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3D Quantitative Assessment of Lesion Response to MR-guided High-Intensity Focused Ultrasound Treatment of Uterine Fibroids

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Abstract

Rationale and Objectives—To investigate the response after MR-guided high-intensity focused ultrasound (MRgHIFU) treatment of uterine fibroids (UF) using a 3D quantification of total and enhancing lesion volume (TLV, ELV) on contrast-enhanced MRI (ceMRI) scans.

Methods and Materials—In a total of 24 patients, ceMRI scans were obtained at baseline and 24 hrs, 6, 12 and 24 months after MRgHIFU treatment. The dominant lesion was assessed using a semi-automatic quantitative 3D segmentation technique. Agreement between software-assisted and manual measurements was then analyzed using a linear regression model. Patients were classified as responders (R) or non-responders (NR) based on their symptom report after 6 months. Statistical analysis included the paired *t*-test and Mann-Whitney-test.

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Conflict of Interest Disclosures

All other authors do not have any conflicts of interest to disclose.

Results—Preprocedurally, the median TLV and ELV were 263.74cm³ (30.45–689.56cm³) and 210.13cm³ (14.43–689.53cm³), respectively. The 6-month follow-up demonstrated a reduction of TLV in 21 patients (87.5%) with a median TLV of 171.7cm³ (8.5–791.2cm³) ($p<.0001$). TLV remained stable with significant differences compared to baseline ($p<.001$ and $p=.047$ after 12 and 24 months). A reduction of ELV was apparent in 16 patients (66.6%) with a median ELV of 158.91cm³ (8.55–779.61cm³) after 6 months ($p=.065$). 3D quantification and manual measurements showed strong intermethod-agreement for fibroid volumes ($R^2=.889$ and $R^2=.917$) but greater discrepancy for enhancement calculations ($R^2=.659$ and $R^2=.419$) at baseline and 6 mo. No significant differences in TLV or ELV were observed between clinical R (n=15) and NR (n=3).

Conclusion—The 3D assessment has proven feasible and accurate in the quantification of fibroid response to MRgHIFU. Contrary to ELV, changes in TLV may be representative of the clinical outcome.

Keywords

MR-guided high-intensity focused ultrasound; ablation; computer applications-3D; pelvic MR-imaging; uterine fibroids

Introduction

Uterine fibroids (UF) represent one of the most common benign tumors that predominantly occur in the perimenopausal years (1, 2). Location, size and multiplicity of UF are varying, resulting in a diversity of clinical presentations that range from asymptomatic to symptoms which highly interfere with the patient's quality of life (1). As for the treatment of UF, surgical removal (myomectomy or hysterectomy) remains the goldstandard and UF represent the major indication for hysterectomy (1). However, there are minimal invasive treatment options including radiofrequency ablation as well as catheter-based approaches such as uterine artery (UAE), which have become well-accepted alternatives to surgery over the last decades (3, 4).

Magnetic resonance-guided high intensity focused ultrasound (MRgHIFU) represents another approach and is the only fully non-invasive alternative in the treatment of UF. MRgHIFU uses targeted energy deposition from focused ultrasound under MR guidance to ablate the tissue by thermal coagulation as well as acoustic cavitation (5, 6). MRgHIFU has proved as safe, feasible and effective in reducing clinical symptoms (7–9).

Contrast-enhanced MRI (ceMRI) can be considered as the most accurate imaging technique to evaluate the extent of the disease prior to therapy and to assess UF response after treatment in terms of necrosis and tumor shrinkage over time. However, no response criteria or standardized imaging protocols have been clearly defined yet. Current UF assessment includes manual measurements of lesion volumes (in three axes) and visual, subjective estimation of total lesion enhancement, which is commonly reported in 10% increments. Specifically, those estimations are commonly based on the simplified assumption that fibroid lesions have perfect ellipsoid shapes (10, 11). Subsequently, those subjective calculations are susceptible to imprecision and reproducibility is limited by individual bias

and interobserver variability. As tumor shrinkage as well as patterns of central necrosis occur asymmetrically, the rationale for the development of a three-dimensional (3D) quantification of tumor volume and enhancement is provided.

