Radiofrequency ablation to treat non-small cell lung cancer and pulmonary metastases

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Radiofrequency ablation is being reported with increasing frequency for the treatment of lung tumors. Several studies have demonstrated that this is a feasible and safe approach. Intermediate outcomes are now becoming available. Although tumors up to 5 cm in size can be effectively treated with radiofrequency ablation, results are better for smaller tumors (3 cm or less). This review describes the techniques, available ablation devices, and the potential role of radiofrequency ablation for non-small cell lung cancer (NSCLC) and pulmonary metastases. Resection (lobar or sublobar) should remain the standard therapy for NSCLC. Radiofrequency ablation may be better than conventional external-beam radiation for the treatment of the high-risk individual with NSCLC. Preliminary results for pulmonary metastases are similar to those reported after resection. In addition, patients with pulmonary metastases have been demonstrated to develop recurrences even after thoracotomy and bimanual palpation of the lung. Radiofrequency ablation may be an alternative to resection for the patient with small-diameter pulmonary metastases, and future study of this may be indicated.

Radiofrequency ablation (RFA) is a relatively new modality that has been successfully used for the treatment of hepatic tumors [1]. During the past few years, an increasing number of reports have described the use of RFA for treatment of malignant lung nodules [2, 3]. Most reports have demonstrated the feasibility of this technique; however, studies with intermediate follow-up are now being reported with increasing frequency [4–6]. As RFA becomes more widely applied in clinical practice, it is important that thoracic surgeons become familiar with this therapeutic modality, its application, and its limitations. This review provides an overview of the technique, indications, and current results of RFA.

Technique

Radiofrequency energy consists of an alternating current that moves from an active electrode that is placed within a tumor to dispersive electrodes (electrosurgical return pads) that are placed on the patient. Radiofrequency ablation systems therefore consist of three components: a generator, an active electrode, and dispersive electrodes. As the RF energy moves from the active electrode to the dispersive electrode and then back to the active electrode, ions within the tissue oscillate in an attempt to follow the change in the direction of the alternating current. This results in frictional heating of the tissue. As the temperature within the tissue becomes elevated beyond 60°C, cells begin to die. It is this phenomenon that causes the region of necrosis surrounding the active electrode.

The advantage of such a thermal intervention system is the capacity to heat tissue to a lethal temperature in a specific anatomic location. This allows for destruction of tumor tissue with minimal damage to surrounding normal tissue, which is particularly important for the patient with pulmonary compromise.

Animal models have been used to investigate the efficacy and feasibility of this technique in lung tissue. Goldberg and colleagues [7] generated a model of lung tumors by infiltrating the pulmonary parenchyma of 11 rabbits with VX2 sarcoma cell suspensions. Seven lesions were treated with RFA for 6 minutes at 90°C, and the remaining 4 tumors were untreated for control. The authors noted computed tomography (CT) scan evidence of coagulation necrosis surrounding the tumor, manifested by increased opacity enveloping the lesion. Histologic analysis revealed that at least 95% of the tumor nodules were necrotic, although some rabbits (43%) had residual tumor nests at the periphery of the tumor.

In another study, Miao and colleagues [8] implanted VX2 tumor tissue in the lung of 18 rabbits (12 treated and 6 controls), and the lesions were then treated with RFA using a cooled-tip electrode for 60 seconds. Efficacy of therapy was followed up with magnetic resonance imaging (MRI), microangiography, and histopathology. Abso-
lute tumor eradication was achieved with RFA in 33% and a partial response in 41.6% of rabbits that survived longer than 3 months. On histopathologic evaluation, the ablated lesion retained its tissue architecture, but with changes consistent with coagulation necrosis with surrounding edema and inflammation of normal surrounding lung. After 1 to 3 months of treatment, the ablated tumor became an atrophied nodule of coagulation necrosis within a fibrotic capsule. The timing and progression of these postablation changes becomes an important issue when treatment response after RFA in patients is evaluated.

Currently, three RFA systems have been approved by the United States Food and Drug Administration for the ablation of soft tissue. These are the Boston Scientific (BOS; Natick, MA), RITA (RITA Medical Systems, Fremont, CA), and Valleylab (VL; Boulder, CO) systems. The BOS and RITA probes contain multiple tines that are expanded within the tumor nodule being ablated. The VL probe consists of either a single needle, or a cluster probe of 3 parallel needles, that is placed into the tumor nodule. The VL probe is also known as the cool-tip probe because the tip of the probe is infused with cold water to prevent charring around the probe as the tumor is heated. Some of the RITA probes allow perfusion of small amount of saline into the tissue that is being ablated. The ions within the saline increase conduction and allow a more rapid and efficient heating of the tumor.

