ANTICANCER RESEARCH *39*: 3071-3077 (2019)
doi:10.21873/anticanres.13442

Comparison of Response and Outcomes of Drug-eluting Bead Chemoembolization (DEB-TACE) *Versus* Radioembolization (TARE) for Patients With Colorectal Cancer Liver Metastases

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Abstract. *Background: To compare outcomes for patients with colorectal cancer liver metastases (CRCLM) treated by drug-eluting bead chemoembolization (DEB-TACE) or radioembolization (TARE). Patients and Methods: A single-center retrospective review was carried out on 202 patients with CRCLM, treated by DEB-TACE (n=47) or TARE (n=155) patients. Propensity-matching yielded 44 pairs. Paired statistical analysis was performed on matched pair demographics, treatment response, and survival. Results: Patients treated with DEB-TACE had worse extra-hepatic metastasis (68.1 vs. 47.7%, p=0.014) and ≥10 liver lesions (42.2 vs. 68.8%, p=0.001). Matched patients treated with DEB-TACE had a trend towards worse toxicity (27% vs. 9.1% (p=0.057). Index DEB-TACE treatment was not a prognostic factor for overall survival (hazard ratio=0.94, 95% confidence intervaI=0.54-1.65; p=0.83). Conclusion: In the matched CRCLM cohort, there was a trend towards worse toxicity post-DEB-TACE treatment, but it was not an independent prognostic factor for survival.*

Metastatic colon cancer is one of the leading causes for colon cancer-driven morbidity and mortality (1). Treatment for colorectal cancer liver metastases (CRCLM) includes hepatectomy with curative intent along with systemic chemotherapy and biological agents (such as bevacizumab, or cetuximab) (1). Treatment can become more challenging for patients who are not candidates for surgery or who have failed multiple lines of systemic therapy.

Transarterial liver therapy can be used to mitigate liver disease and has been shown to achieve good tumor response and disease control in large cohorts (2, 3). Transarterial radioembolization (TARE) involves the infusion of glass (Theraspere; BTG Company), London, UK) or resin (SirSpheres, Sirtex, North Sydney, NSW, Australia) microspheres carrying yttrium-90, a radioactive element that emits pure beta-particle radiation, into liver tumors through their hepatic arterial feeding vessels (4). Chemoembolization (TACE) is another treatment modality that shuts down tumor blood flow, promotes necrosis, and releases chemotherapy (5). TACE with drug-eluting beads (DEB-TACE) has been developed to optimize chemotherapy and embolic particle delivery including *via* delivery of calibrated bead size and longer sustained chemotherapy release (3).

While there are clinical studies suggesting that TARE and DEB-TACE separately have treatment effectiveness against CRCLM (6-15), there are very limited studies comparing TARE and DEB-TACE toxicity and treatment response in patients with CRCLM (16, 17). This study compared the treatment response, toxicity, and survival for patients with CRCLM treated with DEB- TACE or TARE.

Patients and Methods

The study protocol conformed to the 1975 Declaration of Helsinki ethical guidelines and had Institutional Review Board approval (IRB ID#: 201608028). The study was a retrospective analysis of single-institution patients who underwent transarterial treatment for CRCLM. Key demographics included age, gender, sex, weight, baseline medical history (cardiac, vascular, pulmonary), smoking history, prior chemotherapy history, and *KRAS* mutation status. Additional pretreatment factors included number and types of chemotherapy, surgical resection status, Child-Pugh score, Eastern Cooperative Oncology Group (ECOG) score, number and degree of liver lesion involvement, and presence of extrahepatic metastases.

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Key Words: Colorectal cancer liver metastases, drug-eluting bead chemoembolization, radioembolization, propensity matching, survival outcomes.

