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INTERVENTIONAL

Standardizing percutaneous Microwave Ablation in the treatment of Lung Tumors: a prospective multicenter trial (MALT study)

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Abstract

Objectives To prospectively assess reproducibility, safety, and efficacy of microwave ablation (MWA) in the treatment of unresectable primary and secondary pulmonary tumors.

Methods Patients with unresectable primary and metastatic lung tumors up to 4 cm were enrolled in a multicenter prospective clinical trial and underwent CT-guided MWA. Treatments were delivered using pre-defined MW power and duration settings, based on target tumor size and histology classifications. Patients were followed for up to 24 months. Treatment safety, efficacy, and reproducibility were assessed. Ablation volumes were measured at CT scan and compared with ablation volumes obtained on ex vivo bovine liver using equal treatment settings.

Results From September 2015 to September 2017, 69 MWAs were performed in 54 patients, achieving technical success in all cases and treatment completion without deviations from the standardized protocol in 61 procedures (88.4%). Immediate post-MWA CT scans showed ablation dimensions smaller by about 25% than in the ex vivo model; however, a remarkable volumetric increase (40%) of the treated area was observed at 1 month post-ablation. No treatment-related deaths nor complications were recorded. Treatments of equal power and duration yielded fairly reproducible ablation dimensions at 48-h post-MWA scans. In comparison with the ex vivo liver model, in vivo ablation sizes were systematically smaller, by about 25%. Overall LPR was 24.7%, with an average TLP of 8.1 months. OS rates at 12 and 24 months were 98.0% and 71.3%, respectively.

Conclusions Percutaneous CT-guided MWA is a reproducible, safe, and effective treatment for malignant lung tumors up to 4 cm in size.

Key Points

- *Percutaneous MWA treatment of primary and secondary lung tumors is a repeatable, safe, and effective therapeutic option.*
- *It provides a fairly reproducible performance on both the long and short axis of the ablation zone.*
- *When using pre-defined treatment duration and power settings according to tumor histology and size, LPR does not increase with increasing tumor size (up to 4 cm) for both primary and metastatic tumors.*

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Keywords Lung · Neoplasms · Safety · Microwave · Radiofrequency ablation

Abbreviations

AVG	Average
CA	Complete ablation
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CV	Coefficient of variation
D	Ablation short axis (i.e., diameter perpendicular to the microwave probe)
DP	Distant progression
DPR	Distant progression rate
E_d	Microwave energy delivered to the patient
EV	Ex vivo data series (i.e., ablations on ex vivo bovine liver)
GGO	Ground-glass opacity
IV	In vivo data series (i.e., ablations on MALT patients)
L	Ablation long axis (i.e., longest diameter, along the microwave probe track)
LP	Local progression
LPFS	Local progression-free survival
LPR	Local tumor progression rate
MALT	Microwave Ablation of Lung Tumors (study acronym)
MALT1	MALT study arm related to primary lung tumors
MALT2	MALT study arm related to metastatic lung tumors
MAX	Maximum value
MIN	Minimum value
MW	Microwave radiation (2450 MHz)
MWA	Microwave ablation
NSCLC	Non-small cell lung cancer
OS	Overall survival
P	Power of ablation treatment
PA	Partial ablation
RFA	Radiofrequency ablation
S	Ablation sphericity index
SBRT	Stereotactic body radiation therapy
SD	Standard deviation
T	Duration of ablation treatment
TDP	Time to distant progression
TLP	Time to local progression
V_0	Ablation volume measured pre-MWA
V_n	Normalized ablation volume
V_t	Ablation volume measured at time *t* post-MWA

Introduction

Percutaneous thermal ablation is emerging as a safe and effective loco-regional alternative to surgery and stereotactic body radiation therapy (SBRT) for the treatment of either primary early-stage or metastatic pulmonary tumors [1, 2]. Alternating electric current circuits generating electromagnetic waves in the 400–500 kHz range (radiofrequency) have been mostly used for this purpose; they cause tissue heating through ionic agitation and Joule effect. Over the last decade, microwave ablation (MWA) has gained increasing popularity, partly supplanting RF ablation (RFA) for percutaneous thermal ablation of tumors in numerous anatomical districts [3–7]. MW heating is based on a dielectric mechanism, secondary to friction among molecular electric dipoles that are simultaneously rotating due to fast switching electromagnetic waves [3].

However, MWA is a relatively new technique compared with RFA, with a remarkably wider variability in device design and performance, more complex decision-making algorithms for treatment planning, and a less trivial correlation between the expected ablation size and any probe-related feature [4–8]. All these account for a lack of standardization in MWA treatment protocols, especially in extra-hepatic clinical applications such as the ablation of lung tumors. The coagulation charts provided by vendors are the most readily available guidelines to MWA planning, but they are based on ex vivo animal models (usually liver) that differ from the in vivo scenario. Very few published MWA clinical series contribute to build predictive models alternative to the vendors' coagulation charts [9].

