Trials

STUDY PROTOCOL

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Real-time 3D confirmation of complete ablation with margins as a local cure for colorectal liver metastases: the ACCLAIM trial

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Abstract

Background Treatment failure and local tumor progression (LTP) after thermal ablation (TA) have been attributed to insufficient minimal margin (MM) ablation zone coverage of the target tumor.

Methods This prospective, open-label, multicenter, international trial will enroll approximately 275 patients with one to three colorectal liver metastases (CLM) (for a total of 330 tumors) each up to 2.5 cm in largest diameter, eligible for local cure using microwave ablation (MWA). Any FDA cleared or CE-marked MWA device can be used. MWA will be performed with the intent to create a MM of at least 5 mm and ideally ≥ 10 mm. MM size will be documented intraprocedurally with contrast-enhanced computed tomography (CECT) immediately post-MWA and again within 4–8 weeks after MWA using any FDA cleared or CE-marked image-processing software to provide a 3D assessment of the ablation zone (AZ) and MM. An independent assessment of the MM by a central physician reviewer with expertise on AZ assessments will be conducted within 7 days of the MWA with 3D image-processing confirmation software and again within 7 days after the 4–8 weeks post-MWA CECT. A MM of 5.0 mm will represent the necessary condition for technical success of MWA. For MMs under 5 mm, repeat MWA will be performed within the same session whenever feasible/safe, and/or within 30 days from detection of the insufficient MM to create a sufficient MM (> 5 mm). MM size will be correlated with time to local tumor progression (TTLP). Local progression-free (LPFS) and hepatic disease-free survival (accounting for all tumors ablated) stratified by MM of 5.0–9.9 mm and ≥ 10.0 mm will be assessed with Kaplan–Meier and competing risk methodologies.

Discussion This study aims to demonstrate that MWA of CLM ≤ 2.5 cm with 3D image-processing confirmation software of MM over 5 mm achieves definitive local tumor control. This will help establish margin confirmation as a new standard of care for MWA of CLM.

Trial registration ClinicalTrials.gov NCT05265169. Registered on January 13, 2023.

Keywords Colorectal liver metastases, Thermal ablation, 3D assessment of the ablation zone, Minimal ablative margin

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Background and rationale (6a)

Colorectal cancer is a high prevalence disease, with more than one million people affected worldwide, many of whom will develop liver metastasis in the course of their disease [1]. Complete eradication of colorectal cancer liver metastases (CLM) can result in cure and could be achieved by surgical resection. Several large series [2–5] have demonstrated that macroscopically margin-negative resection (R0), clinical risk score (CRS), and presence of metastases outside the liver are independent factors impacting oncologic outcomes including patient survival. A large multi-institutional database described a median recurrence-free survival of approximately 26 months following curative-intent surgery of CLM [3]. In the presence of hepatic recurrence, repeated resection [6, 7] and thermal ablation (TA) represent viable options [8, 9].

Image-guided TA techniques, including radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation, have been used as an alternative local treatment with curative potential, while avoiding the morbidity and mortality of surgery. TA has been increasingly used in the treatment of relatively small colorectal liver metastases (CLM).

Similar rates of hepatic recurrence and survival times were observed in studies comparing TA, resection, and/or intraoperative TA [10, 11]. For well-selected small CLM, ablation can provide durable long-term outcomes similar to surgical resection. Local recurrence rates of 5.5% for CLM ⩽4 cm treated with resection plus perioperative chemotherapy vs 6% for lesions treated with RFA were demonstrated in large prospective trials [12–14]. However, insufficient coverage of the tumor by the ablation zone (AZ) can lead to treatment failure and LTP. The minimum ablative margin (MM), defined as the shortest distance between the boundary of the tumor and the edge of the AZ, is currently the most common metric of quantitative assessment of ablation success and was demonstrated to be an independent predictor of LTP [15, 16].

Conventionally, contrast-enhanced CT has been used to determine the adequacy of the MM by visually comparing the pre- and post-ablation CT images, using anatomical landmarks [17]. Several limitations of this method have been described. Measurements with the standard tools provided by CT software can lead to difficulties in measurement and therefore considerable inter-individual differences. The development of new measurement methods, including tumor segmentation, can aid to achieve more reliable measurement results [18]. Previous studies have described the benefits of image registration and fusion for the assessment of the AZ and ablation margins in all spatial dimensions (3D) [19–30]. Fusion of pre- and post-ablation contrast-enhanced images enables better understanding of the relationship between the tumor and the ablation zone, helping verify and document the creation of the ablation margins in all spatial dimensions (3D). To supplement the registration/fusion with 3D volumetric computation of incomplete AZs, different types of image-processing software can be used. The software performs segmentation of the tumor and AZ volumes, automatically generates the contours of interest (e.g., tumor, theoretical 5- and 10-mm margin volumes) and the volumes of insufficient coverage, when the tumor could not be completely eradicated [31].

This prospective clinical trial aims to standardize the technique of TA with confirmation of adequate margins, regardless of operator. The authors hypothesize that TA of CLM up to 2.5 cm in size with 3D confirmation of ablation MM over 5 mm achieves definitive local tumor control. The study will demonstrate that TA can reach the same historic outcome as limited resection for small CLM when adequate ablation margin is achieved. During this trial, a MM of at least 5 mm will represent the necessary condition for declaring success of the ablation and will be verified immediately post-ablation (no later than 24 h) and at 30 days after ablation. For MMs less than 5 mm, repeat MWA will be performed whenever feasible, within 30 days from detection, in order to achieve sufficient MM (>5 mm).

