Evaluation of tissue shrinkage after CT-guided microwave ablation in patients with liver malignancies using Jacobian determinant

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ABSTRACT
Purpose: To assess short-term tissue shrinkage in patients with liver malignancies undergoing computed tomography (CT)-guided microwave ablation (MWA) using Jacobian determinant (JD).
Materials and methods: Twenty-nine patients with 29 hepatic malignancies (primary n = 24; metastases n = 5; median tumor diameter 18 mm) referred to CT-guided MWA (single position; 10 min, 100 W) were included in this retrospective IRB-approved study, after exclusion of five patients. Following segmentation of lesions and tumors on pre-interventional images, segmentations were registered on post-interventional images. JD mapping was applied to quantify voxelwise tissue volume changes after MWA. Percentual volume changes were evaluated in the ablated tumor, a 5-cm tumor perimeter and in the whole liver and compared in different clinical conditions (tumor entity: primary vs. secondary; tumor location: subcapsular vs. non-subcapsular; tumor volume: >/<6 ml; cirrhosis: yes vs. no; prior chemotherapy: yes vs. no using Shapiro–Wilk, χ² and Wilcoxon rank sum tests, respectively (with p < 0.05 deemed significant).
Results: Tissue volume change was 0.6% in the ablated tumor, 1.6% in the 5-cm perimeter and 0.3% in the whole liver. Shrinkage in the ablated tumor was pronounced in non-subcapsular located tumors, whereas tissue expansion was noted in subcapsular tumors (median −3.5 vs. 1.1%; p = 0.0195). Shrinkage in the whole liver was higher in tumor volumes >6ml, compared with smaller tumors, in which tissue expansion was noted (median −1.0 vs. 2.5%; p = 0.002). Other clinical conditions had no significant influence on the extent of tissue shrinkage (p > 0.05).
Conclusion: 3D Jacobian analysis shows that hepatic tissue deformation following MWA is most pronounced in a 5-cm area surrounding the treated tumor. Tumor location and tumor volume may have an impact on the extent of tissue shrinkage which may affect estimation of the safety margin.

INTRODUCTION

The efficacy of image-guided thermal ablation including microwave ablation (MWA) of malignant liver tumors is well-established [1–3]. Moreover, thermal ablative techniques are increasingly implemented not only for treatment of unresectable, but also for resectable hepatic lesions [3,4]. MWA provides an energy profile which is advantageous in terms of a faster coagulation, more homogenous and more predictable coagulation zones than for example radiofrequency ablation (RFA) [5,6]. In this regard, meticulous placement of the MWA antenna in knowledge of the expected size of the evolving ablation zone is essential for maximum treatment efficacy and patient safety. Furthermore, anticipation and knowledge of adjacent liver tissue behavior during MWA are beneficial for treatment planning and evaluation of post-interventional imaging in terms of treatment outcome [7].

Recently, significant spatial tissue contraction in the first minutes of the ablation cycle has been shown with the use of hyperthermal techniques [8]. Specifically, a volume decrease of the ablated tissue at the end of the ablation procedure compared with the volume occupied by the equivalent untreated tissue has been observed [8,9]. In a few cases, even expansion of the treated organ tissue has been noticed [10]. Furthermore, it has been shown that the observed shrinkage increases with temperature and is directly related to the deployed energy [9,11]. From a clinical perspective, tissue shrinkage may affect treatment safety as, first, it can expose peripheral structures to unwanted heating and, second, the thermally ablated area might be underestimated on post-interventional imaging [12]. Therefore, there is a strong need to quantify the amount of local and peritumoral tissue shrinkage during MWA to facilitate more precise assessment of the ablation outcome. Investigating tissue shrinkage with regard to different clinical conditions such as tumor location or in cirrhosis may further support treatment planning, especially in challenging cases. Clinically applied methods for tissue shrinkage characterization are typically limited to radiological standard evaluation and tumor segmentation. However, plain visual evaluation of pre- and post-MWA CT acquisitions are quantitatively inexact as tissue...
shrinkage in all three dimensions may be displayed unequally [13]. Moreover, conventional tumor segmentation for comparison of volumetric variation can be challenging due to possible partial volume effects or limited tumor-parenchyma contrast [14].

