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Thermal ablation combined with transarterial chemoembolization for hepatocellular carcinoma: What is the right treatment sequence?

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ABSTRACT

Background: The combination treatment regimen of thermal ablation (TA) and transarterial chemoembolization (TACE) has gained a place in treatment of hepatocellular carcinoma (HCC) lesions > 3 cm unsuitable for surgery. Despite a high heterogeneity in the currently used treatment protocols, the pooled results of combined treatments seem to outperform those of TA or TACE alone. TACE preceding TA has been studied extensively, while results of the reverse treatment sequence are lacking. In this retrospective cohort study we compared the two treatment sequences.

Patients and methods: 38 patients (median age: 68.5 yrs (range 40–84), male: 34, liver cirrhosis: 33, early stage HCC: 21, intermediate stage HCC: 17) were included in two tertiary referral centers, of whom 27 were treated with TA and adjuvant TACE (TA + TACE). The other 11 patients received TA with neoadjuvant TACE (TACE + TA). Overall survival (OS), time to progression (TTP) and local tumor progression (LTP) free survival were determined for the entire cohort and compared between the two treatment sequences.

Results: The median OS of all patients was 52.7 months and the median time to LTP was 11.5 months (censored for liver transplantation). No differences were found with respect to OS between the two treatment sequences. Median time to LTP for TACE + TA was 23.6 months and 8.1 months for TA + TACE (p = 0.19).

Discussion: No statistical differences were found for OS, TTP and time to LTP between patients treated with TA combined with neoadjuvant or adjuvant TACE.

1. Introduction

Thermal ablation (TA) is an established treatment for hepatocellular carcinoma (HCC) and considered treatment of choice in HCC lesions < 2 cm, as local tumor progression (LTP) rates are comparable to those after surgical resection [1]. Surgical resection remains the treatment of first choice in larger lesions due to better local control, but carries a high risk of complications, especially in patients with cirrhosis and portal hypertension [2]. In patients who are not suitable candidates for surgical resection, TA or transarterial chemoembolization (TACE) are considered alternative therapies, depending on the tumor characteristics, tumor location, liver function, portal hypertension, performance status [3].

In order to decrease LTP rates after TA treatments of HCC lesions > 3 cm, Lencioni et al. published a first pilot study on the combination of TA with adjuvant TACE (TA + TACE) in 2008 [4]. Subsequent studies most commonly used the reversed sequence of neo-adjuvant TACE before TA (TACE + TA) and confirmed the potential benefit of the combined therapy [5,6]. Over the last decade, the treatment combination has been adopted in many clinical practices. The latest European and American guidelines on HCC management mention the potential benefit of combining TA with TACE for larger lesions, although large phase III trials and validation in western patient populations are lacking [7,8].

A meta-analysis was published on the combined treatment effect of TACE + TA vs. TA alone [9]. The authors included 8 studies in which

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648 patients were evaluated and significantly better hazard ratios with respect to overall survival (OS) and recurrence free survival were found. Most of the included studies were cohort studies, but the results were also confirmed by a randomized controlled trial from China [10]. Although the evidence for the use of combined TA and TACE treatment in either sequence is growing, treatment schedules are currently heterogeneous and unconcise in the optimal interval between TA and TACE. Moreover, there is a paucity of studies directly comparing the treatment sequences.

In 2009, the combined treatment regimen was adopted in our clinical practices. Adjuvant TACE after TA was the initial treatment sequence. This was later changed to neoadjuvant TACE prior to TA, due to growing clinical evidence for that treatment sequence. In this retrospective cohort study we compared the effectiveness of both treatment regimens in terms of local tumor control, time to progression (TTP) and OS.

2. Methodology

2.1. Patients

This was a retrospective cohort study performed in two academic tertiary referral centers. Between January 2009 and April 2020, 38 patients were treated with a combination of TA and TACE and had a minimum follow up duration of one year. All patients had de novo unresectable HCC, diagnosed in accordance with the European Association for the Study of the Liver (EASL) guidelines [7]. Consensus on combined treatment with TACE and TA was reached in multidisciplinary tumor board meetings for all patients, attended by at least a hepatologist, surgeon, (interventional) radiologist, pathologist and oncologist. The preferred treatment order was changed from adjuvant TACE to neoadjuvant TACE prior to TA in 2015 in both centres.