The objective of the present study was to investigate the feasibility and diagnostic accuracy of semi-automatic 3D quantification of lesion volume and enhancement in the assessment of UF response to MRgHIFU treatment on ceMRI scans.

Materials and Methods

Study Cohort

This study included a total of 41 pre- and perimenopausal women, who were treated using MRgHIFU for symptomatic UF within a period of 24 months at our institution and the patients were retrospectively reviewed. Patients were excluded if there was no baseline ceMRI scan available (n=3) or if the patients did not return for 6-month follow-up (n=3). Additionally, 5 patients were excluded due to insufficient imaging quality and exclusion of another 6 patients was due to additional alternative treatments within the time of follow-up. For this type of study formal consent was not required.

Clinical Evaluation

Prior to treatment, all patients underwent a gynecological examination. Clinical symptoms of UF can be divided into menorrhagia on the one hand and bulk-related symptoms (pelvic, leg, back or abdominal pain, urinary frequency, incontinence, dyspareunia, constipation) on the other hand. Symptoms were recorded preprocedurally as well as 6 months after MRgHIFU and assessed using questions included in the previously validated Uterine Fibroid Symptom and Quality of Life questionnaires (12). The severity of symptoms was categorized as worsened, unchanged, improved or resolved. Depending on the changes of symptoms reported at the 6-month follow-up, the patients were classified as responders (R) when the clinical symptoms had improved or resolved or non-responders (NR) in all other cases.

MRgHIFU procedure and Follow-up Imaging

MRgHIFU treatments were performed using a modified MR-guided Focused Ultrasound Surgery System (EXAblate 2000, InSightec, Haifa, Israel), coupled with a 1.5T MR system (General Electric Health Care, Milwaukee, WI).

All patients included in this study were subjected to a standardized ceMRI protocol prior to treatment (baseline) as well as 6 months after treatment (6-month follow-up). The baseline ceMRI scan was acquired within a median of 22.53 days (4–77 days) prior to the MRgHIFU procedure. For 19 out of 24 patients an immediate follow-up ceMRI scan (24 hours) was obtained. 13 and 6 patients underwent additional 12- and 24-month follow-up imaging, respectively.

Imaging Data Evaluation— 3D Quantification of Lesion Response

Lesion Segmentation—The dominant target lesion was determined on the T2-weighted baseline scans as the largest UF by volume. A semi-automatic 3D quantitative measurement of the total lesion volume (TLV) as well as the enhancing lesion volume (ELV) was applied on the baseline and followup arterial-phase ceMRI scans to evaluate UF response to MRgHIFU. This semi-automatic imaging analysis was performed using a software prototype (Medisys, Philips Research, Suresnes, France), which has initially been established for primary and secondary liver malignancies and is here-in referred to as 3D-RESQU (3-dimensional response quantification in uterine fibroids).

This software uses non-Euclidean geometry and theory of radial basis functions that permit the segmentation of 3D objects with straight edges and corners (13). The reader defines an initial control point and the software algorithm creates an image-based mask located in a 3D region of the tumor, yielding the term “semi-automatic”. As opposed to fully automatic segmentation techniques, the user can interactively expand or minimize the 3D mask and its coordinates will be saved within the MRI dataset. In the present study, the resulting 3D segmented lesion masks were used to quantify response to MRgHIFU in the dominant lesion of each patient.

3D-RESQU Technique—The technique was described in detail in earlier works (13–15). In short, in order to calculate the 3D-RESQU (3-dimensional response quantification in uterine fibroids) values, the pre-contrast MRI scan was subtracted from the ceMRI scan in order to remove background enhancement. This step is of major importance to achieve an accurate assessment of lesions with potentially hemorrhagic necrosis and helps mitigate false-positive enhancement from contrast-enhancement. The 3D segmented lesion mask was then applied on the subtracted scan (Figure 2C).

