# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

## Interventional procedure overview of high-intensity focused ultrasound for symptomatic breast fibroadenoma

A fibroadenoma is a very common benign (not cancer) breast condition, the commonest symptom being a lump. If the lump becomes very large or painful, it can be removed using traditional or keyhole surgery. This procedure involves using high frequency sound waves that heat up the tissues in the lump. The aim is to reduce its size over time and possibly completely destroy it.

## Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

## Date prepared

This IP overview was prepared in November 2016.

## Procedure name

- High-intensity focused ultrasound for symptomatic breast fibroadenoma

## Specialist societies

- British Society of Interventional Radiology
- Royal College of Radiologists
- Royal College of Surgeons
- British Society of Breast Radiology

- The Association for Cancer Surgery
- British Association of Plastic Surgeons
- Section of Breast Surgeons at the Royal College of Surgeons.

# Description

## *Indications and current treatment*

Breast fibroadenomas are common benign masses that often develop during puberty, although they can occur in women of any age. The condition is rare in men. Simple fibroadenomas are usually 1–3 cm in size but giant fibroadenomas can be over 5 cm. They do not usually increase in size and some may disappear overtime. The condition is diagnosed by breast examination and ultrasound or mammography. A needle core biopsy can be used for histological confirmation. Fibroadenomas are usually painless but can become painful and cause deformity.

If a fibroadenoma is asymptomatic, it does not need to be treated and no follow-up is necessary. However, any growth or other changes to the fibroadenoma should be reported. When symptomatic, fibroadenomas can be removed surgically or by vacuum-assisted mammotomy, which can be done under general or local anaesthesia.

## *What the procedure involves*

High-intensity focused ultrasound (HIFU) for breast fibroadenomas is a minimally invasive thermoablative technique that can be done at an outpatient clinic under local anaesthesia and sedation. A focusing ultrasound device delivers the treatment and allows for simultaneous imaging of the treatment area. The technology uses sound waves that propagate through the tissues, generating local heat and inducing coagulative necrosis, protein denaturation and cellular destruction. A strong acute inflammatory response follows. Remodelling of the chronic inflammatory response lasts for up to 3 months and involves cellular regeneration, proliferation, migration and removal of debris.

Tumour size reduction should happen gradually with no need for further intervention.

# Literature review

## *Rapid review of literature*

The medical literature was searched to identify studies and reviews relevant to HIFU for symptomatic breast fibroadenoma. The following databases were

searched, covering the period from their start to 8 November 2016: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

**Table 1 Inclusion criteria for identification of relevant studies**

| Characteristic | Criteria |
|---|---|
| Publication type | Clinical studies were included. Emphasis was placed on identifying good quality studies.<br>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.<br>Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature. |
| Patient | Patients with symptomatic breast fibroadenoma. |
| Intervention/test | High-intensity focused ultrasound. |
| Outcome | Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy. |
| Language | Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base. |

## *List of studies included in the IP overview*

This IP overview is based on 121 patients from 4 case series[1, 3, 4] and 1 non-randomised controlled trial[2].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

## Table 2 Summary of key efficacy and safety findings on high-intensity focused ultrasound for symptomatic breast fibroadenoma

## Study 1 Kovatcheva R (2015)

**Details**

| | |
|---|---|
| Study type | **Case series** |
| Country | Bulgaria, France |
| Recruitment period | 2011 to 2013 |
| Study population and number | n=**42** (51 fibroadenomas) |
| Age and sex | Mean 32 years, females |
| Patient selection criteria | Women with fibroadenomas in1 or both breasts. Pregnant or lactating women were excluded. Other exclusion criteria were microcalcifications within the lesion at mammogram, history of breast cancer, previous laser or radiation therapy and breast implants in the same breast.<br>Technical criteria included: fibroadenoma size and distance behind the focal point ≥10mm (to eliminate exteriorisation of the focal energy and damage of vulnerable structures behind it); distance between the skin and the fibroadenoma anterior border ≥5mm, to prevent skin burn; distance between the skin and the fibroadenoma posterior border ≤23mm, as a limit of accessibility for treatment with HIFU. |
| Technique | Forty two women with 51 fibroadenomas diagnosed with core needle biopsy with histological confirmation were selected for HIFU. The procedure was done on the outpatient department under conscious sedation. Fibroadenoma visualisation was done with high-resolution real-time ultrasonography and colour doppler using a 7.5 to 10 MHz linear transducer. Pain after the procedure was assessed using a VAS. |
| Follow-up | **12 months** |
| Conflict of interest/source of funding | The study was supported by Theraclion SAS (Paris, France) which is the manufacturer of the EchoPulse system used in the study. |

**Analysis**

**Follow-up issues**:

**Study design issues**: The study was done at 4 centres

**Study population issues**: Five women had more than 1 fibroadenoma treated: 2 women with 1 fibroadenoma in each breast, 2 women with 3 fibroadenomas (2 in 1 breast and 1 in the other), and 1 woman with 4 fibroadenomas (3 in 1 breast and 1 in the other). Eleven women had a personal history of breast surgery for fibroadenoma.