One established method which allows in vivo measurement of tissue alteration in time is deformable image registration [15,16]. Based on this approach, Jacobian determinant (JD) calculation employs a registration algorithm that provides the transformation at a given voxel by the local volume ratio between the undeformed and deformed voxels [17]. As a result, the deformation of the defined lesion or tissue is captured linearly over time and a Jacobian map of tissue volume changes is created. The local shrinkage obtained from the Jacobian map is integrated voxel-by-voxel to identify the net volume change of the defined tissue [18]. The Jacobian approach was successfully applied to CT-based quantification of lung volume changes depending on ventilation [19,20] and radiation-induced lung disease [21]. In a recent study, the findings of JD and subtraction maps on follow-up CTs were compared with conventional hepatic tumor segmentation outcomes in patients undergoing systemic therapy with promising results [22]. However, tools that quantify in vivo liver and tumor tissue after MWA are still very limited, especially their translation from bench to bedside.

The purpose of our study was twofold. First, it was conducted to quantify tumor and liver shrinkage after hepatic MWA using JD mapping, and second, to assess patient- and tumor-specific factors that may affect the extent of a tissue shrinkage.

Materials and methods

Study design and patients

This study was IRB-approved (Hannover Medical School, approval number 2147-2014) with a waiver of patient consent granted, including patients referred for CT-guided MWA of malignant liver tumors. Respective interventions, follow-up data and demographics were selected retrospectively from a database of all patients treated using percutaneous MWA in our department between December 2012 and February 2021. Inclusion criteria were as follows: patient age ≥18 years; referral for CT-guided MWA of a single malignant hepatic lesion with a curative intent after discussion in our multidisciplinary tumor board; treatment with a single ablation cycle and a single treatment position (power 100 W, 10 min); successful image registration for JD mapping. In addition, all interventions were performed using the same MWA system (Emprint™ Microwave Ablation, Medtronic). Electronic medical patient records were reviewed with regard to demographics, laboratory values and available follow-up data. Initially, 29 patients which were meeting the inclusion criteria were identified from the above-mentioned database. Five patients had to be excluded due to following reasons: incomplete image registration (n = 3); a second indeterminate hepatic lesion identified during MWA (n = 1); one patient with HCC recurrence who was counted twice by mistake (Figure 1). The final study population comprised 24 patients (14 male; median age 61, interquartile range 34–79 years). Patients were further stratified based on tumor location (subcapsular or non-subcapsular), tumor volume (<6 ml or ≥6 ml), underlying cirrhosis (yes or no), tumor entity (primary or secondary liver tumor), and prior chemotherapy including trans arterial chemoembolization (TACE; yes or no). A subcapsular location was defined as a tumor-capsule distance ≤ 5 mm. The cutoff value of 6 ml for tumor volume stratification was based on the median tumor volume of the final study population. Patient demographic data are presented in detail in Table 1.

MWA

MWA was performed under CT-guidance (16 slice scanner; Lightspeed GE Healthcare, Waukesha, WI, USA) and under general anesthesia. Antenna placement was accomplished using the SmartStep mode with single low-dose slices
acquired intermittently. MWA was performed by one of two radiologists with more than 10 years of experience in CT-guided interventions, using the Emprint™ Microwave Ablation System (Medtronic Inc.; Watford, UK). This system consists of a 2.45 GHz generator that can generate a maximum power of 100 W. Pre- and post-interventional CT images were acquired in the arterial and portal venous phase using 60 ml of an i.v. contrast agent (Imeron 300, Bracco Imaging Deutschland GmbH, Konstanz, Germany) injected at a flow of 4 ml/s. Complications after MWA were graded as proposed by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) [23].

**Postprocessing and Jacobian analysis**

First, image evaluation and semi-automatic whole liver and tumor segmentation were performed on pre-interventional portal-venous phase CT scans using a thin PACS client (Visage Imaging© GmbH, Berlin, Germany). Further postprocessing and Jacobian determinant calculation were performed using MATLAB 2018b (The MathWorks, Natick, MA, USA). Prior to the registration of post-interventional on pre-interventional CT images, slice locations in both datasets were determined and only intersected slices were included for further postprocessing. Furthermore, all pre and post CT images were zero padded by 20 voxels in all three dimensions to ease the registration and increase convergence speed.