A 3D ROI of 1cm^3 was placed into hypoenhancing soft tissue (left psoas muscle) of the subtracted image set in order to calculate a reference value for tissue enhancement. Furthermore, in order to avoid corrupted ROIs within focally inhomogeneous muscle tissue, signal intensity statistics were calculated for every 3D ($1\text{cm} \times 1\text{cm} \times 1\text{cm} = 1\text{cm}^3$) ROI with the goal of achieving a maximum of signal homogeneity. The software provided the minimum and maximum voxel brightness values within the cubic ROI. The numeric output was in patient-specific arbitrary units (AU) for each ROI. The software furthermore calculated the mean brightness value (MBV), standard deviation (SD) as well as the coefficient of variation (CV). Empirically, a CV of less than 30% was seen as acceptable, while a CV greater than 30% was rejected leading to ROI repositioning.

Eventually, the TLV was calculated according to the segmentation. In order to estimate the extent of necrosis, the ELV was defined as voxels within the previously calculated TLV (% and cm^3), in which the enhancement exceeded the value of the ROI. A normalized patient-specific color map overlay, which was individually normalized to the maximum intensity in the ceMRI scan, demonstrated the distribution of enhancement within the 3D segmented lesion mask (with red representing maximum enhancement/viable fibroid and blue representing no enhancement, below the threshold/necrotic tissue) (Figure 2D).

Manual Image Analysis—For validation purposes, additional subjective manual measurements of the dominant UF dimensions were performed by two radiologists with 3 and 5 years of experience in abdominal MR imaging who were blinded to the results of the 3D-RESQU analysis. Volumetric calculations were based on a formula for prolate ellipsoid shapes (length×width×height×0.523) (10, 16). Enhancing UF portions (in % of the entire lesion) were visually determined on the ceMRI scans and quantified in 10% increments. Both readers separately evaluated the baseline and 6-month follow-up imaging dataset and the values were used for an interobserver correlation analysis and then averaged for an intermethod correlation analysis with the semi-automatic 3D quantification.

Statistical analysis

Statistical calculations were performed using the commercial software GraphPad Prism (Version 6.1, San Diego, California, USA). The Wilcoxon t-test was used for paired, nonparametric analysis in individual patients to compare imaging parameters before and after treatment. For unpaired, non-parametric analysis, the Mann-Whitney-test was applied to compare the both cohorts, R and NR. A p-value <0.05 was considered statistically significant. A linear regression model was used to calculate the Pearson correlation coefficient (R^2) and analyze the interobserver agreement and the correlation of the radiologic readings with the software-assisted 3D quantification.

This was an institutional review board (IRB) approved and U.S. Health Insurance Portability and Accountability Act (HIPAA) compliant single-institution analysis.

Results

Study Population

The mean age of all 24 patients was 46.1 years (range, 37–58 years). 9 patients had 1 UF, another 9 were observed with 2 and 6 patients with more than 2 lesions. As for technical efficacy and safety, all MRgHIFU interventions were technically successful (sonication accomplished as planned) and no major adverse events were reported intra- or postprocedurally within 6 months of follow-up (8) (Table 1).

Imaging Results

Volumetric Assessment I– Total Lesion Volume (TLV)—The median preprocedural TLV was 263.74 cm³ (range, 30.45–689.56 cm³; n=24) according to 3D-RESQU. The analysis revealed no decrease of TLV immediately after treatment (median TLV, 267.83 cm³; range, 14.69–1063.60 cm³; n=19; p=.374). In contrast to that, a volume reduction was achieved in 21 patients (87.5 %) after 6 months (median TLV 191.27 cm³; range, 8.55–791.24 cm³; n=24), which was highly significant compared to the baseline values (p<.0001). On the 12-month and 24-month follow-up, the TLV remained relatively stable. The median TLV after 12 and 24 months was 192.95 cm³ (range, 5.63–634.4 cm³; n=13; p<.001) and 193.14 cm³ (range, 15.67–459.61 cm³; n=6; p=.047), respectively, indicating a significant change compared to the preprocedural TLV. However, a slight trend towards an increase of TLV at the 12- and 24-month follow-up became apparent (Figure 1A).

