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MAGNETIC RESONANCE

Transarterial chemoembolization of colorectal cancer liver metastasis: improved tumor response by DSM-TACE versus conventional TACE, a prospective, randomized, single-center trial

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Abstract

Objectives To prospectively evaluate the therapy response of third-line TACE with DSM or lipiodol in the treatment of CRLM using MRI.

Methods In this prospective, randomized, single-center trial, patients were randomly assigned to receive TACE therapy with either lipiodol or DSM as the embolization agent. Therapy response was evaluated using MRI. Local tumor response was determined according to RECIST 1.1, and survival data was analyzed using the Kaplan-Meier estimator.

Results Fifty patients (35 male, 15 female) were randomized and included in the survival analysis, whereas 31 patients completed therapy and were considered for evaluation of tumor responses (cTACE: $n = 13$, DSM-TACE: $n = 18$). In the cTACE group, PR was observed in 23%, SD in 15%, and PD in 62%. In the DSM-TACE-group, PR was observed in 22% of patients, SD in 56%, and PD in 22% ($p = 0.047$). In addition, the DSM-TACE group showed statistically significant tumor volume reduction ($p = 0.006$). Median apparent diffusion coefficient values were not significantly different between both groups at baseline ($p = 0.26$) and study endpoint ($p = 0.83$). Median survival in the cTACE group was 13 months (95% confidence interval, range 5–40 months) compared to 16 months (95% confidence interval, range 1–48 months) in the DSM-TACE group, exhibiting no statistically significant difference ($p = 0.75$).

Conclusion DSM-TACE showed a significant difference reducing tumor volume and in tumor response according to RECIST 1.1 compared to cTACE. Thus, patients with CRLM might not only benefit from short embolization effect of DSM-TACE but also from better tumor responses. Apparent diffusion coefficients were not significantly different between both groups and cannot be used as a biomarker for monitoring for therapeutic effect of TACE.

Key Points

- *To our knowledge, this is the first prospective study that directly compared cTACE and DSM-TACE in patients with CRLM.*
- *DSM-TACE showed a significant difference reducing tumor volume ($p = 0.006$) and in tumor response according to RECIST 1.1 ($p = 0.047$) compared to cTACE.*
- *Survival analysis showed a median survival of 13 months in the cTACE group compared to 16 months in the DSM-TACE group ($p = 0.75$).*

Keywords Colorectal cancer · Degradable starch microspheres · Lipiodol · Magnetic resonance imaging

Abbreviations

ADC	Apparent diffusion coefficient
CRLM	Colorectal cancer liver metastasis
CT	Computed tomography
DSM	Degradable starch microspheres
DWI	Diffusion-weighted imaging
FOLFIRI	Irinotecan, leucovorin, and 5-fluorouracil
FOLFOX	5-Flourouracil, leucovorin, oxaliplatin
GFR	Glomerular filtration rate

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HCC	Hepatocellular cancer
MRI	Magnetic resonance imaging
PR	Partial response
ROI	Region of interest
SD	Stable disease
TACE	Transarterial chemoembolization
PD	Progressive disease
VEGF	Vascular endothelial growth factor

Introduction

Colorectal cancer is one of the most frequently diagnosed cancers worldwide with up to 60% of patients developing metastases over the course of the disease [1–3]. Among patients with liver metastases, only 10–25% are candidates for surgical resection [4]. For patients with unresectable liver metastases, transarterial chemoembolization (TACE) has been identified as an effective therapy for neoadjuvant, symptomatic, or palliative therapy indications [5–7] which can significantly increase median survival to 7–14 months [8, 9].

Two embolization agents are commonly used for TACE: lipiodol (ethiodized oil) and degradable starch microspheres (DSMs). Both agents prolong the duration of the chemotherapeutic effects on tumor lesions. While lipiodol has a mean pharmacological embolization time of 4 to 12 weeks, DSMs are characterized by a total pharmacological embolization time of maximal 90–120 min. The temporal occlusion by DSM induces only moderate increases in vascular endothelial growth factor (VEGF) levels as compared to conventional TACE (cTACE) using lipiodol and, therefore, likely induces less neoangiogenesis [10].

Diffusion-weighted imaging analyzes the movement of water molecules and can be used to assess therapy response to TACE and potentially predict whether lesions will respond to treatment [11–13]. Factors that may influence diffusion-weighted imaging measurements include *b*-values, breathing/breath-holding, and vendor platform [14–16].

Current medical literature is lacking prospective, randomized trials comparing lipiodol and DSM as embolic agents for TACE. Therefore, the aim of this study was to prospectively evaluate local tumor response of patients with CRLM treated by TACE to compare the efficacy of DSM-TACE and cTACE regarding RECIST 1.1 criteria, tumor volume/diameter, diffusion-weighted imaging (DWI), and survival data.

Materials and methods

Study design

This prospective, randomized, single-center, investigator-initiated study was performed at the University Hospital Frankfurt. Institutional review board approval was attained before the start of the trial, and informed consent of all patients was obtained.

Patients were allocated in a 1:1 ratio to cTACE or DSM-TACE therapy, each consisting of three TACE sessions at intervals of 4 weeks. Treatment outcome was assessed by magnetic resonance imaging (MRI), which was performed at baseline, after the first and second TACE (4 weeks after the respective TACE session), and 4 weeks after the third TACE session (study endpoint). In total, duration of follow-up was 12–18 weeks.

