varian
A Siemens Healthineers Company

Interventional Solutions
Medical Affairs

COVER-ALL Trial

Lancet Gastroenterol Hepatol 2025

Key Takeaway

The study demonstrated that a novel software-based method for assessing minimal ablative margins during liver tumor thermal ablation significantly improved outcomes compared to traditional visual assessment. The experimental group achieved a mean minimal ablative margin of 5.9 mm, compared to 2.2 mm in the control group, with no severe adverse events reported. These results suggest that incorporating software-based assessment could enhance the precision and effectiveness of liver tumor ablation, making it a valuable tool for improving local tumor control and reducing treatment variability.

Key Points

Objective: Evaluate software-based* method for assessing minimal ablative margins in liver tumor ablation.

Trial: NIH and NCI funded, Phase 2, randomized trial at MD Anderson Cancer Center.

Groups: Experimental (software-based assessment) vs. Control (visual assessment). A non-randomized experimental group was treated after the interim analysis halted control group enrollment.

Primary Endpoint: Minimal ablative margin on post-ablation CT after aiming for a margin of 5 mm or greater.

Results:

- Experimental software-based group: 5.9 mm margin vs. 2.2 mm in the control visual group ($p < 0.0001$).
- Non-randomized experimental group: 7.2 mm margin.

Adverse Events: 5% of patients (12% in control, 3% in experimental).

Conclusion: Software-based assessment improves ablative margin and is safe.

Study Design

Study design and patients

The COVER-ALL trial was a randomized, phase 2 superiority study conducted at MD Anderson Cancer Center, involving adults aged 18+ with primary or secondary liver tumors (1–5 cm) referred for thermal ablation. Only the largest tumor per patient was included to avoid within-patient correlation. Exclusion criteria included prior locoregional treatments, inadequate kidney function for contrast use, and conditions impairing study participation.

Randomization and masking

Participants were randomly assigned (1:1) intra-procedurally to either the control group (visual assessment) or the experimental group (software-based assessment) using the Pocock-Simon dynamic minimization method to balance baseline covariates such as tumor histology, size, location, and number. Randomization occurred after the ablation applicators were placed and before energy delivery by a research nurse, ensuring minimization of operator bias. While the study team could not mask the interventional radiologists, research nurses, or technical staff, patients were under general anaesthesia and unaware of their treatment allocation. Oncological outcomes and adverse events were assessed by masked radiologists and research nurses, respectively.

Procedures

The thermal ablation procedures were performed under CT guidance by experienced interventional radiologists, with patients under general anesthesia. Tumors were treated using radiofrequency or microwave ablation, aiming for complete coverage and a minimal 5 mm ablative margin. Pre-ablation planning involved dual-phase CECT images to identify tumors and guide applicator placement. Post-ablation CECT confirmed tumor coverage, and the minimal ablative margin was assessed either visually (control group) or using a software-based method (experimental group) that combined biomechanical deformable image registration (Raystation with Morfeus: RaySearch Laboratories, Stockholm, Sweden) with custom built AI-based autosegmentation algorithms. The software quantified the margin and provided feedback to radiologists, helping guide the procedure.

Outcomes

The primary endpoint was the minimal ablative margin on post-ablation intraprocedural CT. Secondary endpoints included 2-year local tumor progression, overall survival, local tumor progression-free survival, intrahepatic and extrahepatic progression-free survival, procedure workflow, and adverse event rates. Outcomes were assessed using standard ablation reporting criteria and RECIST version 1.1, with modified RECIST for hepatocellular carcinoma. A 3D ray-tracing method was used to correlate sites of tumor progression with the minimal ablative margin. For the experimental group, the impact of the software-based assessment on workflow and user experience was evaluated via a questionnaire. Adverse events were monitored at each study visit, and patients had regular follow-up imaging to assess oncological outcomes, with images reviewed independently by two radiologists.

Statistical analysis

The study aimed to detect differences in minimal ablative margin between the control and experimental groups, with a sample size of 100 patients (50 per group) based on an estimated 2 mm standard deviation. An interim analysis was planned after 50 patients to assess the superiority of the software-based assessment, with a stopping boundary if p-value < 0.003. Post-hoc analyses explored AI autosegmentation, progression correlation, imaging, radiation dose, and procedure workflow. Statistical significance was set at $p < 0.05$.

