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● *Original Contribution*

QUANTITATIVE MRI OF UTERINE LEIOMYOMAS DURING TRIPTORELIN TREATMENT: REPRODUCIBILITY OF VOLUME ASSESSMENT AND PREDICTABILITY OF TREATMENT RESPONSE

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Magnetic resonance (MR) imaging is increasingly applied for the quantitative evaluation of uterine leiomyomas. MR is thought to be more accurate in comparison to ultrasound (US) techniques. MR signal intensity (SI) may prove to be predictive of myoma response to GnRH agonist treatment. This study aimed to evaluate the precision of uterine volume assessment by a parallel planimetric MR method and the accuracy of the ellipsoid formula based calculations from MR and US images. It was also attempted to analyze the precision of MR leiomyoma volume measurements and examine the relation between pretreatment myoma SI patterns and the response to agonist therapy. Twenty-seven women with a myomatous uterus were scanned three times during GnRH agonist treatment for 6 months. T_1- and T_2-weighted, as well as T_1 contrast-enhanced sequences of the uterus were obtained in the transverse and sagittal plane. Abdominal US of the uterus was performed with a conventional sector scanner. By the use of a software system for analysis of three-dimensional images obtained by MR, uterine volume was measured by a parallel planimetric method (MR-ROI) as well as the use of the ellipsoid formula (MR-ELL). Myoma volume was assessed by the MR-ROI method. SI of the myomas was estimated from selected tissue samples as well as from the integral myoma region of interest. By abdominal US, volume was assessed by the ellipsoid equation (US-ELL). Within- and between-observer and method reliability (*Rw*/*Rb*) was calculated from mean squares obtained by analysis of variance. For uterine volume assessment, reliability between observers and between methods when the MR-ROI and MR-ELL methods were analyzed was excellent. For the US-ELL measurements, the between-observer reliability was limited. Moreover, the reliability of the US-ELL was low when the MR-ROI method was used as the standard. Myoma volume assessment with the MR-ROI method showed high between-observer and between-method agreement. The myoma/fat SI ratio and the mean SI coefficient of variation failed to show a correlation with the degree of response to triptorelin treatment of individual myomas. In MR uterine volume assessment the MR-ELL method is very accurate compared with the more complicated MR-ROI method. The agreement between MR and US is limited. Therefore, the ellipsoid method on MR images is to be regarded as the method of choice for quantitative assessment of uterine volume response to hormonal treatment. Myoma SI patterns were shown to be of no value in the response prediction of myomas to treatment with GnRH agonists. Copyright © 1996 Elsevier Science Inc.

Keywords: **Magnetic resonance imaging; Leiomyoma; GnRH agonist; Ultrasound.**

INTRODUCTION

Uterine leiomyomas are very common benign tumors arising from the smooth-muscle tissue of the uterine wall. Leiomyomas may be the cause of pain and pressure complaints, menstrual disturbances, or reproductive failure. Identification, localization, and size of uterine leiomyomas can readily be assessed by the use of magnetic resonance (MR) imaging.[1–4] GnRH agonist treatment of leiomyomas can be evaluated by mea-

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suring changes in uterine and myoma volume. Uterine and myoma volume can be estimated from MR images by the use of three perpendicular diameters incorporated in the equation of an ellipsoid,[5–7] or by serial measurements of regions of interest (ROIs) on scan sequences.[8] Finally, the response rate to agonist treatment may prove to be predictable by evaluation of the myoma signal intensity (SI) at MR imaging. Signal intensity has been claimed to be predictive of the histological appearance of the fibroid, especially as a marker of degeneration and collagen fiber content.[4,9,10]

Ultrasound (US) imaging techniques have been widely used for the assessment of uterine and myoma size during GnRH agonist treatment.[11–19] In the large myomatous uterus the accuracy of ultrasound volume estimations has been doubted.[20,21] Few authors have addressed the question of comparison between MR and US volume estimations in uterine leiomyomas.[22] Studies on the precision of MR volume estimations are lacking.

The present study was designed to further delineate the role of MR in the quantitative evaluation of uterine leiomyomas.

AIMS OF THE STUDY

The study was designed to evaluate the precision of MR imaging based calculations of uterine and myoma volume. In addition, the reliability of uterine volume assessment applying the ellipsoid equation to MR and ultrasound images was studied, taking the MR planimetric method as the standard.

Furthermore, the reliability of MR signal intensity measurements of myoma tissue and the ability to predict myoma volume response to GnRH agonist treatment from the MR signal intensity pattern were studied.

