Advancements in minimally invasive image-guided liver therapies

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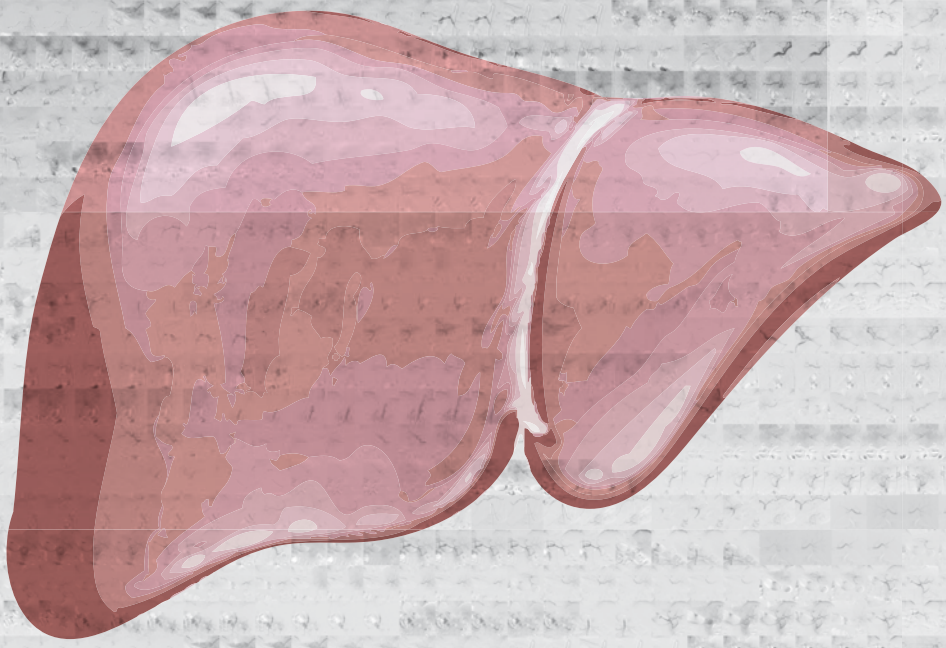
Chapter 4

Local tumor progression and survival rates after combined radiofrequency ablation and drug-eluting bead chemoembolization in unresectable hepatocellular carcinoma



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Submitted for publication

ABSTRACT

Purpose

Local tumor progression (LTP) rates after radiofrequency ablation (RFA) are higher in hepatocellular carcinoma (HCC) >3cm compared to HCCs ≤3cm. Combined RFA and drug-eluting-bead transarterial chemoembolization (DEBTACE) can achieve larger ablation zones compared to RFA alone. This retrospective study describes 3-year LTP free-survival (LTPFS) and overall survival (OS) after RFA and combined RFA-DEBTACE for HCC ≤3 cm and >3cm respectively.

Methods

Local medical ethics committee approved the study. 54 patients (42 males; median 66 years (range: 29-82 years)) were treated with RFA for de novo unresectable HCC. Thirty-nine patients received RFA only. Fifteen patients with HCC >3-7cm underwent RFA-DEBTACE. LTPFS and OS were analyzed using Kaplan-Meier and Cox regression analysis.

Results

In the RFA-group, LTPFS and OS rates at 1-, 2- and 3-years were 81.4%, 66.0% and 59.4% and 87.2%, 81,6% and 69.8% respectively. The LTPFS and OS rates were lower in the RFA-DEBTACE-group: 26.9%, 17.9% and 17.9% and 73.3%, 66.7% and 53.3% respectively.

Conclusion

LTPFS rates after RFA-DEBTACE for HCC >3-7cm are low compared to the results reported after combination therapy of conventional TACE followed by RFA for HCC with similar size.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death in the world (1,2). Surgical resection is the first line treatment for patients with solitary HCC and a well-preserved liver function (1,2). Unfortunately, many patients with HCC are not eligible for surgical resection due to underlying liver disease, i.e. cirrhosis with portal hypertension. Liver transplantation is the preferred treatment for patients with liver cirrhosis and tumors within Milan criteria (single tumor <5cm or up to 3 tumors <3cm) who are unsuitable for resection (1,2). Radiofrequency ablation (RFA) is an effective alternative for surgical resection and may be used as a 'bridge-to-transplant' for patients on the waiting list for liver transplantation (1,2).