Choice of comparator (6a)

In this study, all participants will receive the study intervention (3D confirmation of ablation MM) in addition to all standard of care interventions (MWA, imaging follow-up, QoL assessment). There is no comparator in this study.

Objectives (7)

This study aims to correlate MM with time to LTP. Local disease-free progression (within or abutting the ablation zone) and hepatic disease-free survival (accounting for all tumors ablated) will be assessed.

Study objectives

Primary objective:

To estimate the 24-month local tumor progression-free survival (within or abutting the ablation zone) of colorectal liver metastases treated with MWA with post-MWA ablation margin confirmation using FDA cleared or CE-marked 3D software.

Secondary objectives:

- To estimate the hepatic disease-free survival, the overall progression-free survival, and overall and disease specific survival in patients with colorectal liver metastases treated with MWA, and to compare the

local tumor progression-free survival between sufficient (5.0–9.9 mm) and ideal (≥10.0 mm) minimal ablation margin (MM).
- To determine the technical success rate to create an ablation zone (AZ) that completely covers the target tumor(s) with MM of at least 5.0 mm.
- To assess the incidence and severity of MWA-related adverse events CTCAE grade 3 or greater.
- To determine the secondary rate of local tumor progression-free survival, secondary overall progression-free survival, and secondary hepatic disease-free survival in patients undergoing repeat treatment of an index tumor with MWA.

Exploratory objectives include assessments of the prognostic value of genetic factors (BRAF, KRAS mutation, and microsatellite instability (MSI) status) and the impact of ablation on the quality of life (QOL) via patient questionnaires after MWA.

Trial design (8)

ACCLAIM is an international, multicenter, open-label prospective clinical trial launched by the Society of Interventional Oncology (SIO), expected to accrue approximately 275 participants across sites in the USA and Europe over a 3-year enrollment period. Participating sites include five US and five European high-volume centers that treat CLM with MWA. A Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [32] is presented in Additional file 1.

Methods: participants, interventions, and outcomes

Study setting (9)

The trial is funded via the Society of Interventional Oncology, collectively through grants from Boston Scientific Corporation, NeuWave Medical, Inc. (part of Ethicon, Inc.), and Varian, a Siemens Healthineers company. The study complies with the Declaration of Helsinki/Tokyo/Venice on Experimentation in Humans, the Code of Federal Regulations, Title 21 parts 50, 54, 56, 812, 814.82 (e)[2] as applicable; the Code of Federal Regulations, Title 45 part 46; and the International Conference on Harmonization Good Clinical Practice Guidelines. The trial is registered at clinicaltrials.gov (NCT05265169, January 13, 2023).

The total length of the study will be 5 years, with 3-year enrollment time and 2-year follow-up period. All patients will provide written institutional review board (IRB)/Independent Ethics Committee (IEC)-approved, site-specific informed consent prior to any study intervention.

The trial was designed to prospectively establish the efficacy of MWA as the most suitable curative therapy for selected CLM that can be ablated with margins over 5 mm. MWA will be performed using any FDA/CE-marked, commercially available MWA system, any number of antennas and overlapping ablations at the discretion of the operator. The study will not modify the current clinical treatment protocols at the participating institutions. Imaging assessment after MWA will be performed to assess technique efficacy using triphasic CT (recommended 1.0–2.0 mm slice thickness) at 4–8 weeks, as outlined by the reporting criteria for tumor ablation [33]. This will represent the new baseline for subsequent comparisons to detect local tumor control/progression over time. Subsequent standard of care contrast-enhanced computed tomography (CECT, triphasic preferred) or multiparametric contrast-enhanced magnetic resonance imaging (MRI) with contrast, typically every 3 months in the first year and typically every 3–6 months during the second year to assess local tumor control or local tumor progression (LTP). Additional multiparametric contrast-enhanced MRI with contrast and diffusion weighted imaging (DWI) and metabolic imaging [^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography (FDG PETCT) and/or PETMRI] are recommended when CT results are ambiguous. Patients will be followed for at least 2 years after the last MWA procedure. Subjects without progression at 2 years will be followed according to institutional standard of care (SOC), while the trial is open. Should additional tumors develop subsequently, they will be treated with MWA ablation within trial, provided that the eligibility criteria are still fulfilled. The patient will then be followed for at least an additional 24 months after the last MWA. Tumors developing LTP will be evaluated for feasibility of MWA retreatment within the protocol. Alternatively, they will be offered treatment as per SOC [34–36]. If the subject is retreated with MWA within protocol, secondary local tumor control will be evaluated (Fig. 1).

Eligibility criteria (10)

This study will enroll adult patients with up to three colorectal cancer liver metastases ≤ 2.5 cm judged amenable to complete ablation using microwave. Inclusion and exclusion criteria are presented in Table 1.

Interventions (11a)

Contrast-enhanced MRI with contrast + DWI or triphasic CT of the abdomen and a CT of the chest will be performed within 42 days of MWA treatment. Enrolled patients will undergo image-guided percutaneous MWA using one of the FDA cleared/CE-marked commercially available MWA systems. This study will not modify the current clinical treatment protocol at the participating institutions.

