Percutaneous Thermal Ablation for Lung Cancer: An Update

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ABSTRACT

Lung cancer remains the leading cause of cancer death in the United States, and accounts for more deaths than breast, colon, and prostate cancer combined. Over the past decade, percutaneous thermal ablative therapy (PTA) has become a useful adjunctive therapy in combination with longer-standing methods, or as a standalone treatment.

The physiologic basis of thermal ablation is that coagulative necrosis and cell death occur at temperatures above 60°C. During treatment, PTA of lung tumors routinely achieves temperatures above 70°C. Radiofrequency ablation has fallen out of favor in recent years as microwave ablation has been proven to be effective, with shorter treatment times.

Pulmonary PTA is a routine outpatient procedure in which conscious sedation is used in lieu of general anesthesia. The first post-procedural follow-up imaging is CT at 4 weeks, coinciding with an office visit.

In our most recent review of long-term results, which included 108 patients, all-cause survival at 1, 2, and 3 years was 83%, 59%, and 43%, respectively. When we specifically considered cancer-related survival, these numbers increased to 94%, 79%, and 57%.

Percutaneous thermal ablation has been shown to be a safe and effective treatment for patients with early-stage NSCLC who are not candidates for surgery, as well as a potential treatment for local small cell lung cancers. As the field of oncology, and specifically the treatment of lung cancer, continues to evolve, PTA will represent a useful tool in the arsenal.
INTRODUCTION

Lung cancer remains the leading cause of cancer death in the United States, and accounts for more deaths than breast, colon, and prostate cancer combined. It is the second-most commonly diagnosed cancer in both men and women, and accounts for roughly 25% of all cancer diagnoses in a given year. The American Cancer Society estimates that, in 2018, there will be 234,030 new diagnoses of lung cancer, and 154,050 deaths. While cigarette smoking is the most important epidemiologic risk factor, roughly 25% of lung cancers occur in nonsmokers. Surgical resection remains the standard of care in the treatment of early-stage non-small cell lung cancer (NSCLC), and results in a 5-year survival of up to 70%. Unfortunately, many patients are not candidates for surgery because of their inability to tolerate the physiologic insult of an operation, or because they have multiple early-stage lesions. Traditionally, an alternative to therapy has been external beam radiation therapy, which has offered patients with stage 1 NSCLC a 5-year survival of 21%. However, over the past decade, percutaneous thermal ablation (PTA) has become a useful adjunctive therapy in combination with longer-standing treatments, or as a standalone treatment. Here we examine the technique, results, and complications of PTA in the treatment of early-stage lung cancer.

PRINCIPLES

The physiologic basis of thermal ablation is that coagulative necrosis and cell death occur at temperatures above 60°C. During treatment, PTA of lung tumors routinely achieves temperatures above 70°C. Radiofrequency ablation uses a generator to create high-frequency alternating current (+60-480 kHz), which travels from the active tip of the electrode to grounding pads that are placed on the patient’s back or lower extremity. This generated current meets resistance within the tissues surrounding the tip, which generates frictional heat secondary to molecular collisions. This frictional heat triggers necrosis and cell death. The frictional heat is confined locally, and requires a conductive medium to expand the area of effect. In this way, the aerated parenchyma of the lung provides insulation to the surrounding healthy parenchyma and other nearby structures, and may help to explain why, in our experience, ablating disease within 6mm of the heart has not caused any adverse effects. Microwave ablation (MWA) uses electromagnetic microwaves at ≥ 9.2 x 10^8 Hz to produce friction and heat by agitating water molecules within the surrounding tissues and causing the molecules to flip. This agitation induces necrosis and cell death. Unlike radiofrequency ablation, MWA does not require grounding. Furthermore, treatment times are shorter, and ablation zones are larger, which has allowed MWA to become the thermal ablative treatment modality of choice over the last several years.