Eight of the 51 fibroadenomas were treated a second time between month 3 and month 9 of follow-up. The woman with 4 fibroadenomas and 1 of the women with 3 fibroadenomas were treated in 2 sessions: 1 for the lumps in the same breast and a second for the lesion in the other breast.

**Other issues:** None.

**Key efficacy and safety findings**

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 42 (51 fibroadenomas)<br><br>
84% (43/51) fibroadenomas treated only once<br>
8% (8/51) fibroadenomas treated in 2 sessions<br><br>
Average treatment time: 118 min (60 to 255 min)<br>
Mean fibroadenoma volume at baseline: 3.89ml<br><br>
<table>
<tr><th>Follow-up</th><th>Mean volume reduction</th><th>P value</th></tr>
<tr><td>2 months</td><td>33% (±19%)</td><td>-</td></tr>
<tr><td>6 months</td><td>59% (±18%)</td><td><0.001</td></tr>
<tr><td>12 months</td><td>73% (±17%)</td><td><0.001</td></tr>
</table>
<br>
<table>
<tr><th>Follow-up</th><th>Volume reduction</th><th>% of fibroadenomas</th></tr>
<tr><td>2 months</td><td>30%</td><td>63% (29/46)</td></tr>
<tr><td>6 months</td><td>50%</td><td>67% (32/48)</td></tr>
<tr><td>12 months</td><td>60%</td><td>87% (40/46)</td></tr>
</table>
<br>
<u>Vascularisation</u> (absent)<br>
<table>
<tr><td>2 months</td><td>54% (28/51)</td></tr>
<tr><td>6 months</td><td>64% (33/51)</td></tr>
<tr><td>12 months</td><td>67% (34/51)</td></tr>
</table>
<br>
<u>Pain reduction</u><br>
Discomfort complaints at baseline: 61% (31/51)<br>
Discomfort reduction was absolute in 100% of patients.<br><br>
Pain complaints at baseline: 35% (18/51)<br>
Pain reduction was absolute in 100% of patients.
</td><td>
<u>Pain</u><br>
No need for analgesic drugs post procedure.<br>
VAS post procedure = 29.7±27.5 mm (0 to 80mm)<br><br>
<u>Cosmetic deformity</u><br>
Superficial skin burn with blistering - 6% (3/51)<br>
Hyperpigmentation – 2% (1/51)<br>
Subcutaneous induration – 2% (1/51)<br><br>
All side effects were transient and resolved without treatment with exception of the induration that persisted at the end of the study.
</td></tr>
<tr><td colspan="2">Abbreviations used: HIFU, high-intensity focused ultrasound; VAS, visual analogue scale (0mm = no pain, 100mm = very severe pain).</td></tr>
</table>

## Study 2 Peek MCL (2016)

**Details**

| | |
|---|---|
| Study type | **Non-randomised controlled study** |
| Country | UK |
| Recruitment period | 2014 |
| Study population and number | n=**20** (treatment group), **20** (control group) |
| Age and sex | All female.<br>HIFU group – mean age 30.3 years (18-45 years)<br>Controls – mean age of 31.3 years (21-46 years) |
| Patient selection criteria | Women over the age of 18 with symptomatic breast fibroadenoma (palpable region being painful or not). Patients with more than 25 years of age needed a needle core biopsy for histological confirmation of fibroadenoma. Patients were excluded if they had fibroadenoma with 1 cm or less, were pregnant or lactating, had received ipsilateral laser or radiation therapy, had breast implants, if epithelial atypia was seen or if there was suspicion of phyllodes tumour. |
| Technique | Patients were identified in three ways: in a multidisciplinary meeting, patients were scheduled for a surgical removal, patients were referred to breast clinic. All patients were treated as a day-case under local anaesthesia.<br>The device contained a cooling and coupling disposable unit to cool the skin and prevent burning. Breast lesions were ablated under real-time US guidance using a 7.5–12 MHz diagnostic US transducer.<br>Procedure started with a single pulse in the centre of the fibroadenoma to determine the right energy level, identified by a hyper-echoic mark. During subsequent treatment pulses no hyperechoic mark was needed and pulses were not repeated when no mark was seen. Only the circumferential ring was ablated in this study, with the intention of isolating the fibroadenoma from its blood supply. Two circumferential rings around the FAD were treated and the centre of the FAD was deselected. Pain was assessed during and after the procedure using a VAS. |
| Follow-up | **6 months** |
| Conflict of interest/source of funding | None. |

