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BRIEF REPORT

Transarterial Chemoembolization With Drug-Eluting Beads Versus Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: Outcomes From a Multicenter, Randomized, Phase 2 Trial (the TRENDY Trial)

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Purpose: To compare transarterial chemoembolization delivered with drug eluting beads (TACE-DEB) with stereotactioc body radiation therapy (SBRT) in patients with hepatocellular carcinoma (HCC) in a multicenter randomized trial.

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Research data have been stored in a repository at Erasmus MC. The data are not available for public use, but specific requests will be considered and can be sent to the principal investigator of the study (A.M.R.).

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Methods and Materials: Patients were included if they were eligible for TACE. They could also be recruited if they required treatment prior to liver transplantation. A maximum of four TACE-DEB procedures and ablation after incomplete TACE-DEB were both allowed. SBRT was delivered in six fractions of 8-9Gy. Primary end point was time to progression (TTP). Secondary endpoints were local control (LC), overall survival (OS), response rate (RR), toxicity, and quality of life (QoL). The calculated sample size was 100 patients.

Results: Between May 2015 and April 2020, 30 patients were randomized to the study. Due to slow accrual the trial was closed prematurely. Two patients in the SBRT arm were considered ineligible leaving 16 patients in the TACE-DEB arm and 12 in the SBRT arm. Median follow-up was 28.1 months. Median TTP was 12 months for TACEDEB and 19 months for SBRT (p=0.15). Median LC was 12 months for TACE-DEB and >40 months (not reached) for SBRT (p=0.075). Median OS was 36.8 months for TACEDEB and 44.1 months for SBRT (p=0.36). A post-hoc analysis showed 100% for SBRT 1- and 2-year LC, and 54.4% and 43.6% for TACE-DEB (p=0.019). Both treatments resulted in RR>80%. Three episodes of possibly related toxicity grade ≥3 were observed after TACE-DEB. No episodes were observed after SBRT. QoL remained stable after both treatment arms.

Conclusions: In this trial, TTP after TACE-DEB was not significantly improved by SBRT, while SBRT showed higher local antitumoral activity than TACE-DEB, without detrimental effects on OS, toxicity and QoL. To overcome poor accrual in randomized trials that include SBRT, and to generate evidence for including SBRT in treatment guidelines, international cooperation is needed. © 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

Transarterial chemoembolization (TACE) is a widely used local treatment option recommended for patients with intermediate stage (Barcelona Clinic Liver Cancer stage B) hepatocellular carcinoma (HCC) or for those in early stage for whom techniques such as resection or ablation are not feasible.[1] TACE induces objective sustained responses for at least 6 months and improves survival for patients with unresectable HCC.[2,3] After TACE delivered with drug-eluting beads (TACE-DEB), the following rates of local disease control (complete response [CR], partial response [PR], and stable disease) were reported: 63% at 6 months and 54% and 60% at 1 year.[4-6]

The chance of sustained local tumor control at 1 and 2 years after stereotactic body radiation therapy (SBRT) was shown in phase 1 and 2 trials and retrospective studies to range between 87% and 95%.[7-9] However, despite its antitumor activity, SBRT is not regarded as playing a role within the Barcelona Clinic Liver Cancer treatment strategy, as no randomized trials have compared SBRT with other treatment options.

The TRENDY trial was developed to generate evidence from randomized trials that might support the use of SBRT as a treatment option for HCC.

Methods and Materials

Study design

In this open-label, prospective, multicenter, randomized, phase 2 trial, we randomized patients 1:1 between TACE-DEB (standard arm) and SBRT (experimental arm).

Hypothesis

Our hypothesis was that the time to progression (TTP) would be more favorable after SBRT.