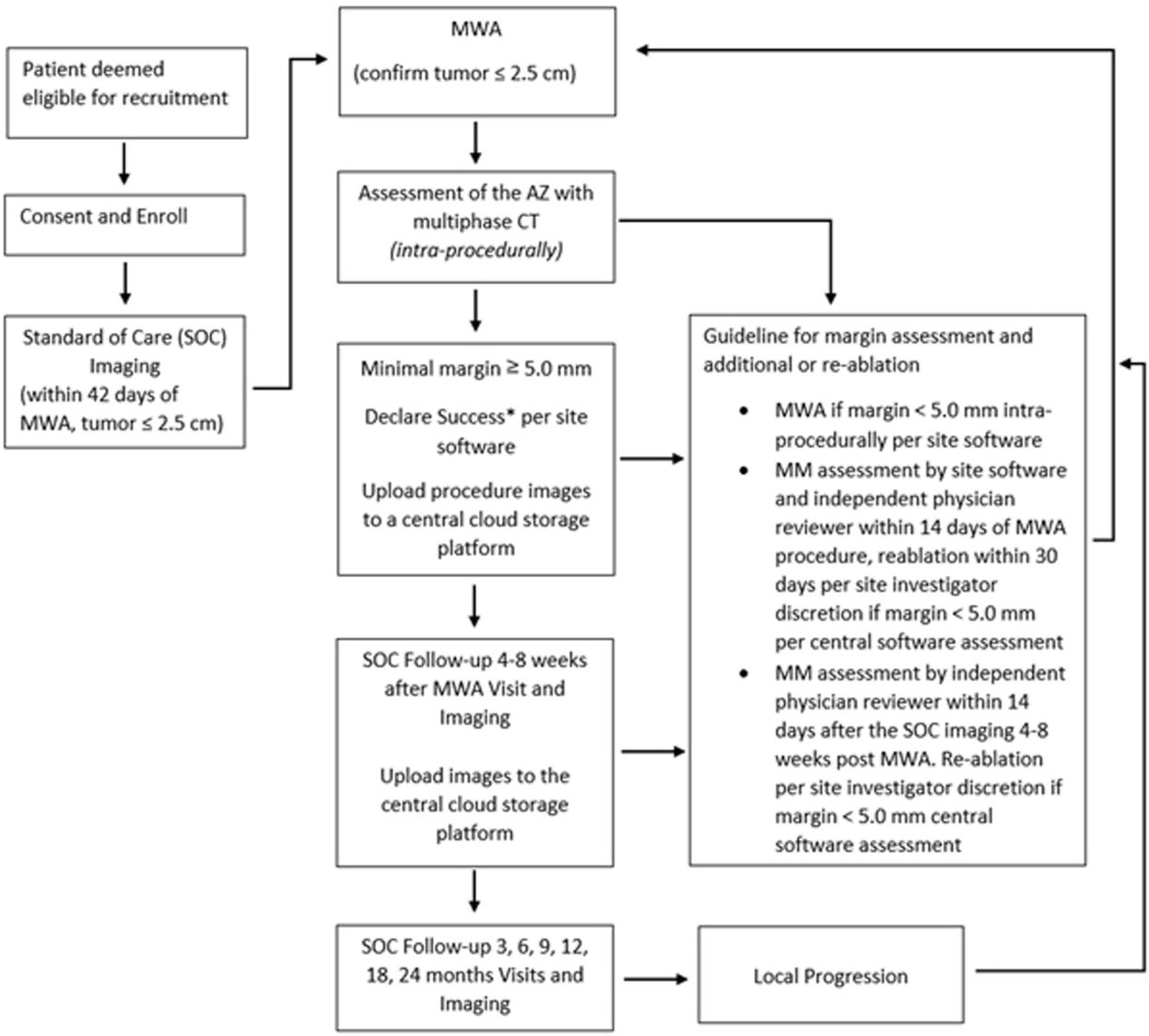

Fig. 1 Study diagram

Microwave ablation procedure

MWA will be performed using one of the FDA cleared/CE-marked commercially available microwave. All eligible CLM will be treated using image-guided percutaneous MWA according to standard clinical protocols. Prophylactic antibiotic according to institutional/SOC may be administered intravenously prior to MWA. Minor variations are expected to occur among institutions' technique, but the treatment endpoint will be identical. A contrast-enhanced triphasic CT examination to localize the target tumor and allow for 3D segmentation will be performed immediately prior to the MWA (recommended at 1 mm or nearest possible slice thickness). Accurate antenna(s) position to cover the entire target CLM will be confirmed with CT imaging prior to the initiation of MWA. Multiple antennas and overlapping ablations are allowed to ensure that the endpoint of ablation is reached. MWA will be performed with the intention to create a diameter of ablation of at least 5 mm (ideally 10 mm) larger than the largest tumor diameter centered on the target tumor. The MWA antenna will be used in accordance with the manufacturer's device instructions. Immediately after MWA (intraprocedurally), assessment of the ablation zone (AZ) will be performed by CECT at the same thickness and at the same position as the pre-MWA CECT. FDA cleared/CE-marked image software

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Written informed consent for the MWA and participation in the study	Patient is unable to lie flat or has respiratory distress at rest
Pathologically confirmed CRC with hepatic metastases confirmed on imaging (e.g., CT or MRI)	Patient has a history of an allergic reaction to intravenous iodine that cannot be pre-medicated or prevents performance of a CT with IV contrast
Age > 18 years	Patient has evidence of active systemic infection
Up to 3 CLMs, each ≤ 2.5 cm in largest diameter (as confirmed at screening and on date of MWA)[a]	Patient has a debilitating medical or psychiatric illness that would preclude giving informed consent or receiving optimal treatment or follow-up
Ability to safely create an AZ that completely covers the tumor with minimal margin (MM) of 5.0 mm[b]	Patient unable to receive general anesthesia or adequate analgesia and sedation
The target tumor(s) is/are visible by US and/or CT in a location where MWA is technically achievable and safe based on the proximity to adjacent structures[c]	Tumor location less than 25.0 mm from hilum
ECOG performance status of 0–1	Patient has uncontrolled and uncorrectable coagulopathy or bleeding disorders
Patient is deemed a suitable candidate for microwave ablation by the investigator	Pregnant or breast-feeding patients
Do not include criteria	
Patient is currently participating in other studies that could affect the primary endpoint	
Patient unable/unwilling to commit time or effort required for the study	

