Are modified RECIST the gold standard for response assessment of lung tumours treated with microwave ablation?

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Abstract: Introduction: mRECIST were introduced in early 2000 for radiofrequency ablation (RFA) of lung tumours. This retrospective study was performed to evaluate mRECIST in the assessment of lung tumours treated with microwave ablation (MWA).

Material and Methods: All percutaneous CT–guided MWA of lung tumours performed between June 2010 and December 2016 were identified and cases with at least 10 months follow-up were included. The therapeutic response was evaluated based on mRECIST.

Results: Of the 35 patients included 23 had non-small cell lung cancer (NSCLC) and 12 patients had colorectal cancer (CRC) metastases. Compared to the 24-h post-ablation scan, at 24 months the median CT mass size had reduced to 51.1% from baseline. Based on mRECIST, at 12 months 84.8% showed partial response and 15.2% had stable disease. At 24 months 90% (n = 20) showed partial response whereas 5% had stable disease and another 5% showed complete response. A large proportion of patients were alive 12 months after MWA with a partial response based on mRECIST; this partial response rate had not changed at the 24 months mark.

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PUBLIC INTEREST STATEMENT

Microwave ablation (MWA) has become an established treatment option for solid tumours and proves to be more potent in the treatment of lung cancers than radiofrequency ablation (RFA), a heat-based thermal ablation modality that has been around for approximately a decade longer. The ablation duration with MWA is much shorter, usually shorter than 10 min, and the thermal damage is much larger and more homogeneous. Ensuing inflammatory reaction locally and along the lymphatic drainage path also tends to be stronger and to last longer than with RFA.

The modified response evaluation in solid tumours (mRECIST) for lung lesion ablation, established and published 2007, was relating to thermal damage produced by RFA. Applying the same criteria to lung tumours treated by MWA may lead to misinterpretation of the radiology findings in the wake of the ablation, potentially labelling the ablation result “progressive disease” when in fact the ablation has been successful.

This article challenges mRECIST for the assessment of lung MWA.
Conclusion: This study challenges the use of mRECIST for the assessment of therapeutic response of lung tumours treated with MWA suggesting that timelines, especially regarding the baseline scan and ablation characteristics, may need to be revised.

Subjects: Medicine, Dentistry, Nursing & Allied Health; Medicine; Oncology; Radiology

Keywords: mRECIST; lung cancer; microwave ablation; thermal ablation

1. Introduction

Lung cancer remains the leading cause of cancer death worldwide. (Wong, Lao, Ho, Goggins, & Tse, 2017) Metastatic deposits from various primary sites are commonly seen in the lung. Surgical resection is the best curative treatment option for lung cancer. However, many patients with lung tumours have significant medical comorbidities, precluding them from operative management (Shirvani et al., 2012). In the last few decades, minimally invasive percutaneous ablative techniques such as radiofrequency ablation (RFA) have been increasingly used as an alternative local therapy to treat both primary and metastatic lung malignancies in selected patients. (Hiraki et al., 2007a, 2007b; Lencioni et al., 2008; Simon et al., 2007; Yamakado, Hase, & Matsuoka et al., 2007)

RFA has been used for many years in different clinical scenarios including the treatment of cardiac arrhythmias caused by aberrant conduction pathways (Calkins et al., 2000). By early 2000, its clinical application in treating lung tumours had been studied and accepted (Dupuy et al., 2000; Hiraki et al., 2007a, 2007b; Lencioni et al., 2008; Simon et al., 2007; Yamakado et al., 2007). After its introduction for the treatment of lung cancer, modified Response Evaluation Criteria in Solid Tumours (mRECIST) had been developed to assess the tumour response to RFA (Table 1). (Herrera et al., 2003)

More recently, microwave ablation (MWA) has gained momentum in treating lung tumours because of its ability to deliver faster and deeper ablation with a uniform distribution of energy (Simon, Dupuy, & Mayo-Smith, 2005) creating larger and uniform zones of ablation. (Brace, Hinshaw, Laeseke, Sampson, & Lee, 2009) However, this technical advantage over RFA poses a special challenge in using mRECIST in evaluating lung cancers treated with MWA. The more potent MWA creates larger volumes of thermal damage and stronger inflammatory response may result in mis-judgement of the therapeutic response using mRECIST criteria. Hence, this retrospective study was conducted to assess the usefulness of mRECIST in the evaluation of MWA-treated lung malignancies, in particular, to challenge the appropriateness of using pre-ablation mRECIST as a baseline measure.

