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Local control, safety, and survival following image-guided percutaneous microwave thermal ablation in primary lung malignancy

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AIM: To determine local control, safety, and survival following percutaneous computed tomography (CT)-guided high-power microwave ablation (MWA) in the treatment of primary lung malignancy at a single institution.

MATERIAL AND METHODS: From July 2010 to June 2016, 52 patients (mean age 76.3 years, range 55–91 years) with 61 unresectable primary lung cancers of mean diameter 23.8 mm (range 26–55 mm) underwent MWA in 55 ablation sessions. Tumours were diagnosed at biopsy, or positron-emission tomography (PET) avidity (mean SUV max = 10.51) and interval growth. Statistical analysis was performed by Kaplan–Meier modelling and Cox and logistic regression.

RESULTS: Local tumour progression (LTP) was diagnosed in six lesions (10%). Median time to local recurrence was 3 months (range 2–14 months). There was a near 12-fold increased odds of local recurrence if the lesion size was >3 cm (95% confidence interval [CI]: 1.84–75.14; p=0.009). The median inpatient stay was 1 day, with no intra-procedural deaths and a 0% 30-day post-ablation mortality rate. Pneumothorax requiring drain was the most serious complication, occurring in 22% (n=12) of patients. Presence of severe emphysema and predicted forced expiratory volume in 1 second (FEV1) of <50% were found to predict future requirement of a drain (odds ratio [OR] 8.17, 95% CI: 1.62–41.37, p=0.01 and OR: 5.14, 95% CI: 1.28–20.68, p=0.02 respectively), when adjusted for age and gender. Tumour size >3 cm had a hazard ratio of 4.37 compared with tumour size ≤3 cm (95% CI: 1.45–13.17, p=0.009) of risk of cancer death at any time, by Cox regression.

CONCLUSION: MWA for primary lung malignancy is a safe and effective treatment for primary lung tumours with outcomes that may be comparable to stereotactic body radiation therapy.

Introduction

Lung cancer is the leading cause of cancer death worldwide.[1] Although surgical resection remains the reference standard of treatment for patients with early-stage non-small cell lung cancer (NSCLC), up to 30% of patients with

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stage I and II disease are deemed to be non-surgical candidates as a result of medical co-morbidities and/or poor performance status.[2] Non-surgical patients with early-stage primary lung cancer are offered stereotactic body radiation therapy (SBRT),[3] or thermal ablative treatments such as radiofrequency ablation (RFA)[4–6] or microwave ablation (MWA).[7–13] SBRT has been shown to be superior to RFA in achieving local control, with a recent systematic review and pooled analysis finding local control rates for RFA to be 77% at 1 year compared with SBRT, which are 97% at 1 year, with 3 year local control rates being 55% for RFA and 88% for SBRT.[14]

Of the percutaneous ablative therapies, RFA remains the technique with the greatest established track record, the safety and efficacy for which has been well-described over the past decade. The newer technique of MWA works by inducing the rapid oscillation of water molecules as they attempt to align with the microwave field, which causes cell death by coagulative necrosis. MWA has purported advantages over RFA, achieving higher temperatures, larger ablation zones, and shorter ablation times, as well as having reduced susceptibility to the heat-sink effect. Recent studies have found 3-year survival following MWA to be comparable to that of RFA (29–56%),[9,15–20] with a particular benefit of MWA being less intraprocedural pain.[21] Early studies reported relatively high local tumour recurrence rates for MWA; however, recent series using higher power MWA have achieved better local control rates of 78–96%[10–12,17] at 1 year, approaching comparison to SBRT.

At Churchill Hospital, MWA is offered to patients with both biopsy-proven diagnosis of NSCLC and imaging-based diagnosis of NSCLC (nodule growth of >25% by serial volumetric computed tomography [CT] performed >3 months apart or 2-[^{18}F]-fluoro-2-deoxy-D-glucose [FDG]-activity above mediastinal avidity).

The primary aim of the present study was to determine local control rates and safety of percutaneous image-guided high-power MWA treatment of presumed early-stage primary lung cancers at Churchill Hospital.