Local tumor progression rates after RFA are significantly higher in tumors >3 cm compared to smaller tumors (1-5). Different strategies have been advocated to reduce local tumor progression rates after RFA in tumors >3cm. Several Asian studies have shown promising results of conventional transarterial chemoembolization (cTACE) as a neoadjuvant treatment preceding RFA. Yet, cTACE has been abandoned in many European centers after a prospective randomized trial (Precision V) comparing cTACE and TACE with doxorubicin-eluting beads (DEBTACE) (6). This trial showed a better safety profile and favorable response rates of DEBTACE compared to cTACE.

There is a paucity of publications on combined treatment with RFA and DEBTACE. In a pilot study, it has been shown that RFA followed by DEBTACE resulted in significant increase in the volume of ablation necrosis compared to RFA alone (7). However, data on long-term results for combined RFA and DEBTACE is absent.

In our institution, a treatment protocol was implemented in January 2009 whereby patients with HCC >3cm were treated with combined RFA-DEBTACE and patients with HCC ≤3 cm were treated with RFA only. The objective of the study was to analyze three year local tumor progression free-survival and overall survival data of patients treated by RFA and combined RFA-DEBTACE for HCC ≤3 cm and >3-7cm respectively.

METHODS

Patients

The institutional review board (IRB) approved the study and informed consent was waived for the retrospective analysis. All patients gave informed consent to undergo treatment. Between January 2009 and July 2012, 54 consecutive patients (42 males;

median age 66 years (range: 29-82 years)) were treated in our institution with RFA for de novo unresectable HCC. The diagnosis was based either on tumor histology or on radiological imaging criteria, according to guidelines by the European Association for Study of the Liver (8). For radiological confirmation of the diagnosis, 4-phase contrast-enhanced computed tomography (CECT) and/or dynamic gadolinium-enhanced magnetic resonance imaging (GE-MRI) was used. All patients were discussed in a multi-disciplinary meeting of hepatologists, surgeons, radiologists and oncologists and consensus about the given treatment was reached in all cases.

Eligibility criteria for local ablation were: Child Pugh A or B, Child Pugh C in a patient eligible to undergo liver transplant, Eastern Cooperation Oncology Group performance status (ECOG) <2, single tumor measuring <7 cm or a maximum of 3 HCCs measuring ≤3cm. Ineligibility criteria were: radiologic evidence of vascular invasion into portal/hepatic vein branches, extrahepatic metastases, severe liver dysfunction (Child-Pugh C) *and* no eligibility for liver transplantation, significant and uncorrectable coagulopathy (International Normalized Ratio (INR) >1.7, platelet count <50x 10^9/mm^3). Patients with a HCC >3cm were scheduled to undergo RFA followed by DEBTACE the next day. All other patients underwent RFA only.

The following baseline information was retrieved from the electronic patient records and Picture and Archiving Computer System (Sectra, Linköping, Sweden): (a) age, (b) gender, (c) size of lesion, (d) number of lesions, (e) baseline serum albumin, (f) baseline serum bilirubin, (g) baseline INR, (h) etiology cirrhosis, (i) Child Pugh status, (j) tumor stage according to Barcelona Clinic Liver Cancer (BCLC) criteria.

The median follow-up for all patients was 23.8 months (quartiles: 15.5-36.9 months).

Radiofrequency ablation

Percutaneous RFA was performed under general anesthesia under ultrasound and/or CT guidance. A single electrode was used (3 cm exposed tip Cooltip (Covidien, Gosport Hamspire, United Kingdom) or StarBurst XL (AngioDynamics, Amsterdam, Netherlands) or multiple electrodes with a switch-control system (3 or 4 cm exposed tip Cooltip). Ablation was performed for 12 (single Cooltip electrode) or 16 minutes (multiple Cooltip electrodes) using standard impedance controlled ablation. Temperature-based ablation was accomplished with the StarBurst XL electrode. CECT was performed immediately after ablation on a 16-slice spiral CT (Toshiba, Tokyo, Japan). Technical success was defined as absence of tumor enhancement after ablation. If the CECT showed residual tumor enhancement, re-ablation was performed in the same session.