Selection criteria for undergoing the treatments included a Child-Pugh classification of A or B and Eastern Cooperation Oncology Group (ECOG) performance status of < 2. Ineligibility criteria were radiologic evidence of vascular invasion into portal/hepatic vein branches, extrahepatic metastases, severe liver dysfunction (Child-Pugh C), significant and uncorrectable coagulopathy (International Normalized Ratio (INR) > 1.7, platelet count $< 50 * 10^9/mm^3$).

2.2. Thermal ablation

Percutaneous TA was performed under general anesthesia with image guidance using ultrasound and/or CT. Three different radiofrequency ablation (RFA) systems were used throughout the study period, of which two were single electrode systems (3 cm exposed tip Covidien (Medtronic Covidien, Fridley, Minessota, USA) and StarBurst XL (Angiodynamics, Amsterdam, The Netherlands)) and one multiple electrodes switch-control system (3 or 4 cm exposed Cooltip (Covidien)). Two microwave ablation (MWA) systems were used: Amica (HS Hospital Service, Rome, Italy) and Emprint (Covidien/Medtronic, Minneapolis, USA). Immediate intraprocedural post-ablation contrast-enhanced computed tomography (CECT) was performed on a 16 or 64 slice spiral CT-scanner. Technical success was defined as 'complete coverage of the tumor by the ablation necrosis as assessed by juxta-positioning of pre- and procedural cross-sectional images and absence of tumor enhancement on the immediate post-ablation CECT'. Immediate re-ablation was performed when no technical success was reached at the first attempt.

2.3. Transarterial chemoembolization

Using a transfemoral approach, selective angiography was performed of the common, lobar and (sub)segmental hepatic arteries. Contrast-enhanced cone-beam computed tomography (CBCT) was performed in most patients to assess the local vascular tumor supply (XperCT, Philips Healthcare, Best, The Netherlands). Catheter positions were chosen as selective as possible and 100–300 μm and 300–500 μm DC Beads were used, loaded with a maximum of 75 mg of doxorubicin per vial (Boston Scientific, Natick, Massachusetts, USA) and up to 150 mg of doxorubicin per patient. In early years of this study, both 100–300 μm and 300–500 μm were used. The treatment protocol was later changed to 100–300 μm beads only, as evidence came available that smaller beads penetrate more distally and may thus cause more extensive tumor necrosis. Endpoints for the treatment were arterial flow stasis or the total infusion of DC Beads with up to 150 mg of doxorubicin. Hepatic angiography was performed immediately after embolization and technical success was defined as the successful delivery of the DC Beads with absence of tumor blush on the last angiogram.

2.4. Follow-up

Imaging was performed 6 weeks after TA and then continued every 3 months until untreatable disease or death, using dynamic gadolinium enhanced magnetic resonance imaging (GE-MRI) or CECT. In one centre, FU was reduced to every 6 months after 2 years of complete remission. Local tumor progression (LTP) was defined as the presence of tumor enhancement on a follow-up scan within or directly bordering the treated tumor. LTP was distinguished from distant intrahepatic recurrence or extrahepatic metastatic disease. Included patients had at least one year follow-up. Patients were followed until death, last follow-up or the end of the study (08-2021).

2.5. Outcomes

Effectivity was evaluated as Time to LTP, TTP of any kind (LTP, intrahepatic metastases or distant metastases) and OS. Complications were evaluated according to the Common Terminology Criteria for Adverse Effects (CTCAE) version 5.0.

2.6. Statistical analysis

Statistical analyses were performed using RStudio 1.4.1106. Continuous variables were compared using an unpaired *t*-test for normally distributed, continuous variables and Mann-Whitney U for non-normally distributed data. The Chi-square test was used to compare categorical variables.

Univariate and multivariate Cox's proportional hazards models were used to evaluate the predictive factors of survival. The factors age, sex, cirrhosis, ECOG score, Child-Pugh score, number of lesions, lesion size, BCLC stage, treatment order, and liver transplantation after treatment were evaluated. Factors with a p-value < 0.2 in the univariate analyses were considered to be potential predictors of survival and were further analysed in the multivariate analysis.