Our study (named "MALT," i.e., Microwave Ablation of Lung Tumors) was designed to fill this gap of knowledge and to prospectively evaluate the performance repeatability of a commercially available 2450-MHz MWA system for the CT-guided percutaneous treatment of primary and metastatic pulmonary tumors up to 4 cm in diameter, using pre-defined treatment settings. We investigated the correlation between applied energy and ablation volume at post-procedural CT scan evaluations. Ablation volumes were also compared with those provided by the manufacturer's ex vivo bovine liver coagulation chart in order to evaluate its capability in predicting clinical performance. Secondary endpoints were safety and clinical efficacy assessments, in terms of immediate and delayed complications and of overall (OS) and local progression-free survival (LPFS) rates.

Materials and methods

Study design

MALT study was designed as a prospective multicenter clinical trial enrolling consecutive patients with inoperable primary ("MALT1" study arm) or metastatic ("MALT2" study arm) lung cancers up to 4 cm in size. It was performed at three

different centers, each with no less than 15 years of prior experience in percutaneous thermal ablation procedures on multiple target organs. The study was conducted in respect of the Declaration of Helsinki, according to the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice. The Institutional Review Board of each participating center approved the study and all enrolled patients signed a specific written informed consent.

A multidisciplinary tumor board deemed patients unresectable and candidates to percutaneous thermal ablation treatment. Inclusion and exclusion criteria for MALT study are listed in Table 1. Pre-treatment work-up included routine physical examination, laboratory tests, and re-evaluation by contrast-enhanced chest computed tomography (CT) when needed. All demographic and clinical data were collected in a study-specific case report form.

In each study arm (MALT1 and MALT2), lesions were classified according to size (group 1: less than 2 cm; group 2: between 2 and 3 cm; group 3: between 3 and 4 cm).

MWA treatment

All thermal ablation treatments were performed via percutaneous approach, under CT guidance, using the HS AMICA™ 2.45-GHz microwave ablation system HS Hospital Service SpA), composed of a solid-state microwave generator with output of up to 140 W (AMICA-GEN, either model AGN-H-1.0 or AGN-3.0), and 14 G internally cooled interstitial applicators (AMICA-PROBE). A single antenna was used in all MWA treatments (Figs.1 and 2).

Each lesion was treated inserting the antenna along the major lesion axis, placing the tip 1 to 5 mm beyond the tumor distal edge in order to obtain a sufficient (5–10 mm) safety margin (Fig. 2). Treatment protocol was standardized to continuous MW energy delivery at a pre-defined power rate (P) for a pre-defined time (T = 10 min), without neither probe repositioning nor power variations during the treatment. P was pre-determined based on the lesion histology (considering that primary lung tumors need a wider safety margin than metastases [10–13]) and size, namely P = 40 W-60 W-80 W for treating tumors belonging to groups 1-2-3 of the MALT1 arm and P = 30 W-50 W-70 W for treating tumors belonging to groups 1-2-3 of the MALT2 arm. Treatment protocols were selected to warrant full coverage of the nodules (including the required safety margin) and equal energy delivery ($E_d = P*T$ in seconds) in all lesions belonging to the same study group (E_d = 24 kJ-36 kJ-48 kJ for groups 1-2-3 of MALT1 and E_d = 18 kJ-30 kJ-42 kJ for groups 1-2-3 of MALT2). In the case of patients with multiple lesions, these were treated in the same session if located in the same lobe or lung (Fig. 2), or in separate sessions otherwise. All procedural data tracked by the generator during MWA procedures were recorded and attached to the correspondent case report form.

Treatments not complying with all listed procedural rules were excluded from the study for the evaluation of treatment repeatability and for comparison with the ex vivo animal model, while being still considered for secondary purposes (complications and clinical success rates).

Ex vivo (ablation chart)/in vivo comparison

Ex vivo coagulation charts are often used as a reference for MWA treatment planning in clinical practice. As for the MWA system used in the MALT study, the coagulation chart provided by the manufacturer is the results of laboratory experiments conducted on ex vivo bovine liver at room temperature using various settings (P = 20, 40, 60, 80, and 100 W; T = 3, 5, 10, and 15 min). The chart reports the long-axis (L_{ev}, i.e., along the MWA probe trajectory) and short-axis (D_{ev}, i.e., perpendicular to the MWA probe) measures of the

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Oral anticoagulant drugs in the days before the procedure.
Signed informed consent	Known allergy to iodinated contrast media
1–5 lung lesions	Need of urgency/emergency treatments
Lesion size: ≤ 4 cm	Moderate/severe kidney function impairment (assessed by the MDRD or by Cockcroft-Gault formula: glomerular filtration rate < 45 mL/min/1.73 m^2)
Platelet count ≥ 50,000/mm^3	Pregnant or lactating women
International normalized ratio < 1.5	Previous pneumonectomy
Prothrombin time < 15 s	Active enrolment in other studies
Thromboplastin time < 45 s	Prior sites of local therapies (including surgery and ablation) less than 2 cm apart from the lesion
Life expectancy > 6 months	Life expectancy ≤ 6 months

