

# Risk factors for occurrence of local tumor progression after percutaneous radiofrequency ablation for lung neoplasms

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## PURPOSE

To examine the characteristics of lung tumors for which radiofrequency (RF) ablation therapy is effective, and to determine what RF ablation parameters are effective for obtaining complete coagulation of the entire ablation zone with a single RF ablation session.

## MATERIALS AND METHODS

Computed tomography (CT)-guided RF ablation of lung tumors was performed on 82 lesions in 34 patients between April 2003 and May 2005. Tumor characteristics and ablation parameters, including tumor size, location, and depth, and ablation duration, power deployed during ablation, and temperatures achieved were analyzed with regard to local tumor progression.

## RESULTS

In all, 103 RF ablation sessions were performed on 82 tumors. As a procedure-related complication, pneumothorax occurred in 27 procedures. During the mean follow-up period of 10 months (range, 6–28 months), local tumor progression occurred in 18 (22.0%) of the 82 ablated tumors (3 months after RF ablation in 10, 6 months after RF ablation in 5, 9 months after RF ablation in 1, and 12 months after RF ablation in 2). Mean local progression-free duration was  $8.7 \pm 4.5$  months (range, 3–28 months). The frequency of local tumor progression was significantly correlated with size, whereas other variables had no statistical association. In tumors with a diameter  $\geq 2.5$  cm, only the period of ablation during the initial session was significantly correlated with subsequent local tumor progression ( $P = 0.000002$ , chi-square test).

## CONCLUSION

A long duration of RF ablation is desirable for large lung tumors. The success of RF ablation is dependent upon tumor size. RF ablation treatment is most effective for lesions  $< 2.5$  cm.

**Key words:** • computed tomography guidance • lung neoplasms • radiofrequency catheter ablation

Following many reports of the usefulness of radiofrequency (RF) ablation for liver tumors (1–8), Dupuy et al. (9) reported in 2000 the use of this technique under computed tomography (CT) guidance for lung tumors. Since that time, reports have gradually increased. Currently, RF ablation has become an accepted therapy for lung tumors, particularly for certain unresectable cases (10, 11).

Nonetheless, the use of RF ablation for treating lung tumors, in contrast to liver tumors, has a short clinical history and is still developing. Thus, there remain many unknowns and much to be clarified. Among these issues are the characteristics of tumors for which RF ablation therapy is effective and identifying the conditions under which RF ablation will result in no evidence of local tumor progression after a single session. In this study, we examined those factors in cases with unresectable lung tumors treated with RF ablation with an internally-cooled electrode.