Patients

Fifty patients with CRLM that had already received second-line therapy (FOLFIRI, FOLFOX, and bevacizumab) were included in this study (Table 1). A complete list of inclusion and exclusion criteria is provided in Table 2. Randomization and patient allocation were performed by our clinical study center using blocked randomization with a fixed block size of ten patients. Patients were blinded to which therapy course they received.

Pre-treatment evaluation

In all patients, we calculated the total volume of all hepatic lesions per patient in addition to the total liver volume in order to estimate the hepatic tumor load. Only those patients with < 70% hepatic tumor involvement were treated (Table 1).

Contraindications to treatment with TACE were presence of extrahepatic metastases, poor performance status (ECOG > 1), tumor involvement of more than 70% of liver volume, high total bilirubin serum levels (> 2.5 mg/dL), poor hepatic synthesis (serum albumin level, < 2.0 mg/dL (20 g/L), INR > 1.5), renal impairment (serum creatinine level, > 2 mg/dL (176.8 μmol/L)), and complete thrombosis of the main portal vein.

TACE procedure

Upon covering the inguinal region in a sterile manner, local anesthesia was injected. Using Seldinger technique, the common femoral artery was punctured, and a 5F sheath (Introducer 2®, Terumo) was introduced. After insertion, an aortography (Artis zeego®, Siemens Healthcare) was performed to gain an exploratory view of the abdomen and the celiac trunk using a 5F pigtail catheter (Boston Scientific). This was followed by selective catheterization of the celiac trunk using a 5F sidewinder (Terumo). A 2.8F coaxial microcatheter system (Progreat®, Terumo) was advanced through the celiac trunk and past the branching of the gastroduodenal artery. The catheter was positioned in the tumor-supplying vessels, and upon confirming correct placement, chemotherapeutic and embolic agents were administered. To

Table 1 Characteristics of patients

Characteristic	cTACE, *N* (%)	DSM-TACE, *N* (%)	Total, *N* (%)	*p* value
No. of patients	25	25	50	
Sex				0.27
Male	19	16	35 (70%)	
Female	6	9	15 (30%)	
Age (years)				0.67
Mean (range)	62.7 (40–77)	60.9 (45–79)	61.8 (40–79)	
TN-stage of TNM classification				0.57
T2N0	1 (4%)	4 (16%)	5 (10%)	
T2N1	3 (12%)	5 (20%)	8 (16%)	
T2N2	6 (24%)	8 (32%)	14 (28%)	
T3N0	2 (8%)	1 (4%)	3 (6%)	
T3N1	7 (28%)	4 (16%)	11 (22%)	
T3N2	5 (20%)	3 (12%)	8 (16%)	
T4N0	1 (4%)	0 (0%)	1 (2%)	
Tumor burden of the liver				0.74
10–30%	13 (52%)	15 (60%)	28 (56%)	
30–50%	7 (28%)	4 (16%)	11 (22%)	
50–70%	5 (20%)	6 (24%)	11 (22%)	
Number of tumor lesions				1.00
1	4 (16%)	3 (12%)	7 (14%)	
2	3 (12%)	3 (12%)	6 (12%)	
3	2 (8%)	3 (12%)	5 (10%)	
4	1 (4%)	2 (8%)	3 (6%)	
Multiple (≥ 5)	15 (60%)	14 (56%)	29 (58%)	
Localization				0.67
Right liver lobe	6 (24%)	10 (40%)	16 (32%)	
Left liver lobe	1 (4%)	1 (4%)	2 (4%)	
Both lobes	18 (72%)	14 (56%)	32 (64%)	

control for correct administration of the drugs and artery occlusion, an additional final angiography was performed.

The following chemotherapeutic agents were used: mitomycin C (mitomycin Medac®; 8 mg/m^2), cisplatin (Cisplatin Teva®; 35 mg/m^2), and irinotecan (Campto®, Pfizer Pharma; 150 mg/m^2). Embolization was performed using a maximum of 10 mL/m^2 ethiodized oil (Lipiodol® Ultra-Fluid, Guerbet) or by injection of 200–450 mg DSM (50 μm) (EmboCept® S, PharmaCept). Each drug was administered in a separate syringe.

MRI evaluation

All images were taken with the same MRI scanner (MAGNETOM Avanto Fit® 1,5 T, Siemens Healthcare).

Table 2 Inclusion and exclusion criteria of the study

Inclusion criteria	Exclusion criteria
• Planned transarterial chemoembolization with third-line tumor therapy, approved by tumor board	• Contraindications for magnetic resonance imaging
• Given written consent by the patient	• Pregnant or breast-feeding women
• Age ≥ 18 years	• Renal insufficiency (glomerular filtration rate ≤ 30 mL/min)
• Histologically or radiologically confirmed colorectal cancer liver metastasis	• Secondary carcinoma
• Liver dominant metastasis	• Known severe allergy to contrast media
• K-Ras status independent	• Contraindications for transarterial chemoembolization
• Prior magnetic resonance imaging with 1.5 or 3 Tesla	
• Tumor size ≥ 1 cm	

Patients were positioned head-first in a supine position and the abdomen was covered with an 18-channel phased-array body coil. Spine coil elements in the patient table were switched on. Sequences were acquired during multiple end-expiratory breath holds. Contrast medium was injected with a flow rate of 1 ml/s and the amount was contingent upon the patient's body weight and the recommended dose from the selected vendor, respectively.

