Radiology

ORIGINAL RESEARCH • VASCULAR AND INTERVENTIONAL RADIOLOGY

^{90}Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial

Elisabeth Dhondt, PhD, MD • Bieke Lambert, PhD, MD[1] • Laurens Hermie, MD • Lynn Huyck, PhD • Peter Vanlangenhove, PhD, MD • Anja Geerts, PhD, MD • Xavier Verhelst, PhD, MD • Maridi Aerts, MD[2] • Aude Vanlander, MD • Frederik Berrevoet, PhD, MD • Roberto Ivan Troisi, PhD, MD[3] • Hans Van Vlierberghe, PhD, MD • Luc Defreyne, PhD, MD

From the Departments of Vascular and Interventional Radiology (E.D., L. Hermie, L. Huyck, P.V., L.D.), Gastroenterology and Hepatology (A.G., X.V., M.A., H.V.V.), and General and HPB Surgery and Liver Transplantation (A.V., F.B.), Ghent University Hospital, C. Heymanslaan 10, 9000 Ghent, Belgium; and the Departments of Diagnostic Sciences (B.L.) and Human Structure and Repair (R.I.T.), Ghent University, Ghent, Belgium. Received July 23, 2021; revision requested September 21; revision received December 1; accepted December 23. **Address correspondence to** E.D. (e-mail: *Elisabeth.dhondt@uzgent.be*).

Current addresses:

[1] Department of Nuclear Medicine, AZ Jan Palfijn and AZ Maria Middelares, Ghent, Belgium.

[2] Department of Gastroenterology, Brussels University Hospital, Jette, Belgium.

[3] Department of Clinical Medicine, Division of HPB Minimally Invasive and Robotic Surgery, Federico II University Hospital, Naples, Italy.

Conflicts of interest are listed at the end of this article.

Radiology 2022; 303:699–710 • https://doi.org/10.1148/radiol.211806 • Content codes: GI IR

Background: Transarterial chemoembolization (TACE) is the recommended treatment for intermediate hepatocellular carcinoma (HCC) according to the Barcelona Clinic Liver Cancer guidelines. Prospective uncontrolled studies suggest that yttrium 90 (^{90}Y) transarterial radioembolization (TARE) is a safe and effective alternative.

Purpose: To compare the efficacy and safety of TARE with TACE for unresectable HCC.

Materials and Methods: In this single-center prospective randomized controlled trial (TRACE), ^{90}Y glass TARE was compared with doxorubicin drug-eluting bead (DEB) TACE in participants with intermediate-stage HCC, extended to Eastern Cooperative Oncology Group performance status 1 and those with early-stage HCC not eligible for surgery or thermoablation. Participants were recruited between September 2011 and March 2018. The primary end point was time to overall tumor progression (TTP) (Kaplan-Meier analysis) in the intention-to-treat (ITT) and per-protocol (PP) groups.

Results: At interim analysis, 38 participants (median age, 67 years; IQR, 63–72 years; 33 men) were randomized to the TARE arm and 34 (median age, 68 years; IQR, 61–71 years; 30 men) to the DEB-TACE arm (ITT group). Median TTP was 17.1 months in the TARE arm versus 9.5 months in the DEB-TACE arm (ITT group hazard ratio [HR], 0.36; 95% CI: 0.18, 0.70; $P = .002$) (PP group, 32 and 34 participants, respectively, in each arm; HR, 0.29; 95% CI: 0.14, 0.60; $P < .001$). Median overall survival was 30.2 months after TARE and 15.6 months after DEB-TACE (ITT group HR, 0.48; 95% CI: 0.28, 0.82; $P = .006$). Serious adverse events grade 3 or higher (13 of 33 participants [39%] vs 19 of 36 [53%] after TARE and DEB-TACE, respectively; $P = .47$) and 30-day mortality (0 of 33 participants [0%] vs three of 36 [8.3%]; $P = .24$) were similar in the safety groups. At the interim, the HR for the primary end point, TTP, was less than 0.39, meeting the criteria to halt the study.

Conclusion: With similar safety profile, yttrium 90 radioembolization conferred superior tumor control and survival compared with chemoembolization using drug-eluting beads in selected participants with early or intermediate hepatocellular carcinoma.

Clinical trial registration no. NCT01381211

Online supplemental material is available for this article.

Hepatocellular carcinoma (HCC) is the most prevalent primary liver tumor, accounting for 8% of cancer-related deaths (1). Prognosis depends on tumor extension, the degree of liver dysfunction, and the patient's performance status. The European Society for the Study of the Liver endorsed the Barcelona Clinic Liver Cancer (BCLC) classification because it links these three major determinants to dynamic treatment guidelines (2). Very early (a single tumor ≤2 cm) and early HCC (single tumor or up to three nodules, with none of them >3 cm) is amenable to curative surgical or ablative treatment. For patients with intermediate-stage (BCLC B) unresectable HCC and preserved liver function, transarterial chemoembolization (TACE) is the standard treatment (2,3). For the advanced BCLC stage C—characterized by vascular invasion, extrahepatic spread, or tumor-induced symptoms—systemic treatment is the standard of care.

Conventional TACE is a level I evidence treatment for intermediate HCC. The major drawback of TACE is the high variability of the procedure: Miscellaneous

Abbreviations

BCLC = Barcelona Clinic Liver Cancer, DEB = drug-eluting bead, HCC = hepatocellular carcinoma, HR = hazard ratio, ITT = intention to treat, ORR = objective response rate, OS = overall survival, PP = per protocol, TACE = transarterial chemoembolization, TARE = transarterial radioembolization, TTP = time to overall tumor progression

Summary

Yttrium 90 radioembolization was superior to chemoembolization using drug-eluting beads for tumor control and survival in nonsurgical Barcelona Clinic Liver Cancer stage A and B hepatocellular carcinoma.

Key Results

- This prospective phase II randomized controlled trial (TRACE) showed the median time to progression was 17.1 months in the yttrium 90 transarterial radioembolization (TARE) arm (n = 38) versus 9.5 months in the drug-eluting bead (DEB) transarterial chemoembolization (TACE) arm (n = 34) (hazard ratio [HR], 0.36; P = .002), justifying early termination of the study.
- Median overall survival was 30.2 months after TARE versus 15.6 months after DEB-TACE (HR, 0.48; P = .006).

transarterial techniques are used to inject different drugs mixed in diverse concentrations. In a high number of patients, conventional TACE is accompanied with a discomforting postembolization syndrome (4). To cope with the limitations and side effects of conventional TACE, TACE with drug-eluting beads (DEBs) was developed (ie, DEB-TACE). In the pilot and later trials, DEB-TACE was better tolerated than conventional TACE for equivalent tumor control (5,6). Similarly, nonbiodegradable microspheres loaded with yttrium 90 (^{90}Y)—a pure beta-emitting isotope—were developed. Retrospective comparative studies of transarterial radioembolization (TARE) with conventional TACE proposed a similar or even superior role for TARE in patients with intermediate HCC, but high-quality prospectively randomized data are lacking (7,8).

The null hypothesis of this prospective randomized trial was that there would be no difference in time to overall progression between TARE and DEB-TACE. The alternative hypothesis is two-sided (TARE could have a shorter or longer time to overall progression compared with DEB-TACE). The aim was to compare the efficacy and safety of ^{90}Y TARE and TACE for nonsurgical early and intermediate HCC. Considering the level I evidence that, compared with conventional TACE, DEB-TACE results in equivalent tumor control with a better safety profile, DEB-TACE was chosen as the comparative arm (5,6).