Survival analyses for OS, TTP and time to LTP were performed using Kaplan Meier estimates. Starting point was set at the date of treatment completion. Censoring was applied in comparative survival analyses to patients that underwent liver transplantation, and in all Kaplan-Meier analyses for cases that were lost to follow up. Moreover, survival was censored for patients who were still alive at the closeout date. Differences in OS, TTP and LTP free survival were tested for using the log-rank test. P-values of <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

Baseline characteristics of all patients are shown in Table 1. In total 38 patients were included with a median age of 68.5 years old, of which 34 were male. Underlying liver cirrhosis was found in 33 patients, all with Child-Pugh A cirrhosis. Most patients had 1 lesion ($n = 21$), 15 patients had 2 lesions and 2 patients had 3 lesions. The median tumor size of the largest lesion was 40 mm (range: 21–69 mm). An example of both treatment sequences can be found in Fig. 1.

Table 1
Patient characteristics of analyzed patients.

		Total		*TA + TACE*		*TACE + TA*		*p-value*
Total		38		27		11		
Age (years)	median (range)	68.5	*(40–84)*	65	*(40–84)*	70	(54–78)	*0.351*
Sex	male	34	*89.5%*	23	*85.2%*	11	100%	*0.238*
Center	Center 1	31	*81.6%*	23	*85.2%*	8	72.7%	*0.370*
	Center 2	7	*18.4%*	4	*14.8%*	3	27.3%	
Cirrhosis	yes	33	*86.8%*	22	*81.5%*	10	90.1%	*0.429*
Etiology of cirrhosis*	Hepatitis B	4		4		0		
	Hepatitis C	11		6		5		
	Alcoholic liver disease	16		11		5		
	NASH	6		3		2		
	Other	3		3		0		
Child-Pugh	A5	22	*66.7%*	18	*81.8%*	4	36.4%	*<0.001**
	A6	11	*33.3%*	4	*18.2%*	7	63.6%	
ECOG score	0	33	*86.8%*	23	*85.2%*	10	90.9%	*0.636*
	1	5	*13.2%*	4	*14.8%*	1	9.1%	
BCLC stage	early	21	*55.3%*	13	*48.1%*	8	72.7%	*0.167*
	intermediate	17	*44.7%*	14	*51.9%*	3	27.3%	
Number of lesions	1	21	*55.3%*	13	*48.1%*	8	72.7%	*0.216*
	2	15	*39.4%*	13	*48.1%*	2	18.2%	
	3	2	*5.3%*	1	*3.8%*	1	9.1%	
Size largest lesion (mm)	median (range)	40	*(21–69)*	43	*(30–69)*	37	(21–55)	*0.034**
Type of TA	RFA	33	*86.8%*	25	*92.6%*	8	72.7%	*0.100*
	MWA	5	*13.2%*	2	*7.4%*	3	27.3%	
Size TACE particles	100–300 μm	32		25		7		
	300–500 μm	6		5		1		
	Unknown	5		2		3		
Dose of doxorubicin (mg)	median (range)	50	*(25–100)*	50	*(25–100)*	67.5	(25–100)	*0.510*
Consecutive treatments	Thermal ablation	15	*39.5%*	12	*44.4%*	3	27.3%	*0.272*
	Liver transplantation	12	*31.6%*	10	*37.0%*	2	18.2%	*0.231*
	TACE	11	*28.9%*	8	*29.6%*	3	27.3%	*0.334*
	TARE	3	*7.9%*	3	*11.1%*	0	–	*<0.001**
	Sorafenib	9	*23.7%*	8	*29.6%*	1	*9.1%*	*0.237*
Year of treatment	2009–2014	25	*65.8%*	24	*88.9%*	1	*9.1%*	*<0.001**
	2015–2020	13	*34.2%*	3	*11.1%*	10	*90.9%*	

NASH = Non-alcoholic steatohepatitis, ECOG = Eastern Cooperative Oncology Group, BCLC = Barcelona Clinic for Liver Cancer, TA = Thermal ablation, RFA = Radiofrequency ablation, MWA = Microwave ablation, TACE = Transarterial chemoembolization, TARE = Transarterial radioembolization. *More etiological factors could apply to one patient. *Statistically significant.

Statistically significant differences between the two cohorts of different treatment sequences were found with respect to Child-Pugh score (higher for patients treated with neo-adjuvant TACE, $p < 0.001$), lesion size (larger for patients treated with adjuvant TACE, $p = 0.034$), the use of TARE as consecutive treatment (used more often in patients treated with adjuvant TACE) and year of treatment (the treatment sequence changed from adjuvant TACE to neoadjuvant TACE). All details can be found in Table 1. Data on the TACE particle size were missing in 5 patients. In 5 patients, both small sized (100–300 μm) and larger sized (300–500 μm) particles were used.

