# Clinical impact of a volumetric image method for confirming tumor coverage with Ablation on patients with malignant Liver Lesions

**(COVER-ALL)**

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## List of Abbreviations

ASA: American society of anesthesiologists

CECT: contrast-enhanced computed tomography

CLM: colorectal liver metastasis

CT: computed tomography

DIR: deformable imaging registration

DTA: distance to agreement

ECOG: eastern cooperative oncology group classification

FEA: finite element analysis

INR: international normalized ratio

LTP: local tumor progression

LTPF: local tumor progression-free survival

MAM: minimal ablation margins

MR: magnetic resonance

MW: microwave ablation

OS: overall survival

PTA: percutaneous ablation

QOL: quality of life

RFA: radiofrequency ablation

TRE: target registration error

## OBJECTIVES

### 1.1 Primary Objective

To evaluate if the intra-procedure feedback of a biomechanical deformable registration volumetric image method during percutaneous ablation will increase the minimal ablation margins on a three-dimensional computed tomography-generated analysis.

### 1.2 Secondary Objectives

1. To assess whether applying the proposed method during percutaneous ablation improves local tumor progression-free survival (LTPFS) rates;
2. Evaluate impact of software use on procedure workflow;
3. Impact of software use on complication rates, quality of life, liver function;
4. Evaluate oncological outcomes (intra-hepatic and overall progression-free survivals, and overall survival)

## BACKGROUND

### 1.3 Rationale

Primary liver cancer is the second leading cause of death worldwide with an estimated 788.000 related-deaths in 2015. The global burden of primary liver cancer can also be demonstrated by the impact on disability-adjusted life-years, which was estimated

in 20.578.000 in 2015. In addition to primary liver cancer, approximately two-thirds of all the 774.000 colorectal cancer-related deaths - the third most common cause of cancer-related death worldwide and the most common cause of metastatic liver cancer - are attributed to the presence of colorectal liver metastasis (CLM). Collectively, primary and secondary liver cancers are responsible for over 1 million deaths per year worldwide. Moreover, it is expected an increase on the incidence on both primary and secondary liver cancers in the next decades owing to population growth and aging. Therefore, effective therapies for the treatment of primary and secondary liver cancers are needed.

Among the curative treatments available for primary liver cancer, surgical resection (or liver transplantation) and ablation are both considered the standard of care on patients with very early and early stage accordingly to the Barcelona Clinic Liver Cancer staging and treatment strategy (1). Contrarily, for secondary liver cancers such as colorectal cancer liver metastasis, surgical resection is still considered the modality of choice. Unfortunately, only 20% of the patients with colorectal liver metastasis are considered surgical candidates (2), with percutaneous thermal ablation used as an acceptable alternative for the remaining of the non-surgical candidates (3), highlighting the importance of this therapy as a therapeutic option. Moreover, results of prospective phase II randomized clinical trial demonstrated improved overall survival rates among patients treated with a combination of percutaneous liver ablation and systemic chemotherapy for CLM when compared to patients treated with systemic chemotherapy alone (4).

Currently, several ablation modalities are available for clinical use. Among those, radiofrequency ablation (RFA) and microwave (MW) coagulation are the most commonly

utilized. Such modalities have fundamental differences in the way tumor destruction is obtained. RFA promotes tumor destruction by the delivery of an alternating electrical current within the tumor resulting in frictional heat and movement of electrons within the lesion and surrounding tissues, whereas MW promotes tissue heating by causing polar water molecules to continuously realign with an oscillating electromagnetical field that emanates from the microwave antenna. Both technologies produces tissue friction and heat induces cellular destruction via coagulative necrosis. More recently, MW has been used more frequently in clinical practice given its advantages in achieving higher ablation temperatures and larger ablation zones. Nevertheless, when compared to RFA, MW is associated with a lower level of predictability between the desired ablation zone planned and the actual ablation zone achieved. Such discrepancy might affect both the safety of the procedure (i.e. larger unanticipated ablation zones with damage of critical structures adjacent to the ablated tumors) as well the oncological outcome of it (i.e. smaller ablation zone not encompassing the entire tumor volume). Moreover, tissue volumetric loss are more prominent with MW coagulation when compared to RFA, which limits the ability of the operator to ascertain with confidence adequate tumor coverage. Therefore, tailored high-precision image-guidance during ablation is critical for reducing procedure-associated complications and achieve optimal outcomes.

### 1.4 Clinical Impact

Among the local therapies utilized for liver cancers, percutaneous thermal ablation has become a widely utilized option for patients not eligible for surgery, with most recent series demonstrating similar 5-year overall survival rates between surgery and ablation

(5-7). This highlights the efficacy of this treatment modality on prolonging OS in patients with liver cancers (4).

In order to achieve optimal results with ablation, low rates of local recurrence (also known as *local tumor progression* [LTP]) at the treated tumors should be obtained. More recently, results of a prospective randomized phase II trial demonstrated that patients with CLM treated liver ablation in association with systemic chemotherapy had significantly longer overall survival rates (OS) when compared to patients treated only with systemic chemotherapy (4), emphasizing the role of aggressive local treatment on prolonging OS in patients with unresectable CLM. In an effort to improve local disease control and oncologic outcomes after liver ablation, several factors have been studied (15-19). Among the known factors associated with improved local tumor control with ablation, lesion diameter < 3 cm, number and location of tumors, and minimal ablation margins achieved around the target tumor(s) are widely recognized as critical variables, with the latter being the only one passive for modification during treatment delivery. Moreover, it has been recently described that biological factors such as the RAS mutational status are also prognostic indicators for local recurrence and survival in patients undergoing ablation of CLM and have prompted recommendations for wider ablation margins in patients with RAS-mutated tumors (8, 20), suggesting that the minimal ablation margin acceptable for optimal disease control needs to be tailored to distinct tumor subtypes.

