Sorafenib Plus Drug-eluting Bead Transarterial Chemoembolization for Early Intrahepatic Stage-progressed Advanced Hepatocellular Carcinoma Refractory to Conventional Transarterial Chemoembolization

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Research Article

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Abstract

Purpose: To investigate the effectiveness and safety of the combination of sorafenib and drug-eluting bead transarterial chemoembolization (DEB-TACE) in the treatment of early intrahepatic stage-progressed advanced hepatocellular carcinoma (ISPA-HCC).

Methods: This study was approved by the ethics committees of six tertiary medical centers in China. Between October 2017 and October 2020, 213 patients with advanced HCC received either sorafenib combined with on-demand DEB-TACE (DTS group, n = 103) or sorafenib monotherapy (S group, n = 110). Overall survival (OS), time to progression (TTP), local tumor response, and adverse events (AEs) were compared between the two groups.

Results: The AEs of patients were similar between the DTS and S groups. The post-treatment partial response, objective response, and disease control rates were significantly higher in the DTS group than in the S group (51.5% vs. 23.6%; 56.3% vs. 25.5%; 77.7% vs. 56.4%, respectively). The median OS was significantly longer in the DTS group than in the S group (16.3 vs. 10.0 months; hazard ratio [HR] = 0.43; $P < 0.001$), as was the TTP (6.7 vs. 4.3 months; HR = 0.60; $P = 0.001$). In the DTS group, patients who received ≥2 sessions of DEB-TACE benefited more than those who received two sessions of DEB-TACE. Multivariate analysis revealed that the α-fetoprotein level and treatment allocation were independent predictors of OS and TTP.

Conclusion: The combination of sorafenib and DEB-TACE is safe and effective for the treatment of early ISPA-HCC.

Introduction

Hepatocellular carcinoma (HCC) is the most frequently occurring and third-deadliest primary liver malignancy worldwide (Sung et al. 2021). Transarterial chemoembolization (TACE) is an effective therapeutic option for unresectable HCC (Sieghart et al. 2015; Lencioni et al. 2016). Conventional TACE (cTACE) with oil-based chemoembolization provides survival benefits, but the five-year tumor recurrence rate is 70% because of TACE refractoriness (Kudo et al. 2011). After cTACE resistance, most intermediate HCC develops to stage progression (SP) HCC. SP serves as the surrogate end-point for TACE refractoriness and a crucial turning point in the survival time of patients with intermediate HCC (Kim et al. 2012). Compared to primary advanced HCC, early intrahepatic stage progression advanced HCC (ISPA-HCC)—which is SP-HCC with portal vein tumor thrombus (PVTT) with/without extrahepatic metastasis—has reduced tumor burden, poor hepatic artery condition, impaired liver function from repeated TACE, and complete response to TACE. However, no standard therapeutic regimen has been established for patients with ISPA-HCC (Yamashita and Kaneko 2013).

Sorafenib is one of the standard therapies for patients with advanced-stage HCC and is recommended for managing cTACE-refractory HCC by the Japan Society of Hepatology's consensus-based clinical practice guidelines (Kudo et al. 2011; Ikeda et al. 2014). An observational study reported that the median overall

survival (OS) of ISPA-HCC patients treated with systematic treatment was only approximately 6.2 months (Kim et al. 2012). Therefore, further investigations are required for the improvement of sorafenib efficacy.

Drug-eluting bead TACE (DEB-TACE) selectively delivers high doses of chemotherapeutic agents over an extended period, thereby minimizing the blood drug concentration, related systemic effects, and need for embolic agents (Brown et al. 2012). Previous studies have shown that DEB-TACE is superior to cTACE considering its high local response rate, reduced implications, and low liver toxicity (Lammer et al. 2010), and has a local effect in cTACE-resistant HCC (Xiao et al. 2019; Song et al. 2013). For advanced HCC, DEB-TACE has been demonstrated as safe and yields an objective response rate of approximately 69.5% (Liu et al. 2020), which can rapidly reduce tumor burden and enhance the anti-tumor effect of sorafenib (Pawlik et al. 2011). Both the TACE-2 and SPACE studies indicate that DEB-TACE combined with sorafenib is safe and has an increased survival effect in patients with unresectable HCC, with progression-free survival rates of 238 and 169 days, respectively (Meyer et al. 2017; Lencioni et al. 2016), providing evidence for the continued use of DEB-TACE in ISPA-HCC patients. DEB-TACE is also a potential synergistic agent with sorafenib for treatment of early ISPA-HCC patients after cTACE resistance.

This study compared the efficacy and safety of this combined treatment with sorafenib monotherapy. We hypothesized that sorafenib plus DEB-TACE is safe and effective in early ISPA-HCC patients with good liver function.

Materials And Methods

Study design

This retrospective multicenter study collected data from six tertiary medical centers. The study protocol was approved by the institutional review boards. As this was a retrospective study, the requirement for obtaining informed consent from the patients was waived.

