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Percutaneous radiofrequency thermal ablation in the management of lung tumors: presentation of clinical experience on a series of 35 patients

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PURPOSE
To present our results in a series of 35 patients with malignant pulmonary lesions, who underwent radiofrequency thermal ablation (RFA) during a period of 18 months.

MATERIALS AND METHODS
In our institution, 55 RFA sessions under computed tomography (CT) guidance were performed on 48 pulmonary malignant lesions (23 inoperable primary and 25 metastatic) in 35 patients.

RESULTS
Total necrosis was noted in 19 primary (82.6%) and in 19 metastatic lesions (76%). In four primary (17.4%) and in six metastatic lesions (14%), partial necrosis was achieved, and a second RFA session was performed. The 6-month spiral CT follow-up demonstrated recurrence in seven lesions (14.5%) (four primary and three metastatic), which were treated with an additional RFA session. Two of the patients who underwent the procedure died of disseminated disease after one year, accounting for a 1-year survival rate of 94.2%. Mean survival was 14.48 ± 3.3 months.

CONCLUSION
RFA is an effective method for treating unresectable lung carcinoma and lung metastases.

Key words: • *radiofrequency catheter ablation* • *lung neoplasms* • *neoplasm metastasis*

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Percutaneous thermal radiofrequency ablation (RFA) under ultrasound or computed tomography (CT) guidance is a cost-effective, minimally invasive modality in treating tumors in different solid organs. It has been used to treat primary and metastatic liver tumors for the past decade with promising results (1). It can be performed on an outpatient basis (or with overnight hospitalization), and has a low rate of complications in experienced hands.

Lung cancer is the leading cause of cancer-related death worldwide. It is most common in males (37.5 new cases vs. 10.8 in females annually per 100,000 population) (2). Patients with advanced non-small-cell lung carcinoma (NSCLC) have a median survival of six to eight months, and a 1-year survival rate of only 10–20% (3). Some patients at diagnosis have disease amenable to surgical treatment; the gold standard therapy for stage I lung tumors is surgical resection, this being the only approach with any prospect of cure or long-term survival. However, only about a third of patients are eligible for surgery, and most patients have widespread disease at the time of diagnosis. Some have comorbid conditions including poor cardiopulmonary status, are in poor general health, or are elderly and have insufficient reserves to withstand lobectomy or pneumonectomy (4). Therefore, they are frequently referred for radiation therapy or palliative treatment (3, 5).

Lung is also a frequent site of metastasis. Pulmonary metastases occur in 30% of all malignancies, mostly from hematogenous dissemination. Unfortunately, chemotherapy and external-beam radiation have not greatly affected outcomes in patients with unresectable disease, and increased efficacy often is accompanied by substantial toxicity, especially for patients with comorbid conditions (5).

There exists controversy regarding treatment of patients who have lung malignancies but who are not eligible for surgery, due to extensive disease or to comorbidities with attendant surgical risk. There is no standard treatment for such patients, so innovative treatments may be employed to manage their malignancies. RFA may be an alternative to surgery or radiation therapy for the elimination of tumors in patients with primary lung cancer or pulmonary metastases. RFA can also be used in conjunction with chemotherapy for better disease control. In contrast to radiation therapy and chemotherapy, RFA has almost no side effects, and may help reduce morbidity and mortality, and prolong survival. In the present report, the authors present their experience with a series of 35 patients who underwent RFA for treatment of malignant lesions of the lung.

