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Association between adipose tissue thickness and fibroid shrinkage using ultrasound-guided-high-intensity focused ultrasound

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ASSOCIATION BETWEEN ADIPOSE TISSUE THICKNESS AND FIBROID SHRINKAGE USING ULTRASOUND-GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND

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In fulfillment of the requirements for the degree of

Master of Medicine in the Clinical Disciplines.

Submitted on 8 October 2020

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Declaration by Candidate:

I hereby declare that this research paper is my own original work and has not been submitted before to any other institution for assessment purposes.

Furthermore, I have acknowledged all sources and have cited these in the references section.

There are no conflicts of interest in creating this research paper.

This paper was prepared in a "submissible" format in line with the guidelines of the South African Medical Journal. These guidelines can be found at the following internet address:

http://www.samj.org.za/index.php/samj/about/submissions

Signed,



_____

Gary Peiser (Candidate)

8 October 2020

Declaration by Supervisors:

The following people contributed as supervisors to the work undertaken by the candidate, Gary Peiser, as part of their research paper entitled "ASSOCIATION BETWEEN ADIPOSE TISSUE THICKNESS AND FIBROID SHRINKAGE USING ULTRASOUND GUIDED HIGH INTENSITY FOCUSED ULTRASOUND" in fulfillment of the requirements for the degree of FC Rad Diag (SA) MMed (Student number: 1821478).

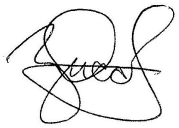
Details of Candidate and Supervisors:

- Candidate: Gary Peiser
- Supervisor 1: Kathleen Jacobs
- Supervisor 2: Richard Spence
- Supervisor 3: Raymond Setzen

Contribution of work by supervisors and candidate for the above-mentioned research paper:

- The research paper is the original work of the candidate, Gary Peiser, who is the author of the above-mentioned research paper.
- Supervisors reviewed draft manuscripts of the protocol and the final research paper and gave guidance regarding research methodology, improvements to content, general conduct and conceptual ideas.
- The proposal and the research paper were submitted to Turn It In concerning plagiarism. The plagiarism certificates were checked and are satisfactory.

Signed,







Kathleen Jacobs	Richard Spence	Raymond Setzen
Primary Supervisor	Supervisor 2	Supervisor 3

8 October 2020

This research paper is dedicated to my aunt.

Presentations:

This study was presented in the form of an E-poster at the RSSA-SASPI-ESNR 2020 Paediatric Imaging congress at the Maslow Hotel, Sandton, South Africa, from 6-9 February 2020.

The submitted poster won the first prize for best poster.

(Please refer to Appendix 1)

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ABSTRACT:

Background:

Ultrasound-guided high frequency focused ultrasound (USgHIFU) is used to treat uterine fibroids that are symptomatic in a non-invasive way. A high frequency focussed ultrasound beam (HIFU) can heat tissue within a fibroid to 65 - 85 degrees celsius where the cells within it denature. The treated fibroid decreases in size over the next 24 months (median follow up period 33.9 months, range 6 - 54 months). A greater thickness of adipose tissue that the HIFU beam travels through is thought to be associated with a decreased treatment effect, although the evidence for this is anecdotal.

Objectives:

This study aims to determine whether the thickness of adipose tissue that the HIFU beam travels through affects the percentage volume shrinkage of the uterine fibroid after treatment.

Method:

A retrospective study was performed at Chris Hani Baragwanath Academic Hospital (CHBAH) of patients who were treated with USgHIFU for symptomatic uterine fibroids between 11 October 2015 and 11 April 2018. Pre- and post-treatment MRI images were used to measure the adipose thickness that the HIFU beam traveled through, as well as the percentage volume shrinkage that the uterine fibroid underwent. Linear regression was used to determine whether there is an association between adipose thickness and the percentage volume shrinkage of the uterine fibroid after treatment.