3.2. Cox proportional hazards model

Table 2 shows the results of the univariate and multivariate analysis for survival. BCLC stage and liver transplantation were the only covariates that showed a p-value < 0.2 in the univariate analysis. After multivariate analysis, only liver transplantation contributed significantly to survival with a hazard ratio of 0.05 (CI 95%: 0.01–0.27) and p-value of <0.001.

3.3. Treatment outcome

Technical success of TA and TACE was achieved in all patients. Two out of 38 patients were lost to follow-up. The median survival was 52.7 months for all patients. Fig. 2 demonstrates the corresponding Kaplan-Meier curve. The 1-year, 2-year, 3-year, 4 year and 5-year OS are respectively 86.5%, 62.3.1%, 55.5%, 51.2% and 47.0%.

Disease progression occurred in 28/38 patients with a median TTP of 4.8 months. LTP occurred in 20/38 patients. Median time to LTP was 11.5 months. Fig. 3 shows the corresponding TTP and time to LTP curves, censored for liver transplantation.

3.4. Treatment sequence

Adjuvant TACE was performed after TA in 27/38 patients with an average interval of 3.52 days (SD = 6.81). In the other 11 patients, patients first underwent neoadjuvant TACE followed by TA with an average interval of 30.73 days (SD = 25.15). OS curves were similar between those groups ($p = 0.68$). Median TTP was 12.8 months for TACE + TA and 2.8 months for TA + TACE ($p = 0.30$). Time to LTP was 23.6 months for TACE + TA and 8.1 months for TA + TACE ($p = 0.19$) The corresponding Kaplan-Meier curves can be found in Fig. 4.

3.5. Complications

One grade CTCAE 5.0 grade 5 complication occurred. In a patient who was treated for a large (47 mm) HCC lesion in the liver dome. This procedure was complicated by a right sided pneumothorax for which a chest tube was inserted. The next day, super selective TACE was performed. Five days later, the patient developed sepsis as a result of *E. coli* peritonitis. Despite treatment with percutaneous drainage and antibiotics, the patient died 23 days after TA as a result of sepsis and hepatorenal syndrome. Two patients developed a liver abscess days after ablation, which were successfully treated with percutaneous drainage and antibiotics (CTCAE 5.0 grade 3 and 4). Moreover 6 complications were graded 1 or 2 (mostly post-TACE symptoms). All grade 2–5 complications (n = 6) were reported in patients who underwent adjuvant TACE.

