

1 **High Intensity Focused Ultrasound in the treatment of breast Fibroadenomata**  
2 **(HIFU-F trial)**

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1 **High Intensity Focused Ultrasound in the treatment of breast Fibroadenomata**  
2 **(HIFU-F trial)**

3 Background: High intensity focused ultrasound (HIFU) is a non-invasive ablative  
4 technique utilising the application of high frequency ultrasound (US) pressure  
5 waves to cause tissue necrosis. This emerging technology is currently limited by  
6 prolonged treatment times. The aim of the HIFU-F trial was to perform  
7 circumferential HIFU treatment as a means of shortening treatment times.

8 Methods: A prospective trial was set up to treat 50 consecutive patients  $\geq 18$  years  
9 of age. Eligible patients possessed symptomatic fibroadenomata, visible on US.  
10 Patients  $\geq 25$  years of age required histological confirmation of the diagnosis.  
11 Primary outcome measures were reduction in treatment time, reduction in volume  
12 on US after 12 months and complication rates.

13 Results: HIFU treatment was performed in 51 patients (53 treatments) with a mean  
14 age of 29.8 years (SD 7.2 years) and diameter of 2.6 cm (SD 1.4 cm).  
15 Circumferential ablation reduced treatment times by an estimated 19.9 minutes (SD  
16 25.1 minutes), which is a 29.4% (SD 15.2%) reduction compared to whole lesion  
17 ablation. Volume reduction of 43.2% (SD 35.4%;  $p < 0.005$ , paired t-test) was  
18 observed on US at 12 months post-treatment. Local complications completely  
19 resolved at one month apart from skin hyper-pigmentation, which persisted in nine  
20 cases at three months, six cases at six months and six at 12 months.

21 Conclusion: Circumferential HIFU treatment for breast fibroadenomata is feasible  
22 to reduce both lesion size and treatment time. HIFU is a non-invasive alternative  
23 technique for the treatment of breast fibroadenomata ~~and required further~~  
24 [evaluation](#).

25 ISRCTN registration: 76622747

26 Keywords: High intensity focused ultrasound (HIFU); breast fibroadenomata  
27 (FAD); ablative technique; ultrasound; minimally invasive surgery.

28

1 **Introduction**

2 Fibroadenomata represent the most common benign breast lumps in women [1, 2].  
3 Fibroadenomata are diagnosed clinically as a palpable lump or incidentally during breast  
4 imaging [2, 3]. The diagnosis is based upon triple assessment (clinical examination,  
5 ultrasound (US) and a core needle biopsy (CNB)) [1, 2, 3]. Patients with asymptomatic,  
6 biopsy-proven breast fibroadenomata are generally managed by reassurance and no  
7 follow-up is deemed necessary. Symptomatic or rapidly growing lesions are suitable for  
8 excision, either surgically or radiologically (e.g. by vacuum-assisted mammotomy)  
9 although these techniques have limitations associated with an invasive procedure [1, 2,  
10 3].

11 High intensity focused ultrasound (HIFU) is a non-invasive ablative technique.  
12 During HIFU treatment, an US beam generated by a transducer propagates through soft  
13 tissue as a high-frequency pressure wave [4, 5]. The beam is focused onto the target tissue  
14 and the energy from the beam elevates the temperature of the targeted area to about 60 to  
15 95 degrees Celsius within seconds, leading to localised protein denaturation and  
16 coagulative necrosis - sparing the surrounding tissues from thermal damage [4, 5, 6].  
17 HIFU provides a completely non-invasive treatment, avoiding the potential complications  
18 associated with general anaesthesia and surgical excision [7].