Results:

The data of 71 female patients who attended the CHBAH HIFU clinic during a 30 month period were analysed. Mean adipose thickness was 17,49mm (95% CI 14,86-19,73). Mean pre-treatment volume of the fibroid was 176ml (95% CI 123,26-208,57). Mean post-treatment volume of the fibroid was 109ml (95% CI 71,75-141,73). Mean fibroid volume reduction was 44.68% ($p <$

0,0001). The analysis indicated that the relationship between adipose thickness and change in volume ratio is not significant.

Conclusion:

In our experience, the adipose thickness does not affect treatment outcome when symptomatic uterine fibroids are ablated using USgHIFU. This is of clinical value as women with an adipose tissue thickness of greater than 6cm are excluded from treatment at CHBAH. The study suggests that the exclusion criteria for USgHIFU treatment of uterine fibroids be reviewed.

Acknowledgements:

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Nomenclature:

HIFU: High Frequency Focused Ultrasound

MRgHIFU: Magnetic Resonance guided High Frequency Ultrasound

USgHIFU: Ultrasound guided High Frequency Ultrasound

CHBAH: Chris Hani Baragwanath Academic Hospital

BMI: Body Mass Index

UAE: Uterine Artery Embolisation

MRI: Magnetic Resonance Imaging

PACS: Picture Archiving and Communication System

V: Volume

CI: Confidence Interval

Introduction:

High frequency focused ultrasound, or HIFU is a minimally invasive, nonsurgical option offered by interventional radiology to treat symptomatic uterine fibroids. HIFU waves are transmitted from a probe placed on a patient's lower abdomen in the midline. The ultrasound waves converge on a single central point, which, as a result, heats the uterine fibroid tissue to a temperature of 65 - 85 degrees celsius to denature cells within it [1]. Reports of fibroid shrinkage of up to 50% have been demonstrated over the 12 to 24 months (median follow up period 33.9 months, range 6 - 54 months) following HIFU treatment [2,3].

Of all the benign tumours of the female reproductive tract, uterine fibroids are the most common. They affect women of reproductive age and cause a significant burden of disease in this population group including heavy or prolonged menses, anaemia, infertility and interference with physical activities[4]. Ultrasound-guided HIFU (USgHIFU) treatment is offered to patients with symptomatic fibroids at Chris Hani Baragwanath Academic Hospital (CHBAH). As far as we can ascertain, this is the only health facility offering this treatment in Southern Africa. This is an important treatment option for women with symptomatic fibroids who wish to preserve their fertility. Preliminary results suggest that uterine fibroid ablation with HIFU is not associated with major risks during subsequent pregnancies, making this treatment option unique[5, 6]. Local studies have demonstrated that the HIFU treatment offered at CHBAH is effective and safe[7], although the treating clinician at CHBAH has offered an anecdotal opinion suggesting that there is variation in the success of treatment outcomes observed on follow-up visits. One possible factor that has been suggested to explain this variability is greater subcutaneous adipose tissue thickness, implying that adipose tissue may attenuate the HIFU beam and decrease its efficacy.

Objectives:

This study aimed to determine whether the thickness of adipose tissue that the HIFU beam travels through plays a role in the percentage shrinkage of uterine fibroids after treatment. A secondary objective is to determine whether there are other variables that could predict the percentage volume shrinkage of uterine fibroids. This study also aims to ascertain whether the HIFU treatment offered to the study population at CHBAH is effective.

Methods:

Study Population:

Only patients who received USgHIFU therapy at CHBAH were considered for the study.

The departmental general inclusion criteria of USgHIFU fibroid ablation therapy at CHBAH are:

- Premenopausal patients;
- Patients with symptomatic fibroids requiring treatment;
- The size of the uterus when measured clinically should be smaller than a gravid uterus of 16 weeks gestation;
- The diameter of the dominant fibroid should measure less than 15cm;
- Patients must be able to lie prone for a minimum of one hour and must be able to communicate with the treating clinician [7].