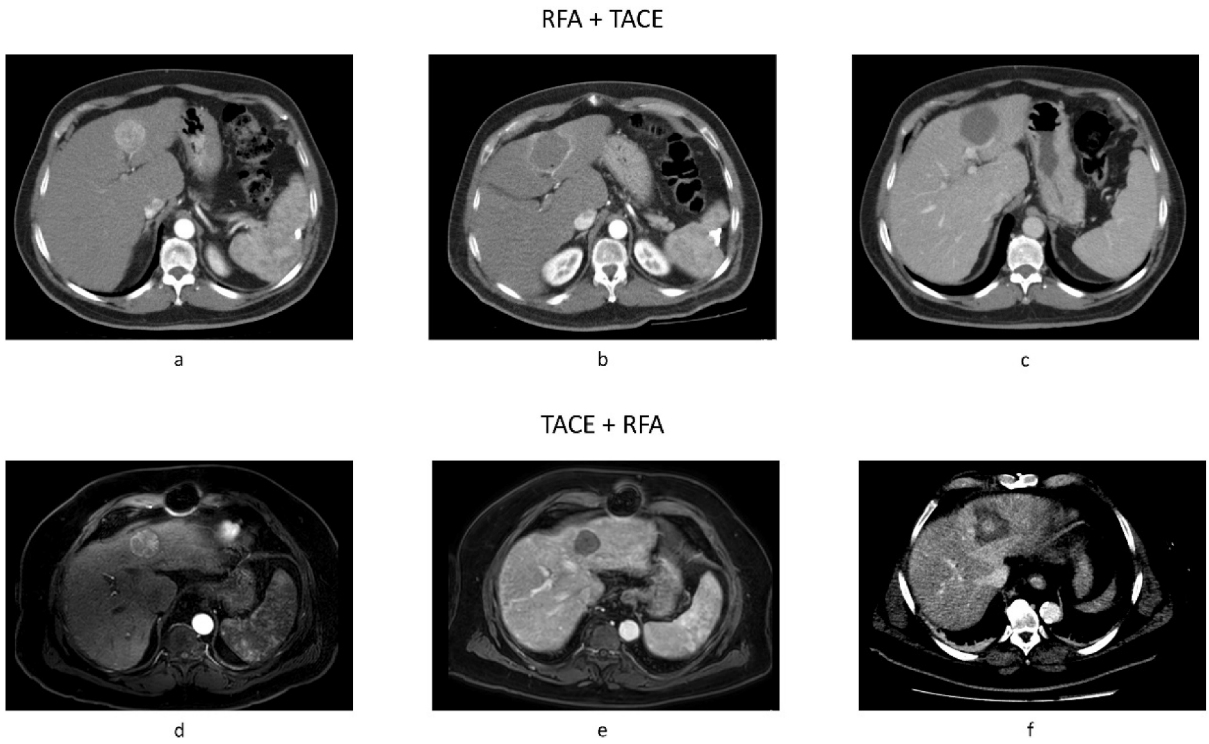

Fig. 1. Two cases of patients treated with different treatment sequences. Adjuvant TACE was used in the first case (A: diagnostic CT, B: post-ablation CT, C: post TACE CT) Neo-adjuvant TACE was used in the second case (D: pre-treatment gadolinium-enhanced MRI in arterial phase, E: pre-treatment gadolinium-enhanced MRI in portal venous phase, F: post-treatment CT scan).

Table 2
Univariate and multivariate analysis for survival.

	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Age	1.03 (0.99–1.07)	*0.178*		
Sex	0.98 (0.28–3.46)	*0.976*		
Cirrhosis	1.15 (0.33–4.03)	*0.830*		
ECOG score	1.75 (0.39–7.85)	*0.466*		
BCLC stage	0.54 (0.21–1.36)	*0.190*	1.65 (0.59–4.61)	*0.337*
Child Pugh	1.79 (0.67–4.82)	*0.246*		
Number of Lesions	0.65 (0.30–1.39)	*0.264*		
Lesion size	1.02 (0.99–1.05)	*0.239*		
Treatment sequence	1.24 (0.44–3.52)	*0.684*		
Liver transplantation	0.07 (0.01–0.31)	*<0.001*	0.05 (0.01–0.27)	*<0.001*

HR = hazard ratio, CI = confide interval, ECOG = eastern cooperative oncology group, BCLC = Barcelona clinic for liver cancer.

3.6. Consecutive treatments

Liver transplantation was performed in 12/38 patients treated with the combined regimen of TA and TACE. The median time to transplantation was 419 days (range: 183–1373 days). In one transplanted patient, recurrent disease was found 3 years after transplantation. No disease progression was found in all other transplanted patients. Details on all other consecutive treatments can be found in Table 1.

4. Discussion

In this retrospective cohort study, we evaluated the effect of combined TA and TACE treatment on OS, TTP and time to LTP. In the multivariate analysis of survival, only liver transplantation as consecutive treatment turned out to be an independent covariate. In the Kaplan-Meier analysis, median time to LTP was 23.6 months for TACE + TA and 8.1 months for TA + TACE ($p = 0.19$). No statistical difference was found between the groups, but local tumor control can be considered a goal itself as combined TA and TACE can be used as bridging therapy to liver transplantation [11].

The median OS of 52.7 months corresponds to expected OS for early and intermediate stage HCC patients according to the BCLC criteria [3]. Table 3 shows an overview of clinical trials studying the TA + TACE treatment combinations with respect to treatment protocol and clinical outcomes. Our results are in general comparable to those of other clinical studies. Very limited data are available on the combination of TA followed by TACE. One clinical study was found comparing TA + TACE with TACE + TA by El Dorry et al. and they found median disease-free survival of 17.1 months for TACE + TA vs 23.2 months for TA + TACE ($p > 0.05$) [12]. These results confirm our results as no statistical differences were found. Uncensored, the TTP in our study was 14.2 months, which is slightly lower than in the study by El Dorry et al.

