

Rate of Recurrence of Non-Small Cell Lung Cancer in Patients Treated with Percutaneous Ablation

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Abstract

Background: Percutaneous ablation therapy as a treatment for non-small cell lung cancer (NSCLC) has been increasingly utilized. There is little data on long term efficacy. Because of this we reviewed the rate of recurrence of all ablation procedures done at our institution for the last 6 years. **Methods:** A total of 36 patients underwent 43 percutaneous procedures from July 2008 until January 2014 at our institution. There were 9 patients treated with radiofrequency ablation (RFA) and 27 treated with microwave ablation (MWA) for Stage I NSCLC. Each patient was reviewed to determine if there was a recurrence, the time to recurrence and the characteristics of the original cancer possibly predisposing the procedure to failure. **Results:** There were 8 recurrences in 9 patients undergoing RFA occurring at a median time of 842 days (range 425 - 1568) after their procedure. MWA was utilized in 27 patients for 34 procedures with 11 patients experiencing recurrences at a median time of 487 days (range 168 - 845). The median follow up time for the RFA patients was 1631 days (4.46 years) and for the MWA patients 751 days (2.06 years). Of the RFA recurrences, 5 involved systemic spread of their cancer and 3 were limited to site recurrences only. Of the MWA recurrences, 5 involved systemic spread of their cancer, 2 had chest wall recurrences and 4 were limited to site recurrences only.

Keywords

Ablative Therapies, Lung Cancer, Surgery

1. Introduction

Percutaneous ablation techniques including radiofrequency ablation (RFA), microwave ablation (MWA), cryoab-

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lation and now, irreversible electroporation (IRE) have all been described as modalities with various efficacies at treating non-small cell lung cancer [1]. The use of these modalities for the treatment of lung cancer is being done with increasing frequency [2]. Despite the increased utilization of the percutaneous modalities surgical resection remains the best chance of cure for a patient with an early stage non-small cell lung cancer [3]. Surgical resection is frequently not feasible in patients diagnosed with early non-small cell lung cancer however due to significant comorbidities or patient refusal to undergo surgical resection. In patients denied lobectomy or sublobar resection percutaneous ablation therapy has emerged as an alternative [4].

Radiofrequency ablation has been used for the last decade as an alternative treatment for patients considered too high a surgical risk for lung resection while microwave ablation has been in use for the last several years [5]. Radiofrequency ablation was first utilized at our institution for poor surgical candidates with non-small cell lung cancer in 2008. Microwave ablation supplanted RFA as the percutaneous ablation modality of choice at our institution in 2010 because of its theoretical benefits with respect to heat deposition and tumor lysis in the *in vivo* lung [1]. Since 2008 over 60 percutaneous ablation procedures for lung cancer have been done at our institution. This paper describes the results of 36 of those patients who presented with clinical Stage I non-small cell lung cancer screened, treated and followed post-operatively by a single surgeon at a single institution. Each patient's medical record was reviewed for the presence and time of recurrence, the outcome when a recurrence occurred, and aspects of the original tumor treated that possibly predisposed the patient to recurrence.

2. Patients and Methods

2.1. Patients

The study was approved by the Institutional Review Board of UPMC Northwest. All of the patients treated in the study were treated and followed at UPMC Northwest between 2008 and 2014 by a single surgeon (JWK). Each of the patients was presented at the institution's multi-specialty tumor board prior to treatment. The patients underwent their pre-operative work up by the thoracic surgery service and were not felt to be candidates for surgical resection due to poor pulmonary function and, or significant comorbidities as defined by the Charlson comorbidity index [6], or patient refusal to undergo an operation. Pre-operative work up consisted of a history and physical, computed tomography (CT), image guided biopsy of the lung nodule and positron emission tomography (PET) to assess the possibility of the presence of metastatic disease prior to undergoing treatment. Patients with any evidence of metastatic disease by CT or PET underwent further work up to pathologically confirm the presence of metastatic disease. Only patients considered having clinical Stage IA (T1a and T1b, N0, M0) NSCLC were included in the study.

2.2. Methods

Image guided RFA or MWA using CT guidance was performed with both an interventional radiologist and a thoracic surgeon (JWK) present for the procedure. RFA was used early in the series (2008-2010). Both the Cool-tipTM RFA system (Valleylab, Boulder, CO) and the RITATM system (RITA Medical Systems, Inc, Mountainview CA) were used. An ablation goal of 60°C and a 0.5 - 1 cm rim of ablation in normal lung parenchyma were the RFA endpoints of treatment. MWA ablation supplanted RFA in 2010 because of the theoretical benefits of its energy dispersal characteristics in lung tissue [1]. All MWA were performed with the EvidentTM system (Covidien, Tyco Healthcare Group, Mansfield, MA). MWA antennae used either a 2.0 or 3.7 cm active tip emitting microwaves at 915 MHz with an output power of 45 W for 10 minutes in each case. The antenna size and the need for multiple antennae were chosen based on the CT dimensions of the nodule to be treated with the desired goal of achieving a 0.5 - 1 cm rim of normal parenchyma ablated with the cancer [7].