Table I. *Clinical characteristics of the pooled cohort.*

		DEB TACE	TARE	*p*-Value*
N		47	155	
Age (years)	Mean±SD	57.2±10.1	57.7±11.5	0.78
Gender (%)	M/F	59.6%/40.4%	64.5%/35.5%	0.54
Weight (kg)	Mean±SD	83.7±22.6	85.5±21.1	0.7
Medical history, n (%)	Cardiac	14 (29.8%)	26 (16.8%)	0.12
	Pulmonary	4 (8.5%)	19 (12.3%)	0.48
	Vascular	9 (19.1%)	17 (11.0%)	0.14
Prior chemotherapy, n (%)	Yes	44 (93.6%)	153 (98.7%)	0.049
	FOLFOX	40 (87.0%)	133 (88.1%)	0.84
	FOLFIRI	23 (50.0%)	81 (54.7%)	0.57
	Bevacizumab	30 (65.2%)	121 (80.1%)	0.036
	Capecitabine	17 (37.0%)	46 (30.3%)	0.39
Colectomy, n (%)	Yes	27 (57.5%)	103 (67.2%)	0.34
KRAS-mutant, n (%)	Yes	9 (19.1%)	56 (36.1%)	0.06
Extrahepatic metastases, n (%)	Yes	32 (68.1%)	74 (47.7%)	0.014
Lung metastases, n (%) (% of total with metastases)	Yes	22 (46.8%) (68.8%)	47 (30.3%) (63.5%)	
Bony metastases, n (%) (% of total with metastases)	Yes	1 (2.1%) (3.1%)	3 (1.9%) (4.1%)	
No. of liver metastases, n (%)	Multiple (≥10)	19 (42.2%)	106 (68.8%)	0.001
	<10	26 (57.8%)	48 (31.2%)	

DEB-TACE: Drug-eluting bead transarterial chemoembolization, TARE: transarterial radioembolization; M/F: male/female, SD: standard deviation. *Statistics by chi-square/Fisher's exact test, ANOVA, Wilcoxon rank-sum tests.

Groups were divided according to their index or first transarterial treatment. Inclusion criteria for transarterial therapy included age >18 years, proof of liver-metastatic disease, ECOG score of 2 or less, and the ability to give consent. Every patient underwent preliminary computed tomography (CT) and magnetic resonance imaging (MRI) of liver disease prior to treatment. A total of 202 patients were included in this study: 47 treated with DEB-TACE and 155 with TARE.

Radioembolization technique. A visceral angiogram was performed to evaluate arterial anatomy approximately 2-3 weeks prior to the procedure. Technetium-99m-labeled macro-aggregated albumin was used to determine hepatopulmonary shunting and radioactive shunting. Planar scintigraphy was used to calculate shunt fractions. Coil embolization of specific vessels were performed when appropriate. TARE was performed using either glass Theraspheres (BTG Company) or resin SIRspheres (Sirtex). Dose calculations were performed according to the respective manufacturer's published guidelines. Patients were evaluated and discharged after the procedure on the same day.

DEB-TACE technique. A visceral angiogram was performed to look at patient anatomy and tumor vascularity. Patients had multiple treatments depending on liver tumor involvement. The procedure involved microcatheter placement close to the liver tumor before infusion of 50-500 μm bead particles (Boston Scientific/BTG) loaded with chemotherapy (primarily irinotecan or doxorubicin). Patients were evaluated for post-embolization symptoms and complications overnight before discharge.

Toxicity, follow-up and outcome measures. CT and MRI follow-up were performed post-procedure at 1 month for TACE and 3 months for TARE. All images were initially read by a radiologist. Treatment efficacy response was assessed by the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (18). All adverse events were recorded and evaluated using the five grade Common Therapy Evaluation Program's Common Terminology Criteria for Adverse Events (CTCAE version 5.0) (19). Overall survival (OS) was defined as the time between treatment start date and the patient's overall status. Progression-free survival (PFS) was defined as the time between initial treatment and progression as determined by CT or MRI follow-up or death.

Statistical analysis. Patients were censored on their tumor progression date, last clinic visit, and survival date, with all data up until August 2016 included in the analysis. Student's *t*-test, one-way ANOVA, and Wilcoxon tests were used for continuous and ordinal data comparisons. Two-tailed Fisher's exact and chi-square test was used for categorical data comparison. OS and PFS probabilities were generated with Kaplan–Meier statistics. Cox regression was used to associate independent variables with survival.