The actual size of the ablation zone is dependent on many variables, including but not limited to generator power, electrode choice and position, location and tissue properties of the tumor, and treatment time. A balance must be struck between the optimal temperature for treatment and overheating. The optimal temperature for cell death is 60°C to 100°C. Temperatures exceeding the upper limits of this range can lead to tissue charring, which limits treatment by increasing impedance, and decreasing current flow, and thus results in a smaller zone of treatment and increases the risk of incomplete treatment. The location of the tumor is important for planning both the location and approach for probe placement, as well as how much energy to use. Peripheral tumors are easier to access and are more displaced from large vessels which may act as a “heat sink” and shunt energy away from the desired area of treatment. This phenomenon has been shown to be less of a factor for MWA methods, compared to radiofrequency ablation.

TECHNOLOGY

Several radiofrequency ablation devices are available in the United States that offer electrodes of various gauges. Some have internal cooling mechanisms to limit the amount of charring. Similarly, several MWA devices are offered by different manufacturers that offer various generator powers and antenna specifications. Specific preferences are largely institution- and operator-based, and are not the focus of this article.

PROCEDURE

There are several reasonable approaches to the PTA procedure. Here we describe the procedure we have
adopted over the past 15+ years. Whether a patient is self-referred or sent to our tumor-ablation service from a clinical colleague, we see all patients in consultation with our radiology nurse practitioners before scheduling the procedure. Each week there is a multidisciplinary clinic for lung cancer involving specialists from pulmonology, oncology, thoracic surgery, radiation oncology, pathology, and interventional oncology. Patients are discussed and then seen later that afternoon. If they are determined to be suitable for PTA, they are referred to our clinic. Pulmonary PTA is a routine outpatient procedure that generally only requires local anesthesia, fentanyl and midazolam, and therefore anesthesia consultations are not routinely obtained. All lung ablations at our institution are performed in the CT suite, with the patient positioned optimally depending on tumor location. These specifics are discussed the morning of the procedure with the proceduralist, any assistants, and the technicians. The patient is appropriately positioned and a pre-procedure contrast-enhanced CT scan is obtained for planning, and often to evaluate any change in the lesion between the prior CT scan and the treatment date. Once the skin is prepped and draped, subcutaneous 1% buffered lidocaine is injected, a spinal needle is advanced to the pleural surface using CT-fluoroscopic guidance, and a 5- to 10-mL bolus of lidocaine is injected. The patient is given conscious sedation, and monitored closely by the radiology nursing staff. The PTA antenna is placed into the tumor under CT-fluoroscopic guidance. All other needles are removed from the skin, and typically a 10- to 20-minute ablation is performed. A second CT scan is performed at this time with the antenna within the tumor, and 3D reconstructions are created to ensure adequate coverage and to evaluate the need for additional treatment (Figure 1). After adequate treatment is confirmed, the PTA antenna is removed and a third CT scan is performed to examine for complications and create an immediate post-treatment baseline (Figure 2). If a complication, such as pneumothorax, is identified, appropriate treatment measures are taken before the patient leaves the CT suite. During the procedure, ice packs are placed on the patient’s skin in an effort to reduce the risk of cutaneous burns (Figure 3). A chest radiograph is obtained for all of our patients 2 hours after they arrive in the recovery suite. If the patient experiences an uneventful recovery, they are discharged home typically within 3-4 hours after the procedure. The first post-procedural follow-up imaging is CT at 4 weeks, coinciding with an office visit.