Materials and Methods

Participants

The Transarterial Radioembolization versus Chemoembolization for the Treatment of Hepatocellular Carcinoma (ie, TRACE) trial is an open-label single-center superiority randomized controlled trial (*ClinicalTrials.gov* identifier: NCT01381211). The study was set up as a two-center trial, but the initial partner withdrew before trial start for logistic reasons. The protocol was approved by the local ethics committee, and written informed consent obtained.

Between September 2011 and March 2018, patients with HCC were screened and enrolled. Patients with BCLC stage B HCC were admitted to the trial, extended to patients with BCLC stage A HCC not amenable to ablation, partial hepatectomy, or transplant. Patients with Eastern Cooperative Oncology Group performance status 1 and/or a Child-Pugh score of 7 were also eligible. HCC diagnosis was established on MRI or CT scan, in accordance with the European Society for the Study of the Liver guidelines (2). Exclusion criteria were greater than 50% liver involvement; extrahepatic disease; invasion of the main, right, or left portal vein; bilirubin over 34 μmol/L, or over 44 μmol/L in case of a single involved segment; and Child-Pugh score higher than 7. An overview of all exclusion criteria can be found in the original protocol (9).

Study Design

Treatment allocation was performed by minimization to balance prognostic factors between trial arms (9). Four parameters were taken into account: Child-Pugh score, Eastern Cooperative Oncology Group performance status, prior curative (resection or ablation) treatment, and bilobar disease. For participants randomized to the TARE arm, TARE-specific work-up was subsequently scheduled. Targeted tumors had to show tracer uptake at technetium 99m–labeled macroaggregated albumin scintigraphy, without extrahepatic microsphere deposition and with lung activity lower than 610-MBq ^{90}Y. If one of these unanticipated situations occurred or angiography demonstrated nonhepatic tumor feeders, TARE was not performed. These participants were included in the intention-to-treat (ITT) but not the per-protocol (PP) analysis.

Procedures

TARE was performed with ^{90}Y glass microspheres (TheraSphere, Boston Scientific) after angiographic tumor mapping with use of cone-beam CT and treatment simulation with 150-MBq technetium 99m macroaggregated albumin. Extrahepatic deposition of radioactivity was avoided and, if needed, the culprit vessels were coiled. Bilobar disease was treated in two separate sessions 30–45 days apart. If the tumor supply at cone-beam CT allowed for a more selective approach, segmental rather than lobar TARE was preferred. ^{90}Y activity was prescribed in accordance with the TheraSphere package insert. We aimed for an absorbed dose of 120 Gy in the treated liver volume except in specific cases (Appendix E1 [online]).

DEB-TACE was performed with doxorubicin DEBs (DC Bead, Boston Scientific) sized 100–300 μm and 300–500 μm (10). The beads were delivered as selectively as possible, with a maximum doxorubicin dose of 150 mg per session. The embolization end point was reached when all the beads were administered, or earlier when sluggish flow was seen in the arterial tumor feeders. If indicated, DEB-TACE was repeated with a maximum of three sessions per lesion and five sessions in total. More details, including procedural and periprocedural pain management, can be found in Appendix E1 (online).

Clinical follow-up visits with blood analysis were scheduled 2 weeks following every treatment and every 3 months thereafter. MRI or CT of the liver was performed at 3-month

intervals. Participants could undergo posttrial local-regional treatment or systemic therapy. If downstaging to within the Milan criteria was achieved, participants could be considered for orthotopic liver transplant. Participants were monitored for 2 years.

Outcomes

The primary end point was defined as time to overall tumor progression (TTP) according to the Modified Response Evaluation Criteria in Solid Tumors, which has become the standard measurement tool for early and intermediate HCC (11–13). TTP was calculated as the time lapse from randomization until progression in target lesions or nontarget lesions or the occurrence of new lesions, including extrahepatic disease. Participants without events were censored at the date of their last follow-up visit or time of death. Participants who underwent transplant were censored at time of last follow-up imaging before transplant. Secondary end points were time to whole-liver progression and time to local progression, defined as the time elapsed from randomization until progression in the whole liver or in the treated liver area, respectively. An additional end point was progression-free survival, defined as the time between randomization and death or radiologic tumor progression, whichever came first. Objective response rate (ORR) was the percentage of participants whose best response was complete or partial according to the Modified Response Evaluation Criteria in Solid Tumors (14). Overall survival (OS) was defined as the time between randomization and death from any cause. Participants who were alive at time of interim analysis (September 2019) were censored. OS was recalculated with censoring of participants who underwent orthotopic liver transplant. Serious adverse events were recorded according to the Common Terminology Criteria for Adverse Events (version 4.03), and participants were monitored for 6 months following the last treatment (15). Thirty-day mortality included all deaths within 30 days after treatment, regardless of the cause of death.

The image analysis and interobserver variation are described in Appendix E1 (online).

Primary and secondary end points were compared between treatment groups by means of ITT and PP analysis. The ITT group included all participants as originally allocated after randomization. The PP group comprised the participants who completed the originally allocated treatment. A subgroup analysis of BCLC stage B participants was performed. Complications and 30-day mortality were evaluated in the safety group, which comprised all participants receiving either TARE or DEB-TACE.

Statistical Analysis

Study sample size for a type I error of 5% with a statistical power of 90% was 136 participants overall based on a 20% improvement in TTP with TARE. A planned interim analysis for efficacy was performed when 45 events (ie, progressions) were observed. At interim analysis, the null hypothesis would be rejected when the hazard ratio (HR) was greater than 2.60 or less than 0.39 or when the *P* value was less than .0024. At final analysis, the null hypothesis would be rejected when the HR was greater than 1.49 or less than 0.67 or when the *P* value was less than .049.

TTP was estimated with the Kaplan-Meier method and compared between both groups by using the log-rank test. HR was calculated with a Cox proportional hazard model. The secondary outcomes of time to whole-liver progression, time to local progression, progression-free survival, and OS were calculated accordingly. Categoric parameters were analyzed with the Fisher exact test. Statistical analyses were performed using IBM SPSS Statistics version 26.

Results

Participant Characteristics

Between September 2011 and March 2018, 487 patients with HCC were screened and 72 enrolled (Fig 1). In the ITT group, 38 participants (median age, 67 years; IQR, 63–72 years; 33 men) were randomized to TARE and 34 participants (median age, 68 years; IQR, 61–71 years; 30 men) to DEB-TACE. Every participant in the DEB-TACE arm received the allocated treatment. Six of 38 participants (16%) randomized to TARE did not undergo the allocated treatment (Fig 1). The PP group comprised 32 participants in the TARE arm (median age, 68 years; IQR, 64–74 years; 28 men) and 34 in the DEB-TACE arm (median age, 68 years; IQR, 61–71 years; 30 men). No participants were lost to follow-up. Median follow-up time was 28 months (IQR, 17–36 months) for participants in the TARE arm and 15.6 months (IQR, 9–31 months) in the DEB-TACE arm. The randomization arms were well balanced regarding baseline characteristics (Table 1). Therapy data in the safety group are shown in Table 2. Because of angiographic work-up, time from randomization to first treatment was longer in the TARE arm. In the DEB-TACE arm, more treatments were carried out, resulting in a longer trial treatment period. Dose and dosimetry data in the safety group can be found in Table E1 (online). Figures 2 and 3 depict typical pre- and posttreatment findings in TARE and DEB-TACE, respectively.

