Systematic review

Systematic review of high-intensity focused ultrasound ablation in the treatment of breast cancer

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Background: **A systematic review was undertaken to assess the clinical efficacy of non-invasive high-intensity focused ultrasound (HIFU) ablation in the treatment of breast cancer.**

Methods: **MEDLINE/PubMed library databases were used to identify all studies published up to December 2013 that evaluated the role of HIFU ablation in the treatment of breast cancer. Studies were eligible if they were performed on patients with breast cancer and objectively recorded at least one clinical outcome measure of response (imaging, histopathological or cosmetic) to HIFU treatment.**

Results: **Nine studies fulfilled the inclusion criteria. The absence of tumour or residual tumour after treatment was reported for 95·8 per cent of patients (160 of 167). No residual tumour was found in 46·2 per cent (55 of 119; range 17–100 per cent), less than 10 per cent residual tumour in 29·4 per cent (35 of 119; range 0–53 per cent), and between 10 and 90 per cent residual tumour in 22·7 per cent (27 of 119; range 0–60 per cent). The most common complication associated with HIFU ablation was pain (40·1 per cent) and less frequently oedema (16·8 per cent), skin burn (4·2 per cent) and pectoralis major injury (3·6 per cent). MRI showed an absence of contrast enhancement after treatment in 82 per cent of patients (31 of 38; range 50–100 per cent), indicative of coagulative necrosis. Correlation of contrast enhancement on pretreatment and post-treatment MRI successfully predicted the presence of residual disease.**

Conclusion: **HIFU treatment can induce coagulative necrosis in breast cancers. Complete ablation has not been reported consistently on histopathology and no imaging modality has been able confidently to predict the percentage of complete ablation. Consistent tumour and margin necrosis with reliable follow-up imaging are required before HIFU ablation can be evaluated within large, prospective clinical trials.**

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Introduction

Breast cancer is the most common cancer in the UK. In 2010, just under 50 000 women were diagnosed with invasive breast cancer, with 11 684 deaths in 2011, making it the second most common cause of death from cancer in women after lung cancer[1].

With the wider use of mammographic screening, breast cancers are being diagnosed at an increasingly earlier stage. Surgery in the form of either breast conservation or mastectomy followed by adjuvant therapy constitutes the mainstay of treatment[2–4]. Breast conservation is dependent on clear margins, defined as no tumour cells visible on ink on the resected specimen according to American Society for Radiation Oncology (ASTRO) guidelines[5]. However, during surgery the surgeon is unable to visualize the tumour to aid in determining clear margins. This lack of intraoperative target definition results in high rates of reoperation to excise residual tumour. There is a clinical need to develop minimally invasive ablative techniques to define better the target and tumour margins during treatment. These techniques potentially benefit from the absence of general anaesthesia, a reduced recovery time and absence of scarring, and consequently also have economic benefits[6].

High-intensity focused ultrasound (HIFU) ablation is a non-invasive technique that has been used for the

treatment of liver, kidney, prostate, brain, bone and breast cancers[7,8]. During HIFU treatment, an ultrasound beam generated by a piezoelectric ultrasound transducer propagates through tissue as a high-frequency pressure wave[8]. The beam is focused on to the targeted tissue, and each treatment volume is approximately $0{\cdot}8 \times 0{\cdot}2 \times 0{\cdot}2\ cm^3$. The energy from the beam raises the temperature of the focused area to 60–95°C within a few seconds without causing damage to the adjacent tissues, thereby leading to very localized protein denaturation and coagulative necrosis[8,9]. Depending on the type of application and penetration depth, ultrasound beams with a frequency between 0·5 and 4 MHz are used[7,8].

The available HIFU devices are generally integrated with either MRI or ultrasound imaging in order to plan treatment and monitor response in real time. MRI has the advantage of excellent anatomical resolution, high sensitivity for lesion detection and temperature mapping; ultrasonography offers real-time visualization of the targeted volume, thereby detecting patient movement, and guidance of energy deposition within the treated area through a hyperechogenic cross visible during pulse application. In addition, ultrasonography provides a rapid real-time assessment of the volume of coagulative necrosis during treatment by visualization of a hyperechogenic spot on the screen[7,8]. Temperature imaging with MRI, on the other hand, is challenging owing to the large amount of fat and lack of reliability of water proton phase-shift-based measurements within fat[10].