**Complications**

Pneumothorax is the most frequent complication of PTA, with rates ranging from 13% to 63%. A recently published review of 108 patients from our...
institution revealed a pneumothorax rate of 32%. They occur, pneumothoraces usually develop within 2 hours of the procedure and may require placement of a chest tube. These pneumothoraces are evaluated by immediate post-procedure CT, and a 2-hour post-procedure chest radiograph in our recovery room. While the development of a pneumothorax in a specific patient is difficult to predict, some factors that may predispose a patient to a pneumothorax include age older than 60 years, emphysema, central or basilar location of the tumor, treatments requiring multiple pleural punctures or probe repositioning, and electrode placement through a lumen. The only independent risk factor that has been identified to date is the length of aerated lung traversed by the PTA antenna, as seen in a study by Gillams and Lees.13 While some of the patients who require placement of a chest tube will be admitted to the hospital for observation and chest tube management, we have been increasingly managing our pneumothoraces in the outpatient setting with Heimlich valves. At our institution, these patients are followed by the interventional oncology service throughout their stay. Additionally, these patients are followed by their pulmonologists while in-hospital. In our most recent review of our procedures, 28% of our ablation procedures required an unplanned hospital admission.10 Pleural effusions are commonly seen after PTA and are likely physiologic responses to heat. The next-most common complication reported in the literature, and in our experience, is pain (20% of RFA cases).10 This pain is both pleuritic, when the tumor or ablation zone abuts the pleura and intercostal nerves, and somatic, most commonly at the site of probe insertion. Pain is controlled in the acute setting with a dose of narcotics, as well as nonsteroidal anti-inflammatory drugs. Additionally, in patients with persistent neuropathic pain, gabapentin has been used to alleviate symptoms. While it is common to see pulmonary parenchymal hemorrhage on the immediate post-treatment CT scan within the treatment area, hemoptysis is rare, and is reported in only 2% of RFA cases.4 An entity known as postablative syndrome is a known complication that presents as fever and/or flu-like symptoms and is merely treated symptomatically. This complication was seen in only 4% of our cohort. In our experience, the development of bronchopleural fistulas requiring extended hospitalization is exceedingly rare. There is a single case report of a stroke due to air embolism immediately following PTA.15 However, given the comorbidities of typical patients undergoing this treatment, this was likely coincidental and not specifically related to the PTA procedure. The risk of complications is associated with the maximum tumor diameter. In our experience, for every 1mm increase in maximal tumor diameter, the complication rate is increased by 3%.10 Larger tumors require longer treatment times, probe repositioning, or multiple probes, each of which exposes the patient to a greater complication risk.

FOLLOW-UP

Surveillance imaging protocols designed to detect primary tumor progression and recurrence in patients treated with PTA need to be more aggressive than those designed to follow postoperative patients because, unlike with resection, the treatment margin is not precisely measured.

While their remains no consensus statement regarding recommendations for postablative imaging, most authors report an every-3-month follow-up with a combination of CT and fluordeoxyglucose (FDG)-positron emission tomography (PET)-CT.16,17 We use surveillance CT with and without contrast at 4 weeks and 3 months, and FDG PET-CT at 6 months. We then alternate CT and PET-CT every 3 months for the first 2 years after PTA. Beyond 2 years, imaging performed every 4 to 6 months with alternating CT and PET-CT is a reasonable approach.17

Computerized tomography imaging performed immediately after successful PTA shows a ground-glass halo surrounding the tumor. This ground-glass opacity typically resolves within the first month after treatment. Histopathology in a pig model showed that these immediate postablative CT findings corresponded to a 3-layer structure. The peripheral layer consisted of necrotic hemorrhagic congestion, which measured up to 4.1 mm. The intermediate layer consisted of effusion in the alveolar lumen. The central layer consisted of cytoplasm, with nuclei having condensed chromatin suggesting cell death. An area of cavitation is usually seen within 3 months, with thickening of the pleura at the site of ablation. Treated tumors can increase in size during the first three months after PTA; however, continued growth 6 months after ablation is suggestive of local tumor progression.19 Focal nodular enhancement on follow-up CT is also suggestive of disease progression.20 While it is common to see reactive lymph nodes after PTA, these normally decrease in size within 6 months. New or increasing FDG uptake on follow-up PET-CT is highly suggestive of disease progression. Some authors use the modified RECIST (Response Evaluation Criteria in Solid Tumors) criteria, under which primary tumor progression is suggested when any 2 of the following 3 imaging features are detected on surveillance CT or PET-CT: increase in sum length of the tumor greater than 20%, solid mass with invasion of adjacent structures, and higher standardized uptake value (SUV) or increasing FDG uptake.1 Local tumor progression has been reported in 30% to 43% of cases and occurs more commonly in larger tumors.17 Hiraki et al17 reported that tumor histology did not significantly affect primary control rates in 105 patients with 252 lung tumors. Unlike external beam radiation therapy, there is no “maximum” ablation dose; therefore, repeat PTA is performed routinely.