Materials and methods

Study design and patient selection

This retrospective study was performed following approval from the institutional review board, with a waiver of informed consent. From May 2010 to January 2016, consecutive patients treated with MWA for single or multiple primary lung malignancy were included in this patient cohort. Patients were selected for treatment following consideration at a weekly multidisciplinary team (MDT) meeting with senior doctors from respiratory medicine, oncology, thoracic surgery, and radiology. Primary lung cancers were referred for ablation when deemed not suitable for resection or SBRT, without evidence of nodal or metastatic disease on combined positron-emission tomography (PET)-CT. Determination of malignancy was obtained either with biopsy or confirmation of FDG activity above mediastinal avidity, along with documented nodule growth of >25% by serial volumetric CT performed >3 months apart. Lung function data, including forced expiratory volume in 1 second (FEV1) and predicted FEV1, was collected pre- and post-ablation where available.

Study population

Fifty-two patients (27 men, 25 women) with a mean age ± standard deviation (SD) of 76.3±8.6 years (range 55–91 years) underwent CT-guided MWA, four patients had multiple lesions treated (2–4), one patient had ablation for different lesions on two separate occasions, and two patients were re-treated for recurrence. Sixty-one lesions were treated, with a mean maximal axial diameter ± SD of 23.8±10.3 mm (range 6–55 mm). Tumours were diagnosed at biopsy in 39% of lesions (24/61) and/or FDG avidity (mean maximum standardised update value [SUVmax] ± SD =10.51±6.4, range 2–28) with interval growth in 61% (37 solitary lesions). For cases with multiple lesions requiring treatment, biopsy or FDG avidity in at least one lesion, combined with interval growth in the other lesions was deemed sufficient to warrant treatment. See Table 1 for patient and tumour characteristics.

Table 1
Patient and tumour characteristics.

Clinical/tumour characteristic	Per patient analysis	Per lesion analysis
Follow-up time		
n	52	61 55 (single tumour 51, multiple tumour 4)
Age (year)		
Mean (range)	76.2 (55.0–91.16)	76.0 (55.10–91.16)
Median (IQR)	75.7 (62.73–88.67)	75.0 (62.10–87.9)
Gender		
Male	27	33
Female	25	28
Biopsy proven		
No	28	37
Yes	24	24
Size (mm)		
Mean (range)		23.82 (6–55)
Median (IQR)		23.00 (11–35)
≤30		49
>30		12
Location		
Upper/middle		27
Lower		34
Radiological		
emphysema	28	
No	24	
Yes	7	
Mild	4	
Moderate	13	
Severe		
FEV1		
<1	7	
≥1	42	
FEV1 percentage		
predicted	12	
<50%	36	
>50%		

IQR, interquartile range; FEV1, forced expiratory volume in 1 second.

Percutaneous MWA

Patients were treated under general anaesthesia in combination with high-frequency jet ventilation.[22,23] General anaesthesia involved intravenous midazolam followed by target-controlled intravenous infusions of remifentanil and propofol. During the procedure, the anaesthetist monitored the patient's heart rate, continuous electrocardiogram, oxygen saturation, and blood pressure. All complications resulting from the ablation procedure were recorded prospectively and classified in accordance with the guidance of the Society of Interventional Radiology.[24,25]

MWA was performed by using a magnetron at a frequency of 2.45 GHz, with fixed power at 180 W until March 2012, and then following a company manufacturing change at 140 W, delivered via an internally-cooled 16-G percutaneous antenna (Accu2i; Angiodynamics, Amsterdam, The Netherlands). The microwave antenna was placed percutaneously into the target lesion using CT fluoroscopic guidance by using the SmartStep technique (LightSpeed VCT, GE Healthcare Milwaukee, WI, USA). The duration of ablation was increased in proportion to lesion volume to achieve complete thermal necrosis.

To treat the lesion with a single applicator position, the operator used a sliding scale of 1.5 minutes for a 1 cm lesion, 3 minutes for a 2 cm lesion, 4 minutes for a 3 cm lesion, and 5 minutes for a 4 cm lesion. If the lesion was not approximately spherical, or any portion of the tumour was not within 0.5 cm of the epicentre of the ablation needle for a 1.5 minute ablation, 1 cm for a 3 minute ablation, 1.5 cm for a 4 minute ablation and 2 cm for a 5 minute ablation, the operator repositioned the needle after the first treatment to achieve complete ablation. When it was anticipated that multiple applicator positions would be required, ablations were at 140 W for 3 minutes each time.

