Radiofrequency Ablation of Primary Lung Cancer*

Results From an Ablate and Resect Pilot Study

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Study objectives: The role of radiofrequency ablation (RFA) for primary lung cancer remains poorly defined. The purpose of this “ablate and resect” pilot study was to evaluate the safety of performing RFA in patients with primary non-small cell lung cancer (NSCLC) and to characterize the histologic changes in tumor tissue following such ablation.

Design: This prospective study was undertaken at a single institution, and 10 patients were accrued from June 2002 to June 2003. Eligible patients included those with clinical stage I or II disease. RFA of the tumor was performed through a standard thoracotomy followed by conventional lobectomy and lymph node dissection. Extent of cell death was determined histologically.

Measurements and results. Following the exclusion of two patients, the treated portions of eight tumors were examined for tumor cell viability. Gross inspection and routine histologic staining could not reliably identify the “immediately ablated” tissue. However, using a supravital staining technique, the treated areas from seven of the eight tumors (87.5%) demonstrated > 80% nonviability (100% nonviability was noted in the treated areas from three of the eight tumors). No bleeding or thermal complications were noted at the time of RFA, and none of the patients had skin burns at the electrode dispersive pad sites.

Conclusions: RFA of primary NSCLC is feasible and can be performed safely in the setting of an open thoracotomy. Complete tumor cell necrosis, as determined by supravital staining, was noted in the treated areas from three of eight tumors (37.5%). Such complete ablation was observed in the treated areas from smaller tumors (< 2 cm), whereas the treated areas from larger tumors demonstrated incomplete ablation. Additional investigation with histopathologic correlation is needed to fully assess the long-term efficacy of RFA for NSCLC.

(CHEST 2005; 128:3507–3511)

Key words: lung cancer; pathology, lung; radiology intervention; surgery

Abbreviations: H&E = hematoxylin-eosin; NADH = nicotinamide dinucleotide-diaphorase; NSCLC = non-small cell lung cancer; RFA = radiofrequency ablation

Primary lung cancer is among the most commonly occurring malignancies in the world and represents the most common cause of cancer-related death in the United States. In addition, the lungs are the second most frequent site of metastatic disease from extrathoracic cancers and are the only site of metastatic disease in 20% of those cases.1,2

Conventional treatment strategies for patients with malignant lung tumors include surgery, chemotherapy, and radiation. Optimal treatments for unresectable primary lung cancer, local recurrence of lung cancer within a previous radiation field, pulmonary metastases, and small lung cancers (< 1 cm) have not been elucidated.3 Alternative forms of local therapy include stereotactic radiation therapy, cryoablation, radiofrequency ablation (RFA), and chemical ablation.

RFA has been used for unresectable liver lesions with success.4 However, its role in the treatment of lung cancer is evolving with as-yet insufficient data on long-term effectiveness. At present, most clinical...
reports\textsuperscript{3–7} of RFA-treated lung tumors have described percutaneous techniques in patients with multiple pulmonary metastases who are not candidates for surgery because of limited lung function or medical comorbidities. In these studies,\textsuperscript{3–7} the effect of RFA on the tumor is generally measured using imaging-based surrogate end points rather than histologic analysis. Although several authors\textsuperscript{8–10} have performed percutaneous biopsies in order to detect persistent or recurrent cancer, there are no guidelines regarding timing of biopsy in the post-RFA setting or data regarding its accuracy. Therefore, it is difficult to determine the true clinical efficacy of RFA, especially since reported follow-up tends to be short and some recurrences may go undetected.

Our study was designed to investigate the histopathologic changes on tumor tissue following RFA, since such information is lacking in the clinical literature on the use of RFA to treat lung tumors. We designed an “ablate and resect” pilot study and enrolled only patients with early stage (resectable) primary non-small cell lung cancer (NSCLC). Following ablation of tumor tissue after a single electrode deployment, we resected the lobe containing the RFA-treated tumor, providing the patients with standard treatment for lung cancer and the pathologist with the entire tumor for histologic analysis including supravital staining techniques.

\section*{Materials and Methods}

\subsection*{Entry Criteria}

This study was a single institution, prospective, single-arm study. Patients were required to meet the following criteria for participation. All of the patients had to be $\geq 18$ years old with documented clinical stage I or II disease. Histologic proof of NSCLC had to be obtained preoperatively or intraoperatively via needle biopsy. Eligible patients were deemed to have adequate pulmonary physiologic reserve so as to tolerate anatomic resection. The location of tumor was such that lobectomy would remove all gross tumor with grossly negative margins.

Criteria for exclusion included the following: (1) age < 18 years; (2) suspected clinical stage III or IV disease; (3) pretreatment chemotherapy or radiation therapy; (4) preoperative or intraoperative proof of malignancy not obtained; (5) centralized tumor not amenable to lobectomy; and (6) resection required greater than lobectomy. Patients were accrued over a 12-month period from June 2002 to June 2003. Approval for this study was obtained through the Internal Review Board of our institution on March 26, 2002. Each patient within this pilot study gave informed consent prior to participation.