DESIGN OF THE STUDY

Study Group

Twenty-seven women with symptomatic leiomyomas diagnosed by US participated in the study. All women had regular menstrual cycles and a total uterine size of at least 300 ml as measured by abdominal ultrasound examination. They were scheduled for either preserving surgery or hysterectomy and received 6 months of GnRH agonist pretreatment. Any previous hormonal treatment was interrupted 2 months before entering the trial. Women with an endocrine disorder, history of urolithiasis, or disease affecting bone metabolism were excluded from the study. Serum creatinine had to be within the normal range.

All women started daily subcutaneous (SC) self-administration of an aqueous solution of triptorelin on the second day of the menstrual cycle. During the first week a daily dose of 500 μg was used, followed by 100 μg daily for a period of 7 weeks. After the initial 8-week period, women were randomized into one of three dosage groups using either 5, 20, or 100 μg triptorelin daily for an additional period of 18 weeks. Thus, the total treatment period was 26 weeks.

Of the total 27, three patients dropped out of the treatment protocol. One patient interrupted treatment in week 10 because of severe complaints of headaches. A second patient, suffering from severe menorrhagia before treatment, experienced heavy bleeding in week 11. Agonist treatment was interrupted, and she was further treated with oral progesterone and received blood transfusions. The third patient revealed herself to be a cocaine addict. She repeatedly violated the medication and monitoring protocol and was not used for the response to treatment evaluation. The former two patients were used only for the initial response to treatment analysis (week 0 vs week 8).

The protocol as described was approved by the Committee on Ethics of Research involving Human Subjects of the Free University Hospital. All volunteers gave oral informed consent before entering the study.

MR Volume Assessment

MR imaging of the lower abdomen was carried out before and after 8 and 26 weeks of agonist treatment. The MR studies were performed with a 0.6-T superconductive magnet (Teslacon II; Technicare). All images were acquired with four excitations and a 160 × 256 matrix. With a spin-echo (SE) T_1-weighted (500–650/20 [repetition time (TR) ms/echo time (TE) ms]) pulse sequence, images were obtained in the sagittal and transverse plane. Using a T_2-weighted (TR/TE 2000/90) SE sequence, imaging was performed in the transverse plane. Finally, transversal T_1-weighted (TR/TE 500–700/20) SE images were acquired after rapid intravenous administration of gadopentetate dimeglumine (0.1 mM/kg body wt; Magnevist, Schering, Weesp, The Netherlands). All images obtained had a 10-mm slice thickness and a 12.5-mm slice-to-slice distance.

Total uterine volume calculation was carried out by means of two distinct methods. First, a software package for the display and analysis of three-dimensional (3D) MR images (Analyze, ver. 6.2; Biomedical Imaging Resource, Mayo Foundation, Rochester, NY) was used. By defining ROIs (i.e. uterine and/or myoma tissue) on transverse and sagittal sections, assessment of the uterine section volumes was performed

(MR-ROI). The 3D volumes of subsequent sections were automatically computed into a total uterine volume value, using the slice thickness and distance. The volume calculations were done by two investigators (FB and MH) from both the T_1-weighted transverse and sagittal sections. Calculations by one author (FB) were done in duplicate on separate occasions.

Second, total uterine volumes were calculated by applying the equation for the volume of an ellipsoid ($L \times W \times D \times \pi/6$; MR-ELL method). The three maximal perpendicular diameters of the uterus from the T_1-weighted sagittal (craniocaudal) and transverse images (dextrosinister and anteroposterior) were measured by the use of 2D calipers in the previously mentioned software system. All measurements were carried out by one author (FB) in duplicate on separate occasions.

Calculations of myoma volume were done for those myomas that could be clearly identified on both the baseline and 8- and 26-week scan sequences. The same Analyze software system was used as for the total uterine volume calculations (MR-ROI). The size assessments were carried out by one investigator (FB) in duplicate from both the T_2-weighted transverse sections as well as the T_1-Magnevist-enhanced transverse image sequence. In addition, MR-ROI myoma size before treatment was measured by another observer (ThF) for both the T_2-weighted and the T_1-Magnevist-enhanced transverse images. Both investigators were blinded regarding the dose of the agonist used.

MR Signal Intensity Assessment

Mean pixel SI and the standard deviation (SD) of the mean SI for a certain region of interest or series of ROIs were measured from both the T_2-weighted and the T_1-Magnevist-enhanced transverse myoma images. Background SI measurements were done at various locations outside the image of the abdomen.