In order to provide adequate ablation margins, several elements are important: firstly, it is critical to have optimal definition of the tumor extent on intra-procedural CT

image; secondly, confirmation of precise probe placement in relation to the tumor is needed intra-procedurally; thirdly, the volumetric loss and peri-tumoral tissue inflammation promoted by the ablation limits the ability to evaluate with confidence the ablation margin intra-procedurally, therefore requiring a magnetic resonance (MR) or computed tomography (CT) study to be performed within 1-2 months following ablation procedure, a long period to evaluate the primary efficacy of this modality. Taking all together, those factors points to the need of having improved intra-procedurally imaging assessment of patients undergoing percutaneous ablation.

Currently, there are no commercially available tools that provide a robust and accurate method for tumor mapping and ablation confirmation that takes in consideration the biomechanical conformational changes promoted by this therapy. We hypothesize that local tumor control following percutaneous ablation of liver cancers will be significantly improved with the application of a dedicated anatomical linear elastic biomechanical model for treatment guidance and efficacy assessment by enabling the operator to accurately identify the tumor for ablation probe placement and assess intra-procedurally the minimal ablation margins, therefore increasing efficacy of percutaneous ablation therapy, ultimately improving liver progression-free survival rates.

Our preliminary data shows that our biomechanical model can accurately map the tumor, defined on pre-treatment computed tomography (CT) imaging, onto an intra-procedural CT image and is insensitive to imaging artifacts associated with ablation probe. We hypothesize that our innovative approach to modeling the tissue changes related to the ablation procedure will enable intra-procedure monitoring of the ablation

margin relative to the tumor. In addition, the combination of these technologies will provide further detailed information on the relationship between progression-free survival local tumor progression-free survival (LTPFS) and the ablation margins achieved.

### 1.5 Mechanism

A multi-organ finite element model (FEM)based deformable image registration (DIR) method (Morfeus) has been developed in a previously funded R01 and extensively validated on several sites including head and neck, lung, liver, stomach, esophagus, pancreas, prostate, rectum, cervix, and extremity sarcoma (8-29). A commercially available FEM pre and post processes (HyperMesh, Altair Engineering, Troy, MI) and a Finite Element Analysis (FEA) software package (ABAQUS, ABAQUS Inc, Pawtucket, RI) are utilized for model creation and analysis. Morfeus, is briefly described below, illustrated in Figure 1, and described in detail in the referenced publications: Briefly, manual contouring of regions of interest are generated and converted to a 2D surface mesh (clouds of nodes, connected to form elements). The number of elements can be reduced, leading to increase in efficiency, by combining elements and smoothing regions of high frequency.

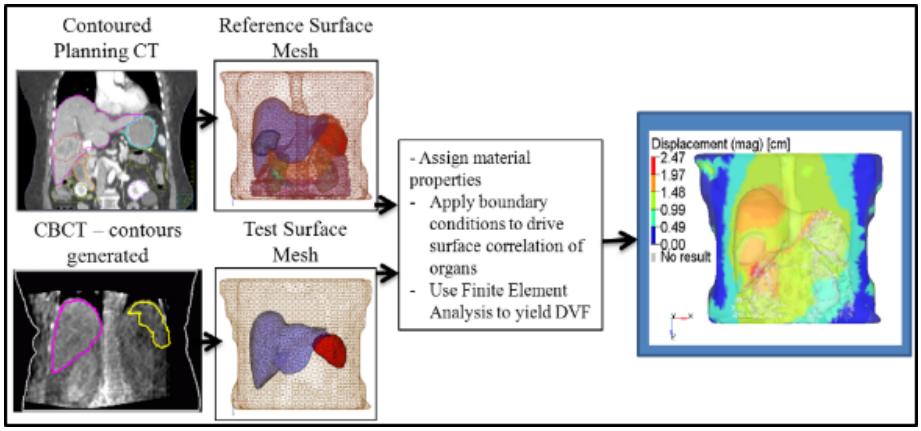



Figure 1. Morfeus schematic. Contours from reference volume (planning CT) and test volume (generated semi-automatically) are matched by Finite Element analysis

This surface mesh is a shell from which a 3D volume mesh is created, consisting of tetrahedral elements. Multi-organ models are created by constructing surface interfaces between neighboring region of interest meshes to govern their interaction. Boundary conditions, or loads applied to the FEM (e.g. force, moment, constraint, or pressure), provide a relationship between the initial and secondary representation of the mesh. Preliminary investigations focused on the use of applied constraints, or set displacements, assigned to a subset of elements in the model, determined by projecting the nodes on the surface of one region of interest onto a surface representation of the same region of interest constructed from another imaging session. Finite Element Analysis (FEA) determines the results of the boundary conditions for all nodes in the model. In summary, the method does not explicitly use intensity information in the registration, only for the manual delineation of regions of interest, the registration process is identical for images of the same or different modalities, the registration is driven by the alignment of a subset of the region of interest surfaces using a guided surface projection method, and the full deformation map (i.e. points in space with defined displacements), relating two images, is calculated using biomechanical models and solving the constitutive equations using FEA.