Propensity matching. Propensity score matching has increased in use among the scientific clinical community. Propensity score matching can help design underpowered observational studies similar to that of randomized controlled trials (20, 21). The estimated propensity model was the predicted probability of treatment with either DEB-TACE or TARE derived from the fitted logistic regression model. A matched sample was created by matching individuals treated with DEB-TACE and TARE on the logit of the propensity score using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score. A greedy, nearest-neighbor matching algorithm was employed to form 44 DEB-TACE and TARE matched pairs. Propensity score match effectiveness was evaluated using standardized differences in the matched sample.

Table II. *Treatment factors for drug-eluting bead transarterial chemoembolization (DEB-TACE) and transarterial radioembolization (TARE).*

	DEB-TACE (n=47 patients)	TARE (n=155 patients)	*p*-Value*
Total embolization treatments, n	92	266	
Cross over between treatments, n (%)	5 (10.6%)	16 (10.3%)	0.95
Chemotherapy during treatment, n (% of treatments)	10 (21.3%)	35 (22.6%)	0.85
DEB-DOX, n (% of treatments)	7 (7.6%)	9 (3.4%)	
DEBIRI, n (% of treatments)	76 (82.7%)	31 (11.7%)	
SIRspheres, n (% of embolization treatments)	9 (9.9%)	204 (76.7%)	
Theraspheres, n (%)	0 (0%)	20 (7.5%)	
Radioactivity delivered (Gbq), median (range)	0.00 (2)	0.99 (6)	
Segmental, n (% of treatments)	13 (14.1%)	18 (6.8%)	

DEB-DOX: Doxorubin-eluting bead therapy; DEBIRI: irinotectan-eluting bead therapy. *Statistics by Pearson chi-squared, Wilcoxon rank-sum, one-way ANOVA.

Table III. *Total complications associated with drug-eluting bead transarterial chemoembolization (DEB-TACE) and transarterial radioembolization (TARE) treatments for the pooled cohort.*

	DEB-TACE (n=47 patients)	TARE (n=155 patients)	*p*-Value*
Total DEB-TACE and TARE treatments in cohort	92	266	
Total adverse events, n treatments (% of total treatments)	15 (16.3%)	37 (13.9%)	0.65
Adverse events CTCAE grade ≥3, n treatments (% of total adverse events) (% out of total # treatments)	2 (13.3%)(2.2%)	9 (24.3%)(3.4%)	0.47

CTCAE: Common Terminology Criteria for Adverse Events. *Statistics by Chi-square/Fisher's exact test when n<5.

Differences between DEB-TACE and TARE matched subject outcomes were evaluated using paired *t*-tests for continuous variables and Mc Nemar's or Bowker's test of symmetry for categorical variables. To estimate the effect of treatment on survival outcomes, a Cox proportional hazards model we used with robust sandwich variance estimator. *p*-Values of less than 0.05 were considered statistically significant. Statistics were calculated by JMP software SAS version 9 (SAS corporation, Cary, NC, USA) and SPSS version 24 (Intel Corporation, Chicago, IL, USA).

Results

Baseline demographics-pooled cohort. From our CRCLM data set, 155 and 47 patients underwent TARE and DEB-TACE, respectively, as index treatments. Patients treated with DEB-TACE or TARE had similar demographics (Table I). Patients treated with DEB-TACE were more likely to have Child-Pugh score B (p=0.048) and frequently had extrahepatic metastases p=0.014). The TARE group had more patients with ≥10 liver metastases than the DEB-TACE group (p=0.001).

Pooled cohort: Treatment factors/adverse events. At total of 47 patients treated with DEB-TACE first had 92 embolization treatments while 155 patients treated with TARE first had 267 embolization treatments (204 of which with SIRSpheres) (Table II). Median radioactivity delivered was 0.99 Gbq for the TARE embolization group. DEBs loaded with irinotecan was the most common DEB-TACE index treatment (76, 82.7%). The majority of DEB-TACE and TARE treatments were lobar.

Patients with DEB-TACE had higher (16.3% *vs*. 13.9%) percentage of total adverse events but the difference was not statistically significant (p=0.65). The rate of severe adverse events (CTCAE grade ≥3) was also similar in both groups (2.2% *vs*. 3.4%, respectively; p=0.47) (Table III).