A pelvic ultrasound is performed and the following criteria had to be met during the ultrasound examination for the patient to be considered for USgHIFU treatment:

- Subcutaneous fat measurement of less than 6cm;
- The minimum diameter of the fibroid should be no less then 3cm;
- The fibroid must not be pedunculated or intra-cavitatory; and
- The uterus must not be larger than a gravid uterus at 16-weeks gestational age.

Patients who met these ultrasound criteria are then referred for an MRI of the pelvis. The fibroids intended for treatment are measured and their exact location is assessed. Bladder or bowel in the line of the intended HIFU beam treatment plane is a contraindication for treatment as these structures could be damaged by the high energy beam, although these structures can be manipulated out of the beam pathway by bowel massage or instillation of saline into the bladder. The patients are then given a date for USgHIFU treatment.

During the procedure, the patient lies prone on the HIFU treatment bed with their abdomen submerged in a water bath. Air bubbles are carefully removed by hand from the patient's abdomen as these would scatter the ultrasound waves and weaken the beam. The HIFU beam probe is placed on the patient's lower abdomen directly anterior to the fibroid. Conscious sedation is administered

(in CHBAH this is done by an anaesthetic registrar). The ultrasound waves are directed towards a single central point within the fibroid which heat and thus denature the targeted cells. These ablated cells result in uterine fibroid shrinkage which is seen over the next 24 months (range 6 - 54 months). A HIFU treatment typically lasts between one and three hours; multiple sessions may be needed to successfully ablate the targeted fibroid depending on the fibroid shrinkage determined by MRI or ultrasound at follow up appointments.

Inclusion Criteria:

A retrospective study was conducted of patients who had received USgHIFU fibroid ablation therapy between 11 October 2015 and 11 April 2018 at CHBAH. Only patients who received an MRI before the procedure as well as an MRI between six and 12 months after the procedure were included in the study. The largest change in fibroid volume occurs within the first 6 months, thereafter the volume continues to shrink but the curve plateaus [7].

MRI images were used to determine the adipose thickness (in millimeters) directly anterior of the treated fibroid on the pre-treatment MRI scan and change in volume between the pre- and post-treatment MRI scans. The software Program R (Version 3.5.1) was used and the results were plotted on scatter graphs.

Results:

71 patients met the selection criteria for the study. All patients were of African descent, and their ages ranged from 31 to 45 years of age. The patients who were selected for the study received treatment between the dates of 11 October 2015 and 12 June 2017 (no patients who were treated met the inclusion criteria after the latter date). All of the patients included in the study received only one treatment session and had an MRI before the procedure and between 6 and 12 months after the procedure. No patients in the study received multiple treatments. In the study population, the thinnest adipose tissue thickness measured was 3,8mm and the thickest was 46,1mm. The mean adipose thickness was 17,49mm (95% CI 14,86-19,73). The mean pre-treatment volume of the fibroid was 176ml (95% CI 123,26-208,57) and the mean post-treatment volume of the fibroid 109ml (95% CI 71,75-141,73). This is a mean reduction of 44,68% in size (95% CI 38.21-51.14)