MWA, microwave ablation; *CRC*, colorectal cancer; *CLMs*, colorectal liver metastases; *AZ*, ablation zone; *ECOG*, Eastern Cooperative Oncology Group

[a] Patient may have up to 5 lesions in the lung (none larger than ≥ 2.0 cm) and/or any lymph node ≤ 2.0 cm in the largest diameter

[b] Subcapsular (any tumor within 5.0 mm from the liver capsule) or perivascular (any tumor within 5.0 mm from a vessel larger than 3.0 mm) tumors may be included. For these tumors, the ablation zone must extend to the capsule, or the vessel and the calculation of the minimal margin will not apply to the area abutting the capsule or the vessel

[c] Protective maneuvers such as hydrodissection for organ mobilization are allowed

for margin assessment that allows for registration/fusion 3D volumetric assessments will be used to assess the ablation margin. If a circumferential MM of ≥ 5.0 mm is not confirmed by the 3D software, then the operator should attempt to complete the ablation within the same session to obtain the required MM of ≥ 5.0 mm. Ultrasound is not permitted for measurement of margins or ablation zone assessments. Patients will recover and be discharged from the hospital when institutional criteria are met.

Minimal margin (MM) assessment and response assessment

The MM will be assessed by independent physician reviewers, Drs. LS, DED, and LC, board certified in radiology with experience in tumor assessment following ablation. Participating sites will submit de-identified DICOM files to a centralized location for independent 3D software assessments. A 1.0 mm slice thickness (or as close to 1 mm as technically feasible) is strongly suggested for imaging tumor margins. Assessment of the MM for the determination of success will be conducted using a central FDA cleared image-processing software to provide 3D assessment of the ablation zone and margins, highlighting the portions of the target CLM and MMs located outside the ablation zones (the volumes of insufficient coverage). The initial assessment of the MM will be conducted using the SOC imaging obtained immediately after the MWA. A MM of at least 5.0 mm represents technical success. The software margin calculation and independent physician review of the MM and technical success will be conducted within 7 days (with a 3-day window for adjudication) from the MWA. Assessment of the MM will be conducted again on the imaging obtained 4–8 weeks post-MWA. The margin calculation and independent physician review of the MM will be conducted typically within 14 days (with a 3-day window for adjudication) of the 4–8-week imaging assessments. This imaging scan is used for the assessment of technique efficacy. It will also be used as the new baseline for future assessments and detection of local tumor progression (LTP). Patients with technically unsuccessful ablation at the time of margin assessment (MM < 5.0 mm) may undergo repeat MWA at the discretion of the site investigator. The need for additional ablation will be recorded. MM size will be recorded and categorized (< 5.0 mm, 5.0–9.9 mm, and > 10.0 mm).

For subcapsular (any tumor within 5.0 mm from the liver capsule) or perivascular (any tumor within 5.0 mm from a vessel larger than 3.0 mm) tumors, the calculation of the margin will not apply to the area abutting the capsule or the vessel.

Follow-up

Follow-up imaging assessment after the initial post-MWA imaging at 4–8 weeks will be performed using triphasic CT or MRI according to the standard of care, as described above in Design section. Patients' imaging follow-up will continue until progression not treatable by MWA or up to 24 months after the last MWA as per protocol. If there is evidence of disease progression and repeat percutaneous MWA is clinically indicated, eligible patients may be retreated at the discretion of the site investigator. Alternatively, they will receive treatment according to the SOC. Subjects with untreatable progression will be followed through medical record assessment for OS. Subjects without progression at 24 months after MWA will continue to be followed through medical record assessments. No additional visits are required per protocol outside of standard of care after 24 months from last MWA. The study will conclude when the final subject treated with MWA has met the above criteria (24 months of follow-up with imaging after the last MWA on protocol).

Time schedule of enrollment, interventions, and assessments is displayed in Fig. 2.

Modifications (11b)

The following circumstances will result in the discontinuation or removal from the study:

- For those participants that will have a repeat thermal ablation, if at any time the subject is found to be ineligible for the protocol as designated in the eligibility criteria, the patient will be removed from the study.
- Subject has hepatic tumor progression not treatable by MWA.
- Non-compliance.
- Inability or refusal to sign informed consent.
- Upon patient's request (participation is voluntary).

Adherence (11c)

The study intervention (assessment of the ablation zone and additional ablation for margin < 5.0 mm per site software) is performed intraprocedurally; therefore,

Items	Screening/ Baseline Visit (within 42 days of MWA)	Intervention (MWA)	Initial outcome (4-8 weeks ±7 days after MWA)	SOC follow-up assessment* (3 months after MWA ±4 weeks)	SOC follow-up* (at 6, 9, 12, 18, 24 months after MWA ±4 weeks)	SOC annual follow-up* (up to 5 years ±4 weeks), medical records only, no visit
Clinic Visit/ Physical Examination – inclusion and exclusion criteria	X					
QoL assessment	X		X	X	X	
ECOG performance status	X					
Blood Tests	X		X	X	X	
Tumor Analysis (e.g., BRAF, KRAS, MSI status)	X					
CT Scan/MRI		X	X	X	X	X
Microwave Ablation		X	X**	X**		
Ablation Margin assessment		X	X			
Adverse Event Assessment		X	X	X	X	
Survival Assessment						X

Fig. 2 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) timeline. SOC, standard of care; CT, computed tomography; MRI, magnetic resonance imaging; QoL, quality of life. *Visits occur per standard of care every 3 months in the first year and every 6 months during the second year. For patients without local tumor progression for 2 years post-ablation, follow-up may be continued at approximately 1-year intervals, per SOC, until the trial ends. **Patients with technically unsuccessful ablation at the time of margin assessment (MM < 5.0 mm) may undergo repeat MWA at the discretion of the investigator

participants' adherence is assured at this point. For patients needing re-ablation as deemed by the central assessment (margin < 5 mm) within 30 days of ablation and/or of the SOC imaging 4–8 weeks post-MWA, comprehensive information about the study's purpose, about the rationale of repeat treatment will be clearly communicated to the participant by the study's team. Regular reminders will be consistently provided by the research staff to reinforce scheduled interventions.