This algorithm was licensed to RaySearch Laboratories (Stockholm, Sweden) for integration into their radiation therapy treatment planning system RayStation. The algorithm was extensively validated to confirm that the integration was performing with the same accuracy as the in-house developed system. Overall, the mean distance to agreement (DTA) was ≤ 1.0 mm for controlling structures (i.e. the liver) and 1.0–3.5 mm

for implicitly deformed structures (i.e. the kidneys) on average. Target registration error (TRE) ranged from 2.0 mm on prostate MR to 5.1 mm on lung MR on average, within 0.1 mm or lower than the image voxel sizes. Accuracy was not overly sensitive to changes in the material properties or variability in structure segmentations, as changing these inputs affected DTA and TRE by ≤ 0.8 mm. Maximum DTA > 5 mm occurred for 88% of the structures evaluated although these were within the inherent segmentation uncertainty for 82% of structures. Differences in accuracy between the commercial and in-house research implementations were ≤ 0.5 mm for mean DTA and ≤ 0.7 mm for mean TRE.

Deformable image registration for multi-modality imaging for treatment planning and guidance has been an area recent advancement. The vast majority of algorithms rely on voxel-based similarity metrics (e.g. mutual information) combined with geometric-based smoothing parameters (e.g. B-splines) (30, 31). The accuracy of these algorithms is often sufficient when contrast is present in the images and the motion is smooth, however, recent studies, such as the one illustrated in Figure 2(32), have indicated that as contrast is reduced and the motion is complex and non-uniform, the accuracy reduces substantially (33-35). In several instances (e.g. contrast-limited images, sliding interfaces) biomechanical models have succeeded in achieving the desired level of accuracy (8, 9, 11, 17, 18, 20, 21). The successful completion of this program of research will expand these proven models to model deformation observed between planning and intra-procedural images for percutaneous ablation (PTA). The development of these models, which maintain accuracy regardless of extent of contrast in the images, will enable the safe use of deformable registration for PTA guidance (integration of pre-treatment

images) and PTA response (e.g. water loss and tissue retraction due to heating and inflammation).

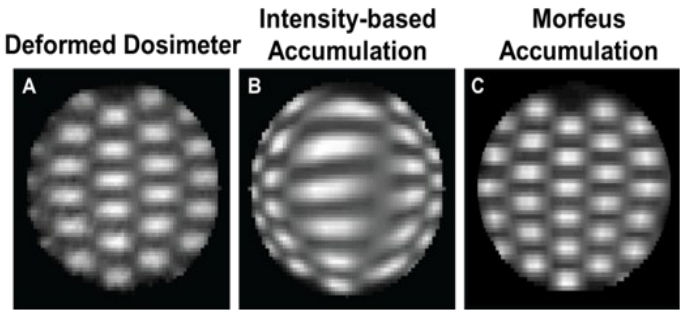



Figure 2. Two methods of dose accumulation were evaluated by deforming a gel dosimeter. Morfeus was more accurate at representing the actual deformation.

## ELIGIBILITY

### 1.6 Inclusion Criteria

1. Patients presenting with ≤ 3 liver tumors (biopsy-proven or documented by imaging) measuring 1 to 5 cm planned to undergo percutaneous thermal ablation with either microwave or radiofrequency ablation. Patients with more than 3 tumors might also be eligible in case other tumors can be treated with another curative-intended loco-regional therapy (i.e. surgical resection, radiation therapy).
2. Ability to completely cover the target tumor with at least a 5 mm ablation margin.
3. Written informed consent to voluntarily participate in the study and follow-up CT scan schedule
4. Age > 18 years-old
5. Performance status 0-2 (Eastern Cooperative Oncology Group Classification [ECOG])

6. Target tumor should be visualized on contrast-enhanced CT
7. Adequate glomerular filtration rate

### 1.7 Exclusion Criteria

1. Active bacterial infection or fungal infection on the day of the ablation that, in the opinion of the investigator, would interfere with safe delivery of the study procedure or with the interpretation of study results.
2. Platelet < 50,000/$mm^3$.
3. INR > 1.5
4. Patients with uncorrectable coagulopathy.
5. Currently breastfeeding or pregnant (latter confirmed by serum pregnancy test).
6. Physical or psychological condition which would impair study participation.
7. ASA (American Society of Anesthesiologists) score of > 4.
8. Any other loco-regional therapies at the target lesion(s) within 30 days of the ablation procedure.

## NUMBER OF PARTICIPANTS

Preliminary retrospective data on the control arm suggest that a minimum ablation margin (MAM) of 2mm (SD 2) is generally achieved when ablation is performed without the use of software guidance. A sample size of 50 evaluable subjects in each group will have 80% power to detect a difference in means of -1.132 (the difference between a control arm mean, of 2 mm and the experimental arm mean of 3.132) assuming that the common

standard deviation is 2 using a two group t-test with a two-sided 0.05 significance level. Assuming an accrual rate of 35 **patients per year**, the study accrual duration will be around 3 years, with follow-up for at least 2 years, totaling 5 years for the entire study duration. We will have an interim look for superiority once half the evaluable subjects (n=50) have been enrolled. A Lan-Demets spending function using an Obrien-Flemming boundary will be used for superiority stopping boundaries. We will stop enrollment at the control arm at our interim look if our p-value is less than 0.003. East v6.5 was used for sample size calculation. The next 50 patients would be enrolled on the experimental arm only to allow further development of the proposed biomechanical model on clinical practice, as well allow other interventional radiologists at our Department to utilize it.

