are transarterial chemoembolization (TACE) or transarterial radioembolization (TARE). However, the evidence for a clinical benefit of TACE in this subgroup of patients is weak because very large tumours or uncountable tumour nodules tend to respond insufficiently to TACE. Patients with CP class B are excluded from this treatment option because of the high expected risk of liver damage following ischaemia due to the large volume of liver that needs to be treated. If the tumour burden is really bulky, for example tumours exceeding 10 cm or uncountable nodules, the probability of a response to TACE is minimal [12] and the risk of decompensation or complications is significant. Promising results have been reported with TARE using ^{90}Y-loaded microspheres in patients with intermediate and more advanced tumours [13–15]. The risk of complications after TARE does not depend on tumour stage [15] and the survival rate among these patients is comparable to that obtained with sorafenib [16]. Moreover, a formal randomized trial comparing TACE and TARE with overall survival as the primary endpoint is lacking. The aim of the present study was to evaluate the outcome in patients with BCLC-B2 substage HCC treated with TARE.

Materials and methods

A retrospective study was carried out in all consecutive patients diagnosed with intermediate stage HCC who were treated with TARE from January 2003 to December 2015 in three European hospitals: Clinica Universidad de Navarra, Pamplona, Spain; Universitätsklinikum Magdeburg, Magdeburg, Germany; and Policlinico Sant'Orsola-Malpighi, Bologna, Italy. Patient and treatment characteristics as well as relevant outcomes were obtained from medical records and missing data were not replaced for analysis. Following the subclassification of intermediate HCC proposed by Bolondi et al. [10], patients with B2 substage were selected.

TARE was performed using ^{90}Y-labelled resin microspheres (SIR-Spheres; Sirtex Medical, Sydney, Australia). The indications for TARE were established by each hospital according to local policies and the decisions of the multidisciplinary team at each site. However, to be considered for TARE in all three hospitals, patients had to have an unequivocal diagnosis of HCC and no recent hepatic decompensation. All patients gave informed consent to TARE. The study was approved by the Institutional Review Board/Ethics Committee of each hospital. Patients received whole-liver or a more selective TARE depending on the distribution of tumour burden and hepatic vasculature. Whole-liver TARE was performed in a single session in two hospitals and using a sequential approach in one centre. For the whole-liver single sessions, the prescribed activity was usually divided into two vials and injected into the right and left hepatic arteries to avoid reflux to collateral vessels connected to the gastrointestinal tract vasculature. For the sequential approach the second injection was delivered 6 weeks after the first to reduce the risk of radioembolization-induced liver disease.

Table 1 Substages of intermediate HCC

	BCLC substage			
	B1	B2	B3	B4
Child-Pugh score	5, 6, 7	5, 6	7	8, 9
Tumour burden	Beyond Milan criteria, within up-to-seven criteria	Beyond up-to-seven criteria	Beyond up-to-seven criteria	Any
ECOG performance status	0	0	0	0/1
Portal vein thrombosis	No	No	No	No

As proposed by the manufacturer, the activity of ^{90}Y-loaded microspheres was calculated in all centres using either the body surface area formula or a dosimetric approach based on Medical Internal Radiation Dose (MIRD) formalism called the "partition model". The MIRD formalism is based on the determination of the fraction of activity (fractional uptake) that is trapped by the tumour, normal liver and lungs, and by the volume of each liver segment calculated using CT images. The fractional uptake was measured using ^{99m}Tc-MAA SPECT images. After TARE, a ^{90}Y PET/CT study was performed to obtain absorbed doses to the tumour and the treated volume, in consideration of the fact that we used the MIRD formalism in the pretreatment phase of the study. ^{90}Y PET/CT was not used in every patient; the transition from SPECT to PET took place at all three centres at different times.

A retrospective statistical analysis of variables that were in many cases obtained prospectively was performed. Categorical variables are expressed as frequencies and percentages. Quantitative variables with asymmetrical distributions are expressed as medians and interquartile ranges. Quantitative variables with symmetrical distributions are expressed as means and standard deviations. Survival was calculated from the date of first TARE until death or last follow-up. Survival was analysed using the Kaplan-Meier method and compared using the Cox regression model. Statistical analysis was performed using SPSS 20.0.

Results

Population

61 patients (41.5%) from Clinica Universitad de Navarra 47 patients (31.9%) from Policlinico S.Orsola of Bologna 39 patients (26.6%) from Magdeburg. According to the subclassification, 15 patients (10.2%) had BCLC-B1 substage, 126 patients (85.7%) had BCLC-B2 substage, 3 patients (2.0%) had BCLC-B3 substage, and 3 patients (2.0%) had BCLC-B4 substage. Table 2 summarizes the main demographic and clinical features of the patients with B2 substage. As expected, most patients were male (88.9%) and cirrhotic (81%), with a mean age of 65.7 years. Six patients (4.8%) had benign occlusive portal vein thrombosis based on the CT or MRI appearance. As a result of the requirement to have preserved liver function to be considered for TARE, most patients had normal albumin and total bilirubin values at baseline.

