Fusion of preinterventional MR imaging with liver perfusion CT after RFA of hepatocellular carcinoma: early quantitative prediction of local recurrence

Kobe, Adrian ; Kindler, Yanick ; Klotz, Ernst ; Puippe, Gilbert ; Messmer, Florian ; Alkadhi, Hatem ; Pfammatter, Thomas

Abstract: **OBJECTIVES:** The aim of this study was to evaluate the ability of fusion of pretreatment magnetic resonance (MR) imaging with posttreatment perfusion-CT (P-CT) after radiofrequency ablation (RFA) of hepatocellular carcinomas (HCCs) and to determine treatment success in an objective, quantitative way. **MATERIALS AND METHODS:** In this institutional review board-approved study, 39 patients (78.4% male; mean age 68.2 ± 8.5 years) with a total of 43 HCCs, who underwent RFA at our institution and had diagnostic pre-RFA MR imaging and post-RFA P-CT, were included in the study. Post-RFA P-CT was performed within 24 hours after RFA. In a first step, the pre-RFA MR imaging, depicting the HCC, was registered onto the post-RFA P-CT using nonrigid image registration. After image registration, the MR data were reloaded jointly with the calculated perfusion parameter volumes into the perfusion application for quantitative analysis. A 3-dimensional volume of interest was drawn around the HCC and the ablation zone; both outlines were automatically projected onto all perfusion maps. Resulting perfusion values (normalized peak enhancement [NPE, %]; arterial liver perfusion [ALP, in mL/min/100 mL]; BF [blood flow, mL/100 mL/min]; and blood volume [BV, mL/100 mL]) and histogram data were recorded. Local tumor recurrence was defined in follow-up imaging according to the EASL guidelines. **RESULTS:** Image registration of MR imaging and CT data was successful in 37 patients (94.9%). Local tumor recurrence was observed in 5 HCCs (12%). In the local tumor recurrence group (LTR-group), HCC size was significantly larger (22.7 ± 3.9 cm vs 17.8 ± 5.3 cm, $P = 0.035$) and the ablation zone was significantly smaller (29.8 ± 6.9 cm vs 39.3 ± 6.8 cm, $P = 0.014$) compared with the no-local tumor recurrence group (no-LTR group). The differences (ablation zone - tumor) of the perfusion parameters NPE, ALP, BF, and BV significantly differed between the 2 groups (all P 's < 0.005). Especially, the difference (ablation zone - tumor) of NPE and ALP, with a cutoff value of zero, accurately differentiated between LTR or no-LTR in all cases. A negative difference of these perfusion parameters identified local tumor recurrence in all cases. **CONCLUSIONS:** Image registration of pre-RFA MR imaging onto post-RFA P-CT is feasible and allows to predict local tumor recurrence within 24 hours after RFA in an objective, quantitative manner and with excellent accuracy.

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Fusion of Preinterventional MR Imaging With Liver Perfusion CT After RFA of Hepatocellular Carcinoma

Early Quantitative Prediction of Local Recurrence

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Objectives: The aim of this study was to evaluate the ability of fusion of pretreatment magnetic resonance (MR) imaging with posttreatment perfusion-CT (P-CT) after radiofrequency ablation (RFA) of hepatocellular carcinomas (HCCs) and to determine treatment success in an objective, quantitative way.

Materials and Methods: In this institutional review board–approved study, 39 patients (78.4% male; mean age 68.2 ± 8.5 years) with a total of 43 HCCs, who underwent RFA at our institution and had diagnostic pre-RFA MR imaging and post-RFA P-CT, were included in the study. Post-RFA P-CT was performed within 24 hours after RFA. In a first step, the pre-RFA MR imaging, depicting the HCC, was registered onto the post-RFA P-CT using nonrigid image registration. After image registration, the MR data were reloaded jointly with the calculated perfusion parameter volumes into the perfusion application for quantitative analysis. A 3-dimensional volume of interest was drawn around the HCC and the ablation zone; both outlines were automatically projected onto all perfusion maps. Resulting perfusion values (normalized peak enhancement [NPE, %]; arterial liver perfusion [ALP, in mL/min/100 mL]; BF [blood flow, mL/100 mL/min]; and blood volume [BV, mL/100 mL]) and histogram data were recorded. Local tumor recurrence was defined in follow-up imaging according to the EASL guidelines.