Primary and Secondary End Points in the ITT Group

In the ITT group, primary and secondary end points were as follows. Median TTP was 17.1 months in the TARE arm versus 9.5 months in the DEB-TACE arm (HR, 0.36; 95% CI: 0.18, 0.70; $P = .002$) (Fig 4A). Median time to whole-liver progression and time to local progression for the TARE arm were identical to TTP (17.1 months), whereas in the DEB-TACE arm, time to whole-liver progression was 9.7 months (HR, 0.38; 95% CI: 0.19, 0.77; $P = .005$) and time to local progression was 10 months (HR, 0.32; 95% CI: 0.16, 0.67; $P = .001$). ORR in the treated area was 94% for TARE versus 100% for DEB-TACE. ORR in the liver was 88% for TARE versus 87% for DEB-TACE. Median progression-free survival was 11.8 months in the TARE arm and 9.1 months in the DEB-TACE arm (HR, 0.40; 95% CI: 0.24, 0.67; $P < .001$) (Fig E1A [online]). Downstaging led to transplant in 10 participants in the TARE arm and four in the DEB-TACE arm. Median OS was 30.2 months in the TARE arm and 15.6 months in the DEB-TACE arm

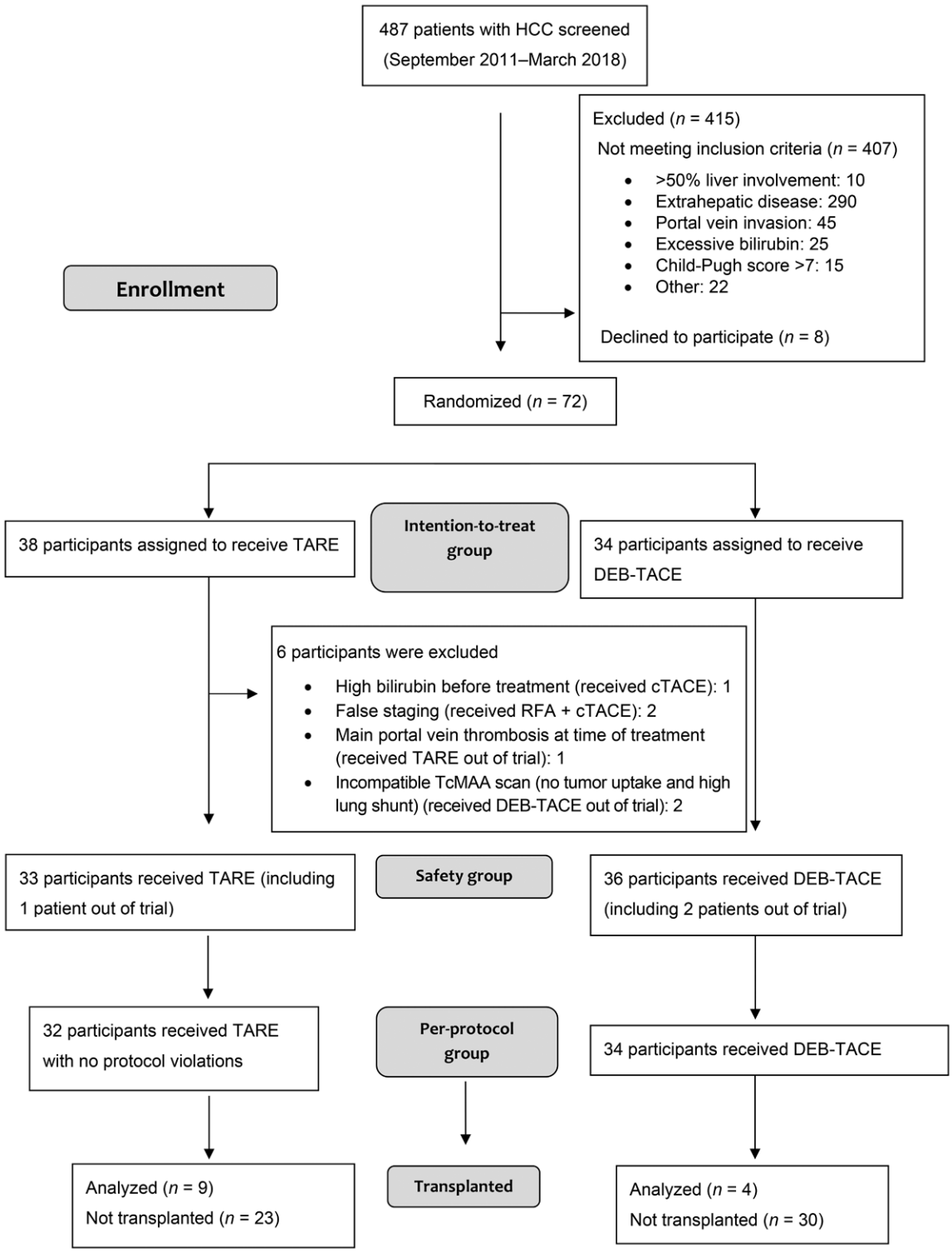

Figure 1: Trial flow diagram. cTACE = conventional transarterial chemoembolization, DEB = drug-eluting bead, HCC = hepatocellular carcinoma, RFA = radiofrequency ablation, TACE = transarterial chemoembolization, TARE = transarterial radioembolization, TcMAA = technetium 99m macroaggregated albumin.

(HR, 0.48; 95% CI: 0.28, 0.82; P = .006) (Fig 5A). Median OS with censoring for orthotopic liver transplant was 27.6 months in the TARE arm and 15.6 months in the DEB-TACE arm (HR, 0.49; 95% CI: 0.28, 0.87; P = .01).

With an HR of 0.36 for the primary end point in the ITT group in favor of TARE, the statistical conditions (HR <0.39) at interim analysis were fulfilled to reject the null hypothesis and request a halt of the study. After observing concordant longer OS

Table 1: Baseline Characteristics in the ITT and PP Groups

Characteristic	ITT Group			PP Group		
	TARE (n = 38)	DEB-TACE (n = 34)	P Value	TARE (n = 32)	DEB-TACE (n = 34)	P Value
Age (y)*	67 (63–72) [51, 85]	68 (61–71) [38, 84]	.81	68 (64–74) [54, 85]	68 (61–71) [38, 84]	.53
Sex			>.99			>.99
M	33 (87)	30 (88)		28 (88)	30 (88)	
F	5 (13)	4 (12)		4 (12)	4 (12)	
Race			.60			>.99
White	37	32		31	32	
Black	1	2		1	2	
Cause of HCC			.56			.79
Alcohol use disorder	27 (71)	24 (70)		21 (66)	24 (70)	
Nonalcoholic steatohepatitis	1 (2.6)	2 (5.9)		1 (3.1)	2 (5.9)	
Hemochromatosis	1 (2.6)	2 (5.9)		1 (3.1)	2 (5.9)	
Viral	5 (13)	5 (15)		5 (16)	5 (15)	
Unknown	4 (10)	1 (2.9)		4 (12)	1 (2.9)	
Child-Pugh score			.24			.43
A	36 (95)	29 (85)		30 (94)	29 (85)	
B	2 (5.3)	5 (15)		2 (6.3)	5 (15)	
ECOG performance status			.73			>.99
0	34 (90)	29 (85)		28 (88)	29 (85)	
1†	4 (11)	5 (15)		4 (13)	5 (15)	
α-fetoprotein (ng/dL)			.73			.71
<400	33 (87)	28 (82)		28 (88)	28 (82)	
≥400	4 (10)	5 (15)		3 (9.4)	5 (15)	
Data missing	1 (2.6)	1 (2.9)		1 (3.1)	1 (2.9)	
Total bilirubin (μmol/L)*	11.1 (8.6–20.5) [3.4, 27.4]	13.7 (10.3–18.1) [1.9, 27.4]	.46	11.1 (8.6–20.5) [3.4, 27.4]	13.7 (10.3–18.1) [1.9, 27.4]	.46
BCLC tumor staging			.52			.73
A	7 (18)	4 (12)		5 (16)	4 (12)	
B	31 (82)	30 (88)		27 (84)	30 (88)	
Prior resection	3 (7.9)	5 (15)	.50	2 (6.3)	5 (15)	.26
Prior ablation	1 (2.6)	1 (2.9)		0 (0)	1 (2.9)	
Tumor burden			>.99			.81
Unilobar	19 (50)	16 (47)		15 (47)	16 (47)	
Bilobar	19 (50)	18 (53)		17 (53)	18 (53)	
Tumor load			.10			.14
≤3 nodules	18 (47)	23 (68)		15 (47)	23 (68)	
>3 nodules	20 (53)	11 (32)		17 (53)	11 (32)	
Lesions			.08			.07
Solitary	8 (21)	4 (12)		7 (22)	4 (12)	
Multifocal	30 (79)	30 (88)		25 (78)	30 (88)	
2–3 foci	10	19		8	19	
4–10 foci	17	10		14	10	
>10 foci	3	1		3	1	
Largest tumor size (cm)			.27			.17
Median with IQR	4.2 (3.1–5.6)	4.7 (3.7–6.7)		4.2 (3.2–5.6)	4.7 (3.7–6.7)	
Mean with 95% CI	4.6 (3.9, 5.3)	5.3 (4.3, 6.3)		4.5 (3.9, 5.1)	5.3 (4.3, 6.3)	
Minimum and maximum	1.5, 12.8	1.3, 15.0		2.0, 9.4	1.3, 15.0	