As shown in Table 3, considerable heterogeneity exist between the treatment protocols in the various studies. Besides the sequence of both treatments, variability exists in patient selection, interval between the treatments, type of ablation (RFA and/or MWA) and type of TACE (conventional TACE (cTACE) or drug-eluting bead TACE (DEB-TACE)). Most clinical evidence is available for the use of TACE + TA. The rationale for this treatment sequence is that TACE causes vessel occlusion and reduced tumor perfusion, potentially resulting in volume reduction, reduction of 'heat-sink' and larger ablation zones [13]. A less studied alternative is TA + TACE. TA causes hyperemia in the liver parenchyma surrounding the area of coagulation necrosis and this

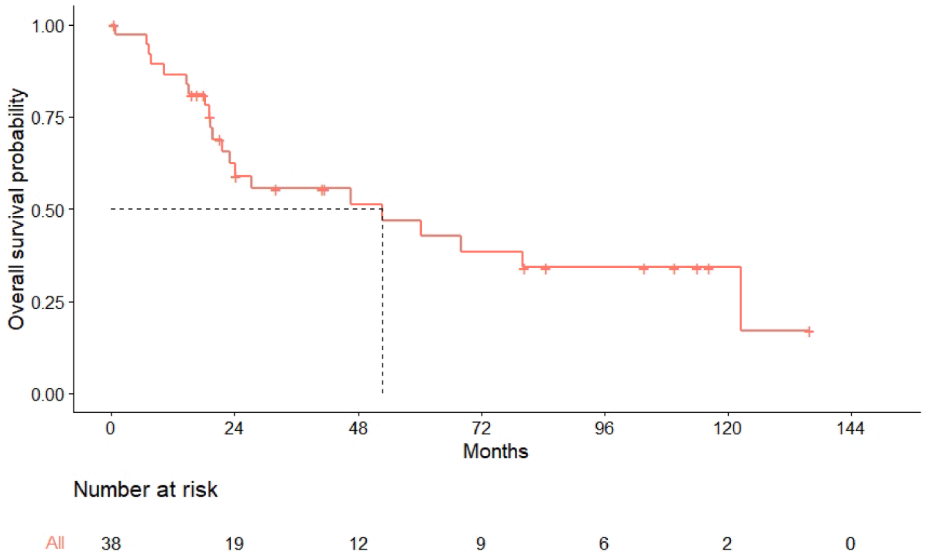

Fig. 2. Kaplan-Meier overall survival function of all patients treated with combined TA + TACE.

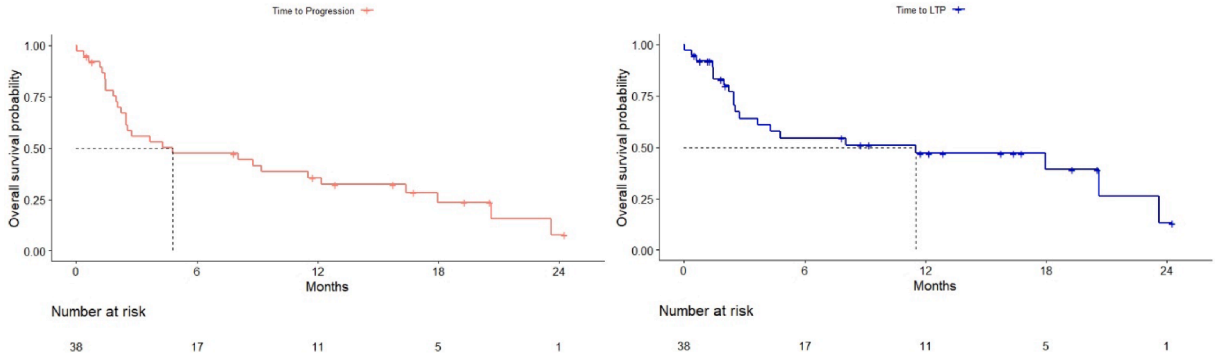

Fig. 3. Left: Kaplan-Meier analysis of the TTP, censored for liver transplantation. Right: Kaplan-Meier analysis of the Time to LTP, censored for liver transplantation.

hyperemia is utilized to target residual tumor cells or satellite lesions. It is hypothesized that by performing TACE within several days after TA, the hyperemia will cause preferential flow and high uptake of chemoembolic drugs in the tissue surrounding the ablation. Furthermore, insufficiently heated tumor tissue may have reduced cell resistance to drugs used in TACE [13]

In our study, RFA and MWA were used interchangeably. The available literature indicates that OS is comparable between the two techniques, but differences between RFA and MWA may affect the combinational effect when ablation is combined with TACE [14–17]. Compared to RFA, MWA is less susceptible to heat-sink and tissue perfusion. This may reduce the added value of TACE in a neoadjuvant setting. Also, ablation times are shorter with MWA and intratumoral temperatures tend to be higher. Both factors would potentially influence the degree of hyperemia that occurs in the surrounding liver parenchyma after ablation. This may potentially reduce the efficacy of TACE in an adjuvant setting [14–17].