Relevant concomitant care (11d)

All SOC treatments will be allowed. Dual enrollment in other interventional studies will not be allowed. Enrollment in registry studies will be allowed if they do not interfere with the study protocol.

Outcomes (12)

The following outcome measures are going to be evaluated in this study: technical success, local tumor progression (LTP), local disease-free survival, overall survival, time to metastatic liver disease progression beyond the index tumor, time to overall cancer progression, time to metastatic liver disease untreatable by microwave ablation, and time to metastatic liver disease untreatable with any focal therapy.

Definitions

Technical success: a tumor that is treated according to protocol and covered completely (i.e., ablation zone completely overlaps or encompasses target tumor plus an ablative margin), with a minimal margin (MM) of at least 5.0 mm as determined at the time of the MWA procedure.

Technique effectiveness: determination of complete ablation with a MM of at least 5.0 mm, as evidenced by first post-ablation imaging at 4–8 weeks post-MWA.

Local tumor progression (LTP): new appearance of enhancement and/or growth within or abutting the ablation zone identified on post-MWA imaging after achieving technical success and technique effectiveness (after the 4–8 weeks imaging).

Local tumor (progression) free survival: time from the first MWA to LTP or last follow-up.

Secondary local tumor (progression) free survival: time from the repeat MWA (accounting for all MWA to treat LTP of the initially treated CLM) to LTP or last follow-up in patients undergoing repeat treatment(s) of an index tumor.

Overall survival: time from the first MWA to death from any cause or last contact.

Secondary overall survival: time from the repeat MWA in patients undergoing repeat treatment of an index tumor to death from any cause or last contact.

Hepatic disease (cancer) specific survival: time from the first MWA to death from the colorectal cancer or last contact.

Secondary hepatic disease (cancer) specific survival: time from the repeat MWA in patients undergoing repeat treatment of an index tumor to death from the colorectal cancer or last contact.

Time to metastatic liver disease progression beyond the index tumor: time from the first MWA date to the date of detection of metastatic disease beyond the index tumor site. Patients without disease progression will be censored at the date of their last visit or the date of their death (due to any cause).

Survival rates will be summarized by using Kaplan–Meier methodology.

Participant timeline (13)

Time schedule of enrollment, interventions, and assessments is displayed in Fig. 2.

Sample size (14)

Hypothesis: MWA of CLM ≤ 2.5 cm with 3D confirmation of the ablation margin > 5 mm achieves definitive local tumor control with minimal morbidity and patient hospital length of stay. The hypothesis is that MWA will have a (tumor-based) liver disease-free survival rate at 2 years at least equal to the historic reference standard of resection with lower morbidity. This study will enroll adult patients with up to three CLMs ≤ 2.5 cm amenable to complete ablation using MWA.

The primary objective of this study is to test the hypothesis that local tumor progression-free survival (LTPFS) is improved with microwave ablation (MWA) in a patient population where we expect two thirds to have ≥ 5.0–9.9 mm minimal ablation margin (MM) and one third to have MM ≥ 10.0 mm. According to past published experience, an overall 85% local progression-free survival at 2 years with radiofrequency ablation for 5.0–9.9 mm margin and > 90% for margin ≥ 10.0 mm has been documented. Our limited data with MWA suggests that these rates can be improved to over 90% and over 95%, respectively. Sample size determination is based on over 90% local tumor control/LPFS at 2 years. We expect to analyze 330 tumors from 275 patients that will provide 86–90% power, depending on intra-patient tumor correlation, to test the null hypothesis that the local progression-free rate will be 87% against the alternative that it will be over 92%, controlling the one-sided type I error at 5% using an exact binomial test. In our past published

experience, intra-patient tumor correlation was negligibly small; hence, we expect to have approximately 90% power [37].

Recruitment (15)

The patients will be identified and recruited from the existing patient population in the Interventional Radiology Service as well as Gastrointestinal Oncology, Hepatobiliary and Colorectal Service. The patients will be presented with a consent form and an explanation of any concerns they may have by the investigator or research team. Patients will be approached for ACCLAIM study if it has already been determined that MWA is the appropriate treatment as determined by routine institutional practice. The participating centers are high-volume centers that could sufficiently enroll patients to meet the sample size required for a powered statistical analysis.

Sequence generation (16)

Not applicable.

Blinding (17)

Trial participants and research study teams will not be blinded to the interventions. Data analysts will be blinded.

Data collection (18a)

Data collection will be handled by the clinical trial team at each site under the supervision of the site investigator, who will be responsible for ensuring the accuracy, completeness, legibility, and timelines of the data reported. Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a REDCap electronic data capture system.

Retention (18b)

Data collection will continue from the participants who have deviations from the protocol interventions or follow-up schedule of assessments. Study documents should be retained for a minimum of 2 years since the formal discontinuation of the clinical investigation.

Data management (19)

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be de-identified, transmitted to and stored with the sponsor. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. Data collected for this study will be analyzed and stored with the sponsor (Society of Interventional Oncology). After the study is completed, the de-identified, archived data will be securely stored as specified in accordance with site regulations and the SIO.