Matched cohort patient characteristics. Propensity matching produced 44 pairs of patients with similar standardized differences for select variables in Table IV. The propensity-matched cohort had similar demographics including weight, age, smoking history, ECOG score, and liver lesion size (Table V).

Treatment adverse events. Propensity-matched patients treated with DEB-TACE as index treatment had a total of 88 treatments *versus* 67 compared with TARE. Patients treated with DEB-TACE had a trend towards more adverse events compared to matched those treated with TARE (27% *vs*. 9.1%, p=0.057) (Table VI).

Common adverse events recorded included abdominal pain, and fever for the DEB-TACE-treated patient cohort. Severe adverse event (CTCAE ≥3) rate was higher for DEB-TACE-treated patients (4.5% *vs*. 2.2%) (Table VI).

Treatment efficacy and survival of the matched cohort. TARE led to a higher overall response rate (partial response + complete response) by mRECIST (15.2%) than DEB-TACE (11.1%) but this was not statistically significant (p=0.71) (Table VII).

Cox regression on the propensity-matched set revealed that index treatment with DEB-TACE was not a significant prognostic factor for PFS (hazard ratio=1.35, 95% confidence intervaI=0.83-2.2; p=0.23) (Figure 1A) and OS (hazard ratio=0.94, 95% confidence intervaI=0.54-1.65; p=0.83) (Figure 1B).

Table IV. *Unmatched and propensity-matched standardized difference (Std. Diff).*

	Absolute Std. Diff.	
Variable	Unmatched	Propensity-matched
Age (at diagnosis)	0.04791	0.01417
Sex, n (%)	0.10196	0.13845
ECOG score 0, n (%)	0.54770	0.04696
Total number of lesions, n (%)	0.22881	0.09975
Extrahepatic metastases, n (%)	0.42109	0.00000
FOLFIRI, n (%)	0.09481	0.00113
Other colorectal cancer treatment procedure, n (%)	0.23284	0.01584

ECOG: Eastern Cooperative Oncology Group.

Discussion

Multiple clinical studies have shown the benefits of both TARE and DEB-TACE for patients with CRCLM (6-15). Our retrospective study is one of the few clinical studies (16, 17) explicitly comparing effectiveness of DEB-TACE and TARE for patients with CRCLM. One meta-analysis compared treatment effectiveness of TARE with TACE and hepatic artery infusion against CRCLM. For patients who failed multiple chemotherapy lines, TARE led to better treatment response (36% TARE *vs*. 29% TACE) and similar toxicity profile to TACE (19% *vs*. 18%, respectively, compared to 40% grade 3 and 4 toxicity in hepatic artery infusion) (16). TARE led to worse median OS (10.7 *vs*. 21.3 months) (16). Similarly, a meta-analysis by Levy *et al*. pooling current TACE and TARE trials on unresectable CRCLM found worse median OS for those treated with TARE compared to DEB-TACE (median OS of 12 *vs*. 16 months, respectively) (17). The worse median OS for the TARE population compared to TACE may have been confounded by the higher frequency of comorbidities and extrahepatic metastatic disease in the TARE population (16). Both comparative meta-analyses pooled data from prior conventional and older DEB-TACE clinical trials (16, 17). These older DEB-TACE trial results were limited by patient numbers, lack of procedure treatment type, and dose standardization (22). Unlike our own study, the meta-analyses of Zacharias *et al*. (16) and Levy *et al*. (17) did not compare DEB-TACE and TARE in a population with similar patient demographics and cancer comorbidities.

Our TARE cohort demographics, treatment toxicity, and survival were similar to those of other studies (6-10). We recorded, however, a lower overall mRECIST response rate and higher frequency of progressive disease for both DEB-TACE and TARE treatments (6-15). Our study's lower overall treatment response rates by mRECIST might be attributed to a sicker cohort and irregular imaging follow-up. Baseline comorbidities and metastatic burden were factored using propensity score matching between cohorts as we found low standardized differences for key variables including ECOG scores, number of liver lesions, and the presence of extrahepatic metastases. Propensity-matching confirmed pooled results with no statistical difference in treatment response or survival even though TARE-treated patients had improved OS compared with DEB-TACE. DEB-TACE treatment group patients had a trend towards worse adverse and even worse CTCAE ≥3 adverse events despite matching for extrahepatic metastases and patient comorbidities. Many of these adverse events were post-embolization symptoms such as abdominal pain, nausea, and fever that resolved with time and were similar to complications observed in previous studies evaluating DEB-TACE (12-14). Our data suggest that DEB-TACE treatment may lead to worse post-treatment patient symptoms than TARE for patients with CRCLM.