With respect to TACE technique, patients in our study underwent TACE with drug eluting beads (DEB-TACE) rather than conventional TACE (cTACE). After cTACE, lipiodol causes visualization of the targeted lesion on a non-contrast CT-scan, which may help needle positioning when TA is performed after TACE. Although limited evidence suggests DEB-TACE may yield better local control when used as single therapy [18,19], the influence of different TACE techniques when combined with TA has not been studied. Further research is warranted to determine how synergy between TA and TACE is best achieved.

The main limitations of this study are its limited number of included patients and its retrospective nature. Comparative analysis to a matching group from our own institutions was not performed as the selection criteria for the combined treatment regimen was distinctly different from patients undergoing either TA or TACE only. Instead, we chose to validate our results with evidence available from other studies to TA and TACE combined treatments and to perform a comparative analysis within our own cohort only between the treatment sequences. Comparison between the two groups was hampered by the low number of patients, in particular in the TACE + TA group.

5. Conclusion

There is growing evidence for the combined treatment regimen of TA and TACE for HCC lesions > 3 cm. The vast majority of clinical evidence is available on TACE as a neoadjuvant treatment prior to TA. Our retrospective clinical data contributes to this field as we have compared the two treatment sequences in a western cohort. No difference in OS or LTP was found between the TA with adjuvant TACE and TA with neoadjuvant TACE groups.

CRediT authorship contribution statement

P. Hendriks: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **D.R. Sudiono:** Conceptualization, Data curation, Writing – original draft. **J.J. Schaapman:** Data curation, Writing – original draft. **M.J. Coenraad:** Methodology, Resources, Writing – review & editing. **M.E. Tushuizen:**