A rigid and non-rigid image registration algorithm using advanced normalization tools [24] was applied to register the post-interventional CT image on the pre-interventional CT image. First, the global structures were aligned using rigid registration. Afterwards, non-rigid registration was necessary, since the location and shape of the liver, heart, lung and other neighboring organs change over time in a complex way. As it was our intention to register only the liver, the semi-automatically segmented liver mask was used to assess the similarity metric between pre- and post-interventional CT image during the registration procedure. To characterize the local structural change (shrinkage/expansion) between both image datasets, the resulting deformation field was further assessed using Jacobian matrix, which is the first derivative of the obtained transformation field. Its determinant, termed Jacobian Determinant (JD), indicates the volumetric change after the registration. The results are interpreted as follows: a JD >1 denotes local tissue expansion; a JD = 1 implies no local volume change; a JD < 1 reflects local tissue shrinkage. JD mapping was performed voxel-wise and evaluated in three specific anatomic zones: (1) ablated tumor zone; (2) a circumferential 5-cm perimeter around the tumor; (3) the whole liver (Figure 2). After creating JD maps, the median of

Table 1. Demographic data of patients included for further evaluation of tissue shrinkage after CT-guided MWA.

| Patient characteristics | Number |
|-------------------------|--------|
| Number of included patients | 24     |
| Sex (number of males/females) | 14/10  |
| Age (years) | 61 (34 – 79)     |
| BMI (kg/m²) | 26 (23 – 27)     |
| Cirrhosis (number) yes/no | 18/6   |
| Prior chemotherapy (number) yes / no | 15/9 |
| Tumor characteristics | |
| Subcapsular (number) yes/no | 10/14 |
| Tumor volume >/<6 ml | 13/11 |
| Primary tumor | 19        |
| Metastases | 5    |
| Localization (number) | |
| Right lobe (S5–8) | 14     |
| Left lobe (S1–4) | 10     |

**Figure 2.** Schematic description of the postprocessing steps for evaluation of tissue shrinkage. 1: Export of pre- and post-interventional CT images. 2: Semi-automatic whole liver (yellow color-coded) and tumor (blue color-coded) segmentation. 3: Image registration. 4: Application of a postprocessing algorithm to quantify voxel wise the deformation volume of the liver tissue. 5: Calculation of JD maps in three defined anatomic regions (green zone = ablated tumor; red zone = 5cm tumor perimeter; blue zone = whole liver). 6: Evaluation of tissue shrinkage considering different patient and tumor settings.
local tissue shrinkage.

Subcapsular tumor

| Condition   | Patients (n = 24) | Number of males/females | Liver volume (ml) | Tumor volume (ml) |
|-------------|-------------------|--------------------------|-------------------|-------------------|
| Yes         | 10/6              |                          | 2699.3 (1999.8–3087.4) | 9.8 (6.5–31.9) |
| No          | 14/10             |                          | 2366.5 (2060.7–2822.1) | 4.4 (2.1–8.3) |

Tumor volume >6 ml

| Condition   | Patients (n = 24) | Number of males/females | Liver volume (ml) | Tumor volume (ml) |
|-------------|-------------------|--------------------------|-------------------|-------------------|
| Yes         | 13/6              |                          | 2803.27 (2215.1–3135.9) | 10.7 (8.3–20.3) |
| No          | 11/8              |                          | 2271.4 (1895.3–2742.3) | 2.2 (1.5–2.9) |

Cirrhosis

| Condition   | Patients (n = 24) | Number of males/females | Liver volume (ml) | Tumor volume (ml) |
|-------------|-------------------|--------------------------|-------------------|-------------------|
| Yes         | 18/11             |                          | 2363.6 (1982.3–2816.3) | 7.9 (2.6–11.3) |
| No          | 6/3               |                          | 2919.8 (2181.7–3582.2) | 5.6 (2.1–12.0) |