**Analysis**

**Follow-up issues**: Follow-up at 2 weeks, 3 and 6 months consisted of physical and ultrasound examination.

**Study design issues**: The ultrasonographers in the US were not blinded but the consultant was blinded from the ultrasound results when doing the physical examination. Both the treatment and control groups were recruited consecutively.

**Study population issues**: Mean age and baseline mean volume were not statistically significantly different in both groups.

**Other issues**: None.

**Key efficacy and safety findings**

Efficacy

**n=40** (20 HIFU, 20 controls )

Baseline fibroadenoma mean volume

HIFU group - 7.3 $cm^3$ (0.4 to 44.0 $cm^3$)

Controls - 3.0 $cm^3$ (0.4 to18.7 $cm^3$)

Treatment time

Sonication time - 34.6 min (SD 10.5 min)

Total theatre time – 68.7 min (SD 16.2 min)

Technical efficacy

Two circumferential rings were successfully treated in 50% (10/20) patients.

One circumferential ring was treated in 45% (9/20) patients[1].

One patient was unable to tolerate a complete circumferential ring of pulses due to arm pain.

Treatment failure – 10% (2/20)[2]

Pain reduction – 75% (6/8)[3]

**Volume reduction**

HIFU group showed a statistically significant change in volume over a period of six months (p=0.002, grouped t-test; U=58, p=0.001).

Complete reduction of FA - 33% (4/20)[3]

| | HIFU group | | | | Controls | | | |
|---|---|---|---|---|---|---|---|---|
| | FA mean size ($cm^3$) | Mean reduction | p | Paired t-test[4] | FA mean size ($cm^3$) | Mean reduction | p | Paired t-test[4] |
| **Baseline** | 7.3 (SD 10.1) | NA | 0.082 | – | 3 (SD 4.1) | NA | 0.082 | – |
| **2 weeks** | 6.1 (SD 8.4) | 16.8% (SD 19%) | 0.021 | 0.007 | – | | | |
| **3 months** | 5 (SD 6.5) | 31% (SD 53%) | 0.022 | 0.11 | | | | |
| **6 months** | 4.6 (SD 6.4) | 44% (SD 39%) | 0.016 | 0.006 | 2.6 (SD 2.3) | 5% (SD 46%) | 0.53 | 0.709 |

[1]Five of these almost completed treatment of 2 rings apart from one or two pulses) due to patient movement or pain during treatment.

[2]Two patients had surgery post-HIFU due to absence of decrease in FAD at 12 months follow-up. In these women histology confirmed the presence of fibroadenomas. These had prominent signs of fibrosis.

[3]At 6 months follow-up.

[4]Kolmogorov-Smirnov test.

[5]Mann Whitney-Wilcoxon signed rank test.

Safety

Pain during treatment[4]

Discomfort or burning sensation - 90%(18/20)

VAS (mean) – 6.4 (SD 3.2)

Pain after treatment

VAS (mean) – 1.6 (SD 1.9)

Persistent pain – 10% (2/20)[5]

Cosmetic deformity

Ecchymosis – 45% (9/20)

Erythema – 30% (6/20)

Dimpling of the skin[6] - 5% (1/20)

First-degree skin burn - 5% (1/20)

Hyperpigmentation

- 3 months – 30% (6/20)
- 6 months – 20% (4/20)

Damage to adjacent structures

Numbness of the skin - 5% (1/20)

[4]Continuing treatment by moving to another part of the fibroadenoma was agreed in 17/18 patients.

[5]Pain resolved completely within 3 months

[6]Lump of thickening that feels different from the rest of the breast.

Abbreviations used: FA, fibroadenoma; HIFU, high-intensity focused ultrasound; SD, standard deviation; VAS, visual analogue scale (0 = no pain, 10 = very severe pain).