Volumetric Assessment II— Enhancement Lesion Volume (ELV)—The median preprocedural ELV was 82.8 % (range, 2.2–100 %) or 210.13 cm³ (14.43–689.53 cm³; n=24). A reduction of ELV was observed in 16 patients (66.6%) at the 6-month followup with a median ELV of 84.24 % (range, 27.73–100 %) or 158.91 cm³ (8.55–779.61 cm³; n=24; p=.065) according to 3D-RESQU. After 24 hrs, the median ELV had decreased to 10 58.70 % (range, 7.50–96.55 %) or 133.01 cm³ (14.17–671.48 cm³; n=19; p=.21). At the 12- and 24-month follow-up, a median ELV of 86.87 % (61.33–100 %) or 163.08 cm³ (5.07–634.41 cm³; n=13; p=.022) and 94.91 % (range, 80.3–99.64 %) or 176.70 cm³ (14.80–369.07 cm³; n=6; p>.999), respectively, was observed (Figure 1B, 2).

However, MRgHIFU resulted in a slightly significant change after 12 months but no significant decrease of ELV at the 6- and 24-month follow-up compared to baseline.

Manual and Visual Image Analysis—The linear regression model revealed a strong interreader agreement of UF volume calculations at baseline as well as 6 mo ($R^2=0.966$ and $R^2=0.879$, respectively) (Figure 3A, B) and the manual volume measurements correlated well with the semi-automatic 3D assessment of the TLV ($R^2=0.889$ and $R^2=0.917$) (Figure 3C, D).

Regarding UF enhancement, the results recorded during visual assessment sessions showed some agreement ($R^2=0.616$ and $R^2=0.695$ at baseline and 6-month follow-up, respectively) (Figure 4A, B), whereas intermethod correlation demonstrated major disagreement between both techniques, particularly at the postprocedural evaluation ($R^2=0.659$ and $R^2=0.419$) (Figure 4C, D).

Clinical Results

Clinical reports were available in 18 out of 24 patients who were included into this study. At the baseline assessment, 3 patients presented with menorrhagia, 6 patients reported bulk-related symptoms and 9 patients had both. At the 6-month follow-up, all 18 patients were asked to report the development of symptoms after treatment. 15 patients (83.3%) reported an improvement of their bulk-related symptoms and menorrhagia (R). However, 3 patients (16.6%) were classified as NR according to their report of clinical symptoms at the 6-month follow-up. All of them had presented with menorrhagia only prior to MRgHIFU treatment. The comparative analysis did not reveal statistically significant differences between clinical R and NR in imaging parameters at baseline or 6-month follow-up.

Discussion

In the present study, we demonstrate the clinical feasibility and accuracy of a 3D quantitative lesion assessment as a novel semi-automatic technique to assess uterine fibroid response after MRgHIFU therapy on ceMRI scans. In vitro and in vivo studies have shown MRgHIFU therapy to cause coagulative necrosis and tumor volume reduction in UF within 6 to 12 months after MRgHIFU therapy (17, 18). Thus, assessing ELV and TLV, 3D-RESQU reflects on the major pathological effects of sonification. As UF response to MRgHIFU occurs gradually, a decrease of TLV is not present immediately after the procedure but becomes highly significant at the 6-month follow-up and remains relatively

stable at 12 and 24 months (Figure 1). The increase of ELV values during the long-term follow-up primarily correlated with the observation of relapsing viable UF tissue at the lesion rim on the ceMRI scans (Figure 2D). A possible explanation could be that remaining vasculature facilitates UF recurrence, which might be a technically reasonable benefit of UAE over MRgHIFU. Based on the principle of devascularization, UAE is known to effectively reduce heavy bleeding symptoms (19, 20). But aiming at UF infarction also implies a threshold tumor volume for successful and realistic UAE treatment, which is reported to be relatively small at 66.0 cm³ (21, 22). In the present study, dominant lesions with a TLV ranging from 30.45 to 689.56 cm³ were successfully treated with MRgHIFU and tumor volume did not limit the application of MRgHIFU or reduce the efficacy of the procedure.