The eligibility criteria for enrollment in this study were: (*a*) age 18–75 years; (*b*) HCC diagnosed according to the European Association for the Study of the Liver/American Association for the Study of Liver Diseases (Bruix et al. 2005; EASL 2018); (*c*) patients with ≥1 typical enhanced measurable target lesion based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria (Lencioni and Llovet 2010), who had not received DEB-TACE or systemic therapy; (*d*) PVTT initially observed during follow-up of cTACE-treated intermediate HCC; (*e*) Child-Pugh class A liver function after stage progression; (*f*) Eastern Cooperative Oncology Group performance status score of 0; and (*g*) adequate renal function (serum creatinine concentration of 1.5-fold the upper limit of the normal range or less).

The exclusion criteria were: (*a*) PVTT in the main portal vein, (*b*) curative treatment including resection or ablation after stage progression, and (*c*) severe dysfunction of the heart, kidney, or other organs.

Electronic medical records of 309 patients with ISPA-HCC from intermediate stage after cTACE—who had been treated with either sorafenib monotherapy or DEB-TACE combination therapy between October 2017

and October 2020—were reviewed. Overall, 213 patients met the inclusion criteria. DEB-TACE combined with sorafenib was administered to 103 patients (DTS group), while the remaining 110 patients received sorafenib monotherapy (S group) (Fig. 1).

Treatments

Sorafenib treatment (400 mg) was administered orally twice a daily after detection of stage progression. The patients received continuous sorafenib with no breaks before or after repeated DEB-TACE. The dose was reduced to 400 mg once daily with grade 3 or 4 hematologic toxicity, skin toxicity, gastrointestinal toxicity, hypertension, or hepatic dysfunction, until the adverse events (AEs) were alleviated or eliminated. If these continued after dose adjustment, sorafenib treatment was halted until their disappearance.

On-demand TACE was performed according to the tumor condition. All TACE procedures were performed by interventional radiologists. Standard angiographic facilities and protocols were used for hepatic angiography and catheterization. Imaging of the celiac and superior mesenteric arteries was performed in all patients to evaluate the circulation of the liver vasculature prior to treatment. Super-selective catheterizations were performed in every embolization of DEB-TACE procedures, if possible. However, in patients with bilobar multinodular disease, the lobar artery was selectively catheterized.

The doxorubicin capable beads (DC Beads™; Biocompatibles, Farnham, UK) used were either 100–300 or 300–500 μm. Each vial of DC Beads (2-mL beads) was loaded with 75 mg of doxorubicin dissolved in sterilized water. After loading for 30 min, at least 5–10 mL of nonionic isotonic contrast (270 mg/mL Visipaque [iodixanol]; GE Healthcare, Princeton, NJ, USA) was injected into the vial per 1 mL doxorubicin-DEB. A 10-mL suspension of doxorubicin-DEB was aspirated into a syringe and injected as recommended previously (Lencioni et al. 2012). The embolization protocols rarely necessitated the use of supplementary embolic materials to avoid doxorubicin-DEB overdose, in which case 300–500-μm Embosphere Microspheres (Merit Medical, Salt Lake City, UT, USA) were required for complete devascularization (Fig. S1 shows a typical patient).

Doxorubicin-DEB doses were adjusted according to the tumor diameter (based on the ellipsoid volume, i.e., height × width × length × π/6). The end-point of primary chemoembolization was complete devascularization of HCC observed on angiograms (Lencioni et al. 2012).

Outcomes and assessments

OS was measured from the first administration of sorafenib until death or the last follow-up. Time to progression (TTP) was defined as the time from the first sorafenib treatment until the detection of progressive disease. Patients followed up once per month. Within one week prior to the treatment, all patients underwent triphasic contrast-enhanced CT or MRI, and all parameters, including serum α-fetoprotein (AFP) level and hepatic function, were documented. Tumor response and safety were assessed at 1-month intervals until death or progression. Once any residual tumor or recurrence was observed, additional DEB-TACE was performed on demand according to the criteria described above. The mRECIST criteria were used to assess the efficacy of local tumor response according to images acquired

one month after TACE (EASL 2018). In each institution, measurements were performed by two independent radiologists from the Department of Medical Imaging, with a consensus review performed for equivocal cases by a third experienced radiologist. Triphasic contrast-enhanced CT and MRI were used for follow-up imaging. The best overall response during treatment was considered the final response. The last follow-up date was June 31, 2021.

AEs were classified according to the Common Terminology Criteria for Adverse Events v. 4.0 (NIH. 2010). Abdominal pain, nausea, and vomiting that occurred within 14 days after the TACE procedure were considered post-TACE syndrome (Vogl et al. 2009) and were not recorded as sorafenib-related AEs. Hepatic reserve function was evaluated using the albumin–bilirubin (ALBI) score. The ALBI score was calculated based on the total bilirubin (TBil) and serum albumin (ALB) levels using the following formula: ALBI score = (-0.085 × ALB [g/L]) + (0.66 × log10 TBil [μmol/L]), and it was categorized into three grades based on the following scores: ≤-2.60 = grade 1, >-2.60 to ≤-1.39 = grade 2, and >-1.39 = grade 3 (Hiraoka et al. 2017).