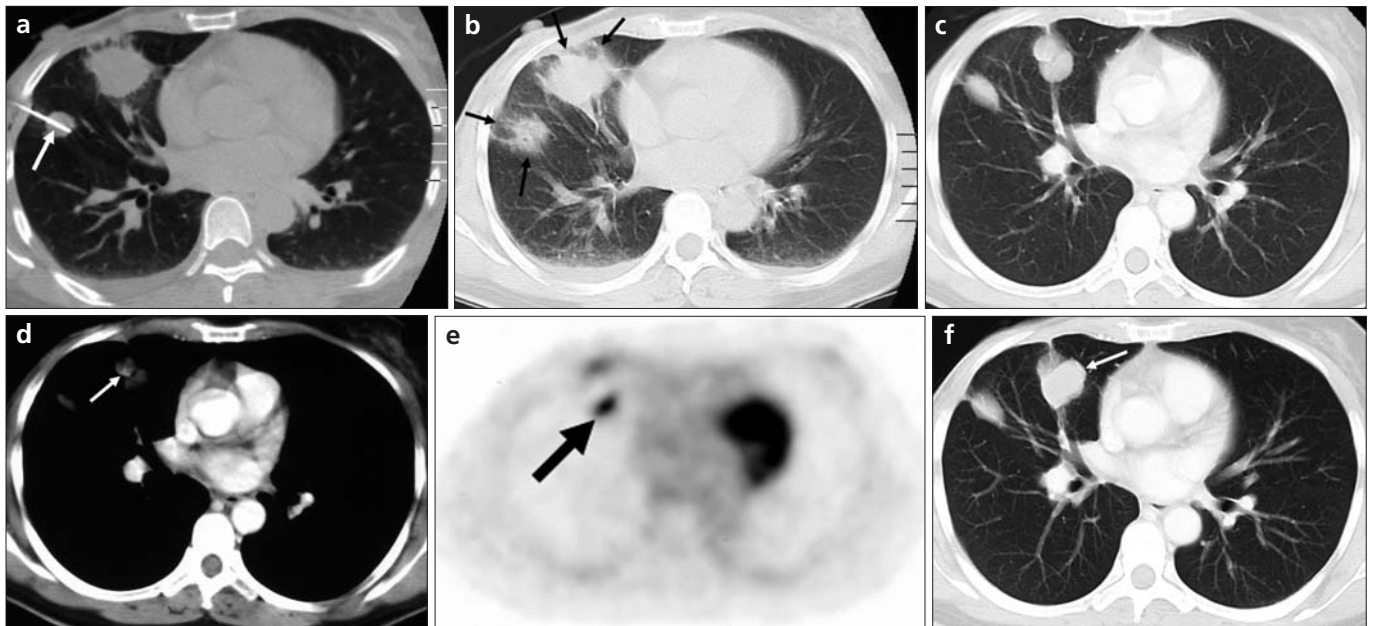
## Materials and methods

### Subjects

Percutaneous CT-guided RF ablation of 82 tumors in 34 patients with inoperable lung neoplasms (21 males and 13 females; age range, 29–80 years; mean, 62 years) was performed in our institution between April 2003 and June 2005. Inoperability was determined as follows: 1) the extent or distribution of disease ( $n = 28$ , another coexistent tumor: 24 patients; multiple lung tumors distributed in both lobes: 4 patients); 2) the presence of comorbid conditions ( $n = 7$ , pulmonary emphysema: 4 patients; hemodialysis: 1 patient; liver cirrhosis: 1 patient; heart failure: 1 patient); 3) previous surgery for pulmonary metastatic disease ( $n = 2$ ); 4) patient refused surgery ( $n = 1$ ). Categories overlapped in 4 patients. Patients selected for RF ablation therapy met the following criteria: (a) histologically-proven non-small-cell carcinoma or metastases, and (b) no coagulation disorders. Candidates for RF ablation were selected by the consensus of interventional radiologists and thoracic surgeons at a case presentation conference. Most of these patients had previously received other treatments, such as systemic chemotherapy or radiation therapy, only to develop intractable disease. Two patients had a primary lung tumor and 32 had metastatic lung tumors that originated from the colorectum ( $n = 13$ ), testis ( $n = 4$ ), thyroid ( $n = 4$ ), breast ( $n = 3$ ), kidney ( $n = 3$ ), liver ( $n = 2$ ), thymus ( $n = 1$ ), urinary bladder ( $n = 1$ ), and uterus ( $n = 1$ ). In the same or different sessions, one tumor was ablated in 16 patients, 2 tumors in 9, 3 tumors in 2, 4 tumors in 3, 5 tumors in 2, 8 tumors in 1, and 12 tumors in 1 patient. In all cases, more than 6 months passed between the first session of RF ablation and the writing of this report or the patient's death. The mean diameter of lung tumors was  $18 \pm 9$  mm (mean  $\pm$  SD; range, 3–42 mm). The mean lesion depth, measured from the surface of the pleura to the edge of the lesion, was  $25 \pm 20$  mm (mean  $\pm$  SD; range, 0–70 mm). Among the tumors, 11 were centrally

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A 42-year-old woman with lung metastasis from the breast. Real-time CT fluoroscopic image (a) with patient in the supine position shows that the radiofrequency (RF) ablation needle tip is advanced into the smaller tumor (arrow). Note that RF ablation was performed for the larger tumor, just before the procedure for the smaller tumor. Transverse contrast-enhanced CT image (b) obtained immediately after RF ablation for 2 tumors show ground glass opacities around both ablated tumors (arrows). Transverse contrast-enhanced CT images (c, d) obtained 3 months after RF ablation show that both ablated tumors decreased in size; however, an enhanced part is included in the larger one (arrow, d). An FDG-PET scan (e) acquired 3 months after RF ablation shows complete reduction of radioactivity in the smaller tumor, but remaining radioactivity in the larger one (arrow). Transverse contrast-enhanced CT image (f) obtained 9 months after RF ablation shows an increase in the size of the larger tumor (arrow). Note that after obtaining this image, a second session of RF ablation was performed for this tumor.

located close to the bronchus and 20 were located peripherally.