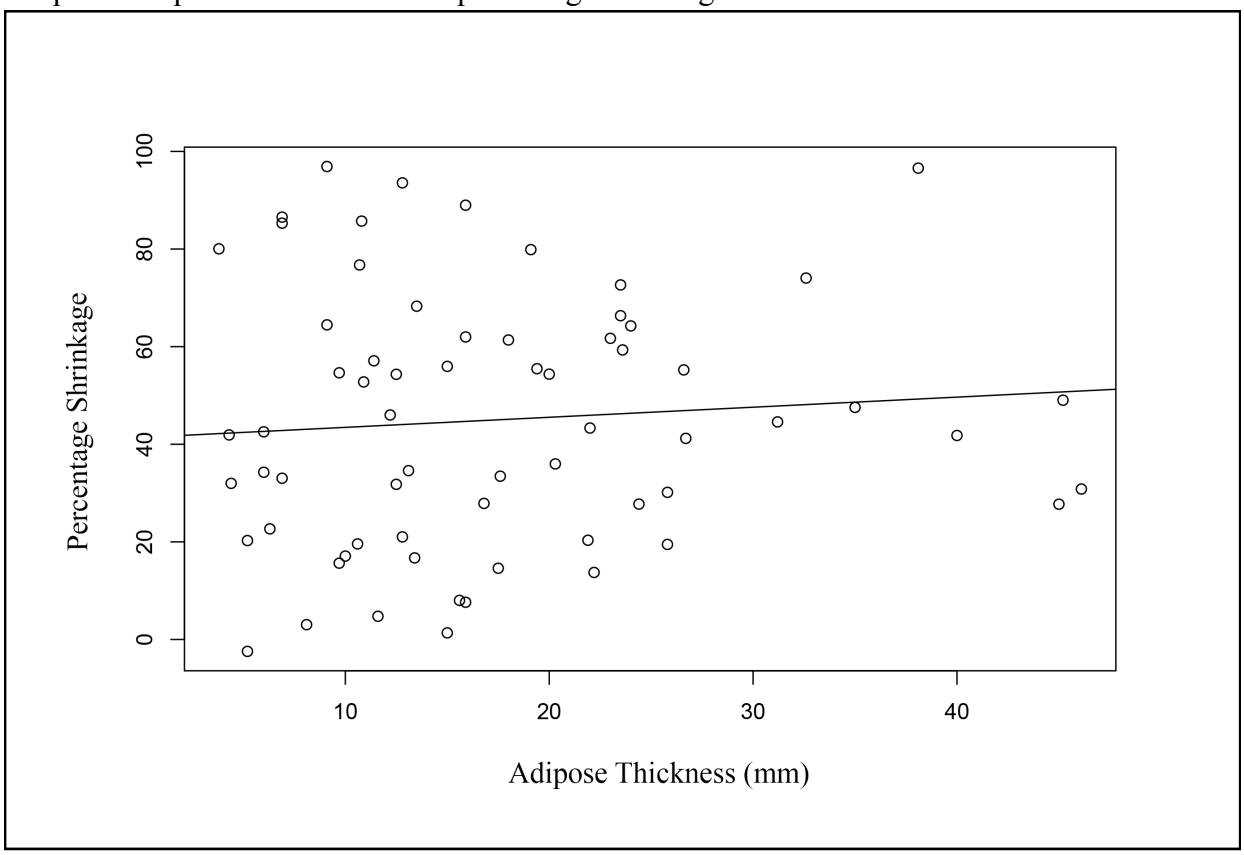
from HIFU treatment in patients treated in this study. The largest percentage volume shrinkage of a fibroid was 96% *(See results summary table).*

Results summary table:

	Minimum	Mean with 95% Confidence Interval	Maximum	Range
Adipose tissue thickness	3,8mm	19,49mm (95% CI 14,86-19,73)	46,10mm	42.3mm
Pre treatment volume	6,28mL	176,21mL (95% CI 123,26-208,57)	1040mL	1033,72mL
Post treatment volume	0,79mL	109,20mL (95% CI 71,75-141,73)	709,63mL	708,84mL
Percentage shrinkage	-2,44%	44,93% (95% CI 38.21-51.14)	96,91%	99,35%

A table depicting the minimum, mean with confidence interval, the maximum, and the range of the adipose tissue thickness, the pre treatment volume, post treatment volume and percentage shrinkage.