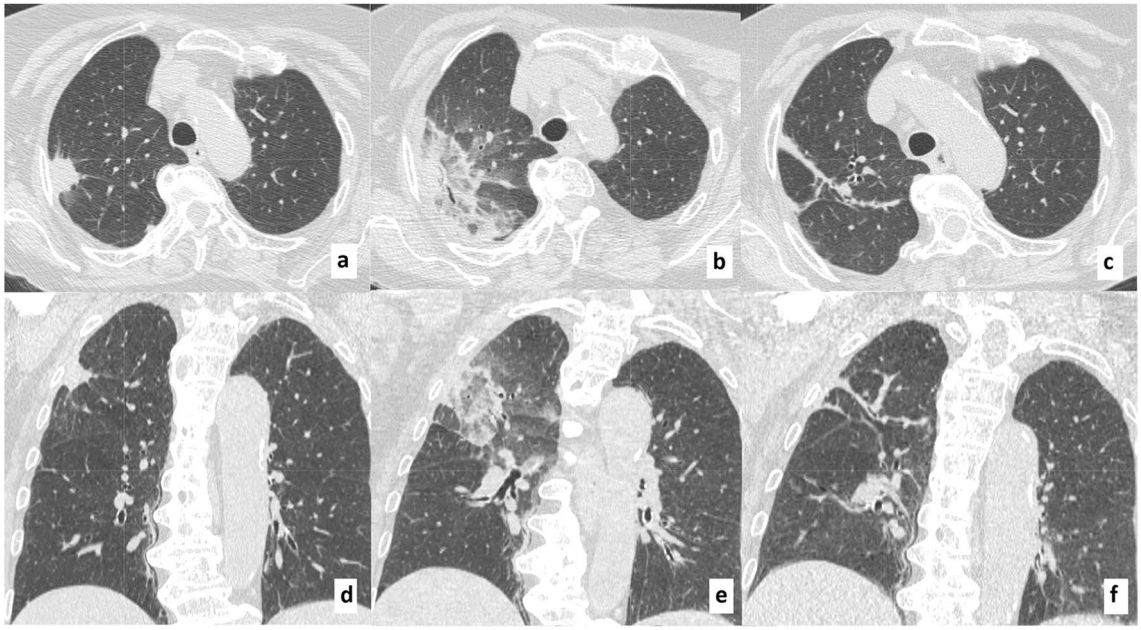

Fig. 1 A 74-year-old man with a 2.8-cm primary tumor in the right upper lobe treated with MWA (60W × 10 min) (**a**, **d**: pre-procedural CT-images) with a large ablation volume obtained at 1-month follow-up (**b**, **e**: 1 month CT images). Primary tumor disappeared at 6 months follow-up CT images (**c**, **f**), without procedural nor delayed complications

coagulation zone produced in liver tissue. Data at 30 W, 50 W, and 70 W were obtained by linear interpolation.

Ex vivo ablation measures (L_{ev}, D_{ev}, and the ablation sphericity index $S_{ev} = D_{ev}/L_{ev}$) were compared with their counterparts in the MALT study (L_{iv}, D_{iv}, and $S_{iv} = D_{iv}/L_{iv}$, respectively, i.e., the radiological measurements of the ablation zones achieved clinically using the same MWA parameters) to assess the predictive accuracy of the manufacturer's chart.

Deviations of the in vivo clinical results from ex vivo predictions were calculated as follows: $\Delta_L = (L_{iv} - L_{ev})/L_{ev}$ and $\Delta_D = (D_{iv} - D_{ev})/D_{ev}$ for the ablation long and short axis, respectively.

Post-treatment and follow-up studies

All patients underwent an unenhanced chest CT scan immediately after the removal of the antenna and a baseline and contrast-enhanced chest CT scan within 48 h post-MWA, to assess volume of ablation (V_0) and exclude complications. Post-treatment chest CT scans and clinical examinations were scheduled at 1, 3, 6, 12, 18, and 24 months post-MWA, according to our standard of care, for the evaluation of the local efficacy and possible delayed complications (Figs. 1 and 2).

All examinations were carried out using 64-channel multidetector-row CT systems (Lightspeed VCT XT, GE; Brilliance 64, Philips) and 120 kV and 100 mA tube voltage and current, respectively. All studies were acquired from the pulmonary apices to the diaphragm, with 1.25-mm-slice thickness reconstruction. A total of 0.4 gI/kg of iodinate low-osmolar non-ionic contrast medium (iopromide, 370 mgI/mL, Ultravist) was injected with a flow rate of 3 mL/s, followed by 60 mL of saline. Arterial phase was acquired at 35 s whereas delayed phase at 60 s [10].

At each post-MWA CT scan, the following were evaluated: size of the ablation zone along three planes (D1, D2, and D3, see below), including the post-ablation peripheral zone of ground-glass opacity (GGO) when present, and occurrence of local or distal tumor progression (LP and DP, respectively).

Measurements were performed by direct visual inspection of the post-ablation CT scans, using the ordinary tools provided by the CT scan viewer software suite. As ablated areas are well approximated by ellipsoids with rotational symmetry around the microwave probe axis, ablation volumes were obtained from linear measurements by applying the ellipsoid formula (π/6*D1*D2*D3, where D1, D2, and D3 are the longest ablation diameters in the *xy*, *yz*, and *xz* planes of an *xyz* orthogonal Cartesian coordinate system).