19 Data from systematic reviews [8, 9] suggest that pilot studies of the treatment of  
20 breast cancer possess prolonged treatment times – of up to three hours – as a significant  
21 disadvantage with the current HIFU technique. The aim of the HIFU-F trial was to  
22 perform circumferential HIFU treatment in order to isolate the fibroadenoma from its  
23 blood supply, resulting in necrosis of the fibroadenoma and a reduced treatment time. In  
24 a recently published article [10], a protocol planned analysis of the first 20 patients  
25 included in this trial were compared to a control group of 20 patients who underwent only

1 an US scan at six months after their initial diagnosis to determine the natural change in  
2 fibroadenoma volume. The study demonstrated that circumferential ablation reduced the  
3 mean treatment time by 37.5% (SD 20.1%) compared to whole lesion ablation. In  
4 addition, a significant mean reduction in fibroadenoma volume of 43.5% (SD 38.8%;  
5  $p=0.016$ , paired t-test) in the HIFU group compared to 4.6% (SD 46.0%;  $p=0.530$ ) in the  
6 control group was demonstrated on US after six months. This mean reduction in volume  
7 between the two groups was statistically significant in favour of the HIFU group  
8 ( $p=0.002$ , grouped t-test). This article reports on HIFU treatment of all 51 patients who  
9 participated in the HIFU-F trial with a minimum follow-up of 12 months.

## 10 **Materials and Methods**

11 A prospective trial was set up to treat 50 consecutive patients with circumferential HIFU.  
12 Written informed consent was obtained from all patients prior to inclusion. This study  
13 was approved by the National Research Ethics Committee (13/LO/1221).

### 14 ***Patient selection***

15 As described in the article by Peek *et al.* [10], patients were eligible for the HIFU-F trial  
16 if they were at least 18 years of age and had been referred to the one-stop Breast Clinic  
17 at Guy's Hospital with a symptomatic fibroadenomata – defined as either a palpable  
18 lesion with or without pain developing from this lesion – which was visible on US.  
19 Patients of 25 years of age or older required confirmation of the diagnosis by US guided  
20 core needle biopsy, as per local Unit protocol. Patients were excluded if they had a  
21 fibroadenoma of less than 1 cm, had previous breast implants, were pregnant or lactating,  
22 had received any laser or radiation therapy to the ipsilateral breast, if epithelial atypia was  
23 seen on histopathology or if there was any suspicion of a phyllodes tumour. No other  
24 exclusions were applied.

1 A control group including 20 patients were consecutively recruited, without matching  
2 with the HIFU group, to determine the natural course in volume change of their  
3 fibroadenoma as assessed by US, six months after initial presentation. Patients were  
4 recruited using the same inclusion and exclusion criteria as the HIFU treatment group,  
5 demonstrating a definite treatment response in the HIFU group -[10].

6 All eligible patients were identified: (1) at the multi-disciplinary meeting (MDM),  
7 (2) as scheduled for surgical excision of a fibroadenoma or (3) as referred to the breast  
8 clinic with a symptomatic breast lump requesting treatment. All eligible patients were  
9 approached and received a patient information sheet if interested in participating in the  
10 HIFU-F trial.

11 Primary outcome measures were the change in treatment time compared to whole  
12 lesion ablation (estimation based on the computerised treatment plan) and the volume  
13 reduction on US after 12 months. Secondary outcomes were the complication rate and  
14 patient recorded outcome measures (palpability of the lump and pain pre- and post-  
15 treatment measured with visual analog scale (VAS)).

### 16 ***HIFU treatment***

17 Patients were treated using the US-guided-Echopulse device (Theraclion Ltd, Malakoff,  
18 France), which is CE marked for the treatment of breast fibroadenomata and thyroid  
19 nodules. The device contains a cooling and coupling disposable unit to cool the skin  
20 during treatment. Treatment was performed under real-time US guidance using a 7.5 to  
21 12 MHz diagnostic transducer and a 3.0 MHz therapeutic transducer with a central hole  
22 measuring 1.1 cm for the coaxial imaging transducer. Oval tissue volumes of  
23 approximately 0.9 cm in length and 0.2 cm in height and width were ablated. No updates  
24 in software or hardware were used during this study.