## Study 3 Marincola BC (2014)

### Details

| | |
|---|---|
| Study type | **Case series** |
| Country | Italy |
| Recruitment period | 2013 to 2014 |
| Study population and number | n=**10** (12 fibroadenomas) |
| Age and sex | Mean age 26 years (18 to 34), females |
| Patient selection criteria | Women with cytological/histological diagnosis of single or multiple fibroadenomas of at least 1.5 cm in diameter. |
| Technique | All procedures were done under local anaesthesia and conscious sedation. The ablation was ultrasound-guided. |
| Follow-up | **3 months** |
| Conflict of interest/source of funding | None |

### Analysis

**Follow-up issues**: None.

**Study design issues**: None.

**Study population issues**: Two patients had bilateral treatment.

**Other issues**: None.

### Key efficacy and safety findings

| Efficacy | Safety |
|---|---|
| n=**10**<br>Fibroadenoma diameter – Median 26.5 mm (19 to 44 mm)<br>Number of sonications – Mean 88 (54 to 148)<br>Total delivered energy - Mean 115.94 Joules/site<br><br><u>Procedure duration</u><br>Sonication time – 57.2 min (40 to 100 min)<br>Theatre time – Mean 136 min (80 to 210 min)<br><br><u>Volume reduction</u><br>At follow-up, all treated fibroadenomas showed a 50% reduction in diameter. | <u>Pain</u><br>During treatment – 0%<br>Follow-up – 0%<br>Mild swelling and hardness of the treated area was mentioned but no frequencies were reported. A non-steroidal anti-inflammatory was given in the first days after treatment to reduce swelling. |
| Abbreviations used: Min, minutes. | |

## Study 4 Hynynen K (2001)

**Details**

| | |
|---|---|
| Study type | **Case series** |
| Country | US |
| Recruitment period | |
| Study population and number | n=**9** (11 fibroadenomas) |
| Age and sex | Mean 29 years, females |
| Patient selection criteria | Women that were suitable to surgical resection of fibroadenoma but preferred HIFU instead. Inclusion criteria were having more than a 1.5-cm distance to the skin and rib cage from the sonication plane, and having histologic confirmation after large-core biopsy. Women who were pregnant, lactating, mammograms showing calcifications or contraindication for MR imaging were excluded. |
| Technique | Sonications were done with a clinical MR imaging–compatible ultrasound surgery system (GE Medical Systems, Milwaukee, Wisconsin). All procedures were done under local anaesthesia and conscious sedation under MR guidance.<br>Initially, a low-energy test pulse starting at 6–7 W was aimed within the target volume. The power was increased until the location of the focus was visible on the temperature-sensitive image. Pre-treatment and follow-up MR images of the breast were routinely obtained by using a dedicated breast coil. |
| Follow-up | **6 months** (median) |
| Conflict of interest/source of funding | GE Medical Systems provided the MR imaging–guided ultrasound system used in the experiments. |

**Analysis**

**Follow-up issues**: None.

**Study design issues**: Routine follow-up included clinical examination and MR imaging.

**Study population issues**: Two women had bilateral fibroadenomas. One fibroadenoma was treated twice.

**Other issues**: None.

**Key efficacy and safety findings**

| Efficacy | Safety |
|---|---|
| n=**9** (11 fibroadenomas)<br>Number of sonications – mean 60.2 (25 to 106)<br>Mean volume at baseline – 1.9 $cm^3$ (SD ±1.5 $cm^3$)<br><br>Treatment time for a 2-cm lesion was approximately<br>2 hours and for a 1-cm lesion, approximately<br>45 minutes<br><br><u>Technical failure</u> – 42% (5/12)[1]<br><br><u>Volume reduction</u><br>Volume reduction was achieved in 50% (6/12) of fibroadenoma treatments<br>Mean fibroadenoma volume was reduced to 1.3 $cm^3$ (SD 1.1 $cm^3$), p=0.01[2].<br><br>[1]Due to patient movement in 2 patients (in 1 of the patients it was not possible to refocus the fibroadenoma and treatment was abandoned), in 1 patient due to pain, in 1 patient due to deliberate administration of below threshold level of energy and in another patient due to excessive local anaesthetic anterior to the fibroadenoma.<br>[2]At 6 months follow-up. | <u>Pain</u><br>During treatment<br>None – 36% (4/11)<br>Slight – 36% (4/11)<br>Moderate – 18% (2/11)<br>Severe – 9% (1/11)<br><br>Mild pain up to 10 days after treatment – 8% (1/11)<br><br><u>Damage to adjacent structures</u><br>Most patients reported tenderness and oedema of the breast up to 10 days after treatment (frequencies not reported).<br>One patient developed an ecchymosis as result of needle biopsy.<br><br><u>Impact on future diagnosis</u><br>In the patient that had treatment abandoned due to movement and inability to refocus, a second treatment attempt was also unsuccessful. Targeting of the fibroadenoma was not possible due to fibrosis caused by the first treatment attempt.<br>Three patients had mammograms that did not report treatment related changes 4 years after HIFU. |
| Abbreviations used: HIFU, high-intensity focused ultrasound; MR, magnetic resonance; SD, standard deviation. | |