We plan to screen 140 subjects and expect approximately 20 subjects to be screen failures. Furthermore, subjects after randomization who drop out due to tumor progression, inability to clearly depict target lesions, and major complications precluding further ablation will be considered inevaluable. To account for an expected 20% inevaluable subjects, we will enroll a total of 120 subjects to ensure 100 evaluable subjects.

## STUDY PLAN/DESIGN

### 1.8 Method

RayStation® is a flexible, innovative treatment planning system. It combines unique features like unmatched adaptive therapy capabilities, multi-criteria optimization,

optimization for HDR brachytherapy and external beam therapy with photons, electrons, protons as well as helium and carbon ions. RayStation supports a wide range of treatment machines, providing one control center to create biomechanical deformable registrations using “Morfeus”. Morfeus lets the investigators focus all their skill and experience on evaluating and refining plan quality.

To investigate the impact of the proposed biomechanical model on clinical decisions during ablation guidance and end-point assessment, patients will be randomized in two treatment arms (i.e. experimental arm - including anatomical modeling of the liver, and control arm) with a 1:1 ratio. The primary objective is to assess whether applying biomechanical models during percutaneous ablation will increase the minimal ablation margins, which will be evaluated at the end of the procedure with the proposed software on both cohorts. Additionally, two other distinct end-points will analyzed: ability of the model to provide tumor identification for ablation probe placement on intra-procedural non-contrast enhanced CT, and local tumor control rates achieved with the clinical application of this model. Operating physicians will be informed in respect which arm the patient was randomized at the time of ablation (figure 3).

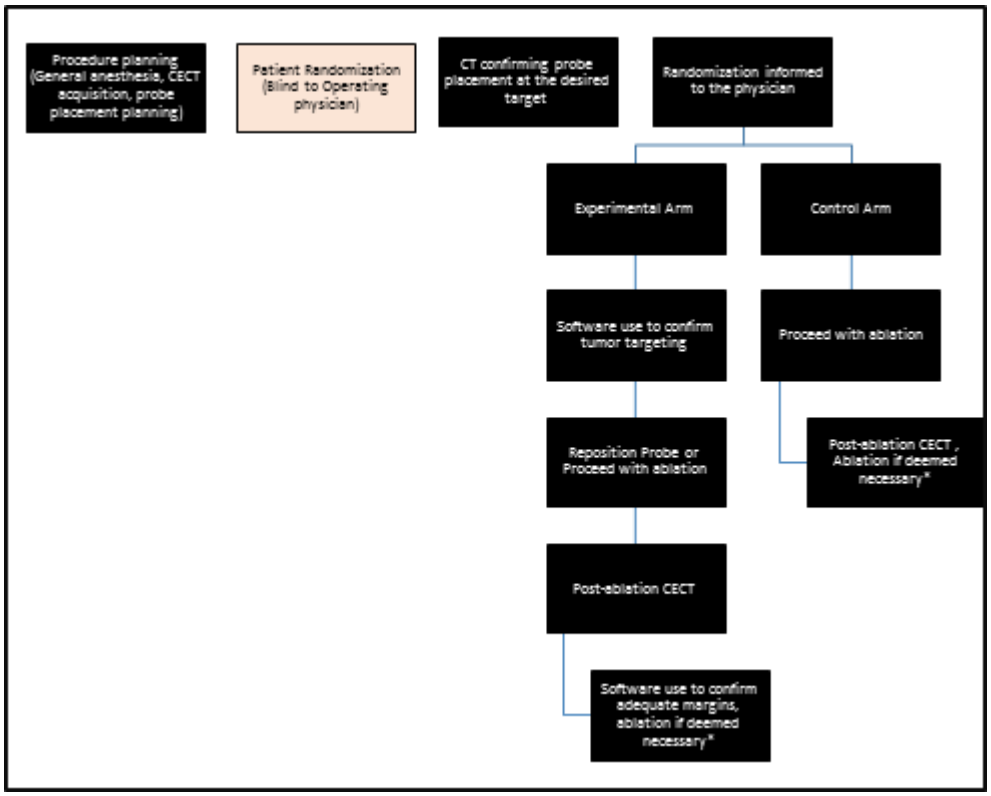



Figure 3: Patient randomization flowchart

### A. Impact on tumor targeting

The clinical trial will be designed according to the optimized parameters from our retrospective analysis. The optimized biomechanical models will be used to assess the accuracy (e.g. the ability of the model to accurately describe the motion, deformation, and volume change and tumor location in the liver between the pre-ablation contrast-enhanced CT and the intra-procedural non-contrast enhanced CT) in both cohort of patients. For the control arm, no information in respect tumor location and targeting will be provided for the operating physician during ablation. Imaging processing using the biomechanical model will be performed after procedure completion. For the experimental

arm, tumor location and confirmation of appropriate targeting with ablation probe will be performed intra-procedurally utilizing the proposed software. Differences in tumor targeting accuracy between the two cohorts will be evaluated. If the accuracy of the cross validation cohort is not statistically significantly different, using a paired Student's T-test based on the preliminary retrospective results with significance defined as a p value of less than 0.05, from the initial optimization and validation results, then the model will be identified as complete. If the results are statistically worse, as an alternative approach, the initial cohort of patients will be used to perform an independent optimization of the model. Collaborations with the statistician will ensure that the appropriate power study has been performed for the analysis. The completion of this investigation will provide the accuracy of the present model in identifying and facilitate targeting of the liver tumors eligible for ablation when compared to the currently utilized standard of care tumor for tumor identification and targeting.