Approval was obtained from the institutional ethics committee before accumulating data for this retrospective study. All procedures were performed under local anesthesia after the patient provided written informed consent. The consent form included permission to use records, images, and data for research purposes.

#### RF ablation

All RF ablation procedures were performed percutaneously with the patient under local anesthesia by one of the 3 interventional radiologists in our institution. An RF generator (Cool-tip Radiofrequency Ablation System, Radionics, Burlington, MA, USA) with an internally-cooled single electrode was used for all procedures (Figure). We used local anesthesia with intradermal and subcutaneous 1% lidocaine, and intravenous conscious sedation using 15 mg of pentazocine. The length of the exposed tip was matched to the size of the tumor; a 1-cm exposed tip was used for tumors  $\leq 2$  cm in diameter, a 2-cm exposed tip for tumors 2–3 cm in diameter, and a 3-cm single exposed tip for tumors  $> 3$

cm. The electrode was placed in the tumor according to tumor size and shape in order to create overlapping volumes of ablated tumor tissue (12).

For tumors  $\leq 3$  cm in diameter, the tip of the RF electrode was inserted into the center, while in larger tumors, overlapping ablations were performed by inserting the electrode into 2–4 different sites within the tumor.

In all procedures, the RF electrode was advanced into the tumor under CT fluoroscopic guidance. The CT unit used was an X Vigor Laudator (Toshiba Medical System, Tokyo, Japan). After confirming that the electrode tip had advanced to the desired location, the generator was switched on and set to 40 W. Every 60 s the wattage was increased by 10 W until the impedance surrounding the RF electrode rose more than 20 ohms above the baseline impedance (break), or until a peak of 140 W was reached. Power was maintained at that level or at 10 W lower than the wattage at which a break occurred for a total duration of ablation of 12 min, at which time the RF application was automatically terminated. These procedures were repeated until at least one of the following criteria was satisfied: 1) a break oc-

curred, 2) the temperature of the ablated tissue increased to over  $60^{\circ}\text{C}$ , and/or 3) ground-glass opacity (GGO) emerged around the ablation zone on CT fluoroscopic images. These criteria were used previously (11, 13, 14) as the endpoints of one session of RF ablation.

After each RF ablation procedure, axial images were obtained during a single breath hold through the whole chest using helical CT scanning in order to evaluate the presence of a pneumothorax or any other complication related to the RF ablation procedure.

A procedure was defined to be technically successful at the point when a break occurred (criteria 1), GGO emerged around the ablation zone (criteria 3), or both. Both criteria have been described to define technical success in previous reports (11, 13).

The efficacy of RF ablation was assessed by enhanced CT obtained within 5–7 days of the initial RF ablation session.

#### Evaluation of therapeutic response

Follow-up studies for all patients included both contrast-enhanced CT imaging and  $^{18}\text{F}$  fluorodeoxyglucose positron emission tomography (FDG-PET)

obtained 3 months after RF ablation. Subsequently, contrast-enhanced CT imaging studies were performed every 3 months. In cases ( $n = 3$ ) in which enhancement in the ablation zone or an increase in the size of the ablation zone, or both were seen, and it was difficult to confirm that such CT findings indicated the presence of local tumor progression, a supplemental FDG-PET study was added to enhance the CT findings.

No local tumor progression was defined as both the complete resolution of FDG-uptake in the ablation zone on PET, and the eradication of tumor enhancement and decrease in size as shown by contrast-enhanced CT images. Local tumor progression was considered to have occurred in the ablation zone when contrast-enhanced CT images revealed an enhanced portion in the ablation zone or an increase in size, and/or when FDG-PET imaging revealed abnormal FDG-accumulation. When there was a discrepancy between CT findings and FDG-PET, the presence of local tumor progression in the ablation zone was confirmed by a percutaneous needle biopsy or carefully-performed follow-up with imaging modalities (CT and FDG-PET). These images were then analyzed and discussed by the 2 authors until a consensus was reached.