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. BCLC = Barcelona Clinic Liver Cancer, DEB = drug-eluting bead, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, ITT = intention to treat, PP = per protocol, TACE = transarterial chemoembolization, TARE = transarterial radioembolization.

* Data are medians, with IQRs in parentheses and minimum and maximum values in brackets.

† ECOG performance status 1 in three participants with BCLC stage A HCC and six participants with BCLC stage B HCC.

Table 2: Treatment Data in the Safety Group

Treatment Parameter of Interest	TARE (n = 33)*	DEB-TACE (n = 36)†	P Value
Time from randomization to first treatment (d)‡	24 (20–29) [7, 118]	7.5 (4.0–15) [1, 69]	<.001§
Treatment sessions per participant			<.001‖
1	16	2	
2	17	11	
3	0	12	
4	0	9	
5	0	2	
Median	2	3	
No. of participants with a lesion treated more than once			
Target lesion 1	NA	19/36 (53)	
Target lesion 2	NA	11/32 (34)	
Nontarget lesions	NA	14/28 (50)	
Time interval between treatment sessions (d)‡	46 (41–54) [32, 84]	39 (29–49) [6, 87]	.03§
Total treatment period (d)‡	32 (0–46) [0, 84]	82 (56–122) [0, 266]	<.001§
Approach			>.99‖
Unilobar	16	17	
Bilobar	17	19	
Treatment approach			<.001‖
Selective	7	29	
Lobar	10	3	
Near whole liver	7	4	
Whole liver	9	0	

Note.—Unless otherwise specified, data are numbers of participants, and data in parentheses are percentages. DEB = drug-eluting bead, NA = not applicable, TACE = transarterial chemoembolization, TARE = transarterial radioembolization.

* Thirty-two participants as per protocol plus one participant originally randomized to the TARE arm but who received TARE out of trial (main portal vein thrombosis).

† Thirty-four participants as per protocol plus two participants originally randomized to the TARE arm but who received DEB-TACE out of trial (incompatible technetium 99m–labeled macroaggregated albumin scintigraphy).

‡ Data are medians, with IQRs in parentheses and minimum and maximum values in brackets.

§ P values were calculated by using the Mann-Whitney U test.

‖ P values were calculated by using the Fisher exact test.

with TARE, the trial board considered continuation of the study ethically unjustified, and the trial was stopped.

Primary and Secondary End Points in the PP Group

In the PP group, median TTP was 17.1 months in the TARE arm and 9.5 months in the DEB-TACE arm (HR, 0.29; 95% CI: 0.14, 0.60; $P < .001$) (Fig 4B). Median OS was identical to the ITT group for both arms (HR, 0.47; 95% CI: 0.26, 0.83; $P = .008$) (Fig 5B). The other end points corresponded to the outcomes in the ITT group (Table E2, Fig E1B [online]). Subgroup analysis of participants with BCLC stage B HCC showed a median TTP of 12.8 months in the TARE arm and 9.6 months in the DEB-TACE arm (HR, 0.37; 95% CI: 0.17, 0.83; $P = .009$) (Table E3 [online]). Thirteen of 32 participants (41%) in the TARE arm and 18 of 34 participants (53%) in the DEB-TACE arm underwent posttrial treatments ($P = .34$) (Appendix E1, Table E4 [online]).

The Cox proportional hazard assumption for the different end points was verified by evaluating the log-minus-log plots. The log-minus-log plots showed noncrossing curves for all end points. Hence, there was no strong indication that the proportional hazard assumption was violated. Conditional HRs for all end points in the ITT and PP groups were recalculated with a Cox proportional hazard model adjusted for the prespecified stratifying covariates (Tables E5, E6 [online]). As the HRs in the adjusted models differed minimally from the HRs in the unadjusted models, it was decided to report the latter HRs, as described in the original study protocol.

Complications and 30-day Mortality in the Safety Group

In the TARE arm, 13 of 33 participants (39%) experienced at least one serious adverse event grade 3 or higher compared with 19 of 36 participants (53%) in the DEB-TACE arm ($P = .47$) (Table 3). Six deaths within 6 months after last treatment were noted as serious adverse event grade 5 toxicities (Table 4).

Discussion

In this randomized controlled phase II trial, TRACE, yttrium 90 transarterial radioembolization (TARE) resulted in a significantly slower tumor progression compared with drug-eluting bead (DEB) transarterial chemoembolization (TACE) for treatment of intermediate- and early-stage hepatocellular carcinoma