Statistical methods (20)

Populations for analyses

Intention-to-treat (ITT) analysis dataset (i.e., all consented participants).

Modified intention-to-treat analysis dataset (e.g., participants who are treated with MWA).

Safety analysis dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who are treated with MWA).

Per-protocol analysis dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model.

General analysis: data will be analyzed using descriptive statistics. Continuous variables (e.g., age) will be summarized by the number of subjects, mean, standard deviation, median, interquartile range, minimum, and maximum. Categorical variables (e.g., race) will be summarized by frequencies and percentages of subjects in each category.

Statistical methods for primary and secondary outcomes (20a)

Patients are allowed up to 3 tumors and tumor progression will be calculated on a per tumor level as well as per patient level. The local tumor progression-free survival counts and rates will be presented along with the 95% two-sided confidence intervals for the rate. The rate will be defined as estimated proportion of tumors/patients with local tumor progression-free survival at 24 months after the initial MWA using a Kaplan–Meier analysis, adjusting for intraclass correlations needed.

Additional analyses (20b)

All analyses for secondary progression/control will involve two parts: (1) an analysis of post-progression survival using Kaplan–Meier methods and Cox regression and (2) a time-dependent covariate analysis for time from initial treatment, using the secondary treatment as a covariate.

Quality of life assessments will be made by examining the change in the baseline scores to those reported

postoperatively at quality of life (SF-12) assessments at 3, 6, 9, 12, 18, and 24 months post-MWA.

Safety analyses: the incidence and severity of microwave-related adverse events that occur during the course of the study will be assessed.

Missing data (20c)

Missing data (specific items missing or attrition) will be an important issue to address. We will examine and compare patient characteristics between patients who are missing data and those who are not to explore potential bias and missing data mechanisms. Linear mixed models can be applied when there are incomplete records for a participant and yield valid inference under a "missing at random" assumption. Sensitivity to the missing at random assumption will be examined, and if needed, models for non-ignorable missing data mechanisms will be determined [38, 39].

Data monitoring (21a)

Independent medical monitors (IMM) will conduct regular review and analysis of the safety data. The IMM will communicate the results of the review and make recommendations to the trial steering committee/sponsor. Drs. MCS and PP will serve as IMMs.

Interim analyses (21b)

As MWA is an established technique for the treatment of liver malignancies, no interim analyses will be performed for determination of efficacy.

Harms (22)

All adverse events and treatment-related adverse events will be assessed by incidence and severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE). CTCAE is a set of criteria for the standardized classification of adverse effects of drugs used in cancer therapy. The CTCAE system is a product of the US National Cancer Institute (NCI). The CTCAE manual (version 5.0) provides standard AE names and grades. The principal investigator will indicate a preliminary determination of whether an event is related to a study procedure and/or to the study device (i.e., adverse device effect). An event may be both procedure and device related.

The occurrence of a MWA-related adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. MWA-related AEs occurring during the follow-up period will be assessed and followed as reported by all subjects or observed by the investigational site and shall be reported to the study. A representative of the sponsor will work with the investigator to complete the SAE report. Investigators are required to submit to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and the sponsor a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator learns of the effect. The sites will maintain adequate documentation of timely event reporting.

Auditing (23)

Each clinical site will perform internal quality management of study conduct, and data collection, documentation, and completion. Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the International Conference on Harmonization Good Clinical Practice (ICH GCP) and with applicable regulatory requirements.

All participating sites will permit study-related monitoring, audits, and inspections by the ethics committee, IRB, sponsor, and government regulatory bodies of all study-related documents (e.g., source data/documents, regulatory documents, data collection instruments, study data).

Research ethics approval (24)

The study complies with the Declaration of Helsinki/Tokyo/Venice on Experimentation in Humans, as required by the US Food and Drug Administration regulations, the Code of Federal Regulations, Title 21 parts 50, 54, 56, 812, 814.82 (e)[2] as applicable; the Code of Federal Regulations, Title 45 part 46; and the International Conference on Harmonization Good Clinical Practice Guidelines.

The study protocol and any amendments will be submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for formal approval of the study conduct. The participant will sign the informed consent document, using the ethics committee/IRB-approved consent form, prior to any procedures being done specifically for the study. The consent form will be signed by the participant or legally acceptable surrogate and by the investigator-designated research professional. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and

password protected. At the end of the study, all study databases will be de-identified and archived.

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Protocol amendments (25)

Any protocol modifications including eligibility criteria, outcomes, or statistical analyses will be assessed by the steering committee and submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for formal approval. Substantive changes will be communicated to the sponsor and the participating sites.

Who will obtain informed consent (26a)

The site investigator and/or the study personnel will explain the study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

Additional consent provisions for collection and use of participant data and biological specimens (26b)

Participants will consent to their de-identified data being stored electronically with password protection. The informed consent form specifies that de-identified participant data and biospecimens could be used for future research studies without additional informed consent.

Confidentiality (27)

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor. All research activities will be conducted in as private a setting as possible. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/EC, institutional policies, or sponsor requirements.

Declaration of interests (28)

CTS—Ethicon, Sirtex, Terumo, and Medtronic (consultancy, research support); Varian (consultancy/advisory, research support); Ethicon (payment/honoraria for lectures, presentations, speakers bureaus, manuscript writing, educational events); is on the Executive Council of the Society of Interventional Radiology (SIR); is on the Board of Directors 2017–2023 for the Society of Interventional Oncology; and reports research support of the SIR Foundation (grant) and the Society of Interventional Oncology (ACCLAIM Trial Global PI). MRC—Boston Scientific, Pulse Biotherapeutics (consultancy), and UptoDate (royalties). MA—Sirtex Medical Inc. and GE Healthcare (consultancy). DED—Varian Medical (consultancy), Springer Verlag, and UptoDate (royalties). ENP, MG, WR, AK, MCS, PP, LC, and LS have no COI associated with this work.