Transarterial chemoembolization

TACE was scheduled 1 day after RFA. After introduction of a 5F/6F vascular sheath in the common femoral artery, angiography was performed from the common, lobar and (sub) segmental hepatic arteries. Cone-beam CT (CBCT) was performed in individual cases to better delineate vascular tumor supply (XperCT, Philips Healthcare, Best, Netherlands). TACE was performed as selective as possible using 100-300 micrometer and 300-500 micrometer DC Bead® with a total of 100mg doxorubicin (Biocompatibles UK Limited, Surrey, United Kingdom). Endpoints for embolization were complete administration of 2 vials of DC Bead® or arterial flow stasis. Hepatic angiography was performed immediately after embolization. Technical success was defined as successful delivery of DC Bead® into the tumor feeding artery with absence of tumor blush on the completion angiogram.

Complications

Complications were evaluated according to the Common Terminology Criteria for Adverse Effects version 4.0 (CTCAE 4.0).

Follow-up

Four-phase CECT or dynamic GE-MRI was performed 6 weeks after treatment and repeated every 3 months thereafter. Local tumor progression was defined as the presence of tumor enhancement on a follow-up scan at the location of the treated tumor. Local tumor progression was distinguished from distant recurrence (i.e. a new intrahepatic tumor distant from the treated tumor). Patients were followed until last follow-up date, death or the end of the study. The endpoints were local tumor progression-free survival and overall survival.

Statistical analysis

The statistical analyses were performed using SPSS 21 (IBM, Armonk, NY, USA). Comparisons between the two groups were done by student t-test for continuous variables and the Chi-square test for categorical variables. Survival curves for overall survival and local tumor progression-free survival were constructed by the Kaplan-Meier method and compared with the Cox regression analysis. The impact of liver transplantation on overall survival was assessed using a time-dependant covariate with a log-rank test. All statistical tests were two-sided, and a difference was considered significant when $p < 0.05$.

RESULTS

Patient characteristics

Baseline demographics of all patients are shown in Table 1. All patients had hepatocellular carcinoma in the setting of liver cirrhosis. Of the 54 patients, 39 patients were treated with RFA and 15 with RFA-DEBTACE.

Table 1. Baseline patient and tumor characteristics of 54 patients.

Characteristic		Value
Median age (range)		66 years (29-82 years)
Male gender		42
ECOG		
	0	53 (98.1)
	1	1 (1.9)
Cause of cirrhosis (n (%))		
	Hepatitis B	6 (11.1)
	Hepatitis C	14 (25.9)
	Alcohol	31 (57.4)
	Other	11 (20.4)
Child Pugh score (n (%))		
	A	48 (88.9)
	B	4 (7.4)
	C	2 (3.7)
No. nodules per patient (n (%))		
	1	40 (74.1)
	2	11 (20.3)
	3	3 (5.6)
Maximal tumor diameter in mm (n=71)		Median 22.0 Range 8-69

* The sum of percentages is >100% as the etiology of cirrhosis may be multifactorial. ECOG = Eastern Cooperative Oncology Group

Baseline parameters per group are described in Table 2. The mean maximal diameter of tumors at baseline was 45.7 mm in the combined RFA-DEBTACE group and 21.5 mm in the RFA group. In one patient in the RFA-DEBTACE group the maximal diameter of the largest tumor was <3cm. This patient had two tumors in segment 6 of respectively 24 mm and 22 mm that were in close relation to each other. It had been decided to consider the two tumors as one larger tumor area and perform RFA combined with DEB-TACE. In the RFA-DEBTACE group, the percentage of patients with multifocal disease (>1 lesion)

Table 2. Baseline patient and tumor characteristics per treatment group.

	RFA (n=39)	RFA and TACE (n=15)
Median age (range)	62.5 years (29-79 years)	65.2 years (47-82 years)
Male gender (%)	30 (76.9)	12 (80.0)
ECOG (n (%))		
0	38 (97.4)	15 (100)
1	1 (2.6)	0 (0)
Cause of cirrhosis in (n (%))*		
Hepatitis B	3 (7.7)	3 (20.0)
Hepatitis C	10 (25.6)	4 (26.7)
Alcohol	23 (59.0)	8 (53.3)
Other	9 (23.1)	2 (13.3)
Child Pugh score (n (%))		
A	34 (87.2)	14 (93.3)
B	3 (7.7)	1 (6.7)
C	2 (5.5)	0 (0)
Nodules per patient (no. of patients per arm (%))		
1	31 (79.5)	9 (60.0)
2	6 (15.4)	6 (33.3)
3	2 (5.1)	1 (6,7)
Mean maximal diameter of largest tumor (mm)	21.5 Range 10-30	45.7 Range 24-67

* The sum of percentages is >100% as the etiology of cirrhosis may be multifactorial. ECOG = Eastern Co-operative Oncology Group

was 40.0%. In the RFA group, 20.5% of patients had multifocal disease. The difference between the two groups was not statistically significant (p=0.175).

