Magnetic resonance imaging-guided focused ultrasound surgery for symptomatic uterine fibroids: Estimation of treatment efficacy using thermal dose calculations

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Purpose

Over the past decade, magnetic resonance-guided focused ultrasound surgery (MRgFUS) has emerged as a non-invasive treatment tool for uterine fibroid; utilizing focused ultrasound waves to accurately target and thermally coagulate fibroids. The safety of this treatment is maintained through the utilization of high resolution anatomical imaging used for planning and thermal-monitoring images obtained during the energy delivery into the target [1 on page ...].

During the course of MRgFUS, treating physicians are often faced with the challenge of estimating the level of ablation based on the thermal dose maps accumulating on their control workstation. Given the increasing body of evidence which shows that most of the fibroid volume should be ablated in order to achieve lasting results[2 on page ...], this knowledge is increasingly becoming more important.

The purpose of this study was to analyze the correlation between the predicted ablation and the actual outcome in a large consecutive group of patients and to follow on these patients throughout the first year following their MRgFUS (tracking the level of symptomatic relief as well as the size of the treated fibroids).

Methods and Materials

Patients
This retrospective analysis reviews sixty consecutive women, who were treated in our hospital for the indication of uterine fibroids, between August 2006 and May 2007. The women were screened using an MRI to verify that the acoustic beam would reach the target efficiently without compromising safety (ensuring that there will not be unintentional heating of bowel or bone) [3]. The mean age and mean body mass index (BMI) of the 60 women treated with MRgFUS were 41.3 ± 6.3 years (range, 30 to 52) and 22.0 ± 2.6 (range 18.0 - 28.3 Kg/m²). The 60 patients had 98 fibroids; of which 84 fibroids were deemed to contribute to the patients’ symptoms and were accessible for treatment. A summary of patient and fibroid demographics is provided in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>41.3 ± 6.3</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>41.3 ± 6.3</td>
</tr>
</tbody>
</table>
Range            30 to 52
Race
Asian             60 (100)
Number of Fibroids (98)
1               38 (39)
2 - 3             40 (41)
4                20 (20)
Dominant Fibroid location (84)
Intramural          31 (37)
Submucosal         27 (32)
Subserosal        26 (31)
Treated Fibroid Volume
Mean ± SD          200 ± 160
Median              172
Range              17 - 650
Treated Fibroid Volume (per patient)
#100 cm³           21 (35)
101 - 200 cm³      17 (28)
201 - 300 cm³      9 (15)
301 - 400 cm³      6 (10)
#400 cm³           7 (12)

Table 1: Patient and Fibroid characteristics. Values in parentheses are percentages.

MR-guided Focused Ultrasound Treatments

Treatment devices:
The MRgFUS system was comprised of the ExAblate 2000 (InSightec, Haifa, Israel) integrated with a 3.0-T MRI scanner (Signa HDx, GE Healthcare, Milwaukee, WI, USA).

Pre-treatment patient preparation:
Patients were advised to shave hair from the umbilicus to the pubis and to lie prone on an acoustic coupling gel-pad located above the ultrasound transducer. A Foley catheter was inserted in order to minimize uterus movement during the treatment due to the natural filling of the bladder. All women were administered with one ample of Fentanyl during the procedure to reduce possible motion and to reduce procedure related pain.
**Treatment:**
The treating physician prescribed the target on the ExAblate workstation using the recently acquired MRI anatomical images, taking into consideration the symptomatic lesions and areas which ultrasound energy should not pass (such as bowel or nerves near bony structures). Sufficient levels of energy, enough to raise the temperature in the designated targeted region to 70-80 °C, were delivered in order to coagulate the volume traced on the screen.

Volumetric thermal dose maps were created by adding all the regions which have reached thermal dose beyond 240 equivalent minutes at 43°C. Following each energy delivery - the software accumulated the treated volume from the thermometry images supplied by the MRI and marked the treated area to enable the physician to proceed to the next sonication (refer to Figure 1). Throughout the treatment, the software kept accumulating the thermal dose maps and displayed it to the physician, overlaid on the anatomical MRI images. The cumulative volumetric sum of all these thermal maps is constantly displayed to the physician as the Thermal Dose Volume (TDV).