For the initial and final MRI, gadobutrol (Gadovist, Bayer Vital), (2) gadoteric acid (Dotarem, Guerbet) were utilized. Initial and final MRI scans were acquired using the following protocol: Localizer, T2w, T1w-FLASH-2D, EP-2D-Diff (b50, b400, b800), T1w-3D (VIBE) unenhanced, application of contrast media with monitoring, 3 dynamic T1w-3D (VIBE), T1w-FLASH-2D. Additionally, prior to each TACE, a non-contrast MRI was performed using another protocol: Localizer, T2w, T1w-FLASH-2D, EP-2D-Diff (b50, b400, b800).

MRI analysis

All datasets were evaluated directly on the picture archiving and communication system (GE Centricity PACS, GE Healthcare). For the evaluation of diameter, volume, Volume viewer 2® (AW Suite 2.0, GE Healthcare) was used. RECIST 1.1 is defined as the ratio between the longest diameter in the final MRI and in the initial MRI of a maximum of two liver lesions. The progress was analyzed according to the RECIST 1.1 protocol [17]. A Siemens Leonardo workstation® (Siemens Healthcare) was used for lesion detection, region of interest (ROI) placement, and apparent diffusion coefficient (ADC) measurements. Diffusion-weighted sequences (DWIs) were acquired with *b*-values of b50, b400, and b800 and ADC maps were calculated and evaluated using a MRI-connected workstation. ADC map registration was confirmed manually with T2-wighted images. A manually drawn region of interest (ROI) was defined for each lesion and the resulting mean ADC value was recorded.

All image analysis was performed by two senior radiologists with more than 7 and 27 years of experience in abdominal imaging in consensus. The examinations were split up among both radiologists. Both radiologists were informed about the patient's medical history. Each radiologist could individually change order of sequences of MR images and could individually regulate the windowsettings.

Statistical analysis

Differences between trial groups were analyzed using the Friedman test, the Mann-Whitney *U* test, the Cox-Mantel log-rank test, Fisher's exact test, and the Kaplan-Meier survival estimates using BIAS® (Version 11.06, epsilon-Verlag); $p \leq 0.05$ was considered significant. Sample size was determined using an alpha-coefficient of 0.05, and a test power of 0.80 yielding a result of 23 patients per group. Considering the asymptotic relative efficiency correction, a sample size of 25 patients per study arm was determined.

Results

Study population

Fifty patients (35 male, 15 female) were included in the study and equally randomized to both treatment groups. Median age of all patients was 62.5 years (range 40–79). Ten patients in the cTACE group and seven patients in the DSM-TACE group discontinued treatment due to patient decision before receiving all planned chemoembolization cycles. In the cTACE group, two patients had to be excluded from the local tumor response analysis since they received ablation therapy before the final contrast MRI was taken (Fig. 1). In total, 31 patients (13 in the cTACE group, 18 in the DSM-TACE group) were considered for evaluation of local tumor responses, yielding a test power of 53% with the initial assumptions of the study protocol. All 50 patients were included in the survival data analysis.

Tumor volume

The volume of the five largest definable liver metastases was determined for each patient at baseline and after every TACE. Patients in the cTACE group who completed the study had a mean tumor volume of 14.7 cm^3 (SD ± 16.3, range 0.9–62.5 cm^3) at baseline. The tumor volume increased gradually to 19.3 cm^3 (SD ± 25.5, range 0.6–85.3 cm^3) after the first therapy cycle, 21.9 cm^3 (SD ± 31.7, range 0.3–117.7 cm^3) after the second cycle, and 23.9 cm^3 (SD ± 32.7, range 0.2–115.3 cm^3) at study endpoint (Table 2). In the DSM-TACE group, mean tumor volume at baseline was 35.3 cm^3 (SD ± 71.6, range 1.2–306.5 cm^3). After the first and second intervention cycle, the value increased to 39.4 cm^3 (SD ± 71.4, range 1.2–286.9 cm^3) and 42.1 cm^3 (SD ± 78.7, range 0.6–260.2 cm^3), respectively. However, mean tumor volume had decreased to 33.5 cm^3 (SD ± 58.4, range 0.4–223.3 cm^3) at the study endpoint (Table 3).

Differences in mean tumor volume between the cTACE and DSM-TACE group were not statistically significant according to Mann-Whitney *U* test, neither at baseline ($p = 0.82$) nor at the study endpoint ($p = 0.59$). However, mean tumor volume was significantly reduced in the DSM-TACE group at endpoint as compared to baseline (Friedman test, $p = 0.006$) (Fig. 2), whereas in the cTACE group, no significant mean tumor volume change was observed ($p = 0.68$) (Fig. 2). Also analyzed were the differences in the tumor volume changes between the study groups over the course of the therapy. No