Pathophysiological rationale of radiofrequency ablation

The goal of thermal tumor ablation is to destroy the entire tumor by using heat to kill the malignant cells in a minimally invasive fashion,

without damaging adjacent vital structures (6). The treatment includes a 0.5–1 cm margin of healthy tissue adjacent to the lesion because of uncertainty regarding the precise location of tumor margins, and to eliminate microscopic tumor foci. On elevation of temperature to approximately 40°C, cellular homeostasis can be maintained; at temperatures above this threshold, cellular damage ensues, with protein coagulation occurring between 60°C and 100°C (7). The term "coagulation necrosis" is used to denote irreversible thermal damage to cells, even if the ultimate manifestations of cell death do not fulfill the strict histologic criteria of coagulation necrosis. Temperatures above 105°C cause tissue boiling, vaporization, and carbonization. These processes usually retard optimal ablation, because of the resultant decrease in energy transmission. Gas formation increases tissue impedance, which prevents deposition of the heating current (6). Thus, the aim of ablative therapy is to achieve and maintain a 50–100°C temperature range throughout the entire volume of the target tumor.

Hypoxic cells with limited blood supply such as those found in the center of necrotic tumors can be resistant to chemotherapy and external-beam radiation therapy, but might be more sensitive to RFA because of their increased sensitivity to heat in the hypoxic state, and because dissipation of heat is decreased due to poor tumor perfusion (8).

Multiple energy sources have been used to provide the heat necessary to induce coagulation necrosis. RFA utilizes an electromagnetic form of energy, radio waves, which emanate from the non-insulated distal portion of the electrode. Heat is produced by resistive forces (i.e., ionic agitation) surrounding the implanted electrode tip, as the radio waves find their ground, usually a foil pad attached to the patient's back or thigh (6).

Several strategies have been developed to improve tissue-energy interaction for optimal thermal ablation therapy. These can be classified as those permitting an increase in the total amount and rate of deposited energy (inserting multiple RF probes into the tissue, or cooling the tissues nearest the probe), those that improve heat conduction within the target (injection of saline and other compounds inside the tumor), and those that decrease tumor tolerance to heat (prior tumor cell damage; e.g., chemotherapeutic agents) (6).

Clinical indication

RFA is indicated in patients with early-stage (T1–T2, N0, M0) NSCLC who are not eligible for surgery because of coexisting morbidity; in patients with late-stage NSCLC; in patients who underwent surgical treatment for NSCLC and in whom tumor has recurred; and in patients with metastatic lung disease. Ablation must be targeted to each individual lesion, RFA is best suited for a small number (four or fewer) of slow-growing metastases. RFA may also be suitable for palliation of larger lesions causing symptoms such as cough, dyspnea, hemoptysis, or pain.

Materials and methods

At our institution, patients are referred for RFA therapy by their physicians, surgeons, or oncologists. Lung RFA is performed with approval from the institutional ethics committee, and in accordance with the ethical principles of the Helsinki Declaration. Written informed consent is obtained from each patient prior to treatment, after the risks and benefits of the procedure are fully explained.

Patients eligible for lung RFA must not be surgical candidates. Such patients include those with inoperable or non-resectable tumors, or those who have resectable lesions but cannot tolerate surgery due to poor general health, advanced age, or comorbid conditions such as poor cardiopulmonary reserve. The decision to exclude a patient from surgery must be made by a multidisciplinary team. Patients who have undergone pneumonectomy and present with a lesion in the remaining lung would be excluded from clinical trials involving RFA because of the high risk it would confer in such patients. Especially under these circumstances, RFA requires an experienced team and appropriate information for patients on the inherent risks of the procedure.

During an eighteen month period, we performed 55 RFA sessions under CT-guidance on 48 malignant pulmonary lesions (23 inoperable primary and 25 metastatic) on 35 patients. Diameter of the lesions ranged from 1.0 to 5.5 cm; there were 23 lesions ≤3 cm and 25 lesions >3 cm. Of the 48 lesions, 17 were located centrally, and 31 lesions were located peripherally. None of the lesions was invading the major vessels, the heart, or the trachea. Of the 23 primary carcinomas, nine were inoperable cases of early stage (IA, IIA, IB, IIB, IIIA) due to other comorbidities. The remaining were cases of advanced carcinoma.