All patients underwent unenhanced CT examination of the chest (LightSpeed VCT; GE Healthcare) with the following parameters: 120 kV, automated 100–650 mA, and 0·625-mm contiguous sections, within 24 hours of ablation. Technical success was defined when the index tumour was treated according to the protocol, with complete coverage of the index tumour by the ablation zone on CT.[25]

Follow-up

Patients were followed with contrast-enhanced CT 3-monthly until either death or local tumour progression was identified, or for at least 12 months post-procedure. Local tumour progression (LTP) was defined as contiguous enlargement or a change in the shape of the ablation zone other than a reduction in size or the development of contrast enhancement in part of the zone.[7,8,26] Mortality data were recorded from the electronic patient medical records. Cancer-specific cause of death was determined from patient records or via cross-sectional imaging showing local or distant disease progression <3 months prior to death.

Statistical analysis

Local control was analysed on a per-lesion basis and using binary logistic regression models. Safety and complications per procedure were recorded, and logistic regression with multivariate analyses used to determine risk factors. Specific complications and 30-day mortality rates were determined. Survival rate was evaluated by Kaplan–Meier and Cox regression analysis on a per-patient basis. Data were analysed using commercially available statistics software (SPSS, IBM (UK) Portsmouth, UK. PO6 3AU).

Results

A total of 61 unresectable primary NSLC lesions were ablated, in 55 ablation sessions, in 52 patients. The procedure was technically successful in 60 lesions (98%) with only one case of technical failure, which was caused by an inability to ablate the upper portion of the tumour due to its proximity to the oesophagus (Fig 1). The median total ablation duration was 4±4.09 minutes (range 1–24 minutes) and the mean size of lesions was 23.8±10.3 mm (range 6–55 mm).

Local control

Sixty-one lesions were followed-up for a median of 12 months (95% CI: 12.1–17, range 1–42 months). Local control was estimated at 88% at a 14-month time period by Kaplan–Meier analysis (Fig 2), with the median time to local tumour recurrence of 3 months (range 2–14 months). Local recurrence occurred in 6/60 cases in which technical success was achieved, with local control for the duration of follow-up achieved in two of these cases following re-ablation, resulting in an overall local control rate of 93% (56/60) for the study period. The relationship between tumour size and local recurrence was determined by binary logistic regression. For every 1 mm increase in tumour size, there was a 14% higher odds of local recurrence (95% CI: 1.04–1.25; p=0.005). Using a cut-off value, there was an 11.8 higher odds of local recurrence if lesion size was >3 cm (95% CI: 1.84–75.14; p=0.009; Fig 3). There was no statistically significant difference in the rate of local recurrence between patients with biopsy diagnosis or imaging diagnosis of NSLC. The presence of emphysema and its severity, occurrence of pneumothorax and/or chest drain, FEV1 or FEV1 percentage predicted, age at procedure, or gender did not have an effect on local recurrence.

Safety

The median inpatient stay was 1 day (SD 3.50 range 0–21), with six patients remaining in hospital for >72 hours. In all cases, discharge was delayed due to the development of pneumothorax. No intra-procedural deaths occurred, and the 30-day post-ablation mortality rate was 0%. Sixteen cases of pneumothorax were diagnosed on chest radiography 1 hour post-ablation (29% of ablation sessions); 12 were deemed Common Terminology Criteria for Adverse