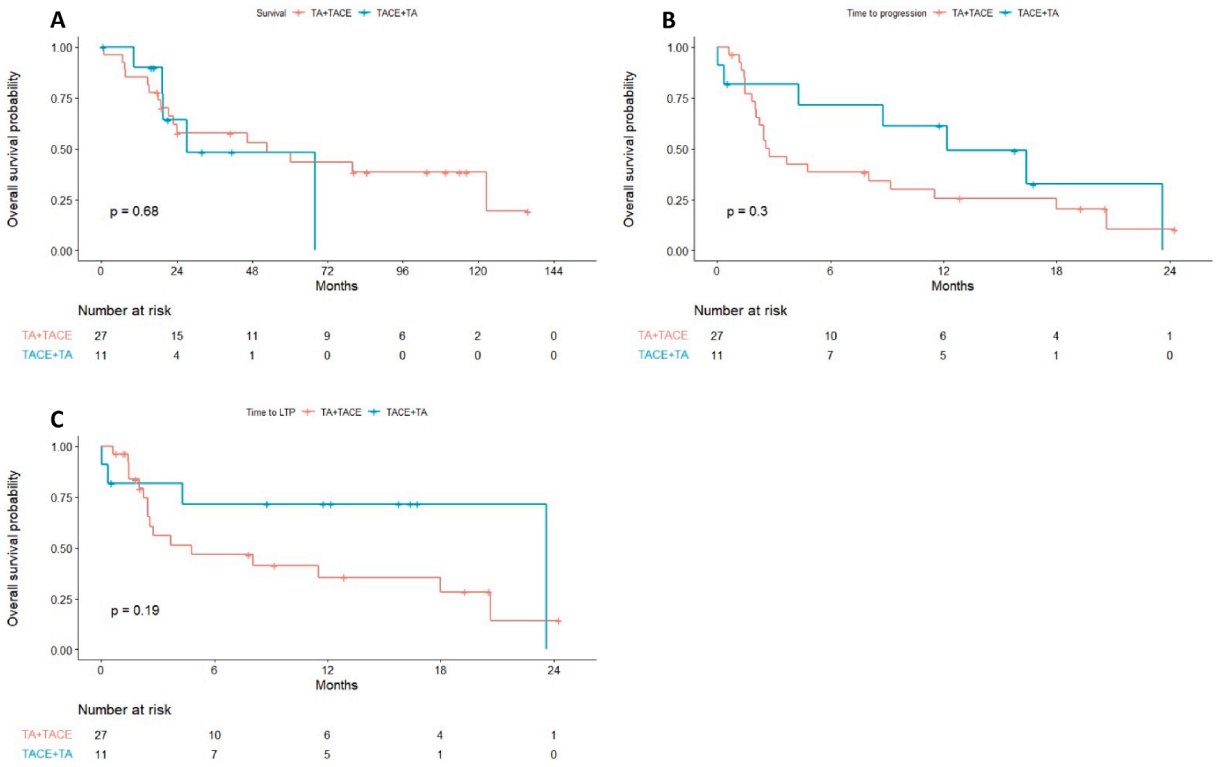

Fig. 4. Kaplan-Meier curves of differences between treatment sequences TA + TACE (orange) and TACE + TA (turquoise). A: overall survival. B: Time to progression. C: Time to local tumor progression.

Table 3
Overview of treatment regimens and clinical outcomes of previous studies. All survival data are in months. OS = Overall survival, PFS = Progression free survival, TTP = Time to progression, RFA = radiofrequency ablation, MWA = microwave ablation, DEB-TACE = drug-eluting beads transarterial chemoembolization, cTACE = conventional transarterial chemoembolization.

Article	Lesion size	Treatment	Interval	Overall Survival (OS in %)			Progression Free Survival (PFS in %)			Median/ Mean OS	Median/ Mean TTP
				1 year	2 year	3 year	1 year	2 year	3 year		
Lencioni et al. [4]	5.0 cm (3.3–7.0)	RFA + DEB-TACE	<24 h	–	–	–	–	–	–	–	–
Sheta et al. [17]	4.2–5.6 4.8–5.6	RFA + cTACE MWA + cTACE	same session same session	–	–	–	–	–	–	–	–
Wang et al. [20]	1.5–10 cm	RFA + cTACE	1–2 months	83.1	55.7	43.7	–	–	–	–	–
El Dorry et al. [12]	–	RFA + TACE* TACE* + RFA	same session same session	100 85	74 64	–	–	–	–	–	23.2 17.1
Lin et al. [21]	3–5 cm	TACE* + RFA	1 week	90.6	72	53.1	75	50	34	–	–
Peng et al. [10]	<7 cm	cTACE + RFA	<2 weeks	92.6	66.6	–	79.4	60.6	–	–	–
Morimoto et al. [22]	3.1–5.0 cm	cTACE + RFA	same day	100	93	93	67	19	–	–	–
Shibata et al. [23]	0.8–3.0 cm	cTACE + RFA	1 week	100	100	84.8	85.6	82.4	82.4	–	–
Yan et al. [24]	1.1–15.6	cTACE + RFA	1–14 days	–	–	–	–	–	–	46	28
Zhang et al [25]	3.75 (SD: 1.21)	DEB-TACE + RFA	1–2 weeks	97.5	84.7	66.1	75	51.7	35.4	–	–
Liu et al. [26]	<5 cm	cTACE + RFA	7–15 days	76.2	–	37.1	43.2	–	18	27.6	9.1
Sun et al. [27]	<7 cm	cTACE + RFA	1 week	94.4	–	70.8	76.4	–	37.1	–	–
Abdelaziz et al. [15]	4.6 ± 1.9 cm 4.2 ± 1.9 cm	cTACE + RFA cTACE + MWA	<2 weeks <2 weeks	–	–	–	73.1 83.3	40.6 64.7	16.2 64.7	–	–
Zhu et al. [28]	2.7 (2.1–4.8)	DEB-TACE + RFA	1–3 months	–	–	–	–	–	–	12.5	8.8

*Type of TACE not specified.

Methodology, Resources, Writing – review & editing. **R.B. Takkenberg:** Resources, Writing – review & editing. **T.T.M. Oosterveer:** Data curation, Formal analysis, Writing – review & editing. **L.F. de Geus-Oei:** Methodology, Supervision, Writing – review & editing. **O.M. van Delden:** Data curation, Resources, Supervision, Writing – review & editing. **M.C. Burgmans:** Conceptualization, Investigation, Methodology,

Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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