HIFU ablation provides a completely non-invasive therapy, thus avoiding potential complications associated with general anaesthesia and surgery[11]. It has been evaluated for treatment of fibroadenomas in a single clinical trial[12]. For breast cancer, HIFU treatment has the potential to improve cosmetic outcomes as scarring is prevented, and earlier administration of systemic therapies is possible as postoperative recovery times are shorter[11]. This systematic review evaluates the current evidence for HIFU ablation in the management of breast cancer, with a focus on residual disease, establishing treatment response through imaging and cosmetic outcome.

Methods

Study selection

A systematic review of the literature was performed using MEDLINE/PubMed library databases to identify all studies published up to December 2013 that evaluated the role of HIFU in the treatment of breast cancer. The medical subject heading (MeSH) search terms used were: 'High Intensity Focused Ultrasound', 'HIFU', 'focused ultrasound ablation' and 'FUS', all in combination with 'breast'. The search was restricted to reports in the English language and human subjects; there were no further restrictions. The related articles function was used to broaden the search, and all abstracts, studies and citations obtained were reviewed. References of the articles acquired were also searched by hand. The last search was conducted on 20 December 2013.

Inclusion criteria

Studies were considered eligible for the systematic review if they were performed on patients with breast cancer, and objectively recorded at least one clinical outcome measure of response (cosmetic, imaging and/or histopathology) to HIFU treatment.

Exclusion criteria

Studies that failed to fulfil the inclusion criteria, and those in which the outcomes of interest were not reported or could not be analysed from published reports, were excluded. Conference abstracts, letters, editorials and case reports were also excluded.

Data extraction

Each study was evaluated initially for either inclusion or exclusion. The data extracted from included studies were: first author, year of publication, study design, number of patients included, mean patient age, lesion type, lesion size, type of guided imaging, frequency, dose, treatment margin used, total treatment time, whether resection was carried out, follow-up, cosmetic outcome, imaging outcome, histopathology staining, histopathological outcome, complications, retreatment of lesions and recurrence. One reviewer extracted data for all selected studies, and a second reviewer verified the accuracy of the extracted data.

Risk of bias in individual studies

The risk of bias tool in the Cochrane Handbook[13] was used to determine the suitability of randomized clinical trials (RCTs) selected for inclusion in the quantitative analysis. The quality of cohort studies was assessed according to the recommendations of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement[14]. Seven items of the STROBE statement were considered relevant for quality evaluation. Studies with a score of less than 4 were excluded. Two reviewers did the

assessment independently. In the event of disagreement, a consensual decision was made.

Statistical analysis

All extracted data were tabulated and presented as means with percentages. Numerators and denominators were provided to address outcomes of included studies. The mean proportion of patients with no residual tumour left after HIFU treatment was evaluated by calculating the pooled inverse-variance weighted proportion. Studies with a standard deviation of 0 (where there was 100 per cent ablation) were excluded from the analysis. A random-effects analysis was performed in view of the suspected high degree of heterogeneity among the included studies. All statistical analyses were carried out in Stata® version 12.0 (StataCorp LP, College Station, Texas, USA).

Results

Selected studies

A total of 140 articles published up to December 2013 were identified from the literature search (*Fig. 1*). After reviewing the abstracts, 101 non-relevant articles were excluded and 39 articles underwent full-text examination. A total of nine studies matched the selection criteria, of which six[6,15–19] were feasibility studies, one[20] was a prospective cohort study and one[9] was a retrospective cohort study. A single RCT[7] was identified in which HIFU ablation followed by mastectomy was compared with mastectomy alone.