\subsection*{Surgical Procedure and RFA Technique}

Tumors were ablated with a radiofrequency ablation system (RF 3000; Boston Scientific Corporation; Natick, MA) and a needle electrode (LeVeen; Boston Scientific Corporation; either 3.0 cm or 3.5 cm depending on tumor size). The needle introducer utilized was 15 gauge in diameter, and patient grounding was achieved by placing two electrosurgical dispersive pads on each thigh.

RFA was performed at the time of thoracotomy. Patients underwent general anesthesia and were intubated with a double-lumen endotracheal tube. A standard posterolateral thoracotomy was performed, and ventilation of both lungs was maintained throughout the entire ablative procedure. The tumor was identified by careful palpation, and the pulmonary vessels were dissected in preparation for resection.

Through the thoracotomy incision, the needle electrode was placed into the tumor. Electrode placement was verified by palpation. An attempt was made to include the entire tumor within the span of the electrode array. For the purpose of this study, all tumors regardless of size were treated with a single placement of the electrode. Multiple overlapping zones of ablation were not created. Thus, only a portion of larger tumors was ablated. Radiofrequency energy was applied using a standard two-phase algorithm according to the protocol of the manufacturer for treating lung tumors. RFA was initiated at a power of 10 W and increased in 5-W increments until the system impedance rose $>400$ ohms. The ablation session was terminated when a sudden loss of impedance was noted in the treated tissue (“roll-off”), suggesting complete tissue necrosis. A second round of RFA was administered in the same location after waiting for 30 s and continued until a second “roll-off” was noted.

The power and impedance were monitored continuously during the RFA process. The power at the time of attaining the critical tissue impedance was recorded in all patients. The total time needed to complete the two-step algorithm treatment was recorded in all patients. After completion of RFA, the electrode array was retracted into the introducer, and the introducer was withdrawn from the lung parenchyma. Any evidence of bleeding and/or thermal injury along the needle/introducer tract was noted. Subsequently, a standard lobectomy and lymph node dissection were performed.

\subsection*{Pathologic Examination}

The resected specimens were transported immediately to our pathology laboratory and evaluated by the pathologist. The size of the ablated tumor was measured, and the lung parenchyma was bisected centrally along the tract created by the electrode array (Fig 1). The tumor and surrounding lung tissue were then serially sectioned in a “bread-loaf” fashion on either side of the electrode tract at 5-mm increments. Sectioning continued 1 cm beyond the gross lesion.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Lobectomy specimen bisected centrally along the RFA tract. CM = centimeters.}
\end{figure}
Representative sections were fixed in formalin, embedded in paraffin, sectioned, and stained with hematoxylin-eosin (H&E). The mirror-image section was then processed for nicotinamide dinucleotide-diaphorase (NADH) cell viability. This cell viability stain utilizes the reduction of nitroblue tetrazolium chloride by cells expressing NADH. Therefore, viable cells stain blue. The sections selected for NADH staining were immediately snap frozen in liquid nitrogen, stored at −75 C, and sent to the University of California, Davis, via overnight express for processing. Our pathologist reviewed both H&E and NADH specimens, and the percentage of cell nonviability in areas of tumor treated with RFA was assessed.

**RESULTS**

A total of 10 patients were enrolled in our study. However, two patients were excluded from analysis. In one patient, a diagnosis of cancer could not be obtained prior to lobectomy; in another patient, the NADH supravital staining was incorrectly performed. Information regarding the eight remaining patients is depicted in Table 1. There were six men and two women (mean ± SD age, 63.5 ± 6.2 years). Seven of the eight patients presented with clinical stage I. Histologic examination revealed five patients with adenocarcinoma and three patients with squamous cell carcinoma (Table 2). The average number of processed sections per tumor specimen was 4.5 ± 0.4. Mean tumor dimension was 2.2 ± 0.6 cm, with six of the eight tumors having a dimension ≤ 2.0 cm. The mean dimension of the RFA lesion was 3.0 ± 0.5 cm. Median time of RFA was 12 min, 9 s (range, 8 min, 22 s to 15 min, 57 s).

Gross examination of RFA-treated areas demonstrated a failure of the electrode array to encompass the entire tumor in five of eight cases. In addition, a distinct zone of ablation was absent in all of the specimens. Routine H&E staining of treated areas could not differentiate viable from nonviable cells. NADH supravital staining was the only histopathologic method capable of differentiating viable from ablated tissue (Table 2). Successful ablation of tumor cells was noted in 37.5% of the treated areas (from three of the eight tumors). All three of these tumors were ≤ 2 cm in greatest dimension. Incomplete ablation, defined by the presence of viable tumor cells within zones of tumor cell nonviability, was noted in the treated areas of the other five tumors. Examination after NADH staining demonstrated that the RFA-treated areas from four of five tumors demonstrated ≥ 80% nonviability. In one patient (patient 7), several NADH-stained sections from the RFA-treated area revealed viable tumor cells within a larger area of nonviable tumor (estimated < 80% tumor ablation).