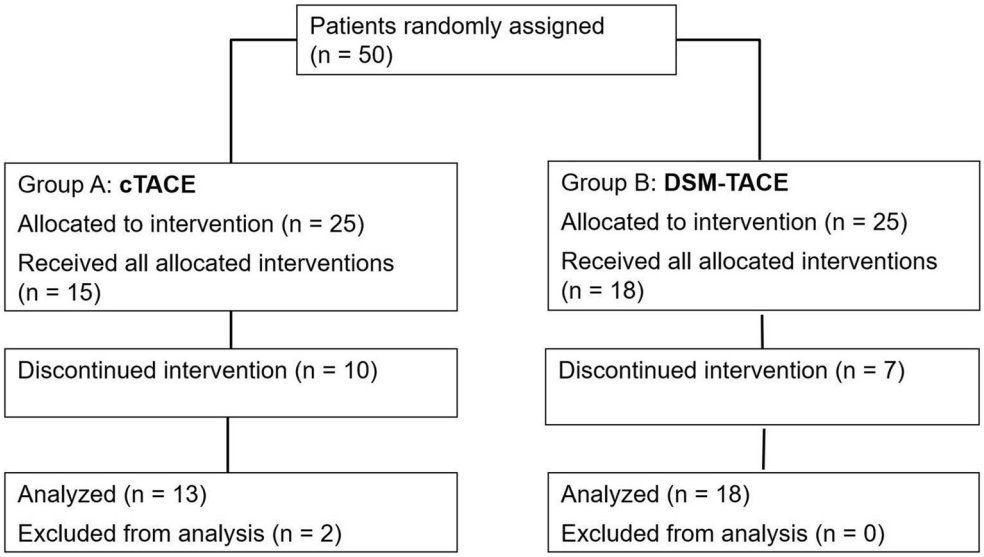

Fig. 1 Flow diagram of the patient population. DSM: degradable starch microspheres

statistically significant differences in tumor volume change could be found after the first ($p = 0.62$), second ($p = 0.065$), and third therapy cycle ($p = 0.35$). An initially planned analysis of the tumor necrosis volume change could not be completed because the tumor necrosis volume could not be reliably measured in smaller metastasis.

Evaluation of the baseline tumor volume in responders (33.8 cm^3) vs non-responders (15.4 cm^3) according to RECIST 1.1 (responder: partial response [PR] + stable disease [SD], non-responder: progressive disease [PD]; see below) revealed no statistically significant difference ($p = 0.88$) between both groups.

Tumor diameter

In addition to tumor volume, the diameter of the two largest liver metastases was determined and totaled in each patient at the different time points. In the cTACE group, patients completing the study had a mean tumor diameter of 25.6 mm (SD ± 9.4, range 12.7–44.0 mm) at baseline. After the first and second intervention cycle, the value increased to 26.7 mm

Table 3 Mean tumor volume, tumor diameter, ADC values, and tumor response according to RECIST 1.1 for cTACE and DSM-TACE groups as well as the respective *p* values. *cTACE* conventional transarterial chemoembolization, *DSM-TACE* degradable starch microspheres transarterial chemoembolization, *mADC* mean apparent diffusion coefficient, *PD* progressive disease, *PR* partial response, *RECIST 1.1* Response Evaluation Criteria in Solid Tumors, *SD* stable disease. Responder = PR + SD, non-responder = PD

	cTACE ($n = 13$)	DSM-TACE ($n = 18$)	*p* value
Mean tumor volume (± SD):			
Baseline	14.7 cm^3 (± 16.3)	35.3 cm^3 (± 71.6)	$p = 0.82$
Endpoint	23.9 cm^3 (± 32.7)	33.5 cm^3 (± 58.4)	$p = 0.59$
Mean tumor diameter (± SD):			
Baseline	25.6 mm (± 9.4)	31.5 mm (± 20.1)	$p = 0.95$
Endpoint	30.4 mm (± 16.5)	28.9 mm (± 20.5)	$p = 0.37$
Tumor response (RECIST 1.1)	PR, 23% ($n = 3$)	PR, 22% ($n = 4$)	
	SD, 15% ($n = 2$)	SD, 56% ($n = 10$)	$p = 0.046$
	PD, 62% ($n = 8$)	PD, 22% ($n = 4$)	
Median ADC (mm^2/s)			
Endpoint	1.2845×10^{-3}	1.1941×10^{-3}	$p = 0.83$
Overall response:			
Responder	38% ($n = 5$)	78% ($n = 14$)	$p = 0.027$
Non-responder	62% ($n = 8$)	22% ($n = 4$)	