Some limitations of our study include its retrospective nature with a limited patient population. A smaller DEB-TACE patient population can limit propensity score matching and OS analysis. We had to rely more on secondary outcomes for treatment response and effectiveness including tumor response rate *via* mRECIST criteria (23). Furthermore, transarterial treatments in this study were not standardized; there were discrepancies in treatment radiation dose, administered chemotherapy, and treatment types during and after initial index transarterial therapy.

While our study found no significant difference in mRECIST response and survival between patients treated with TARE or DEB-TACE, TARE was tolerated better than DEB-TACE and demonstrated a trend towards better OS. We recommend larger prospective studies in order to make definite conclusions on DEB-TACE *versus* TARE for the CRCLM population.

Table V. *Selected demographics for matched cohort*.

Variable	DEB-TACE (N=44)	TARE (N=44)
Weight, mean±SD (kg)	84.2±23.3	84.5±19.6
Age, median (min-max)	59.0 (30.0-75.0)	57.0 (33.0-86.0)
Number of packs/day, median (min-max)	0 (0-3.0)	0 (0-2.5)
Number of pack years, median (min-max)	0 (0-80.0)	0 (0-50.0)
ECOG score post procedure, median (min-max)	2.0 (0-4.0)	1.5 (0-4.0)
Liver lesion size (mm), median (min-max)	20.1 (1.5-174.8)	19.8 (1.8-177.5)
DEB-TACE treatments, median (min-max)	2.0 (0-4.0)	0 (0-1.0)
TARE treatments (only for patients with multiple treatments), median (min-max)	0 (0-3.0)	0 (0-2.0)
Number of treatments, median (min-max)	2.0 (1.0-6.0)	2.0 (1.0-2.0)

DEB-TACE: Drug-eluting bead chemoembolization; TARE: transarterial radioembolization; ECOG: Eastern Cooperative Oncology Group.

Table VI. *Matched cohort toxicity and Common Terminology Criteria for Adverse Event (CTCAE) adverse events*.

Type of complication	DEB-TACE (n=44 patients)	TARE (n=44 patients)	*p*-Value*
Abdominal pain, no. patients	5	1	
Fever, no. patients	4	0	
Nausea/vomiting, no. patients	1	0	
Pneumonitis/renal failure, no. patients#	1	0	
Portal HTN, no. patients#	0	1	
Death, no. patients#	1	0	
Adverse events, no. patients (% of total matched patients)	12 (27%)	4 (9.1%)	0.057
CTCAE grade ≥3 adverse events, no. patients (% of matched patients)	2 (4.5%)	1 (2.2%)	

*Mc Nemar's test; #CTCAE grade≥3 complications.

Table VII. *Matched cohort tumor response by modified Response Evaluation Criteria in Solid Tumors (mRECIST)*.

	DEB-TACE (n=44)	TARE (n=44)	*p*-Value*
PD, n (%)	27 (75%)	19 (57.6%)	0.36
PR, n (%)	4 (11.1%)	5 (15.2%)	
SD, n (%)	5 (13.9%)	9 (27.3%)	

PD: Progressive disease; PR: partial response; SD: stable disease. *Mc Nemar's test of binomial proportions.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

Authors' Contributions

MM collected the data, conceived and designed the analysis, contributed data or analysis tools, and wrote the article. CN collected the data and revised the article. CM and RR revised the article. OA conceived and designed the analysis, contributed data or analysis tools, and revised the article.