Treatment

TARE was the first treatment for HCC in 50 patients (39.7%). The remaining patients had relapsed or progressed following a variety of treatments that included liver resection (24 patients, 19%), percutaneous ablation (16 patients, 12.7%), TACE (45 patients, 35.7%), sorafenib (11 patients, 8.7%), and capecitabine (1 patient, 0.8%). TARE was performed as a lobar treatment (preserving an entire liver lobe) in 99 patients (78.6%), and as a whole-liver treatment in 27 patients (21.4%). The median activity delivered was 1.53 GBq (interquartile range 1.18–1.95 GBq). Patients received further treatment for HCC after TARE for downstaging, for residual disease that could be ablated, or for tumour progression. Treatments performed included liver resection (8 patients, 6.3%), ablation therapy (17 patients, 13.5%), TACE (33 patients, 26.2%) in the presence of residual tumour, sorafenib (35 patients, 27.8%), and other treatments (12 patients, 9.5%).

Survival

For the entire cohort, median survival was 18.43 months (95% CI 15.46–21.40 months; Fig. 1) and median progression-free survival was 6.17 months (95% CI 3.96–8.38 months; Fig. 2). In relation to tumour characteristics, overall median survival was 19.35 months (95% CI 8.27–30.42 months) in patients with a single large (>7 cm) HCC nodule and 18.43 months (95% CI 15.08–21.77 months) in patients with multinodular HCC beyond the up-to-seven criterion ($p = 0.27$; Fig. 3). The long-term survival rates at 24 and 36 months were higher among patients with a single large tumour (36.3 and 29%, respectively) than among those with multiple tumours (34.6 and 16.8%, respectively).

Table 2 Demographic and clinical characteristics of patients with BCLC-B2 substage HCC treated with TARE

Number of patients	126
Age (years), mean ± SD	65.7 ± 10.78
Sex, *n* (%)	
Male	112 (88.9)
Female	14 (11.1)
Cirrhosis, *n* (%)	102 (81)
Number of nodules, *n* (%)	
One	19 (15.1)
Two or three	26 (20.6)
More than three	81 (64.3)
Tumour size (mm), median (interquartile range)	60.0 (47.0–82.5)
Non tumoral portal vein thrombosis, *n* (%)	6 (4.8)
Albumin (g/dL), median (interquartile range)	3.90 (3.50–4.26)
Bilirubin (mg/dL), median (interquartile range)	0.77 (0.50–1.11)
Aspartate aminotransferase (IU/L), median (interquartile range)	41 (27–71.5)
Alpha-fetoprotein (ng/mL), median (interquartile range)	47 (7–414)

Discussion

The BCLC staging system for HCC is a prognostic classification and also provides guidance for therapeutic decisions based on factors related to the tumour, patient and liver function [6]. The intermediate BCLC-B stage includes a heterogeneous group of patients with different tumour burden, liver function and other associated factors [12]. The recommended treatment option as the standard-of-care for patients with stage BCLC-B is TACE [17]. However, a large proportion of patients with intermediate stage HCC are not suitable for TACE due to decompensated liver disease or advanced liver dysfunction [5]. Even more relevant in the selection of the best candidates for TACE is the tumour burden, which can be highly variable among patients with intermediate stage HCC and can influence the response to treatment. Indeed, it has recently been reported that patients with nodules >5 cm in diameter or more than five nodules are significantly less likely to achieve a complete response following TACE [12, 18, 19]. In a study comparing selective/superselective and lobar TACE by analysing explanted livers [20], histological necrosis after TACE was complete in about 53.8% of lesions and was maximal in tumours between 3 and 5 cm (91.8% after selective/superselective TACE and 66.5% after lobar procedures).

Given the controversy surrounding the efficacy, safety and technique of TACE in a proportion of patients with intermediate HCC and the introduction of novel treatment strategies,