Integral signal intensity (SI integral) was assessed during myoma volume measurements by investigator FB, in which automatically the overall mean and SD of the SI of all the pixels contributing to the myoma volume were calculated using the Analyze software package. The coefficient of variation of the SI, as measured for a given ROI or series of ROIs, was calculated by dividing the SD by the mean. The CV of the Integral signal intensity of a myoma was considered a quantitative marker for the degree of homogeneity of the myoma SI pattern.

Selected samples of the SI of the myomas and SC adipose tissue as close to the myoma as possible were calculated by choosing ROIs with a minimum of 100 pixels that were thought to well represent the overall SI pattern of the myoma. The SI samples were performed in duplicate from two adjacent MR slices of the myoma by the same observer (FB). Arbitrarily, only myomas present on four subsequent MR slices were used for SI samples. Otherwise, the SI sample would have almost been equal to the integral SI measurement. To minimize the effect of variations in SI from other sources, the SI sample of the myoma was expressed as the proportion of the SI sample of adjacent adipose tissue, creating the SI ratio. SI assessments at various sites in the SC tissue were carried out to assess the variablity of SI raised by this type of tissue.

US Volume Assessment

Abdominal US scanning of the lower abdomen with the use of the full-bladder technique was carried out before treatment and after 8 and 26 weeks of agonist treatment. The three maximal perpendicular diameters of the uterus in the craniocaudal, dextrosinister, and anteroposterior direction were measured after defining the contour of the uterus. The total uterine volume was then calculated by applying the equation for the volume of an ellipsoid (US-ELL). Measurements were performed by one author (FB) in duplicate at the same occasion. The Acuson 128 Computed Sonography system was used, applying either the electronic 3.5-mHz sector array (S 328) transducer or the 3.5-mHz curved array (C 366) transducer (Acuson Corporation, CA). In addition, following the same technique, single total uterine volume estimates were carried out by another investigator (MH). Scanning was performed using the Toshiba Sonolayer system SSA/270A, applying an electronic 3.5-mHz convex sector scanner (Toshiba Medical Systems, Europe BV, Woerden, The Netherlands). Both investigators were blinded with regard to the agonist dose used by the patient.

Statistical Analysis

The ability of the first of two measurements to predict the result of a second measurement using the same method was calculated from the between- and within-subject mean squares, obtained from analysis of variance (BMDP Dynamic, Release 7; BMDP Statistical Software, Los Angeles, CA) and expressed as within-Reliability (*Rw*) (intraclass coefficient of correlation[23]). The interobserver or intermethod reliability was calculated from the between-observer, between-patient, and error type II mean squares obtained by analysis of variance. This reliability was expressed as the between-reliability (*Rb*).[23] Values for reliability are given as point estimates with the 95% confidence interval between brackets.

Triptorelin treatment effects during the first 8 weeks

of treatment were studied by using all available myomas. As there was no dose-related effect on myoma size it was thought justified to pool the data of the three dose groups for the response to treatment analysis. The treatment effect on the SI ratio of the myoma during the first 8 weeks was assessed by analysis of variance. The prediction of the myoma volume reduction during agonist treatment by the initial SI ratio and by the CV of the SI was calculated by linear regression analysis.

RESULTS

Clinical Data

Twenty-seven patients were entered in the study. Two patients interrupted treatment in week 10 owing to side effects and bleeding problems. A third patient completed the study but revealed herself to be a cocaine addict. There was evidence of repeated violation of the medication protocol; therefore, she was regarded as not evaluable for response to treatment. The remaining group of 24 patients was used for analysis of response to treatment. The total group of 27 patients was included in the MR and US imaging reliability studies. A full description of patient characteristics and response to treatment has been published elsewhere.[24]

Uterine Volume Assessment

A total of 78 scans analyzed by observer FB were available for precision calculations and between-method comparisons. Duplicate assessments of total uterine volume by the MR-ROI method from T_1 transverse and sagittal images showed an *Rw* of 0.99 (0.99–1.00) for both methods. The prediction of the T_1 transverse uterine volume by the measurement from the sagittal T_1 images showed an *Rb* of 0.97 (0.97–0.99) for observer FB and 0.99 (0.97–0.99) for observer MH (Fig. 1). Duplicate assessments of uterine volume by the MR-ELL method showed an *Rw* of 0.98 (0.97–0.99). When the mean values from the MR-ELL method were compared with the mean from the MR-ROI measurements, the *Rb* appeared to be 0.97 (0.95–0.98) (Fig. 1).