Statistical analysis

Continuous variables and categorical data were expressed as mean ± standard deviation and frequencies, respectively, whereas between-group comparisons were evaluated using either Student's *t*-test or Pearson's chi-squared test. Survival curves were estimated using the Kaplan–Meier analysis, and univariate analysis was performed using the log-rank test. Multivariate analysis was performed using Cox regression analysis for the significant variables identified in the univariate analysis. All statistical tests were two-sided, and between-group differences were considered significant at $P < 0.05$.

Results

Patient characteristics

A retrospective review of the records of 309 consecutive patients with stage-progressed advanced HCC between October 2017 and October 2020 was performed. A total of 213 patients were enrolled in the study. Of these, 103 patients consented to receiving the combination of sorafenib and DEB-TACE (DTS group), whereas the remaining 110 patients consented to receive sorafenib monotherapy (S group) (Table 1). The median follow-up duration was 11.3 months (2.4–36.6 months) and 9.5 months (2.4–27.5 months) in the DTS and S groups, respectively. The average pre-cTACE times were 2.6 and 2.4 in the DTS and S groups, respectively. In the DTS group, all patients received repeated on-demand DEB-TACE; 56 (54.4%) patients received two DEB-TACE sessions and 47 (45.6%) patients received ≥3 DEB-TACE sessions. No significant differences were observed in the baseline characteristics between the two groups.

Table 1
Comparison of characteristics between patients in the DTS and S groups

Characteristic	DTS Group (n = 103)	S Group (n = 110)	*P*-value
Age (y)	49 ± 11	50 ± 12	0.477
<50	56 (54.4%)	53 (48.2%)	
≥50	47 (45.6%)	57 (51.8%)	
Sex (n, %)			0.188
Male	94 (91.3%)	94 (85.5%)	
Female	9 (8.7%)	16 (14.5%)	
HBV (n, %)			0.397
Absence	11 (10.7%)	16 (14.5%)	
Presence	92 (89.3%)	94 (85.5%)	
AFP (n, %)			0.613
<400 ng/mL	47 (45.6%)	54 (49.1%)	
≥400 ng/mL	56 (54.4%)	56 (50.9%)	
WBC ($\times 10^9$)	6.7 ± 2.6	7.1 ± 3.1	0.309
RBC ($\times 10^{12}$)	4.7 ± 1.2	4.6 ± 1.1	0.459
Platelet count ($\times 10^9$)	178 ± 90	168 ± 66	0.320
ALT (IU/L)	48.8 ± 51.6	43.7 ± 32.8	0.390
AST (IU/L)	72.8 ± 65.9	60.7 ± 64.4	0.178
ALB (g/dL)	38.0 ± 5.0	37.7 ± 4.6	0.638
TBil (mg/dL)	19.2±10.9	19.3±15.4	0.954
PT (s)	12.8 ± 1.2	13.6 ± 7.7	0.273
ALBI score	-2.447 ± 0.446	-2.388 ± 0.444	0.331
ALBI grade			0.223

AFP, α-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; APS, arterioportal shunt; AST, aspartate aminotransferase; DTS group, patients treated with drug-eluting bead transarterial chemoembolization plus sorafenib; HBV, hepatitis B virus; PT, prothrombin time (international ratio); PVTT, portal vein tumor thrombus; RBC, red blood cell; S group, patients treated with sorafenib monotherapy; TBil, total bilirubin; WBC, white blood cell.

Characteristic	DTS Group (n = 103)	S Group (n = 110)	*P*-value
1	42 (40.3%)	36 (32.7%)	
2	61 (59.2%)	74 (67.3%)	
Intrahepatic tumor number (n, %)			0.915
≤3	20 (19.4%)	22 (20.0%)	
>3	83 (80.6%)	88 (80.0%)	
Main tumor size (cm; n, %)	8.1 ± 3.7	8.1 ± 5.0	0.965
<5 cm	26 (25.2%)	21 (19.1%)	
≥5 cm	77 (74.8%)	89 (80.9%)	
Location of PVTT (n, %)			0.834
Second- or lower-order	86 (83.5%)	93 (84.5%)	
First-order	17 (16.5%)	17 (15.5%)	
Extrahepatic metastasis (n, %)			0.952
Absence	83 (80.6%)	89 (80.9%)	
Presence	20 (19.4%)	21 (19.1%)	
Previous cTACE			0.482
1	50 (48.5%)	44 (40.0%)	
≥2	53 (51.5%)	66 (60.0%)	

AFP, α-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; APS, arterioportal shunt; AST, aspartate aminotransferase; DTS group, patients treated with drug-eluting bead transarterial chemoembolization plus sorafenib; HBV, hepatitis B virus; PT, prothrombin time (international ratio); PVTT, portal vein tumor thrombus; RBC, red blood cell; S group, patients treated with sorafenib monotherapy; TBil, total bilirubin; WBC, white blood cell.