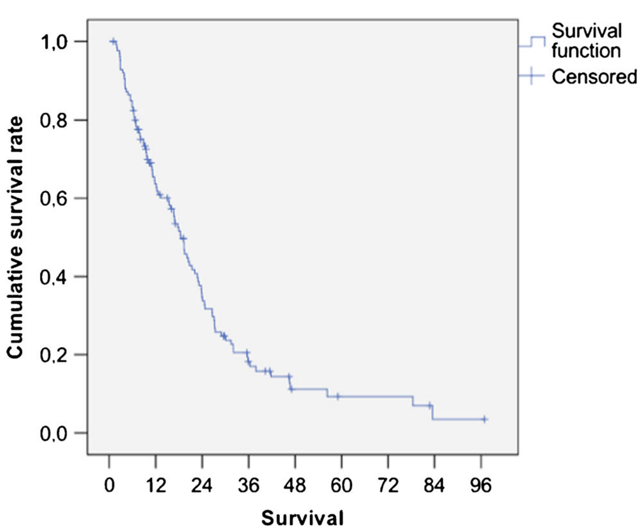

Fig. 1 Overall survival in patients with BCLC-B2 substage HCC treated with TARE

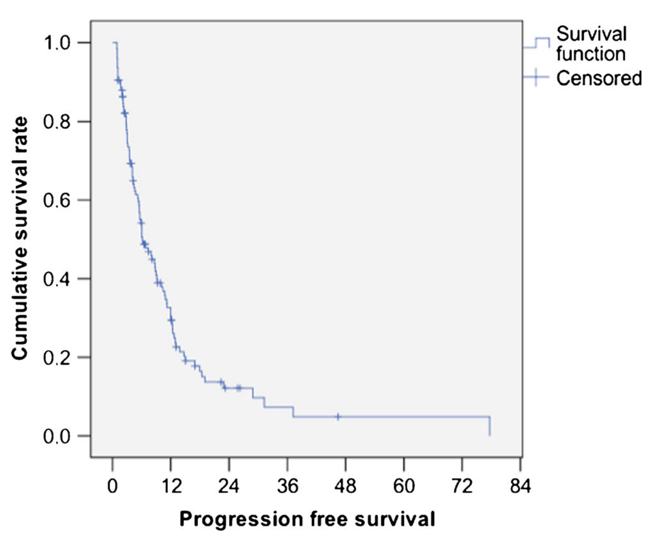

Fig. 2 Progression-free survival in patients with BCLC-B2 substage HCC treated with TARE

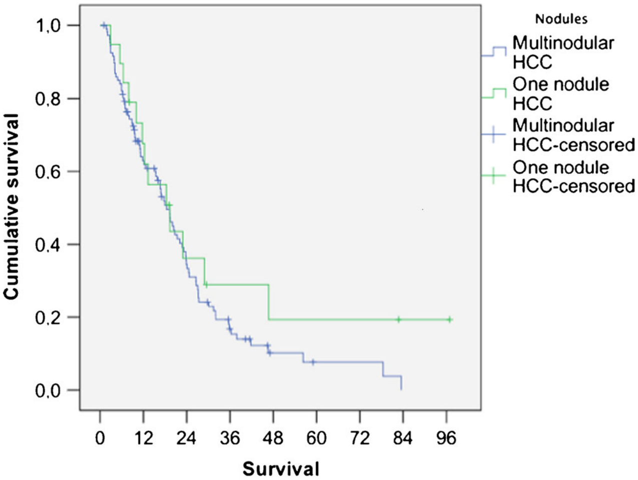

Fig. 3 Overall survival in patients with BCLC-B2 substage HCC treated with TARE comparing those with a single or multinodular tumours

new tools are required to identify patients who will derive most benefit from TACE [12]. TARE has been proposed for treating patients with unresectable HCC who are unsuitable for percutaneous ablative treatments, although all studies published on TARE treatment to date included patients with both intermediate and advanced disease [13–15, 21–23]. In these studies, TARE showed promising antitumoral effects with an acceptable safety profile [24]. Several studies have shown comparable median survival rates and toxic effects among patients treated with TACE and TARE, and therefore no defined selection criteria to determine which technique is better have yet been established.

In nonrandomized studies, the rates of patients achieving downstaging with TARE and with TACE enabling radical therapies were similar [25, 26]. Among patients with intermediate HCC, median overall survival after TARE compares favourably with that after TACE [16, 22, 27–35]. Median survivals ranging from 6 to 18 months after TACE and 6 to 18.6 months after TARE have been reported. In a randomized control trial, Pitton et al. [36] also found no significant difference in survival between patients with stage BCLC-B treated with TACE and those treated with TARE: 788 days (26.2 months) vs. 592 days (19.7 months; p not significant). However, the survival times of patients with the different BCLC-B substages were not reported, but the population was most likely similar to ours (CP class A patients, corresponding to BCLC-B1 and BCLC-B2 substages). In a meta-analysis, Facciorusso et al. [37] found no significant differences in survival at 1, 2 and 3 years between patients treated with TARE and those treated with TACE ($p = 0.71$, odds ratio 1.01, 95% confidence interval 0.78–1.31; $p = 0.93$, 1.42, 1.08–1.89; and $p = 0.44$, 1.48, 1.03–2.13, respectively). However, most of the studies discussed above showed a longer times to progression, less toxicity and shorter hospital stays after TARE than after TACE.