For between-observer comparisons of uterine volume assessments using the MR-ROI technique by observers FB and MH, a total of 72 scans were available. The reliability of uterine volume calculations by MR-ROI, when the two observers were compared, showed an *Rb* value of 0.98 (0.93–0.99) (Fig. 1).

A total of 77 abdominal ultrasound scans performed by observer FB were available for analysis. For the uterine volume assessments by the US-ELL method, the within-observer reliability was 0.97 (0.96–0.98). When the US-ELL measurements by FB were compared with those performed by observer MH, the between-observer reliability was found to be 0.75 (0.61–0.83) (Fig. 2). Comparing US-ELL with MR-ROI volume assessments carried out by FB, the *Rb* value was 0.78 (0.62–0.85), while the same comparison for observer MH revealed an

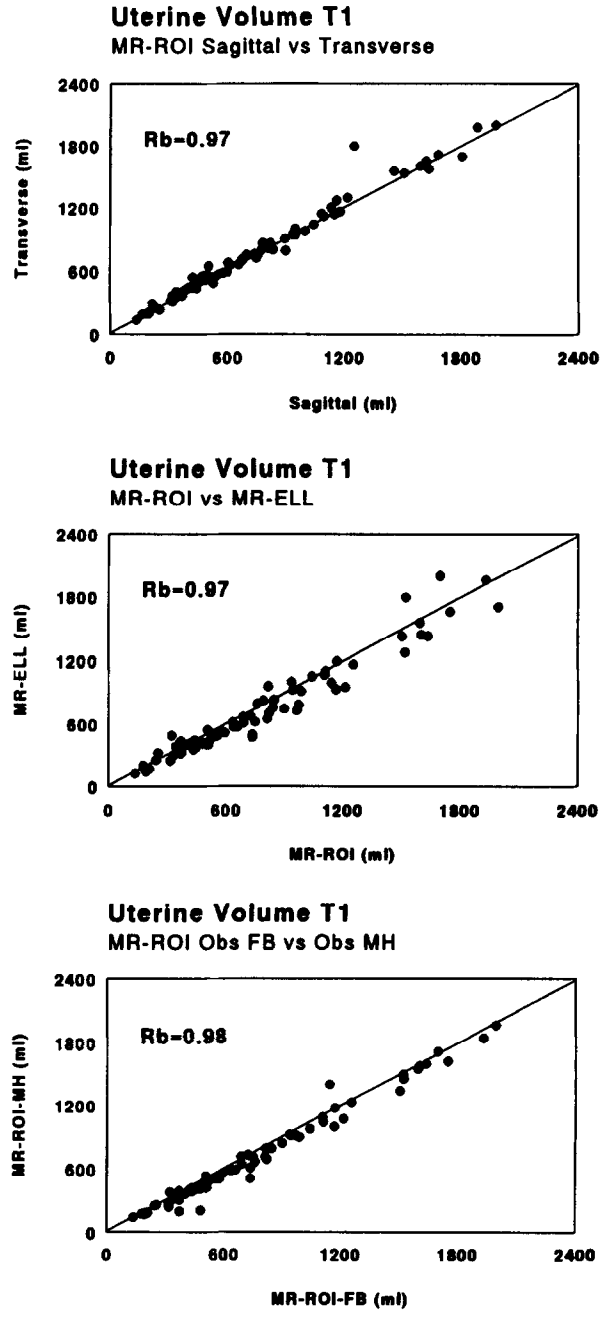

Fig. 1. Scatter plots of the reliability of total uterine volume assessment by MR imaging. The relation is shown between MR-ROI sagittal and transverse measurements (upper panel), between MR-ROI and MR-ELL measurements (middle panel), and between MR-ROI measurements of two different observers (lower panel).