#### *Investigated parameters*

We retrospectively investigated the following: 1) technical success rate; 2) procedure-related complications according to the Society of Cardiovascular and Interventional Radiology (SIR) standards (15); 3) present status (dead or alive) of each patient; 4) detection rate of local tumor progression in treated tumors and their management; 5) the relationship between the incidence of local tumor progression and several variables (tumor size, tumor depth as measured from the surface of the pleura to the edge of the tumor, existence of a tumor portion in contact with the pleura, large vessels  $>1$  cm in diameter, and bronchi  $>1$  cm in diameter); 6) various conditions for the RF ablation procedure according to tumor size; 7) correlation between the detection of local tumor progression and conditions for RF ablation of relatively large tumors ( $\geq 2.5$  cm in diameter). Conditions referred to in 6) and 7) were: maximum power of the generator during RF ablation, duration of ablation, temperature of the ablated tissue at the end of RF ablation, the occurrence of a break

during RF ablation, and the appearance of GGO at the end of RF ablation.

#### *Statistical analysis*

For statistical analysis, commercial software (Statview, Abacus Concept, Berkeley, CA, USA) was used. Quantitative variables were compared using the Student's *t*-test. Qualitative variables were compared using the chi-square test.

#### **Results**

As of December 2005, 4 of the 34 patients died. The time from the first ablation of each tumor until the present (December 2005) or the patient's death ranged from 6 to 28 months (mean  $\pm$  SD,  $10.1 \pm 4.6$  months). Progression of lung malignancy was not the cause of death in any of the 4 patients. In 3 of these 4 patients, local tumor progression after ablation was not observed.

Overall, 103 RF ablation sessions were performed on a total of 82 tumors (1 session,  $n = 68$ ; 2 sessions,  $n = 9$ ; 3 sessions,  $n = 3$ ; 4 sessions,  $n = 2$ ). All RF ablations were technically successful. At least 1 of 3 parameters per lesion was satisfied, as required, before an RF session was completed: in 71 (87%) of the 82 ablated tumors, a break occurred during RF ablation; in 41 (50%) the temperature of the ablated tissue increased to over  $60^\circ\text{C}$ ; and in 80 (98%) GGO emerged around the ablation zone. All 3 parameters were satisfied for 33 tumors. After all RF ablation sessions, contrast-enhanced CT obtained 5–7 days later showed no enhancement within the boundaries of the ablation zone.

A major procedure-related complication occurred in 5 (4.9%) of the 103 sessions; all were pneumothoraces requiring treatment with chest tube placement. Regarding minor complications, there were 22 pneumothoraces that disappeared spontaneously without treatment with chest tube placement, 6 cases of transient hemoptysis, and 5 episodes of pleural effusion of small amounts of fluid.

In 18 (22.0%) of the 82 ablated tumors, local tumor progression was observed 3 months after RF ablation in 10 tumors, 6 months after RF ablation in 5, 9 months after RF ablation in 1, and 12 months after RF ablation in 2 of the treated tumors. A second RF ablation session was added for 14 tumors after local tumor progression was noted. Furthermore, a third session was added for 5 lesions that were resistant to the

repeat RF ablation and a fourth session was added for 2 such tumors. Mean local progression-free duration was  $8.7 \pm 4.5$  months (range, 3–28 months).

Table 1 summarizes the correlation between several variables of the treated tumors in which local tumor progression was seen. Only lesion size was significantly correlated with the frequency of local progression after RF ablation. Local tumor progression was revealed in 5 (62.5%) of 8 tumors  $>3$  cm in diameter; in 9 (45.0%) of 20 tumors 2–3 cm in diameter; in 3 (9.7%) of 31 tumors 1–2 cm in diameter; and in 1 (4.3%) of 23 tumors  $\leq 1$  cm in diameter. Table 2 shows the conditions for the first session of ablation according to tumor size.

When the frequency of appearance of local tumor progression was compared between tumors  $\geq 2.5$  cm in diameter ( $n = 20$ ) and those  $< 2.5$  cm ( $n = 62$ ), in the former cohort local progression appeared in 12 (60.0%) ablated tumors, while in the latter cohort it appeared in 6 (9.7%). The difference between the 2 groups was significant ( $P = 0.000002$ , chi-square test). In those tumors  $\geq 2.5$  cm, among the factors shown in Table 3, only the duration of ablation during the initial session was significantly correlated with the subsequent appearance of local tumor progression.

#### **Discussion**

No firm conclusions can be made with regard to establishing the parameters of RF ablation for lung tumors. Based only on reports of RF ablation with an internally-cooled electrode, the maximum RF generator power during lung tumor ablation ranged from 10–90 W (11) to 50–200 W (14). With regard to criteria for determining the completion of a single session of RF ablation, the occurrence of a break (13), temperature of ablated tissues exceeding  $60^\circ\text{C}$  (11), and the appearance of GGO (11, 14) have been suggested; however, no conclusions have been reached. In most previous reports the duration of a single session was shorter than 12 min (9, 10, 16); however, others have recommended that if the above-mentioned factors were not satisfied within 12 min, the procedure should continue until sufficient ablation was confirmed (11, 13, 17, 18).