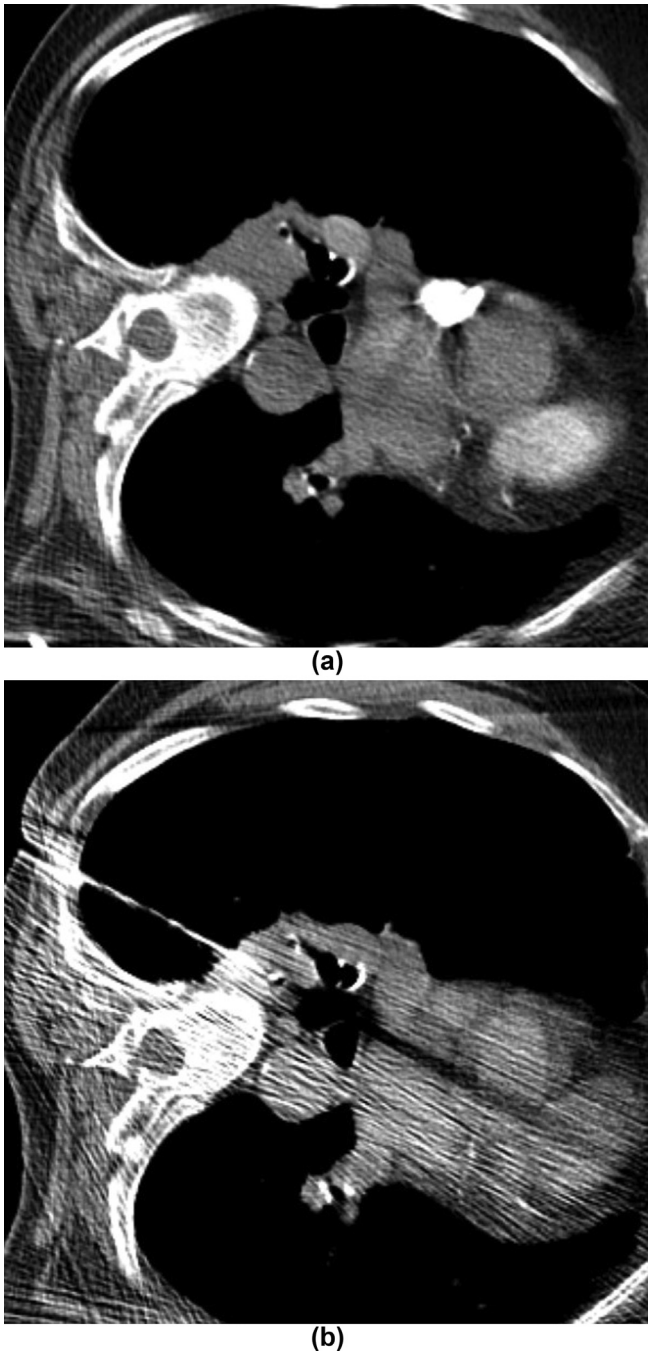

Figure 1 Ablation of tumour in close proximity to the oesophagus.

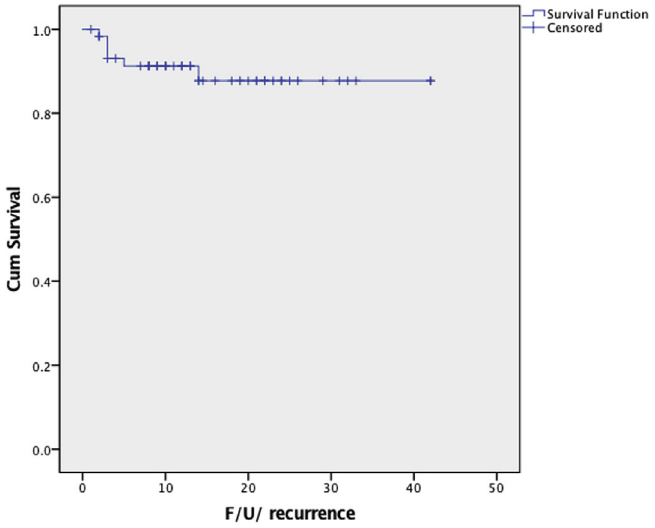

Figure 2 Months to recurrence by Kaplan–Meier analysis.

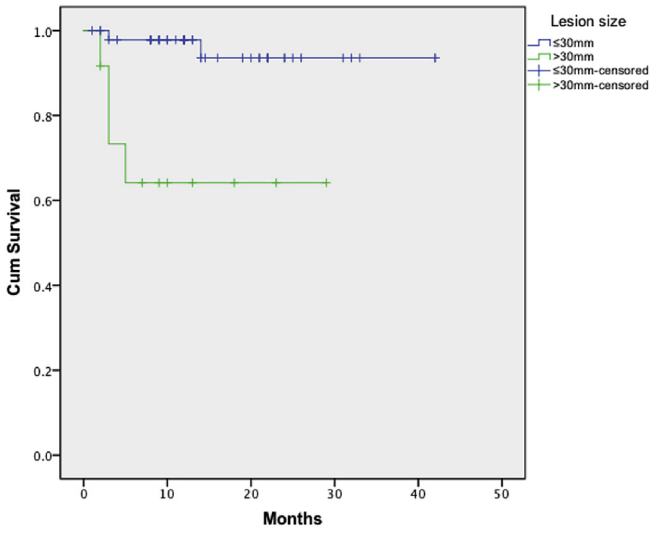

Figure 3 Months to recurrence by original tumour maximal diameter.