Results: Image registration of MR imaging and CT data was successful in 37 patients (94.9%). Local tumor recurrence was observed in 5 HCCs (12%). In the local tumor recurrence group (LTR-group), HCC size was significantly larger (22.7 ± 3.9 cm vs 17.8 ± 5.3 cm, $P = 0.035$) and the ablation zone was significantly smaller (29.8 ± 6.9 cm vs 39.3 ± 6.8 cm, $P = 0.014$) compared with the no-local tumor recurrence group (no-LTR group). The differences (ablation zone – tumor) of the perfusion parameters NPE, ALP, BF, and BV significantly differed between the 2 groups (all P 's < 0.005). Especially, the difference (ablation zone – tumor) of NPE and ALP, with a cutoff value of zero, accurately differentiated between LTR or no-LTR in all cases. A negative difference of these perfusion parameters identified local tumor recurrence in all cases.

Conclusions: Image registration of pre-RFA MR imaging onto post-RFA P-CT is feasible and allows to predict local tumor recurrence within 24 hours after RFA in an objective, quantitative manner and with excellent accuracy.

Key Words: computed tomography, perfusion, RFA, HCC, local tumor recurrence (*Invest Radiol* 2020;00: 00–00)

Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver cancer and is one of the leading causes of cancer-related death worldwide.¹ Minimal invasive treatment options such as radiofrequency ablation (RFA) are accepted alternatives to surgery and recommended in very early stage and early stage HCC.^{1,2}

Radiofrequency ablation shows, compared with surgery, no difference in overall mortality at long-term follow-up with a lower rate of adverse events, shorter hospital stay, and favorable cost-effectiveness. Nevertheless, RFA is associated with a higher local recurrence rate than surgery, especially in larger tumors.³

It has been shown that the safety margin between the tumor and ablation zone after RFA plays a crucial role in local tumor recurrence and should be at least 5 mm.⁴ Most interventionalists estimate treatment success on post-RFA contrast-enhanced computed tomography (CT) by visual side-by-side comparison and a qualitative estimation whether the ablation zone contains the tumor or not. A few studies evaluated non-rigid fusion of pre-RFA and post-RFA CT images to improve the assessment of the safety margin.^{5,6} Shin et al⁵ were able to demonstrate in a prospective study on 150 patients that, when using such techniques for immediate postablation assessment, 15% were deemed insufficient and that, with immediate reablation, the 42 months local tumor progression rate was 11% compared with 23% in a standard control group.

Previous work on image fusion was mostly done using single-phase CT, which limits the correct assessment of the size of the ablation zone.^{7,8} A recent study by Bressen et al⁹ showed that subtraction CT was superior to nonsubtracted contrast-enhanced CT in an in vivo porcine model in terms of visibility of the ablation zone after microwave ablation, whereas nonsubtracted contrast-enhanced CT images showed an overestimation of the ablation zone compared with subtracted images after correlation with pathologic assessment.

Perfusion-CT (P-CT) of the liver permits quantitative evaluation of liver tumors with a reported sensitivity of HCC diagnosis superior to that using multiphase CT.^{10,11} In addition, P-CT has shown to allow for prediction of local tumor recurrence after RFA.^{12–14} However, these studies were performed months after treatment when reactive hyperemia around the ablation zone, which could be misinterpreted as viable tissue, is less prominent.^{15,16}

Nowadays, pre-RFA imaging in HCC patients is often done by magnetic resonance (MR) imaging. Thus, the attempt of this study was to fuse pre-RFA MR imaging with post-RFA P-CT, the latter being a valuable imaging technique for both HCC and ablation zone depiction.

Hence, we evaluated the ability of fusion of pretreatment MR imaging with post-RFA P-CT in patients with HCC to determine early treatment success in an objective, quantitative way.

MATERIALS AND METHODS

Patients

From 67 patients (74 HCCs) that underwent percutaneous RFA between April 2013 and November 2018, we retrospectively selected 39 patients with a total of 43 HCCs that had a complete diagnostic MR imaging examination and a post-RFA perfusion scan on a CT scanner that allowed for sufficient liver coverage. Two patients were later excluded due to technical issues (Fig. 1).