Tumor entity

| Condition   | Patients (n = 24) | Number of males/females | Liver volume (ml) | Tumor volume (ml) |
|-------------|-------------------|--------------------------|-------------------|-------------------|
| Primary     | 19/11             |                          | 2455.9 (2006.2–2854.1) | 7.9 (2.7–11.2) |
| Secondary   | 5/3               |                          | 2848.6 (2086.2–3058.5) | 2.9 (1.9–11.4) |

Prior chemotherapy

| Condition   | Patients (n = 24) | Number of males/females | Liver volume (ml) | Tumor volume (ml) |
|-------------|-------------------|--------------------------|-------------------|-------------------|
| Yes         | 15/9              |                          | 2704.9 (2068.8–2990.9) | 7.7 (2.1–11.1) |
| No          | 9/6               |                          | 2271.4 (1654.7–2798.2) | 2.9 (1.7–11.2) |

Registration performance

To assess registration accuracy, a pair of anatomical landmarks was placed on the bifurcation of the portal vein in the pre-interventional CT images. Also, a pair of anatomical landmarks was placed on the bifurcation of the portal vein in the registered CT images and in the post-interventional CT dataset, respectively, as described by other study groups before [25]. Distance differences of the same anatomical landmarks placed on the bifurcation of the portal vein between pre- and post-interventional CT datasets and between pre-interventional and registered post-interventional CT datasets were calculated in all patients (Figure 3).

Statistical analysis

Statistical analysis was performed using MATLAB 2018 b (The MathWorks, Natick, MA, USA) and JMP (pro16 software, USA). Data are presented as median and interquartile range (25–75%). Patients’ characteristics were compared between subgroups using $\chi^2$ and Wilcoxon rank sum test, respectively. After creating JD maps, the median of all voxels was calculated for each patient for assessment of the percental tissue volume change in different anatomic zones (i.e., ablated tumor, 5-cm tumor perimeter and the whole liver). Furthermore, volume changes in each zone were compared between different subgroups (tumor location, tumor volume, presence of cirrhosis, tumor entity, history of chemotherapy) using Wilcoxon rank sum test. For evaluation of registration accuracy, the landmark differences were compared using Wilcoxon rank sum test. In addition, a post hoc power calculation was performed to calculate the minimal detectable difference for each parameter in all three anatomical zones [26]. A $p$-value less than 0.05 was deemed statistically significant for all calculations.

Results

Patients and MWA procedure

There were no significant differences of all analyzed clinical conditions regarding patients sex and patients liver volumes (Table 2) (all $p > 0.2$). There were no significant differences of all analyzed clinical conditions (except tumor volume > 6 ml) regarding patients tumor volumes (all $p > 0.2$) (Table 2). All tumors were treated according to the protocol and covered completely by the respective ablation zone, as confirmed on post-interventional contrast-enhanced CT. The median liver and tumor volumes were 2595 ml (2046–2915 ml) and 6 ml (2–10 ml), respectively. All ablations were performed using a single- or double-angulated approach, technical success was 100%. There was one grade 1 complication reported in a male patient in terms of a local hematoma which was treated conservatively. One patient died in the later course due to a separate preexisting comorbidity (chronic heart failure) and another patient underwent liver transplantation shortly after MWA. At follow-up, two patients with HCC showed local tumor recurrence.

Evaluation of image registration

A significant difference between the median distance pre- to post-MWA CT landmarks (median 5.2 mm, inter quartile
range 3.9–7.8 mm, \( p < 0.001 \) vs. pre- to registered post-MWA CT landmarks (median 2.1 mm, inter quartile range 1.4–3.1 mm, \( p < 0.001 \)) was found.

**Evaluation of tissue shrinkage**

In all patients, median percental tissue volume changes in the ablated tumor zone, the 5-cm perimeter and in the whole liver were 0.6, 1.6 and 0.3%, respectively.