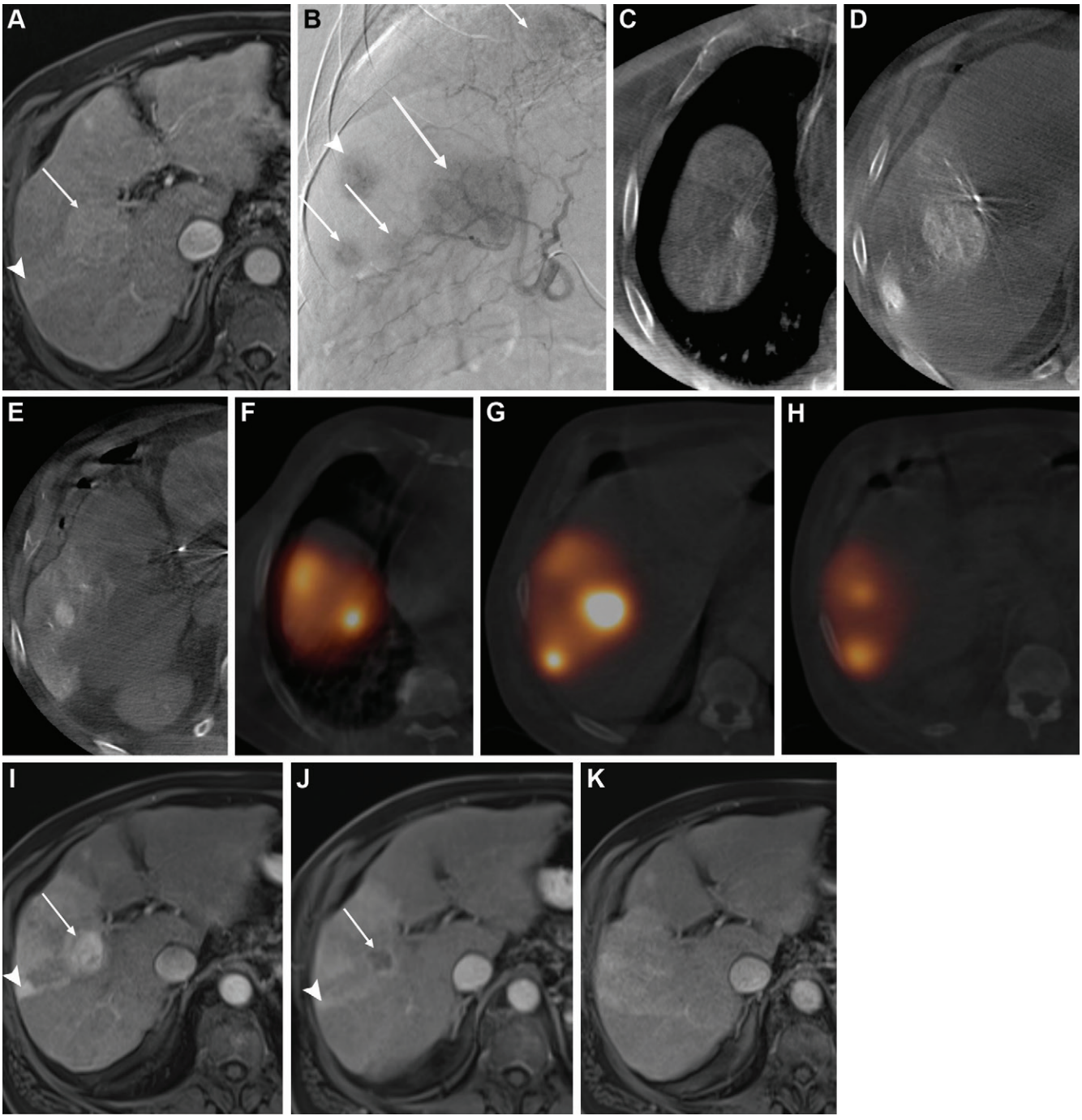

Figure 2: Images in a 64-year-old man with multifocal hepatocellular carcinoma (HCC) in the right lobe. **(A)** Arterial phase axial T1-weighted gadolinium-enhanced volumetric interpolated breath-hold examination (VIBE) image shows two HCCs (arrow and arrowhead) on the border of segments V and VIII. Three other HCCs in segments VIII and V are not shown. **(B)** Selective arteriographic image of the right hepatic artery shows five HCCs, two corresponding to those in **A** (large arrow and arrowhead) and three additional (small arrows). **(C–E)** Axial intra-arterial cone-beam CT images confirm the HCCs within the arterial territory of the anterior right hepatic artery. **(F–H)** Axial SPECT images after administration of 150-MBq technetium 99m–labeled macroaggregated albumin in the anterior right hepatic artery confirm tracer uptake by the HCCs. **(I,J)** Arterial phase axial T1-weighted gadolinium-enhanced VIBE images 3 months after selective yttrium 90 radioembolization at the level of **A** still show hypervascularity in the segment V and VIII HCCs (arrow and arrowhead), which disappeared 6 months later. **(K)** Arterial axial T1-weighted VIBE image at 15 months: no HCCs could be identified in the radiation-induced shrunken part of the right liver lobe. Ultimately, the participant was downstaged and underwent transplant 17.4 months after randomization.

not amenable to curative treatment (median time to overall tumor progression of 17.1 months vs 9.5 months, respectively). Time to local progression for the TARE arm was 17.1 months versus 10 months in the DEB-TACE arm.

By achieving a median TTP of 9.5 months both in the ITT and PP groups, DEB-TACE did not underperform compared with data in the literature (5.5–10.5 months) (5,6,16–18). The assumption of 13.3-month median TTP for TARE at sample