Treatment outcome

Technical success was achieved in 98.1% (n=53) of RFA procedures and 100% (n=15) of TACE procedures.

Figure 1 shows the local tumor progression-free survival of the RFA and RFA-DEBTACE group. The mean local tumor progression-free survival for all patients was 30.7 months (95% CI: 23.9-37.5 months). Patients in the RFA group had a mean local tumor progression free-survival of 36.9 months (95% CI: 29.6-44.3 months). Mean local tumor progression free-survival in the RFA-DEBTACE group was 11.0 months (95% CI: 2.8-19.4 months). The difference between the two groups was statistically significant: HR 0.211; 95% CI: 0.094-0.471. In the RFA group, the local tumor progression free-survival rates at 1-, 2- and 3-years were 81.4%, 66.0% and 59.4% respectively. These rates were 26.9%, 17.9%

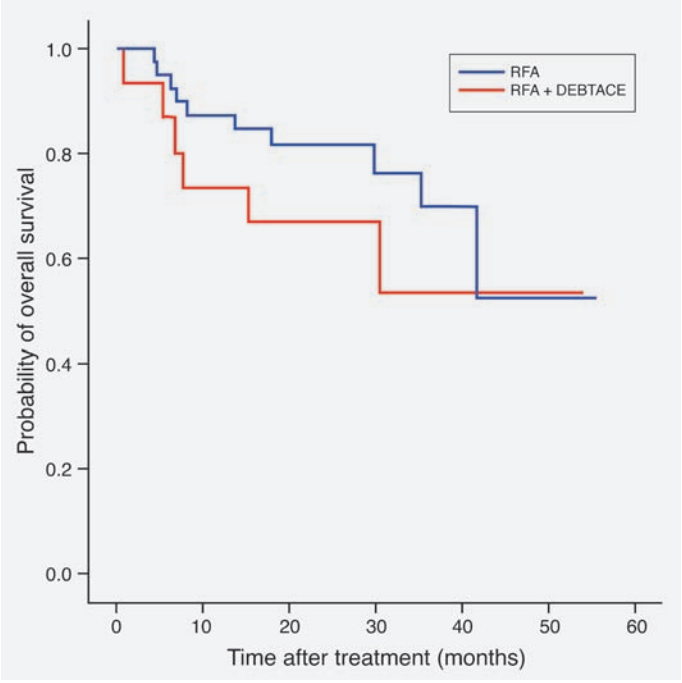

Figure 1. Overall survival rate per treatment group

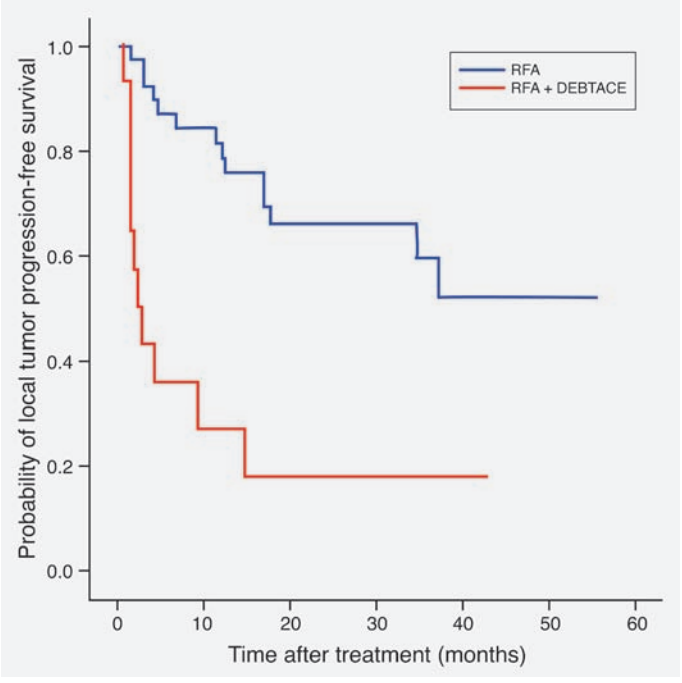

Figure 2. Local tumor progression-free survival rate per treatment group

and 17.9% respectively in the RFA-DEBTACE group. The differences in local tumor progression free-survival rates at 1-, 2- and 3-years were statistically significant (p=0.0001, p=0.0004 and p=0.0045 respectively).
Figure 2 shows the overall survival of the RFA and RFA-DEBTACE group. The mean overall survival of all patients was 40.4 months (95% CI: 34.5-46.2 months). The mean overall survival in the RFA group was 41.6 months (95% CI: 34.6-48.6 months) and 34.8 months (95% CI: 23.5-46.1 months) in the RFA-DEBTACE. The overall survival at 1-, 2- and 3-years was 87.2%, 81,6% and 69.8% respectively in the RFA group. In the RFA-DEBTACE group, these rates were 73.3%, 66.7% and 53.3%. The difference in overall survival between the two groups at 1-, 2- and 3-years was not statistically significant (p=0.27, p=0.28 and p=0.36 respectively).

Complications

CTCAE grade 3-4 complications occurred in one patient in the RFA group (2.6%) and 2 patients in the RFA-DEBTACE group (13.3%). The patient in the RFA group had a puncture site bleeding, which was treated successfully with transarterial embolization. One patient in the RFA-DEBTACE group developed a liver abscess 6 days after the ablation and was successfully treated with percutaneous drainage and antibiotics. The other patient in the DEBTACE group had a 47mm HCC high up in the dome of the liver. The RFA procedure was complicated by a right-sided pneumothorax for which a chest-tube was inserted. The next day, TACE of the liver dome tumor was performed. Five days after the TACE, the patient developed sepsis as result of Escherichia coli peritonitis. Despite treatment with percutaneous drainage of the ascites and intravenous antibiotics, the patient passed away 23 days after RFA as a result of sepsis and hepatorenal syndrome.