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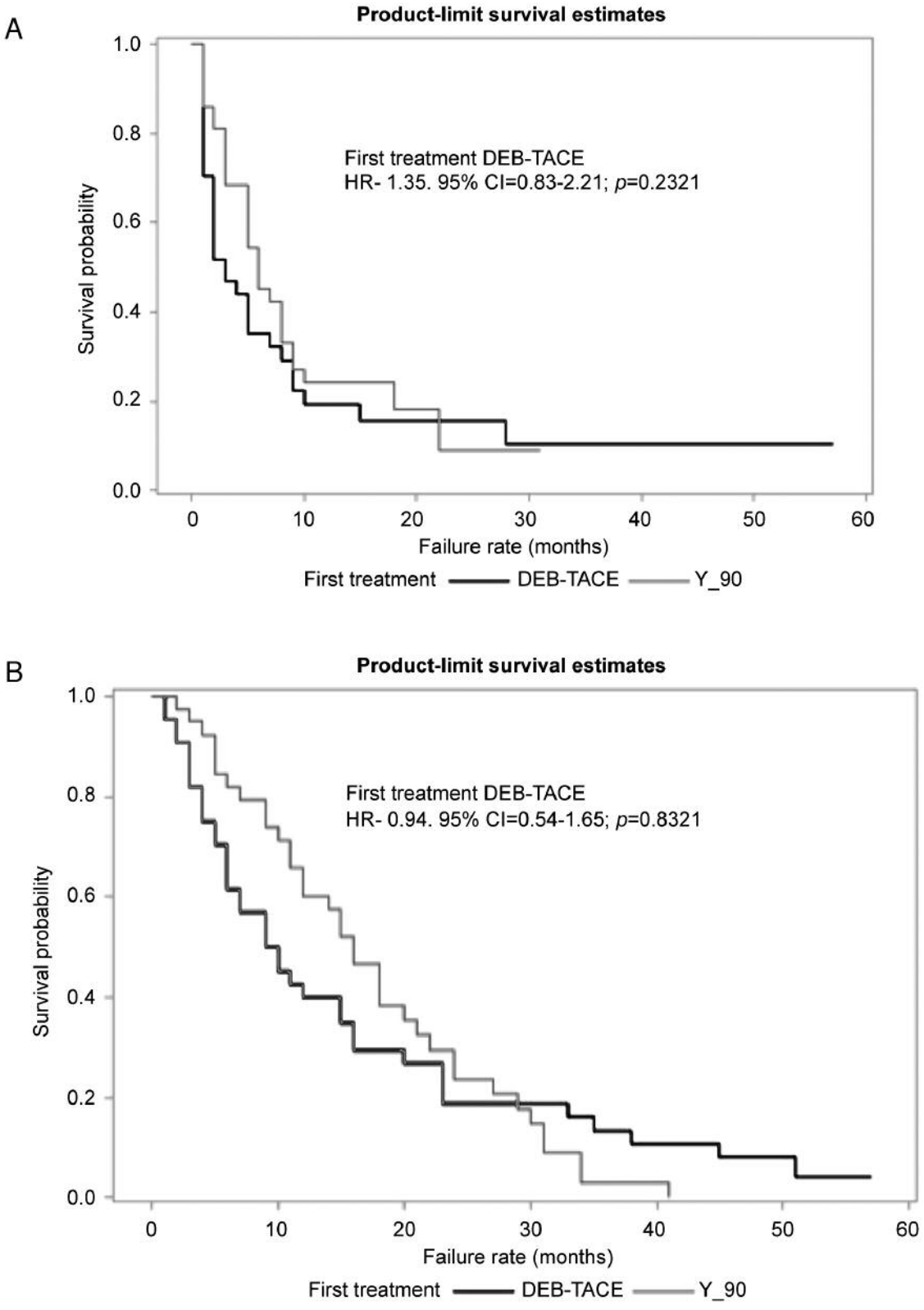

Figure 1. *Kaplan–Meier curves for matched cohort showing no difference in progression-free (A) and overall (B) survival between treatments. Hazard ratios (HRs), confidence intervaIs (CI) and p-values were calculated using univariate Cox analysis. DEB-TACE: Drug-eluting bead chemoembolization; TARE: radioembolization.*

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Received April 5, 2019
Revised May 8, 2019
Accepted May 13, 2019