Study population

Patients were candidates for the study if they were ineligible for surgery or ablation. This included those who required treatment before liver transplantation and those who relapsed after surgery or ablation. All patients had to be discussed in a multidisciplinary tumor board. Two additional inclusion criteria were a noncirrhotic liver or a liver with cirrhosis Child-Pugh A and 1 to 3 tumors up to a cumulative diameter of ≤6 cm. Table E1 specifies the other inclusion and exclusion criteria.

Treatment

TACE-DEB

Chemoembolization was performed by delivering DEB, that is, hydrogel-based microspheres (Biocompatibles UK, Ltd, HepaSphere Biosphere Medical) loaded with the chemotherapeutic agent doxorubicin. If 1-, 3-, or 6-month follow-up computed tomography or magnetic resonance imaging scan showed residual enhancement of the treated lesion, a second, third, or even fourth TACE-DEB procedure was allowed. After randomization and TACE-DEB, the centers delivered ablation to the tumor remnant at their own discretion.

SBRT

The radiation therapy approach used for this study had already been tested with favorable outcome and limited hepatic toxicity in a phase 1-2 trial.[8] A risk-adapted dose prescription was applied with a maximum dose of 6 × 9 Gy

(Canadian protocol), while 6 × 8 Gy was acceptable as lowest total dose. See the Appendix E1 for information about respiratory control and the SBRT quality assurance (QA) protocol (Table E2).

Study parameters

The primary endpoint was TTP.[10] Secondary endpoints were local control (LC), overall survival (OS), response rate (CR and PR), toxicity scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, and quality of life (QoL). More information on study parameters is provided in the Appendix E1.

Patients who received a transplant before progression were censored for TTP at the date of transplantation. Similarly, patients who received a transplant before local recurrence were censored for LC on the date of transplantation.

Sample size calculation

To calculate the sample size, we selected the median TTP of 2 studies.[7,11] Median TTP was 16 months for the TACE-DEB group and 36.5 months for the SBRT group. For the sample size calculation, we used these results to derive a hazard ratio (HR) of 0.438 with power $1 - ß = 0.80$ (2-sided significance level $\alpha = 0.05$). One hundred patients had to be randomized 1:1 to both arms. See Appendix E1 for additional information.

Statistics

Analyses were performed according to the modified intention-to-treat (m-ITT) principle. In other words, patients were analyzed according to the arms to which they had been assigned, but only after the exclusion of patients who had retrospectively been considered ineligible on the basis of information that should have been available before randomization. A post hoc analysis was performed, in which TTP was not censored at liver transplantation. Also, a post hoc analysis for LC was performed in the per-protocol population, that is, in the patients in the m-ITT population who had received the treatment to which they had been assigned, also taking into account compliance with the treatment protocol. For SBRT, this meant compliance with the SBRT QA planning protocol (absence of major deviations). A third post hoc analysis was performed that took into account the treatment the patients had actually received ("as treated"). Safety data were analyzed according to the treatment the patients had undergone. A P value $\leq .05$ was considered statistically significant. More information on the statistical methods is presented in Appendix E1.

Results

Study population

Between May 1, 2015, and April 14, 2020, 30 patients were included and randomized in the study (Fig. 1). As recruitment was very slow and numbers lower than anticipated, the study was closed on June 1, 2020.

Two of the 30 included patients, both randomized to the SBRT arm, were retrospectively considered to be ineligible, one because of a low thrombocyte count at randomization and the other because of the number of tumors in the liver at randomization (Fig. 1). Exclusion of these 2 patients resulted in 28 patients in the m-ITT population with 16 randomized and treated with TACE-DEB and 12 randomized and planned for SBRT. One patient in the SBRT group was ultimately treated with TACE-DEB, as the implanted fiducial markers were not visible to the tracking system in the linear accelerator. Median follow-up was 28.1 months (range, 12.5-51.3 months). Table 1 presents the patient and tumor characteristics of the 28 eligible patients. There was a major SBRT QA protocol deviation in 1 patient (87% planning target volume coverage).