The BOS device is an impedance-based device. The tumor is slowly heated, with power increased at 1-minute intervals, until the impedance rises to a high level that prevents further heating of the tissue. The RITA system is a temperature- and time-based device. With this system, the multiple tines are serially expanded at 1-cm intervals to the target diameter. Temperature is continuously monitored, and the tumor is cooked at a temperature of 90° at each deployed size. The VL system is also an impedance-based device; however, unlike the BOS system, it is also possible to measure temperature during the procedure.

There have been two animal studies involving ablation of the liver [9, 10]. Of interest is that the two reports had different conclusions. In one study involving 16 pigs, ablation length and volumes were significantly less with the expandable probes compared with the cool-tip probes [9]. The other study used both an in vivo and ex vivo component, and the expandable probes (BOS and RITA) were seen to be superior, with larger volumes and more spherical ablation zones compared with the VL system [10].

A recent study from Japan reported results after RFA of 342 pulmonary tumors in 128 patients [11]. The VL probe was used for 200 tumors nodules, and the BOS probe was used for 142. On multivariate analysis, larger tumor size (> 2 cm) and use of the VL probe were associated with local progression. It should be noted, however, that most of the VL ablations were performed with the single-needle probes. Only five of 200 were performed with the cluster probes, which allow for a wider area of ablation. Further studies specifically looking at lung ablation will need to be performed to better determine this issue.

Although RFA can be performed in the operating room with thoracotomy, most cases can and should be performed percutaneously with CT guidance, because ablation is usually used in patients with marginal lung function. Procedures can be performed under sedation or with general anesthesia. Thoracic surgeons familiar with performing video-assisted procedures should be able to master the skills required for percutaneous placement of ablation probes.

One technique involves using a thin (22-gauge) spinal needle to determine the trajectory and subsequent placement of the larger-diameter RFA probe. Other techniques involve using an external skin marker or CT fluoroscopy to directly place the ablation probe into the target tumor. Probe size is selected according to the diameter of the target lesion. We generally strive to achieve an ablation at least 1 cm greater in diameter than the maximum diameter of the cancer; therefore, an active electrode that will ablate to at least 1 cm larger than the maximum diameter of the tumor is usually selected.

### Indications

**Lung Cancer**

The primary treatment for patients with stage I or II non-small cell lung cancer (NSCLC) is resection. For this reason, a thoracic surgeon should initially determine whether the patient is a candidate for lobar or even sublobar resection before proceeding with RFA or referral to another physician for the procedure. It is reasonable to use RFA as a single modality for stage I cancer; whereas RFA should be used in combination with another therapy for stage II or above because the ablation will not address any nodal disease that may be present. Radiofrequency ablation will be more effective for smaller tumors. In a previous study using the BOS system, we found that RFA was ineffective for tumors greater than 5 cm in maximum diameter [12].

Biopsy should be performed before the RFA to confirm the diagnosis of cancer; however, in some high-risk patients, it is better that the patient undergo the risk of the biopsy and RFA in one setting. The disadvantage of this approach is that this adds time to the procedure, and sometimes parenchymal hemorrhage will occur around the tumor that will make it difficult to then localize the tumor for subsequent ablation. Occasionally, if a lesion is suspicious by CT and positron-emission tomography (PET) scans and the pathologist is unable to make a diagnosis of cancer at the time of biopsy, we will proceed with ablation rather than subject the patient to further biopsy and general anesthesia.

Radiofrequency ablation is suitable for lesions in the outer two-thirds of the lung parenchyma. Ablation in the inner one-third should be approached with caution and should be avoided for any lesion abutting a hiliar blood vessel. We have previously reported a patient who died from massive hemoptysis several days after RFA of a...
central lung nodule [12]. This same patient had also received brachytherapy for an endobronchial tumor after the RFA. Although we cannot be certain whether it was the RFA or the brachytherapy that resulted in death, we remain concerned about ablating these central lesions.

External-beam radiation has traditionally been used for high-risk patients with NSCLC, but outcomes have been poor. In one study of 71 node-negative patients who received at least 60 Gy to their cancers, survival was 19% at 3 years and 12% at 5 years [13]. In another report of 60 patients with stage I and II cancers, local progression occurred in 53% of patients, with a median progression-free survival of 18.5 months and overall median survival of 20 months [14].

It could be argued that most patients with significant cardiopulmonary compromise will likely die of their comorbid diseases and that the benefits of treating an asymptomatic early-stage cancer are minimal. In a study of 128 patients with stage I and II NSCLC, median survival was 46.2 months in patients undergoing resection, 19.2 months in patients undergoing radiation, and 14.2 months in patients who received no therapy [15]. Cancer was the cause of death in 53% of the 49 patients who had no therapy, whereas it was the cause of death in 43% of the 36 patients treated with radiation.