This retrospective study was approved by the local ethics committee. Written consent requirement was waived.

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FIGURE 1. Study flowchart.

Pre-RFA MR Imaging

In all patients pre-RFA MR imaging of the liver was obtained for HCC diagnosis and treatment planning. As most of the patients were referred for treatment to our hospital from other institutions, there was a large heterogeneity in pre-RFA MR imaging protocols, including different MR scanners and field strength. In total, 39 examinations were analyzed—21 with a hepatobiliary-specific contrast agent (54%) and 18 with an extracellular contrast agent (46%). In patients with MR imaging and hepatobiliary-specific contrast agent, the hepatobiliary phase was used for registration due to its high tumor-to-liver parenchyma contrast and good visibility of nearby vessels. In patients with MR imaging and extracellular contrast agent, a postcontrast phase was used for registration where the tumor and the maximum of the nearby vessels were depicted (either late arterial or venous phase).

All liver lesions were classified according to the LI-RADS (Liver Imaging Reporting and Data System).⁸ LI-RADS category 4 and 5 lesions were included and treated with RFA.

Post-RFA Perfusion CT Imaging

A total of 39 P-CTs were performed within 24 hours after RFA. All scans were done using a 4D spiral mode (repetitive scanning for 45 seconds) and mixed cycle times of 1.5 and 3.0 seconds. Thirty-four scans were done on a 192-section CT scanner providing 18-cm coverage (SOMATOM Force; Siemens Healthineers, Forchheim, Germany), 5 scans on 128-section CT scanners providing 15-cm coverage (SOMATOM Definition Edge and SOMATOM Definition Flash; all Siemens Healthineers, Forchheim, Germany). Fixed tube voltage and current-time product at 80 kVp and 100 mAs, respectively, were used. Image reconstruction was done with a slice width of 4 mm and an increment of 3 mm resulting in typically 1450 images per scan.

A total of 50 mL of iopromide (Ultravist 370, 370 mg iodine/mL; Bayer Schering Pharma, Berlin, Germany) at 6 mL/s with a 7-second scan delay was used. After initial breath hold, the patients were asked to breath superficially during the rest of the scan for minimal motion artifacts.

FIGURE 2. Image postprocessing flowchart.

TABLE 1. Baseline Characteristics

	All
Patients	37
Age, mean $\pm$ SD, y	68.2 $\pm$ 8.5
Male, n (%)	29 (78.4)
Liver cirrhosis and etiology, n (%)	37 (100)
HBV	7 (18.4)
HCV	13 (34.2)
Alcohol	12 (31.6)
NASH	6 (15.8)
HCC location, n (%)	41 (100)
Segment II	6 (14.6)
Segment III	3 (7.3)
Segment IV	5 (12.2)
Segment V	6 (14.6)
Segment VI	6 (14.6)
Segment VII	6 (14.6)
Segment VIII	9 (22)

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.

The automatically generated dose reports including the volume CT dose index (CTDI_{vol}; mGy) and dose length product (DLP; mGy $\times$ cm) were taken for estimations of the radiation dose. Effective dose was calculated using a conversion coefficient for the abdomen ($\kappa = 0.015$ mSv/[mGy $\times$ cm]).

Analysis Concept

We hypothesized that, if the original tumor volume is completely contained within the ablation zone, then the mean values of suitable measures of enhancement or perfusion should be lower than the respective values of the ablation volume. We exported detailed volume histogram data to cross-check this effect. This approach led to the following analysis steps:

1. Creation of suitable perfusion parameter volumes;
2. Registration of a pre-RFA MR volume to a suitable anatomical reference created from the 4D data;
3. Additional DICOM relabelling of the registered MR volume as a dummy perfusion parameter, so it could be reloaded together with the perfusion parameters, which will then all have the same frame of reference; and
4. Manual 3-dimensional (3D) volume definition of tumor and ablation zone and storage of numerical results.

