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Radio-frequency Ablation of Hepatic Tumor: Subjective Assessment of the Perilesional Vascular Network on Contrast Enhanced CT Before and After Ablation can Reliably Predict the Risk of Local Recurrence

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Abstract

OBJECTIVE—To determine whether simple, subjective analysis of the peri-lesional vascular network can predict the risk of local recurrence after radio-frequency ablation (RFA) of liver malignancies on contrast-enhanced computed-tomography (CECT).

METHODS—CECT's of 103 patients (59 men and 44 women; mean age, 63 years (range 31-84 years) with 134 lesions who underwent RFA between 2000 and 2010 were retrospectively analyzed. The primary tumors include colorectal carcinoma (58 patients), hepatocellular carcinoma (n=13), breast carcinoma (n=8), neuroendocrine tumor (n=5) and others (n=19). 3 blinded radiologists independently reviewed the CECT (a triple phase liver protocol for

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CONFLICTS OF INTEREST

None

hypervascular tumors and a single phase for the hypovascular tumors) before and 6 weeks after RFA and subjectively estimated the width of the ablative margin on a 3-point scale (optimal-1, suboptimal-2 and residual tumor-3). Local recurrence was determined on follow up CECT.

RESULTS—The consensus score was 1 in 94, 2 in 28 and 3 in 12 lesions. Kappa among readers was 0.75. Local recurrence occurred in 3 lesions with a score of 1 and 12 lesions with a score of 2. The consensus score was a significant univariate predictor of local recurrence.

CONCLUSION—Subjective estimation of the width of ablative margin can reliably predict the risk of local recurrence.

Keywords

Computed tomography; Radio-frequency ablation; Liver; Ablation margin; Primary and metastatic liver lesions

INTRODUCTION

Radiofrequency ablation (RFA) is used routinely to treat malignant hepatic tumors, especially early-stage hepatocellular carcinoma and unresectable metastases that are smaller than 5 cm¹⁻³. After 2 decades of practice and technical refinements, the main issue with the technique is neither the choice of targets nor the incomplete necrosis of the tumor but the difficulty in ensuring the eradication of viable cells at the edge of the ablation zone, an inherent but understandable risk owing to the lack of visual assessment of the precise extent of ablation during the procedure. The selection of optimal candidates for RFA is based on imaging: tumor size, number and the location of target lesions, invasion of adjacent structures have an impact on the success rate⁴. An accurate assessment of the completeness of ablation likewise relies on imaging. The best predictor of successful ablation has been shown to be the width of the ablative margin, defined as the thickness of the normal peritumoral parenchyma included in the ablation zone^{5,6}.

No simple, reliable method exists for estimating the width of the ablative margin. Therefore, the purpose of this retrospective study was to determine whether a subjective morphologic analysis that is focused primarily on the peri-lesional vascular network (normal opacified portal and hepatic veins, and arterioles around the lesion) allows consistent prediction of the completeness of ablation on contrast-enhanced computed tomography (CT).

SUBJECTS AND METHODS

Patients

We searched a prospectively maintained surgical database and identified 103 patients (59 males and 44 females; mean age, 63 years; age range 31-84 years; and standard deviation, 11.5 years) with 134 lesions who had undergone RFA for primary and metastatic hepatic tumors between 2000 and 2010, either during open surgery (54 patients [52%]) or percutaneously by interventional radiologists (49 patients [48%]). The number of lesions RF ablated in a patient ranged between 1 and 4. The study only included patients for whom contrast-enhanced CT images were available from before and at least within 6 months after

RFA. The most common primary tumors were colorectal carcinoma (58 patients), hepatocellular carcinoma (n=13), breast carcinoma (n=8), and neuroendocrine tumor (n=5). Other tumors included melanoma (n=4), pancreatic adenocarcinoma (n=3), cholangiocarcinoma (n=2), anal squamous cell carcinoma (n=2), renal cell carcinoma (n=2), gastrointestinal stromal tumor (n=1), granulosa cell tumor of the ovary tumor (n=1), duodenal carcinoma (n=1), thyroid carcinoma (n=1), non-small cell lung cancer (n=1) and hemangioendothelioma (n=1). The lesions ranged in size from 0.4 cm to 4.7 cm (mean ,1.8 cm; standard deviation, 0.8 cm) . This retrospective study including a waiver of informed consent was approved by our institutional review board.