![Figure 1](image1.png)

**Fig. 1:** Figure 1: Temperature-sensitive phase-difference fast spoiled gradient-echo MR images acquired during sonications. Magnitude images (left) provide the physician information about the clinical orientation of the targeted myoma and the thermal images (right) provide thermal information using color-coded overlays. Green dose overlay corresponds to areas, in current sonication, which have passed the thermal dose threshold of 240 equivalent minutes at 43°C. Blue dose overlay corresponds to the accumulated thermal dose from all previous sonications.

**References:** Diagnostic Radiology, College of Medicine, CHA University, CHA Bundang Medical Center - Gyunggi-Do/KR
At the end of the treatment, when the intended volume was treated, T1 weighted contrast-enhanced images were acquired to evaluate the outcome by inspection of the non-enhancing regions (which correspond to absence of blood perfusion to these areas) (refer to Figure 2).

**Fig. 2:** Figure 2: Accumulated thermal dose overlaid on the sagittal T2-weighted images used for planning of the treatment (left). Non-perfused regions seen post treatment on T1-weighted images after contrast injection (right).

**References:** Diagnostic Radiology, College of Medicine, CHA University, CHA Bundang Medical Center - Gyunggi-Do/KR

**Data Analyses**

A comparison has been made between the non-perfused volume (NPV) and the TDV. In addition, the NPV and the TDV were both divided by the initial treatment volume to arrive at the NPV ratio and TDV ratio values, respectively, to gauge the treatment effectiveness.

**Symptom Severity Score**

Symptom Severity Score (SSS) of the treated women has been tracked using a validated tool, uterine fibroid symptom and quality of life - UFS-QoL[4]. The numerical sum was later transformed to a 100-point scale, for which a higher score indicates worse symptoms. This evaluation was repeated during the follow-up period at the 3, 6 and 12 months intervals.

**Statistical analysis**
Statistical analysis was performed using R 2.12.1 software[5]. Descriptive statistics were used to evaluate the baseline and outcome data, and the data is presented in the form of mean ± standard deviation.

Paired t-tests were used for statistical comparisons of mean SSS values between baseline and that reported at later follow-up visits.

Correlation coefficient was calculated between the TDV and the NPV.

A p value below 0.05 was considered to indicate a significant difference.

**Images for this section:**

![Figure 1](image_url)

**Fig. 1:** Figure 1: Temperature-sensitive phase-difference fast spoiled gradient-echo MR images acquired during sonications. Magnitude images (left) provide the physician information about the clinical orientation of the targeted myoma and the thermal images (right) provide thermal information using color-coded overlays. Green dose overlay corresponds to areas, in current sonication, which have passed the thermal dose threshold of 240 equivalent minutes at 43°C. Blue dose overlay corresponds to the accumulated thermal dose from all previous sonications.
**Fig. 2:** Figure 2: Accumulated thermal dose overlaid on the sagittal T2-weighted images used for planning of the treatment (left). Non-perfused regions seen post treatment on T1-weighted images after contrast injection (right).
Results

Thermal dosimetry analysis

Mean NPV ratio : 40% ± 20% (range 0% - 92%)
Mean TDV ratio : 30% ± 15% (median 27%, range 0% - 87%)
NPV/ TDV ratio : 1.5 ± 1.0

Relation between the TDV and the NPV : strongly correlated (r=0.84, P<0.0001)

When analyzing the group of patients for which the TDV ratio was larger than the median (>27%, n=30), the mean ratio between the NPV and the predicted dose volume was 1.1 ± 0.5 compared with the relation at the lower TDV ratio group (1.9 ± 1.3, P=0.0029) (refer to Table 2).

<table>
<thead>
<tr>
<th>Large TDV ratio group (&gt;27%, n=30)</th>
<th>Lower TDV ratio group (&lt;27%, n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPV/TDV ratio</td>
<td>1.1 ± 0.5</td>
<td>1.9 ± 1.3</td>
</tr>
</tbody>
</table>

Table 2: Comparison of the mean ratio between the NPV and the predicted dose volume between Large TDV ratio group and lower group.