**B. Impact on minimal ablation margins**

A post ablation contrast-enhanced CT will be performed as per standard of care to assess the minimal ablation margins. Such assessment is currently performed manually using local rigid anatomic landmarks of the liver between the pre-ablation and post-ablation contrast-enhanced CTs. In this aim, we will evaluate the impact on the use of the advanced biomechanical model-based deformable alignment incorporating motion, deformation, and ablation-related volume loss in the liver between the pre-ablation contrast-enhanced CT and the post-ablation contrast-enhanced CT. The model will

automatically generate a minimal ablation margin on a three-dimensional Cartesian plan. Such information will be utilized by the operator physician on the experimental arm to determine whether additional ablation is needed at a particular region surrounding the target tumor using a cut-off of at ≥ 5 mm of minimal ablation margins in relation to the tumor borders in all planes (treatment arm). The ≥ 5 mm minimal ablation margin will be used to account for the margin of error of the software, which is currently 3 mm. Frequency of total coverage of the target tumor, minimal ablation margins distance, and

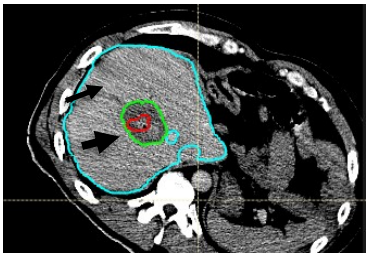


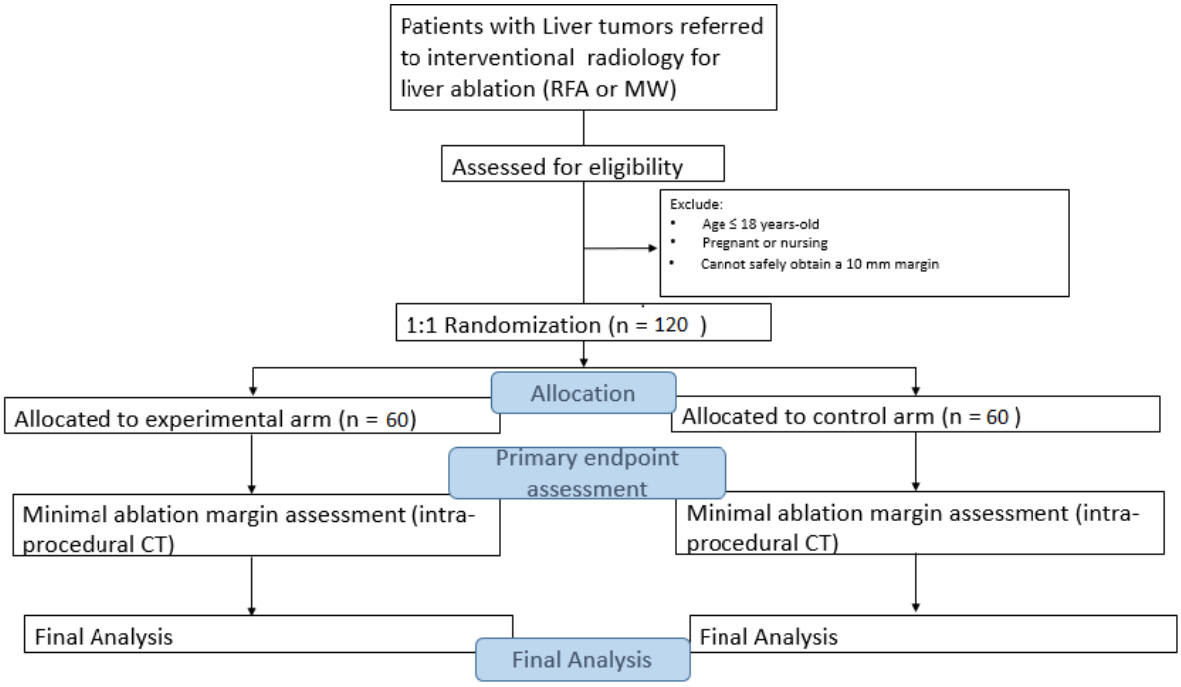
Figure 4: Image fusion of pre- and post-ablation contrast-enhanced CT using the proposed biomechanical model-based deformable image registration (Morfeus). Blue line: deep learning-based segmentation of the liver; Red line: gross-tumor volume (GTV) contouring; Green line: gross-ablation volume. A minimal ablation margin of < 5 mm was detected on the latero-posterior aspect of the GTV (arrow).

need for re-ablation between the two cohorts will be analyzed to identify the impact of this model on intra-procedural decision-making.