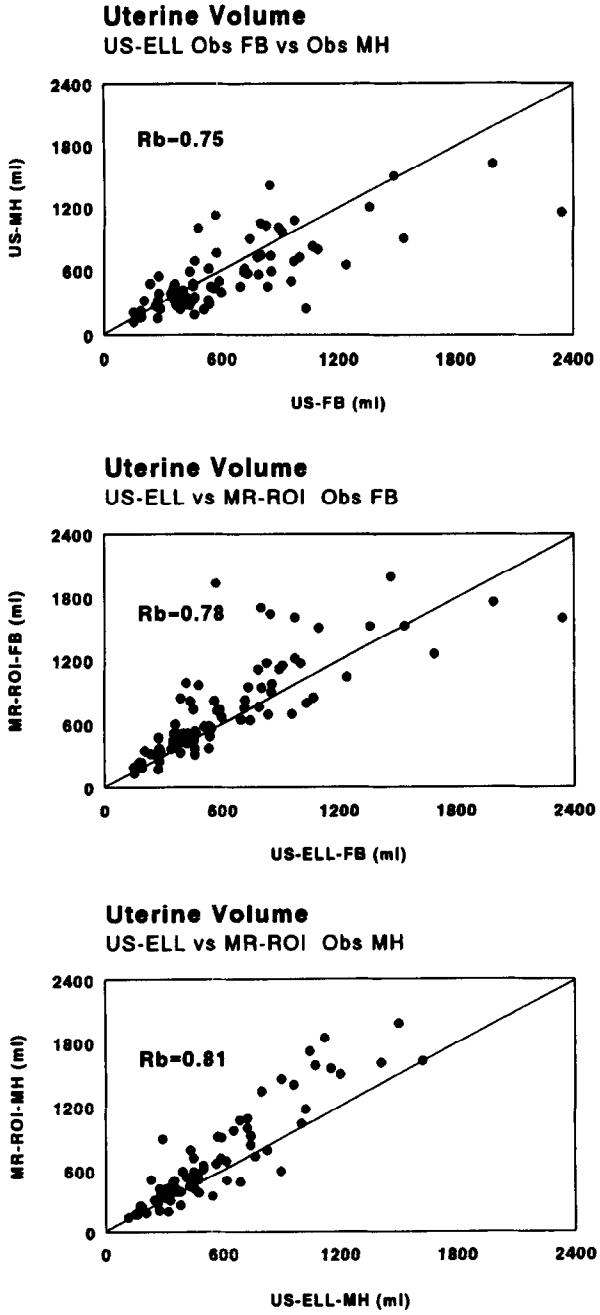

Fig. 2. Scatter plots of the reliability of total uterine volume assessment by US imaging. The relation is shown between US-ELL measurements by two different observers (upper panel), between MR-ROI and US-ELL measurements by observer FB (middle panel), and between MR-ROI and US-ELL measurements by observer MH (lower panel).

Rb of 0.81 (0.54–0.90) (Fig. 2). When US-ELL and MR-ROI measurements of uterine volumes under 700 ml were compared with those over 700 ml in volume, the reliability was lower in the higher uterine volume group. For examiner FB the *Rb* values were 0.50 (0.16–0.72) for the higher volumes and 0.81 (0.67–0.89) for the lower volumes (Fig. 2).

Myoma Volume Assessment

The number of available scans for evaluation of the precision of myoma volume measurements by FB was 139 for both the T_2- and T_1-Magnevist-enhanced images. The within-observer reliability for the two scanning techniques appeared to be 0.98 (0.97–0.98) and 0.99 (0.99–1.00), respectively. Comparing the means of duplicate measurements from both techniques (T_1 and T_2) used, the between-method reliability appeared to be 0.99 (0.98–0.99).

For comparison of myoma volume assessments by the two different observers, FB and TF, a total of 79 scans were used. Between-observer reliability was 0.98 (0.95–0.99) and 0.99 (0.99–1.00) for the T_2 and T_1-Magnevist images, respectively (Fig. 3).