1 All patients received treatment as a day-case procedure using local anaesthesia  
2 (1.0% Lidocaine with adrenaline with or without 0.25 to 0.5% Bupivacaine, ratio 1:1).  
3 In cases where the fibroadenoma was located close (<0.5 cm) to the skin or pectoralis  
4 major muscle, local anaesthesia was injected between the fibroadenoma and the skin or  
5 muscle. Depending on the size of the breast and the position of the fibroadenoma, the  
6 patient was placed in either a supine or lateral position and the breast was fixed using an  
7 immobilisation system. Retro-areolar FAD were treated with the patient placed in a lateral  
8 position. After an US scan with a handheld probe was performed to locate the  
9 fibroadenoma, the device head was positioned on top of the fibroadenoma to outline the  
10 fibroadenoma and the skin in the radial and anti-radial view. For every radial slice, all  
11 treatment pulses were visualised and adjusted if required. The procedure started with a  
12 single pulse in the centre of the fibroadenoma in order to determine the correct energy  
13 level, identified by a hyper-echoic mark (HEM) visible during administration of the pulse.  
14 The HIFU device calculated the energy and power level of each pulse during treatment.  
15 In this study, only the circumference of the fibroadenoma was ablated; two  
16 circumferential rings were treated and the centre was deselected (figure 1). The Echopulse  
17 device treats only one central, top or bottom disc shaped target volume (curved or  
18 horizontal) during one treatment session. The optimal target volume was selected in order  
19 to avoid thermal damage to skin and pectoral muscle and to cover the most central part  
20 of the fibroadenoma. After the treatment, the patient's skin was observed for any  
21 treatment related changes. Patients were asked to provide a pain score after the procedure  
22 for pre-, intra- and post-treatment pain using a VAS scoring system between 0 to 10.  
23 Patients followed nurse-led discharge policies in accordance with local protocol.

24 Circumferential treatment time was recorded from the beginning of the first pulse  
25 to the end of the last pulse, along with the number of pulses delivered. The average time

1 to deliver a treatment pulse was calculated (including any delays between pulses due to  
2 prolonged treatment pauses) and used to estimate the total treatment time required to treat  
3 the whole lesion. In addition, total procedure time – including treatment planning and  
4 administration of local anaesthesia - was recorded.

### 5 ***Follow-up***

6 Patients were followed up at two weeks, three, six and 12 months - with a physical  
7 examination and US scan. Clinicians were blinded from the US results during physical  
8 examination but ultra-sonographers performing the scans were not blinded from previous  
9 scan results. The fibroadenoma volume was calculated using standard formulae in which  
10 V is the volume and A, B and C are the maximum diameters measured on US. [11]

$$11 \quad V = \frac{4}{3} * \pi * (\frac{1}{2} A) * (\frac{1}{2} B) * (\frac{1}{2} C)$$

### 12 ***Statistical analysis***

13 Statistical analysis was performed using IBM SPSS statistics version 23 (SPSS Inc.,  
14 Chicago, IL). A paired t-test and Wilcoxon signed rank test were used to determine the  
15 significance of the reduction in fibroadenomata volumes. The logarithms of the initial  
16 and final volumes were calculated and a Pitman-Morgan test was used to determine if the  
17 percentage in volume reduction varies within initial fibroadenomata volumes. An  
18 independent t-test was used to determine if the patients lost to follow-up had different  
19 initial volumes compared to those who completed follow-up and if there was a significant  
20 difference in volume reduction after 12 months between patients with two successfully  
21 treated rings and patients with less than two successfully treated rings.

22 A Mann-Whitney U-test was used to determine if there were any statistically  
23 significant differences in distribution between the patients with or without post-treatment  
24 hyper-pigmentation in terms of distance of fibroadenomata to the skin, distance of

1 fibroadenomata to the pectoralis major muscle, mean power and mean energy used during  
2 the treatment.

### 3 **Results**

#### 4 *Patient screening*

5 A total of 262 patients with fibroadenomata were screened between December 2013 and  
6 September 2015. 46.6% of these patients (122 of 262) were potentially eligible for HIFU  
7 treatment and were approached by our team of which 19.5% (51 of 262) were included  
8 in the trial and treated with HIFU and an additional 20 patients were included in the  
9 HIFU-F trials as control patients (7.6%, 20 of 262). Another 19.5% (51 of 262) were  
10 excluded as they were not contactable or did not want to participate in the trial, 18.3%  
11 (48 of 262) had incidental fibroadenomata, 23.7% (62 of 262) had fibroadenomata smaller  
12 than 1 cm, 3.1% (8 of 262) had giant fibroadenomata and 8.4% (22 of 262) were excluded  
13 due to our exclusion criteria.