CLINICAL OUTCOMES

Percutaneous PTA has been used in the treatment of lung tumors for roughly 20 years. Each year, more and more studies are published to help us better understand the efficacy of this treatment and which patients are most appropriate for it. Numerous early studies validated the safety and efficacy of the procedure,21-39 and the ABLATE and RESeCT trials showed that RFA results in complete cell death on pathological specimens.39 In our most recent review of long-term results, which included 108 patients, all-cause survival at 1, 2, and 3 years was 83%, 59%, and 43%, respectively. When we specifically focused on cancer-related survival, these numbers increased to 94%, 79%,
and 57%. Palussiere et al. examined 87 patients with clinical N0 NSCLC from two centers and found that 5-year survival was 27.9%. Both studies demonstrated that lesion size was directly related to disease-free survival: 3 cm lesions in our study and 2 cm lesions in their study were identified as important thresholds for helping to predict survival. These patients received PTA as their only treatment, and our center continues to explore novel approaches using both PTA and radiation therapy. One study reported improved primary control rates and survival when RFA was performed before radiation therapy, as opposed to radiation alone, in patients with stage I NSCLC. In a study of 41 patients with stage I or II NSCLC treated with a combination of thermal ablation (RFA in 37 and microwave in 4) and either external beam radiation or brachytherapy, Grieco et al. reported 1-, 2-, and 3-year survival rates of 86.8%, 70.4%, and 57.1%, respectively.

FUTURE DIRECTIONS

As we continue to expand the treatment options for cancer patients to tailor treatment at an individual level and balance risks and benefits, it is imperative that our treatments evolve as fast as the disease. At our institution, we recently published a pilot study that looked at 10 patients with small-cell lung cancer who received MWA as part of their treatment regimen. Three of the patients had definitive local disease. MWA alone was enough for 32 months and 48 months of disease-free survival, respectively, in two of the patients, while the third developed local recurrence and underwent additional treatment. While this cohort is very small, early results are promising and may reveal that MWA has a role to play in the treatment of small-cell lung cancer as well as a growing role in the treatment of NSCLC. Additionally, while the complication rates and types of complications have been well described, this does not account for all of the patients that may have been candidates for PTA if not for the location of the tumor and its presumed risks. We previously demonstrated in a small cohort of patients that PTA adjacent to the heart is not associated with any additional risks, and there is ongoing research on para-aortic cancers to better understand both complications and the so-called “heat sink” of the aorta. As more applications for PTA are verified to be both safe and effective, a growing number of patients will be able to benefit from this evolving technology.

CONCLUSIONS

Percutaneous thermal ablation has been shown to be a safe and effective treatment for patients with early-stage NSCLC who are not candidates for surgery, as well as a potential treatment for definitively local small-cell lung cancers. Additional large multicenter prospective randomized control trials are needed to further compare this treatment with alternatives such as surgery and radiation, both stereotactic body radiation therapy and intensity-modulated radiation therapy, in terms of long-term survival, toxicity, and cost-benefit. Combined multimodality treatment is an area of continued exploration and may provide additional benefits to some patients. As the field of oncology, and specifically the treatment of lung cancer, continues to evolve, PTA will represent a useful tool in the arsenal.

AUTHORS’ DISCLOSURES

The authors have no conflicts of interest to report.

REFERENCES

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