Creation of Perfusion Parameter Volumes

Image postprocessing was performed on commercially available software (syngo.via VB30; Siemens Healthineers, Erlangen, Germany)

TABLE 2. RFA Procedure and Outcome Data

	All	No-LTR	LTR	P
RFA, n (%)				
Anesthesia				
Analgesedation	36 (87.8)	32 (88.9)	4 (80)	
General anesthesia	5 (12.2)	4 (11.1)	1 (20)	
Modality				
Sonography	38 (92.7)	34 (94.4)	4 (80)	
CT	3 (7.3)	2 (5.6)	1 (20)	
Electrodes, n (%)				
Single-probe	9 (22)	8 (22.2)	1 (20)	
Two probes	2 (4.9)	1 (2.8)	1 (20)	
Triple probe	30 (73.2)	27 (75)	3 (60)	
Ablation time, min	12.8 $\pm$ 3.4	12.8 $\pm$ 3.3	12.8 $\pm$ 4.6	0.976
End temperature	82.8°C $\pm$ 10.2°C	83.9°C $\pm$ 9.5°C	74.6°C $\pm$ 12.9°C	0.055
Post-RFA P-CT, mean $\pm$ SD				
Time to P-CT, h	7.5 $\pm$ 5.8	7.4 $\pm$ 5.8	8.4 $\pm$ 6.4	0.714
DLP, mGy $\times$ cm	959.7 $\pm$ 155	945.6 $\pm$ 132.3	1055.5 $\pm$ 265.3	0.141
CTDI _{vol} , mGy	51.6 $\pm$ 10.6	50.6 $\pm$ 7.8	58.9 $\pm$ 22.3	0.104
Effective dose, mSv	14.4 $\pm$ 2.3	14.2 $\pm$ 2	15.8 $\pm$ 4	0.141
In-hospital outcome, n (%)				
Complications	3 (7.3)	2 (66.7)	1 (33.3)	
In-hospital mortality	0 (0)			
Outpatient setting	31 (75.6)	28 (77.8)	3 (60)	
Inpatient setting	10 (24.4)	8 (22.2)	2 (40)	
Follow-up period, mean $\pm$ SD, mo	16.3 $\pm$ 11.9	17.8 $\pm$ 12	6.1 $\pm$ 3.7	0.039
Local tumor recurrence, n (%)	5 (12.2%)			

Non-LTR, no-local tumor recurrence; LTR, local tumor recurrence; RFA, radiofrequency ablation; P-CT, perfusion CT; CTDI_{vol}, volume CT dose index; DLP, dose length product.

TABLE 3. Perfusion Analysis Data

	All	No-LTR	LTR	P
Diameter HCC, median (IQR), mm	16.9 (14.6–22.4)	15.7 (14–21.2)	22.3 (19–26.6)	0.035
Diameter ablation zone, median (IQR), mm	37.4 (32–44.8)	38.3 (33.5–45.5)	28.3 (24.2–36.2)	0.014
D_A – D_HCC, median (IQR), mm	19.6 (15.1–23.5)	20.9 (18–24.5)	6.5 (2.4–12.2)	0.001
NPE_A – NPE_HCC, median (IQR), %	1.1 (0.7–1.7)	1.2 (1–1.8)	–3.1 (–4.6 to –1.6)	0.0003
ALP_A – ALP_HCC, median (IQR), mL/min/100 mL	4.3 (2.1–6.8)	4.8 (3–7)	–10.2 (–26.9 to –3.8)	0.0003
BF_A – BF_HCC, median (IQR), mL/100 mL/min	8.8 (–1.3–12.9)	10.4 (4–13.7)	–15.6 (–26.5 to –8.7)	0.0006
BV_A – BV_HCC, median (IQR), mL/100 mL/min	0.8 (0.1–1.1)	0.9 (0.4–1.3)	–2 (–2.3 to –0.8)	0.0006

IQR, interquartile range; D_A – D_HCC, difference of diameter of ablation zone and HCC; NPE_A – NPE_HCC, difference of normalized peak enhancement between ablation zone and HCC; ALP_A – ALP_HCC, difference ALP ablation zone and HCC; BF_A – BF_HCC, difference BF ablation zone and HCC; BV_A – BV_HCC, difference BV ablation zone and HCC.