#### 14 *Patient characteristics*

15 Circumferential HIFU treatment was performed in 51 patients (53 treatments) with a  
16 mean age of 29.8 years (SD 7.2 years) and a mean fibroadenomata size of 2.6 cm (SD 1.4  
17 cm). The mean distance between the skin and the fibroadenomata was 0.4 cm (SD 0.2  
18 cm) and between the pectoralis major and the fibroadenomata 0.5 cm (SD 0.3 cm). 45.3%  
19 of lesions (24 of 53) were located in the left and 54.7% (29 of 53) in the right breast.  
20 35.8% of lesions (19 of 53) were located in the upper outer quadrant, 18.9% (10 of 53) in  
21 the lower outer quadrant, 28.3% (15 of 53) in the upper inner quadrant and 17.0% (9 of  
22 53) in the lower inner quadrant (table 1a).



1 ***HIFU treatment***

2 Two circumferential rings were completed in 67.9% (36 of 53) of treatments, one ring in  
3 30.2% (16 of 53; only one or two treatment pulses were missing to complete the second  
4 ring in 22.6% (12 of 53)) and in 1.9% (1 of 53) no circumferential ring was completed  
5 and treatment had to be abandoned (table 1b). The central layer was treated in 94.3% (50  
6 of 53) of treatments, the bottom in 3.8% (2 of 53) and the top in 1.9% (1 of 53).

7 A mean of 16.6 ml (SD 8.3 ml) local anaesthesia was administered prior to the  
8 treatment. HIFU treatment was performed with a mean of 117.2 Joule per pulse (SD 29.6  
9 Joule per pulse; 52 treatments) and 29.1 Watt per pulse (SD 7.3 Watt per pulse; 52  
10 treatments). A mean volume of 0.9 cm<sup>3</sup> (SD 0.3 cm<sup>3</sup>; 52 treatments) was treated during  
11 each treatment session.

12 Out of 29 patients who were asked if they would have HIFU treatment for  
13 fibroadenomata again, 19 patients replied “yes”, seven patients replied “no” (because of  
14 pain in all cases) and three patients were indecisive.

15 ***Treatment times***

16 The mean procedural circumferential treatment time was 32.9 minutes (SD 9.8 minutes).  
17 Circumferential ablation shortened the estimated procedural treatment time by 19.9  
18 minutes (SD 25.1 minutes), which is a mean reduction of 29.4% (SD 15.2%) compared  
19 to whole lesion ablation. Total procedure time – including treatment planning and  
20 administration of local anaesthesia - was 66.0 minutes (SD 16.5 minutes).

21 ***Response to treatment***

22 Prior to HIFU treatment the mean fibroadenoma volume was 6.1 cm<sup>3</sup> (SD 12.1 cm<sup>3</sup>). At  
23 two weeks (49 patients (n)) the fibroadenomata showed a slight decrease in volume of  
24 12.3% (SD 27.1%; paired t-test  $p=0.007$ ; Wilcoxon signed ranks test  $Z=-2.91$ ,  $p=0.004$ )

1 to 5.7 cm<sup>3</sup> (SD 11.0 cm<sup>3</sup>). At three months (n=48) the decrease was 14.3% (SD 124.4%;  
2  $p=0.002$ ;  $Z=-3.87$ ,  $p<0.005$ ) to 3.5 cm<sup>3</sup> (SD 4.6 cm<sup>3</sup>). At six months (n=42) a reduction  
3 of 35.0% (SD 102.8%;  $p<0.005$ ;  $Z=-4.47$ ,  $p<0.005$ ) to 2.8 cm<sup>3</sup> (SD 4.3 cm<sup>3</sup>) was seen.  
4 At 12 months (n= 40) a reduction in volume of 43.2% (SD 35.4%;  $p<0.005$ ;  $Z=-4.65$ ,  
5  $p<0.005$ ) to 3.0 cm<sup>3</sup> (SD 5.3 cm<sup>3</sup>) was seen (figure 2+3, table 1).