Following ablation patients were followed by the thoracic surgery service at scheduled intervals with clinical exams and appropriate radiological studies. In general, patients underwent surveillance with CT scans at 6 weeks, 3 months, 9 months and 6 month intervals post ablation. Tumor response was evaluated with respect to the Modified Response Evaluation Criteria in Solid Tumors (RECIST) criterion [8]. Patients failing to demonstrate a complete response or a continued partial response by serial CT scans received more aggressive work up including the addition of PET scanning to determine metabolic activity or repeat biopsy of the previously ablated lung cancer.

2.3. Analysis

The medical records of all patients treated with percutaneous ablation at our institution between 2008 and January 2014 were retrospectively reviewed and the patients who experienced recurrence of their lung cancer were reviewed. The site of recurrence, the time to recurrence as evidenced by the first radiological test suggesting it, and the respective outcomes were determined. Additionally, in those patients who experienced a recurrence, their initial presentation findings were reviewed to determine if there were any parameters identifiable predisposing them to recurrence.

3. Results

Radiofrequency ablation was utilized in 9 patients. 8 of the 9 patients experienced cancer recurrence (**Table 1**). The median time until recurrence was 842 days with a range of 425 days to 1,568 days (**Figure 1**). Of the 8 recurrences 3 had site recurrences only, with 2 undergoing re-ablation and 1 undergoing a sublobar resection. All of these patients continue to be disease free following re-treatment. 3 patients failed without evidence of recurrent disease at the treated site but with significant nodal spread. 1 of these patients succumbed to cancer while 2 remain alive on maintenance adjuvant therapy. 1 patient experienced widely disseminated metastatic disease and succumbed to cancer while 1 patient was found to have a malignant pleural effusion and remains alive on maintenance chemotherapy. A single patient did not experience a cancer recurrence but died from benign pulmonary disease over 5 years after her ablation.

Microwave ablation was utilized in 27 patients for 34 total procedures. 11 of these patients have experienced recurrences (**Table 2**). The median time until recurrence was 487 days with a range of 165 - 845 days (**Figure 2**). The follow up interval for the MWA patients is not as mature as the RFA interval due to the transition to MWA during the treatment period. 9 of the recurrences were site recurrences with 4 patients undergoing re-ablation all of whom remain disease free at the present time. 2 patients who experienced site recurrences underwent re-ablation and subsequently developed progressive disease; 1 developed ipsilateral hilar disease and ultimately succumbed to cancer during chemotherapy while the other developed widely metastatic disease and died with palliative chemotherapy. 2 patients presented post-ablation with widely metastatic disease and remain alive on adjuvant therapy. 2 patients, both of whom had peripheral pleural based nodules at their initial ablation, have had chest wall recurrences treated with subsequent external beam radiation. 6 patients treated with MWA were lost to follow up.

After review of both the RFA and MWA results it was felt that further statistical analysis of the patient populations would be of limited value due to the preponderance of recurrence in both groups of patients. Review of all of the patients revealed that all of the originally ablated nodules were no larger than 3 cm in the greatest dimension with the majority < 2 cm. Additionally, each of the patients underwent pre-treatment PET evaluation and was without evidence of the presence of metastatic disease at the time of their initial ablation procedure. All patients reviewed were thus clinical Stage IA biopsy proven non-small cell lung cancer patients.

4. Comment

The American Cancer Society estimates that in 2014 there will be over 220,000 new cases of lung cancer in the United States with over 159,000 cancer deaths. The same report also estimates that greater than two thirds of the patients newly diagnosed will be older than age 65 [9]. It has also been estimated that only 15% of patients diagnosed with Stage I or II NSCLC meet the physiological criteria for parenchymal resection [10] [11]. The aging of the population in the United States has been well documented; it is estimated that by 2030 the elderly population of the United States will reach 70 million people [12]. It has been demonstrated that CT screening for lung cancer has the potential to detect early stage lung cancers effectively [13]. The combination of the aging population in the U.S. with the increased use of CT scanning is likely to result in more patients with early stage lung cancers that are marginal candidates for surgical resection.

