Radiofrequency Ablation—A New Treatment Option for Non-small Cell Lung Cancer Patients

a report by

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Damian E Dupuy, MD, is the Director of Tumor Ablation at Rhode Island Hospital and a Professor of Diagnostic Imaging at Brown Medical School. A pioneer in the use of image-guided ablation, he has helped broaden clinical applications to successfully combat cancer of the kidney, lung, adrenal, thyroid, and skeleton. Other newer technologies, such as microwave ablation, and combination therapies using radiofrequency ablation (RFA) with external radiation or brachytherapy, have been pioneered by Dr Dupuy, who is the principal investigator or co-investigator of several National Cancer Institute (NCI)-funded multicenter trials. Dr Dupuy has published over 130 publications and given over 60 invited lectures in the field of radiology and image-guided tumor ablation.

Lung cancer is the most common cancer worldwide, with an estimated five-year survival rate of 15% for the majority of histologies (e.g. non-small cell). Surgery is the primary treatment for resectable non-small cell lung cancer (NSCLC). The five-year survival rates after surgical treatment are 63–67% in stage IA, 46–57% in stage IB, 52–55% in stage IIA, 33–39% in stage IIB, and 19–23% in stage 111A.[1–3] However, only one-third of patients are surgical candidates due to their advanced stage at presentation or medical co-morbidities.[4] In these patients, the treatment options rely on radiotherapy (RT) with or without chemotherapy. In a meta-analysis determining the effectiveness of radical RT for stage I/II medically inoperable NSCLC patients, overall five-year survival ranged 0–42%, with complete response rates of 33–61% and local failure rates ranging 6–70%.[5] The role of chemotherapy in NSCLC has primarily been for patients with more advanced disease alone or in conjunction with radiotherapy. Recently, two large studies evaluating the addition of chemotherapy to surgery for stage I and II NSCLC showed a 12–15% improvement in survival in the chemotherapy group compared with surgery alone.[6,7] Clearly, even in early-stage disease, systemic failures can be problematic.

The fact that many patients are not candidates for resection or radiation has led to alternative modalities that could accomplish tumor destruction. Percutaneous image-guided thermal ablation with radiofrequency (RF) energy has been used as a minimally invasive approach for a variety of solid tumors, including liver, kidney, bone, and adrenal gland.[8–11] The technique for thermal ablation utilizing RF was first described in animal lung tumor models in 1995 and was reported in human lungs in 2000.[12,13] Since 2000 the worldwide experience of RF ablation (RFA) of lung neoplasms has grown (see *Table 1*) as a minimally invasive option for non-surgical candidates, not only for local control but also for symptom palliation.

Clinical Applications of RFA for Primary Lung Neoplasms

RFA of lung neoplasms is a technique, the clinical applications of which are just beginning to be developed. It has some advantages over traditional RT and chemotherapy. Its safety profile is similar to percutaneous image-guided lung biopsy. Almost all RF procedures can be performed in an out-patient setting, mostly with conscious sedation. Multiple applications can be performed in a single session or over several sessions.

RFA of lung malignancies is performed with two basic rationales. In the first group it is used with an intention of achieving definitive therapy. These are patients who are not candidates for surgery because of co-morbid medical conditions. This cohort could potentially derive significant benefit from a minimally invasive alternative therapy. In the second group it is used as a palliative measure:

- to achieve tumor reduction before chemotherapy;
- to palliate local symptoms related to aggressive tumor growth, such as chest pain, chest wall pain or dyspnea;
- for hematogenous painful bony metastatic disease; and
- tumor recurrence in patients who are not suitable for repeat radiotherapy or surgery.

The most promising application for RFA is in the treatment of primary NSCLC. With the overall five-year survival rate for all stages of NSCLC being less than 15%, newer treatment modalities are needed. RFA is a local therapy and potentially can be utilized for incidental or screen detected stage I disease, where the tumor size is less than 3cm and there is no evidence of regional or distant tumor spread by staging computed tomography (CT) and/or positron emission tomography (PET) scanning. Currently, the gold standard of therapy for such patients is lobectomy with a five-year survival rate of 65–70%. Current studies report overall five-year survival rates from 53% to 82% when both anatomic (lobectomy) and non-anatomic (limited/wedge resection) are included.[14,15] Wedge resection is associated with an increased risk of local recurrence when compared with lobectomy but appears to be a viable