6 A Pitman-Morgan test showed that large fibroadenomata do not decrease by as  
7 large a percentage of volume as small fibroadenomata (figure 4). In addition, comparing  
8 the patients who completed follow-up with those who were lost to follow-up, it was seen  
9 that there was no statistical difference in initial fibroadenomata volume (independent t-  
10 test, unequal variances,  $t(18)=0.282$ ,  $p=0.781$ ). No significant difference was seen  
11 between the reductions in fibroadenomata volumes after 12 months for patients with one  
12 or two treatment rings treated (independent t-test, unequal variances,  $t(26)=0.152$ ,  
13  $p=0.880$ ).

14 All patients were able to feel their fibroadenoma prior to treatment. A total of  
15 24.5% of patients (13 of 53) could no longer feel the fibroadenoma after treatment, in  
16 11.3% (6 of 53) this data was not available and 64.2% (34 of 53) were still able to feel a  
17 residual lump – although reduced in size. An increase in volume was seen in nine patients  
18 at 12 months follow-up. A total of three patients decided to undergo surgery after follow-  
19 up (figure 5) due to a lack of response on US. On histopathology, residual fibroadenoma  
20 tissue was seen with areas of fibrosis and fat necrosis.

### 21 *Pain symptoms*

22 During treatment, the maximum pain felt by patients scored 7.1 (SD 2.6) on a 0-10 VAS  
23 score. [If the application of a sonication was paused due to pain, the sonication and](#)  
24 [treatment were only completed with consent of the patient. In the single abandoned](#)

1 [treatment consent to continue treatment was not given.](#) Immediately after treatment pain  
2 was scored 1.6 (SD 1.8).

3         Pre-treatment a total of 21 patients had pain at the site of the fibroadenoma (VAS  
4 score 1.5 (SD 2.7)). Two weeks post-treatment, 11 patients no longer experienced any  
5 pain and two patients developed pain from the area of the fibroadenoma. At three months  
6 pain was reduced in 15 patients, one patient had recurrent pain, an additional two patients  
7 developed pain and one of two patients who developed pain at two weeks follow-up no  
8 longer felt any discomfort. At six months, 15 patients were pain free, the patient with  
9 recurrent discomfort still had pain near the FAD and all but one patient who developed  
10 pain post-treatment were now pain free. At 12 months, 14 patients with pre-treatment  
11 pain were pain free, all but one patient who developed post-treatment pain were now pain  
12 free and the patient with recurrent discomfort still had pain near the FAD.

### 13 ***Local complications***

14 At two weeks post-treatment, bruising of the skin (n=15 patients), skin erythema (n=12),  
15 skin numbness (n=3) and single cases of hypo-pigmentation, hyper-pigmentation, skin  
16 burns, skin blisters, skin dimpling and pain in the ipsilateral axilla were reported. At three  
17 months post-treatment only one case of skin erythema persisted and at 12 months one  
18 case of skin numbness persisted.

19         Skin hyper-pigmentation was observed in nine and six cases at three and 12  
20 months respectively (figure 6). There was no significant difference between the distance  
21 from the fibroadenoma to the skin and pectoralis major and the occurrence of hyper-  
22 pigmentation (p=0.748 and p=0.969, respectively). No significant difference was  
23 identified between mean power and energy levels used during the treatments and the  
24 occurrence of hyper-pigmentation (p=0.461 and p=0.511, respectively).

## 1 **Discussion**

2 Our study has shown that with circumferential HIFU treatment, a treatment time  
3 reduction of 29.4% (SD 15.2%, 32.9 minutes (SD 9.8 minutes)) and a fibroadenoma  
4 volume reduction of 43.2% (SD 35.4%) after 12 months was achieved. The combination  
5 of circumferential treatment and performing this treatment under local anaesthesia  
6 resulted in a treatment, which reduced the fibroadenoma volume but did not make the  
7 lump non-palpable in the majority patients (64.2%; 34 of 53).