CT Technique

Contrast-enhanced CT studies had been performed with a multidetector row 4- or 16-slice CT scanner (Light-Speed, GE Healthcare, Piscataway, NJ) using a collimation of 5 mm and reconstruction at 2.5 mm. Contrast enhancement was performed with a triphasic liver protocol in the case of hepatocellular carcinoma and neuro endocrine tumors or single-phase technique for hypovascular tumors. Axial images were reviewed on our institutional PACS (Philips IntelliSpace PACS Radiology).

RF ablation Technique

All CT-guided RF ablations were performed under general anesthesia using an impedance-based Cool-Tip RF ablation system (Valleylab, Boulder, Colorado). One or more electrodes were used depending on the tumor's size and location, and overlapping ablations were performed to adequately cover the entire tumor. A contrast-enhanced CT examination was frequently performed immediately after the ablation to assess the efficacy of the ablation. Surgical patients were treated during a laparoscopic or open surgical procedure under general anesthesia. Intraoperative or laparoscopic ultrasonography was used to place the RF needle into the target lesions.

Image Analysis

Two radiologists with more than 20 years of experience (EL and SG) and a junior faculty member with 2 years of experience (ST), all blinded to the outcome, independently reviewed the pre-procedure images and the images obtained within 6 weeks of the RFA. The radiologists estimated the ablative margin by comparing the size of the RFA defect on post procedure CT with that of the treated tumor on pre-procedure CT evaluating for gross misalignment and residual tumor by comparing the alignment of the boundaries of the RFA defect with that of the tumor before RFA. A more refined evaluation was performed next, focusing on the respective relationships of the tumor before treatment and the RFA defects with the peri-lesional vascular network, including a meticulous assessment of the effects of RFA on these vessels. Peri-lesional vessels are affected differently depending on their location in relation to the index tumor. Vessels closest to the tumor may be incorporated into the post-RFA defect and disappear; those further away are not affected by RFA, although they may change orientation when the defect is large. Segments of vessels obliterated during RFA are direct markers of the extent of peri-lesional parenchymal destruction at a particular point. The segments of vessels that are not ablated can also be used as points of reference to gauge the width of ablated peri-tumoral parenchyma by subjectively comparing the distance

between the non-ablated vessels and the edge of the tumor on the pre-RFA scan with the distance between the same vessels and the edge of the RFA defect (Fig. 1).

The completeness of RFA at the first restaging was scored on a scale of 1-3 on the basis of the subjective estimation of the width of the ablative margin. A score of 1 was given when the edge of the RFA defect, estimated subjectively, clearly extended beyond the contours of the treated tumor by at least 3-5 mm (Figs. 1 B and Fig. 2); 2 was given when the contours of the defect were very close to the contours of the treated tumor at any point (Fig. 1 C, Figs 3 and 4); and 3 was given when the ablation was incomplete, with residual tumor seen at the margin of the defect (Fig. 1 D and Fig 5)

Imaging follow up for lesions given a score of 1 and 2 ranged from 103 to 2965 days with a median of 743 days. Recurrence was diagnosed radiographically using established morphologic patterns⁷. Discrepancies between readers were resolved by consensus.

Statistical Analysis

Each liver lesion was treated independently since each lesion could recur independently of any other lesion that had or had not been ablated. Kappa statistics were calculated to assess inter-reader agreement among the 3 readers. Time to recurrence was calculated from the date of RFA to recurrence or last follow-up. Kaplan-Meier survival curves were used to estimate the time to recurrence, and the log-rank test was used to assess the difference in recurrence time by consensus CT score. Type of radio-frequency ablation (surgical versus interventional radiology treatment), patient age, size of the lesion and consensus score were assessed to predict the time to recurrence. Univariate Cox proportional hazards regression was used to assess the impact of selected predictors on time to recurrence. The Akaike information criterion (AIC), which is a measure of the variability of the outcome explained by the predictor(s) in the model, was examined to help identify which predictors might explain more of the outcome. All statistical analyses were performed using STATA 12.0 and SAS 9.3 software.