Table 1: Literature Summary—RFA of Lung Neoplasms

Author	Title	Journal	n=	Significant Findings
Bojarski J D, Dupuy D E, Mayo-Smith W W	"CT Imaging Findings of Pulmonary Neoplasms After Treatment with RFA Results in 32 Tumors"	AJR (2005); 185: pp. 466–471	26 patients (32 thoracic neoplasms)	Many treated neoplasms increase in size from baseline on one- to three-month follow-up CT scans and remain stable thereafter.
El-Sherif A, Luketich J D, Landreneau R J, Fernando H C	"New therapeutic approaches for early stage non-small cell lung cancer"	Surg Oncol. (July 2005);. 14(1): pp. 27–32	Lit. review	Alternatives to surgical resection including RFA, sublobar resection with brachytherapy, and stereotactic radiosurgery. for early-stage NSCLC that cannot be treated by surgical resection were examined; concluding that all three methods are viable non-surgical alternatives for patients not be able to tolerate curative resection.
Fernando H C, Hoyos A D, Lanreneau R J, Gilbert S, Gooding W E, Nuenaventura P O, Christie N A, Belani C, Luketich J D	"Radiofrequency ablation for the treatment of non-small cell lung cancer in marginal surgical candidates"	J. Thorac Cardiovasc Surg. (March 2005);129 (3): pp. 639–44	18 (21 tumors)	This study demonstrates the feasibility of RFA for small, peripheral NSCLC tumors. Local control is comparable to, if not better than, that provided by RT.
VanSonnenberg E, Shankar S, Morrison P R, Nair R T, Silverman S G, Jaklitsch M T, Liu F, Cheung L, Tuncali K, Skarin A T, Sugarbaker D J	"Radiofrequency ablation of thoracic, lesions: part 2initial clinical experience—technicaland multidisciplinary considerations in 30 patients"	AJR (February 2005); 184(2): pp. 381–390	30 (36 lesions)	All ablations were technically successful. No periprocedural mortality occurred. Necrosis of tumor was greater than 90% in 26 of 30 lesions based on short-term follow-up imaging (CT, PET, MRI). In the 11 patients who underwent ablation for pain, relief was complete in four and partial in the other seven. RFA for a variety of thoracic tumors can be performed safely and with a high degree of efficacy for pain control and tumor killing.
Suh R, Reckamp K, Zeidler M, Cameron R	"Radiofrequency Ablation in Lung Cancer: Promising Results in Safety and Efficacy"	Oncology (October 2005);(suppl.) 19(11): pp. 12–20	Lit. review Patient Selection	The results regarding RF lung ablation are comparable to other therapies currently available, particularly for the conventionally unresectable or high-risk lung cancer population.
Gadaleta C, Catino A, Ranieri G, Armenise F, Colucci G, Lorusso V, Cramarossa A, Fiorentini G, Mattioli V	"Radiofrequency thermal ablation of 69 lung neoplasms"	J. Chemother. (November 2004);16 (suppl. 5): pp. 86–89	34 (69 tumors)	The rate of complete necrosis of lung neoplasms was high (92%). Lung RFA is an attractive technique suitable for patients not otherwise eligible for surgery.
Jin G Y, Lee J M, Lee Y C, Ha Y M, Lim Y S	"Primary and secondary lung malignancies treated with percutaneous radiofrequency ablation: evaluation with follow-up CT"	AJR (October 2004) ;183(4): pp. 1,013–1,020	21 (nine classified as complete ablation; 12 classified as partial ablation)	In the complete ablation group, ablated lesions were completely without contrast enhancement on follow-up CT. In the partial ablation group, the ablated lesions had various degrees of enhancement, and the mean percentage of ablated lesion size gradually increased after the six-month follow-up CT examination.
Gadaleta C, Mattiolo V, Colucci G et al.	"Radiofrequency Ablation of 40 Lung Neoplasms: Preliminary Results"	AJR (2004); 183: pp. 361–368	18 (40 nodules)	The authors wish to emphasize the safety of lung RFA. It is a conservative, minimally invasive treatment that can be administered multiple times; it could be effective especially in patients not eligible for surgery or with slow-growing lesions.
Joos L, Tamm M, Chhajed P N	"Radiofrequency tumor ablation for lung tumors: is there a role for neoadjuvant and/or adjuvant chemotherapy?"	J. Chemother. (December 2004); 16(6): pp. 561–569	Comment	A number of studies have provided evidence that RFA is a valuable and relatively safe alternative for inoperable patients or in patients with lung metastases.
Steinke K, Glenn D, King J et al.	"Percutaneous Imaging-Guided Radiofrequency Ablation in Patients with Colorectal Pulmonary Metastases: 1-Year Follow-Up"	Ann. Surg. Oncol. (2004);11(2): pp. 207–212	23 (52 metastases)	Eighteen patients with CT scan follow-up at one year have 40 lesions classified as disappeared (n=17), stable/same size (n=4), or increased (n=14)
Lencioni R, Crocetti L, Cioni R, Mussi A, Fontanini G, Ambrogi M, Franchini C, Cioni D, Anucchi O, Genignani R, Baldassari R, Angeletti C A, Bartolozzi C	"Radiofrequency ablation of lung malignancies: where do we stand?"	Cardiovasc. Intervent. Radiol. (November—Dec 2004); 27(6): pp. 581–590	Lit. review	RFA could represent a viable alternate or complementary treatment method for patients with NSCLC or lung metastases of favorable histology who are not candidates for surgical intervention.
Kang S, Luo R, Liao W, et al.	"Single group study to evaluate the feasibility and complications of radiofrequency ablation and usefulness of post treatment position emission tomography in lung tumours"	World Journal of Surgical Oncology (2004);2: p. 30	50	Tumors smaller than 3.5cm were completely killed after RFA. In tumors larger than 3.5cm, the part within 3.5cm was killed. While CT showed that tumors became larger one to two weeks after RFA procedure. PET demonstrated tumor destruction in 70% cases, compared with 38% in CT.
Akeboshi M, Yamakado K, Nakatsuka A et al.	"Percutaneous Radiofrequency Ablation of Lung Neoplasms, Initial Therapeutic Response"	JVIR (May 2004); 15: pp. 463–470	31 (54 tumors)	Complete necrosis was achieved in 32 of the 54 tumors (59%) after initial RF session.