CT: Computed tomography, CECT: Contrast-enhanced computed tomography, AI: Artificial intelligence, RECIST: Response evaluation criteria in solid tumors. QR700022294 April 2025

Patients	
	Study Enrollment Period: June 15, 2020 – October 5, 2023 **Control Group**: 26 patients (mean age 58.1 years, 69% male, 31% female), with 42% having colorectal cancer liver metastasis. Median tumor diameter: 1.7 cm. Ablation modality: RFA=1, MWA=25. **Experimental Group**: 24 patients (mean age 60.5 years, 67% male, 33% female), with 42% having colorectal cancer liver metastasis. Median tumor diameter: 1.8 cm. Ablation modality: RFA=0, MWA=24. **Non-randomized Experimental Group**: 50 patients (mean age 56.5 years, 54% male, 46% female), with 60% having colorectal cancer liver metastasis. Median tumor diameter: 1.5 cm. Ablation modality: RFA=0, MWA=50.
Primary Endpoint	
Minimal Ablative Margin (MAM)	- At the interim analysis, MAM was significantly higher in the experimental group (5.9 mm) compared to the control group (2.2 mm, p<0.0001) with IDSMB recommending halting control group enrollment. - For the non-randomized experimental software-based assessment group, the mean MAM was 7.2 mm. - The proportion of patients with an optimal MAM of ≥ 5 mm was higher in the experimental group (75%) compared to the control group (15%); and 84% in the non-randomized experimental group.
Secondary Endpoints – Experimental and Control Group	
Local Tumor Progression	- Local tumor progression was lower in the experimental group (4%) compared to the control group (15%), though the difference was not statistically significant (p=0.24). - Intrahepatic and extrahepatic progression were similar.
Local Tumor Progression-Free Survival	- The 2-year cumulative incidence of local tumor progression was 16% in the control group and 5% in the experimental group (p=0.24).
Procedure Workflow	- Overlapping ablations were more common in the experimental group (92%) compared to control (62%). - The procedure duration was longer in the experimental group (112 min) than in the control group (91.5 min).
Adverse Event Rates (All Three Groups)	- Adverse events occurred in 5% of patients, with 12% in the control group (26 patients) and 3% in the two experimental groups (74 patients). - No grade 4 or 5 adverse events were reported.

Discussion

- **Significance**: This phase 2 RCT is the first to show the feasibility and efficacy of using a software-based assessment to optimize the minimal ablative margin during thermal ablation of liver tumors.
- **Software-Based Assessment Efficacy**: The software-based assessment significantly improved the minimal ablative margin (5.9 mm vs. 2.2 mm in the control group, p<0.0001).
- **Procedure Duration**: The experimental group had longer procedures due to more overlapping ablations and re-ablations, but software processing time was quick (3 minutes).
- **Adverse Events**: Low adverse event rates (5%), with no major events, indicating safety of the procedure with the software.
- **Limitations**: Study had small sample sizes, potential selection bias, and underpowered analysis for oncological outcomes.
- **Potential for Integration into Standard Care**: Software-based assessment improved the ablative margin and reduced local tumor progression (5% vs. 16% in control), highlighting its potential for integrating into standard care.
- **Future Validation and Generalization**: The study supports the use of the proposed software for real-time, intraprocedural decisions, but findings should be validated in larger, multi-center trials to further assess its general applicability across different tumor types and ablation methods.

Research in Context

- **Evidence Before the Study**: Retrospective studies show varying rates of local tumor progression (12%-54%) after liver thermal ablation, with minimal ablative margin being a key factor, often assessed visually. There was a lack of prospective studies on software-based ablation confirmation during the procedure.
- **Added Value of This Study**: This is the first randomized clinical trial to assess the intraprocedural use of a software-based ablation confirmation method, demonstrating its safety and significant improvement in the minimal ablative margin.
- **Implications of Available Evidence**: Retrospective studies link minimal ablative margin with local tumor progression, but this trial is the first to show that software-based assessment during ablation can directly improve procedure efficacy and safety.
- **Study Results**: The software-based method was found to significantly improve the minimal ablative margin, making it a valuable tool for liver thermal ablation procedures.
- **Clinical Implications**: The findings support the integration of software-based assessment into routine thermal ablation procedures to enhance local tumor control and improve patient outcomes.

Software-based versus visual assessment of the minimal ablative margin in patients with liver tumours undergoing percutaneous thermal ablation (COVER-ALL): a randomised phase 2 trial

Bruno C Odisio, Jessica Albuquerque, Yuan-Mao Lin, Brian M Anderson, Caleb S O'Connor, Bastien Rigaud, Maria Briones-Dimayuga, Aaron K Jones, Bryan M Fellman, Steven Y Huang, Joshua Kuban, Zeyad A Metwalli, Rahul Sheth, Peiman Habibollahi, Milan Patel, Ketan Y Shah, Veronica L Cox, HyunSeon C Kang, Van K Morris, Scott Kopetz, Milind M Javle, Ahmed Kaseb, Ching-Wei Tzeng, Hop-Tran Cao, Timothy Newhook, Yun Shin Chun, Jean-Nicolas Vauthey, Sanjay Gupta, Iwan Paolucci, Kristy K Brock

Lancet Gastroenterol Hepatol 2025

Published Online March 13, 2025 https://doi.org/10.1016/S2468-1253(25)00024-X

See Online/Comment https://doi.org/10.1016/S2468-1253(25)00061-5

IDSMB: Institution Data and Safety Monitoring Board, RCT: Randomized Controlled Trial.