## Study 5 Kovatcheva R (2017)

**Details**

| | |
|---|---|
| Study type | **Case series** |
| Country | Bulgaria |
| Recruitment period | 2011 to 2015 |
| Study population and number | **n=20** women (26 fibroadenomas) |
| Age and sex | Mean 29 (±10.2) years |
| Patient selection criteria | Inclusion criteria:<br>- Over 18 years or age,<br>- Clinical diagnosis of breast fibroadenoma based on palpation,<br>- US examination alone for patients < 35 years of age, and mammography in addition for women older than 35 years,<br>- BI-RADS score ≤2,<br>- Histological confirmation after large-core biopsy using a 16-gauge needle size done at least 2 weeks before therapy and verified by 2 independent readers,<br>- Fibroadenoma larger than 1 mm, without macrocalcifications inducing a substantial shadowing and situated within the treatable area, which was 5 to 28 mm from the skin surface,<br>- The intended size of the ablation unit was 9 mm in length and 1.8–2.5 mm in width and the depth of each ablation unit was adjusted automatically to be centred with the antero-posterior diameter of the target,<br>- The rib cage had to be outside the treatment cone or at least 10 mm behind the focal point. Those criteria had to be fulfilled in treatment conditions, once the breast was immobilised and eventually compressed.<br><br>*Exclusion criteria:*<br>- Pregnant or lactating women,<br>- US suspicions for malignancy,<br>- History of breast cancer, history of laser or radiation therapy of the targeted breast,<br>- Women with breast implants. |
| Technique | Treatment done in an outpatient clinic in 1 single centre. Post-procedure pain was assessed using a VAS (0 = no pain to 100 = extreme pain) and adverse events were assessed. After the 6-month follow-up, patients completed a satisfaction questionnaire assessing symptoms and cosmetic changes (1 = no, 2 = low, 3 = high, 4 = complete satisfaction). |
| Follow-up | **2 years** |
| Conflict of interest/source of funding | None. |

**Analysis**

**Follow-up issues**: Follow-up visits were done at 1, 3, 6, 12 and 24 months. At 6-month follow-up, if the fibroadenoma volume reduced by less than 50% or its absolute volume exceeded 1.5 ml, a second ablation was done. All patients were followed-up.

**Study population issues**: There were 35% (7/20) women who had previously been operated for fibroadenoma on the same breast and 35% (7/20) had more than 1 fibroadenoma. Treatment was done in 1 session in 73% (19/23 of fibroadenomas (group 1) and in 2 sessions (6 to 7 months after) in 27% (7/26, group 2) of fibroadenomas. Fibroadenomas were statistically significantly larger at baseline in group 2 (8.14 ml [1.53–10.39] versus 1.82 [0.35–5.95] in group 1), groups were otherwise identical.

**Key efficacy and safety findings**

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>

**n=20 women (26 fibroadenomas)**

Fibroadenoma volume reduction compared to baseline (ml)

<table>
<tr><th></th><th>Group 1 (n=20)<br>(Treated once by HIFU)</th><th>Group 2 (n=7)<br>(Treated twice by HIFU)</th></tr>
<tr><td>Baseline size (median, range)</td><td>0.78 (0.35 to 2.24)</td><td>Before first ablation: 2.66 (0.52 to 3.01)<br>Before second ablation: 1.34 (0.65 to 2.24)</td></tr>
<tr><td>1 month (median, range)</td><td>1.44 (0.2 to 5.18), p<0.001</td><td>–</td></tr>
<tr><td>3 months (median, range)</td><td>–</td><td>4.70 (0.88 to 8.02), p=0.005</td></tr>
<tr><td>24 months (median, range)</td><td>0.35 (0.06 to 1.21), p<0.001</td><td>0.21 (0.09 to 1.66), p=0.003</td></tr>
</table>

Volume reduction was 95%in group 1 and 99% in group 2 at 24 months follow-up.

Patient satisfaction

<table>
<tr><td>Symptom disappearance</td><td>50% (10/20) high, 45% (9/20) satisfied completely, 5% (1/20) low</td></tr>
<tr><td>Cosmetic results</td><td>95% (19/20) satisfied completely, 5% (1/20) high</td></tr>
</table>

</td><td>

Pain

Mean pain score was 40.7 (± 24.6) after first session and 34.9 (±17.9) after the second treatment (p value not reported).