Access to data (29)

Access to the final trial dataset could be available from the principal investigator upon reasonable request.

Ancillary and post-trial care (30)

MWA is an established treatment for liver malignancies; therefore, participants receive standard of care treatment/follow-up parallel to study participation, which will continue following the trial. Post-trial provisions are not applicable.

Dissemination plans (31a)

The principal investigator is responsible for publication of the results of this study, both positive and negative. The study's outcomes will be presented at relevant national and international scientific meetings and published in a peer-reviewed scientific journal.

Authorship (31b)

Authorship of future publications will be in accordance with the guidelines of the International Committee of

Medical Journal Editors (ICMJE). Authors must fulfill the requirements to be included. Others who contribute but do not fulfill all criteria will be mentioned in the acknowledgements.

Plans to give access to the full protocol, participant-level data, and statistical code (31c)

The full protocol, participant-level data, and statistical code will be available upon request by contact with the corresponding author.

Discussion

A large body of research data on thermal ablation for the treatment of CLMs have focused on the effectiveness, safety, procedural outcomes, and comparison of different thermal ablation modalities (mainly radiofrequency and microwave ablation) [37, 40–45]. Early studies have established the role of TA as a salvage treatment for CLMs recurring after hepatectomy [8, 46], demonstrating comparable rates of LTP for radiofrequency ablation (RFA) and MWA when sufficient ablation margins are achieved [44], and proposed potential markers to aid in prognosis after ablation [37, 45]. Ablation margins ≥ 10 mm were demonstrated to achieve optimal local tumor control [21, 23, 26, 27, 30, 44, 47–50]; however, studies indicated that TA may be associated with a relative risk of complications in high-risk patients such as those previously treated with hepatic artery infusion pump chemotherapy, pre-existing biliary dilatation, prior exposure to bevacizumab, and MM > 10 mm [37].

For well-selected small CLMs, ablation can provide durable long-term outcomes, similar to metastasectomy, as shown by a study [12] that compared the CLOCC trial [51] with the EPOC [14] trial. The EPOC trial randomized 364 patients with resectable CLM to metastasectomy ± perioperative FOLFOX chemotherapy. In the EPOC trial, tumors ≤ 4 cm in the perioperative chemotherapy arm achieved identical rates of local tumor control following resection as tumors treated by RFA in the CLOCC trial. A meta-analysis [52] that included 48 studies (8 systematic reviews, 2 randomized studies, 26 comparative observational studies, 2 guideline-articles, and 10 case series) assessing safety and outcomes of RFA and MWA versus systemic chemotherapy and partial hepatectomy in the treatment of CLM concluded that further randomized comparisons of ablation to current-day chemotherapy alone should no longer be undertaken as the highest level of evidence has been achieved.

The accumulation of these data thus created the research base for establishing the role of thermal ablation (TA) as an alternative to surgery in selected patients with CLMs through prospective clinical trials [49, 53–56]. The prospective randomized CLOCC trial [53] demonstrated a significant prolongation of patients' overall survival by combining standard chemotherapy with TA. Results from the recently presented randomized control COLLISION trial (NCT03088150) showed better local control for TA and a favorable morbidity profile when compared to liver resection for small CLMs [57]. The trial stopped early due to the high likelihood of overall survival and local control benefit, as well as decreased adverse events following TA [58]. The prospective multi-institutional observational CIEMAR study (NCT03775980) evaluating the effectiveness of MWA in real-world clinical practice have enrolled 500 patients with 976 CLMs [59]. Along with the ongoing NEW-COMET (NCT05129787) and HELARC (NCT02886104), these trials are expected to provide further support for the role of TA as a curative-intent treatment for patients with CLM.

Another locoregional treatment for CLMs is stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR). Although SBRT has demonstrated good local tumor control [60], frequent toxicities, including gastrointestinal and liver toxicities, advise against the use of SBRT in CLMs patients that are candidates for surgery or thermal ablation. The prospective SABR-COMET (NCT01446744) [61–63] showed a potential improvement in survival when image-guided SABR is added to standard of care treatment in a variety of tumors in different locations in patients with oligometastatic cancers. Despite the positive signal, the limitations in the design of these trials do not allow the universal use of SABR in patients with CRC liver metastases that can be treated with limited resection or ablation (NCCN Guidelines-Colon Cancer Version 3.2024, [64]). Very few studies have compared SBRT/SABR to TA. The results of these comparisons are extremely limited mostly due to lack of stratification of outcomes by treatment margin [65, 66]. The multicenter randomized controlled trial COLLISION-XL [67] (NCT04081168) comparing SBRT with MWA for unresectable intermediate-size (3–5 cm) CLMs is expected to provide more definitive answers regarding the optimal treatment option for these patients.

LTP rates after TA have ranged between 2.8 and 60% [11, 41, 68], thus precluding the widespread use of this technology as a cancer treatment. Insufficient coverage of the tumor by the AZ results in ablation failure and LTP, regardless of the TA modality used [44, 69]. The size of

the minimum ablative margin (MM) is an independent predictor of LTP [15] and, currently, it is the most common metric of quantitative assessment of ablation success. Inadequate ablative margins were shown to have a high concordance rate with the exact site of LTP [17, 19, 47, 70]. According to the Standardization of Terminology and Reporting Criteria for image-guided tumor ablation [33], technically successful ablation is defined as tumor that is treated according to the protocol and covered completely including the ablation margin (at least 5 mm and ideally 10 mm all around the target tumor, analogous to a surgical margin).