Graph 1- Adipose thickness versus percentage shrinkage:

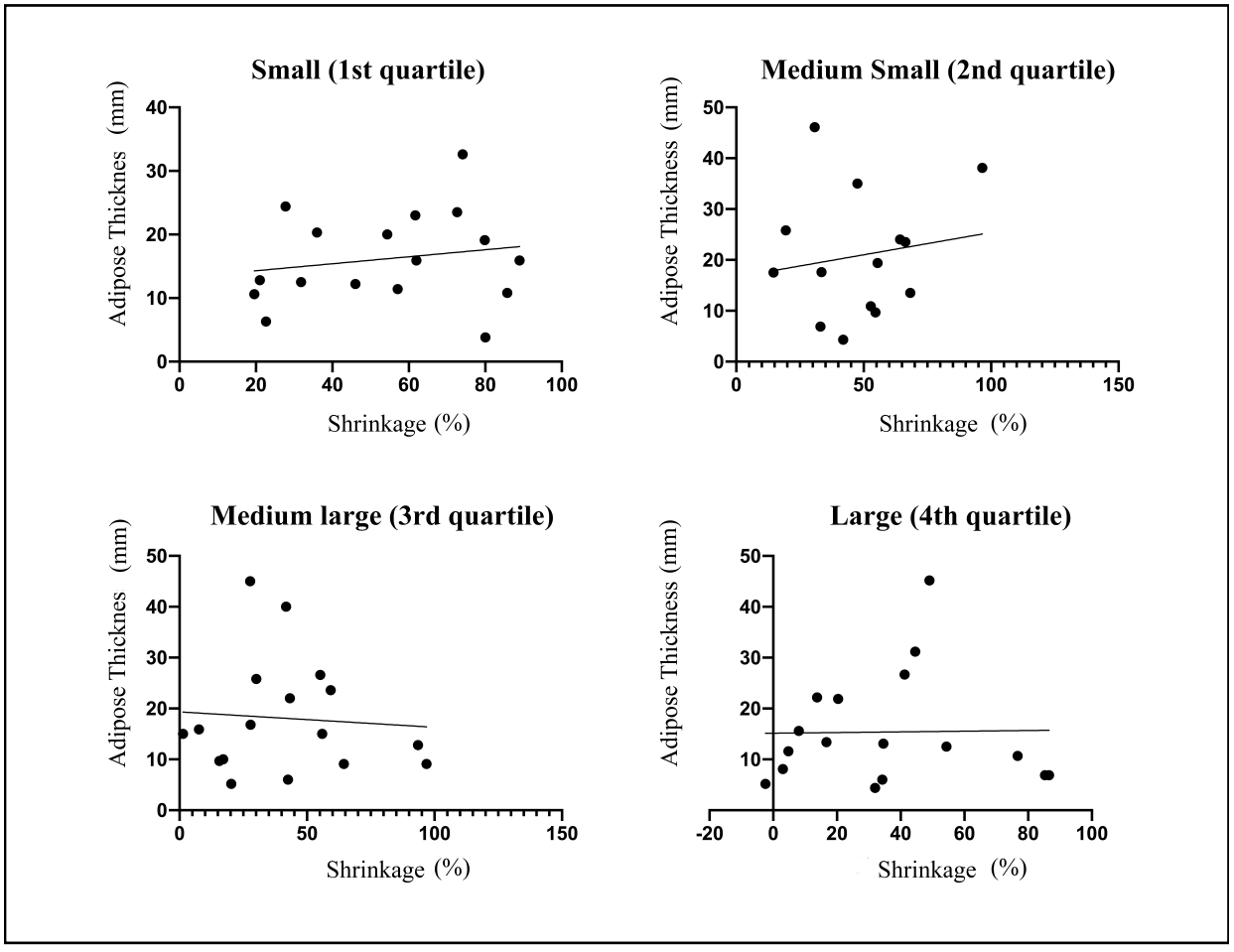


A linear regression model demonstrating a statistically insignificant relationship between adipose tissue and percentage shrinkage of a uterine fibroid after HIFU treatment ($p > 0.05$).