Normalized ablation volumes ($V_n = V_t/V_0$, where V_t is the measured volume at time t post-MWA) were calculated at each follow-up control, to identify the time constant τ characteristic of tissue repair mechanisms, i.e., the mean time to complete "re-absorption" of the thermal lesion.

Treatment-related morbidity and mortality rates were based on the incidence of complications during the first 7 days post-treatment. Complications were assigned a severity grade using the SIR latest classification [14]: 0 = no complications; 1 = mild adverse event (requiring no therapy or non-substantial therapy); 2 = moderate adverse events (with moderate escalation of care, requiring substantial treatment); 3 = severe adverse events (with marked escalation of care); 4 = life-

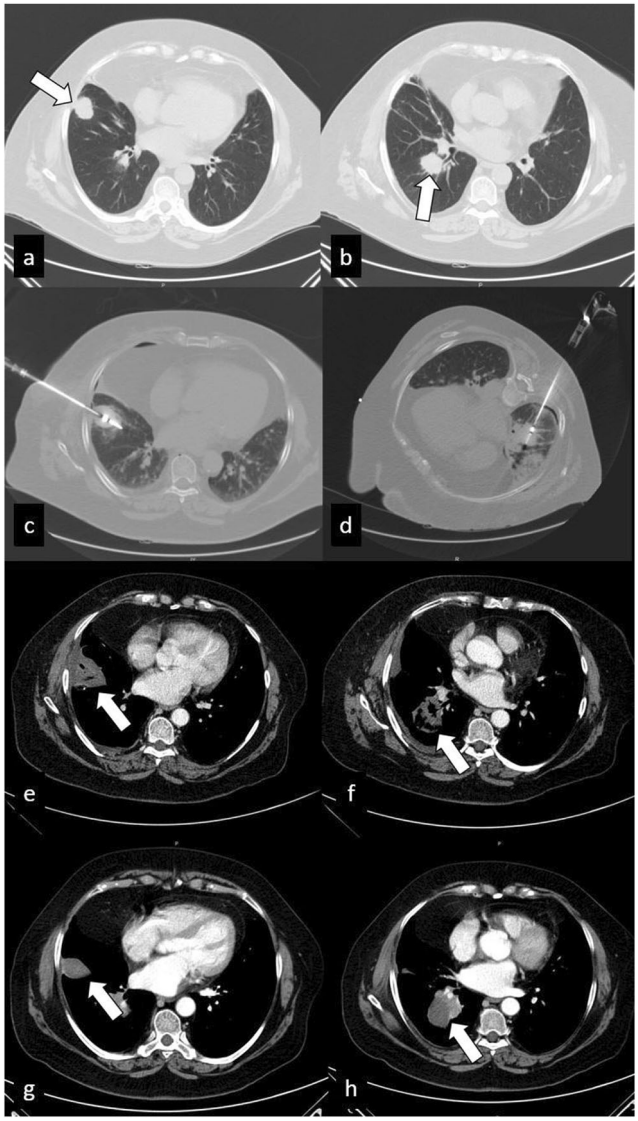

Fig. 2 A 70-year-old female with two 3-cm metastases in the middle (**a**), and right lower lobe (**b**), treated with MW ablations (70 W × 10 min), in supine (**c**) and right lateral-prone (**d**) decubitus, respectively. Apparent complete ablation of both tumors obtained at 1-month post-treatment CT scan, with sufficient safety margin without procedural complications (**e**, **f**). At 9-month CT follow-up, complete ablation was maintained in the peripheral metastasis (**g**), while a recurrence occurred on the hilar side of the central lesion, possibly due to heat sink effect of relatively large adjacent vessels (**h**)

threatening or disabling event; 5 = patient death. The same severity scale was also used for delayed complications (later than 7 days post-MWA). Complication score, defined as mean severity grade, was calculated for all treatments in MALT1/MALT2 groups.

Based on the follow-up CT scans, treatment efficacy was evaluated as complete ablation (CA) (Figs. 1 and 2) or partial ablation (PA), according to CT analysis of lesion size and absence or persistent enhancement. Persistence or appearance (after CA) of enhancing areas was classified as LP (Fig. 2). Local and distant disease progression rates (LPR and DPR, respectively) and time to local and distant progression (TLP and TDP) were recorded. Finally, OS and LPFS curves were estimated.

Statistical analysis

A specific statistical analysis plan, to obtain a sample sizing, was not pre-designed due to lack of preliminary information from pilot studies.

Quantitative variables were reported with average (AVG) value, standard deviation (SD), minimum (MIN) value, maximum (MAX) value, and coefficient of variation (CV = SD/AVG).

The p value threshold for statistical significance was set to $p = 0.05$, based on a two-tailed, unpaired, heteroskedastic Student's t test. The analyses of OS and LPFS were conducted using the Kaplan-Meier method. All calculations were performed using Excel worksheets and validated with software SPSS v16.0 (IBM).