| Table 1. Modified RECIST criteria for thermal ablation of lung tumours |
|---------------------------------------------------------------|
| **Response** | **CT mass size** | **CT mass quality** | **PET** |
| Complete (2 of the criteria) | Lesion disappearance or <25% of original size | Cyst or cavity formation; low density | SUV <2.5 |
| Partial (1 of the criteria) | >30% decrease in sum LD of target lesions | Mass central necrosis or central cavity with liquid density | Decreased SUV or area of FDG uptake |
| Stable lesion (1 of the criteria) | <30% decrease in sum LD of target lesions | Mass solid appearance, no central necrosis or cavity | Unchanged SUV or area of FDG uptake |
| Progression (2 of the criteria) | Increase >20% in sum LD of target lesions | Solid mass, invasion of adjacent structures | Higher SUV or larger area of FDG uptake |

LD = largest diameter; FDG = 18-Fluorodeoxyglucose; SUV = standard uptake value
2. Methods

2.1. Patients and study period
Institutional ethics approval was obtained (HREC/14/QRBW/553). In this retrospective cohort study, searching our departmental thermal ablation database, we identified a total of 70 patients who underwent CT-guided MWA of pulmonary tumours at our institution between June 2010 and December 2016. Inclusion criteria consisted of a follow-up period of more than 10 months. Patients were excluded if they had a repeat ablation of the same lesion within a 12-month period, or other concurrent or sequential therapies including surgery, radiotherapy or chemotherapy. Thirty-five patients were included in this study.

2.2. Instrumentation
All ablations were performed under CT guidance. The Acculis microwave tissue ablation system (AngioDynamics, Latham, NY, USA) was used in 30 cases. The system operates at 2.45 GHz with a maximum power output of 140 W. Three cases were treated with the Amica MWA system (HS hospital Service, Rome, Italy), which also operates at 2.45 GHz with a maximum output of 140 W. The Evident TM system (Covidien, Boulder, CO, USA) was used in two cases, operating at 915 MHz with a maximum power output of 45 W.

2.3. Procedure
One interventional radiologist with more than 15 years of experience in image-guided thermo-ablation performed all ablations. Written informed consent was obtained. Anticoagulation or antiplatelet therapies were stopped for 1 to 7 days prior to the procedure. No antibiotic prophylaxis was administered. Conscious sedation or general anaesthesia was used during all ablation sessions, as per the preference of the anaesthetic team.

Immediately prior to each MWA, a non-contrast CT scan of the target area was obtained for approach planning. Under sterile conditions and CT guidance, the antenna was inserted into the target lesion. Multiplanar reformats were used for confirmation of the final antenna position. Some patients underwent over-lapping ablations, depending on the size and shape of lesions. In addition, power output and ablation duration were carefully considered and chosen based on the lesion size, shape and proximity to vessels.

2.4. Post-procedural follow-up
In addition to the limited non-contrast CT scan immediately after removal of the antenna, a routine chest X-ray was performed 3 h after MWA to assess post-procedure complications. All patients were admitted overnight post ablation and underwent a non-contrast CT scan of the ablation site on the following day to evaluate the thermal damage and assess potential complications not identified on X-ray imaging. This 24-h CT scan was also used as a baseline scan for comparison with all future scans.

Further follow-up imaging with contrast-enhanced CT, unless contra-indicated, was performed at 3, 6, 12, 18, 24 months post-MWA and yearly thereafter for a total of five years. A two-month window either side of each target follow-up was accepted and included as that target interval's scan.

DICOM data of follow-up scans were uploaded and reviewed on an AFGA IMPAX 6 workstation, and measurements of ablated lesions were performed in the lung window on axial images. The longest diameters of an ablated lesion were compared on subsequent scans. The mass quality was also noted as defined by mRECIST criteria.

Fludeoxyglucose-positron emission tomography (FDG-PET) performed 3 to 24 months after MWA was included. Not all patients had an FDG-PET scan pre- and/or post-ablation, as it often had not been readily available. Post-ablation FDG-PET results were only evaluated in patients with a pre-MWA FDG-PET for comparison. The maximum standard uptake value (SUVmax) was established...
with syngo.via (Siemens imaging software). The value was calculated from the FDG dose, time of administration and imaging, and patient's weight and height. The therapeutic response to MWA was then determined using mRECIST criteria.