Inadequate ablative margins were shown to have a high concordance rate with the exact site of LTP [71]. Local tumor progression commonly occurs within 5 mm from the tumor border, most likely due to residual viable tumor cells. Currently, there is consensus that a MM of at least 5 mm (ideally 10 mm) is required for ensuring local tumor control following TA [37, 44, 72].

Methods for the measurement of the minimal margin (MM) after TA using anatomical landmarks on pre- and post-ablation CT have been described [16, 17]. A number of challenges compromise the value of the conventional ablation zone assessment approach. First, its accuracy suffers from the mismatch in the imaging slices' position between pre- and post-TA CT images due to liver motion, subjectivity of visual side by side image comparisons and overall cumbersomeness. Second, the size of the MM in the axial plain does not inform on the extent of the additional ablation that may be necessary when the coverage of the tumor within the AZ is sub-optimal. Many recurrences emerge from the caudal or cranial ends of the ablation zone, where the MM is not accurately assessed on single-section CT scans obtained after TA.

Previous studies have described the benefits of image registration and fusion for the assessment of the AZ and AM in all spatial dimensions (3D) [19, 20, 22, 25, 73]. Fusion of pre- and post-ablation contrast-enhanced images enables better understanding of the relationship between the tumor and the ablation zone, helping verify and document the creation of the AM in all spatial dimensions (3D). To supplement the registration/fusion with 3D volumetric computation of incomplete ablation zones, different types of image-processing software can be used. The software performs segmentation of the tumor and AZ volumes, automatically generates the contours of interest (e.g., tumor, theoretical 5- and 10-mm margin volumes) and the volumes of insufficient coverage, when the tumor could not be completely eradicated [74].

Fusion, using image registration and segmentation, is versatile and does not consume much time. Automatic/semiautomatic image registration and segmentation technique take approximately 2–3 and 5 min, respectively. Total time required for the creation of fusion images is generally less than 10 min [73].

Prior studies have demonstrated that the assessment of the ablation zone using 3D image registration software has higher accuracy in identifying the MM and local tumor progression than the 2D landmark-based method [21, 27, 74]. The concordance between the location of the MM and the location of local tumor progression during follow-up has been shown in both studies using the conventional 2D landmarks assessment [17, 47] and in those using the 3D software assessment of the ablation zone [21, 27, 74].

A prior study [47] showed that the assessment of the AZ and margins with immediate post-ablation triple-phase CT resulted in a significantly lower LTP rate when compared LTP rates of ablations performed prior to the establishment of this immediate imaging assessment. Within the 55-month median follow-up, tumors ablated with sufficient MM (5–10 mm) developed LTP more often when compared to those ablated with MM greater than 10 mm (LTP: 15% vs 5%) [47]. In another study comparing RFA to MWA in the treatment of CLMs, no LTP was noted for ablation zones with a MM larger than 10 mm [44]. MMs less than 5 mm and perivascular tumor localization were significant predictors of shorter time to tumor progression for RFA. Perivascular tumor location was not significant for MWA. Several subsequent studies validated the 5 mm as a critical technical end point of ablation technical success [21, 27, 28, 31, 37, 50, 75, 76].

A recent meta-analysis solidified that a minimal ablation margin over 5 mm is a required critical endpoint, whereas a minimal margin of at least 10 mm yields optimal local tumor control after TA of CLMs [75].

Image fusion, using anatomic image registration and segmentation, is versatile and time efficient. Automatic/semiautomatic image registration and segmentation technique take approximately 2–3 and 5 min, respectively. Total time required for the creation of fusion images is generally less than 10 min [73]. Recent publications have shown the importance of ablation margins in local tumor control for CLM [21, 26, 27, 29, 30, 49, 75] and the superiority on the intraprocedural vs the 4–8 weeks 3D margin assessments as a predictor of LTP [49, 50]. Recent findings from the randomized controlled COVER-ALL trial demonstrated that software-based assessment of the ablation margins is superior to that using a visual comparison approach in patients with a variety of primary and metastatic liver tumors treated with thermal ablation [77].

Well-designed prospective clinical trials are needed to further refine patient selection criteria, optimize and standardize treatment protocols, and assess long-term

outcomes. The ACCLAIM trial established a uniform MWA technique throughout 10 centers in the USA and EU, with a measurable and reproducible technical endpoint, and is aspiring to establish the minimum required standard of care of thermal ablation when used as a local cure for selected CLM.

Trial status

Protocol version 4.0. Open to accrual: 26-April-2023. Latest approval date: 09-Dec-2024. Estimated completion date: 01-Dec-2025.

Abbreviations

AZ	Ablation zone
CECT	Contrast-enhanced computed tomography
CLM	Colorectal liver metastases
CRS	Clinical risk score
DWI	Diffusion weighted imaging
ECOG	Eastern Cooperative Oncology Group
FDG PETCT	^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography
LPFS	Local progression-free survival
LTP	Local tumor progression
TA	Thermal ablation
MM	Minimal margin
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MWA	Microwave ablation
QOL	Quality of life
RFA	Radiofrequency ablation
SABR	Stereotactic ablative radiotherapy
SBRT	Stereotactic body radiotherapy
SIO	Society of Interventional Oncology
SOC	Standard of care

Supplementary Information

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Additional file 1. SPIRIT checklist

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Not applicable.

Authors' contributions
CTS is the principal investigator; he conceived the study and led the proposal and protocol development. MG provides statistical expertise and will be performing the analysis. MRC, WR, MA, and MCS contributed to the study design and to development of the proposal. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interest

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