Prior to the procedure, each patient underwent meticulous clinical examination, laboratory testing, imaging, and pulmonary function testing. Blood coagulation analysis is mandatory prior to the procedure. The following thresholds should have been achieved: platelet count >50,000/mL, and international normalized ratio <1.3. If the patient was taking warfarin sodium and/or acetylsalicylicacid, medication was withdrawn at least three days prior to therapy. The RFA procedure was performed by a consultant radiologist specializing in biopsies and liver RFA, and was performed on an outpatient basis, or with one-day hospitalization. No antibiotic prophylaxis was administered, although antibiotic prophylaxis is routine at some centers (9, 10).

In our department, we administer an analgesic agent 45 min prior to RFA. Patients receive 3 mg oral bromazepam, and 0.05 g pethidine hydrochloride by intramuscular injection to decrease anxiety prior to the procedure. This intervention lowers cost, decreases side effects, and achieves adequate analgesia, thus permitting the patient to tolerate the ablation with minimal pain. If pain is intolerable early in treatment, the generator may be turned down or off and the pain should abate in under 30 seconds. Treatment may then resume after more sedation is administered.

Our CT scanner is a Picker 5000® (Philips Medical Systems, Best, The Netherlands). We begin CT-guided RFA by placing the patient in the appropriate position (prone, supine, or lateral decubitus, depending on tumor location and route of approach). An initial scan of the desired area with 5 mm collimation is performed. The precise location and depth of the lesion in relation to the overlying skin is determined by inspection of the CT images. Thus, the appropriate skin entry for the procedure is chosen (the shortest, most vertical path that avoids bullae, interlobar fissures, pulmonary

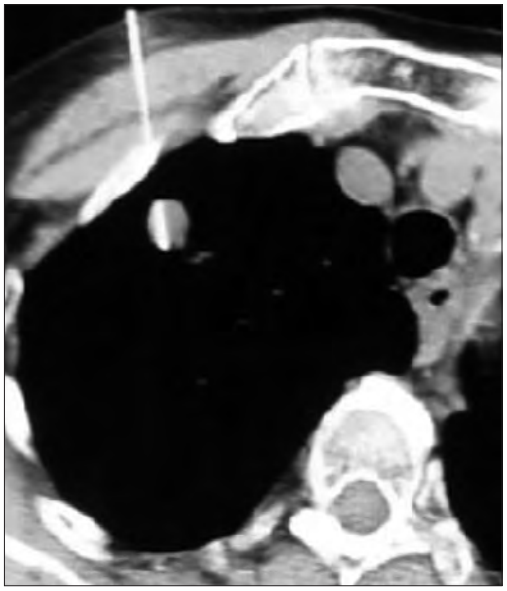

Figure 1. CT image shows a patient undergoing radiofrequency ablation. The tip of the device is inside the lesion.

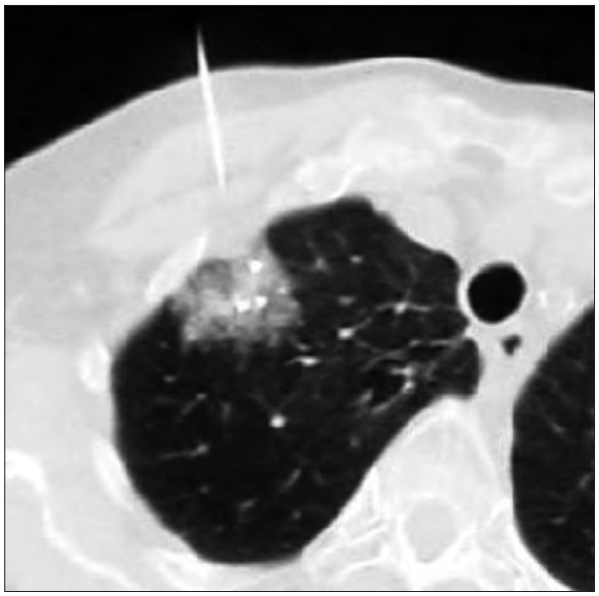

Figure 2. CT image of the same patient shown in Fig.1, at pulmonary window setting. The ablated lesion is surrounded by ground-glass opacification, and this represents an optimal result immediately after radiofrequency ablation.