Consecutive treatment

Twenty-two patients (40.7%) underwent liver transplantation with a median of 7.0 months (range 0.3-28.6 months) after the first RFA treatment. The transplant rate for patients in the RFA group was 43.6% and 33.3% in the RFA-DEBTACE group. The difference in transplantation rate between the groups was not statistically significant (p=0.551). None of the patients that were transplanted had recurrent HCC. Liver transplantation resulted in a non-significant increase in survival with a hazard ratio of 0.452 in favor of transplantation (95% CI: 0.116-1.768).

Nineteen out of 54 patients (35.2%) received additional loco-regional treatment after the initial RFA or RFA-DEBTACE. In the RFA group, 28.2% patients underwent further loco-regional treatment after the initial RFA compared to 53.3% in the RFA-DEBTACE group (table 3). The difference between the two groups was statistically significant (p=0.022).

Table 3. Additional treatment during follow-up per treatment group

	RFA n (%)	RFA-TACE n (%)	Overall n (%)
Transplantation	17 (43.6)	5 (33.3)	22 (40.7)
Resection only	1 (2.6)	0 (0)	1 (1.9)
Resection and RFA and TACE	1 (2.6)	0 (0)	1 (1.9)
RFA only	3 (7.7)	3 (20.0)	6 (11.1)
RFA and TACE	3 (7.7)	2 (13.3)	5 (9.3)
TACE only	3 (7.7)	3 (20.0)	6 (11.1)

RFA = radiofrequency ablation. TACE = transarterial chemotherapy

DISCUSSION

To our best knowledge, this is the first reported study on the long-term efficacy of combined treatment with RFA and DEBTACE in patients with unresectable HCC. In our institution, we performed RFA for HCCs ≤3cm with a maximum of 3 tumors and combined treatment for HCCs >3-7cm. This treatment strategy was adopted on the premise that adjuvant DEBTACE would result in similar outcomes in patients with larger tumors compared to those with tumors ≤3cm. Despite the additional treatment with DEBTACE however, patients in the combined treatment group had significantly lower mean local tumor progression free-survival rates compared to the RFA-only group at 1, 2 and 3-years: 81.4%, 66.0% and 59.4% versus 26.9%, 17.9% and 17.9% respectively. The overall survival rate at 1, 2 and 3-years was also lower in the RFA-DEBTACE group compared to the RFA group, but the difference between the two groups did not reach statistical significance.