Study characteristics

In total, nine studies with 167 patients (mean age 58·5 years) and 169 breast lesions were included in the review. In three studies[9,17,18] the breast cancer types were not specified. In the remaining studies[6,7,15,16,19,20] the included breast cancer types were: invasive ductal carcinoma (83·5 per cent, 106 of 127 patients), ductal carcinoma *in situ* (5·5 per cent, 7 of 127 patients), adenocarcinoma (2·4 per cent, 3 of 127), invasive lobular carcinoma (2·4 per cent, 3 of 127), invasive mucinous adenocarcinoma (0·8 per cent, 1 of 127 patients) and unknown breast carcinoma (5·5 per cent, 7 of 127 patients). The characteristics of the studies are summarized in *Table 1*. Six studies[6,15–19] (116 patients) used MRI as the mode of guided imaging for HIFU ablation, and the remaining three[7,9,20] (51 patients) used ultrasonography. After HIFU treatment, resection of the lesion was performed in six studies[6,7,15,16,18,19], follow-up with

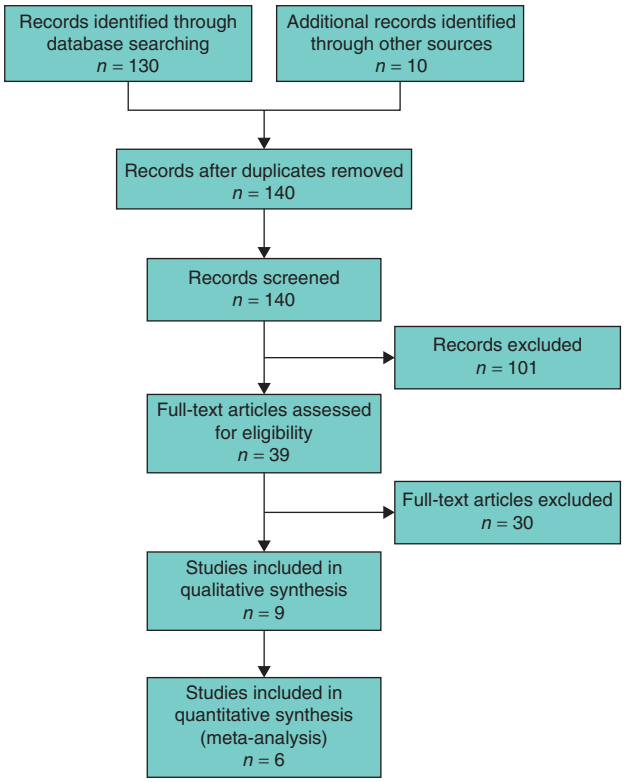

Fig. 1 PRISMA flow diagram showing selection of studies for systematic review

biopsies in two[17,20], and follow-up by both surgery and biopsy in one study[9]. The cosmetic outcome was described in two studies[18,20], histopathology results were discussed in all nine papers[6,7,9,15–20], and imaging results were reported for six series[7,9,16,17,19,20]. The outcomes are described in *Tables S1* and *2*.

Quality assessment

Seven items of the STROBE statement[14] were used for quality assessment of the included cohort studies (*Table 3*). One study with of quality score below 4 was excluded. All studies included specified study objectives and all had clear inclusion criteria and used standard imaging. A standard technique was used in six studies and five reported standard histopathology. Patient follow-up was undertaken until surgery in six studies and further follow-up carried out in two. In three studies, patients withdrew during the course of treatment. The overall STROBE score ranged from 4 to 6 (mean(s.d.) 5·3(0·71)). The Cochrane checklist[13] was used to assess the quality of the single RCT[7] (*Table 4*). The study was randomized, and contained complete outcome data with no short-term outcome data missing; it was free

Table 1 Patient and treatment characteristics of studies using HIFU in breast cancer