Mild to moderate tenderness up to 1 week after first treatment – 45% (9/20)

Mild to moderate tenderness up to 1 weeks after second treatment – 57% (4/7)

Subcutaneous oedema - 25% (4/20)

Mild to moderate erythema resolving within 1 week – 29% (2/7)

First-degree skin burn with hyperpigmentation visible after 6 months – 1/7

</td></tr>
<tr><td colspan="2">Abbreviations used: BI-RADS, breast Imaging and reporting data system; HIFU, high-intensity focused ultrasound; US, ultra-sound; VAS, visual analogue scale.</td></tr>
</table>

## *Efficacy*

### Clinical efficacy

In a case series of 42 women (51 fibroadenomas) treated by high-intensity focused ultrasound (HIFU), 63% (29/46) of the fibroadenomas had reduced in size by 30% at 2 months, 67% (32/48) had reduced by 50% at 6 months and 87% (40/46) had reduced by 60% at 12 months. The same study reported that vascularisation was absent in 54% (28/51), 64 % (33/51) and 67% (34/51) of the fibroadenomas at 2, 6 and 12 months respectively.[1]

In a non-randomised controlled study of 40 women, in which 20 were treated by HIFU and 20 were in a control group, fibroadenoma size was statistically significantly reduced by 17% at 2 weeks (standard deviation [SD] 19%, p=0.021), and by 31% at 3 months (SD 53%, p=0.022) in the HIFU group. In the same study, fibroadenoma size reduction was statistically significantly different in women treated by HIFU (44%, SD 39%, p=0.016) compared with women in the control group (5%, SD 46%, p=0.53) at 6-month follow-up; complete fibroadenoma reduction was reported in 33% (4/20) of women in the HIFU group at 12-month follow-up.[2]

In a case series of 10 patients treated by HIFU, fibroadenoma diameter was reduced by 50% in 100% (10/10) of patients at 3-month follow-up.[3]

In a case series of 9 patients treated by magnetic resonance (MR)-guided HIFU, fibroadenomas size was reduced to 1.3 $cm^3$ (mean, SD 1.1 $cm^3$) from a baseline of 1.9 $cm^3$ (mean, SD 1.5 $cm^3$) in 50% (6/12) of treatments at 6-month follow-up.[4]

In a case series of 20 patients, fibroadenoma size was statistically significantly reduced in patients treated only once by HIFU from 0.78 ml (0.35 to 2.24) at baseline to 0.35 ml (0.06 to 1.21, p<0.001) at 2-year follow-up, and in patients treated twice from 2.66 ml (0.52 to 3.01) to 0.21 ml (0.09 to 1.66, p=0.003) at 2-year follow-up.[5]

### Treatment failure

In the non-randomised controlled study of 40 women, 10% (2/20) of fibroadenomas treated by HIFU did not change in size at 6-month follow-up.[2]

### Technical efficacy

In the case series of 9 patients treated by MR-guided HIFU, technical failure was reported in 42% (5/12) of fibroadenoma treatments.[4]

### Pain reduction

In the case series of 42 women, 61% (31/51) of the fibroadenomas had caused discomfort before the procedure, which had resolved in 100% of the women at 12-month follow-up. In the same study, at baseline, 35% (18/51) of fibroadenomas were associated with pain, which had resolved in 100% of patients at 12-month follow-up.[1]

In the non-randomised controlled study of 40 women, complete pain reduction was reported by 6/8 women treated by HIFU at 6 months follow-up.[2]

### Patient satisfaction

In the case series of 20 patients treated by HIFU, for symptom disappearance, 45% (9/20) of patients were completely satisfied, and satisfaction was high in 50% (10/20) and low in 5% (1/20) of patients. In the same case series, for cosmetic results, 95% (19/20) of patients were completely satisfied and satisfaction was high in 5% (1/20) of patients.[5]

## *Safety*

### Pain during treatment

Discomfort or burning sensation assessed with a visual analogue scale (0=no pain, 10=very severe pain) was reported by 90% (18/20) of women (mean score 6.4; SD 3.2) treated by HIFU in a non-randomised controlled study of 40 women.[2]

Pain during treatment was reported as being slight in 36% (4/11), moderate in 18% (2/11) and severe in 9% (1/11) of the procedures, in the case series of 9 women treated by magnetic resonance-guided HIFU.[4]