In a study analyzing results from 30,790 patients in the Surveillance Epidemiology and End Results (SEER) database, 4357 patients (14.1%) who did not have an operation were identified [16]. Survival in stage I patients who had radiation was significantly \( p = 0.0001 \) better compared with those who had no therapy (21 vs 14 months). Stage II patients also demonstrated a significantly \( p = 0.001 \) superior survival in the radiation group compared with the no treatment group (14 vs 9 months). Multivariate analysis also demonstrated that radiation was associated with better lung cancer-specific survival.

These data support the continued use and development of low-morbidity therapies to treat NSCLC in high-risk patients. There are a significant number of such patients. The SEER study demonstrated that about 14.1% of patients with early-stage disease are not candidates for operation. Another study also reported that among a group of 14,555 stage I and II NSCLC patients, 15.7% did not undergo resection [17], which increased to 30.4% in patients aged older than 75 years.

**Pulmonary Metastases**

The benefits of resection of pulmonary metastasis have been demonstrated in several retrospective studies. Patients most likely to benefit from intervention are those in whom local control of the primary tumor has or can be achieved, who have experienced a long disease-free interval from the primary tumor resection, who do not have any extrathoracic metastases, and who have a limited pulmonary metastatic burden that can be completely resected [18]. In the International Registry of Lung Metastases trial of 5206 patients, the 5-year survival was 45%, with a disease-free interval of 36 months or more [19].

As with NSCLC, RFA can be used to ablate pulmonary metastases but should be reserved for patients who are considered to be at increased operative risk. We have also found RFA to be useful for patients presenting with recurrent metastatic disease after a previous thoracotomy because it avoids some of the morbidity of a redo thoracotomy. This approach can be justified because these patients have already demonstrated more aggressive tumor biology and have at least a 60% chance of presenting with recurrent disease after a redo resection [20].

We have also found RFA to be a useful adjunct when treating a patient with multiple metastases. Wedge resection of peripherally located metastases and RFA of the more central metastases can be undertaken to avoid performing a lobar or larger resection. In this instance, RFA would be performed using an open approach to ensure that no injury occurs to the pulmonary vasculature or a major bronchus.

One of the difficulties in assessing therapeutic results for pulmonary metastases is the variable biologic behavior of different tumor types. Most reported series include a mixture of different primary tumors rather than a single tumor type. Probably the best tumor type to help determine the relative role of resection and ablation of pulmonary metastasis is with colorectal cancer. Colorectal cancer is the second most common visceral malignancy in the United States, with approximately 130,000 cases per year. The lungs are the most common site of extra-abdominal disease. Approximately 30% of patients with colorectal cancer have pulmonary metastases, and in about 2% to 4%, these metastases are isolated [21, 22].

Thoracotomy and resection is an acceptable approach for patients with metastatic colon cancer to the lungs. Survival in one series of 144 patients was 40% at 5 years and 30% at 10 years [23]. A more recent report of 153 patients who also underwent thoracotomy for resection of colorectal metastases demonstrated similar early results, with survival of 64% at 2 years and 37% at 5 years [24]. In another series, 80 patients with colorectal metastases underwent video-assisted thoracic surgical resection [18]. Mean survival was 30.4 months for patients with single tumors compared with 26.5 months for patients with multiple tumors.

**Results of Radiofrequency Ablation**

An international study of RFA combined results from 7 centers around the world providing initial outcomes in 493 patients [25]. Two deaths were reported in this combined series. The most common complication was pneumothorax in 30% of patients. Pleural effusion occurred in less than 10% of patients.

In our initial series of RFA, 33 tumors were treated in 18 patients [12]. At a mean follow-up of 6 months, a radiographic response was seen in 66% of patients with tumors 5 cm or less compared with only 33% in patients with tumors larger than 5 cm. Similarly, 33% of the patients with tumors 5 cm or less died during follow-up compared with 66% of patients with larger tumors. For
this reason, we have limited RFA to tumors of 5 cm or less.

Lung Cancer
In 2005 we reported our results in treating 18 NSCLC patients with RFA, 9 of whom had stage I cancers [4]. The median tumor diameter was 2.8 cm. Fifteen patients (83.3%) were alive at a median follow-up of 14 months.

A problem that is challenging after RFA is assessment of treatment response. There is usually a residual mass associated with some degree of scarring after RFA. In some cases, this scarring may involve a larger area than the original tumor. Results of PET sans may continue to be positive, making it difficult to assess whether viable tumor or scarring is present.