Bojarski et al. (16) evaluated CT findings of lung tumors following RF ablation and reported that tumor size in the ablation zone was variable during

the first 6 months after RF ablation. In the present study, tumor growth 1–3 months after RF ablation was common, irrespective of the presence of local tumor progression; compared to the pre-RF ablation baseline, 64% were larger and 32% were unchanged 1 month after ablation, and 30% were larger and 50% were unchanged 3 months after ablation. All neoplasms that continued to grow beyond 6 months post-ablation were shown on follow-up scans to be

suspicious or recurrent disease. Yasui et al. (11), in describing their experiences with the RF ablation of 99 lung tumors, reported that the size of the ablation zone, including the tumor, did not significantly change 2 months after the initial RF ablation. Considering such results (11, 16), change in size of the ablation zone alone is not sufficient for evaluating the therapeutic effectiveness of RF ablation for lung tumors, especially in the first few months fol-

lowing the procedure. To achieve more precise evaluation, the use of contrast-enhanced CT or the additional use of FDG-PET is recommended (13, 17, 18). The rate of complete necrosis obtained by a single RF ablation session, as revealed by these imaging studies, ranged from 43%–91% (11, 13–15, 17–20).

The rate of local tumor progression is known to increase with tumor size (13, 14, 17). In summarizing the RF ablation of 54 lung tumors, Akeboshi et al. (13)

**Table 1.** Parameters affecting the appearance of local tumor progression after a single radiofrequency ablation session

Parameter	Later appearance of local tumor progression		Statistical test	P value
	Present (n = 18)	Absent (n = 64)		
Females [n (%)]	5 (27.8)	26 (40.6)	Chi-square test	0.3207
Age (years) (range)	62.2 ± 10.7 <sup>a</sup> (42-80)	58.7 ± 14.6 <sup>a</sup> (29-77)	Student's t-test	0.3408
Size (mm) (range)	25.6 ± 7.6 <sup>a</sup> (10-36)	15.4 ± 8.3 <sup>a</sup> (3-42)	Student's t-test	< 0.0001
Depth of lesion (mm) (range)	21.8 ± 21.2 <sup>a</sup> (0-60)	25.4 ± 19.6 <sup>a</sup> (0-70)	Student's t-test	0.4951
Tumor contacting				
Pleura [n (%)]	7 (38.9)	13 (20.3)	Chi-square test	0.1176
Large vessel [n (%)]	4 (22.2)	14 (21.9)	Chi-square test	0.9749
Bronchus [n (%)]	4 (22.2)	7 (10.9)	Chi-square test	0.2381

<sup>a</sup> mean ± SD

**Table 2.** Summary of conditions for radiofrequency ablation according to tumor size

	Overall (n = 82)	> 3 cm (n = 8)	2-3 cm (n = 20)	1-2 cm (n = 31)	< 1 cm (n = 23)
Maximum power (W) (range)	65 ± 25 <sup>a</sup> (40-140)	113 ± 13 <sup>a</sup> (100-140)	84 ± 16 <sup>a</sup> (60-110)	58 ± 14 <sup>a</sup> (40-90)	42 ± 9 <sup>a</sup> (40-80)
Period (min) (range)	16 ± 7 <sup>a</sup> (12-48)	29 ± 12 <sup>a</sup> (12-48)	17 ± 6 <sup>a</sup> (12-29)	14 ± 5 <sup>a</sup> (12-36)	14 ± 4 <sup>a</sup> (12-24)
Tissue temperature (°C) (range)	58 ± 12 <sup>a</sup> (37-80)	72 ± 5 <sup>a</sup> (60-77)	69 ± 6 <sup>a</sup> (60-80)	56 ± 9 <sup>a</sup> (37-73)	46 ± 7 <sup>a</sup> (37-66)
Break present [n (%)]	71 (87)	6 (75)	16 (80)	29 (94)	20 (87)
GGO present [n (%)]	79 (96)	8 (100)	19 (95)	30 (97)	22 (96)

GGO: ground-glass opacity.