**Pain after treatment**

Persistent pain assessed with a visual analogue scale (0=no pain, 10=very severe pain) was reported by 10% (2/20) of women (mean score 1.6 [SD 1.9] in the non-randomised controlled study of 40 women, within 3 months of treatment.[2]

Mild pain was reported by 1 woman after the treatment of 1/11 fibroadenoma in the case series of 9 women treated by MR-guided HIFU.[4]

Pain after treatment measured by a visual analogue scale (VAS, 0 = no pain to 100 = extreme pain) was 40.7 (± 24.6) after the first ablation and 34.9 (±17.9) after the second ablation (p value not reported), in the case series of 20 patients treated by HIFU.[5]

**Damage to adjacent structures**

Numbness of the skin was reported by 1 woman of 20 treated by HIFU in the non-randomised controlled study of 40 women.[2]

Mild to moderate tenderness was reported by 45% (9/20) of patients up to 1 week after the first HIFU session and by 57% (4/7) of patients, in the case series of 20 patients.[5]

**Cosmetic deformity**

*Skin burn*

Superficial skin burn with blistering was reported in 6% (3/51) of fibroadenomas after the procedure in a case series of 42 women (51 fibroadenomas) treated by HIFU.[1]

A first-degree skin burn was reported in 1 woman of 20 in the non-randomised controlled study of 40 women treated by HIFU.[2]

A first-degree skin burn with hyperpigmentation visible after 6 months was reported in 1 women of 7 in the case series of 20 women treated by HIFU.[5]

*Hyperpigmentation*

Hyperpigmentation of the skin was reported in 1 woman within days after the procedure in the case series of 42 women treated by HIFU.[1]

Hyperpigmentation of the skin was reported by 30% (6/20) of woman treated by HIFU at 3 months and 20% (4/20) at 6 months in the non-randomised controlled study of 40 women .[2]

*Subcutaneous induration or oedema*

Subcutaneous induration was reported in 1 woman of 42 at 12-month follow-up in the case series of 42 women treated by HIFU.[1]

Subcutaneous oedema was reported in 25% (4/20) of women in the case series of 20 women treated by HIFU.[5]

*Ecchymosis*

Ecchymosis was reported by 45% (9/20) of women in the non-randomised controlled study of 40 women treated by HIFU. [2]

*Erythema*

Erythema was reported by 30% (6/20) of women treated by HIFU in the non-randomised controlled study of 40 women.[2]

Mild to moderate erythema that resolved within 1 week was reported by 29% (2/7) of women, who had more than 1 fibroadenoma, treated by HIFU in the case series of 20 patients.[5]

*Dimpling of the skin*

Dimpling of the skin was reported by 1 woman of 20 treated by HIFU in the non-randomised controlled study of 40 women.[2]

### *Validity and generalisability of the studies*

- None of the studies reported a mean follow-up period greater than 12 months.[1]
- No randomised data was found in the literature.
- Some studies report fibroadenomas that were treated twice but it is not possible to isolate this data from the overall efficacy estimates.[1, 4]
- Methodology and duration of treatment was not homogeneous among studies.[2]

### *Existing assessments of this procedure*

There were no published assessments from other organisations identified at the time of the literature search.

### *Related NICE guidance*

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

**Interventional procedures**

Interstitial laser therapy for fibroadenomas of the breast. NICE Interventional Procedures Guidance 131 (2005). Available from https://www.nice.org.uk/guidance/ipg131

## Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are

considered voluminous, or publication would be unlawful or inappropriate. Four Specialist Advisor Questionnaires for high-intensity focused ultrasound for symptomatic breast fibroadenoma were submitted and can be found on the NICE website.

## Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

## Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

## Issues for consideration by IPAC

- One study on this procedure was published in Spanish in 1965. NICE IP methods exclude non-English language studies from consideration. This paper was excluded.
- Ongoing studies:

- NCT01422629 - High Intensity Focused Ultrasound (HIFU) to Treat Breast Fibroadenoma. Completed, not yet reported.
- NCT02488655 - Treatment of Breast Fibroadenoma with FastScan HIFU. Expected completion date: December 2017.
- NCT02011919 - Treatment of Breast Fibroadenoma with High Intensity Focused Ultrasound (HIFU. Expected conclusion date: December 2018.
- NCT02078011 - Treatment of Breast Fibroadenoma with High Intensity Focused Ultrasound (HIFU-FA-001. Expected conclusion date: October 2017.
- NCT01331954 - Treatment of Breast Fibroadenoma with High Intensity Focused Ultrasound (HIFU. Expected completion date: December 2017.
- NCT02139683 - Feasibility Study Assessing the Treatment of Fibroadenomata with a Circumferential Sonication Treatment with HIFU. Expected completion date: December 2017.