The few recent studies that have tried to assess the prognostic ability of the BCLC subclassification were mainly carried out in patients treated with TACE, and found contrasting results [38–41]. Despite a similar patient distribution in the various substages, survival is difficult to compare among these studies. The series presented by Ha et al. [38] and Wang et al. [39] included patients who were fit enough to undergo TACE and were of Asian ethnicity. Moreover, in the study by Wang et al. >70% of the patients had chronic HBV infection and an unknown proportion had cirrhosis. Furthermore, transarterial embolization (TAE), which is not yet a validated technique as specified above, and not TACE, was performed in both studies. Mazzaferro et al. [42] reported a median survival of 18 months in a subgroup of 15 patients with stage BCLC-B treated with TARE.

Therefore, choosing the best treatment in patients with intermediate stage HCC is still a challenge. In the current scenario the proposal of the expert panel (Bolondi subclassification) as the first approach in patients with BCLC-B2 substage is TACE, or alternatively TARE. This subclassification has been fully validated [38, 43, 44], but the outcomes following TARE treatment in patients with BCLC-B2 substage have been reported in few studies. Recently, Salem et al. [45] reported the outcomes in 91 patients with stage BCLC-B and CP class A. The authors found a median censored survival of 25 months (95% CI 17.3–30.5 months) and an intention-to-treat (ITT) survival of 30 months (95% CI 21.4–33 months). In our study, patients with BCLC-B2 substage treated with TARE had a median survival slightly shorter than those reported by Salem et al. (18.4 months) probably because the large majority of patients in the study by Salem et al. had United Network for Organ Sharing (UNOS) T2 stage, in contrast to our patients who were by definition beyond the Milan criteria and within up-to-seven criterion. In our study, patients with BCLC-B2 substage treated with TARE had a median survival of 18.4 months. Those results are quite good when compared with survival reported by Giannini et al. [46] in untreated patients with BCLC-B2 substage (16 months).

A recent study by Kim et al. [47] analysed for the first time survival after TACE in relation to BCLC-B substage and found excellent survival in patients with BCLC-B2 substage (26 months). Similar results have been reported by Scaffaro et al. [48] who found a median survival of 28.6 months in 27 patients with BCLC-B2 substage treated with TAE using polyvinyl alcohol particles. The significant difference in these results (between TARE and TACE) may be mainly attributable to different patient selection. As reported, patients undergoing TARE were generally suboptimal candidates for TACE because of bearing larger tumours and/or their unresponsiveness to previous treatments, suggesting the likelihood of more aggressive tumour behaviour. This selection bias could have reduced the overall survival of the whole group with BCLC-B2 substage. Furthermore, Kim et al. [47] also considered that their results may not be pertinent for patients with HCC in Western countries, mainly due to differences in demographics and underlying causes of liver disease. The only study including a Western population similar to ours was performed by Weinmann et al. [40]. In that study, 67 patients with BCLC-B2 substage were treated with TACE or TARE with a survival of 18.6 months. Moreover, in our patients with BCLC-B2, substage, survival was 5 months shorter in those who had received previous treatment, although not significantly ($p = 0.5$), than in treatment-naive patients.

Lastly, in our study patients with a single large (>7 cm) HCC nodule showed better median survival than patients with multinodular HCC. Since the poor efficacy of TACE in treating large (>5 cm) tumours has already been demonstrated (both in terms of local response and survival) [18, 19, 49], patients with BCLC-B2 substage and large nodules could be the real field of application of TARE. In this scenario, tumours beyond the up-to-seven criterion with a single nodule larger than 7 cm could benefit more from TARE, and those with BCLC-B2 substage and multinodular disease could be effectively treated with TACE, even if the real efficacy of TACE in this setting has still to be fully proven, or more likely with the systemic agent sorafenib. Stage BCLC-A according to the more recent suggestions, when used for classifying single lesions, might be further divided into two substages: single tumours <5 cm which could be more likely to benefit from resection, and single/large tumours >5 cm which could be more likely to benefit from TARE. In this latter situation a double advantage could be obtained: downsizing the lesion and inducing hypertrophy of the contralateral lobe, thus switching patients to surgical treatment.

The present study had obvious limitations related to its retrospective nature, and also included not only patients naive for TARE. Thus some bias affecting survival outcome may have been introduced. However, our study population came from three different centres that collected data as a large series treated in a similar way, making the population treatment homogeneous.

In conclusion, patients with BCLC-B2 substage and in particular with large HCC could mainly benefit from TARE treatment if TACE is ineffective or not feasible. Future studies with larger sample sizes are warranted to validate our results.

Authors' contributions Alberta Cappelli, Paloma Sangro, Cristina Mosconi, Eleonora Terzi, J Jose I. Bilbao, Jens Ricke, Rita Golfieri and Bruno Sangro participated in the design of the study.

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All authors participated in the elaboration and interpretation of the results and reviewed the final manuscript.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The study was approved by the Institutional Review Board/Ethics Committee of each hospital. This article does not describe any studies with animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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