Reference	*n*	Age (years)	Tumour size	Ablation margin (cm)	Image guiding modality	Maximum power/ pulse (W)‡	Treatment time (min)	Complications and cosmetic results
Gianfelice *et al.*[15] (2003)	12	60	2·77 (0·11–8·80) cm^3	0·5	MRI	400	80 (35–133)	Pain/discomfort: slight (4), moderate (8) Tenderness: mild (1), moderate (2) Second-degree burn (2)
Gianfelice *et al.*[17] (2003)	24	74·2	1·51 (0·6–2·5) cm	–	MRI	60	–	Pain: moderate (14), mild (10) Second-degree skin burn (1)
Gianfelice *et al.*[16] (2003)	17	61·2	2·49 (0·11–8·80) cm^3	–	MRI	–	–	–
Wu *et al.*[7] (2003)	23	46·5	3·1(0·79) (2·0–4·7) cm*	1·5–2·0	US	545	78 (45–210)†	Minimal skin burn (1), mild local pain, warmth and sensation of heaviness in breast (14), oedema (unknown)
Wu *et al.*[20] (2005)	22	48·6	3·4 (2·0–4·8) cm	1·5–2·0	US	545	132 (60–180)†	Local oedema (all patients), mild local pain (14; oral analgesics 6) Cosmesis: good–excellent (16 of 17), acceptable (1 of 17)
Zippel and Papa[18] (2005)	10	56	2·2 cm	0·5	MRI	–	Maximum 240	Second-degree burn (2), pain during procedure Cosmesis: good–excellent (9), acceptable (1)
Furusawa *et al.*[6] (2006)	28	56·9	1·3 (0·5–2·5) cm	0·5	MRI	400	140 (76–231)	Third-degree skin burn (1), minor adverse events (claustrophobia 1, abdominal and breast skin redness 1, pain 2, shoulder pain 1)
Khiat *et al.*[19] (2006)	25	61·3	3·29 (0·11–11·2) cm^3	–	MRI	–	–	–
Kim *et al.*[9] (2010)	6	62·1	2·56 (1·2–3·7) cm	1·0	US	240	171 (80–285)	Mammary oedema (6), pectoralis major muscle injury (6), skin and trabecular thickening

Values are mean (range) unless indicated otherwise; *values are mean(s.d.) (range) and †median (range). ‡Defined before surgery. US, ultrasonography. All ablations were performed by ExAblate® 2000 (InSightec, Haifa, Israel), with the exception of references 7, 9 and 20 where Haifu Model JC (Chongqing Haifu Medical Technology, Chongqing, China) was used.

from selective reporting and other biases. It did not, however, contain a power analysis, or blind patients, participants or results.

Types of imaging used to assess response to high-intensity focused ultrasound ablation

Different imaging modalities have been used to determine the response to HIFU ablation (*Table S1*). In all studies both pretreatment and post-treatment imaging was performed. In two studies[7,20] (26·9 per cent, 45 of 167 patients) ultrasonography with colour Doppler imaging was performed before the treatment and in one study[20] after treatment to determine perfusion of the lesion. In one study[20] single-photon emission CT was carried out both before and after treatment (3·6 per cent, 6 of 167 patients). MRI was undertaken before and after treatment in 77·8 per cent of all patients (130 of 167)[6,7,9,15–20].

Although all nine studies used MRI before and after treatment, different MRI systems and sequences were used. The systems used were the 1·5-T Signa® Excite® (GE Medical Systems, Milwaukee, Wisconsin, USA) in four studies[9,15,16,19], a non-specified 1·5-T system (GE Medical Systems) in two[6,17] and the 1·0-T Impact® (Siemens, Erlangen, Germany) in two[7,20]; in one report[18] the MRI system was not specified.

MRI-based assessment of high-intensity focused ultrasound treatment

Of the 130 patients (77·8 per cent of 167) who underwent post-treatment MRI, the results were not reported in one study (12 patients)[15]. In four studies[6,16,18,19] (80 patients), general descriptive findings were reported without quantitative findings. Contrast enhancement was seen on pretreatment scans and no enhancement was observed after treatment. In four studies[7,9,17,20], 82 per cent of patients (31 of 38; range 50–100 per cent) showed an absence of enhancement at the index tumour and a thin rim of enhancement at the periphery. In 18 per cent of patients (7 of 38) nodular enhancement was seen at the periphery of the tumour, consistent with residual disease.

Two studies[9,20] recorded a reduction in tumour size by post-treatment MRI. A mean(s.d.) reduction of 26·7(12·2)