A linear regression model demonstrates that the relationship between adipose thickness and change in volume ratio is not significant ($p > 0.05$) (*see adipose thickness versus percentage shrinkage*

graph above). A further generalised linear model was generated where the change in size was the response variable with both adipose tissue thickness and pre-treatment fibroid size included as predictor variables (an interaction term was included). It was found that even after accounting for pre-treatment fibroid size, the adipose thickness was insignificant ($p > 0.05$). To represent this visually, we created 4 graphs dividing the fibroids into quartiles by their pre-treatment volume (*see quartile graphs below*). The fibroid volume was used to divide the fibroids into 4 equal groups. There is a positive trend seen in the medium-small group but this trend did not reach significance. This positive trend line is likely an artifact. The thickness of the adipose tissue that the HIFU beam travels through is not a good predictor of the percentage volume shrinkage of the uterine fibroid.

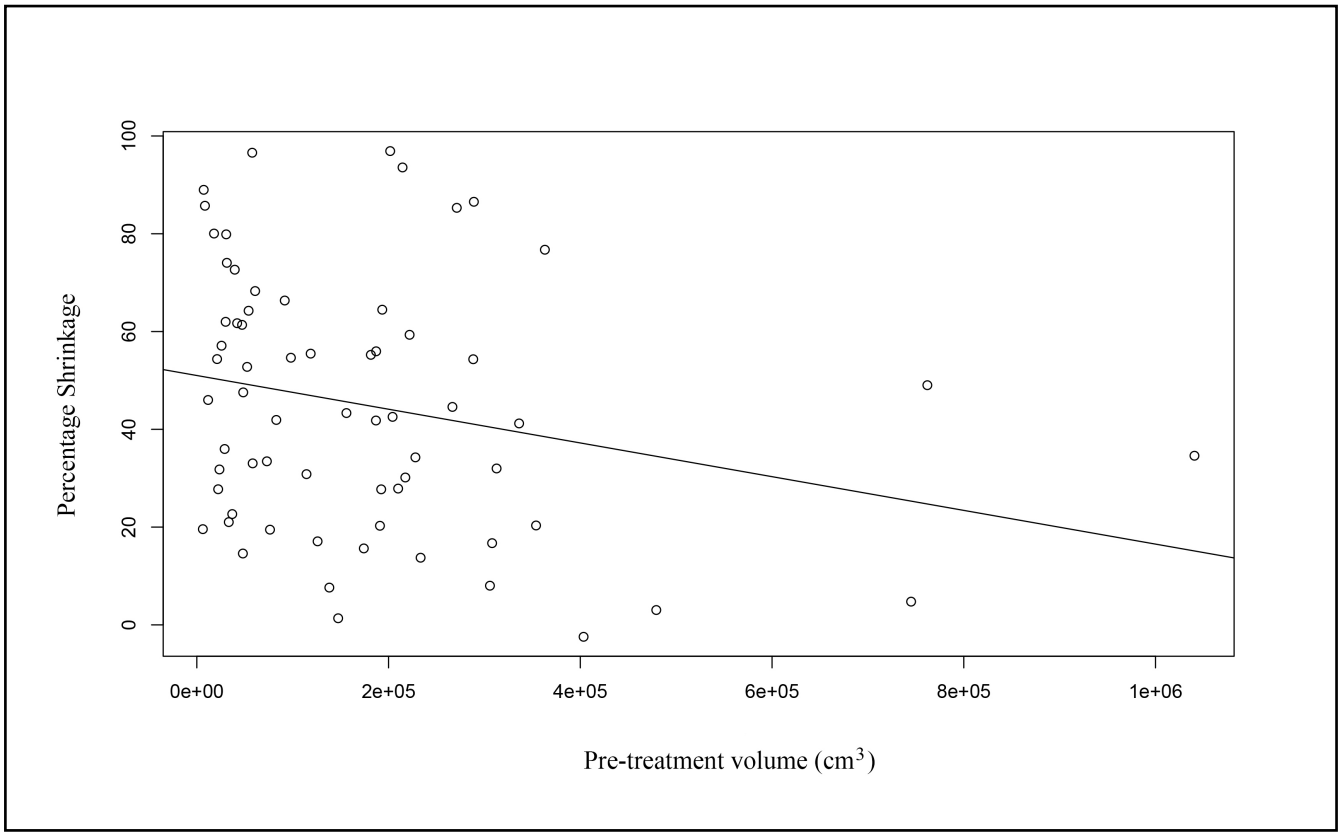
Graph 2- Quartile graphs:



In a generalised linear model where pre-treatment fibroid size divided into quartiles and included as a predictor variable, depicted above, it was found that the adipose thickness was not an important predictor of the treatment outcome ($p > 0.05$).