Results

From September 2015 to September 2017, 54 patients with a total of 69 nodules were enrolled in our study; more than one tumor was ablated in 11 treatment sessions, with a maximum number of 3 tumors per session.

The main features of patients and tumors are reported in Table 2. Technical success (i.e., complete tumor ablation, with margin) was achieved in all cases (69/69). However, the planned treatment protocol, based on the use of a single antenna without probe re-positioning nor power variations, was performed in 61 out of the overall 69 treatments (88.4%). In the other 8 treatments (11.6%), two consecutive overlapping ablations were performed for ensuring complete tumor coverage with safety margins, due to the impossibility of precisely accessing the target tumor along its longest axis. These 8 treatments were excluded from the evaluation of MWA repeatability and comparability with the ex vivo bovine liver model and retained only for safety and efficacy assessments.

The onset of GGO at the ablation site, partially or completely encompassing the tumor, was reported in the majority of cases (61.5% of overall treated lesions), with a statistically significant difference between the MALT1 arm (50.0%) and the MALT2 arm (69.2%) ($p = 0.0034$).

In terms of MWA repeatability assessment (Table 3), the 48-h CT study showed a wider variability in the long axis (CV = 25.3 ± 5.5%) than in the short axis (CV = 17.5 ± 7.3%) of the ablated zone. Table 3 also shows how ablation sizes measured in the clinical series were systematically smaller than those in the ex vivo model for all investigated settings, nearly to the same extent in the long and short axes ($\Delta_L = -24.0 \pm 21.8\%$ vs $\Delta_D = -27.0 \pm 15.6\%$, $p = 0.27$).

Table 2 Overview of MALT1 and MALT2 patients' population and treated tumors

		MALT1	MALT2	All	*p* value
Patients (*n*)		25	29	54	
Gender	Male	19	16	35	0.110
	Female	6	13	19	
Age (years ± SD)		76.4 ± 7.0	66.6 ± 13.5	71.1 ± 12.0	0.001
Previously treated patients		Overall: 11 (44.0%) CT: 2 (8.0%) SBRT: 5 (20.0%)	Overall: 9 (31.0%) CT: 6 (20.7%) SBRT: 3 (10.3%)	Overall: 20 (37.0%) CT: 8 (14.8%) SBRT: 8 (14.8%)	0.247
Risk factors	Smoke addiction	14 (56.0%)	5 (17.2%)	19 (35.2%)	0.018
	Emphysema	9 (36.0%)	5 (17.2%)	14 (25.9%)	0.188
	Smoke addiction and emphysema	8 (32.0%)	5 (17.2%)	13 (24.1%)	0.339
Treated tumors		28 (1.12 ± 0.33 per pt.)	41 (1.41 ± 0.57 per pt.)	69 (1.28 ± 0.49 per pt.)	0.035
Lesion size (mm)		24.7 ± 8.5 (min 5.3 ÷ max 37.7)	20.1 ± 8.1 (min 7.7 ÷ max 38.0)	22.0 ± 8.6 (min 5.3 ÷ max 8.0)	0.013
Tumor histology	SCLC	7 (25.0%)	-	7 (10.1%)	
	NSCLC	21 (75.0%)	-	21 (30.4%)	
	CRC metastases	-	22 (53.7%)	22 (31.9%)	
	Breast metastases	-	6 (14.6%)	6 (8.7%)	
	Other metastases	-	13 (31.7%)	13 (18.8%)	
Tumor location	Sub-pleural	22 (78.6%)	28 (68.3%)	50 (72.5%)	0.290
	Central	3 (10.7%)	8 (19.5%)	11 (15.9%)	
	Close to hilum	3 (10.7%)	5 (12.2%)	8 (11.6%)	
	Left lung	11 (39.3%)	17 (41.5%)	28 (40.6%)	
	Right lung	17 (60.7%)	24 (41.5%)	41 (59.4%)	
Tumor stratification by size	Group 1 (< 2 cm)	5 (17.9%)	18 (43.9%)	23 (33.3%)	0.078
	Group 2 (≥ 2 cm and < 3 cm)	9 (32.1%)	14 (34.1%)	23 (33.3%)	
	Group 3 (≥ 3 cm and < 4 cm)	14 (50.0%)	9 (22.0%)	23 (33.3%)	

SCLC/NSCLC, small/non-small cell lung cancer; *CRC*, colorectal cancer; *CT*, chemotherapy; *SBRT*, stereotactic body radiation therapy

Figure 3 shows the dependence of the ablation measures (*L* and *D*) on deposited energy E_d, both in the ex vivo model and in the MALT series. While L_{ev} and L_{iv} grow almost equally fast with increasing E_d, in terms of the short ablation axis the performance gap between ex vivo and in vivo appears to reduce as E_d grows.

At 1-month post-treatment CT scan, volume of ablation was on average 40% larger than at immediate post-MWA CT.

Figure 4 depicts how the ablated tissue shrinks over time, as monitored through the follow-up CT scans: normalized ablation volumes appear to undergo an exponential decrease (i.e., $V_n = V_0 * e^{-t/\tau}$), with a time constant τ of approximately 9.2 months.