Safety

AEs associated with sorafenib treatment are shown in Table 2. Only events that occurred in ≥10% of the patients in each group were recorded. The median duration of sorafenib administration was 5.9 and 4.0 months in the DTS and S groups, respectively. The median daily dose of sorafenib was 600 mg for both groups. The rates of dose reduction and interruption due to AEs were 57.3% and 47.3% in the DTS group and 47.6% and 34.5% in the S group, respectively. No unexpected AEs or drug-related deaths occurred within 30 days of final dose administration. Compared to the AEs in the S group, the most common AEs

in the DTS group included decreased appetite (61.2% vs. 58.2%, *P* = 0.657) and fatigue (54.4% vs. 50.0%, *P* = 0.524). Only a few Grade 3 AEs were observed in the DTS group. There were no significant differences in the incidence of AEs between the two groups for either all grades or grades ≥3. The mean changes in the ALBI score seven days after chemoembolization were consistent between the two groups (*P* = 0.407) (Fig. S2).

Table 2
Comparison of adverse events related to sorafenib between patients in the DTS and S groups

	All grades		*P*-value	Grade 3		*P*-value
	DTS Group (n = 103)	S Group (n = 110)		DTS Group (n = 103)	S Group (n = 110)	
Hand-foot skin reaction	49 (47.6%)	45 (41.0%)	0.328	14 (13.6%)	12 (10.9%)	0.550
Diarrhea	51 (49.5%)	59 (53.6%)	0.547	7 (6.8%)	7 (6.4%)	0.899
Hypertension	31 (30.1%)	25 (22.7%)	0.222	4 (3.9%)	3 (2.7%)	0.636
Alopecia	24 (23.3%)	37 (33.6%)	0.095	2 (1.9%)	1 (0.9%)	0.523
Nausea/Vomiting	51 (49.5%)	50 (45.5%)	0.553	2 (1.9%)	3 (2.7%)	0.705
Fatigue	56 (54.4%)	55 (50.0%)	0.524	9 (8.7%)	5 (4.5%)	0.217
Decreased appetite	63 (61.2%)	64 (58.2%)	0.657	7 (6.8%)	7 (6.4%)	0.899
Proteinuria	14 (13.6%)	12 (10.9%)	0.550	2 (1.9%)	1 (0.9%)	0.523
Abdominal pain	14 (13.6%)	14 (12.7%)	0.852	1 (1.0%)	1 (0.9%)	0.963
Rash	29 (28.2%)	39 (35.5%)	0.253	4 (3.9%)	5 (4.5%)	0.810
ALT/AST increased	49 (47.6%)	39 (35.5%)	0.073	4 (3.9%)	9 (8.2%)	0.190

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DTS group, patients treated with drug-eluting bead transarterial chemoembolization plus sorafenib; S group, patients treated with sorafenib monotherapy

Survival outcomes and local efficacy

The median OS was 16.3 months (95% confidence interval [CI]: 14.1–18.5) for the DTS group and 10.0 months (95% CI: 7.9–12.1) for the S group (stratified hazard ratio [HR] for death = 0.43; 95% CI: 0.31–0.61; *P* < 0.001). Estimated OS rates at 6 and 12 months were 95.0% (95% CI: 88.4–97.9) and 62.6% (95% CI: 51.2–72.0) in the DTS group, respectively, versus 67.0% (95% CI: 57.3–75.0) and 44.1% (95% CI: 34.5–53.2) in the S group, respectively (Fig. 2).

In terms of TTP, the DTS group (6.7 months; 95% CI: 4.7–8.6) was superior to the S group (4.3 months; 95% CI: 3.2–5.5) (HR = 0.60; 95% CI: 0.45–0.81; *P* = 0.001). Estimated no-disease-progression rates at 6 and 12 months were 52.9% (95% CI: 42.6–62.1) and 23.7% (95% CI: 15.6–32.8) in the DTS group, respectively, versus 37.4% (95% CI: 28.4–46.4) and 12.6% (95% CI: 7.0–19.9) in the S group, respectively (Fig. S3).

In the DTS group, 6 (5.8%), 53 (51.5%), and 22 (21.4%) patients exhibited complete response, partial response, and stable disease, respectively (shown in Fig. 3). Compared with the S group, the DTS group had high partial response (51.5% vs. 23.6%; *P* < 0.001), objective response (56.3% vs. 25.5%; *P* < 0.001), and disease control (77.7% vs. 56.4%; *P* = 0.001) rates.

The forest plots show the results of the subgroup analysis of OS and TTP (shown in Fig. 4 and S4). The DTS group was superior to the S group for the OS in most subgroups except without HBV-infection, main tumor size ≤5 cm, PVTT in first portal vein branch, and with extrahepatic spread. Similar advantages of the DTS group were observed in the subgroup analysis of TTP. In the DTS group, the patients who received more sessions of DEB-TACE (≥2 sessions) benefited more from the combined therapy, regarding OS (HR = 0.53, *P* = 0.027), than those who received two sessions of DEB-TACE (Fig. S5).