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry has previously found survival results for early stage NSCLC to be as high as 75% at 8 years for patients treated by surgical resection [13]. Conversely the survival results for patients with early stage NSCLC who do not undergo any treatment were found to be, at best, 13% by the same registry data [14]. Additionally, review of patients with untreated Stage I NSCLC from the California Cancer Registry has previously found that the median survival for patients not undergoing any treatment is 13 months [15].

Table 1. Original tumor characteristics, site of recurrence and time from ablation to recurrence in patients treated with Radiofrequency Ablation.

Patient Demographics	Nodule Characteristics	Site of Recurrence	Time to Recurrence (days)
60 Years Old Male	19 mm LUL Peripheral	N3; Left Supraclavicular Lymph Nodes	892; Cancer Mortality
81 Years Old	16 mm LLL Peripheral	M1b; Bilateral Adrenals and Pelvis	755; Cancer Mortality
68 Years Old Female	15 mm LUL Peripheral	Site Recurrence	1568; Re-ablated
82 Years Old Male	13 mm RUL Peripheral	Site Recurrence with N1, N2 and M1b Disease	792; Cancer Mortality
76 Years Old Female	19 mm RLL Peripheral	M1a; Right Pleura	1435; Chemotherapy
68 Years Old Female	10 mm LUL Peripheral	Site Recurrence	425; Re-ablated
83 Years Old Male	16 mm LUL Peripheral	Site Recurrence	1120; Segmentectomy
64 Years Old Female	19 mm LUL Peripheral	N2; AP Zone Nodes	655; Chemotherapy

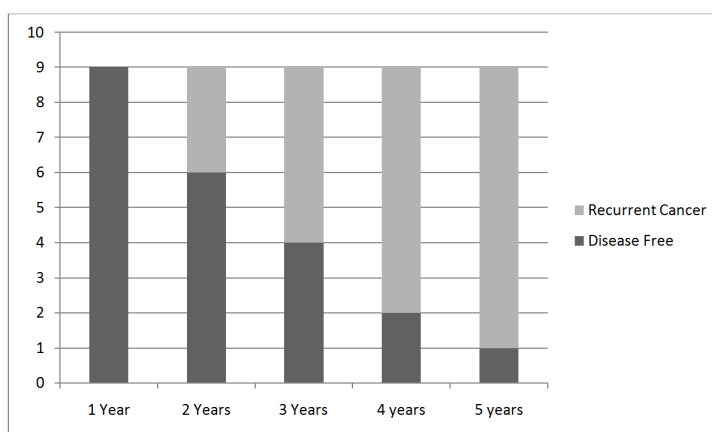


Figure 1. Disease free and recurrent cancer patients from the time of their initial RFA.

Table 2. Original tumor characteristics, site of recurrence and time from ablation to recurrence in patients treated with Microwave Ablation.

Patient Demographics	Nodule Characteristics	Site of Recurrence	Time to Recurrence (days)
48 Years Old Male	16 mm LUL Perihilar	Site Recurrence	439; Re-ablated
71 Years Old Male	18 mm RUL Peripheral Abutted Chest Wall	Chest Wall	569; Chemotherapy & External Beam Radiation
69 Years Old Female	8 mm LUL Peripheral	Site Recurrence	492; Re-ablated
78 Years Old Female	17 mm RUL Peripheral	Site Recurrence (first)	368; Re-ablated
		Hepatic Metastatic disease	440; Cancer Mortality
81 Years Old Male	21 mm RUL Peripheral	Site Recurrence	845; Re-ablated
	17 mm LLL Peripheral	Site Recurrence (first)	248; Re-ablated
		Site & N1 Recurrence	313; Cancer Mortality
64 Years Old Female	20 mm RLL Abutted Chest Wall	Site & Chest Wall	168; Chemotherapy & External Beam Radiation
63 Years Old Male	28 mm LUL Peripheral	Site & N1 Recurrence	296; Chemotherapy
88 Years Old Male	13mm LUL Mid-lobar	Site Recurrence	530; Re-ablated
80 Years Old Female	16 mm LUL Mid-lobar	M1a & N2 Recurrence	350; Chemotherapy
84 Years Old Male	14 mm RUL Peripheral	M1; Widespread	487; Chemotherapy
70 Years Old Male	19mm RLL Mid-lobar	Site Recurrence	669; Chemotherapy

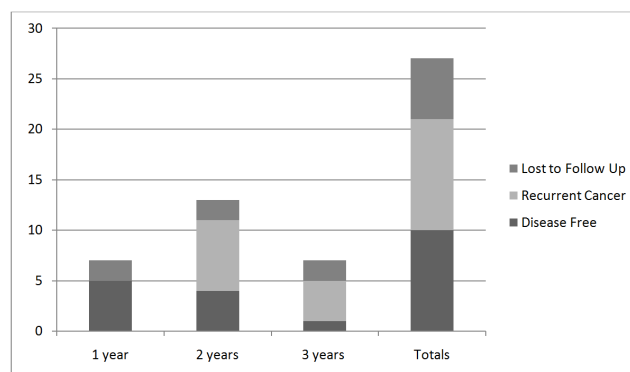


Figure 2. Disease free, recurrent cancer and patients lost to follow up from the time of their initial MWA.