In the 2005 study of 18 NSCLC patients, we used a modification of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria to assess tumor progression after RFA [4]. Because the inflammatory changes after RFA usually start to subside by 3 months, the 3-month scan is often more useful as a new baseline scan against which local progression can be judged. For stage I cancers, the mean progression-free interval was 17.6 months. The median progression-free interval was not reached, with only 3 patients (33%) demonstrating local progression. Morbidity occurred in 10 patients (55.6%) but was minor in most cases. The most common complication, the need for a chest tube or pigtail catheter for pneumothorax, was required in 7 patients (38.9%). The median duration of the chest-tube was less than 24 hours (range, 0 to 14 days). Prolonged air leak (> 4 days) occurred in only 1 patient (5.6%). A pulmonary embolus developed in 1 patient (5.6%) and pneumonia developed in 2 patients (11.1%) after RFA; however, both cases occurred after open rather than percutaneous procedures.

More recently, these results have been updated in a group of 19 stage I NSCLC patients [5]. Median percentage of forced expiratory volume in 1 second for these high-risk patients was 29%. During follow-up, local progression occurred in 8 patients (42%). The median time to progression was 27 months. There were no procedurally related deaths, and 6 patients died during follow-up. The estimated probability of survival at 1 year was 95%.

A large multicenter study known as the Radiofrequency Ablation of Pulmonary Tumors Response Evaluation (RAPTURE) trial included 106 patients [26]. Although not yet published, these results provide additional outcomes for both lung cancer and metastatic colorectal cancer. This study comprised 33 NSCLC patients. The 2-year overall survival was 48%; however, most of these high-risk patients were dying from non-cancer-related causes, as indicated by their cancer-specific survival, which was much higher at 92%.

The long-term outcomes in a cohort of 153 patients were recently reported by Simon and colleagues [6]. This study included 75 stage I NSCLC patients, who had a median survival of 29 months. Overall survival at 1, 2, 3, 4, and 5 years was 78%, 57%, 36%, 27%, and 27%, respectively. Local tumor progression was reported for all tumors rather than by tumor type. The key finding was that there were differences in local control between tumors 3 cm or less in size compared with tumors larger than 3 cm. In the patients with smaller tumors, median time to progression was 45 months, and progression-free rates at 1, 2, 3, 4, and 5 years were 83%, 64%, 57%, 47%, and 47%, respectively. In the patients with larger tumors, median time to progression was 12 months, and the progression-free rates at 1, 2, 3, 4, and 5 years were 45%, 25%, 25%, 25%, and 25%, respectively. One factor that may have affected these results is that all ablations were performed using the single-needle or cluster-tip VL probes, which may not as effective for tumors larger than 3 cm.

These results are considerably worse than that reported after resection, and surgical resection (lobar or sublobar) should continue to remain the standard of care for NSCLC. On the other hand, these preliminary results are potentially superior to those of conventional radiation and support further investigation of RFA for the high-risk patients with NSCLC.

Pulmonary Metastases
The study by Simon and colleagues [6] of 153 patients included 18 patients with colorectal metastases who underwent ablation, and 57% were alive at a median follow-up of 27 months. Overall survival at 1, 2, 3, 4, and 5 months was 87%, 78%, 57%, and 57%, respectively. The RAPTURE trial also included a relatively large cohort of 53 patients with colorectal metastases [26]. Overall 2-year survival was 62%, and cancer-specific survival was better at 82%.

The largest reported single-center experience of RFA for colorectal metastases has been from the group at St. George Hospital in Sydney, Australia [27]. This study included 55 patients with a median follow-up of 2 years. Median overall survival was 33 months, and 1-, 2-, and 3-year survivals were 85%, 64%, and 46%, respectively. On multivariate analysis, the only significant factor associated with impaired survival was tumor size greater than 3 cm. The 3-year survival was 52% for tumors 3 cm or smaller compared with 31% for tumors larger than 3 cm (p = 0.032).

These results for the smaller tumors are similar to those reported after resection of colorectal metastases. The main advantage of thoracotomy when pulmonary metastases are treated is the identification of radiologically occult metastases that may be present in up to 56% of patients [28]; however, the identification of occult disease has not been demonstrated to confer a survival advantage [29, 30]. For these reasons, as more experience with RFA is obtained, it may be reasonable to compare RFA with resection for small pulmonary metastases in future trials.

In conclusion, RFA has been demonstrated to be a safe modality for the local control of pulmonary tumors. Efficacy is better for smaller compared with larger tumors. Local control is inferior to resection, and for this reason, RFA should be reserved for the compromised patient where resection otherwise makes sense from a biologic standpoint.
Radiofrequency ablation may be preferable to conventional external-beam radiation for NSCLC, and future studies will help determine this. Patients with metastases to the lungs are often treated with resection; however, these patients have a high incidence of recurrence within the same or contralateral lung after complete resection. Future studies comparing RFA with resection for patients with small diameter metastases may be appropriate as more data become available.

References