Events (CTCAE) grade 2 requiring chest drain insertion (22% of ablation sessions). Of these 12 patients, six were discharged within 72 hours of the ablation procedure. The remaining patients were discharged at 4, 6, 7, 11, 14, and 21 days. The patients discharged at 14 and 21 days had hospital stays complicated by hospital-acquired pneumonia. There were no major complications (grade 3 or higher).

Post-ablation pleural effusion was diagnosed after 12 procedures (22%), none required drainage. Three patients developed mild track haemorrhage post-procedure that did not require treatment (CTCAE grade 1). Twelve patients had surgical emphysema post-procedure. No patients were diagnosed with post-ablation syndrome.

Univariate analyses did not show age, gender, whether the lesion was upper or lower lobe, presence/absence of emphysema, size of lesion, FEV1 or percentage predicted FEV1 to be statistically significant risk factors for the development of pneumothorax. Multivariate logistic regression adjusted for age and gender (see Table 3) showed the presence of severe emphysema to have an eightfold increase in developing pneumothorax requiring an intercostal drain (OR: 8.17, 95% CI: 1.615–41.37 p=0.011). Although FEV1 was not shown to have an impact, a 10% increase in predicted FEV1 was shown to have 35% reduction in odds of requiring a chest drain (OR: 0.65, 95% CI: 0.473–0.925 p=0.016). Using a cut-off value, predicted FEV1 <50% was associated with a fivefold increased odds of

Table 2
Complications following ablation.

	Number (percentage of ablation sessions)
Pneumothorax	16 (29%)
Pneumothorax requiring drain	12 (22%)
Pleural effusion	12 (22%)
Surgical emphysema	12 (22%)
Pulmonary haemorrhage	3 (5%)

pneumothorax requiring a chest drain (OR: 5.14, 95% CI: 1.28–20.68, p=0.02), when adjusted for age and gender.

Survival

During the study period, 32/52 patients (61.5%) died. The Kaplan–Meier median time to death from any cause for all patients (n=52) was 22 months (95% CI: 19–25, range 1–57). The 11-, 24-, and 33-month overall survival was 71%, 37%, and 21%, respectively (see Fig 4). The mean time to cancer-specific death was 33 months (95% CI: 18.9–47.1, range 3–57 months) and the 10- and 24-month survival rates were 86% and 63%, respectively.

There was a 5.5% higher odds of risk of death by cancer-specific mortality at any point in time per 1 mm increase in tumour size (HR: 1.055, 95% CI: 1.011–1.101, p=0.014) by Cox regression. Fig. 5 shows the Cox regression model for lesion size with a cut-off diameter of 3 cm, indicating that tumour size >3 cm was associated with quadruple the odds of death by cancer-specific mortality at any point in time (HR: 4.37, 95% CI: 1.45–13.17, p=0.009). There was no difference in cancer-specific mortality or all-cause mortality between those with biopsy-proven and those with image-proven diagnosis. Presence of emphysema and its severity, occurrence of pneumothorax and/or chest drain, FEV1 or FEV1 percentage predicted, age at procedure, or gender did not have an effect on cancer-specific or all-cause mortality.

Discussion

Percutaneous high-energy MWA is a safe and effective therapy in the treatment of inoperable NSCLC. The technical success rate in the present study was 98% (60/61 cases), and overall local control following re-ablation in two cases was 93% (56/60 cases), at a median duration of follow-up of 13 months. The six cases of local tumour recurrence all

Table 3
Multivariate logistic regression analysis on risk factors for pneumothorax requiring an intercostal chest drain

	n	Univariate analysis			Multivariate analysis			Multivariate analysis		
		OR	95% CI:	p-Value	OR:	95% CI	p-Value	OR	95% CI	p-Value
Age (years)	52	0.97	0.89–1.04	0.37	0.99	0.91–1.08	0.87	1.00	0.91–1.11	0.94
Gender	52									
Male		Reference								
Female		0.66	0.17–2.61	0.57	1.55	0.32–7.42	0.58	0.79	0.20–3.23	0.75
Emphysema	55									
Absence		Reference								
Presence		2.78	0.724–10.66	0.14						
Severe emphysema	55									
Absence		Reference								
Presence		7.20	1.77–29.33	0.01	8.17	1.62–41.37	0.01			
FEV1 (10ml)	55	0.99	0.98–1.00	0.10						
FEV1	55									
>1 l		Reference								
<1 l		1.52	0.26–9.028	0.65						
FEV1 percentage predicted (10%)	55	0.65	0.463–0.93	0.02				0.65	0.44–0.96	0.031
FEV1 %predicted	55									
>50%		Reference								
<50%		5.14	1.28–20.68	0.02						
		3								
Lobe	61									
Lower		Reference								
Upper	61	0.76	0.22–2.63	0.67						
Lesion size (mm)	61	0.98	0.90–1.03	0.31						

OR, odds ratio; CI, confidence interval; FEV1, forced expiratory volume in 1 second.