Table 1: Continued

Author	***Title***	***Journal***	***n=***	***Significant Findings***
Steinke K, Sewell P E, Dupuy D, Lencioni R, Helmberger T, Kee S T, Jacob A L, Glenn D W, King J, Morris D L	*"Pulmonary radiofrequency ablation -- an international study survey"*	Anticancer Res. *(January–February 2004);24(1): pp. 339–343*	*493*	*Seven centers reported 493 percutaneous procedures in lung tumors. With almost 500 procedures carried out to date, percutaneous pulmonary RFA appears to be a safe, minimally invasive tool for local pulmonary tumor control with negligible mortality, little morbidity, short hospital stay and gain in quality of life.*
Min Lee J, Yong Jin G, Nahum Goldberg S et al.	*Percutaneous Radiofrequency Ablation for Inoperable Non–Small Cell Lung Cancer and Metastases: Preliminary Report*	Radiology *(2004);230: pp. 125–134*	*26 (32 lesions)*	*Complete necrosis was attained in 12 (38%) of 32 lesions; partial (>50%) necrosis, in the remaining 20 (62%) lesions. Complete necrosis was attained in all six (100%) tumors smaller than 3cm but only in six (23%) of 26 larger tumors (P <.05). Mean survival of patients with complete necrosis (19.7 months) was significantly better than that of patients with partial necrosis (8.7 months) (P <.01).*
Yasui, K; Kanazawa, S; Sano, Y et al.	*"Thoracic Tumors Treated with CT-Guided Radiofrequency Ablation: Initial Experience"*	Radiology *(2004);231: pp. 850–857*	*35 (99 tumors; 54 sessions)*	*Ninety tumors showed no growth progression at follow-up CT. Probable complete coagulation necrosis obtained with initial RFA was achieved in 91% (90 of 99) of the tumors.*
Belfiore G, Moggio G, Tedeschi E, Greco M, Cioffi R, Cincotti F, Rossi R	*"CT-Guided Radiofrequency Ablation: A Potential Complementary Therapy for Patients with Unresectable Primary Lung Cancer—A Preliminary Report of 33 Patients"*	AJR *(2004); 183: pp. 1,003–1,011*	*33 (35 sessions)*	*Constrast-enhanced CT at six-month follow-up showed four cases of complete and 13 cases of partial lesion ablation, 11 cases of stabilized lesion size, and one case of increased lesion size. Contrast-enhanced CT at one-year follow-up showed unchanged lesion size in six cases and reduction in four cases. RFA can be used successfully in unresectable lung cancer as an alternative or complementary treatment to radio- or chemotherapy.*
Jain S, Dupuy D E, Cardarelli G E et al.	*"Percutaneous Radiofrequency Ablation of Pulmonary Malignancies: Combined treatment with Brachytherapy"*	AJR *(2003);181: pp. 711–715*	*3*	*Percutaneous RFA in conjunction with brachytherapy is a promising minimally invasive combination modality. It may be a treatment option for patients with primary, recurrent, or metastatic malignancies of the lung that are not amenable to surgery or further external beam radiotherapy.*
Herrera L J, Fernando H C, Perry Y et al.	*"Radiofrequency ablation of pulmonary malignant tumors in nonsurgical candidates"*	J. Thorac. Cardiovasc. Surg. *(2003);125(4): pp. 929–936*	*18 (13 from a percutaneous approach)*	*RFA achieved a radiographically determined response in eight of 12 patients with treated tumors smaller than 5cm. This pilot study demonstrates the feasibility of RFA for small peripheral lung tumors.*