All patients tolerated the RFA procedure without complications. No patient had hemoptysis during RFA, and no additional hemorrhage was noted during insertion or removal of the needle electrode. There were no thermal injuries to adjacent structures within the chest or at the site of the grounding pads. Following RFA, standard lobectomy and mediastinal lymph node dissection were performed in all patients. No increased incidence of postoperative bronchopleural fistula or prolonged air leak was seen in these patients.

**DISCUSSION**

Standard surgical resection and lymph node dissection remain the foundation for the treatment of early stage NSCLC and isolated pulmonary metastases. Alternative strategies for local control of early stage NSCLC, such as limited resections and high-dose radiotherapy, are less effective. Parenchymal sparing resection for primary lung cancer is associated with increased rates of locoregional recurrence. Furthermore, outcome data for medically inoperable early stage NSCLC treated with standard radiotherapy alone suggests variable response rates with local failure rates of 42 to 44%. Although the clinical experience of using RFA in the management of hepatic malignant tumors is evolving, its role in the treatment of lung malignancies remains poorly defined. Most of the percutaneous lung RFA studies to date have used radiographic rather than histopathologic end points to measure therapeutic responses. Even when percutaneous biopsy of RFA-treated lung was employed, its use was inconsistent and typically reserved for equivocal findings on CT or positron emission tomography scans. To our knowledge, this pilot study represents the largest experience with an ablate and resect model in patients with resectable primary NSCLC. RFA was safely performed through a thoracotomy on noncentrally located primary lung tumors. All tumors were resected via lobectomy and immediately processed.
NADH supravital staining, not routine H&E, proved to be the most reliable method of determining lung cancer cell nonviability in the “immediately ablated” tissue. Examination of RFA-treated areas from each tumor demonstrated regions with > 80% nonviable tumor cells in seven of eight cases. RFA-treated areas from three of these seven tumors demonstrated 100% nonviable tumor cells and were obtained from tumors ≤ 2 cm in greatest dimension. Evidence of incomplete ablation was noted in the RFA-treated areas of the remaining tumors and was especially evident in one patient. Technical explanations for this inconsistent ablation include improper electrode size selection, failure to completely encompass the tumor with the electrode array, and duration of RFA. The total time for RFA in this particular patient was only 7 min, 55 s (below the lowest range of the 95% confidence interval), suggesting insufficient time for ablation.

An important technical feature of this study is the dependence on palpation for electrode placement within the tumor. Precise deployment of the electrode array within the center of the tumor without radiologic guidance proved difficult and may explain the incomplete ablation in the other < 2 cm tumors. Intraoperative ultrasound, which is used to guided electrode placement in liver RFA, is ineffective on lung tissue due to interference of air on sound-wave reflection. However, CT-guided placement of the RFA electrode may provide more accurate information regarding its location within the center of the tumor. In addition, achieving complete tumor encompassment by the electrode array may be facilitated by the availability of newer electrodes (range, 2 to 5 cm), which may produce more accurate ablation zones.

Another limitation of this study relates to the histopathologic processing of “immediately ablated” RFA lung specimens. Although it has proven reliable in the analysis of liver RFA specimens,18–20 routine histopathologic processing of lung RFA tissue in our study failed to reliably identify the margins of the zone of ablation. This finding may be explained by the kinetics of tissue necrosis. Animal models of RFA suggest that the full extent of lethal injury following ablation occurs 24 to 72 h after treatment.21,22 Therefore, the performance of lung tissue analysis by routine staining techniques immediately following RFA may underestimate the full treatment effect.

In our ablate and resect series, RFA appears to be a safe and feasible technique for ablating primary NSCLC. However, only 37.5% of the RFA-treated tumor areas demonstrated complete necrosis with supravital staining after open RFA. With the methodology employed in our study, current results with RFA are likely to be inferior to surgical resection. Yet, we hesitate to conclude that treatment of lung tumors solely with RFA would be associated with an increased local recurrence rate based on this study alone because the study design did not call for multiple ablations of larger tumors. Although the success rate of ablating < 2 cm lesions in our study was only 50%, results of other studies6,10,17 suggest that RFA is more effective for smaller tumors. Should future studies consistently confirm complete tumor cell necrosis on histopathologic analysis, RFA may become an alternative treatment for T1N0 NSCLC, small pulmonary metastases, and local recurrence in patients who either refuse surgery or who are considered poor surgical candidates.

### References