There is, however, a significant linear relationship between the pre-treatment volume of the uterine fibroid and the percentage shrinkage of the uterine fibroid. The correlation was determined with the input variable set as the pre-treatment volume of the uterine fibroid and the output variable the percentage shrinkage (*see pre-treatment volume versus percentage shrinkage graph below)*. A statistically relevant relationship was demonstrated where the uterine fibroids with a larger volume before USgHIFU treatment demonstrated a smaller percentage volume shrinkage than the uterine fibroids with a smaller volume before treatment ($p < 0,05$). In other words, the larger uterine fibroids did not shrink as much as the smaller uterine fibroids after treatment. This finding demonstrates that the pre-treatment volume is important when predicting fibroid shrinkage.

Graph 3 - Pre-treatment volume versus percentage shrinkage:



This linear regression model depicts a significant linear relationship between the pre-treatment volume of the uterine fibroid and the percentage shrinkage the uterine fibroid undergoes after HIFU treatment.

Discussion:

The primary goal of the HIFU ablation of uterine fibroids is to reduce or alleviate the symptoms of uterine fibroids by shrinking their size[7]. It can, therefore, be inferred that the percentage volume change ratio can be seen as an indication of the efficacy of the USgHIFU treatment as smaller uterine fibroids cause fewer symptoms. The study population achieved an average shrinkage rate of 44% within six to 12 months following the HIFU treatment. This is in line with standard predicted outcomes indicating that the treatment offered at CHBAH is successful[8]. The percentage volume shrinkages seen in this study would most likely result in symptomatic improvement although a qualitative questionnaire was not performed.

Addressing the primary outcome, this study determined that the thickness of adipose tissue that the HIFU beam travels through is not a good predictor of the treatment outcome. There was a weak correlation between the adipose thickness and the percentage volume shrinkage, but this relationship was not statistically significant. This is significant because an exclusion criterion for HIFU treatment at CHBAH is an adipose thickness of more than 6cm. This has been set in place because the chances of thermal damage to adipose tissue are increased with an increased adipose thickness that the HIFU beam travels though. It is important to investigate the incidence of this side-effect and its correlation with fat thickness as it is not documented in the available literature. Furthermore, this study suggests that the adipose tissue thickness does not affect the treatment outcome. In CHBAH, women who may benefit from this treatment but have an adipose tissue thickness of more than 6cm are not being offered this therapy as a treatment option. The reason for the adipose thickness exclusion criterion should be explored and potentially revised. This is important because patients with higher body mass indices are at higher risk of developing uterine fibroids [9]. Furthermore, USgHIFU uterine fibroid ablation offers a valuable and unique treatment option for females of childbearing age as it allows them to preserve their fertility[5].

The rationale for this exclusion criterion is that the energy of the HIFU beam is attenuated as it travels through tissue. There exists a proportional relationship between tissue thickness and beam scatter, with the potential for non-target organ heating and tissue damage. Although adipose thickness is a contributing factor, the distance of the probe to the fibroid being treated is more likely to predict whether patients will suffer this side-effect. A fibroid situated anteriorly is much closer to

the HIFU probe than a posteriorly located fibroid, and so the chances of a patient suffering from this side-effect in the case of the former are therefore lower.

Unfortunately, the exclusion criterion of patients with an adipose thickness larger than 6cm could contribute to bias in this study as we are unable to determine whether there would be a correlation between adipose tissue thickness and fibroid shrinkage in patients with a greater adipose tissue thickness than 6cm.