8 This study is the largest cohort of patients with benign breast lesions treated with  
9 HIFU. Circumferential HIFU treatment showed a mean volume reduction of 43.2% (SD  
10 35.4%) after 12 months, an improvement compared to the 35.0% (SD 102.8%) reduction  
11 seen at six months, suggesting that the treatment effect continues up to 12 months post-  
12 treatment. Recently, several trials have been published treating fibroadenomata.  
13 Kovatcheva *et al.* [12] published on 42 women with 51 fibroadenomata who underwent  
14 whole lesion ablation using US guided HIFU and found a 72.5% reduction in volume  
15 after 12 months follow-up. The mean treatment time was 118 minutes and at 12 months,  
16 only one patient with asymptomatic subcutaneous induration was seen. Cavallo  
17 Marincola *et al.* [13] performed whole lesion US guided HIFU on ten patients and showed  
18 a 50% reduction after three months follow-up and no adverse events. The mean treatment  
19 time from first to last pulse was 57.2 minutes and the mean procedure time was 136  
20 minutes. These studies suggest that whole lesion ablation might be more effective than  
21 circumferential ablation but there are no comparative studies.

22 Treatment times were reduced by 29.4% and the total amount of time the patient  
23 spent in the treatment room (procedure time) was just over an hour. This treatment  
24 duration is more acceptable to patients than the one to three hour treatment times  
25 described for whole tumour ablation, traditionally seen [8, 9].

1 ~~Circumferential HIFU treatment showed a mean volume reduction of 43.2% (SD~~  
2 ~~35.4%) after 12 months, an improvement compared to the 35.0% (SD 102.8%) reduction~~  
3 ~~seen at six months, suggesting that the treatment effect continues up to 12 months post-~~  
4 ~~treatment. Volume reduction may have plateaued due to the reduced amount of necrosis~~  
5 ~~after treatment compared to whole lesion ablation. The epicentre of the fibroadenoma~~  
6 ~~might not have been necrosed completely as the treatment was unsuccessful in treating~~  
7 ~~the centre. The Circumferential HIFU treatment aims to cut off the blood supply and if~~  
8 this is not successful, the reduction might not be as significant as expected. An increase  
9 in volume was seen in 15 patients at two weeks, which can be explained by inflammation  
10 and oedema causing difficulty in determining the size of the fibroadenoma. An increase  
11 in volume was seen in nine patients at 12 months, which might be due to an incomplete  
12 ablation of two circumferential rings. In some patients, an increase of over 100% was  
13 seen which reduced to a decrease or milder increase in volume at the next follow-up. This  
14 might be as a result of unclear borders caused by defragmentation of the fibroadenoma,  
15 leading to an over-estimation of the size. Due to this difference in response to treatment,  
16 patient selection is very important. Patients should be made aware of this gradual decrease  
17 in volume compared to the instant and complete removal of the lesion with surgical  
18 excision. Patients might otherwise become anxious about the persistence of a lesion.

19 ~~In our study, 13 patients were lost to follow up, 3.9% (2 of 53) due to surgical~~  
20 ~~excision of the FAD prior to end of follow up and 21.6% (11 of 53) were no longer~~  
21 ~~contactable for the study. Ou *et al.* [14] performed a study on the lost to follow up~~  
22 ~~numbers in high level evidence based studies related to benign prostatic enlargement and~~  
23 ~~included 41 studies. After 12 months an average lost to follow up of 12% was found in~~  
24 ~~39 studies. Our numbers are higher than reported in this study reflecting higher lost to~~  
25 ~~follow up rates in patients with benign breast disease.~~

1 HIFU treatment does seem particularly effective for pain management as only  
2 three out of 21 patients with pre-treatment pain still felt pain from the area of the lump  
3 after 12 months. This could be due to treatment pulses being administered to local sensory  
4 pain receptors, hence why locations where patients initially had pain were no longer  
5 painful following subsequent treatment pulses. Patients who presented with pre- or inter-  
6 treatment pain however would like to have the treatment again if they found another  
7 fibroadenoma.

