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 for breast fibroadenoma 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 regional monitoring. The technology uses sound waves that propagate through the tissues. This generates local heat, inducing coagulative necrosis, protein denaturation and cellular destruction. A strong acute 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 high-intensity focused ultrasound 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. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. 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 101 patients from 3 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. 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)

84% (43/51) fibroadenomas treated only once
8% (8/51) fibroadenomas treated in 2 sessions

Average treatment time: 118 min (60 to 255 min)
Mean fibroadenoma volume at baseline: 3.89ml

<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>

<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>

<u>Vascularisation</u> (absent)
<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>

<u>Pain reduction</u>
Discomfort complaints at baseline: 61% (31/51)
Discomfort reduction was absolute in 100% of patients.

Pain complaints at baseline: 35% (18/51)
Pain reduction was absolute in 100% of patients.
</td><td>
<u>Pain</u>
No need for analgesic drugs post procedure.
VAS post procedure = 29.7±27.5 mm (0 to 80mm)

<u>Cosmetic deformity</u>
Superficial skin burn with blistering - 6% (3/51)
Hyperpigmentation – 2% (1/51)
Subcutaneous induration – 2% (1/51)

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. HIFU group – mean age 30.3 years (18-45 years) 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. 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. 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** Fibroadenoma diameter – Median 26.5 mm (19 to 44 mm) Number of sonications – Mean 88 (54 to 148) Total delivered energy - Mean 115.94 Joules/site <u>Procedure duration</u> Sonication time – 57.2 min (40 to 100 min) Theatre time – Mean 136 min (80 to 210 min) <u>Volume reduction</u> At follow-up, all treated fibroadenomas showed a 50% reduction in diameter.	<u>Pain</u> During treatment – 0% Follow-up – 0% 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. 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) Number of sonications – mean 60.2 (25 to 106) Mean volume at baseline – 1.9 cm^3 (SD ±1.5 cm^3) Treatment time for a 2-cm lesion was approximately 2 hours and for a 1-cm lesion, approximately 45 minutes <u>Technical failure</u> – 42% (5/12)[1] <u>Volume reduction</u> Volume reduction was achieved in 50% (6/12) of fibroadenomas Mean fibroadenoma volume was reduced to 1.3 cm^3 (SD 1.1 cm^3), p=0.01[2]. [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. [2]At 6 months follow-up.	<u>Pain</u> During treatment None – 36% (4/11) Slight – 36% (4/11) Moderate – 18% (2/11) Severe – 9% (1/11) Mild pain up to 10 days after treatment – 8% (1/11) <u>Damage to adjacent structures</u> Most patients reported tenderness and oedema of the breast up to 10 days after treatment (frequencies not reported). One patient developed an ecchymosis as result of needle biopsy. <u>Impact on future diagnosis</u> 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. 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.	

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 treated by HIFU, 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 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 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 women at 6-month follow-up.[4]

Treatment failure

In the non-randomised controlled study of 40 women treated by HIFU, 10% (2/20) of fibroadenomas 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 women.[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 treated by HIFU, complete pain reduction was reported by 6/8 women at 6 months follow-up.[2]

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), in a non-randomised controlled study of 40 women treated by HIFU.[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 MR-guided HIFU.

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]

Damage to adjacent structures

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

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]

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

Subcutaneous induration

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]

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 in the non-randomised controlled study of 40 women treated by HIFU.[2]

Dimpling of the skin

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

Section to be inserted if there is patient commentary

NICE's Public Involvement Programme sent xxx questionnaires to xxx NHS trusts for distribution to patients who had the procedure (or their carers). NICE received xxx completed questionnaires.

Section to be inserted if there is no patient commentary at IPAC 1

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Section to be inserted if there is no patient commentary at IPAC 2

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

Section to be inserted if patient commentators raised no new issues

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Section to be inserted if patient commentators raised new issues

The patient commentators raised the following issues about the safety/efficacy of the procedure, which did not feature in the published evidence or the opinions of specialist advisers, and which the committee considered to be particularly relevant:

- [insert additional efficacy and safety issues raised by patient commentators and highlighted by IPAC, add extra rows as necessary].
- [Last item in list].

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.

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).** 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. 1.2 Clinicians wishing to undertake interstitial laser therapy for fibroadenomas of the breast should take the following actions. • Inform the clinical governance leads in their Trusts. • Audit and review all patients having interstitial laser therapy for fibroadenomas of the breast. • 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. 1.3 This procedure should be carried out only within specialist breast services. 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 Library)	22/09/2016	Issue 9 of 12, September 2016
HTA database (Cochrane Library)	22/09/2016	Issue 3 of 4, July 2016
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	22/09/2016	Issue 8 of 12, August 2016
MEDLINE (Ovid)	22/09/2016	1946 to September Week 2 2016
MEDLINE In-Process (Ovid)	22/09/2016	September 21, 2016
EMBASE (Ovid)	22/09/2016	1974 to 2016 Week 38
PubMed	22/09/2016	n/a
BLIC	22/09/2016	n/a

Trial sources searched on 05 07 2016

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

Websites searched on 05 07 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 Endoscopy, Gastrointestinal/ or Endoscopes, Gastrointestinal/

2 Colonoscopes/ or Colonoscopy/

3 1 and 2

4 ((endoscop* or endo or colonoscop*) adj2 (full thick* or full-thick* or total wall or total-wall) adj2 (remov* or resect* or excis* or surger* or procedure* or polypectom* or treat* or therap* or device* or probe*)).tw.

5 (full* adj2 thick* adj2 (resect* or excis* or remov* or device* or probe*)).tw.

6 FTRD.tw.

7 EFTR.tw.

8 OTSC.tw.

9 (over-the-scope or "over the scope" or (over adj2 scope*)).tw.

10 ((endoscop* or endo) adj4 clip*).tw.

11 or/3-10

12 Colonic Polyps/

13 ((transanal* or anal* or anus* or colon* or colorect* or rectal* or rectum* or bowel* or hyperplastic* or neoplastic* or ademomat* or homartomat* or subepithelial or gastro*) adj4 (polyp* or lesion* or growth* or tumour* or tumor*)).tw.

14 ((transanal* or anal* or anus* or colon* or colorect* or rectal* or rectum* or bowel* or hyperplastic* or neoplastic* or ademomat* or homartomat* or subepithelial or gastro* or non-lift*) adj4 (adenom* or cancer* or carcinoma* or neoplasm*)).tw.

15 or/12-14

16 11 and 15

17 ovesco.tw.

18 16 or 17

19 animals/ not humans/

20 18 not 19