vessels, and bronchi). The skin at the site of needle entry is prepared with povidone iodine 10% solution. A 22 G needle is then inserted through the skin as a marker, and three contiguous CT images are obtained to ensure that the point is appropriate. If so, local anesthetic (2% lidocaine hydrochloride) is then instilled through this needle for anesthetization of skin and subcutaneous tissue. The needle is then removed, and an incision is made with a surgical blade to facilitate insertion of the electrode cannula. After preparation is complete, two dispersive electrodes are applied to the patient's abdomen, back, or thighs, depending on the position of the patient.

We subsequently insert the device through the same skin entry site in a stepwise fashion, checking the tip of the trocar each time with three contiguous 5-mm CT images. After confirmation that the tip is placed approximately 1 cm proximal to the center of the target area, we slowly deploy the tines of the device (Fig. 1). After confirming correct positioning of the tip of the device with an additional 3-mm contiguous CT image, we connect the dispersive electrodes and the device to the RF generator.

Three types of expandable needle RFA models are used: RITA Medical Systems (Mountain View, California, USA), Boston Scientific (Watertown, Massachusetts, USA; formerly Radio Therapeutic Corporation, Mountain View, California, USA), and MIRAS (INVATEC S.r.l., Roncadelle, Italy). The controls are set at the desired settings at the start of the procedure, and are changed during the ablation according to each manufacturer's instructions. A pulsed RF is then applied for 12 to 20 min, causing a gradual local rise of the target temperature to 80–110°C, while the impedance of the lesion is continuously monitored during the procedure. To minimize patient discomfort (if necessary) and to reduce tissue overheating and vaporization (which results in greater coagulation), we also infuse 2% lidocaine hydrochloride through the infusion port (for the RITA model); for the other models, local anesthetic is infused through the skin incision. After the ablation is completed, the needle electrodes are retracted, and the device is removed.

Immediately after RFA is completed, we turn the patient to a supine position to image the ablation result and possible complications that may have occurred with a dual-phase CT acquisition following administration of contrast material. Successfully ablated lesions are surrounded by ground-glass opacification in the adjacent lung parenchyma, representing localized edema and hemorrhage (Fig. 2).

Any residual portion of a lesion enhancing more than 10 Hounsfield units (HU) after administration of contrast material post-ablation is regarded as an unablated (untreated) viable tumor (9), while previously enhancing but currently nonenhancing tumor areas are considered to represent RF-induced necrosis (11). Tumor necrosis is considered complete when the nonenhancing area at the treatment site has a diameter greater than or equal to that of the initially viable mass (9).

If a complication occurs (e.g., pneumothorax or hemorrhage), the patient returns to the depending position of the ablated lesion; otherwise, he/she remains supine. If the procedure is per-

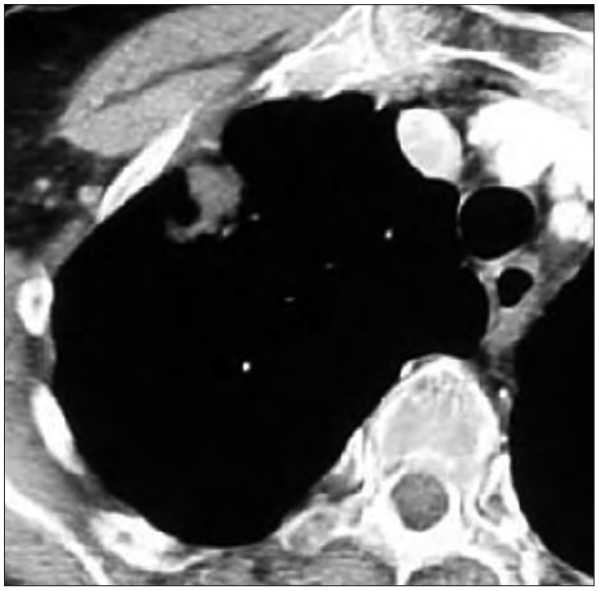

Figure 3. CT image of the ablated lesion of the patient shown in Fig. 1, at mediastinal window setting. The lesion is totally necrotized immediately after the radiofrequency ablation.