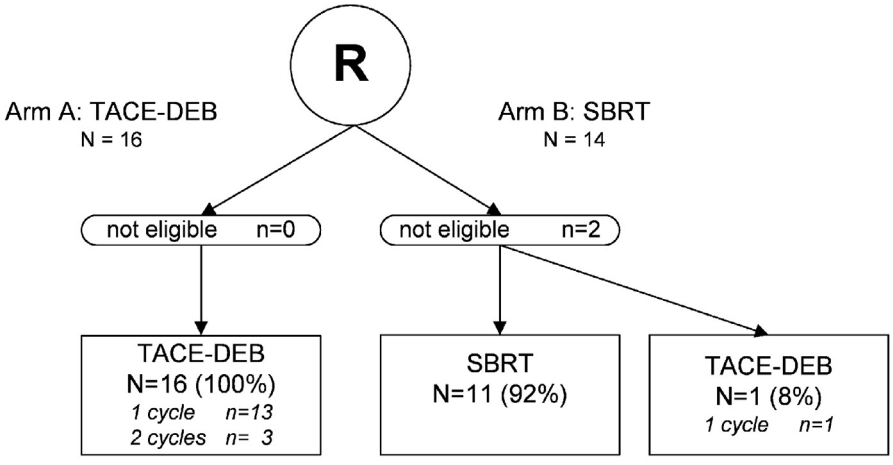

Fig. 1. Diagram showing the flow of patients through the TRENDY study. *Abbreviations:* N and n = number; R = randomization.

Table 1 Demographics

	TACE-DEB	SBRT	Total	*P* value
Total	16	12	28	
Age (y)				.24
Median (range)	69 (55-78)	62 (50-85)	67 (50-85)	
Sex, no. (%)				1.00
Male	14 (88)	10 (83)	24 (86)	
Female	2 (12)	2 (17)	4 (14)	
ECOG, no. (%)				.24
0	4 (25)	6 (50)	10 (36)	
1	12 (75)	6 (50)	18 (64)	
Cirrhosis, no. (%)				1.00
Yes	13 (81)	10 (83)	23 (82)	
No	3 (19)	2 (17)	5 (18)	
Etiology cirrhosis, no. (%)				.90
HVB	1 (6)	2 (17)	3 (11)	
HVC	3 (19)	1 (8)	4 (14)	
Alcohol	6 (38)	4 (33)	10 (36)	
Other	3 (19)	3 (25)	6 (21)	
No cirrhosis	3 (19)	2 (17)	5 (18)	
Portal hypertension, no. (%)				.12
No	4 (25)	7 (58)	11 (39)	
Yes	12 (75)	5 (42)	17 61)	
MELD score				.09
Median (range)	10 (6-19)	9 (5-14)	10 (5-19)	
AFP (ng/mL)				.23
Median (range)	8 (2-1400)	5 (1-623)	6 (1-1400)	
Interquartile range	4-22	4-8	4-13	
Previous treatments for other tumors in the liver, no. (%)				.20
Surgery	1 (6)	2 (17)	3 (11)	
RFA	0 (0)	2 (17)	2 (7)	
Intention liver transplant, no. (%)				.77
No	7 (44)	6 (50)	13 (46)	
Yes, for bridging	6 (38)	5 (42)	11 (39)	
Yes, for downstaging	3 (19)	1 (8)	4 (14)	
Current liver tumor, no. (%)				.71
New	15 (94)	10 (83)	25 (89)	
Local relapse after surgery	0 (0)	1 (8)	1 (4)	
Local relapse after RFA	1 (6)	1 (8)	2 (7)	
Tumors per patient, no. (%)				1.00
1	16 (100)	12 (100)	28 (100)	
Tumor diameter (mm)				.29
Median (range)	30 (11-50)	35 (15-64)	34 (11-64)	
Interquartile range	25-38	26-43	25-40	
Satellite nodules, no. (%)				.43
0	16 (100)	11 (92)	27 (96)	
1	0 (0)	1 (8)	1 (4)	

Abbreviations: AFP = alpha fetoprotein; ECOG = Eastern Cooperative Oncology Group; HVB = hepatitis virus B; HVC = hepatitis virus C; MELD = model for end-stage liver disease; RFA = Radiofrequency ablation; SBRT = stereotactioc body radiation therapy; TACE-DEB = transarterial chemoembolization delivered with drug eluting beads.