- using a dedicated application (CT Body Perfusion). After automatic non-rigid motion-correction, the following 3D volume sets were generated:
1. As anatomical reference for registration a temporal maximum intensity projection (MIP), which depicts the maximum CT number over the whole scan;
 2. For further reference, the precontrast baseline volume, which depicts the average CT number before contrast arrival in the aorta. This volume was later substituted with the registered MR data; and
 3. Quantitative and color-coded perfusion maps of
 - a. Peak enhancement normalized to the peak enhancement of the aorta (NPE, %),

FIGURE 3. Liver perfusion analysis in a 62-year-old male patient with hepatocellular carcinoma (HCC) in segment VIII and no local tumor recurrence after radiofrequency ablation (RFA). Panel A and B show baseline pre-RFA magnetic resonance (MR) images in the hepatobiliary phase. Temporal maximum intensity projection (MIP), parametric blood volume (BV), and arterial liver perfusion (ALP) maps from posttreatment perfusion-CT (P-CT) in panels C, D, and E, respectively. After manual placement of a 3D volume of interest around the ablation zone (dotted arrow) and HCC (white arrow), the volume of interest is delineated in all perfusion maps and in baseline MR images. The quantitative difference between the ablation zone and HCC in this patient was 5.8 mL/min/100 mL for ALP and 1.5% for normalized peak enhancement (NPE). Fourteen months after RFA follow-up MR imaging (F) showed no tumor recurrence, but minor hemorrhage centrally in the ablation zone (double-lined arrow).

FIGURE 4. Liver perfusion analysis in a 64-year-old female patient with HCC in segment VI and local tumor recurrence after RFA. Panel A and B show baseline pre-RFA MR images in the hepatobiliary phase. Temporal MIP, parametric BV, and ALP maps from P-CT in panels C, D, and E, respectively. After manual placement of a 3D volume of interest around the ablation zone (dotted arrow) and HCC (white arrow), the volume of interest is delineated in all perfusion maps and in baseline MR images. The quantitative difference between the ablation zone and HCC in this patient was -38.1 mL/min/100 mL for ALP and -6.2% for NPE. Two months after RFA the follow-up MR imaging (F) showed local tumor recurrence (double-lined arrow) in the arterial phase, exactly where the P-CT found high perfusion parameters next to the ablation zone.

- b. Arterial liver perfusion (ALP, in mL/min/100 mL) calculated from the initial phase maximum slope of the voxel TAC, and
- c. Blood flow (BF, mL/100 mL/min) and blood volume (BV, mL/100 mL) calculated using a deconvolution algorithm with the aorta as input.

Registration of Pre-RFA MR Data Onto Post-RFA P-CT Data

Registration was based on the P-CT temporal MIP volume and the respective MR imaging volume. Both volumes were loaded into prototype software (Hepacare; Siemens Healthineers, Erlangen, Germany). This software uses a deformable registration algorithm that is also contained in the Body Perfusion software for aligning changing breathing states during dynamic scanning. It has previously been successfully used for CT on CT registration after RFA^{5,6} and for CT on MR registration^{17,18} after RFA.

Magnetic resonance images were registered onto CT using CT as the registration template. After first performing automatic registration, local alignment around the tumor was checked by examining vascular and surface structures. If not acceptable, 1 or maximally 2 well-defined 3D anatomical landmarks (vascular branchpoints, surface indentations) were placed in MPR mode in both volumes, and the registration was repeated.

The resulting deformed MR volume was cut or filled depending on FOV differences such that it was in the same frame of reference and identical in size to the CT volume and stored as a DICOM series. Then, the DICOM Header information was exchanged with one of the existing CT baseline volume scans by custom software to allow joint loading into the perfusion software.

Combined Analysis

After image registration, the MR imaging data were reloaded jointly with the calculated parameter volumes into the perfusion application for quantitative analysis.

In a first step, a 3D volume of interest (VOI) was drawn around the tumor within the MR scan. The 3D tumor outline is automatically projected onto all perfusion maps. Then, a similar VOI was drawn encompassing the ablation zone. This was performed on BV images, as the ablation zone was best depicted in these images.

The resulting perfusion values (mean of the VOIs) and histogram data were recorded. The effective diameter of the tumor and the ablation zone was determined by calculating the diameter of a sphere with the same volume as the respective irregular VOI.

Local Tumor Recurrence Evaluation

Follow-up imaging consisted of MR imaging with extracellular fluid contrast agent (Dotarem; Guerbet AG, Zurich, Switzerland) in 36 patients (97%), and 1 patient (3%) had a multiphase CT (native,

arterial, and portal venous phase) for follow-up. Imaging follow-up was performed every 3 months for detection of local tumor recurrence and/or detection of new lesions. According to the EASL guidelines, typical imaging features of HCC such as nodular arterial enhancement and portal washout in the ablation zone were classified as local tumor recurrence.¹ Figure 2 summarizes the process of image postprocessing.