# References


1. Kovatcheva K, Gugliemina JN, Abehsera M et al. (2015) Ultrasound-guided high intensity focused ultrasound treatment of breast fibroadenoma – a multicentre experience. Journal of Therapeutic Ultrasound, 3:1-8
2. Peek MCL, Ahmed M, Scudder J et al. (2016) High intensity ultrasound in the treatment of breast fibroadenomata: Results from the HIFU-F feasibility study. International Journal of Hyperthermia (Online) http://dx.doi.org/10.1080/02656736.2016.1212278
3. Marincola BC, Amati G, Napoli A (2014) High-intensity focused ultrasound in breast pathology: Non-invasive treatment of benign and malignant lesions. Expert Review of Medical devices, online: 1-9
4. Hynynen K, Pomeroy O, Smith DN et al. (2001) MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: a feasibility study. Radiology 219:176-185.
5. Kovatcheva R, Zaletel K, Vlahov J et al. (2017) Long-term efficacy of ultrasound-guided high-intensity focused ultrasound treatment of breast fibroadenoma. Journal of Therapeutic Ultrasound 5:1.

# Appendix A: Additional papers on high-intensity focused ultrasound for symptomatic breast fibroadenoma

There were no additional papers identified.

# Appendix B: Related NICE guidance for high-intensity focused ultrasound for symptomatic breast fibroadenoma

| Guidance | Recommendations |
|---|---|
| Interventional procedures | **Interstitial laser therapy for fibroadenomas of the breast. NICE Interventional Procedures Guidance 131 (2005).**<br>1.1 Current evidence on the safety and efficacy of interstitial laser therapy for fibroadenomas of the breast does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research.<br><br>1.2 Clinicians wishing to undertake interstitial laser therapy for fibroadenomas of the breast should take the following actions.<br><br>• Inform the clinical governance leads in their Trusts.<br>• Audit and review all patients having interstitial laser therapy for fibroadenomas of the breast.<br>• Ensure that patients understand the benign nature of fibroadenomas, and that watchful waiting is an option. Patients should be provided with clear written information and use of the Institute's information for the public is recommended.<br><br>1.3 This procedure should be carried out only within specialist breast services.<br><br>1.4 Publication of safety and efficacy outcomes will be useful. The Institute may review the procedure upon publication of further evidence. |

# Appendix C: Literature search for high-intensity focused ultrasound for symptomatic breast fibroadenoma

| Databases | Date searched | Version/files |
|---|---|---|
| Cochrane Database of Systematic Reviews – CDSR (Cochrane) | 05/06/2017 | Issue 5 of 12, May 2017 |
| Cochrane Central Database of Controlled Trials - CENTRAL | 05/06/2017 | Issue 5 of 12, May 2017 |
| HTA database (Cochrane) | 05/06/2017 | May 2017 |
| MEDLINE (Ovid) | 05/06/2017 | 1946 to May Week 4 2017 |
| MEDLINE In-Process (Ovid) | 05/06/2017 | June 02, 2017 |
| EMBASE (Ovid) | 05/06/2017 | 1980 to 2017 Week 23 |
| PubMed | 05/06/2017 | - |
| JournalTOCS [for update searches only] | 05/06/2017 | - |

Trial sources searched on 11th August 2016

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 11th August 2016

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases

1 High-Intensity Focused Ultrasound Ablation/

2 (HIFU or HIFU-F MRgHIFU MR-HIFU MRgFUS).tw.

3 (High* adj4 Intens* adj4 focus* adj4 ultrasound*).tw.

4 exp Ultrasonic Therapy/

5 (Ultrasonic* adj4 therap*).tw.

6 hemi-ablat*.tw.

7 or/1-6

8 neoplasms, fibroepithelial/ or adenofibroma/ or fibroadenoma/

9 breast diseases/ or breast cyst/ or fibrocystic breast disease/

10 (breast* adj4 (fibroaden* or adenofibro* or fibroepith* or FA or FAD or lump* or lesion* or cyst*)).tw.

11 Breast Neoplasms/

12 (breast* adj4 (cancer* or carcinoma* or adenocarcinom* or neoplasm* or beign * or tumo?r* or metasta*)).tw.

13 or/8-12

14 7 and 13

15 Echopuls*.tw.

16 14 or 15 (262)

17 Animals/ not Humans/

18 16 not 17

19 limit 18 to ed=20161101-20170630