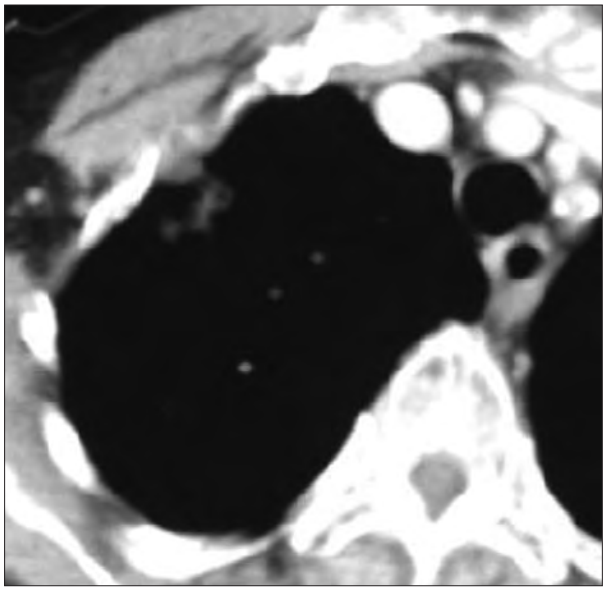

Figure 4. CT image obtained 6 months after radiofrequency ablation. The ablated lesion of the patient shown in Fig. 1 appears hypodense, unenhanced, and decreased in size. These findings indicate complete ablation.

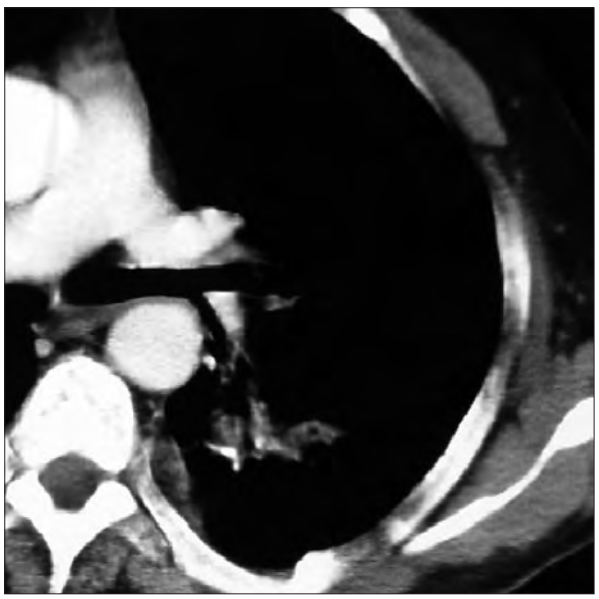

Figure 5. CT image obtained 6 months after radiofrequency ablation. These findings indicate complete ablation.

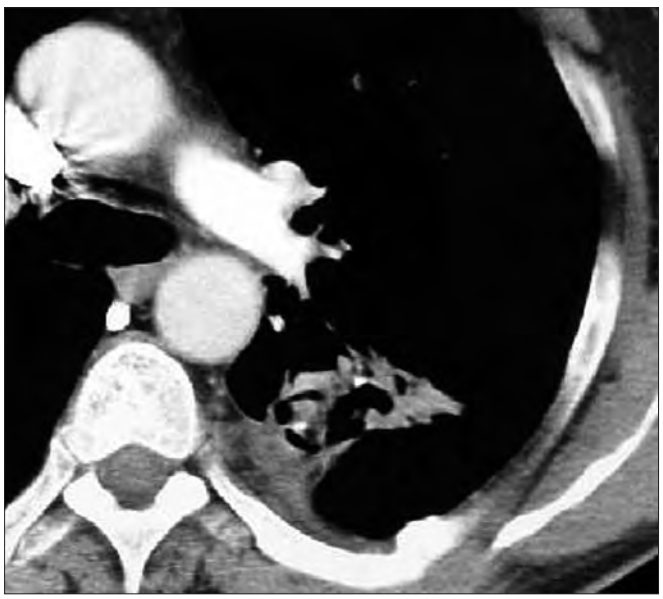

Figure 6. Contrast enhanced follow-up CT image at one year reveals local recurrence of the lesion shown in Fig. 5.