RESULTS

A consensus score of 1 was given to 94 (70%) lesions, 2 to 28 (21%) lesions and 3 to 12 (8%) lesions. Recurrence was observed in 3 out of 94 lesions given a consensus score of 1; and in 12 out of 28 lesions with a consensus score of 2. The scores of individual readers and agreement between the readers is summarized in Table 1. Each reader observed a score of 1 in 71%-72% of all RFAs and a score of 2 in 20% of RFAs. Incomplete ablation, or a score of 3, was observed in 8% of cases. Among all readers, the kappa was 0.75, which indicates substantial agreement, according to Landis and Koch⁸. In the univariate models, the size and consensus score were significant univariate predictors of time to recurrence. For each unit increase in size, the risk of recurrence increased 86.2% (HR: 1.862, 95% CI: 1.364 -2.542 and p-value of <0.001). Compared to a score of 1, a score of 2 was associated with a highly increased risk of recurrence (HR: 15.478, 95% CI: 4.364-54.898 and p-value<0.0001). Age and percutaneous ablation by interventional radiology were not significant predictors of time to recurrence in this sample of patients. The Akaike information criterion (AIC) was

242.730 for size and 183.797 for score, implying that score may be a better predictor than size, although both variables were significant (Table 2).

In 10 of the 12 lesions with a score of 2 who presented with recurrence, the recurrence site was concordant with the site of the insufficient margin. In the 16 lesions with a score of 2 that had no local recurrence, the site judged to have an insufficient margin was at the top or bottom of the defect in 6 and closely abutted a vessel in 4. Three lesions (one metastatic renal cell carcinoma and two metastatic colorectal carcinomas) with a score of 1 developed recurrence.

The results in the subgroup of patients presenting with hepatocellular carcinoma are similar to the results of the entire group. There were 13 patients (4 females and 9 males; mean age, 63 years; age range 51-83 years; and standard deviation, 9.3 years) with 19 hepatocellular carcinoma lesions. The lesions ranged in size from 0.9 cm to 4.7 cm (mean, 1.9 cm; standard deviation, 0.8 cm). A consensus score of 1 was given to 14 (74%) lesions, 2 to 3 (16%) lesions and 3 to 2 (10%) lesions. None of 14 patients with a consensus score of 1 recurred. Recurrence was observed in 1 out of 3 lesions given a consensus score of 2.

DISCUSSION

The appearance of the ablation zone and the pattern of involution on CT and magnetic resonance imaging have both been extensively described for RFA, as have the patterns of local recurrence^{7,9,10}. The size and optimal centralization of the ablation defect over the target tumor are both predictive of complete ablation^{6,11,12}. Optimal centralization essentially controls the width of the ablative margin, which is defined as the thickness of the normal peri-tumoral parenchyma included in the zone of RFA. The width of the ablative margin on imaging is an independent surrogate biomarker of local recurrence after RFA and is the most important parameter to be assessed after the procedure^{5,13,14}, as local recurrence occurs with a high concordance rate at sites of insufficient ablative margin^{6,7,14}. A margin of at least 5 mm has been shown to be associated with the best local control in colorectal carcinoma and hepatocellular carcinoma^{5,13}. Our results are in agreement with the published data. In our patients, both tumor size and ablation score were shown to be significant univariate predictors of recurrence.

While measuring the size of the tumor is usually simple, estimating the ablative margin in routine clinical practice however remains challenging. In this study, we demonstrated that a simple, subjective anatomic evaluation of the post-RFA defect with contrast-enhanced CT can identify sites of insufficient margin and consequently patients who are at high risk of local recurrence. It can also help recognize incomplete ablation when the residual tumor at the margin of the defect is very small. This method shifts the focus of the analysis from the ablation zone and its margins to the spatial concordance between the RFA defect and index tumor using the anatomic changes induced in the peri-tumoral vessels as landmarks or reference points.

Standard follow-up at our institution is performed with contrast-enhanced CT imaging within 6 weeks of the procedure. Importantly, patients who have undergone RFA for

hypervascular tumors, such as hepatocellular carcinoma, are followed up using a multiphasic technique, including non-contrast evaluation of the liver, arterial, portal and delayed phases to increase the likelihood of detecting residual/recurrent tumor⁴.

In our approach, after the elimination of gross residual tumor, the goal is to triangulate the position of the tumor in relation to the peri-tumoral vessels on pre-treatment images. The need for a safe margin indicates that vessels that are close to the tumor will be ablated and not appear on post-procedure scans. The comparison of the peri-lesional vascular network before and after RFA provides an estimate of the ablation margin. The length of the vascular segments that have been ablated directly reflects the width of the margin at that point. The vessels that are not directly affected by the ablation provide numerous additional points of reference. The width of normal parenchyma that has been ablated (i.e., the ablative margin) can be inferred by comparing subjectively the distance between the point of reference in the liver parenchyma (ie, vessels) and the tumor edge with the distance between the same point and the edge of the RFA defect. For each RFA defect, several reference points are used.