Univariate analysis revealed that the AFP level (*P* < 0.001), intrahepatic tumor number (*P* = 0.038), and treatment type (*P* < 0.001) were significant prognostic factors of OS, whereas the AFP level (*P* < 0.001) and treatment type (*P* = 0.001) were significant determinants of TTP. Multivariate analysis showed that the AFP level (HR = 1.96; *P* < 0.001) and treatment type (HR = 0.44; *P* < 0.001) were independent predictors of OS, whereas the AFP level (HR = 1.97; *P* < 0.001) and treatment type (HR = 0.60; *P* = 0.001) were independent predictors of TTP (Table 3).

Table 3
Univariate and multivariate analyses of factors associated with overall survival after treatment

	Overall survival				Time to progression survival			
	Univariate	Multivariate			Univariate	Multivariate		
Factor	P-value	HR	95% CI	P-value	P-value	HR	95% CI	P-value
Sex	0.274				0.449			
Age [1]	0.565				0.723			
HBV	0.583				0.609			
AFP [2]	<0.001	1.96	1.40–2.76	<0.001	<0.001	1.97	1.45–2.66	<0.001
ALBI grade	0.182				0.298			
Number of intrahepatic tumors [3]	0.038	1.44	0.94–2.20	0.098	0.141			
Main tumor size [4]	0.511				0.903			
Branch of PVTT	0.269				0.250			
Extrahepatic spread	0.154				0.119			
Treatment [5]	<0.001	0.44	0.31–0.61	<0.001	0.001	0.60	0.44–0.80	0.001
The cut offs were [1] 50 years, [2] 400 ng/mL, [3] 3, [4] 5 cm, and [5] S group as reference.								
AFP, α-fetoprotein; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; PVTT, portal vein tumor thrombus.								

Discussion

Survival time is poor once a patient enters ISPA-HCC, and the treatment at this stage seriously affects the OS. This study evaluated the efficacy of the combined treatment with sorafenib plus DEB-TACE in patients with early ISPA-HCC. We found that the combined therapy was superior to sorafenib monotherapy with respect to OS (16.3 months vs. 10.0 months) and TTP (6.7 months vs. 4.3 months). This result was similar to prospective studies of primary unresectable HCC treated with DEB-TACE combined with sorafenib, including TACE-2 (TTP 7.9 months) (Meyer et al. 2017) and SPACE (TTP 5.6 months) (Lencioni et al. 2016), and is superior to the trials of primary advanced HCC with PVTT treated with cTACE combined with sorafenib upon STAH (OS 12.8 months) (Park et al. 2019) or Zhu's study (OS 11.0 months) (Zhu et al. 2014). According to the latest result of IMbrave150 (Finn et al. 2020; Finn et al.

2021), the median OS of patients treated with atezolizumab plus bevacizumab was 19.2 months, which is longer than our study. The participants in IMbrave150 included BCLC stage A (2%), BCLC stage B (15%), which may account for this difference. The OS and TTP of our study were calculated from the administration of sorafenib instead of the diagnosis of HCC, indicating that all patients had suffered disease progress, while all patients in IMbrave150 were treated since the diagnosis of primary HCC, making it difficult to directly compare the results. Compared to those with primary advanced HCC, patients with early ISPA-HCC normally have less tumor burden and poor liver functional reserve. However, with portal invasion, the intrahepatic tumor burden of these patients is still in the early progression stage, similar to that of HCC patients at intermediate substage B3a, as reported by Kudo et al. (Kudo et al. 2015). At this stage, local treatment to minimize liver function damage, such as super-selective TACE, could still have a high response rate in intrahepatic tumor control on the premise of systemic treatment. Therefore, early ISPA-HCC patients are most likely to benefit from selective DEB-TACE when they are refractory to cTACE.

Although the STAH trial failed to achieve a survival benefit, the results of post-hoc analysis showed that the subgroups of cTACE ≥2 could benefit from sorafenib plus TACE (Park et al. 2019). In the present study, all patients received ≥2 DEB-TACE sessions in the DTS group, and the patients who received more than two sessions of DEB-TACE had longer median OS than those who received two sessions. This suggested that for whom repeated DEB-TACE is tolerable, sorafenib combined with DEB-TACE might be more effective.

Except for the characteristics of early ISPA-HCC itself, the survival advantages in our study might be due to the mutual benefits for efficacy improvement of both DEB-TACE and sorafenib treatments. First, intrahepatic tumor burden appears to be an important predictor of survival in patients with advanced HCC. Tumor size, tumor number, and PVTT have been found to be predictors of TACE response (Vogl et al. 2011). DEB-TACE promptly reduces the tumor burden refractory to cTACE, which could further enhance sorafenib efficacy. Conversely, in our study, sorafenib was initiated before DEB-TACE, as previous studies suggested that early administration of sorafenib suppresses the post-TACE angiogenesis resulting from increased levels of vascular endothelial growth factor and other angiogenic factors after TACE (Hatooka et al. 2016; Park et al. 2012). As such, sorafenib shows marked efficacy against local tumors and extrahepatic metastases when combined with TACE. Furthermore, sorafenib can normalize the tumor blood vessels and reduce numerous bilobar HCCs simultaneously, which creates opportunities for super-selective embolization by DEB-TACE. Our sub-analyses demonstrated that DEB-TACE was more effective in patients with more advanced-stage HCC, including AFP ≥400 ng/mL, intrahepatic tumor number ≥3, and main tumor size ≥5 cm. On-demand DEB-TACE for patients could quickly reduce tumor burden, thereby protecting liver function from intrahepatic lesion progression.