formed on an outpatient, the patient remains on a stretcher for observation for four hours, and then leaves with post-care instructions. Hospitalized patients are released the next day.

Follow-up was performed at one, three, and six months post-RFA and every six months thereafter.

Results

During the eighteen-month period, we performed 55 RFA sessions under CT-guidance on 48 malignant pulmonary lesions (23 inoperable primary and 25 metastatic) in 35 patients. Total necrosis was noted in 38 lesions (79.1%) of which 19 were primary (82.6%) and 19 were metastatic (76%) lesions (Figs. 3–5). In four primary (17.4%) and in six metastatic lesions (14%), partial necrosis was achieved, and a second RFA session was performed. All cases of partial necrosis involved tumors >3.5 cm. The follow-up demonstrated recurrence in seven lesions (14.5%) (four primary and three metastatic), which were treated with a new RFA session (Fig. 6). One-year survival rate was 94.2%. Mean survival was estimated at 14.2 ± 3.3 months.

Our patients generally experienced no major complications. We had only four cases of minimal complications (two pneumothoraces, one pulmonary hemorrhage, and one pleural effusion) that did not require treatment, and one pneumothorax that required intubation.

Discussion

The results of many clinical studies reported in the literature suggest that RFA can play a significant role in

the treatment of unresectable lung tumors, prolonging patient survival.

All cases of NSCLC involved patients who either could not undergo surgery because of comorbidities or advanced disease, or who refused to undergo surgery. Specifically, six studies included patients with NSCLC and metastatic lung disease originating from other primary tumors (9, 12–16), two studies included only patients with colorectal metastases (CRM) (17, 18) and four studies included only patients with inoperable NSCLC (19–22). Of the studies with patients with inoperable NCSLC, two included patients with stage I carcinoma (20, 22), whereas in our study the patients with primary lung tumors had stage II–IV disease (15). Numbers of patients in the above series ranged from 18 to 153.

The recent study conducted by Simon et al. (16) included the largest number of patients. These investigators presented data on long-term survival rates up to five years for primary (both early and advanced stage) and metastatic lesions and disease free survival rates and progression free intervals for lesions measuring <3 cm and >3 cm. Longest survival rates for patients with metastases were reported in the study conducted by Hiraki et al. (17), while Pennathur et al. (22) reported the highest 1-year survival rate for patients with stage 1 carcinoma.

A meta-analysis was not feasible because the studies did not follow a similar protocol, different ablation systems and algorithms were used, and tumor stage (including presence and extent of extrapulmonary disease) and tumor type (primary or metastatic), as well as endpoints of each study, were not uniform.

Akeboshi et al. (12) achieved a higher response rate (63%) in patients with pulmonary metastases compared with that achieved by chemotherapy (23, 24). However, long-term follow-up is required to show if RFA actually prolongs survival in patients with pulmonary metastases. In patients with primary lung cancer, fluorodeoxyglucose (FDG) accumulation disappears in 5% of patients after chemotherapy and in 9–33% after radiation therapy (25, 26). Akeboshi reported complete response in 46% of the primary lung tumors, suggesting that RFA may have a significant role in the treatment of unresectable primary lung cancer (12).

According to several studies (9, 12–14), there was better response of small lesions (<3 cm) to ablation. Complete tumor necrosis was significantly higher in tumors 3 cm or less, as compared with lesions greater than 3 cm. In the study by Rossi et al. (13), three patients whose post-treatment scans revealed incomplete radiological necrosis had lesions measuring 3.1–3.5 cm in diameter and underwent a second RFA session. The post-treatment CT scans revealed no residual enhancement. Ambrogi et al. (14) reported a higher response rate in metastatic lesions (70.8% vs. 56.4%) and in those smaller than 3 cm (69.7% vs. 50%), although neither reached statistical significance.