Statistical Analysis

For descriptive data, mean values and standard deviations as well as median and interquartile ranges are provided, as appropriate. Continuous, nonnormally distributed variables were compared using the Mann-Whitney *U* test. Continuous, normally distributed variables were compared using the independent 2-sample *t* test. Categorical variables were compared using the χ^2 test. The performance of the different perfusion parameters for predicting local tumor recurrence was measured by plotting curves and by calculating the area under the curve (AUC). All statistical analyses and plots were performed with a commercially available software (SPSS Statistics v. 25; IBM, Chicago, IL). A 2-tailed *P* value of less than 0.05 was considered significant.

RESULTS

In 1 patient, the ablation zone was not completely covered by P-CT; in a second, 1 registration of pre-RFA MR imaging to P-CT failed. So, in total, 37 patients (78% male) with 39 P-CT scans and with 41 HCCs were included in the study. The mean age was 68.2 ± 8.5 years. All patients experienced liver cirrhosis. The HCCs were located in all liver segments except for segment I (Table 1).

MR Imaging to CT Registration

In 1 patient, registration failed due to suboptimal MR positioning and complex anatomy that caused extreme distortions. In 11 cases, registration worked fully automatically; in the remaining 28, 1 or 2 manually placed landmarks were necessary to achieve acceptable registration.

RFA Outcome

The RFA was performed under analgosedation (88%) or general anesthesia (12%). In most of the cases (93%), sonography was used for RFA needle placement. In 22% of the cases, a single-probe RFA needle was used; in 5% of cases, 2 probes were used; and in the majority of cases (73%), a triple probe was used. No significant differences were seen in ablation time (12.8 ± 3.3 minutes vs 12.8 ± 4.6 minutes, $P = 0.976$) and end temperature ($83.9^\circ\text{C} \pm 9.5^\circ\text{C}$ vs $74.6^\circ\text{C} \pm 12.9^\circ\text{C}$, $P = 0.055$) after RFA between the no-local tumor recurrence group (no-LTR group) and the local tumor recurrence group (LTR group). No in-hospital deaths occurred. In 3 cases (7%), minor complications occurred (urinary tract infection, atelectasis of the posterobasal right lung, and fever of unknown origin) that did not require further intervention. Most patients (31 patients, 76%) were treated in an outpatient setting.

The mean clinical and imaging follow-up was 16.3 ± 11.9 months. Local tumor recurrence was observed in 5 HCCs (12%) occurring after a mean follow-up period of 6.1 ± 3.7 months (Table 2).

Perfusion-CT

The average CTDI_{vol}, DLP, and effective dose of P-CT was 51.6 ± 10.6 mGy, 959.7 ± 155 mGy $\times$ cm, and 14.4 ± 2.3 mSv, respectively. The average time between RFA and P-CT was 7.5 ± 5.8 hours (all P-CT examinations within 24 hours after ablation).

The mean HCC size was significantly larger in the LTR-group than in the no-LTR group (22.7 ± 3.9 cm vs 17.8 ± 5.3 cm, $P = 0.035$). The ablation zone was significantly smaller in the LTR-group than in the no-LTR group (29.8 ± 6.9 cm vs

39.3 ± 6.8 cm, $P = 0.014$). Consequently, the difference between the diameter of the ablation zone and the diameter of the HCC, representing the safety margin, was significantly higher in the no-LTR group than in the LTR-group (21.6 ± 5.9 cm vs 7.1 ± 5.3 cm, $P < 0.001$) (Table 3).

Figure 3 and Figure 4 illustrate the perfusion analysis after image fusion of pre-RFA MR imaging and post-RFA P-CT in a patient without and with local tumor recurrence, respectively. Figure 5 illustrates the corresponding histograms.

The differences (ablation zone – tumor) of the perfusion parameters NPE, ALP, BF, and BV between the no-LTR group and LTR-group can be found in Table 3; all of which were statistically significant. Especially, the difference (ablation zone – tumor) of NPE and ALP, with a cutoff value of zero, accurately differentiated between LTR or no-LTR in all cases. A negative difference of these perfusion parameters identified local tumor recurrence in all cases. Figure 6 shows boxplots demonstrating the data distribution of the difference of perfusion parameters (ablation zone – tumor).