In previous studies, post-procedural enhancement on ceMRI was suggested as a good surrogate for UF necrosis after MRgHIFU and a predictor for clinical outcome (8, 9). Contrary to those results, the ELV measured with 3D-RESQU does not seem to be representative of the clinical outcome. Instead, the major decrease in lesion volume at the 6-month follow-up corresponds well to the improvement of symptoms in the majority of patients. Accordingly, our analysis suggests that volume reduction is essential for symptom resolution and that TLV has a strong diagnostic value after MRgHIFU treatment of symptomatic UF. In particular, our preliminary results indicate that bulk-related symptoms are more likely to resolve after volume reduction rather than menorrhagia. All 3 patients classified as NR only reported menorrhagia at the preprocedural examination, whereas all R presented with bulk-related symptoms with or without menorrhagia. From a technical point of view, MRgHIFU does not achieve complete devascularization of the UF as opposed to UAE, which would allow for continuous abnormal bleeding after treatment. However, this aspect requires further investigation.

From a clinical perspective, MRgHIFU is a newer intervention with a smaller body of evidence compared to myomectomy and UAE but there continues to be development. As an example, the Sonalleve Fibroid Ablation Pivotal Clinical Trial for MR-HIFU of Uterine Fibroids (SOFIA) represents an ongoing randomized double-blind interventional study that investigates the efficacy and safety of MRgHIFU compared to sham treatment in the therapy of symptomatic UF with an estimated enrollment of 224 patients (NCT01504308).

With regards to current error-prone manual measurements, there is growing evidence in support of the use of 3D quantitative methods for lesion response evaluation and the present study demonstrates major advantages of 3D-RESQU after MRgHIFU. The semiautomatic approach allows for manual adjustments at all steps and furthermore, the 3D approach overcomes technical errors, which may occur with manual assessment of tumor volume on planar scans. In particular, we suggest a major benefit of the 3D-based calculation of enhancement as well as the subtraction-based analysis of the lesion mask. Moreover, the segmentation-based software is capable of calculating absolute numeric values for ELV, which enable the user to evaluate lesion enhancement in consideration of postprocedural tumor shrinkage based on a voxel-by-voxel threshold analysis. This allowed for a rigorous evaluation that determined that the enhancement based metric (ELV) did not show a diagnostic value. Most importantly, a good intermethod correlation for the quantification of

lesion volume could be shown to confirm the results and validate the technique in this setting (Figure 3). By contrast, the results of the present study outline the limitations of visual enhancement estimation for response evaluation purposes in UF. Asymmetric necrosis with rim tissue enhancement and scattered viable foci within the lesion is a common phenomenon after MRgHIFU therapy and may explain the great extent of interreader disagreement and discrepancy between software-assisted 3D ELV quantification and planar visual attempts (Figure 4). Subsequently, the 3D segmentation technique overall provides a feasible, reproducible and accurate basis to evaluate tumor response to treatment (23).

However, this study has several limitations. First, the small number of patients as well as the large drop-out range for patients after the 6-month follow-up. The latter might be a result of incompliance due to clinical improvement or due to the retrospective design that has prevented us from consistently acquiring MRI scans for every patient. Additionally, one might argue that the stratification of clinical symptoms was insufficient. In particular, 87.5% of clinically assessed patients in this study were categorized as R at the 6-month follow-up. However, 6 patients were excluded from this study due to additional treatments such as hysterectomy or UAE within the time of follow-up. These patients were not included in the statistical analysis but clearly have to be considered as clinical NR. As the patients presented with a large range of tumor volume, a correlation analysis did not reveal significant differences in the imaging parameters between the two cohorts. Assessment of the clinical outcome at the 12- and 24-month follow-up could have clarified possible correlations. Taking into account that most women presented with numerous fibroids, this selective evaluation of the dominant lesion as a surrogate for overall tumor response appears to be another limiting factor.