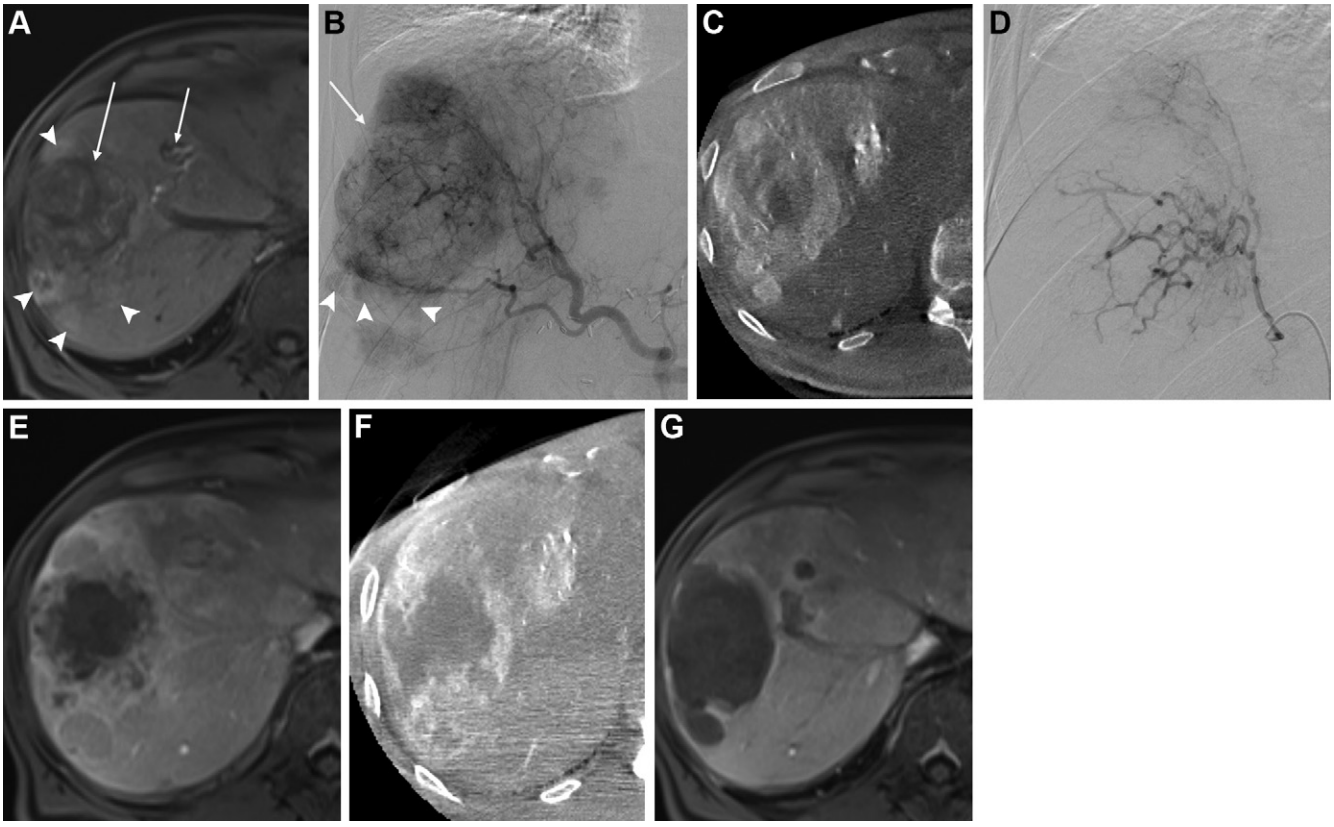

Figure 3: Images in a 67-year-old man with multifocal hepatocellular carcinoma (HCC). **(A)** Arterial phase axial T1-weighted gadolinium-enhanced volumetric interpolated breath-hold examination (VIBE) image shows one large HCC (large arrow) in segments VII and VIII, multiple satellite HCCs (arrowheads), and an HCC in segment IVA (small arrow). Other HCC foci in segments IV, V, VI, and VII are not shown. **(B)** Arteriographic image of the celiac trunk shows the large lesion (arrow) with multiple satellite lesions (arrowheads) and lesions in segments IV and VI. **(C)** Axial intra-arterial cone-beam CT image confirms the HCCs. **(D)** Arteriographic image of one major feeder of the largest HCC. Superselective injection of 100 mg doxorubicin-loaded DC Bead 100–300 μm (Boston Scientific) was performed. **(E)** Arterial phase axial T1-weighted gadolinium-enhanced VIBE image 1 month after the second drug-eluting bead (DEB) transarterial chemoembolization (TACE) session shows central necrosis of the largest HCC. **(F)** Axial intra-arterial cone-beam CT image at the beginning of the third DEB-TACE session confirms the findings in **E**. **(G)** Arterial phase axial T1-weighted gadolinium-enhanced VIBE image 1 month after the fourth and final DEB-TACE session proves necrosis of the large HCC and all satellite HCCs. Unfortunately, the participant developed new HCCs in a nontreated area.

size calculation was consistent with the findings in a sample of participants with intermediate HCC published after trial start (19,20) and with the data herein (median TTP of 12.8 months for intermediate HCC). During TRACE trial recruitment, a pilot study comparing TARE with DEB-TACE for intermediate HCC, including 12 participants in each arm, reported no difference in median TTP (12.2 months and 11 months, respectively, compared with 12.8 months and 9.6 months in the BCLC B subgroup of the current study) (21).

One randomized controlled trial comparing ^{90}Y resin TARE with conventional TACE found no difference between the two arms. Median progression-free survival was 3.6 months (95% CI: 2.3, 6.2) and 3.7 months (95% CI: 1.6, 11.0), respectively (22). A second randomized controlled trial showed a significantly better outcome with ^{90}Y glass TARE compared with conventional TACE (median TTP was not reached [>26 months] vs 6.8 months, respectively) (23). The fewer treatments and lower dosage administered on average might explain the shorter TTP with TACE in the latter study. In view of the small study samples, the impact of these randomized controlled trials is relative.

In our study, TARE and DEB-TACE had equally high ORR. A high ORR of almost 90% or more is what can be expected with TARE (23). For DEB-TACE, however, reported ORRs are much lower (42%–52%) (5,14,17). Definitions of ORR vary, but more importantly, many investigators adhered to less stringent treatment protocols (14,17). In our study, DEB-TACE was pushed to the limit by allowing five sessions. As such, each lesion could be targeted with a maximum doxorubicin dose up to three times, a strategy that resulted in a high ORR. A downside of the superselective and repetitive strategy in DEB-TACE is the reported tumor progression in the nontreated area during the longer treatment period. This is reflected in a 13% lower ORR in the liver (87%) compared with the ORR in the treated area (100%).

In our study, local tumor control (time to local progression) was more durable with TARE. As in DEB-TACE, time to local progression was significantly shorter, and evidence arises that the circumferential parenchyma, most vulnerable for tumor progression, was undertreated with the standard superselective approach (5,6). TARE treatment was lobar in 26 of 33 participants (79%), preemptively exposing the tissue surrounding the tumor to brachytherapy.

The trial demonstrated a TTP-concordant significant survival benefit for the participants in the TARE arm. Indeed, OS after

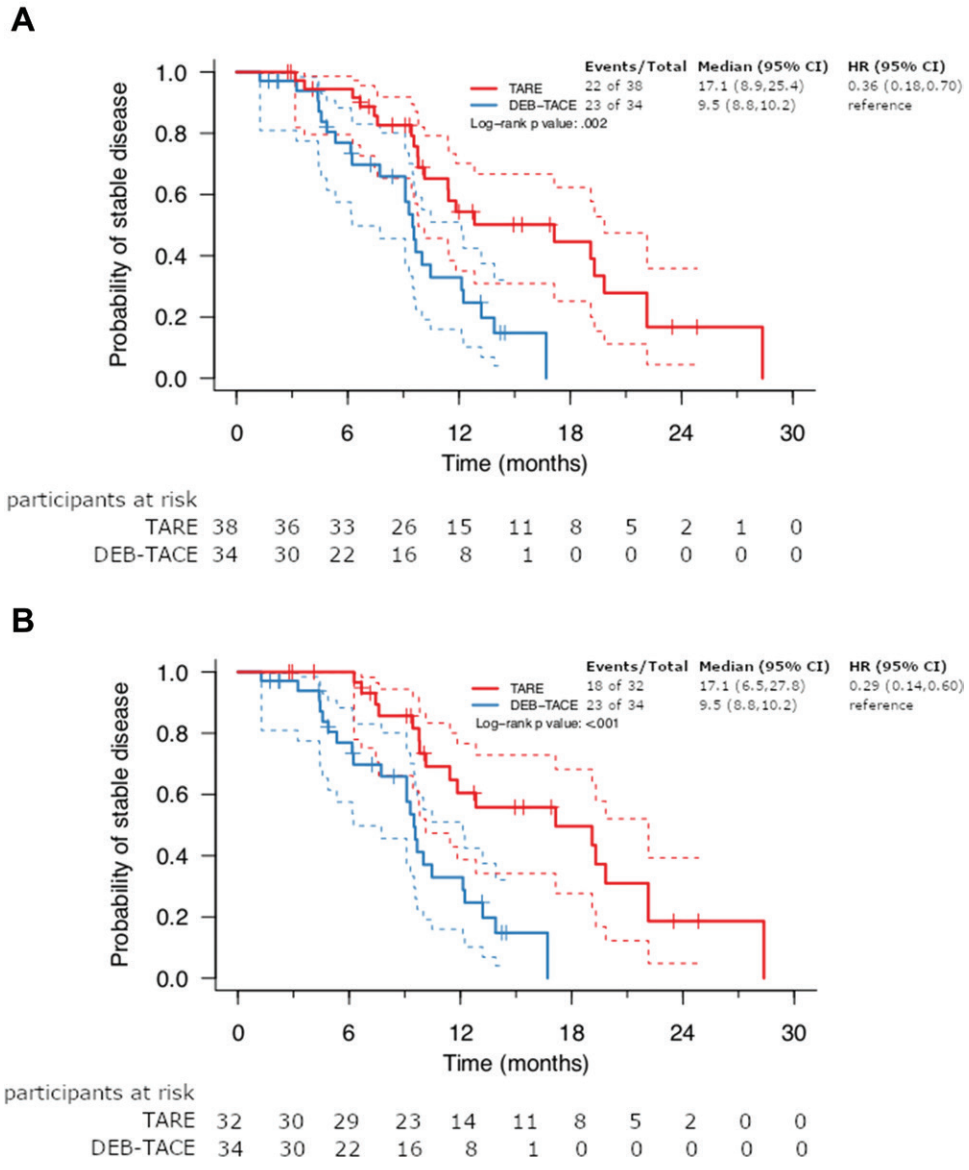

Figure 4: Efficacy outcomes in participants in the Transarterial Radioembolization versus Chemoembolization for the Treatment of Hepatocellular Carcinoma (ie, TRACE) trial randomized to transarterial radioembolization (TARE) or drug-eluting bead (DEB) transarterial chemoembolization (TACE). Kaplan-Meier plots show time to overall tumor progression in **(A)** the intention-to-treat group and **(B)** the per-protocol group. *P* values were calculated by using the log-rank test. Dashed lines indicate 95% CIs. HR = hazard ratio.