### C. Impact on local tumor control

Rates of local recurrence following ablation in the most recent series varies from 20% to 45%. Although re-ablation on a different session is a feasible option in a minority of patients with recurrence at the ablated tumors, this incurs several disadvantages associated with the need to undergo another invasive procedure such as emotional stress, increased exposure to complications related to anesthesia and ablation procedure, radiation exposure, additional use of intravenous contrast media, and

increased associated costs. Given the complex volumetric and spatial changes of the liver post-ablation, the ability to map the previous treatment onto the new treatment plan is critical not only to avoid treatment related toxicities, but also to ensure that the patients receive adequate treatment with optimal coverage. We hypothesize that the use of this current model might improve local tumor control rates at 2-years follow-up. The completion of this aim will evaluate our hypothesis that the applied biomechanical model will improve local tumor control at 2-year when compared to the standard of care control arm.




Note: Final Analysis (n = 100 evaluable subjects)

Figure 5: Clinical Trial schema

## 1.9 Collecting Time Points

| Visit No. | Visit 1 | Visit 2 | | | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 |
|---|---|---|---|---|---|---|---|---|---|
| Visit | Screening | Ablation day | | | 45 days | 3 months | 6 months | 1 year | 2 years |
| Interval Window | Within 30 days ablation | Day 0 = ablation of target lesion | | | (± 14 days) postablation | 3 months ( ± 1 month) postablation | 6 months ( ± 1 month) postablation | 12 months ( ± 1 month) postablation | 24 months ( ± 3 months) postablation |
| Study Activity | | pre | during | post | | | | | |
| Informed consent | x | | | | | | | | |
| Demographic information | x | | | | | | | | |
| Medical, surgical, radiation history | SOC | | | | | | | | |
| BMI and ECOG performance | SOC | SOC | | | SOC | SOC | SOC | SOC | SOC |
| Child-Pugh, ASA scores, BCLC staging | SOC | | | | SOC | SOC | SOC | SOC | SOC |
| CBC, Coagulation, liver function, renal tests | SOC | | | | SOC | SOC | SOC | SOC | SOC |
| Alpha-fetoprotein | SOC | | | | SOC | SOC | SOC | SOC | SOC |
| Carcinoembryonic antigen | SOC | | | | SOC | SOC | SOC | SOC | SOC |
| Pregnancy test | SOC | | | | | | | | |
| Inclusion/exclusion | x | x | | x | | | | | |
| Concomitant medications | SOC | SOC | | | SOC | SOC | SOC | SOC | SOC |
| QOL questionnaire | x | | | | x | x | x | x | x |
| Numeric Pain Rating Scale | SOC | | | | SOC | SOC | SOC | SOC | SOC |
| CT scan | SOC | SOC | SOC | SOC | SOC | SOC | SOC | SOC | SOC |
| Ablation procedure information | | SOC | SOC | SOC | | | | | |
| Liquid biopsy (ctDNA) | | SOC | | | SOC | | SOC | SOC | SOC |
| Physician assessment of software utility | | | | x | | | | | |
| Device user experience | | | | x | | | | | |
| Technical success assessment | | | | SOC | | | | | |
| Technical efficacy assessment | | | | | SOC | | | | |
| Follow-up postablation treatment | | | | | SOC | SOC | SOC | SOC | SOC |

Legend: SOC: Standard of care (data collected as available per standard of care)

## PROCEDURE TO OBTAIN CONSENT

The patients will be approached by either the Interventional Radiology Faculty or Research Staff, including research nurses and research coordinators. The principal investigator or designee who are licensed as physician in the state of Texas will obtain informed consent of participants prior to their procedure. During the consenting process patients will be educated and consented for their research participation in this study. The study will follow the Office of Research SOP04 – Informed Consent Process.

## PATIENT INFORMATION AND CONFIDENTIALITY PLAN

Confidentiality will be maintained throughout the study. An informed consent will be obtained prior to the percutaneous ablation procedure. No identifying information will

be used in any publication from this study. Patient identifiers will be available only to the investigators for the study and will be kept in a password-protected database and locked file cabinet. Unique patient identifiers will be used to replace patient name and medical record number. Paper records (data forms, list of patient names and unique identifiers), will be kept in a locked file cabinet with access granted only to study investigators. In the conclusion of the study, patient identifiers will only be maintained with the principal investigator to allow future review of the research. The protected health information used in this study will not be reused, nor will it be used for other research. As this is a prospective study, an informed consent will be obtained and authorization to use and disclose protected health information is requested.

Morfeus, a software-aided imaging application, is located within MD Anderson password protected behind the institutional firewall with access only granted to authorized study investigators. Morfeus will be provided at no cost to the study participants. There is no foreseeable injury or risk to subjects using Morfeus. Participants may withdraw from the study at any time for any reason and are not obligated to reveal their reasons for withdrawal, the data and test results already collected will be kept and may be used. All study data will be stored in password-protected computers and/or locked file cabinets and will continue to be stored securely after the study.

## STATISTICAL CONSIDERATIONS

### Statistical Design

The primary endpoint is to assess whether applying biomechanical models increase the minimal margins of ablated lesions properly covered by ablation on a three-dimensional analysis. The secondary endpoints of our study will compare the two arms in respect local and systemic oncological outcomes following liver ablation, procedure-related complications, and quality of life via a quality of life (QOL) questionnaire. Specifically, we will analyze the 2-years local tumor progression free-survival rates at the ablated lesions. On the experimental arm, we will evaluate the impact of software use on procedure workflow as well user's experience.

## Statistical Methods

### A. Analysis Plan

Statistical analysis of this study will be the responsibility of the principal investigator (PI) and statistician. The PI and statistician will also be responsible for the appropriate conduct of an internal review for the final dataset and any study-related material to be authorized for publication.