Surgical resection, including lobectomy, anatomic segmentectomy and wedge resection, for the treatment of early stage NSCLC remains the most effective treatment to optimize both survival and freedom from recurrence [16]. The ideal treatment for patients who are not candidates for surgical resection remains to be delineated. Several modalities exist including ablation therapies (RFA, MWA, cryoablation and possibly IRE) and stereotactic ablative radiotherapy (SBRT). All of these modalities appear to be inferior to surgical resection but superior to standard external beam radiation therapy [17]. This paper reviews the results of RFA and MWA at a single institution over a 6-year period. Survival rates for early stage NSCLC treated with RFA have been reported to be as high as 55.7% at 5 years [5] and as high as 61% with MWA at 3 years [18].

Our results reflect similar cancer survival results with an overall rate in the RFA group of 66% (6/9) and 93% (27/29) in the MWA group. The recurrence rate however is much higher with a rate of 89% (8/9) and 41% (11/27) respectively. Although the majority of the recurrences were at the ablation site a significant number represented disease progression: 44% (4/9) for the RFA group and 45% (5/11) for the MWA group with subsequent need for adjuvant therapy and the high probability that these patients will eventually succumb to their malignancy. The median follow-up periods for the RFA and MWA patients in this series were 4.46 and 2.06 years respectively.

All of the patients in this series were followed prospectively by a single surgeon at a single institution during their presentation, workup, treatment and follow-up. This is the strength of the study. Although the data reflects a retrospective analysis of their outcomes they were meticulously followed after undergoing their ablation. Each ablation was performed with both an interventional radiologist and thoracic surgeon present minimizing the probability of poor technique in the performance of the procedure. The results indicate that RFA and MWA rarely render a patient free of cancer but their performance extends the overall survival of patients with NSCLC. The results also indicate that RFA and MWA can be performed safely for NSCLC and that close follow-up is required for patients undergoing either of the procedures.

Percutaneous ablation procedures, like SBRT, risk under staging patients due to the lack of histological lymph node evaluation [17]. It has been reported previously that for clinical Stage I NSCLC the risk of nodal metastases may be as high as 26% [19]. This appears to have been true in 5 of the 9 RFA recurrences in our series and 5 of 11 of the MWA patients with recurrent cancer. Only 3 of these 10 patients had clinical evidence of their recurrences within 1 year of their ablation however. It is therefore unclear whether their recurrences occurred from disease that was occult on their pre-procedural radiological work-up or due to persistent site disease that eventually disseminated. Only 3 of these patients had concomitant evidence of persistent disease at the site when their metastatic disease was identified. It is interesting to note that the median time to recurrence was 842 days for the RFA group and 487 days for the MWA group.

The optimum method for follow-up for patients undergoing ablation for NSCLC remains to be elucidated. It has been previously reported that factors predictive of tumor progression for MWA in the treatment of NSCLC include irregular shape of the tumor and an energy application of less than 26.7 J/mm^3 to the tumor [7]. Cavitation of the treated tumor after ablation has also been reported as a positive prognostic sign [18]. It has also been reported that early changes in tumor size as represented by the RECIST criteria have little impact on survival [8]. Our series suggests that energy application and the presence of cavitation are poor surrogates for a histologically

negative margin and lymph nodes. Meticulous follow-up reveals a high level of recurrence despite energy application rates greater than $1,900 \text{ J/mm}^3$ (45 watts for 10 minutes in tumors with a maximum volume of 14.1 mm^3) and the presence of cavitation on follow-up CT scans which was present in greater than 50% of our patients with recurrence demonstrated.

Radiofrequency and microwave ablation are safe techniques in the treatment of Stage I NSCLC. When compared to a median survival of 13 months in untreated patients with similar tumors [15] it appears that they extend survival. Patients should be advised however that cancer recurrence is likely even at a relatively remote date from their treatment. Consideration for surgical resection should be made in all but the most medically unfit patients. Long term, meticulous follow-up is required in the surveillance of patients undergoing percutaneous ablation for non-small cell lung cancer to optimize their survival.

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