TARE improves substantially because of its success in down-staging to orthotopic liver transplant (24). In our study, the high number of participants who underwent transplant in the TARE arm only partially explained OS discrepancy. Whether participants were censored for transplant or not, the median OS remained better in the TARE arm. The recently updated BCLC staging system adheres to TACE for intermediate-stage HCC but with an optimistic OS target of 26–30 months (3). TARE meets the expectations, but DEB-TACE would underperform by 10 months. The pursuable OS target was derived from three phase III trials, revealing a wide range of median OS times, from 21 to 33 months (14,17,25). In the non-Asian subsample of these TACE trials, median OS drops to 17.5–19.6 months, approximating the OS of our study. The former studies also included more patients with lower tumor burden, a factor prolonging OS (14,17).

Posttrial therapy may confound OS (3). An equal number of participants in both trial arms underwent conventional TACE or DEB-TACE treatment. Based on DEB-TACE and conventional TACE equivalence, posttrial local-regional treatments confounded OS to a lesser degree (5,6,26).

An excess of adverse event grade 5 deaths in the DEB-TACE arm (five of 36 participants vs one of 33 after TARE) contributed to the divergence of the survival curves. The maximum doxorubicin dose and the superselective approach conformed to the pivotal DEB-TACE trial (5). Similarly, other DEB-TACE trials observed 2%–9% therapy-related deaths (5,17,18). The lobar or whole-liver approach

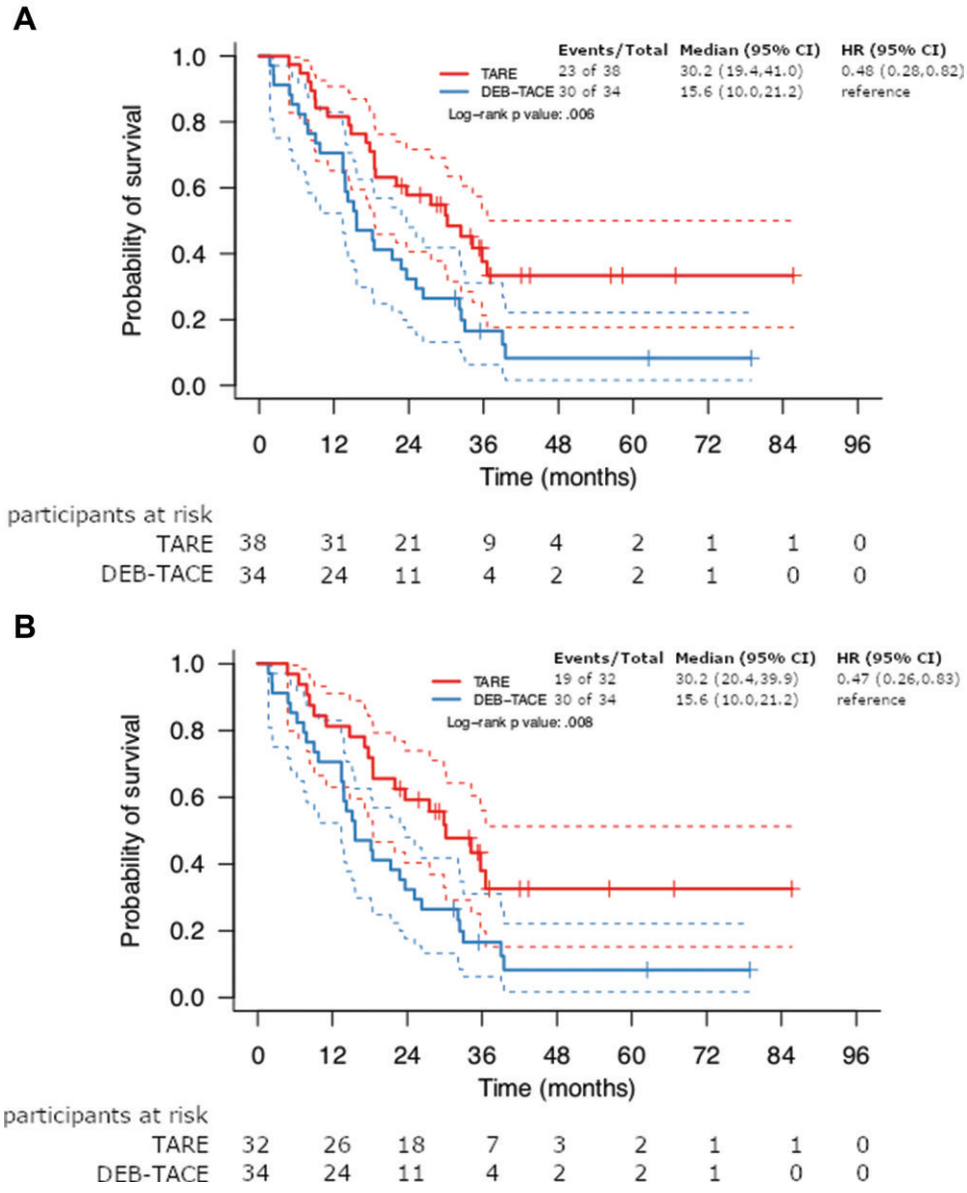

Figure 5: Survival outcomes in participants in the Transarterial Radioembolization versus Chemoembolization for the Treatment of Hepatocellular Carcinoma (ie, TRACE) trial randomized to transarterial radioembolization (TARE) or drug-eluting bead (DEB) transarterial chemoembolization (TACE). Kaplan-Meier plots show overall survival in **(A)** the intention-to-treat group and **(B)** the per-protocol group. *P* values were calculated by using the log-rank test. Dashed lines indicate 95% CIs. HR = hazard ratio.

in TARE entails an inherent risk of liver failure. With the standard dosimetry in the current study, the risk turned out to be low; only one participant died due to radioembolization-induced liver disease.

Our study had several limitations. First, participant accrual was slow. To improve accrual, patients with nonsurgical BCLC stage A HCC were also eligible for inclusion, in accordance with the approach in the investigational hospital. Second, personalized dosimetry, as advocated in guidelines released in 2020 by an expert group, was not applied in this trial (27–29). Such an approach might have further improved the over 90% ORR in TARE.

In view of the high ORR in DEB-TACE as well, future strategies should not focus on smaller bead size but on preemptive treatment of the peritumoral liver tissue (30,31). The investigational biodegradable DEBs might allow lobar treatment with an acceptable risk of parenchymal damage for equivalent antitumor activity.

In conclusion, yttrium 90 (^{90}Y) glass radioembolization, when compared with drug-eluting bead chemoembolization, resulted in superior tumor control and survival in participants with nonsurgical Barcelona Clinic Liver Cancer (BCLC) stage A and B hepatocellular carcinoma (HCC). Because the safety profile was similar for both arms, ^{90}Y glass radioembolization may become a legitimate local-regional treatment option in this patient population. To grant ^{90}Y radioembolization a place in HCC treatment algorithms such as the BCLC classification, randomized phase III trials are warranted.