AE occurrence was routinely checked prior to each TACE session. However, abnormal liver function or post-embolization syndrome was not included as part of the safety analysis, as such events are known to occur shortly after TACE. Patients from the TACE group did not experience AEs ≥grade 3. The incidence of AEs associated with sorafenib was similar to that reported by Zhu et al. and Wu et al. when treating

advanced HCC with sorafenib combined with TACE (Zhu et al. 2014; Wu et al. 2017). Only two grade 3 and no grade 4 AEs were observed in this study. The most common grade 1 or 2 AEs were hand–foot syndrome, diarrhea, and fatigue. These AE results indicate that sorafenib combined with DEB-TACE is well tolerated by patients with early ISPA-HCC after cTACE-refractory.

Previous studies have suggested that DEB-TACE might be effective in cTACE refractoriness. The causes of resistance to cTACE include cTACE-induced liver function impairment (Johnson et al. 1991), heterogeneous lipiodol retention (Lee et al. 2002), and arterioportal shunt formation caused by vascular invasion (Seki and Hori 2012). HCC patients with heterogeneous lipiodol retention have poor blood supplies that are unlikely to be effectively perturbed with arterial embolization alone. In contrast, positive response to DEB-TACE may be associated with the slow release of doxorubicin from the beads in the tumor vascular plexus. Additionally, the lipiodol used during cTACE may pass through the arterioportal shunt, which would not produce embolization of the arterial blood supply to the HCC but would cause extensive ischemia in the normal liver tissue (Oh et al. 2015). However, DEB beads are inherently larger than lipiodol particles and cannot traverse arterioportal shunts; hence, shunts with diameters < 300 μm would be occluded, and continuous doxorubicin delivery would eventually kill the tumors.

There are several limitations to our study. First, as this was a retrospective study, further prospective randomized controlled studies are required to confirm our findings. Second, to date, the first-line treatments for advanced HCC include sorafenib, lenvatinib, and atezolizumab plus bevacizumab. The most suitable systemic therapy for combination with TACE remains to be explored. Last, although early detection of advanced HCC is addressed, it is difficult to define the time limit for early detection from complete cTACE resistance to early progression, and preoperative BCLC B-stage tumor burden and cTACE sessions could affect the degree of ISPA-HCC progression, all of which should be considered in further research.

In conclusion, sorafenib plus DEB-TACE is safe and effective for the treatment of early ISPA-HCC with well-preserved liver function. Combination therapy improves OS, TTP, and local tumor response and does not increase AEs compared to sorafenib monotherapy.

Declarations

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Competing Interests

Authors declared no competing interests.

Author Contributions

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Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

Flowchart showing the procedure for the selection of patients.

BCLC, Barcelona Clinic Liver Cancer; DTS group, patients treated with drug-eluting bead transarterial chemoembolization plus sorafenib; ECOG, Eastern Cooperative Oncology Group (performance status); S group: patients treated with sorafenib monotherapy.