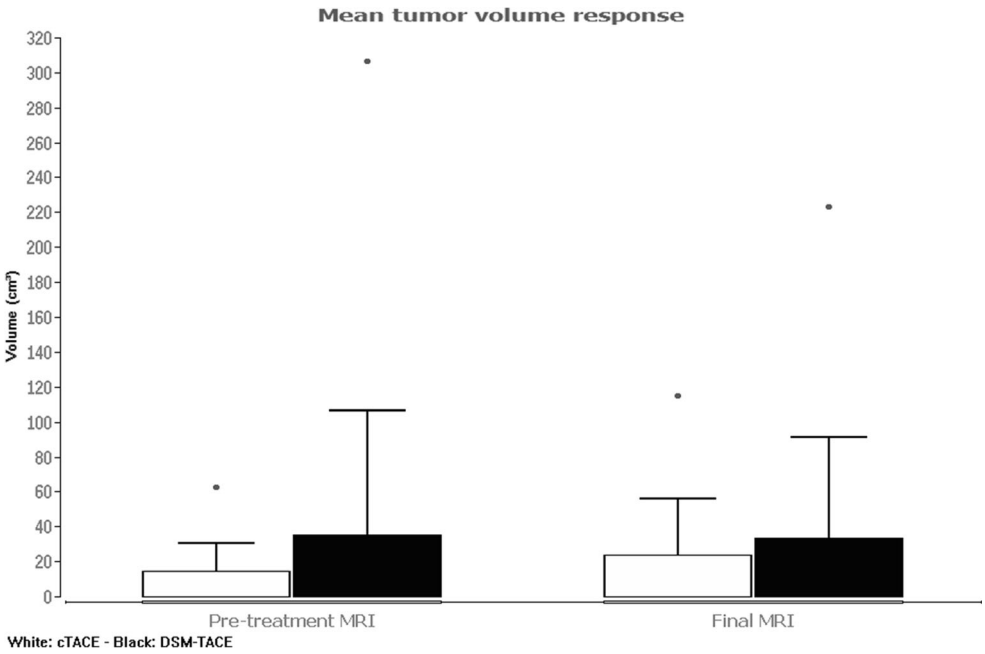

Fig. 2 Mean tumor volume response in the DSM-TACE group and cTACE group. Bar plot showing mean, standard deviations, and maxima of the pre- and post-treatment tumor volumes in the DSM-TACE group ($p = 0.006$). DSM: degradable starch microspheres, TACE: transarterial chemoembolization, MRI: magnetic resonance imaging

(SD ± 12.6, range 9.3–50.0 mm) and 28.8 mm (SD ± 14.9, range 7.9–60.7 mm), respectively. Mean tumor diameter at study endpoint was 30.4 mm (SD ± 16.5, range 6.5–58.8 mm) (Table 2). In contrast, tumor diameter in the DSM-TACE group decreased from 31.5 mm (SD ± 20.1, range 11.1–89.5 mm) at baseline to 30.7 mm (SD ± 21.6, range 9.6–87.5 mm) after the first therapy cycle and 28.9 mm (SD ± 21.8, range 9.1–78.8 mm) after the second intervention. At study endpoint, the mean diameter remained stable at 28.9 mm (SD ± 20.5, range 7.7–69.1 mm) (Table 3).

Statistical analysis showed no significant difference in baseline diameters between the cTACE and DSM-TACE groups ($p = 0.95$). Likewise, tumor diameters did not significantly differ between both groups at study endpoint ($p = 0.37$). Evaluation of differences in tumor diameter change over the course of the therapy between the study groups revealed no statistically significant changes after the first ($p = 0.77$), second ($p = 0.065$), and third therapy cycle ($p = 0.35$).

Diffusion-weighted imaging

ADC values were determined during every MRI measurement. Exemplary pre- and post-treatment MRI scans including ADC maps are shown in Figs. 3 and 4. In patients who completed the study, median baseline ADC values were 1.0677×10^{-3} mm^2/s in the cTACE group and 1.1734×10^{-3} mm^2/s in the DSM-TACE group. After the first and second therapy cycle, median ADC values were 1.2635×10^{-3} mm^2/s (1st cTACE) vs 1.2593×10^{-3} mm^2/s (1st DSM-TACE) and 1.2287×10^{-3} mm^2/s (2nd cTACE) vs 1.2999×10^{-3} mm^2/s (2nd DSM-TACE), respectively. At the study endpoint, median ADC values were 1.2845×10^{-3} mm^2/s in the cTACE group and 1.1941×10^{-3} mm^2/s in the DSM-TACE group (Table 2). There were no significant differences in the baseline ($p = 0.26$), inter-treatment (after 1st cycle: $p = 0.71$, after 2nd cycle: $p = 0.68$), and endpoint ($p = 0.83$) median ADC values between both groups.

Differences in ADC changes over the therapy course were also calculated for the study groups. No statistically different changes could be found after the first ($p = 0.49$), second ($p = 0.43$), and third therapy cycle ($p = 0.18$). We also compared ADC values according to therapy response and found no significant difference in MRIs between responder and non-responder groups at baseline ($p = 0.92$) and study endpoint ($p = 0.65$).

Tumor response according to RECIST 1.1

Evaluation of tumor response according to RECIST 1.1 exhibited three patients with PR in the cTACE group and two patients with SD, while eight patients showed PD. In the DSM-TACE group, four patients revealed PR (Fig. 4), 10 patients SD, and four patients PD (Table 2). In total, 19 patients (61%) belonged to the responder group representing patients with PR or SD (cTACE: $n = 5$ vs DSM-TACE: $n = 14$).

Application of the Fisher's exact test exhibited a statistically significant difference between cTACE and DSM-TACE groups considering the distribution of RECIST 1.1 criteria ($p = 0.047$).