To assess the effect of applying biomechanical image registration models during percutaneous microwave ablation, the primary endpoint of this intent-to-treat randomized trial will be on the impact of the software use on the minimal margins of ablated lesions properly covered by ablation on a three-dimensional analysis. Patients will be evenly randomized (i.e., 1:1 ratio) to two treatment arms (i.e. experimental arm - including anatomical modeling of the liver, and control arm) using the Pocock-Simon dynamic allocation method to balance the baseline covariates: tumor histology

(colorectal vs other histologies), RAS mutation (for colorectal only, yes vs. no vs. undetermined), lesion size (<2cm, 2.0-3.0cm, >3cm-≤5cm), subcapsular location, defined as tumor within 1 cm from the liver capsule (yes vs no) and presence of multiple lesions (yes vs. no). At the end of the study, the average minimum ablation margins will be compared between two arms using a 2-sample t-test (or Wilcoxon rank-sum test). The means and corresponding 95% confidence intervals will be reported for both arms of the study.

As a secondary objective, the Kaplan-Meier method will be used to estimate local tumor progression-free survival (LTPFS) and 95% confidence intervals for the quantiles of the LTPFS function based on the method of Brookmeyer and Crowley will be calculate for each arm. Time point probabilities (e.g., 2-year LTPFS) and the associated log-log transformed pointwise 95% confidence will also be reported. A multivariate Cox-proportional hazards model will be fitted to the data with ablative margin as a continuous variable to assess the significance of study arm and ablative margin size on LTPFS while simultaneously adjusting for known covariates that effect LTPFS. LTPFS will be measured from date of ablation to earliest date of progression at the ablated lesion, death. Those progression free and alive will be censored at their date of last clinic visit. Similar analysis will be used for 2-years intra-hepatic (progression at any site of the liver) progression-free survival and overall survival. Standard summary statistics will be computed for complication rates, quality of life, and liver function and compared between arms. Statistical significance will be defined as $p < 0.05$.

### B. Randomization

A dynamic randomization method by Pocock and Simon will be used with a minimization probability parameter of 0.90. The randomization process will be controlled to ensure a balanced stratification by treatment arm for the factors listed above. Patients will be randomized to either experimental arm or no control arm using the Clinical Trial Conduct (CTC) website (https://biostatistics.mdanderson.org/ClinicalTrialConduct), which is housed on a secure server at MDACC and maintained by the MDACC Department of Biostatistics. Access to the website will be gained through usernames and passwords provided by the MDACC Department of Biostatistics to the clinical team. Training on the use of the CTC website to randomize patients on the study will be provided by the biostatistical collaborators. This is an open-label trial with stratified randomization. When a patient is enrolled on the study, the research nurse or coordinator of the study will enter patient's information including medical record number and stratification factors. Through the web interface, after the randomization button is clicked, the result of the randomization will be displayed on the screen for users to view. All data on randomization will be stored in a secure SQL server database.

## PROTOCOL MONITORING PLAN

MD Anderson's Data Safety Monitoring Board (DSMB) will monitor the conduct of the study. The principal investigator will be responsible for the management of the protocol. Identifiers (name, medical record number) will be collected but will be replaced by study numbers in the analytical file. They key linking these numbers will be retained in a locked file by the principal investigator. All study personnel have

completed training in methods of maintaining the confidentiality of health information. Electronic records will be stored on password protected institution computers behind the institution firewall. Only the principal investigator and research staff in Interventional Radiology will have access to the study. Data will not be transferred to laptop computers that are removed from the institution. Complete confidentiality will be maintained during this evaluation, manuscript preparation and submission. Information from individual Case Report Forms (CRFs) will be saved in an institutionally-based and approved electronic database. Adverse events such as inaccurate tumor localization and ablation coverage, as well as subsequent local tumor progression will be captured and recorded in OnCore.

**DATA COLLECTION PLAN**

All subjects will be registered in OnCore and data will be entered in an UT MD Anderson Cancer Center approved electronic database. The institutionally approved database is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. It is hosted on a secure server by MD Anderson Cancer Center that has undergone an annual Governance Risk & Compliance Assessment by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy

165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335.

Those having access to the data include the study PI and research team personnel. Users are authenticated against MDACC's Active Directory system. The application is accessed through Secure Socket Layer (SSL). All personal identifying information will be removed from the data when it is exported for analysis.

Following publication, study data will be archived in the electronic database indefinitely, since study data may be useful for future research studies performed under separate IRB approved protocols. Since this is a secure electronic database with controlled access, and because subject identifiers may be needed to link study data to data from other sources under future IRB approved protocols, subject identifying information will be retained in the archived database. No specific subject identifiers will be collected in this study. We acknowledge that there is a theoretical chance that the participants may be identified from their combined responses to the demographic questions. However, no attempt will be made by the research personnel to identify the survey respondents. Also, data will only be reported in aggregate form. The demographic information in the survey, along with all other survey responses, will be stored securely in the database. Up to five fully deidentified CT images will be shared with RaySearch Laboratories for joint development purposes directly related to the NIH-funded Academic-Industry Partnership R01 for the COVER-ALL clinical trial and project. RaySearch Laboratories is the industry partner for this grant.