Safety and clinical efficacy

No treatment-related deaths were recorded. Two (2.9%, on a per treatment basis) grade-2 peri-procedural complications occurred (pleural effusions requiring drainage, both in the MALT2 arm). A pneumothorax was reported in 29/69 procedures (42.0%): 17/28 in MALT1 (60.7%) and 12/41 in MALT2 (29.3%); chest tube placing or prolonged hospital stay was never needed, but post-procedural pneumothorax drainage was performed in 4 cases, all belonging to the MALT 2 arm. An overall treatment-related complication score of 0.49 ± 0.55 was reported (MALT1: 0.64 ± 0.48; MALT2: 0.39 ± 0.58; $p = 0.056$). Only 1 (1.4%) grade-2 delayed complication occurred (a bronchial fistula, in the MALT1 arm). The overall delayed complication score was 0.25 ± 0.47. A statistically significant difference ($p = 0.023$) was observed between MALT1 and MALT2 in terms of delayed complication scores (0.42 vs 0.12, respectively, $p = 0.033$).

All patients were hospitalized overnight and discharged within 2 days post-MWA, except for the two subjects with grade-2 complications (2 and 3 days additional hospital stay, respectively).

LPR and DPR of 24.7% and 33.3% were reported (TLP: 8.1 ± 6.0 months; TDP: 9.0 ± 7.0 months); a remarkably higher DPR was registered in MALT2 (54.3% vs 4%). Subgroups analysis for LPR is shown in Table 4.

Table 3 Ablation zones obtained both in the MALT clinical series (*iv*) and on ex vivo bovine liver (*ev*) (excerpted from the official ex vivo coagulation chart of the HS AMICA 2.45-GHz MWA system). Both disaggregate (for each MWA parameters set) and overall deviation data are shown

MWA settings (power × time)	E_d (kJ)	L_{iv} (mm)	D_{iv} (mm)	L_{ev} (mm)	D_{ev} (mm)	S_{ev}	Δ_L	Δ_D
30 W × 10 min	18	32.4 ± 10.8	20.2 ± 4.5	40	32	0.80	− 19.1% ± 29.6%	− 37.0% ± 16.6%
40 W × 10 min	24	32.7 ± 7.6	26.8 ± 3.9	49 ± 1.8	36 ± 1.9	0.73 ± 0.03	− 33.3% ± 15.5%	− 25.5% ± 10.7%
50 W × 10 min	30	38.8 ± 8.9	27.5 ± 2.6	51	38	0.75	− 23.9% ± 17.5%	− 27.8% ± 6.9%
60 W × 10 min	36	48.6 ± 15.7	35.1 ± 10.9	54 ± 2.1	40 ± 2.3	0.74 ± 0.02	− 10.0% ± 29.2%	− 12.3% ± 27.4%
70 W × 10 min	42	40.1 ± 7.7	32.0 ± 4.7	59	42	0.71	− 32.0% ± 13.0%	− 23.8% ± 11.1%
80 W × 10 min	48	49.1 ± 10.3	36.1 ± 4.6	66 ± 2.6	46 ± 4.0	0.70 ± 0.02	− 25.6% ± 15.6%	− 21.6% ± 10.0%
		L_{iv} (mm)	D_{iv} (mm)				Δ_L	Δ_D
Overall coefficient of variation		25.3% ± 5.5%	17.5% ± 7.3%	Overall average ± standard deviation			− 24.0% ± 21.8%	− 27.0% ± 15.6%

$D_{iv/ev}$, in vivo/ex vivo short ablation axis; E_d, deposited energy; $L_{iv/ev}$, in vivo/ex vivo long ablation axis; S, ablation sphericity index; Δ, deviation of the clinical outcomes from the corresponding ex vivo model predictions ($\Delta_L = L_{iv}/L_{ev} - 1$) ($\Delta_D = D_{iv}/D_{ev} - 1$)

Over the entire MALT cohort, estimated OS and LPFS rates at 12 and 24 months were 98.0% and 71.3%, and 80.2% and 64.7%, respectively (Fig. 5). MALT1 resulted in OS = 95.7% and LPFS = 71.4% at 12 months, and OS = 78.1% and LPFS = 62.5% at 24 months; MALT2 yielded OS = 100.0% and LPFS = 68.6% at 12 months, and OS = 81.6% and LPFS = 64.6% at 24 months. No statistically significant difference was demonstrated between the two arms (p = 0.456 for OS and 0.461 for LPFS).

However, differences in oncological management between primary and secondary tumors were remarkable, considering the higher number of patients subject to systemic therapy in the MALT2 arm.

Discussion

MALT trial confirmed the clinical viability of percutaneous MWA in the treatment of lung tumors up to 4 cm in size, with performance variability comparable to that reported in previous series, reporting the results of treatment of hepatic metastases and hepatocellular carcinomas with the same MWA system [15]. The cause of residual variability, despite the strict control of MW energy dosing provided by the MALT protocol, is probably intrinsic to the relatively coarse classification criteria used for this study, in which target tumors were grouped only according on histology (primary or metastatic) and size. Additional and more refined stratification criteria—e.g., anatomic factors, characteristics of surrounding parenchyma, and prior systemic or regional treatments—are probably needed. Moreover, the different responses to MWA between primary and metastatic lesions in terms of immediate appearance of GGO pattern at the treatment site may be due to the differences of the respective tissue backgrounds.