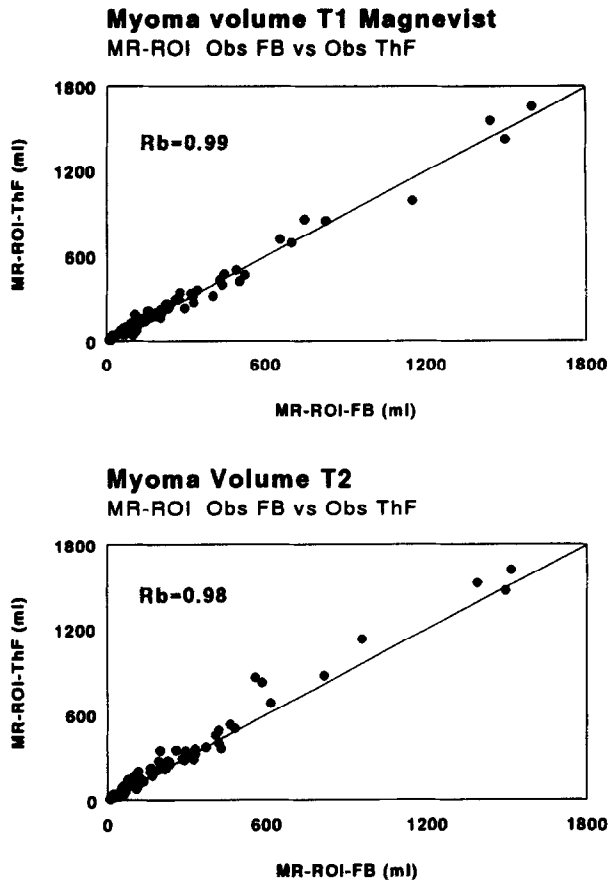

Fig. 3. Scatter plots of the reliability of myoma volume assessment from MR imaging. The relation is shown between MR-ROI measurements by two different observers on T_1-Magnevist-enhanced (upper panel) and T_2-weighted (lower panel) images.

Signal Intensity Measurements

Data for evaluation of the accuracy of sample and integral SI were available from 98 T_2- and 96 T_1-Magnevist-enhanced myoma scans. The signal-to-background noise ratio was 4.2% for the T_2- and 1.7% for the T_1-weighted images. The within-observer (FB) reliability of duplicate SI samples for the two scanning techniques was 1.00 (1.00–1.00) and 0.90 (0.86–0.93), respectively. The ability to predict integral SI of the myomas by the use of the mean of the two SI samples in the T_2 images showed a between-reliability of 0.97 (0.96–0.98). The reliability of SI samples from T_1-Magnevist images in predicting the integral SI was 0.98 (0.97–0.99) (Fig. 4).

The reproducibility of various adipose tissue SI samples from the same image was high, showing an *Rw* value of 0.96 for the T_2 and 0.97 for the T_1 sequences.

During treatment with the GnRH agonist, the SI (myoma/adipose tissue) ratio, as calculated for all the measurable myomas, did not show any change after 8 weeks of treatment, either in the T_1-Magnevist or in the T_2 sequences. After 26 weeks of treatment, the SI ratio in both scanning modes was slightly decreased in the study group as a whole, without any significant dose response relationship ($p = .01$). The prediction of the myoma volume response to agonist treatment at weeks 8 and 26 by the SI ratio before treatment was analyzed by linear regression. Neither in the T_1-Magnevist nor in the T_2-weighted images could a significant correlation be found (Fig. 5).

Regression analysis for the relation between the CV of the integral SI and the treatment response showed no correlation after 8 or 26 weeks for either of the scanning techniques. Finally, treatment response at 8 and 26 weeks could not be predicted by the baseline size of the myoma (Fig. 5).

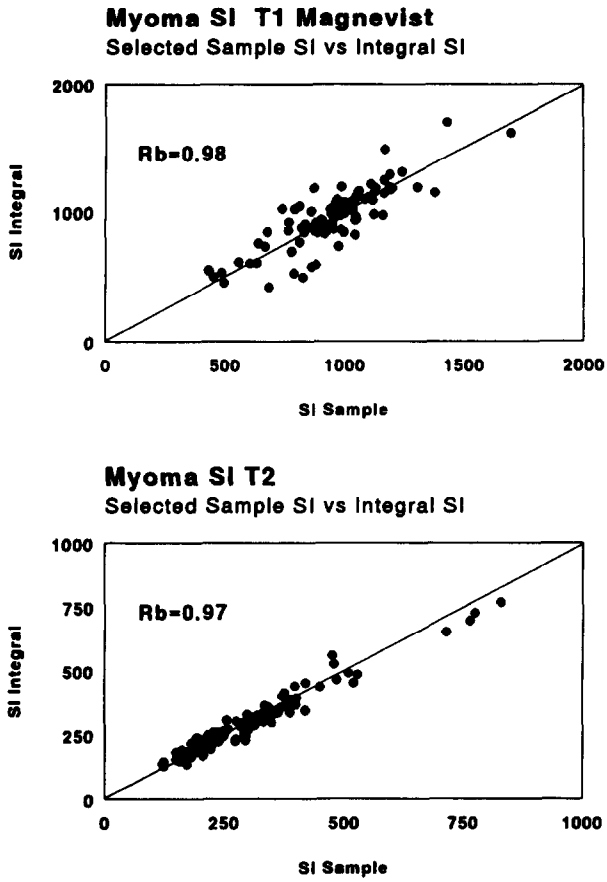

Fig. 4. Scatter plots of the reliability of myoma SI assessment from MR imaging. The relation is shown between the selected SI sample and the integral SI as measured from T_1-Magnevist-enhanced (upper panel) and T_2-weighted (lower panel) images.