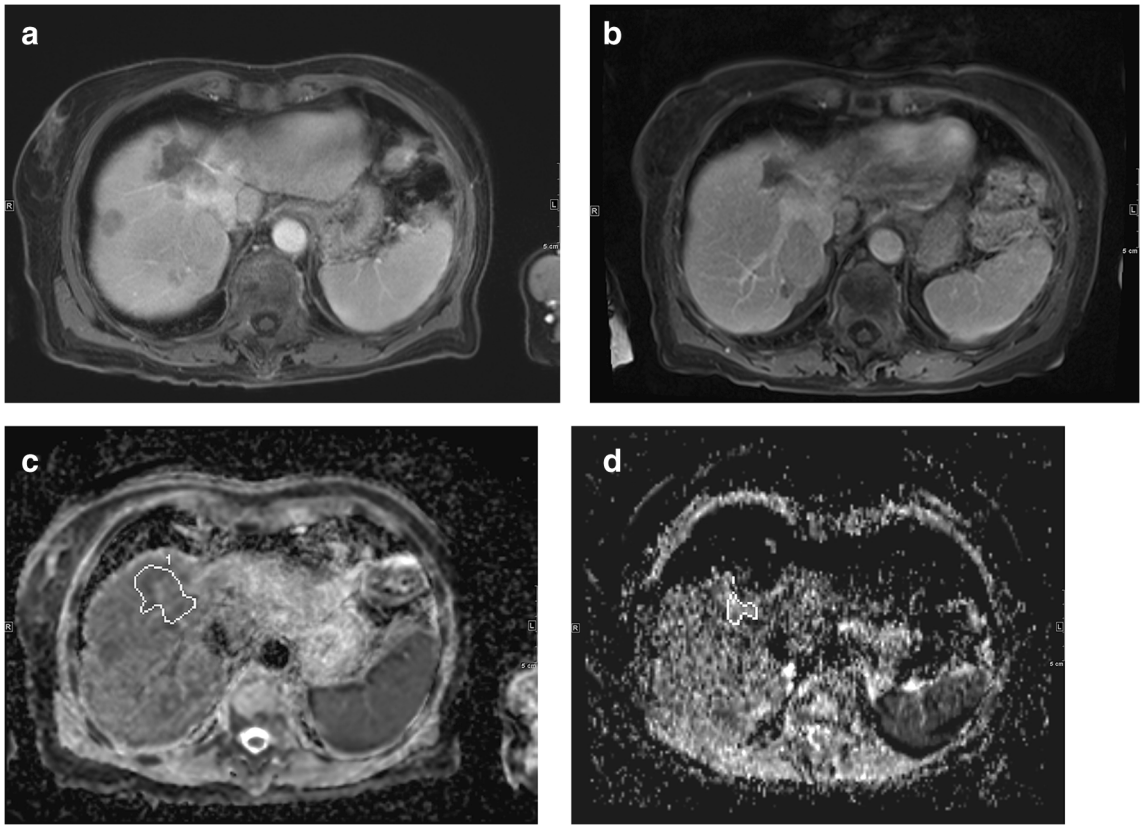

Fig. 3 An 81-year-old woman with hepatic metastasis of a colorectal carcinoma. Palliative indication after first being diagnosed in 12/2012 with pT3, pN2a, L1 G3, wild-type K-Ras, and already receiving second-line chemotherapies as well as a sigmoid resection (11/2014) over the last 5 years. Now third-line transarterial chemoembolization (TACE) with mitomycin C, irinotecan, cisplatin as chemotherapeutics, and degradable starch microspheres (DSM) for vessel occlusion. **a** Pre-treatment contrast-enhanced axial magnetic resonance imaging (MRI) scan showing colorectal liver metastasis in segment IV/VIII with a volume of 23.4 cm^3. **b** Post-treatment contrast-enhanced axial MRI: tumor volume of 6.8 cm^3, approx. 30% of initial tumor mass. **c** Pre-treatment axial apparent diffusion coefficient (ADC) map with region of interest (ROI) of lesion in segment IV/VIII (ROI mean ADC 1.0051×10^{-3} $mm^2/s \pm 0.1486 \times 10^{-3}$ mm^2/s). **d** Post-treatment axial ADC map with ROI of lesion in segment IV/VIII (ROI mean ADC 1.2240×10^{-3} $mm^2/s \pm 0.3806 \times 10^{-3}$ mm^2/s)

Survival data

Survival analysis included all 50 randomized patients and showed a median survival of 13 months (95% confidence interval [CI], range 5–40 months) in the cTACE group compared to 16 months (95% CI, range 1–48 months) in the DSM-TACE group (Fig. 5). No statistically significant difference in survival was observed between both groups ($p = 0.75$). One-year survival rate was 62% (95% confidence interval [CI], range 35–89%) in the cTACE as well as the DSM-TACE group (95% confidence interval [CI], range 31–93%).

Discussion

To our knowledge, this is the first prospective randomized study that directly compared cTACE and DSM-TACE in patients with CRLM. For this purpose, we analyzed local tumor response according to RECIST 1.1, tumor volume/diameter, DWI, and survival. DSM-TACE showed a significant difference in tumor response according to RECIST 1.1 compared to cTACE with an increased proportion of responders (78% vs. 38% in the cTACE group). In the responder group, the tumor diameter at study endpoint was significantly smaller than that in the non-responder group (23.3 mm vs 39.4 mm). Furthermore, DSM-TACE was proven to be significantly effective in reducing tumor volume (35.3 cm^3 at baseline vs. 33.5 cm^3 at endpoint), which was not the case for cTACE.