2.5. Statistical analysis
Patient characteristics and tumour responses were summarised using mean (standard deviation (SD)) or median (interquartile range (IQR)) for continuous variables and frequencies and percentage for categorical variables. Stata15 was used for analyses and graphs.

3. Results
Thirty-five patients met the inclusion criteria with a mean age of 68.2 years (SD 12.5) and 66% male. Twenty-three patients had NSCLC, and 12 patients had CRC metastases. The pre-ablation median size of the treated lesions was 20 mm (IQR 16.0–26.0 mm).

CT mass size was evaluated on serial follow-up CT scans (Table 2). Median follow-up was 26 months (range 12 to 68 month). When the pre-ablation size was considered as baseline, the CT mass size increased to 219.7% of the original lesion on the 24-h post-ablation scan (Table 3). At 24 months, the median lesion CT mass size was still larger than its baseline.

On the other hand, when the 24-h post-ablation size was considered as baseline, the lesion was 70.5% of the baseline at 3 months and reached 51.1% at 24 months. Irrespective of the baseline used, the lesion size seemed to reach a plateau by the 24-month period, although there were 15 missing data points at that stage.

CT mass quality was also evaluated over time with comparison to the 24-h post-ablation scan. At 3 months post-ablation, 66.7% were classified as stable disease and 26.7% demonstrated partial response. At 24 months, 85% were stable disease and 10% showed partial response.

Out of 35 patients, there were 17 patients with complete pre- and post-ablation SUVmax measurements. Fourteen (82%) of these patients had a reduction in a SUVmax whereas 3 (18%) had an increase in SUVmax.

Using pre-ablation size as baseline, the final mRECIST outcome (Table 3) at 12 months resulted in 84.8% (n = 28) with partial response and 15.2% (n = 5) with stable disease. At 24 months post-ablation (n = 20), 90% had partial response. None of the patients with partial response showed clinical features of disease recurrence or progression.

### Table 2. Absolute and percentage CT mass size change over time

| Time         | Size (mm)    | % CT mass size |
|--------------|--------------|----------------|
|              | pre-ablation | 24hrs post-ablation baseline | pre-ablation baseline |
|              | 20.0 (16.0–26.0) | 100 | 219.7 (182.4–250.7) | 100 |
| 24 hrs post-ablation | 45.0 (36.8–50.0) | 141.9 (123.1–180.0) | 70.5 (62.2–81.1) |
| 3 months post (n = 35) | 28.8 (24.7–35.0) | 125.4 (106.2–159.3) | 62.5 (50.9–77.8) |
| 6 months post (n = 31) | 25.0 (20.0–32.6) | 111.2 (101.2–132.6) | 56.0 (45.8–71.3) |
| 12 months post (n = 33) | 24.8 (17.6–30.5) | 113.7 (102.3–186.9) | 55.7 (47.1–66.4) |
| 18 months post (n = 19) | 23.8 (16.5–31.6) | 111.9 (94.9–156.5) | 51.1 (43.6–63.9) |
| 24 months post (n = 20) | 23.0 (19.1–29.4) | 111.9 (94.9–156.5) | 51.1 (43.6–63.9) |

Data presented as median (IQR)
4. Discussion

Over the past decade, MWA has gained in popularity, as it has theoretical advantages over RFA. Recent studies (Acksteiner & Steinke, 2015; Han et al., 2015; Sun, Song, Guo, & Sheng, 2015) show promising results in local tumour control and overall survival with comparable complication rates. (Egashira, Singh, Bandula, & Illing, 2016; Ni, Han, Ye, & Wei, 2015; Splatt & Steinke, 2015; Vogl et al., 2017)

As ablative techniques gain popularity in treating both primary and secondary lung cancers, therapeutic evaluation becomes challenging, as pathological assessment is not an option the ablated lesions show different courses of evolution. When RFA initially gained momentum as a minimally invasive alternative treatment option for pulmonary malignancies, modified RECIST criteria were developed in 2003 (Herrera et al., 2003). The new criteria incorporated the size, characteristics, and PET avidity of an ablated lesion to account for the difference in the therapeutic response—opposed to tumours treated with other means, usually chemotherapy, where only unidimensional size is taken into account (RECIST criteria).