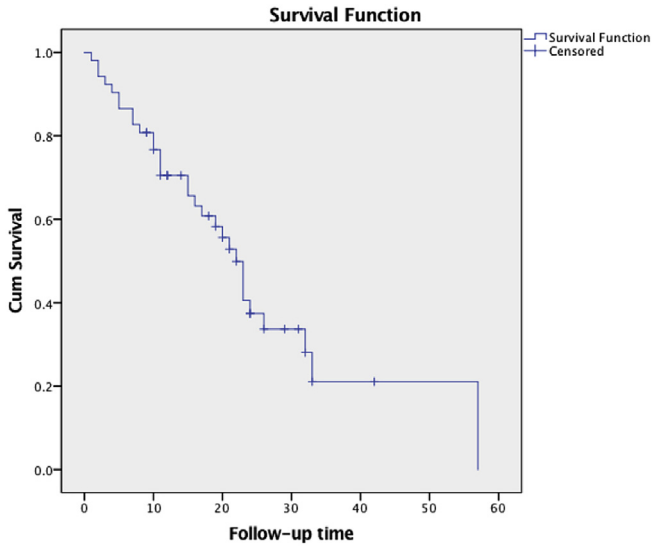

Figure 4 Overall survival by Kaplan–Meier analysis.

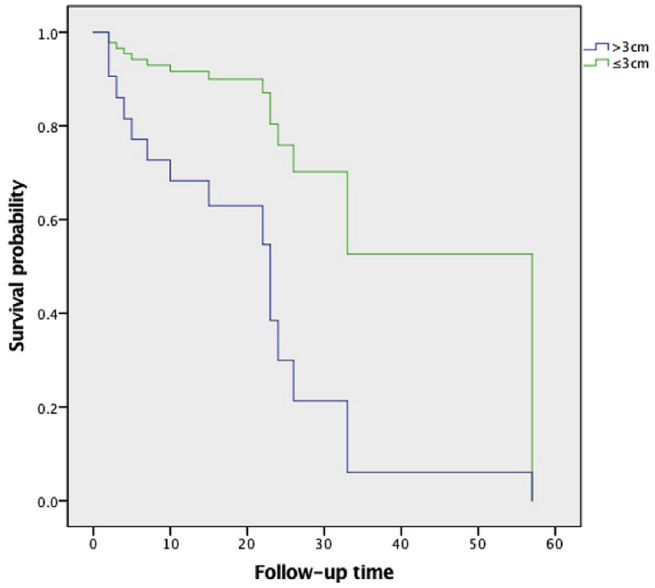

Figure 5 Multivariate Cox regression hazard analysis adjusted for age and gender.

occurred within 14 months of ablation and local control was estimated at 87% at a 14-month time period. The present findings compare favourably with the literature for the use of MWA in lung tumours (both primary and metastatic), with the largest study with the longest follow-up time periods finding local control to be estimated at 75% at 12 months, 59% at 24 months and 40% at 40 months.[10]

Increased lesion size increases risk of local recurrence, a relationship that has also been shown by other authors using thermal ablation, including MWA, in lung tumours.[6,8,10] An important difference when compared to RFA, however, is that local control for tumours >3 cm was 83% for the duration of follow-up whereas the RFA literature shows incomplete tumour necrosis in the majority of treated tumours >3 cm in size. In the present series, no other tumour characteristic was found to correlate with local recurrence.

Local recurrence has been shown to occur as a result of failure of adequate conductive heating at the periphery of the ablation zone. The experience from RFA literature is that LTP occurs early in follow up, with late failure uncommon.[27,28] The present authors' experience is similar, the present treatment failures all occurred within 14 months. No LTP was seen in the group of 21 patients in whom there is >18 months of follow-up.