So far, the efficacy of DSM-TACE has been mainly investigated in single-arm studies missing a control group [18–20]. Other studies tested the combined application of DSM and lipiodol in the same TACE procedure [21–25]. It should be noticed that in our study, initial tumor diameter and tumor volume even tended to be higher in the DSM-TACE than in the cTACE group, although this difference was not statistically significant. A study of Niessen et al, which compared DSM- and cTACE with doxorubicin in 69 patients with intermediate-stage hepatocellular carcinoma (HCC), showed a similar proportion of responders (complete response + PR + SD) of 82% in patients treated with DSM-TACE [26]. In

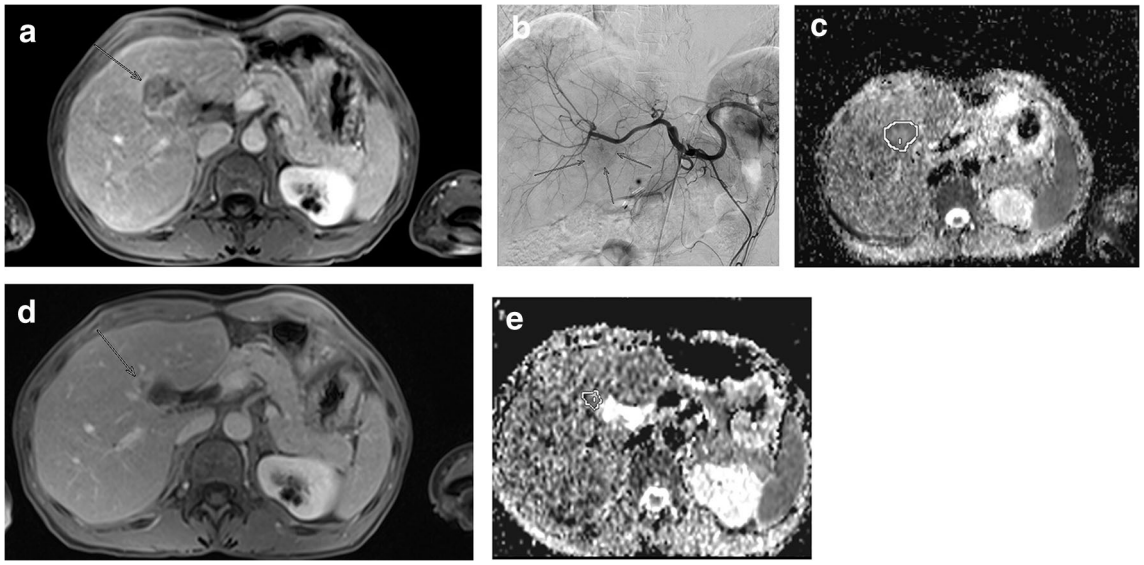

Fig. 4 A 57-year-old female patient with recurrence liver metastases after first neoadjuvant systemic chemotherapy with FOLFIRI and after curative atypical resection of liver metastasis in liver segment 2 and 3 (T3N1M0). After systemic chemotherapy with FOLFOX and Cetuximab®, a new liver metastasis has been diagnosed. Because the redenominated systemic chemotherapy has shown no effect, the patient was treated with DSM-TACE. Partial response achieved after 3 sessions of DSM-TACE. **a** Pre-treatment transverse contrast-enhanced T1-weighted MR image shows a metastatic liver lesion (arrow) in segment IV. **b** DSA image shows the metastasis in liver segment IV (arrow) without hypervascularity of lesion. **c** Pre-treatment axial apparent diffusion coefficient (ADC) map with region of interest (ROI) of lesion in segment IV (ROI mean ADC 1.2711×10^{-3} mm^2/s). **d** Post-treatment transverse contrast-enhanced T1-weighted MR image after 3 sessions of DSM-TACE shows partial response of metastatic liver lesion (arrow). **e** Post-treatment axial apparent diffusion coefficient (ADC) map with region of interest (ROI) of lesion in segment IV (ROI mean ADC 1.8602×10^{-3} mm^2/s)

contrast to our results, there was no significant difference in the proportion of responders compared to the cTACE group [26]. Our survival analysis did not detect any difference between the cTACE and DSM-TACE group in treating patients with CRLM with both showing a 1-year survival rate of 62%. A similar result regarding DSM-TACE was presented by Iezzi et al for patients with advanced HCC (1-year survival rate, 66.6%), although these preliminary data were based on only six patients [18]. Median survival in our cTACE group was 13 months, falling within the expected range for this procedure of 7–14 months according to the current literature [8]. The median survival of patients in the DSM-TACE group exceeded the cTACE group by 3 months. In previous studies, overall survival after DSM-TACE treatment was shown to be 13.8 months (median) in a retrospective analysis of patients with CRLM and 15.5 months (mean) in patients with HCC [9,