Suh R D, Wallace A B, Sheehan R E, Heinze S B and Goldin J G	*"Unresectable Pulmonary Malignancies: CT-guided Percutaneous Radiofrequency Ablation—Preliminary Results"*	Radiology *(2003); 229: pp. 821–829*	*12 (19 tumors)*	*RFA was well tolerated by all patients. In the eight patients with three-month follow-up, lesion size increased in two and remained stable in six. Mean contrast enhancement, however, decreased from 46.8HU (range, 19–107HU) at baseline to 9.6HU (range, 0–32HU) at one- to two-month follow-up. In the one patient with 12-month CT densitometry follow-up, lesion enhancement was less than 50% of that at baseline, and lesion diameter remained stable.*
Steinke K, King J, Glenn D, Franz C R, Morris L D	*"Radiologic Appearance and Complications of Percutaneous Computed Tomography-Guided Radiofrequency-Ablated Pulmonary Metastases from Colorectal Carcinoma"*	Journal of Computer Assisted Tomography *(September/October 2003);27(5): pp. 750–757 [Abstract only available]*	*20 (41 tumors)*	*At three months after RFA, the lesion was approximately the same size as at baseline. The lesion subsequently shrank within the following three months, usually with a small scar remaining. Ablated lesion size usually exceeds the dimensions of the initial tumor for the first three months after ablation and continuously shrinks thereafter.*
Dupuy D E, Mayo-Smith W W, Abbott G, DiPetrillo T	*"Clinical applications of radio-frequency tumor ablation in the thorax"*	Radiographics *(2002): pp. S259–269*	*Presentation of procedure protocol and thoracic applications for RFA*	*In patients with non-small cell lung malignancy who are not candidates for surgery owing to poor cardiorespiratory reserve, RFA alone or followed by conventional radiotherapy with or without chemotherapy may prove to be a treatment option. In patients with metastatic disease, RFA may be suitable for treatment of a small tumor burden or for palliation of larger tumors that cause symptoms such as cough, hemoptysis, or pain. Patients with chest wall or osseous metastatic tumors in whom other therapies have failed may benefit from RFA as an alternative to radiotherapy.*
Dupuy D E, Zagoria R J, Akerley W, Mayo-Smith W W, Kavanagh P V, Safran H	*"Percutaneous radiofrequency ablation of malignancies in the lung"*	AJR *(2000);174(1): pp. 57–59*	*3*	*RFA is a promising new minimally invasive technique for the treatment of solid malignancies. Unlike other percutaneous techniques, RFA can provide controlled regions of coagulation necrosis with a single application to an area as large as 3–5cm depending on the blood flow in the treated tissue. RFA may result in reduced tumor burden when combined with external beam radiation or systemic chemotherapy.*

compromise for patients with cardiopulmonary impairment when considering the operative risks.[16] RFA ± RT can be offered as a limited local therapy in patients who are poor surgical candidates, thus providing them with additional local control and possible benefit in survival.[17]