8 The most common local complication found during this trial was altered skin  
9 pigmentation. In some cases, the altered pigmentation was not noticeable by the patients;  
10 ~~but~~ nevertheless this is a complication, which was reported more often within our study  
11 than any other studies. This might be due to a higher level of cosmesis expected by the  
12 reviewing clinicians. The patients included had fibroadenomata closely located to the skin  
13 and this might be a cause for the hyperpigmentation due to the skin being heated more  
14 than initially expected even though the skin was cooled by the treatment probe. However,  
15 no correlation could be found between the location of the fibroadenoma to the skin,  
16 location of the fibroadenoma to the pectoralis major muscle, energy level used during  
17 treatment and power level used during treatment and the incidence of skin hyper-  
18 pigmentation. Neither was a darker pigmented skin a risk factor for altered pigmentation  
19 due to HIFU treatment.

20 Our study adds to the existing published evidence confirming that HIFU is a  
21 viable alternative option for the treatment of fibroadenomata. Further clinical  
22 implementation and cost-effectiveness analysis is required. Also, aesthetic outcome in  
23 management of symptomatic fibroadenomata is very important in younger women.  
24 Therefore, patient reported outcome measures (PROMS) should also be considered in  
25 order to evaluate aesthetic benefits for patients.

1           The initial aim was to recruit 50 control patients in order to compare volume  
2 reduction within the HIFU group with the control group. However, initial assessment of  
3 20 HIFU patients versus 20 control patients showed a statistically significant difference  
4 ( $p=0.002$ , grouped t-test) between these two groups after six months, and therefore it was  
5 decided to stop recruitment of the control group. [10]

6           The immediate, future research evaluation of HIFU would be progression to the  
7 treatment of small [\(with a diameter of 1 to 3 cm\)](#), good prognostic, screen-detected breast  
8 cancers [which should aim to demonstrate consistent and complete pathological ablation](#).  
9 These could be feasibly treated in short timeframes under local anaesthetic. The HIFU  
10 system could also potentially allow US-guided axillary management of suspicious nodes  
11 - in keeping with the emergence of increasing axillary conservatism. This application will  
12 be bolstered by continual technological advancements from manufacturers to enhance  
13 resolution and allow multiple treatment sites during the procedure. [However, the first step](#)  
14 [should be the standardisation of HIFU treatment for fibroadenomata in the clinical setting](#)  
15 [before breast cancer treatment is evaluated within clinical studies](#).

## 16 **Conclusion**

17 Circumferential HIFU treatment for breast fibroadenomata is feasible to reduce both  
18 lesion size and treatment time. HIFU is a non-invasive alternative technique for the  
19 treatment of breast fibroadenomata and required further evaluation.

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18 **Disclosure statement**

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- 1 Table 1. a) Patient and b) HIFU treatment characteristics (SD: standard deviation).
- 2 Table 2. Fibroadenomata volumes over time measured with ultrasound (mean (standard  
3 deviation)).
- 4 Figure 1. HIFU treatment planning showing the two circumferential treatment rings  
5 (green) and the deselected centre of the fibroadenoma (grey).
- 6 Figure 2. Change in fibroadenomata volume on ultrasound over time by patient (n) in  
7 percentage reduction.
- 8 Figure 3. Ultrasound images of three patients showing change in volume over time; pre-  
9 treatment (a-c), two weeks (d-f), three months (g-i), six months (j-l) and 12 months (m-  
10 o) follow-up.
- 11 Figure 4. Boxplot of the logarithm of the fibroadenoma volume as seen on ultrasound at  
12 each follow-up moment (1: pre-treatment, 2: two weeks, 3: three months, 4: six months  
13 and 5: 12 months follow-up, °: outliers).
- 14 Figure 5. Ultrasound images (pre-treatment - 22\*12\*12 mm, two week follow-up -  
15 19\*8\*10 mm and three months follow-up - 19\*8\*10 mm) showing no change in volume  
16 and histopathology outcome of a patient who underwent surgical excision three months  
17 after HIFU treatment.
- 18 Figure 6. Complications recorded during the study (l) skin burn at two weeks and (r)  
19 hyperpigmentation at three months.