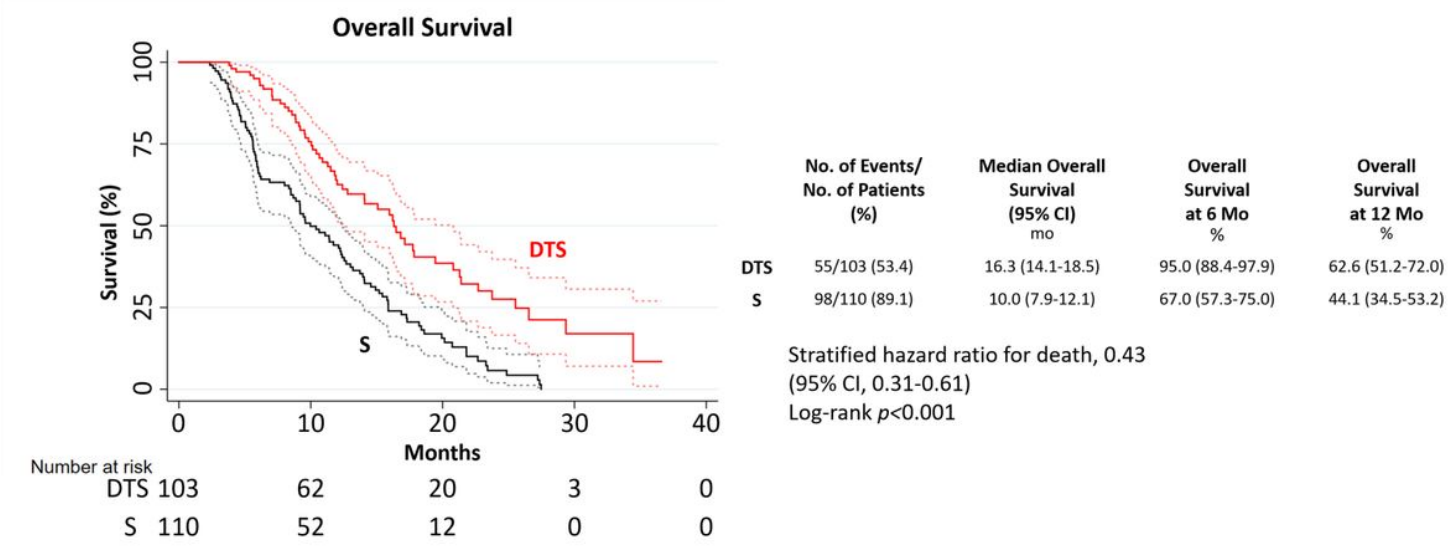

Figure 2

Kaplan–Meier curves showing overall survival in patients in the DTS and S groups.

The dotted lines represent the 95% confidence intervals. DTS group: patients treated with drug-eluting bead transarterial chemoembolization plus sorafenib; S group, patients treated with sorafenib monotherapy; HR, hazard ratio.

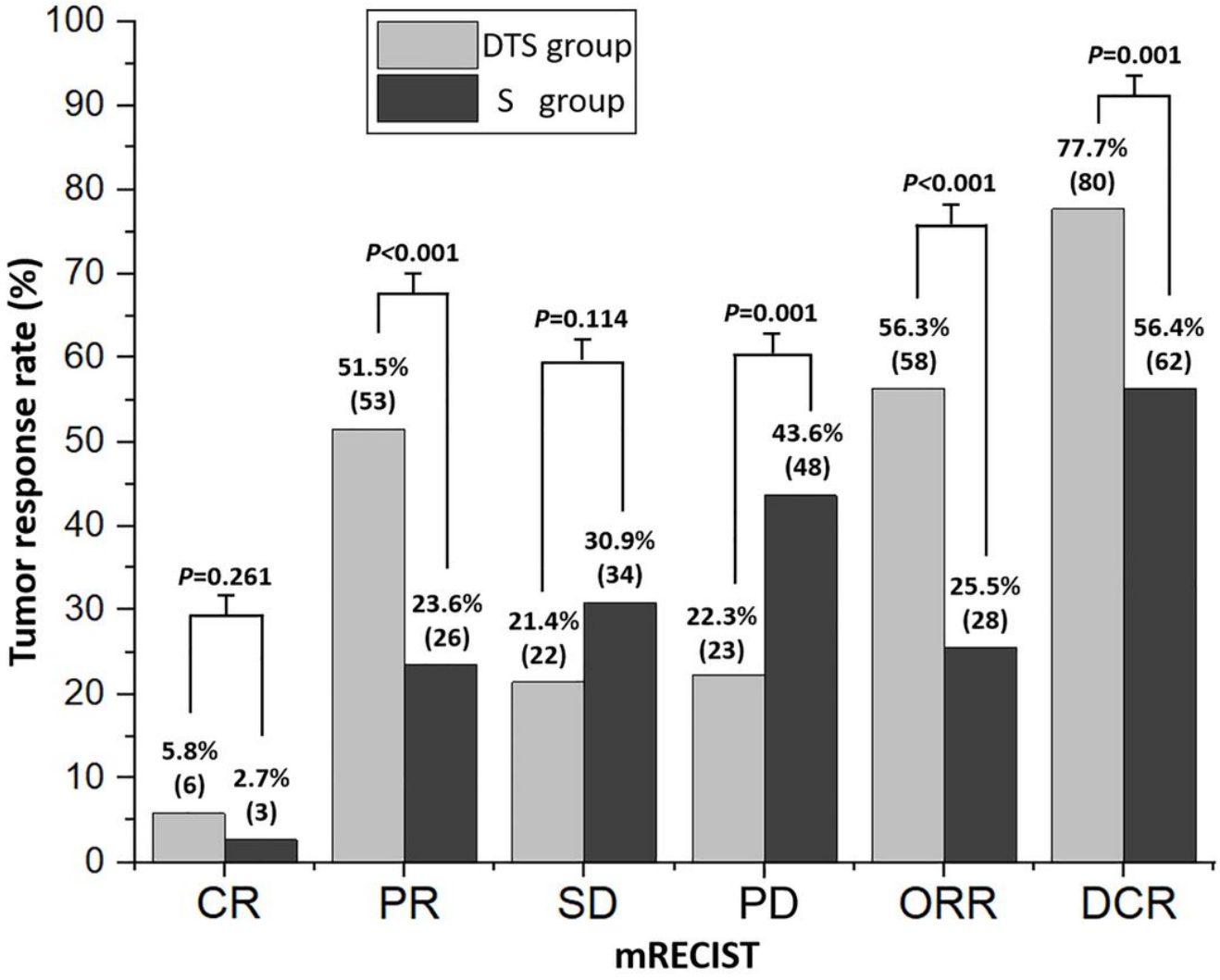

Figure 3

Response assessment of patients in the DTS and S groups according to the mRECIST.