Receiver operating characteristics analysis of the difference (ablation zone – tumor) of NPE and ALP parameters predicting local tumor recurrence showed an AUC of 1 ($P < 0.001$). For the

FIGURE 5. Histogram data showing the distribution of the quantitative parameter NPE, derived from P-CT, for the patient illustrated in Figure 3 (no-LTR, A) and for the patient in Figure 4 (LTR, B). Shown is the distribution for the tumor volume (red) and the ablation zone (blue). In the no-LTR case (A), the tumor distribution is fully contained within the ablation zone; in the LTR case (B), the tumor distribution exceeds the ablation zone distribution at higher values.

FIGURE 6. Boxplots demonstrating the difference of perfusion parameters (ablation zone – HCC) for NPE (A), ALP (B), BF (C), and BV (D) between local tumor recurrence versus no local tumor recurrence. Note the difference between groups without overlap for the parameters NPE and ALP.

difference (ablation zone – tumor) of BF and BV, the AUC was 0.976, respectively ($P < 0.001$).

DISCUSSION

The present study indicates that the registration of pre-RFA MR images with post-RFA P-CT allows for an objective, quantitative assessment of local tumor recurrence of HCC. The difference (ablation zone – tumor) of perfusion parameters (NPE, ALP, BF, and BV) robustly predicted local tumor recurrence after RFA with excellent accuracy when the resulting value was negative.

So far, the technical success of RFA is estimated by eyeballing whether or not the ablation zone in post-RFA multiphase CT includes the entire tumor volume. There are few studies attempting to fuse pre- and post-RFA images. Kim et al⁶ analyzed the interobserver agreement regarding the safety margin assessment by eyeballing versus fusion of pre- and post-RFA CT images. A significant increase in interobserver agreement was found after image fusion. Furthermore, the study showed an excellent registration accuracy of the pre- and post-RFA CT images (gap of 1.3 ± 1.1 mm between related landmarks). A first attempt of pre-RFA MR imaging and post-RFA CT registration was done by Park et al¹⁷ using nonrigid registration to divide the patients into risk groups for local tumor recurrence according to the safety margin. A safety margin of at least 5 mm seemed to be a good cutoff value and showed significantly less local tumor recurrence. Same was found in a study conducted by Yoon et al.¹⁸ Both studies used a similar nonrigid registration approach guided by additional anatomical landmarks in which post-RFA CT was deformed to match pre-RFA MR imaging.

The main complexity of intermodality image registration, such as MR on CT in our study, is not the different matrix sizes and slice

widths, which can be accommodated by using a world coordinate system. Also, different breathing phases during image acquisition can usually be accommodated well by using deformable registration as long as positioning is similar. A major challenge consists in the different arm positioning between modalities. Strong local difference gradients caused by a different rib and surface configuration make it difficult even for deformable registration to attain an acceptable match everywhere. Therefore in our study, additional guidance by 1 or 2 anatomical local landmarks in the vicinity of the tumor were required in 28 of 39 cases to achieve acceptable match of the tumor. Failure of registration in 1 patient was due to complex anatomy with the HCC located subcapsularly in segment V near the gallbladder and abdominal wall. The distortion of the liver between pre- and post-RFA images made it impossible, even using landmarks, to register the 2 modalities.

There are few studies analyzing the posttreatment effects of RFA in HCC using P-CT as an outcome predictor.^{13,14,19} None of these studies combined image fusion with post-RFA P-CT evaluation. These studies focused on an analysis of perfusion parameters of the ablation zone alone. As seen before, a safety margin of less than 5 mm seems to be a predictor for local tumor recurrence.^{4,5} This is also confirmed by our data. In our morphological results; 80% of recurrences had a difference of ablation zone diameter and lesion diameter of less than 10 mm, which renders a safety margin of greater than 5 mm impossible. Therefore, in cases of local tumor recurrence, it can be assumed that the HCC is not fully covered by the ablation zone. Thus, it is crucial to achieve a good visibility of the ablation zone in post-RFA imaging. A recent study by Bressem et al⁹ showed that subtraction CT was superior to nonsubtracted contrast-enhanced CT, in an in vivo porcine model in terms of visibility of the ablation zone after microwave ablation. Interestingly, nonsubtracted, standard contrast-enhanced CT images showed

an overestimation of the ablation zone compared with subtracted images after correlation with pathologic measurements. Bresslem et al²⁰ analyzed the visibility of the necrotic zone after microwave ablation using perfusion CT. Hepatic blood volume and hepatic arterial BF significantly better depicted the necrotic zone compared with contrast-enhanced CT.