At subgroup analysis, significant differences of tissue shrinkage in the tumor region dependent on tumor location were observed. Although in patients with non-subcapsular located tumors pronounced tissue shrinkage (−3.5% (−6.9 to 2.4%) was visible, ablation of subcapsular located tumors resulted in a local volume increase (1.1% (−0.1 to 2.1%), \( p = 0.0195 \)). Exemplary results of two patients with differently located tumors and their corresponding JD maps are demonstrated in Figure 4. Similarly, significant differences of tissue shrinkage in the whole liver dependent on tumor volume could be observed. Specifically, in patients with tumors >6 ml, liver volume shrinkage (−1.0% (−1.5 to 1.1%) was more pronounced as opposed to patients with tumor volumes <6 ml (2.5% (−0.2 to 5%), \( p = 0.002 \)). Results of the post hoc power calculation and volume changes in each subgroup are presented in detail in Table 3 and in Figure 5 (Table 4).

**Discussion**

In this study, we systematically assessed the extent of short-term hepatic tissue shrinkage and expansion in patients undergoing CT-guided MWA using JD mapping. Jacobian 3D tissue volume analysis showed that tissue deformation following MWA is most pronounced in a 5-cm zone surrounding the treated tumor. Furthermore, tumor location and tumor volume may have an impact on the extent of tissue shrinkage.

The presented postprocessing algorithm was able to detect regional differences in tissue deformation following MWA in various clinical subgroups of patients with malignant liver tumors. Similar to previous studies [27,28], postprocessing was based on a non-rigid and a rigid image registration.
algorithm. A non-rigid and a rigid image registration algorithm were chosen, as two different image acquisition time points and two different breathing states in each patient had to be considered. In the validation part of the applied registration algorithm, a significant difference was observed with regard to the distance (mm) of the anatomical landmarks corresponding to the portal vein, between the pre- and post-interventional registered liver CT images. This finding suggests a successful image registration step and is in accordance with previously reported results [25].

Figure 5. Results of volume changes for all subgroups (A–E) in the ablated tumor, 5-cm perimeter and the whole liver, respectively, are demonstrated. Hepatic tissue volume changes were compared depending on different clinically preconditions including tumor location (subcapsular vs. non-subcapsular, A), tumor volume (6/<6 ml, B), presence of cirrhosis (yes vs. no, C), tumor entity (primary vs. secondary, D), history of chemotherapy (yes vs. no, E).
There are only few studies that have assessed tissue volume changes quantitatively after percutaneous thermal ablation [29], especially using MWA. Recently, no significant difference of post MWA hepatic shrinkage in centrally vs. peripherally located lesions was described in a living, hepatic porcine non-survival model [30]. However, there are three important differences as compared with our study, which are worth mentioning. First of all, in the above-mentioned study by Awad et al., ablations were performed in non-tumor-bearing porcine hepatic tissue. Second, ablation times were not uniform, varying between 2 and 8 min. And third, the number of included animals was very limited (three animals per group). In the study at hand, a percental volume change of hepatic tissue may be affected inter alia by reactive hyperemia, edema or carbonization [33]. A regional non-uniform liver tissue change with an asymmetry between the radial and the longitudinal axis, as described before, might also play a role [34].

To the best of our knowledge, there are no previous studies that evaluated systemically the short-term extent of tissue shrinkage with regard to different patient- and tumor-specific preconditions. As a novelty, the overall findings of our study indicate the importance to additionally evaluate the clinical context of the patients referred to hepatic MWA ensuring precise tissue deformation analysis.

This study has some limitations. It is a single center, retrospective study with a limited number of patients. However, the presented results are based on a very patient homogeneous cohort with regard to matching MWA specific parameters (single ablation position, 10 min ablation cycle). Another limitation is that the majority of patients had underlying cirrhosis and prior treatment with transarterial chemotherapy. Therefore, the results of our study need to be further validated in larger, preferably multicenter studies.

In conclusion, evaluation of tissue shrinkage after CT-guided MWA based on Jacobian determinant mapping seems feasible. In the study at hand, tissue deformation in different anatomical zones in the liver was not uniform and dependent on tumor location and tumor volume. In this sense, larger cohort studies focusing on the impact of tumor- and patient-specific parameters, which may affect a defined safety margin, are highly warranted. Predictable shrinkage cutoff values in patient subgroups could be valuable for computer-assisted simulations, to improve treatment outcome and patient safety.

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