DISCUSSION

From the results of this study it can be concluded that uterine volume assessment by a parallel planimetric, computerized technique (MR-ROI method) is very precise, as indicated by the high within- and between-observer reliability. Accuracy may best be analyzed by comparing uterine volume measurements with volumes obtained from water displacement studies after surgical removal of the uterus. However, changes in blood perfusion during the removal procedure may influence the final volume of this standard. Phantom studies have shown that the MR-ROI analyzing system is precise in repeated measurements as well as unbiased when the calculated volume is compared with water displacement of the phantom. The highly defined margins of the myomatous uterus both in the sagittal and transverse MR sequences, as was noted by several authors,[8,25] make the parallel planimetric MR uterine volume assessment very suitable to serve as the standard. With the use of this standard, other techniques to assess uterine volume can be evaluated as for their accuracy.

From a comparison of different methods of MR uterine volume calculation, it was shown that agreement between the sagittal MR-ROI, the transverse MR-ROI, and the MR-ELL method is very high. This suggests that in using the MR-ROI method for the follow-up of uterine volume, the use of either the sagittal or the transverse scanning direction is sufficient. Of course, the use of thinner, nongapped sequences may further limit volume averaging caused by the use of the planimetric method. Several studies have used the ellipse equation for MR volume measurements of the myomatous uterus before and during GnRH agonist

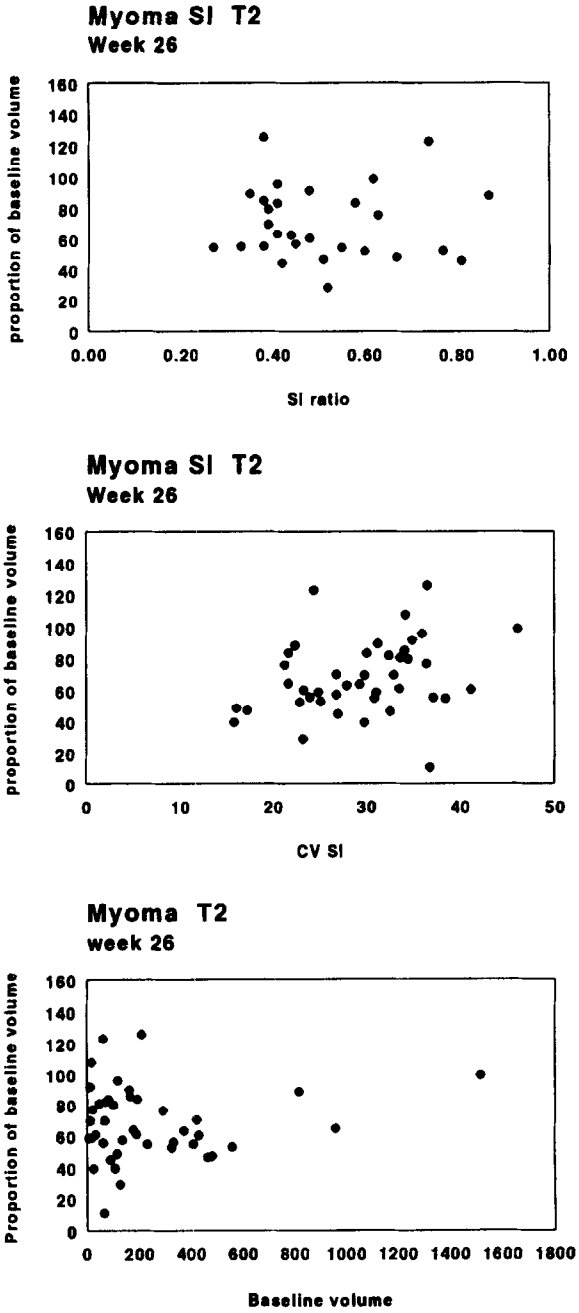

Fig. 5. Scatter plots showing the relation between proportional myoma volume in T_2-weighted images and the baseline SI ratio (upper panel), baseline CV of the mean SI (middle panel), and the baseline myoma volume (lower panel).

treatment,[5-7] Only one author used the planimetric method.[8] Studies on the accuracy of the ellipsoid formula in measuring uterine volume are lacking. With the MR-ROI method as the standard, the MR-ELL method as used in our study has excellent performance, is considerably less time consuming, and is therefore to be preferred in studies evaluating medical treatment of uterine leiomyomas.