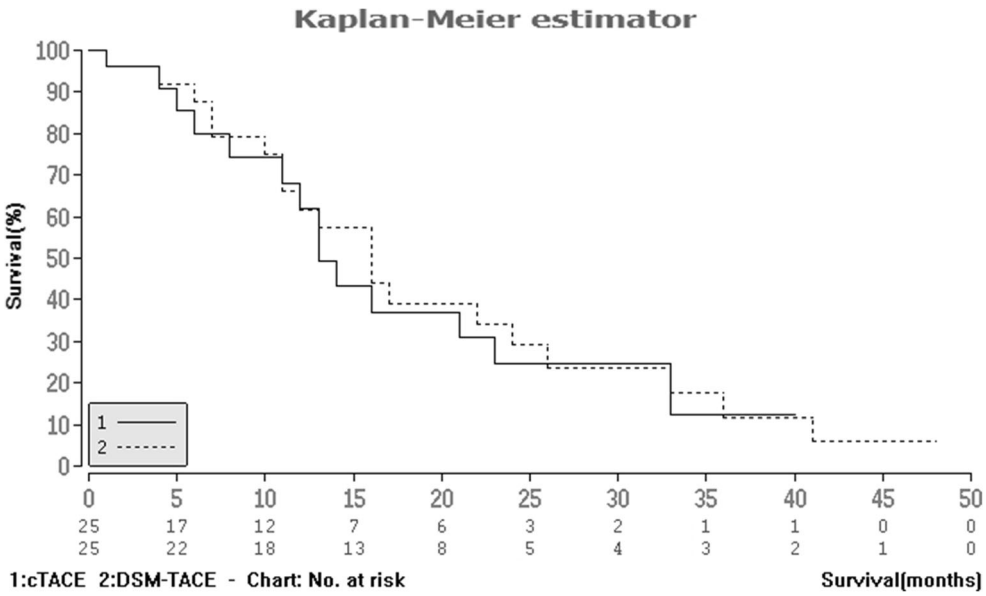

Fig. 5 Survival data of cTACE and DSM-TACE groups shown as Kaplan-Meier estimator. cTACE: conventional transarterial chemoembolization, DSM-TACE: degradable starch microspheres transarterial chemoembolization

26]. Considering that more than 20 patients in our study had more than five separate large, confluent metastases, cTACE and DSM-TACE are both viable therapy options with respect to patient survival. This applies especially to patients with a palliative therapy indication. Regarding DWI, some studies report that lesions which respond to chemotherapy show a significant increase in ADC values at the end of the treatment, suggesting a change to a less cellular or necrotic phenotype. These studies also state that among non-responding lesions or within normal appearing liver parenchyma, no significant ADC change can be observed [27]. On the other hand, it has been shown that a high ADC at baseline correlates with a poor response to chemotherapy [27–29]. While several studies have already analyzed the predictive qualities of baseline ADC values in tumor therapy, few trials have been specific to colorectal cancer [30, 31]. In our study, the correlation of high baseline median ADC (mADC) values with poor therapy response could not be confirmed, since mADC values at baseline did not differ significantly between the responder and non-responder group ($p = 0.92$).

Earlier studies suggest that high ADC values may be caused by increased necrosis within a tumor [28]. This theory is further supported by a study investigating the correlation of change in ADC values and histopathological findings [32]. Tumor necrosis, for example, induced by chemoembolization, changes the microenvironment around the necrotic areas, leading to hypoxia and increased acidity. The remaining tumor cells in these necrotic zones consequently decrease their rate of proliferation and become less sensitive to further chemotherapy [33]. This may explain why mADC values were not significantly influenced by the different occlusion times of lipiodol and DSM after any of the therapy cycles (after 1st cycle: $p = 0.71$; after 2nd cycle: $p = 0.68$; at endpoint: $p = 0.83$). Moreover, this may partly explain why the response group in our study showed no significantly different mADC values in the final MRIs compared to the non-responder group ($p = 0.65$).

Results of this study must be evaluated considering the following limitations. Due to 15 patients discontinuing the intervention, we were not able to reach our predetermined number of patients per study arm, limiting the reliability of our statistical results. Also, examinations were conducted at a single center only which limits the application of our results to the general population. Thus, future research should include multicenter trials with larger cohorts to verify our results. We used ROI ADC measurements to determine ADC values, which cannot account for and track the sometimes heterogeneous composition and change within the metastases [34]. In addition, MRI images of the left liver lobe may be degraded by artifacts arising from cardiac pulmonisations and obscure lesions [27]. Also, lesions smaller than 10 mm cannot be reliably measured with DWIng [28]. Yet, over the course of TACE therapy, some of the target lesions shrank below 10 mm and, therefore, were difficult to measure. To increase time efficiency, we used the same patient appointment to assess tumor response and to start the next cycle of TACE (4 to 6 weeks after the previous treatment). For optimal ADC measurements, however, MRIs may have to be scheduled separately within a week after the chemoembolization. Our study was limited in the generalizability of our ADC value measurements as previously described by Ma et al and Gianotti et al [35, 36]. These ADC values are affected by confounding variables including inherent properties of the scanners and receiver coils, patient BMI, environmental conditions including ambient temperature, and the inherent low spatial resolution of ADC maps. We attempted to mitigate the variability of scanner technology by using the same scanner and coils and the low spatial resolution of ADC maps by delineating ROIs on T2 and post-contrast T1 sequences. Despite these limitations, this is the first prospective, randomized study that directly compared efficacy of DSM-TACE with cTACE as third-line therapy in patients with CRLM. In conclusion, our results demonstrated improved tumor response according to RECIST 1.1 and significantly reduced tumor volume after three DSM-TACE sessions as compared to cTACE treatments. DSM-TACE may therefore be a valuable therapy option for patients with CRLM providing the additional advantage of short-term vessel occlusion, which reduces VEGF induction and risk of postembolization syndrome as compared to lipiodol [9, 10].

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Thomas J. Vogl.

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Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- prospective
- randomized controlled trial
- performed at one institution

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