Time to progression

Median TTP was 12.0 months in the TACE-DEB arm (95% confidence interval [CI], 4.9-15) and 18.8 months in the SBRT arm (95% CI, 7.6 to not reached) (HR, 0.45; 95% CI, 0.16-1.32; P = .15) (Fig. 2a). Treatments delivered after disease progression are presented in the Appendix E1. A post hoc analysis was performed, in which TTP was not censored at liver transplantation. Median TTP was 12.0 months in the TACE-DEB arm (95% CI, 4.9-31.7) and 18.8 months in the SBRT arm (95% CI, 7.6 to not reached) (HR, 0.47; 95% CI, 0.17-1.29; P = .14) (Fig. 2b).

Local control

Median time to local recurrence was 12.0 months in the TACE-DEB arm (95% CI, 4.9 to not reached). In the SBRT arm, it has not been reached (>40 months) (HR, 0.15; 95% CI, 0.02-1.21; P = .075) (Fig. 3a). TACE-DEB was delivered according to protocol in all patients. Taking account of the compliance with the SBRT QA dosimetry protocol (absence of major planning target volume coverage deviations), a post hoc analysis was performed, in which the patient randomized for SBRT but treated with TACE-DEB was taken out of the SBRT arm. Similarly, the patient treated with SBRT with a major deviation of the protocol was also taken out of the SBRT arm. LC at 1, 2, and 3 years for the SBRT arm was 100%. This exploratory analysis showed a difference in LC between the 2 arms (stratified log rank test P = .019) (Fig. 3b). A third post hoc analysis was performed that took into account the treatment the patients actually received ("as treated"). LC at 1, 2, and 3 years for patients treated with TACE-DEB was 57%, 48%, and not reached. For the patients treated with SBRT it was 91% (HR, 0.18; 95% CI, 0.02-1.43; P = .10) (Fig. 3c).