The use of abdominal US in assessing uterine volume in this study showed that this method presumably is precise when used in one observer's hand, as indicated by the high reliability for duplicate measurements. However, in the comparison with the measurements performed by another observer or by the use of the MR methods, the US scan reveals itself to be inaccurate. This inaccuracy presumably stems from the frequent inability to define the margins of the uterus, especially where the size of the uterus is in the higher range, owing to the limited field of view. For the same reason the use of transvaginal ultrasound probes would have failed to adequately visualize the margins of the uterus and its myomas. Our findings confirm the impressions stated by other authors. Zawin et al.[22] compared MR and US uterine volume assessment and concluded that the largest volume that could accurately be measured on US was 140 ml, while with MR all uterine sizes could be analyzed. Kurtz and collegues[20] compared the total uterine volume in pregnant women, assessed by the use of the ellipsoid formula, with the true volume assessed by stepped area-to-volume values from transverse and sagittal waterpath scans. The mean error of the ellipsoid method appeared to be 24%. Failure to define the correct margins of the uterus and possible inappropriateness in the application of the ellipsoid formula to the uterine shape were held responsible.

Myoma volume measurements can be accurately performed with the use of the MR-ROI method, as indicated by the high reliability, both within and between observers. Accuracy parameters did not differ between the two scanning techniques (T_2 and T_1 enhanced). Therefore, as the use of Magnevist is expensive, T_2-weighted images are to be preferred for volume estimations of myomas.

As myoma identification by the use of abdominal US was frequently difficult in this series of patients, comparison between US and MR was not possible. From other studies using the ellipsoid formula, it has become clear that the reliability of US scanning in predicting true myoma volume at water displacement is limited and shows a high degree of overestimation.[21] Postoperative ellipsoid measurements of the myomas had a very high correlation to the true myoma volume, indicating the appropriateness per se of this method for myoma volume estimation.[21] Bias may derive from difficulties in defining the true margin of the myoma in in vivo scanning, as mentioned by other authors.[22]

Prediction of the overall MR SI of a certain myoma by the use of a selected, representative area of interest from which the SI is computed, was shown to be highly reliable, irrespective of the MR technique used (T_2 or

T_1 contrast enhanced). MR SI of myomas, with or without contrast enhancement, has been studied as a marker for the histological appearance of the tumor and response to hormonal treatment.[4,5,9,10,26–28] No study has used an integral assessment of the myoma SI; rather, a selected sample of the myoma area was analyzed. The use of the selected sample method in these studies appears to be justified in retrospective.

The quantitative SI pattern of a leiomyoma showed no ability to predict response to GnRH agonist therapy in our study. This finding is in contrast to suggestions from the literature. Leiomyomas with the same collagen content as normal myometrium tend to have an SI almost equal to that of myometrium. When the collagen fiber content increases, the SI decreases, especially on T_2-weighted images.[4,10] Furthermore, leiomyomas with hyaline, myxomatous, or fatty degeneration show various degrees of inhomogeneity in SI.[9,26,29] Based on this knowledge it was presumed that myomas emitting highly variable signals (indicative for degeneration), would tend to be unresponsive to hypoestrogenism, while leiomyomas with high SIs (suggesting low fiber content) would respond well to agonist therapy. Yamashita and coworkers[28] showed that cellular myomas were homogenous and hyperintense on MR imaging and responded well to therapy. Degenerated myomas appeared as inhomogenous masses with a highly variable signal pattern, and responded only minimal to hypoestrogenism. Our quantitative approach to the prediction of myoma volume reduction, which included both the height and variability of the SI, failed to support the assumptions made by Yamashita. Possibly, the considerable overlap in histological picture, degree of homogeneity, and SI prevents a straightforward quantitative preassessment of the myoma response pattern to hormonal therapy.

This study has shown that MR imaging presents a highly accurate method for both uterine and myoma volume assessment. The MR ellipsoid method is an excellent alternative to US scanning in uterine volume estimations. T_1 contrast-enhanced sagittal and transversal sequences may offer the possibility of applying this ellipsoid method to myoma volume measurements. Although severe inhomogeneity on T_2-weighted images may predict a low response of myoma size to GnRH agonist treatment, a more quantitative approach failed to prove its usefulness.

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