CT scans performed within 48 h after MWA completion clearly showed an ablation size inferior by about 25% in each linear dimension compared with what was predicted by the ex vivo coagulation chart. This may be due to the tissue

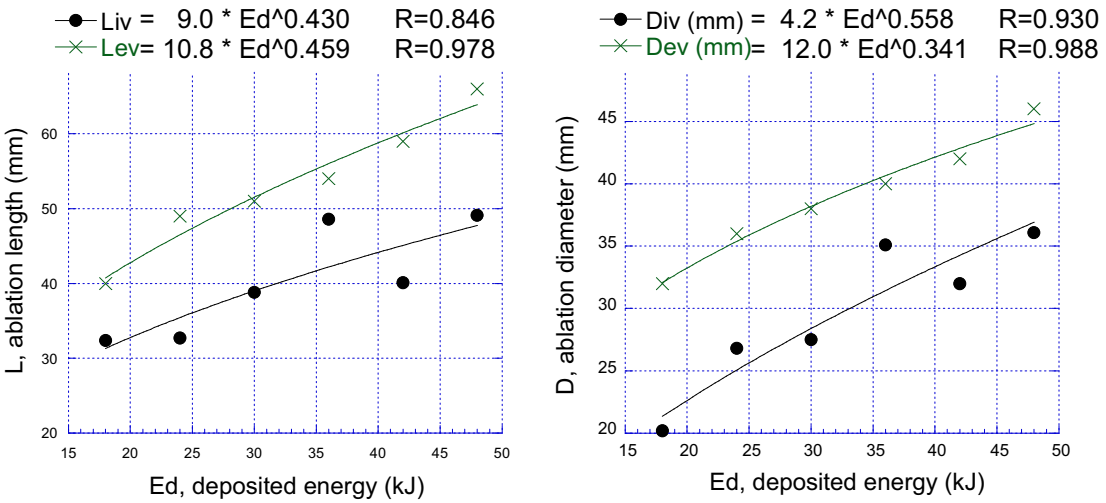

Fig. 3 Ablation long (L) and short (D) axes dependence on deposited energy (E_d), both for the ex vivo bovine liver model (crosses, *ev* subscript) and for the MALT clinical series (circles, *iv* subscript). Solid lines are power numerical fits

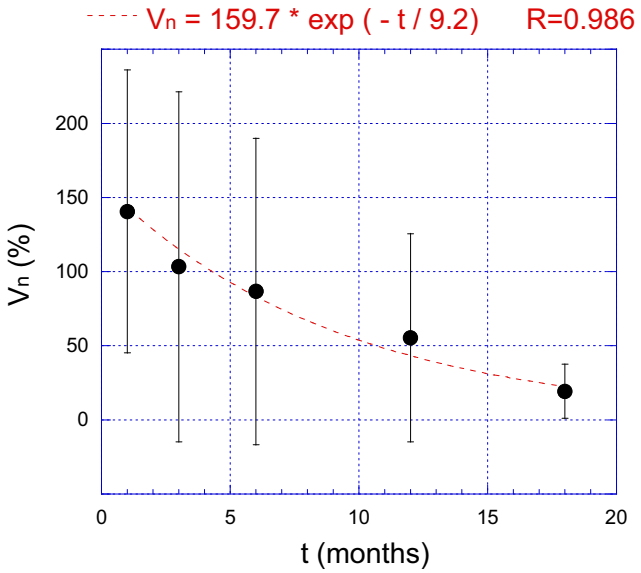

Fig. 4 Volume of the treated tissue area (V_n, normalized with respect to the ablation volume measured immediately after treatment) as a function of time (T, expressed in months post-MWA). Black circles: average of V_n values measured from follow-up CT scans at 1, 3, 6, 12, and 18 months post-MWA; error bars: standard deviation of measurements at each time point; dashed curve: exponential data fit

shrinkage phenomenon induced by thermal treatments: the MWA contraction ratio (i.e., pre-MWA to post-MWA ratio of a tissue segment length comprised in the treated volume) reported in the literature for lung parenchyma (~ 50%) is appreciably higher than its counterpart for liver parenchyma (~ 30%) [16–21].

Standard deviations of Δ_L (21.8%) and Δ_D (15.6%) are comparable with the intrinsic MWA performance variability observed in our study. Therefore, we have to conclude that, when cutting down all table entries by 25%, the standard ex vivo coagulation chart may still be used as a valid reference when planning pulmonary MWA treatments.

It is worthwhile to note that, at 1-month post-treatment CT scan, the ablation volume was approximately 40% larger in volume than that at previous post-MWA CT scan: delayed necrotizing mechanisms, secondary to thermal treatment, may cause further enlargement of the radiologically detectable ablation zone in the short term. These findings should be taken into account in the clinical practice for the timely and correct assessment of MWA of lung tumors.