CR, complete response; DCR, disease control rate; DCR = CR + PR + SD; DTS group: patients treated with drug-eluting bead transarterial chemoembolization plus sorafenib; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; ORR = CR + PR; PR, partial response; SD, stable disease; S group, patients treated with sorafenib monotherapy.

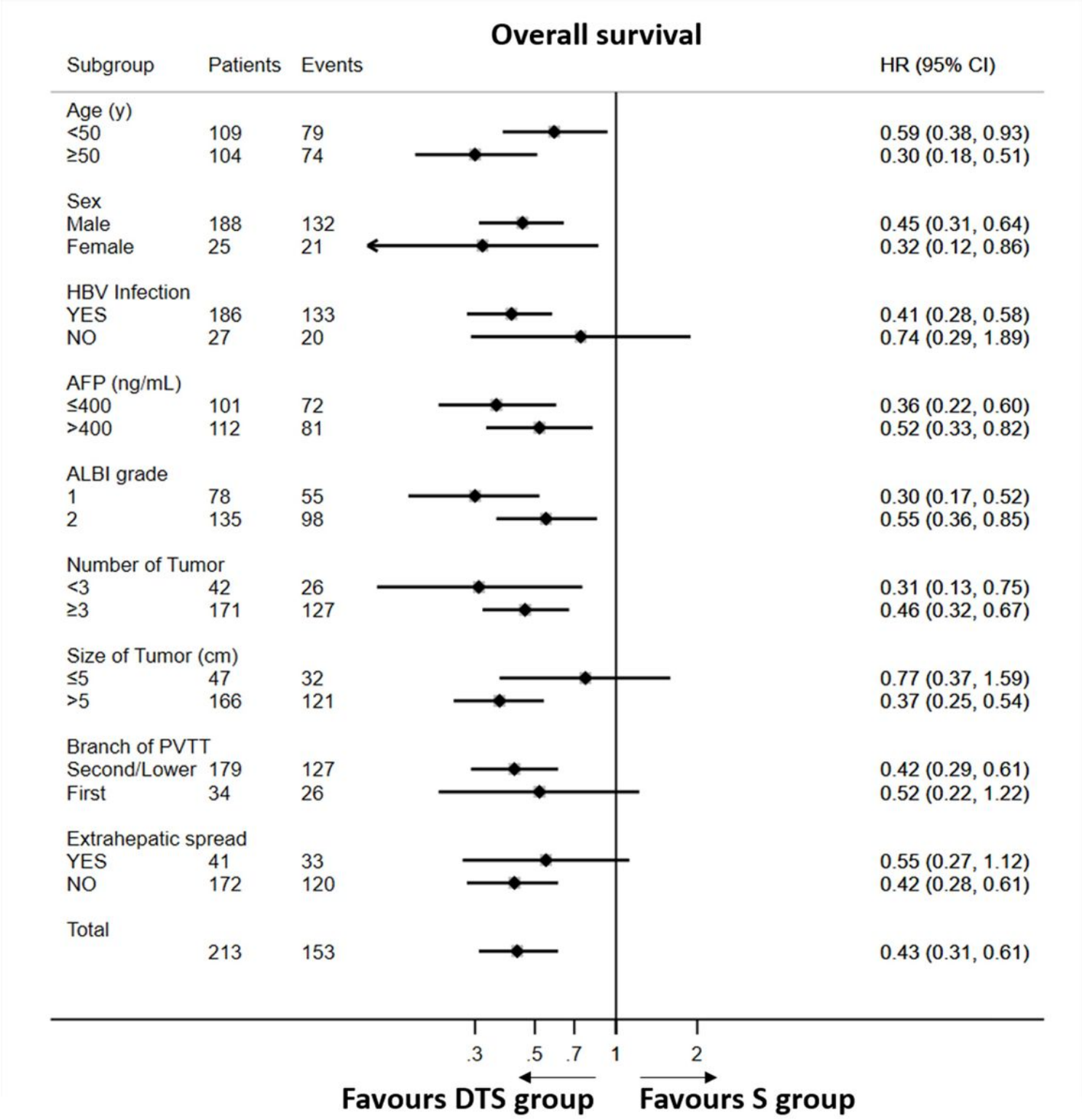

Figure 4

Forest plots of overall survival in the patient subgroups.

Subgroup analyses for overall survival. AFP, α-fetoprotein; HBV, hepatitis B virus; HR, hazard ratio; PVTT, portal vein tumor thrombus; Second/Lower, PVTT in the second- or lower-order branches; First, PVTT in the first-order branches.

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