mRECIST criteria have failed to unequivocally instruct clinicians when to perform the first post-ablation scan as a baseline for future serial imaging. Multiple studies (Goldberg et al., 2009; Zaheer, Whitley, Thomas, & Steinke, 2015) have established their baseline scan at different time points, including at 24 h, 1 month and 3 months post-ablation. Our study demonstrates how different baseline scans (pre-ablation and 24hrs post-ablation) can lead to drastically different therapeutic evaluations. The CT mass size dramatically increased from pre-ablation to 24-h post-ablation (Figure 1 a-c) and gradually decreased thereafter (Figure 2 a-c) with many patients’ CT mass size not reaching their pre-ablation levels over the follow-up period (Figure 3 a-c). Furthermore, most lesions showed the greatest size reduction within 3 to 6 months post-ablation (Table 2). Thus, if a baseline scan were performed at a time later than 24 h post ablation, the size reduction would be less over time leading to underestimation of the therapeutic response. Therefore, this inconsistency can influence the therapeutic evaluation and conclusions derived using mRECIST.

In our study, the use of MWA in lung has demonstrated at times a large circumscribed density at the ablation site that can persist over time. This persistence influences the therapeutic response establishment both in size and mass quality in mRECIST criteria. Our study demonstrates that CT size reaches a plateau after a period of regression. None of the ablated lesions was considered as a complete response by size (Table 3). In addition, an increasing proportion of the treated lesions showed stable disease in CT mass quality over time. Our study also demonstrated that a significant proportion of patients were alive and well with no clinical signs of residual disease despite that therapeutic response was evaluated as an overall partial response for more than 2 years post ablation based on mRECIST. These results indicate that mRECIST use in evaluation of MWA treated lung tumours could be misleading.

In addition, FDG-PET, often used to clarify uncertainty in therapeutic response on serial CTs, is not always readily available everywhere. Thus, post-ablative tumour response is often limited to its

| Time post ablation               | mRECIST outcome |
|----------------------------------|-----------------|
|                                 | Complete response | Partial response | Stable disease | Progressive disease |
| 12 months post (n = 33)          | 0 (0%)           | 28 (84.8%)       | 5 (15.2%)      | 0 (0%)             |
| 18 months post (n = 19)          | 0 (0%)           | 16 (84.2%)       | 3 (15.8%)      | 0 (0%)             |
| 24 months post (n = 20)          | 1 (5.0%)         | 18 (90.0%)       | 1 (5.0%)       | 0 (0%)             |

Data presented as n (%)
diameter and mass characteristic using mRECIST. As seen in our study, this has likely resulted in an underestimation of therapeutic response if evaluated by mRECIST, resulting in a partial response or stable disease even years following MWA.

Although SUVmax decreased over time in most cases in our study, suggesting disease response, however only in a minority of the cases Zaheer et al. warned that not all persistent, increased or even new FDG avid uptake at the ablation site is necessarily indicative of local recurrence. (Durick et al., 2008)

mRECIST criteria have been developed based on experience with RFA and have been adopted as a guide for monitoring therapeutic response post ablation of lung tumours. However, MWA with a much more powerful output causes larger ablation volumes and associated architectural distortion persisting for a long time. Furthermore, increased inflammatory reactions appear to ensue (personal observation).
Whether treatment response is under- or overestimated will depend on the choice of baseline scan: with pre-ablation size underestimation will happen, whereas with post-24-h ablation size, over-estimation is likely.

The challenge comes from difficulty in differentiating between inflammatory response and treatment response based on CT mass size and quality.

This retrospective study was limited by the fact that not all patients had their follow-up CT scan at the same recommended time interval or had FDG-PET scans pre- and post-MWA to fully assess the appropriateness of mRECIST. A considerable proportion of records were missing from 18 months post-ablation onwards with a decreasing number of patients with serial scans. The exploration of patients’ discharge letters from hospital admissions after the lung tumour ablations often failed to mention the lung cancer treatment all along.

The results should be interpreted with caution as there may be a selection bias owing to missing records.

5. Conclusion
This study challenges the use of mRECIST criteria for the assessment of therapeutic response of lung tumours treated with MWA. It is suggestive that timelines, especially regarding the baseline scan and ablation characteristic criteria may need to be revised. Given the inherent limitations of this retrospective study, prospective studies are required to corroborate these results.

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