Both rate and type of complications of percutaneous MWA reported in MALT study are very similar to those of previously published studies [21, 22]. Globally, MALT trial confirmed safety and tolerability of percutaneous lung MWA. A trend towards increased likelihood and/or severity of complications when treating primary compared with metastatic tumors has emerged, probably due to the increased respiratory co-morbidities in patients with primary tumors [23–27].

The LPRs observed in the MALT study are slightly lower than those reported in the literature for RFA series, particularly with regard to the treatment of pulmonary metastases [28, 29]. Increasing tumor size up to 4 cm did not negatively affect LPR: this may be interpreted as an indirect proof of the capability of MWA, compared with RFA, of achieving good locale disease control also when dealing with large tumors, possibly raising the bar of ablatable lesion size from 3 cm at least up to 4 cm [30–32]. The increased heat sinking rejection, the higher intra-tumoral temperatures, and the local tissue inhomogeneity ensured by MWA provide a robust physical explanation to our findings [33, 34].

Nevertheless, several partial ablations occurred, possibly also due to some procedural rules imposed by MALT protocol, such as the mandatory use of a single probe in a single position, at a pre-set power, for a pre-set time. In fact, the use of one specific MWA technology and strict procedural protocols were key for the assessment of performance repeatability. On the other hand, these features circumscribe the scope of the study to the explored MWA system and settings only. Ad hoc procedural adjustments in routine clinical practice may indeed help to further improve outcomes in terms of local disease control. The other main limitation of the MALT study is the relatively low number of enrolled patients and treated tumors, especially in view of the further sub-grouping according to tumor histology and dimensional class.

Table 4 Local tumor progression rates (LPR). *AVG* average; *D*, diameter

Local progressions/treated tumors (%)	Overall	MALT1	MALT2
Group 1 (D_{avg} < 2 cm)	8/23 (34.8%)	2/5 (40.0%)	6/18 (33.3%)
Group 2 (2 cm < D_{avg} < 3 cm)	4/23 (17.4%)	3/9 (33.3%)	1/14 (7.1%)
Group 3 (3 cm < D_{avg} < 4 cm)	5/23 (21.7%)	3/14 (21.4%)	2/9 (22.2%)
Groups 1 and 2 (D_{avg} < 3 cm)	12/46 (26.1%)	5/14 (35.7%)	7/32 (21.9%)
Groups 2 and 3 (2 cm < D_{avg} < 4 cm)	9/46 (19.6%)	6/23 (26.1%)	3/23 (13.0%)
AVG, all groups	17/69 (24.6%)	8/28 (28.6%)	9/41 (22.0%)

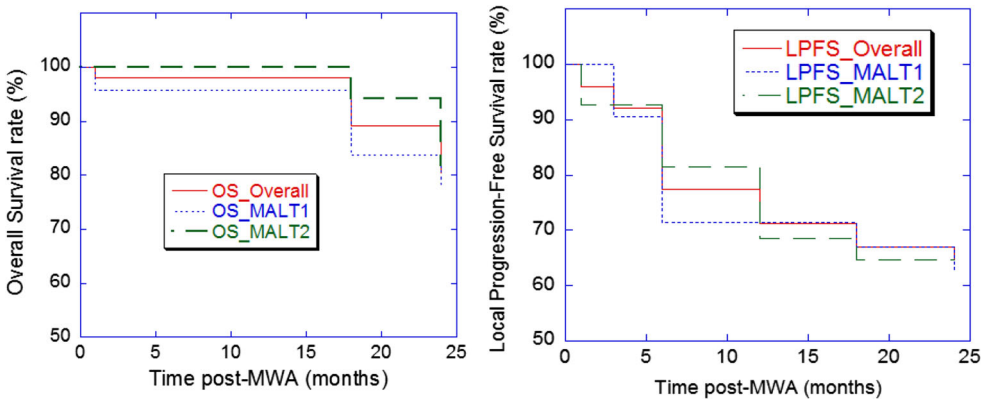

Fig. 5 Kaplan-Meier curves for overall survival (OS, left) and for local progression-free survival (LPFS, right), calculated with respect to the entire study population (overall), to MALT1 patients only and to MALT2 patients only

Numbers at risk							
Time post-MWA (months)	0	1	3	6	12	18	24
MALT1	25	23	20	19	18	12	5
MALT2	29	27	25	23	20	9	4
OVERALL	54	50	45	42	38	21	9

Conclusions

The prospective multicenter MALT trial confirmed that percutaneous MWA treatment of primary and metastatic lung tumors using a 2450-MHz ablation system is a repeatable, reproducible, safe, and effective therapeutic option. Local progression of treated tumors up to 4 cm did not correlate to their initial size.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Roberto Iezzi.

Conflict of interest One author of this manuscript (NT) declares relationships with the following companies: Nevio Tosoratti is an employee of H.S. Hospital Service SpA, the company manufacturing the MWA apparatus used in the study.

The other authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- prospective
- case-control study/experimental study
- multicenter study

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