Posttreatment perfusion-CT alone is probably not sufficient to predict local tumor recurrence. A major issue is reactive hyperemia around the ablation zone that should not be misinterpreted as viable, residual tumor.²¹ This problem can be overcome by correctly reprojecting the tumor volume into the P-CT. In addition to a visual feedback, whether the tumor is fully covered by the ablation zone or not, the perfusion data allow for a quantitative evaluation of the reprojected tumor volume and ablation zone. As ablated parenchyma becomes necrotic, low (or absent) perfusion is expected. In contrast, areas with residual tumor high perfusion are found. Therefore, the difference of perfusion parameters of the ablation zone and reprojected tumor volume turns negative, as shown in our study. In this context, the NPE parameter is particularly interesting. As only the sign of the difference is important, it might be substituted by simpler CT measures that only reproducibly measure local enhancement.

Dual-energy CT could be an alternative to predict local tumor recurrence after image fusion using iodine quantification in the ablation zone and reprojected tumor volume from preinterventional MR imaging. A study by Gordic et al²² showed a good correlation between iodine density quantified with dual-energy CT and arterial perfusion quantified by P-CT in HCC. Same was found for pancreatic carcinoma.²³ In addition, Lee et al²⁴ proved better conspicuity of the ablation zone after hepatic RFA using iodine maps. Postulating that in a necrotic ablation zone only minimal iodine concentration will be detectable, the difference of the ablation zone and reprojected tumor volume might also turn negative in local tumor recurrence in dual-energy CT. The major advantage of dual-energy CT is the simpler scanning (just 1 time point) and its lower radiation dose compared with P-CT.^{22,25} By using a low tube voltage (80kVp) and with a tube current-time product of 100 mAs, radiation dose in our study was on average 14 mSv. This is within the limits of diagnostic reference levels for CT, especially when taking into account that normal liver CT consists of a multiphase CT (native, arterial, portal venous, and delayed phase).²⁶ Another advantage of scanning at low tube voltages is the increased attenuation of contrast media, which can be used to reduce the volume of administered contrast media.^{16,27} Accordingly, our P-CT scan protocol only used 50 mL of contrast media. Another recently described promising technique is the use of dynamic contrast-enhanced golden-angle radial sparse parallel MR imaging, which provided quantitative results comparable to P-CT in patients with HCC undergoing transarterial chemoembolization.²⁸ Here pre-RFA MRI could be fused with post-RFA MR imaging perfusion data sets to further reduce radiation exposure.

We must acknowledge some study limitations. First, we retrospectively investigated a small study population with 41 HCCs. In only 5 HCCs, local tumor recurrence occurred. Even though we found a clear cutoff value of 0 (difference perfusion parameters ablation zone – tumor) for prediction of local tumor recurrence, this has to be investigated in a larger patient cohort. Second, pre-RFA MR imaging in our patients was heterogeneous in terms of protocol parameters, MR scanners, and field strengths. Nevertheless, for image fusion with post-RFA P-CT, we do not think that heterogeneous pre-RFA MRI data is a serious issue. As described above it is crucial to have a high tumor-to-liver parenchyma contrast and good visibility of the vessels to perform rigid or nonrigid image fusion. This requirement was met by all pre-RFA MR imaging examinations. Moreover, our results were consistent and accurate despite of this heterogeneity in MR imaging, which indicates a certain generalizability of the approach described herein. Finally, the evaluation of local tumor recurrence was only based on imaging features. No histopathologic correlation, as the criterion standard, was available.

In conclusion, our study indicates the feasibility of pre-RFA MR imaging registration on post-RFA P-CT for predicting local tumor recurrence within 24 hours after RFA in a highly accurate, quantitative manner.

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