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## QUESTIONNAIRES

Software user's experience

| Specific Use | Definition | Software helped me (1: no; 2: somewhat; 3: yes) | Comments |
|---|---|---|---|
| **Probe Placement** | Ability to understand probe positioning in relation to the target lesion | | |
| **Ablation confirmation** | Evaluating technical success of the procedure (full coverage of the tumor) | | |

Procedure Details

| **Variable measured** | Definition | Answer |
|---|---|---|
| Number of probes utilized on the target lesions | 1 – 3 | |
| Number of overlapping ablations | 0 – 3 | |
| Total duration of ablation (counting overlaps) | In minutes (5-20) | |
| Post-ablation Contrast-enhanced CT after first round of ablation? | Yes/No | |
| Need to re-ablation? | Yes / no | |
| Number of probes utilized on the target lesions | 1-3 | |
| Number of overlapping ablations | 0-3 | |
| Total duration of ablation (counting overlaps) | In minutes (5-20) | |
| Post-ablation Contrast-enhanced CT after second round of ablation? | Yes/No | |
| Need to re-ablation? | Yes / no | |
| Number of probes utilized on the target lesions | 1-3 | |
| Number of overlapping ablations | 0-3 | |
| Total duration of ablation (counting overlaps) | In minutes (5-20) | |

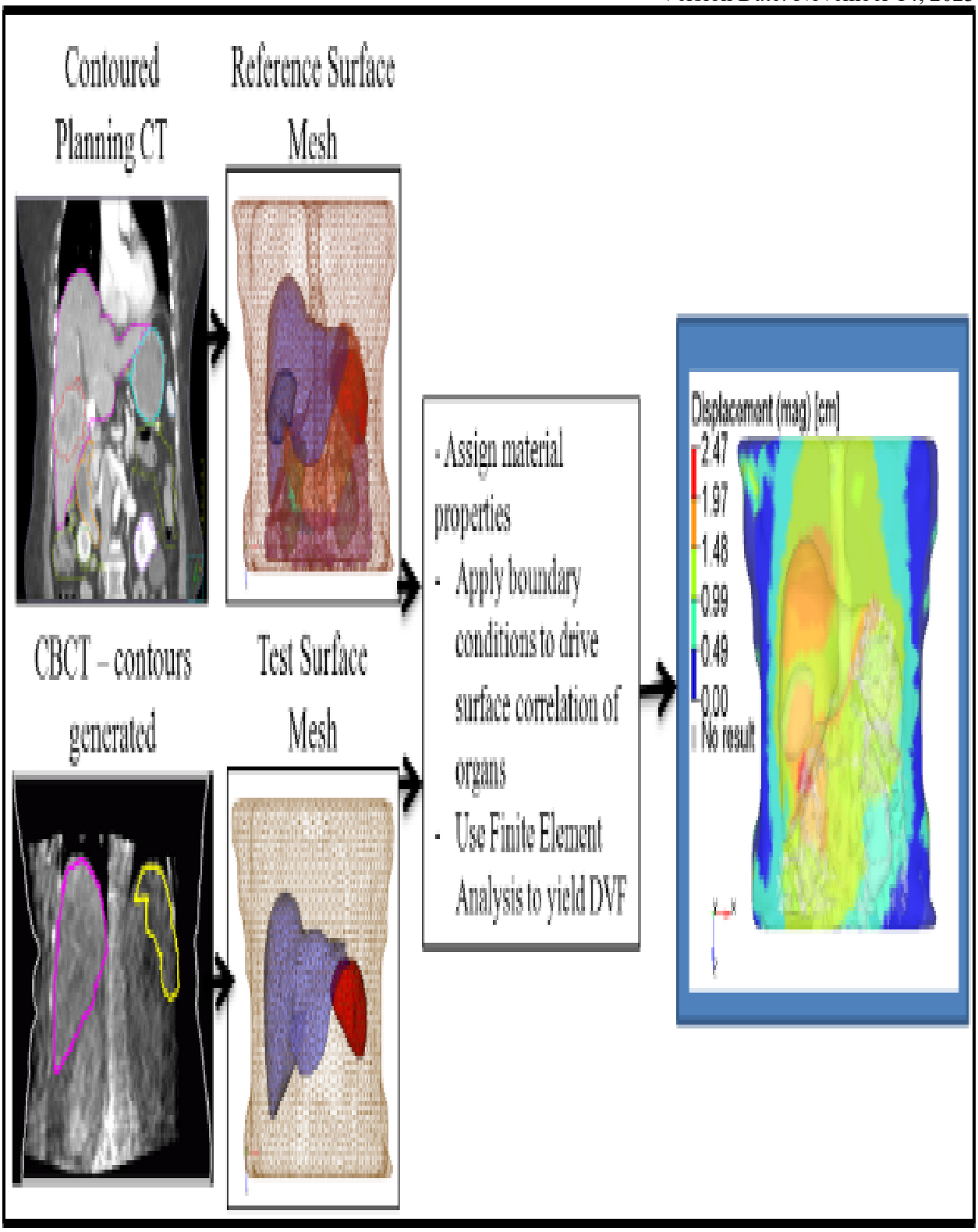
# QUALITY OF LIFE QUESTTIONAIRE

## EORTC QLQ-C30 Questionnaire

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers.

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |


Contoured Planning CT
Reference Surface Mesh
CBCT – contours generated
Test Surface Mesh
- Assign material properties
- Apply boundary conditions to drive surface correlation of organs
- Use Finite Element Analysis to yield DVF
Displacement (mag) [cm]
2.47
1.97
1.48
0.99
0.49
0.00
No result