The most frequent complication in the present study was pneumothorax (41%), with pneumothorax requiring a chest drain in 22% of cases (see Table 2). This is similar to the quoted rate of pneumothorax from thermal ablation of lung tumours as 15–45%[27,29–31] using either MWA or RFA. The presence of severe emphysema, as determined by CT, and percentage predicted FEV1 were the only risk factors to the development of pneumothorax requiring a drain. The fact that percentage predicted FEV1, and not FEV1 or FEV1 <1 l as used in most studies, was shown to be predictive of a pneumothorax requiring a drain, may have implications for future patient selection and determination of risk of pneumothorax in MWA. Previously described significant variables, such as lesion size, upper versus lower lobe, and FEV1 were not found to have a significant impact in the present study. No other post-procedural complications required further management or intervention and the 30-day mortality was 0.

Overall survival in the present patient cohort was 61% at 1 year. Previous studies have shown overall survival for MWA at 1 year to range between 55–100%.[9,10,17,19,21,32,33] The difference in overall survival likely reflects the inclusive eligibility criteria and resulting differences in the patient characteristics of the present cohort, in particular older median age and multiple co-morbidities. Meanwhile, the present 10- and 24-month cancer-specific survival rates of 86% and 63%, respectively, is lower than that of Healey *et al.* with 11- and 24-month survival rates of 89% and 75%, respectively.[10] The difference may in part be due to the present series solely including primary lung cancer and including patients with other synchronous lung tumours and those with multiple primaries. Unlike the findings of previous studies[910], tumour size was found to have an effect on cancer-specific survival, independent of local recurrence in a Cox regression model.

The mean length of ablation in the present study was of only 4 minutes with a maximum total ablation time of 24 minutes. In order to achieve good local control with RFA, ablation times of up to 50 minutes are required, as well as an ablation zone very much larger than the original tumour. Shorter ablation times allow less use of sedation and anaesthetics, and theoretically reduce complication rates.[20,34]

There are number of potential weaknesses of the present study. Firstly, in all cases recurrence was diagnosed by imaging features rather than confirmed histologically. Further, this study is unusual in that image-diagnosed NSCLC was included in the eligibility criteria. This pragmatic approach reflects clinical practice, in which patients referred for

treatment often have a low FEV1 and the additional risk from biopsy was balanced against the diagnostic benefit. It is consistent with clinical practice for primary lung tumours, whether treated with surgery, ablative radiotherapy, or thermal ablation, and is also consistent with published guidelines[35]; however, this introduces selection bias as there is the possibility that some of these lesions were not primary NSCLC, but metastases with an unknown primary, or small cell lung cancer. Nevertheless, there was no statistically significant difference in local tumour recurrence, and overall and cancer-specific mortality between biopsy-proven and imaging-diagnosed NSCLC. It is also important to note that a change in power output during product development of the microwave system used did not have an impact on outcomes.

The treatment options for primary lung malignancy when for a non-surgical candidate is SBRT or thermal ablation, which can be via RFA or MWA. The overall recurrence rates reported in the present series suggest that MWA may be superior to RFA, and even as good as SBRT at achieving local control. The pattern of LTP occurrence with SBRT is one of increasing incidence with increasing length of follow-up, in distinction to the pattern of early LTP seen with ablation.[27] Although the diagnosis of LTP after MWA appears reliable, recurrence after SBRT may be difficult to diagnose with certainty on CT.[28] SBRT has the advantage of being non-invasive and does not require an anaesthetic or an overnight stay in hospital; however, it does require multiple hospital visits. SBRT also has the recognised complications of radiation-induced pneumonitis,[36] chronic chest wall pain, and rib fractures,[37] and appears to be less effective when the radiation dose is reduced because of lesion adjacency to significant mediastinal and hilar structures[38] and the chest wall.[39] For the more elderly patients as in the present cohort, SBRT may be more toxic and less effective.[40] Further studies and longer follow-up data are required to determine how MWA compares with SBRT and RFA, in particular in terms of local control rates.

The present study was limited by its retrospective nature, relatively short follow-up, small sample size, and heterogeneity in diagnosis; however, it adds to the safety and efficacy literature of the use of MWA in primary lung cancer. The present study demonstrates that high-power MWA in presumed non-operable primary lung tumours is both safe and effective with outcomes that may be comparable to SBRT.

Conflict of interest

Dr. Anderson reports personal fees from AngioDynamics, outside the submitted work.

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