A secondary outcome finding suggests that the uterine fibroid volume before the HIFU treatment is a better predictor of the percentage shrinkage after the treatment. The HIFU treatment is less effective with a larger uterine fibroid. A possible explanation of this could be due to the HIFU ablation mechanism of action. The beam is focused on a single point and then moved in 3D space to cover the central volume of the uterine fibroid that is to be ablated. A margin of 1cm around the edges of the fibroid is left untreated to avoid damage to adjacent structures. This process is time-consuming and, for larger uterine fibroids, it may not be practical or feasible to ablate the entire fibroid. The larger area could also result in fewer points being covered. Fibroids that were larger than 16 weeks in size were excluded from the study due to the standard manufacturer's criteria for treatment eligibility.

Strengths and weaknesses:

The study sample size was restricted by our inclusion policy. A total of 236 patients who received treatment during the study period were excluded because they either did not receive an MRI scan within the allocated time frame after treatment or they did not receive an MRI scan after treatment at all. One of the two MRI scanners at the data collection site became dysfunctional during the allocated time frame for retrospective data collection and the machine was not repaired. The dysfunctional MRI scanner, therefore, put a strain on the MRI department and decreased the number of MRI scans that the department was able to perform. As a result, the non-urgent MRI lists were restricted and a decision was eventually made to stop MRI scans after treatment for women receiving USgHIFU fibroid ablation entirely.

Our study is also limited by its retrospective nature. Although the treatment was shown to be effective in the majority of our patients, it is unclear if this was directly as a result of the USgHIFU treatment or due to the natural progression of uterine fibroids as 7 to 40% of uterine fibroids may

regress within six months to three years[10]. Confounding factors have not been excluded from our analysis but this was a secondary outcome.

Although we found no association between adipose tissue thickness and fibroid volume shrinkage, we were not able to analyse the effect of HIFU in patients with an adipose thickness of greater than 6cm. There may be a threshold thickness above which HIFU becomes ineffective but we were not able to explore this further given the inherent exclusion criteria at CHBAH.

Recommendations:

This study suggests that there is no statistically significant relationship between the percentage volume shrinkage after HIFU treatment of a uterine fibroid and the adipose thickness the HIFU beam travels through. This study recommends that the selection criteria be revised at CHBAH to include patients with an adipose thickness of greater than 6cm. A suggestion is that the distance between the center of the uterine fibroid to be treated and the skin surface should be determined on pre-treatment MRI, and that measurement be set as the maximum distance acceptable for HIFU treatment. The maximum range of a HIFU beam is 12cm. An exclusion criterion of more than this distance should be used instead of an adipose thickness of greater than 6cm. This revision – which takes into account both the mechanism of the treatment and the potential side-effect of thermally damaging tissue – will assist by not excluding patients with an adipose thickness of 6cm who could benefit from this therapy.

The distance of the uterine fibroid from the ultrasound transducer is conceivably a better predictor of percentage fibroid shrinkage than adipose thickness. This is because the energy from the HIFU beam is attenuated by the tissues that it passes through. The uterine fibroid's location within the uterus (and therefore its distance to the anterior cutaneous surface) will likely have a greater effect on the efficacy of treatment than the adipose thickness that the HIFU beam travels through. Further research to determine whether there is a relationship between the distance from the center of the fibroid being treated to the cutaneous surface (where the HIFU transducer is situated) and the percentage shrinkage of the fibroid being treated may be helpful. A qualitative study on the patient's experience of the sensation of skin burning and the correlation of this with adipose tissue thickness would be helpful to understand whether a 6cm adipose tissue thickness is an appropriate exclusion criterion.

Conclusion:

USgHIFU uterine fibroid ablation provides a valuable treatment option for women of childbearing age who want to preserve their fertility and improve other aspects of their wellbeing. These study results suggest that the adipose tissue thickness that the HIFU beam travels through does not affect the percentage volume shrinkage of the treated uterine fibroid. This suggests that using adipose thickness as an exclusion criterion for patient selection could be resulting in patients who may benefit from this therapy being excluded from treatment unnecessarily.

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