Utilization of RFA for lung tumors has been gaining momentum in the past few years, as an increasing amount of much required data is reported confirming the safety and efficacy of this technique. Although RFA has been used in a heterogeneous cohort of lung tumor patients, the initial results are encouraging. In medically inoperable patients with NSCLC, Herrera et al. report rates of 40% for partial response, 60% for stable disease with no evidence of disease progression, and death from an unrelated cause.[18] Cosmo et al. treated 40 lung neoplasms with RFA and had a local relapse rate of 2.5% in a mean follow-up of eight months.[19] Kotaro et al. treated 99 malignant thoracic tumors (three primary and 96 secondary) with complete ablation of 91% of the tumors after the first RFA and 9% local recurrences or residual tumors that were treated with repeat RFAs.[20] Jeong et al. treated 32 malignant lung masses (27 NSCLC and five metastasis) with CT-guided RFAs. In their study, lung cancers smaller than 3cm had a higher complete necrosis rate when compared with larger tumors (100% versus 8%). They also found an increased mean survival in patients with complete necrosis versus partial necrosis (19.7 versus 8.7 months).[21]

Pulmonary RFA alone for the treatment of primary lung cancer is not validated at this time, given the prospective surgical data demonstrating a three- and 2.4-fold increase in local–regional recurrence rate with local treatment wedge resection and segmental resection, respectively, compared with lobectomy.[22] However, for less than 2cm stage IA NSCLC, several studies comparing limited resection (segmentectomy) and lymph node (LN) assessment versus lobectomy have shown equivalent five-year survival rates (87.1% versus 93%) and local recurrence.[23–25] These recent studies and the data by Jeong et al. lead to the speculation that for tumors less than 2cm in size, RFA might provide an alternative for local disease control. The explanation for recurrence includes inadequate resection of the primary tumor, as well as presence of microscopic lymphatic disease within the ipsilateral hilar nodes. Unfortunately, detection of these deposits is not possible by the current imaging methods and RF technology does not allow the treatment regimen to extend extensively into the normal lung parenchyma, yet for patients who are non-surgical candidates due to co-morbid conditions, poor cardiopulmonary reserve or prior RT with recurrence in the treatment field, RFA provides an alternative treatment modality.

RFA can also be used in conjunction with other treatment modalities. In addition to the previously mentioned combination with external beam radiotherapy (EBRT) there are studies that focus on combining RFA with brachytherapy in patients with either metastatic lung malignancies or prior treatment that precludes additional EBRT.[26] The rationale is to enhance the local control by magnifying the cytoreduction and the effect of radiation by destroying the central hypoxic area of the tumor. CT can be utilized for brachytherapy catheter placement and the entire treatment can be accomplished in one day. Tumors that tend to be more encapsulated with a sharper lung/tumor interface (e.g. well differentiated squamous cell carcinoma) may be more suitable for candidates for local therapy alone.

The cytoreductive effect of RFA in lung cancer shows promise for symptom palliation. Patients with inoperable lung cancer and tumor size too large for radical RT have a poor prognosis with limited therapeutic options. The majority of lung cancer patients die from their cancer, and the most common symptoms from which they clinically manifest are cough, dyspnea, hemoptysis, and pain.[27] Symptom palliation is therefore an important part of treatment, yet current medical literature reflects failure, with 50% of patients dying without adequate pain relief.[28] Jeong et al. demonstrated 80% relief in mild hemoptysis, but less than ideal relief of chest pain, dyspnea, and coughing. Conventional treatment of osseous metastatic disease involves RT and chemotherapy. RT has been shown to palliate respiratory symptoms and improve quality of life in NSCLC patients, but if the symptomatic areas were included in the prior radiation field they can be difficult to treat.[29] RFA has been shown to provide substantial decrease in pain from skeletal metastasis and improved quality of life.[30,31]

Conclusion

To date, RFA has shown promise for the treatment of lung cancer either alone or in combination with traditional therapies. The advantages of RFA include precise control, relatively low cost, decreased morbidity and mortality compared with surgery, and its use in the out-patient setting. There are many questions as to which patients may benefit most and what imaging tests are best to monitor treatment efficacy. Local control and symptom palliation are clearly areas of important clinical application. However, to achieve a greater utilization and a true paradigm shift toward the use of alternative methods, such as RFA, future controlled multicenter trials are necessary. ■

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