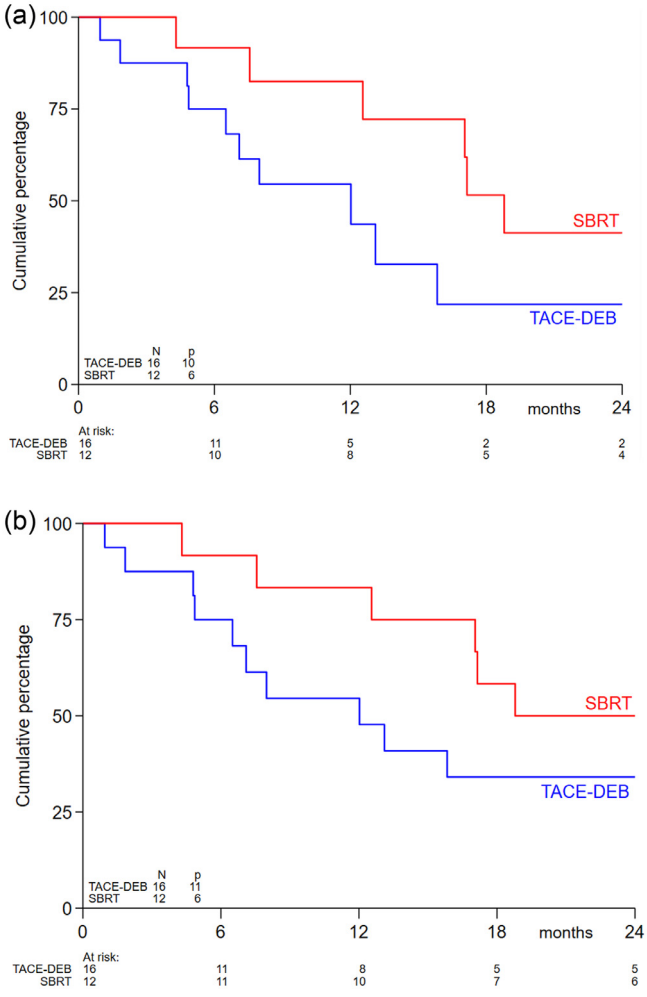

Fig. 2. Time to progression by randomization arm. (a) Original analysis, with censoring at liver transplantation. (b) Post hoc analysis, without censoring at liver transplantation. *Abbreviations:* N = number of patients; p = number of progressions.

Overall survival

Median OS time was 36.8 months in the TACE-DEB arm (95% CI, 18.1 to not reached) and 44.1 months (95% CI, 20.3 to not reached) in the SBRT arm (HR, 0.58; 95% CI, 0.18-1.85; P = .36) (Fig. 4).

Response rate

Response rates were 81% (56% CR + 25% PR) in the TACE-DEB arm and 92% (67% CR + 25% PR) in the SBRT arm.

Liver transplantation

Nine patients had been treated with TACE-DEB with the intention of liver transplantation at a later stage. Ultimately, 5 of these patients underwent transplantation. Median time from randomization to liver transplant was 10.7 months (range, 9.8-17.1 months). The other patients were not transplanted, either because they did not wish to undergo transplantation (2 patients) or because of disease progression (2 patients). Six patients in the SBRT group were considered for liver transplant, 4 of whom ultimately received a transplant. Median time from randomization to liver transplant was 10.3 months (range, 5.2-14 months). Because of disease progression, 2 patients did not undergo a transplant. See Appendix E1 for more information.

Toxicity

Table 2 presents related and unrelated toxicity Common Terminology Criteria for Adverse Events grade ≥3 after TACE-DEB and SBRT. If unrelated toxicity is taken into account, 1 patient in the TACE-DEB arm had a maximum grade 5 (cerebral hemorrhage between 1-3 months of treatment). Only considering adverse events that may have been related to the treatment delivered, 2 of the 16 patients in the