Our results show good inter-observer agreement and a significant difference in the rate of local recurrence between RFAs scored as 1 (3/94) and those scored as 2 (12/28). A score of 2 was given to 16 of 28 lesions that did not develop local recurrence. The site of the suspected insufficient margin was at the superior or inferior margin of the defect in 6 patients. An inadequate estimation of the margin is likely due to the lack of multiplanar reformat in these older studies; better results would likely be obtained today with the use of the routine multiplanar reformat. In 4 patients, the insufficient margin closely abutted a vessel. The lack of recurrence in these patients is in agreement with the results of Kei et al⁷. Three lesions that were scored as type 1 showed local recurrence. One of them had been the object of disagreement between readers and was a difficult case. For the two remaining lesions there was no morphologic reason to explain the recurrence even in retrospect.

Our results corroborate those of a recent study by Wang et al¹³, who performed a thorough analysis using anatomic landmarks on pre-RFA and post-RFA scans to measure the ablative margin. Their approach was essentially the same as the one we have described, focused on the peri-tumoral liver; however, contrary to our subjective approach, they obtained objective measurements between the lesion and points of reference. They showed that a margin of 5 mm was associated with the most effective local control of hepatic colorectal metastasis. Schraml et al¹⁵ also evaluated immediate post-RFA scans using extra-tumoral anatomic references but used the centers of the RFA defect and the index tumor as the reference for their respective locations.

Other methods of assessing RFA margins have been described over the years. Nishikawa et al¹⁴ proposed a grading method that predicted the risk of recurrence on the basis of the width of the margin. The grade C and some of grade B in their method correspond to our type 2 and are likewise associated with an increased risk of local recurrence. Their cohort provided an excellent model to demonstrate the relationship between the margin and the treated tumor but was best suited for cases in which embolization with lipiodol had been performed before RFA and allowed easy visibility of the target tumor after RFA. Indeed, the authors reported that it was difficult to determine the exact location of the index tumor and

hence the width of the margin when the accumulation of lipiodol was suboptimal. Several authors have proposed the use of fusion CT techniques ⁶, while others have used simpler means of comparing the size or volume of the index tumor with that of the defect or the width of the hypo-enhancing peri-tumoral zone on the immediate post-procedure scan^{7,16-18}. These methods require that the defect is centered perfectly over the index tumor. In cases in which optimal centering of the RFA over the tumor is not achieved, these methods are not reliable for predicting the width of the ablative margin.

In this study, by shifting the focus from the RFA defect to the peri-lesional vascular network, we showed that the radiologists can appraise subjectively the congruence between the RFA defect and the index tumor and estimate the width of the ablative margin. We demonstrate that this simple subjective assessment of the ablative margin is, as the size, a univariate predictor of complete ablation and accurately predict the risk of local recurrence and hence identify patients that would benefit from close follow-up.

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Abbreviations

RFA	Radio-frequency ablation
AM	Ablation margin

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Key points

1. Evaluating the completeness of RFA is very difficult during the procedure.
2. Adequate width of ablative margin (AM) is the best predictor of completeness.
3. No simple reliable method for estimating the RFA ablative margin is available.
4. Subjective assessment of the vascular network predicts the risk of recurrence.

FIGURE 1.

Schematic representation of the scoring of the ablation margin. (a) Schematic representation of an index liver lesion with normal vessels around the lesion. (b) Schematic representation of the RFA defect (dotted line) superimposed on the index liver lesion illustrates a good RFA margin given a score of 1. (c) Schematic representation of the RFA defect (dotted line) superimposed on the index liver lesion illustrates close RFA margin given a score of 2. (d) Schematic representation of the RFA defect (dotted line) superimposed on the index liver lesion illustrates incomplete RFA margin with a gross residual tumor given a score of 3.

FIGURE 2.