For the large TDV ratio group, the graphical relation between the TDV and the NPV is shown in Figure 3 exhibiting a very strong correlation (r=0.9, P<0.0001).
**Fig. 3**: Figure 3: Comparison between predicted thermal dose and non-perfused volume for the large TDV ratio group. The line indicates unity. Correlation coefficient of 0.90 indicates a very strong correlation (P

**References**: Diagnostic Radiology, College of Medicine, CHA University, CHA Bundang Medical Center - Gyunggi-Do/KR

**Symptom Severity Score**

Mean baseline SSS : 50 ± 22
3 months follow up SSS : 33 ± 16 (P<0.0001)
12 months follow-up SSS : 19 ± 12 (P< 0.0001) (refer to Figure 4)
**Fig. 4:** Figure 4: Continuous improvement of symptom severity score throughout the first 12 months post treatment. The number of available patients at each visit is shown beneath the graph.

**References:** Diagnostic Radiology, College of Medicine, CHA University, CHA Bundang Medical Center - Gyunggi-Do/KR

**Fibroid volume analysis**

<table>
<thead>
<tr>
<th></th>
<th>Measured volume</th>
<th>Percent shrinkage</th>
<th>Comparison with the initial volume</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial</strong></td>
<td>200 ± 16 cc</td>
<td>29% ± 23%</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>(range 17 - 650 cc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6 months follow-up</strong></td>
<td>150 ± 130 cc</td>
<td>29% ± 23%</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>(range 16 - 607 cc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>12 months follow-up</strong></td>
<td>140 ± 130 cc</td>
<td>32% ± 27%</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>(range 8 - 524 cc)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3:** Measured volume change of the treated fibroid on follow-up MRI.
Fig. 3: Figure 3: Comparison between predicted thermal dose and non-perfused volume for the large TDV ratio group. The line indicates unity. Correlation coefficient of 0.90 indicates a very strong correlation (P
**Fig. 4:** Figure 4: Continuous improvement of symptom severity score throughout the first 12 months post treatment. The number of available patients at each visit is shown beneath the graph.
Conclusion

This report has presented the clinical data using a cohort of 60 consecutively treated women. When looking at the large treatments (those which resulted in more than 27% TDV ratio) - the ratio between the NPV and TDV has been found to be $1.1 \pm 0.5$. These results are superior to those reported in previous studies (McDannold et al. reported on $1.9 \pm 0.7$ [6 on page ], Voogt et al. reported on $1.4 \pm 0.6$ ratio [7 on page ], and Kim et al. reported on $1.8 \pm 0.6$ [8 on page ]). The close correspondence we have found between the TDV and NPV at these large volumes provides the treating physician a better understanding of the level of thermal ablation for the fibroid being treated and therefore provides more knowledge as to when the ablation level is sufficient. This increased level of control corresponds to the accuracy and safety of the MRgFUS technique.

The symptoms, as measured by the SSS, were reduced significantly by the 3 months follow-up, but interestingly, the trend of symptom reduction continued throughout the first year in our study. This trend compares favorably with the one portrayed in earlier studies (Stewart et al [1 on page ], Kim et al [9 on page ]) where there was no additional improvement beyond the significant symptom reduction measured at the first follow-up, 3 months post treatment. We speculate that this is also due to the relatively low NPV ratios which were allowed in those studies.

The large shrinkage rate measured at the 12 months visit (32%) compares favorably with the 25.8% shrinkage reported by Kim et al [9 on page ] and the 9.3% shrinkage reported by Lenard et al [10 on page ], most likely due to the modest NPV ratios attained during the initial stages of those studies, imposed by the strict FDA regulations at the time, which limited the treatments and allowed up-to 50% of the fibroid volume to be targeted.

Our report contains limitations in the design, since the patients were not participating in a clinical trial. This posed difficulties in following-up on all patients and limited our follow-up period at 12 months post treatment. However, we believe that despite these limitations, the data we have managed to collect provides accurate and sufficient longitudinal information on patients undergoing MRgFUS.

We have shown that when the TDV ratio larger than 27% of the fibroid volume there is good correspondence between the thermal information provided to the MRgFUS operator during treatment (TDV) and the final outcome, allowing physicians to safely increase the percentage of the ablation levels - which would have a positive effect on the long-term outcome of this treatment modality. In addition, this study provides further clinical
evidence that MRgFUS provide a safe and effective non-invasive option for patients suffering from uterine fibroids. Our study adds to a growing body of evidence, showing the importance of safely reaching high NPV levels during MRgFUS. We have demonstrated that patients experience fast and significant reduction of symptoms, and that over the course of the first year there is continuous improvement.

References


5. R Development Core Team . R: a language and environment for statistical computing. 2010; http://www.R-project.org:


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