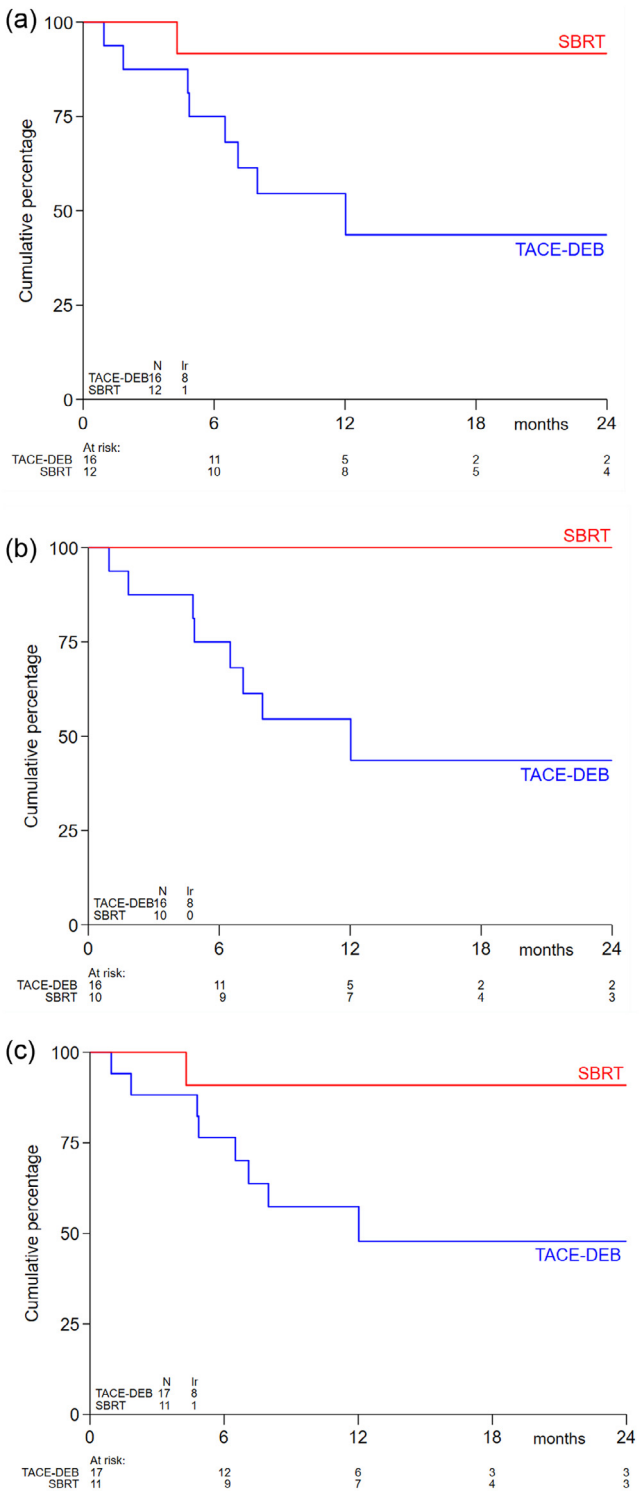

Fig. 3. Local control by randomization arm. (a) Modified intention-to-treat population. (b) Per-protocol population taking into account compliance with the stereotactic body radiation therapy quality assurance planning protocol. (c) Population according to the treatment the patients actually received ("as treated"). *Abbreviations:* lr = number of local recurrences; N = number of patients.

TACE-DEB arm had between them a total of 3 episodes (13%) of grade ≥3 toxicity. In the SBRT group, there were no such episodes. In the TACE-DEB arm, 1 patient developed an infection with sepsis within 1 month after treatment. This was scored as grade 4 and as probably related to the procedure. One patient who developed a hepatobiliary disorder grade 3 (hepatic encephalopathy) between 1 and 3 months after treatment was also scored as possibly related. In the same period, the same patient developed an increase in bilirubin. This was possibly related and scored as grade 3 (grade 2 at base line).

QoL

QoL remained stable after both treatment arms. For the results of the QoL analyses see Appendix E1 and Figs. E1 to E3.

Discussion

The TRENDY randomized phase 2 trial was designed to generate evidence that could support the role of SBRT within the treatment options for patients with HCC. In this trial, TTP after TACE-DEB was not significantly improved by SBRT, while an explorative analysis showed higher local antitumoral activity after SBRT than after TACE-DEB and no detrimental effects on OS, toxicity, and QoL.

Previously, 3 retrospective series used propensity score analysis to compare TACE and SBRT.[12-14] Two showed that LC at 2 years was significantly lower after TACE than after SBRT (23% vs 78.2% and 67.2% vs 91%, respectively).[13,14] However, a third study observed comparable LC between the 2 groups (1 year 82.9% for TACE and 84.8% for SBRT).[12] Although our results fit well with the first 2 series, showing higher LC values after SBRT, these studies reported no information on TTP.