In conclusion, the results of the present pilot study provide initial evidence for the advantages of a segmentation-based semi-automatic 3D quantification of UF response to MRgHIFU. Applied on ceMRI scans, the segmentation is accurate and feasible for daily clinical practice and reveals a beneficial diagnostic value of TLV in this setting. This study may drive research in the field of image-based 3D response evaluation for further validation of the presented results in larger prospective trials.

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Dr. Hamm is a board member of several European radiological and research societies and reports personal fees from Consultant to Toshiba. As the chief director of the Department of Radiology at Universitätsmedizin Charité Berlin, Dr. Hamm reports grants from multiple companies and NGO to the department, outside the submitted work.

Abbreviations

UF	uterine fibroid
MRgHIFU	MR-guided high-intensity focused ultrasound
TLV	total lesion volume
ELV	enhancing lesion volume
3D-RESQU	3-dimensional response quantification in uterine fibroids

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Figure 1. Quantification of the Total Lesion Volume and Enhancing Lesion Volume

The graph (median and standard error) demonstrates the **A** total lesion volume (TLV) and the **B** enhancing lesion volume (ELV) assessed by 3D-RESQU on contrast-enhanced MRI (ceMRI) scans at baseline as well as 24 hrs, 6 months, 12 months and 24 months after MR-guided high-intensity focused ultrasound (MRgHIFU). A TLV decrease of statistical significance compared to baseline was observed after 6, 12 and 24 months. A significant decrease of ELV is apparent after 12 months. * $p < .05$, ** $p < .01$, *** $p < .001$

Figure 2. 3D Quantitative Assessment of Uterine Fibroids

The graph illustrates representative changes in the total lesion volume (TLV) and the enhancing lesion volume (ELV) of a uterine fibroid after MR-guided high-intensity focused ultrasound (MRgHIFU) in a 44-year old patient. In the vertical, the contrast-enhanced MRI (ceMRI) scans are arranged according to the time of acquisition. In the horizontal, **A** and **B** demonstrate the ceMRI scans at 0 and 20 sec, respectively. **C** represents the volume rendering for the segmented lesion on a ceMRI scan. **D** demonstrates the color map of the lesion using 3-dimensional response quantification in uterine fibroids (3D-RESQU); the color coding varies from red representing maximum enhancement to blue representing no enhancement.

Figure 3. Correlation Analysis: Uterine Fibroid Volume

The graph illustrates the interreader agreement for manual volume measurements **A**, **B** as well as the inter-method correlation between manual and 3D-RESQU evaluation of the total lesion volume (TLV) on contrast-enhanced MRI scans **C**, **D** at baseline and 6 months after MR-guided high-intensity focused ultrasound (MRgHIFU). According to the linear regression model and the calculation of the Pearson correlation coefficient (R^2), volumes assessed manually by both readers demonstrate good agreement and the strong correlation of both attempts validates volumetric calculations by the semi-automatic 3D-RESQU technique in this setting.

Figure 4. Correlation Analysis: Uterine Fibroid Enhancement

The graph illustrates the inter-reader agreement for visual enhancement assessment **A, B** as well as the inter-method correlation between visual and 3D-RESQU evaluation of the enhancing lesion volume (ELV) on contrast-enhanced MRI scans **C, D** at baseline and 6 months after MR-guided high-intensity focused ultrasound (MRgHIFU). According to the linear regression model and the calculation of the Pearson correlation coefficient (R^2), visually estimated enhancements only show slight agreement and thereby demonstrate limited reproducibility. The correlation analysis of both attempts reveals strong discrepancy, particularly at the 6-month follow-up, suggesting a benefit of the semi-automatic 3D-RESQU technique over a planar visual approach.

Table 1

Patient Characteristics

Parameter	Study population
Age (n=24)	46.13 [*] years (range, 37–53)
Race	
African-American	n=9
White	n=13
Other	n=2
Clinical symptoms at presentation (n=19)	
menorrhagia	n=13 (68 %)
bulk-related symptoms	n=16 (84 %)
Number of uterine fibroids	
1	n=9
2	n=9
>2	n=6
Baseline TLV (n=24)	263.74 [*] cm ³ (range, 30.45–689.56)

* Mean