<sup>a</sup> mean ± SD

**Table 3.** Summary of conditions for radiofrequency ablation of tumors ≥ 2.5 cm in diameter

	Later appearance of local tumor progression		Statistical test	P value
	Present (n = 12)	Absent (n = 8)		
Maximum power (W) (range)	101 ± 20 <sup>a</sup> (100-140)	89 ± 20 <sup>a</sup> (60-110)	Student's t-test	0.2016
Period (min) (range)	19 ± 5 <sup>a</sup> (12-24)	28 ± 13 <sup>a</sup> (12-48)	Student's t-test	0.0279
Tissue temperature (°C) (range)	70 ± 6 <sup>a</sup> (60-80)	70 ± 5 <sup>a</sup> (60-76)	Student's t-test	0.9514
Break present [n (%)]	8 (67)	7 (88)	Chi-square test	0.2756
GGO present [n (%)]	12 (100)	8 (100)	NA	

GGO: ground-glass opacity.

<sup>a</sup> mean ± SD

reported that there was no appearance of local tumor progression in 69% of 36 tumors  $\leq 3$  cm in diameter after a single RF ablation session versus in only 39% of 18 tumors  $>3$  cm in diameter, a difference that was significant. Additionally, Lee et al. (14) suggested that the rate of achieving no local tumor progression after RF ablation was significantly lower in tumors  $>3$  cm. Kang et al. (17) evaluated 50 patients and reported that local tumor progression was not observed following RF ablation of tumors that were  $\leq 0.5$  cm, but that it was observed in tumors  $>3.5$  cm.

In the present study, the technical success rate was 100%. The complete response rate, that is, the rate of treated tumors in which a residual part was not present after the first session of RF ablation, was 78%, and the rate of pneumothorax was 26.2%. These results were similar to those previously reported, suggesting that the patients and operator skill in our CT-guided RF ablation of lung tumors did not differ appreciably from those of earlier studies. Our criteria for determining the completion of one RF ablation session satisfied at least 1 of the 3 criteria suggested in previous reports (11, 13, 14), which were the occurrence of a break, temperature of ablated tissues exceeding  $60^{\circ}\text{C}$ , or the appearance of GGO. A break and GGO occurred in the majority of our cases, 87% and 96%, respectively. To evaluate the therapeutic effectiveness of RF ablation, both contrast-enhanced CT and FDG-PET were used.

Our investigation of the factors that might have influenced the appearance of local tumor progression after the initial RF ablation session of lung tumors revealed that only tumor size was significantly correlated with the appearance of local tumor progression. There was no significant correlation with any other factor under examination. Thus, the tendency of local tumor progression to appear was greater in larger tumors, although conditions for the performance of RF ablation were stricter for such tumors. As shown in Table 2, maximum power during RF ablation was higher, duration of ablation was longer, and temperature of ablated tissue upon the completion of RF ablation was higher in tumors  $>3$  cm. Previous reports also showed similar ineffectiveness of RF ablation for large tumors (13, 14, 17).

In considering strategies for the performance of RF ablation for relatively

large tumors, our results suggest a longer duration of ablation. Our comparison of the rate of the appearance of local tumor progression in the ablation zone between tumors  $\geq 2.5$  cm in diameter ( $n = 20$ ) and those  $<2.5$  cm ( $n = 62$ ) showed a significantly higher rate in the larger tumors (60.0% vs. 9.7%). Regarding the conditions of RF ablation of large tumors ( $\geq 2.5$  cm in diameter), the duration of ablation during the first session was significantly correlated with the later appearance of local recurrence; however, there was no significant correlation with other conditions examined.

In conclusion, RF ablation is a feasible and useful therapy for unresectable lung tumors. Nonetheless, imaging studies should be repeated periodically to determine if local tumor progression appears, especially in tumors  $>2.5$  cm in diameter. In larger tumors, there is only a slight possibility of achieving complete necrosis with a single RF ablation. Thus, in addition to the conditions already examined and described above, a long duration of ablation is necessary to achieve complete necrosis with a single session. This is based on our finding that the later appearance of local tumor progression in ablated tumors was significantly greater in large tumors compared to small ones, but that such an appearance significantly decreased as the ablation duration increased. Based on the results of the present study, the duration of RF ablation for large tumors should be at least 28 minutes, which was the mean duration that resulted in complete necrosis with a single session of ablation.

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