Studies on TACE-DEB reported a median TTP between 9 and 16 months, a range within which our own finding fits well (median TTP of 12 months after TACE).[4,11,15] The high objective response rates of 81% we found after TACE-DEB also fit well with the values in the published literature (51.6%-84.6%).[5,11,16] TTP after SBRT has been reported only in a small number of papers, with median values ranging from 6 to 47.8 months.[7,8,17] Although our median TTP after SBRT fits well within these values, it is remarkable that the range is very broad. These differences may have been influenced by patient selection criteria. After SBRT, authors have reported overall objective response rates of between 54% and 80%.[7-9,18] Our 90% response rate compares favorably with those in the published series. The 2-year survival rates found after TACE-DEB and after SBRT fit well with published data.[4,8,19,20]

Table 2 Maximum toxicity scored in the TACE-DEB (n = 16) and in the SBRT (n = 11) safety populations after treatment

System organ class	CTCAE grade 3 no. (%)		CTCAE grade 4 no. (%)		CTCAE grade 5 no. (%)		CTCAE grades 3-5 no. (%)	
	TACE	SBRT	TACE	SBRT	TACE	SBRT	TACE	SBRT
Any AE	4 (25)	6 (55)	1 (6)	1 (9)	1 (6)	-	6 (38)	7 (64)
Blood and lymphatic	2 (13)	-	-	-	-	-	2 (13)	-
Cardiac	-	1 (9)	-	1 (9)	-	-	-	2 (18)
Gastrointestinal	1 (6)	-	-	1 (9)	-	-	1 (6)	1 (9)
Hepatobiliary	1 (6)	-	-	-	-	-	1 (6)	-
Infections/infestations	1 (6)	2 (18)	1 (6)	-	-	-	2 (13)	2 (18)
Procedure complications	1 (6)	1 (9)	-	-	-	-	1 (6)	1 (9)
Investigations	2 (13)	2 (18)	-	-	-	-	2 (13)	2 (18)
Metabolism and nutrition	2 (13)	-	-	-	-	-	2 (13)	-
Nervous system	-	1 (9)	-	-	1 (6)	-	1 (6)	1 (9)
Renal and urinary	1 (6)	-	-	-	-	-	1 (6)	-
Respiratory/thoracic/ Mediastinal	1 (6)	1 (9)	-	-	-	-	1 (6)	1 (9)

The maximum follow-up considered for the table was 2 years.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SBRT = stereotactioc body radiation therapy; TACE-DEB = transarterial chemoembolization delivered with drug eluting beads.

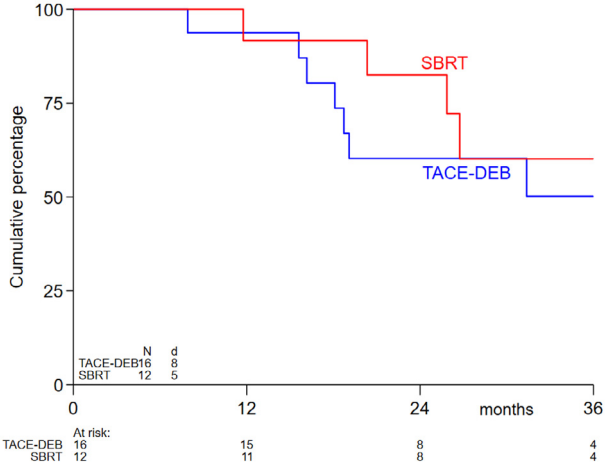

Fig. 4. Survival by randomization arm. *Abbreviations:* d = number of deaths; N = number of patients.

Possibly related grade ≥3 toxicity was limited in our study. No grade 5 related episode was observed. Two patients in the TACE-DEB arm (13%) suffered 3 episodes of grade 3 or 4 toxicity within 1 to 3 months after treatment. In a retrospective study, Sapir et al[13] reported grade ≥3 acute toxicity in 13% of TACE treatments and 8% of SBRT treatments. The limited liver toxicity after SBRT in our study may have been related to our liver constraints or to our patient selection (Child-Pugh grade A).

The limitation of our study is the small number of patients, and large numbers are needed to validate our results. Conceivably, the reasons for the low accrual included the restricted inclusion criteria, the low incidence of HCC in the Netherlands, and the commitments to include patients in studies, which may have varied widely. International collaboration is needed to generate the evidence needed to include SBRT as a treatment option in treatment guidelines.

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