A 66-year-old man with metastatic melanoma and a score of 1. (a) Contrast-enhanced CT in the portal phase shows metastasis (white arrow) abutting the anterior aspect of the portal vein to segment IVa (arrowhead) posterior to the fissure for the falciform ligament and anterior to the bifurcation of the middle hepatic vein (black arrow). (b) Contrast-enhanced CT in the portal phase obtained 3 months after RFA shows the RFA defect extending anteriorly to the fissure for the falciform ligament and the surface of the liver, with obliteration of the portal branch to segment IVa (arrowhead). The posterior edge of the RFA defect is closer to the bifurcation of the middle hepatic vein (black arrow). The ablative margin is at least 3 to 5 mm along the circumference of the tumor. (c). Schematic representation, with the contours of the RFA defect (red) drawn on the index lesion in image A, depicts the use of vascular landmarks (blue).

FIGURE 3.

A 91-year-old man with metastatic colorectal carcinoma and a score of 2 who did not develop local recurrence. (a). Contrast-enhanced CT in the portal phase shows metastasis in segment VIII (white arrow). Note the small portal vein branch abutting the anterior aspect of the metastasis (arrowhead) and its relationship to other vessels (black arrows) surrounding the metastasis. (b) Contrast-enhanced CT in the portal phase, obtained 3 months after RFA, shows an RFA defect extending posteriorly and medially to vessels that were distant from the tumor on the pre-procedure scan (black arrows). The margin along the posteromedial aspect of the defect is 3 to 5 mm. Anteriorly and laterally, the tumor remains in contact with small portal branches (arrow head), indicating the lack of margin at that level and the reason for a score of 2. (c) Schematic representation with the contours of the RFA defect (red) drawn on the index lesion in image A depicts the use of vascular landmarks (blue) as a spatial reference.

FIGURE 4.

A 60-year-old woman with metastatic papillary carcinoma of the thyroid and a score of 2 who developed local recurrence. (a) Contrast-enhanced CT in the portal phase shows metastasis in segment IVa (white arrow). Note the relationship of the tumor with a portal branch to segment IVa (arrowheads) and a branch of the middle hepatic vein (black arrows). (b) Contrast-enhanced CT in the portal phase obtained 3 months after RFA shows the ablation defect extending posteriorly to the branch of the middle hepatic vein, indicating a 3-5-mm margin; the parenchyma between the RFA defect and the portal branch to segment IV appears intact, suggesting that the margin along the anterior aspect is insufficient. (c) Contrast-enhanced CT in the portal phase obtained 5 months after RFA shows recurrence along the anterior margin of the RFA defect (arrow). (d). Schematic representation, with the contours of the RFA defect (red) drawn on the index lesion in image A depicts the use of vascular landmarks (blue) as a spatial reference.

FIGURE 5.

A 75-year-old woman with metastatic colorectal carcinoma and a score of 3. (a) Contrast-enhanced CT in the portal phase shows metastasis in segment VIII (white arrow). Note the relationship with the small branch of the right hepatic vein (black arrows). (b) Contrast-enhanced CT in the portal phase obtained 3 months after RFA. The anterior margin of the defect has the same relationship with the branch of the right hepatic vein as the tumor (black arrows), indicating an insufficient margin. On closer inspection, a small focus of residual tumor is visible at the edge of the RFA defect. (c) Schematic representation, with the contours of the RFA defect (red) drawn on the lesion index lesion in image A, depicts the use of vascular landmarks (blue) as a spatial reference.

Table 1

Reader Scores and Agreement in the Assessment of Radiofrequency Ablation Margins (n = 134)

Score	Reader, (%)		
	1	2	3
1 = Optimal	97 (72)	96 (72)	95 (71)
2 = Risk of recurrence	26 (19)	25 (19)	28 (21)
3 = Incomplete	11 (8)	13 (10)	11 (8)

Combined kappa among all readers: 0.7572.

Kappa 1/2: 0.6928 (87% agreement)

Kappa 1/3: 0.7692 (91% agreement)

Kappa 2/3: 0.7821 (90% agreement)

Table 2

Univariate Cox proportional hazards regression results for time to recurrence after radiofrequency ablation (N = 134, recurrences = 27)

Variable	Hazard ratio	95% CI for hazard ratio	p value
Treatment [†]	0.798	0.370-1.720	0.5643
Age (years)	0.995	0.964-1.027	0.7623
Size (cm)	1.862	1.364-2.542	<.0001
		4.364-	
Score = 2 [*]	15.478	54.898	<.0001

[†]Interventional radiology versus surgical ablation

^{*}A score of 1 was used as the reference.