Akeboshi et al. (12) observed that the 1-year survival rate was higher in patients with primary tumors than in patients with metastatic disease, and higher in patients with tumors smaller than 3 cm; however, the difference was not statistically significant. As reported by Lee et al. (9), complete necrosis was attained in all six tumors smaller than 3 cm, versus 6/26 of larger tumors (23%). Lee et al. (9) also verified a trend toward greater survival rates in patients with small tumors, although the difference between the two groups did not achieve statistical significance. Simon et al. (16), however, found that the difference between the local tumor progression associated with large tumors (>3 cm) and that of small tumors (<3 cm) was significant (P = 0.002). Yamakado et al. (18) reported a significant difference in the local tumor progression rate between patients with small tumors (<3 cm) and those with large tumors (>3.1).

While Akeboshi et al. (12) reported no significant difference in the 1-year survival rate between patients with complete tumor necrosis versus those with residual tumor (81% vs. 91%, respectively; P = 0.92), Lee et al. (9) reported that mean survival in patients with complete necrosis was significantly longer than that in patients with partial necrosis (19.7 vs. 8.7 months, respectively; $P < 0.01$).

Simon et al. (16) found that survival rates from colorectal metastases are promising; however, because most of these patients received neoadjuvant and/or adjuvant chemotherapy, the sole effect of RFA cannot be reliably estimated.

It is encouraging that this therapeutic modality may help to improve quality of life for some patients (9, 27, 28). Belfiore et al. (28) found that clinical improvement in pre-treatment symptoms was observed in 12 of 29 patients seen at 6-month follow-up. In addition, Lee et al. (9) demonstrated excellent palliation of mild hemoptysis (80%), but relatively less satisfactory palliation of chest pain (36%), dyspnea (36%), and cough (25%). Although the palliative response rates were less than ideal, it is worth mentioning that this patient population had poor prognostic indicators, including advanced age (mean, 70 years), poor performance status, and prior treatment failure.

As observed by Jin et al. (29), the enhancement pattern and change in size of the ablated lesion are the most important CT findings of lung malignancy for determining whether a complete ablation has been achieved. In order to achieve complete ablation, the ideal is to ablate a peripheral margin of 0.5–1 cm of normal tissue surrounding the tumor, as well as the entire tumor itself (30, 31). Thus, the size of the ablated lesion immediately after the procedure usually appears larger than that of the tumor before ablation. Hypodensity, lack of contrast enhancement, and decrease in size (or no change in size) of the treated areas during follow-up are features suggestive of complete ablation (Figs. 4 and 5). On the other hand, various degrees of contrast enhancement of ablated regions represent viable residual tumor (8, 30, 31) that may progressively increase in size, thus indicating partial ablation (32). Reasons for the existence of residual tumor may be intrinsic heat-resistant properties of a tumor, and residual vascular flow, or reperfusion of an ablation zone (33). One should also keep in mind that surrounding inflammation after RFA affects apparent tumor size. It has been reported that apparent tumor size may increase at 1 week after RFA, probably as a result of surrounding atelectasis (31). For this reason, some authors suggest that lesion size is not a reliable measure of ablation efficacy (12, 33).

The ground-glass opacity surrounding the tumor is interpreted as pulmonary hemorrhage or hyperemia that has occurred during the ablation (30, 31). For complete ablation, the

ideal is to achieve complete peripheral ground-glass opacity surrounding the tumor, which is not always possible due to emphysema, large tumor size, and structures adjacent to the tumor margin such as a fissure, pleura, or a pulmonary vessel (32).