Clearly, direct comparison between the two groups in our study is flawed because of selection bias. Treatment selection was dependent on tumor size and as a result the mean maximal tumor diameter in the RFA-DEBTACE group was significantly larger than in the RFA group. Tumor size >3cm is a known risk factor for tumor recurrence after RFA and this is confirmed by our study (1-5). Different strategies are have been studied trying to reduce HCC recurrence rates after RFA and the debate is still open on what the best strategy is. Most studies have used a combination of RFA and TACE, but others have combined RFA with ethanol injection or sorafenib (9-12). In our study, RFA was performed first followed by DEBTACE the next day. After RFA-DEBTACE, the local tumor progression-free survival at 3 years was 17.9%. This compares favorable to previous studies that have reported 3-year recurrence free-survival rates of only around 10% after RFA for HCC >3cm (13,14). Yet, our results are poorer than those reported in studies that used a sequence whereby cTACE was performed prior to RFA (4,15-19). In a randomized controlled trial by Peng et al. in patients with unresectable HCC with ≤3 nodules smaller

than 7cm, cTACE followed by RFA (n = 94) was significantly better than RFA alone (n = 95) (15). For patients with tumor diameters of 3.1–5.0 cm, the 3-year recurrence free survival rate was 40% for the combined treatment group (compared to 10% for the RFA group). In a smaller randomized controlled study by Morimoto et al. (4), patients with solitary HCC of >3-5cm were allocated to treatment with either cTACE followed by RFA (n=19) or RFA only (n=18). Local tumor progression at the end of the third year in the cTACE-RFA group was 6% compared to 39% in the RFA group (p = 0.012).

Comparison of the results of the studies by Peng and Morimoto with our study results suggests that better outcomes may be achieved with a sequence of cTACE followed by RFA rather that with RFA followed by DEBTACE. It can be debated whether the better outcome after cTACE-RFA is a result of the difference in the type of TACE or of the difference in the treatment sequence.

In our opinion, the type of TACE is less likely to have significant impact on treatment outcome. In the Precision V trial, the objective response rate after DEBTACE was higher than after cTACE, but the difference between the two treatments did not reach statistically significance (6). We believe that differences in efficacy between cTACE-RFA and RFA-DEBTACE are more likely due to the difference in treatment sequence. It has been a long lasting debate in the interventional radiology community whether TACE should be performed before or after RFA when combining both treatments. The rationale for one or the other sequence is different. RFA induces hyperemia in a marginal zone between the ablated area and surrounding tissue. This marginal zone encompasses the periphery of the tumor in which viable tumor cells may be present as well as the area where most satellite nodules tend to be (20). When TACE is performed within several days after RFA, the hyperemia can be used to deliver a high dose of the chemotherapeutic agent to this marginal zone. This marginal zone is not specifically targeted when TACE precedes RFA. The most important theoretical advantage of this sequence is that it may reduce local tumor progression caused by heat sink. Embolization of the hepatic arteries feeding the tumor will result in reduced intra- and perilesional blood flow during the ablation. When TACE is performed after RFA, nothing is done to prevent heat-sink during the ablation. Our study results now allow comparison of long-term results of RFA-DEBTACE with those of cTACE-RFA. Local tumor progression free-survival rates in our study were lower compared to those reported in studies on cTACE-RFA. The most likely explanation for this would be that cTACE-RFA reduces the risk of tumor recurrence due to heat-sink, whereas RFA-DEBTACE does not prevent this type of recurrence. To date, there is limited data on the efficacy of combined RFA and TACE for inoperable HCC. The optimal treatment strategy in HCCs >3cm is yet to be determined and further studies are warranted. Based on a comparison of our results with results of studies using cTACE-RFA, we would argue

that a sequence of TACE followed by RFA should be the preferred sequence in further studies combining both treatments.

The retrospective nature of our study and the relatively small number of patients are limitations of this study. We did not randomize patients to treatment with either RFA or RFA-DEBTACE and therefore direct comparison between the two treatments is not possible. Furthermore, we were only able to compare our results of RFA-DEBTACE with historical data on cTACE-RFA.

In conclusion, local tumor progression free-survival rates for HCC >3cm-7cm are low compared to those after RFA for smaller tumors. The 3-year local tumor progression free-survival rate after RFA-DEBTACE was 17.9% in our study and this is low compared to results reported after cTACE-RFA for HCC with similar size.

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