Table 3: SAEs until 6 Months after Treatment and 30-day Mortality in the Safety Group

No. and Type of SAEs	TARE (*n* = 33)	DEB-TACE (*n* = 36)	*P* Value*
No. of participants with at least one SAE†	13 (39)	19 (53)	.47
Total no. of SAEs	20	34	
No. of grade 3 toxicities	19	29	
Blood and lymphatic system disorders	0	1	
Musculoskeletal and connective tissue disorders	0	2	
Nervous system disorders	0	1	
Cardiac disorders	0	2	
Renal and urinary disorders	5	5	
Hepatobiliary disorders	14	12	
Respiratory, thoracic, and mediastinal disorders	0	6	
No. of participants with grade 5 toxicities	1 (3.0)	5 (14)	.21
Thirty-day mortality	0 (0)	3 (8.3)	.24

Note.—Data in parentheses are percentages. DEB = drug-eluting bead, SAE = serious adverse event, TACE = transarterial chemoembolization, TARE = transarterial radioembolization.

* *P* values were calculated by using the Fisher exact test.

† Adverse event grade 3–5 according to the Common Terminology Criteria for Adverse Events version 4.03.

Table 4: Grade 5 Serious Adverse Events

Participant No.	Treatment Arm	Treatment Session Closest to Event	Days Since Last Treatment	Days Since First Treatment	CTCAE Category	Detailed Information	Relation with Treatment
1	TARE	Second	87	122	Hepatobiliary	Radiation-induced liver disease	Definite
2	DEB-TACE	Third	86	142	Unknown cause	Sudden death while listed for transplant	Unlikely
3	DEB-TACE	Second	6	59	Infections and infestations	Septic shock	Definite
4	DEB-TACE	Second	78	112	Infections and infestations	Liver abscess with septic shock	Definite
5	DEB-TACE	Third	16	180	Infections and infestations	Metabolic lactate acidosis and acute kidney injury	Definite
6	DEB-TACE	First	24	24	Cardiac	Non–ST segment elevation myocardial infarction	Unlikely

Note.—CTCAE = Common Terminology Criteria for Adverse Events version 4.03, DEB = drug-eluting bead, TACE = transarterial chemoembolization, TARE = transarterial radioembolization.

Author contributions: Guarantors of integrity of entire study, **B.L., H.V.V., L.D.**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **E.D., B.L., P.V., A.G., X.V., M.A., H.V.V., L.D.**; clinical studies, **E.D., B.L., L. Hermie, L. Huyck, P.V., A.G., X.V., M.A., F.B., R.I.T., H.V.V., L.D.**; statistical analysis, **E.D., B.L., L. Huyck, P.V., A.G., M.A., L.D.**; and manuscript editing, **E.D., B.L., P.V., A.G., X.V., M.A., A.V., F.B., R.I.T., H.V.V., L.D.**

Data sharing: Data generated or analyzed during the study are available from the corresponding author by request.

Disclosures of conflicts of interest: **E.D.** No relevant relationships. **B.L.** No relevant relationships. **L. Hermie** No relevant relationships. **L. Huyck** No relevant relationships. **P.V.** No relevant relationships. **A.G.** No relevant relationships. **X.V.** No relevant relationships. **M.A.** No relevant relationships. **A.V.** No relevant relationships. **F.B.** No relevant relationships. **R.I.T.** No relevant relationships. **H.V.V.** No relevant relationships. **L.D.** No relevant relationships.

References

1. Global Burden of Disease Liver Cancer Collaboration; Akinyemiju T, Abera S, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. JAMA Oncol 2017;3(12):1683–1691.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69(1):182–236. [Published correction appears in J Hepatol 2019;70(4):817.]
3. Llovet JM, Villanueva A, Marrero JA, et al. Trial design and endpoints in hepatocellular carcinoma: AASLD Consensus Conference. Hepatology 2021;73(Suppl 1):158–191.
4. Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JF. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. Hepatology 2016;64(1):106–116.
5. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33(1):41–52.

6. Golfieri R, Giampalma E, Renzulli M, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014;111(2):255–264.
7. Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer 2010;116(5):1305–1314.
8. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2011;140(2):497–507.e2.
9. Seinstra BA, Defreyne L, Lambert B, et al. Transarterial RAdioembolization versus ChemoEmbolization for the treatment of hepatocellular carcinoma (TRACE): study protocol for a randomized controlled trial. Trials 2012;13(1):144.
10. Malagari K, Chatzimichael K, Alexopoulou E, et al. Transarterial chemoembolization of unresectable hepatocellular carcinoma with drug eluting beads: results of an open-label study of 62 patients. Cardiovasc Intervent Radiol 2008;31(2):269–280.
11. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30(1):52–60.
12. Llovet JM, Lencioni R. mRECIST for HCC: performance and novel refinements. J Hepatol 2020;72(2):288–306.
13. Ghosn M, Derbel H, Kharrat R, et al. Prediction of overall survival in patients with hepatocellular carcinoma treated with Y-90 radioembolization by imaging response criteria. Diagn Interv Imaging 2021;102(1):35–44.
14. Kudo M, Han G, Finn RS, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial. Hepatology 2014;60(5):1697–1707.
15. Common Terminology Criteria for Adverse Events. U.S. Department of Health and Human Services. http://evs.nci.nih.gov/ftp1/CTCAE/About.html. Published May 28, 2009. Updated June 14, 2010. Accessed October 13, 2021.
16. Facciorusso A, Mariani L, Sposito C, et al. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Gastroenterol Hepatol 2016;31(3):645–653.
17. Meyer T, Fox R, Ma YT, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. Lancet Gastroenterol Hepatol 2017;2(8):565–575.
18. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. J Hepatol 2016;64(5):1090–1098.
19. El Fouly A, Ertle J, El Dorry A, et al. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? Liver Int 2015;35(2):627–635.
20. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 2010;138(1):52–64.
21. Pitton MB, Kloeckner R, Ruckes C, et al. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol 2015;38(2):352–360.
22. Kolligs FT, Bilbao JI, Jakobs T, et al. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. Liver Int 2015;35(6):1715–1721.
23. Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2016;151(6):1155–1163.e2.
24. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 2009;9(8):1920–1928.
25. Kudo M, Cheng AL, Park JW, et al. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. Lancet Gastroenterol Hepatol 2018;3(1):37–46.
26. Facciorusso A, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: a meta-analysis. Dig Liver Dis 2016;48(6):571–577.
27. Salem R, Padia SA, Lam M, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. Eur J Nucl Med Mol Imaging 2019;46(8):1695–1704.
28. Garin E, Tselikas L, Guiu B, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol 2021;6(1):17–29.
29. Hermann AL, Dieudonné A, Ronot M, et al. Relationship of tumor radiation–absorbed dose to survival and response in hepatocellular carcinoma treated with transarterial radioembolization with ^{90}Y in the SARAH study. Radiology 2020;296(3):673–684.
30. Malagari K, Moschouris H, Kiakidis T, et al. Five-years outcome analysis of 142 consecutive hepatocellular carcinoma patients treated with doxorubicin eluting microspheres 30-60 μm: results from a single-centre prospective phase ii trial. Cardiovasc Intervent Radiol 2019;42(11):1551–1562.
31. Kang YJ, Lee BC, Kim JK, et al. Conventional versus small doxorubicin-eluting bead transcatheter arterial chemoembolization for treating Barcelona Clinic Liver Cancer Stage 0/A hepatocellular carcinoma. Cardiovasc Intervent Radiol 2020;43(1):55–64.