Suh et al. (33) observed that at the 3-month follow-up, there was an increase in contrast enhancement compared with that observed at the 1–2-month CT scan. Nevertheless, all enhancement profiles remained lower than those recorded before treatment. The authors attributed this relative increase in contrast enhancement to recovering circulation rather than to tumor growth. However, to distinguish conclusively between normal circulation and viable tumor, biopsy or long-term follow-up is necessary. In the same study, Suh suggests that densitometry of the lesion before and after RFA might be a reliable indicator of effectiveness of treatment.

Besides CT, FDG-PET has also been used to determine the therapeutic response after local treatment of lung cancer by radiofrequency in some of the above reported studies (12, 14–16, 22.). In the study by Akeboshi et al. (12), PET showed higher sensitivity and specificity than contrast-enhanced CT in the early period post-ablation to detect residual tumor. On the other hand, Belfiore et al. (28) suggest that CT scan follow-up in association with CT-guided biopsy are superior to CT findings alone in the assessment of treated lesions.

An important problem often encountered is that of treating lesions that are located adjacent to critical structures, such as major thoracic vessels, or that are difficult to approach (34, 35). In our opinion, it is not prohibitive to perform RFA in such difficult cases. However, the experience and the training of the operator are crucial in minimizing side effects.

Generally, the RFA procedure is followed by an acceptable rate of complications that can be managed with relative ease. Pneumothorax is a very common complication. Increased incidence of pneumothorax is associated with central location of the tumor, chronic obstructive airway disease/emphysema, and multiple electrode insertions (9). If possible, therefore, the needle path should minimize the amount of lung that must be traversed to avoid crossing large bullae or interlobar fissures. However, patients suffering from emphysema can tolerate RFA (15), although in such cases it is very important that the procedure be performed by experienced and well-trained operators. Pneumothoraces are usually small (9, 27, 32–34) and when less than 30%, they require no intervention. However, in patients with underlying lung disease, even small scale pneumothoraces (less than 30%) may require evacuation.

Post-procedural pleurisy and small pleural effusions are observed mainly in patients with pleural-based and peripheral lesions, but thoracentesis is usually not required, because these lesions are self-limited (9, 33, 34, 36). Cough productive of brown sputum lasting 1–2 weeks after ablation is observed in a small number of cases (36). Mild to moderate pain may be present in the majority of patients during the procedure (9). For energies greater than 100 W, ablation of central lesions abutting large bronchi resulted in intractable cough in some patients (34).

Major complications include massive hemorrhage and hemoptysis, pulmonary abscess, and broncho-pleural fistula (9, 12, 33, 37).

Our patients experienced a 1-year survival rate similar to that reported by Pennathur et al. (22) for patients with NSCLC stage 1, and by Hiraki et al. (17) for patients with metastases. We believe that experience of the interventionalist, and patient tolerance and cooperation are the most important factors determining the clinical results and the rate of complications. We have been performing the RFA in cases of early unresectable lung cancer, in cases of advanced disease, in recurrences post surgery, and in metastatic lesions as indicated. We exclude patients who have numerous lung lesions (usually > 5) and patients with lesions surrounded by emphysematous parenchyma. Patients who are not co-operative are also excluded. Large tumors are not a contraindication; however, patients with large tumors will require more than one session). Duration of RFA ranges between 10 and 20 min, depending on the type of electrode and the size of the tumor.

We try to avoid multiple paracenteses, in order to reduce the risk of pneumothorax, and we choose the shortest route, avoiding crossing lung parenchyma as much as possible. RFA is always performed also on the needle track as a precaution at the end of the RFA procedure in order to avoid seeding along the electrode route. In addition, we always perform the RFA sessions under sedation using the aforementioned antidepressant and analgesic medication. In this way, the patient can follow instructions and cooperate in order to achieve optimal results.

Although the initial results concerning technical feasibility, therapeutic response, short-term survival, and rate of complications are encouraging, the long-term clinical benefits of RFA for the treatment of malignant tumors are still to be proven. Improvements in radiofrequency equipment, ablation techniques, and imaging follow-up procedures would contribute to better results.

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