Table 2 Histopathology outcomes of studies

Reference	Type of specimen collected	Time of specimen collection	Complete histopathological response (% of patients)			
			< 1 month	1–3 months	3–6 months	> 6 months
Gianfelice *et al.*[15] (2003)	Resection	Unknown	–	–	–	–
Gianfelice *et al.*[17] (2003)	Biopsy	6 months	–	–	Complete necrosis (58%)	Second treatment: total complete necrosis (79%)
Gianfelice *et al.*[16] (2003)	Resection	3–21 days	Complete necrosis (24%), residual tumour < 10% (53%), residual tumour 30–75% (24%)	–	–	–
Wu *et al.*[7] (2003)	Resection	1–2 weeks	Complete necrosis of tumour (100%) and margin of mean(s.d.) 1·80(0·58) cm	–	–	–
Wu *et al.*[20] (2005)	Biopsy	2 weeks, 3, 6, 12 months	Complete necrosis of tumour and adjacent margin (100%)	Partial fibrosis (100%, $n = 18$)	Complete fibrosis (100%, $n = 14$)	Complete fibrosis (100%, $n = 14$)
Zippel and Papa[18] (2005)	Resection	7–10 days	Complete necrosis (20%), microscopic foci of residual tumour (20%), 10% residual tumour (30%), 10–30% residual tumour (30%)	–	–	–
Furusawa *et al.*[6] (2006)	Resection	5–23 days	Complete necrosis (54%), < 10% residual disease (36%), 10–15% residual disease (10%)	–	–	–
Khiat *et al.*[19] (2006)	Resection	3–21 days	Complete necrosis (31%), residual tumour < 10% (42%), residual tumour 20–90% (27%)	–	–	–
Kim *et al.*[9] (2010)	Resection and biopsy	2–20 months	–	Viable tumour (50%)	No viable tumour (67%)	No viable tumour (67%)

Table 3 Study quality assessment of included cohort studies

Reference	Study objectives	Clear inclusion criteria	Standard technique	Standard histopathology	Standard imaging	Patient follow-up	Withdrawals from study
Gianfelice *et al.*[15]	Yes	Yes	No	Yes	Yes	No*	No
Gianfelice *et al.*[17]	Yes	Yes	No	Unknown	Yes	No*	No
Gianfelice *et al.*[16]	Yes	Yes	Yes	Yes	Yes	No*	No
Wu *et al.*[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zippel and Papa[18]	Yes	Yes	Yes	Unknown	Yes	No*	No
Furusawa *et al.*[6]	Yes	Yes	Yes	Yes	Yes	No*	Yes
Khiat *et al.*[19]	Yes	Yes	Yes	Yes	Yes	No*	No
Kim *et al.*[9]	Yes	Yes	Yes	No	Yes	Yes	Yes

Assessed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. *Studies in which the lesion was resected and follow-up was until surgery.

per cent was reported after 6 months, 45·2(22·1) per cent after 12 months, 72·3(32·1) per cent after 24 months[20], and a reduction of 46·3 per cent between 11 and 24 months[9]. MRI within the first 2 weeks after treatment showed transient oedema surrounding the target volume[7]. Any change in lesion size as a result of oedema was not documented.

MRI was carried out immediately after HIFU treatment in three studies[6,18,19], within the first 2 weeks in eight[6,7,9,15–19] and at an unknown subsequent time in one study[20]. MRI immediately after HIFU treatment showed decreased enhancement, although not sufficient to determine treatment response.

Two studies[16,19] showed a good correlation between the increase in signal intensity (ISI) ($r = 0·897$ and $r = 0·749$ respectively), maximum difference function (MDF) ($r = 0·789$)[16], positive enhancement integral (PEI) ($r = 0·859$ and $r = 0·778$ respectively) and the percentage of residual tumour. In one of these studies[16] a stronger correlation was seen ($r = 0·932$ for ISI and $r = 0·964$ for PEI) when only MRI performed 7 days after HIFU treatment was included.

Table 4 Study quality assessment of included randomized clinical trial

Reference	Adequate sequence generation	Power analysis	Concealed allocation	Blinding	Incomplete data addressed	Free from other bias	Free from selective reporting
Wu *et al.*[7]	Yes	No	Unknown	No	No	Yes	Yes

Assessed according to the risk of bias tool in the Cochrane Handbook.

One study[17] with 24 patients, 18 of 19 patients who were considered to have had successful treatment based on biopsy results, demonstrated a lack of enhancement on MRI; three of five patients whose treatment was deemed to have failed, because residual tumour was found on biopsy, demonstrated persistent enhancement on MRI after two HIFU sessions.

Histopathological outcome after high-intensity focused ultrasound treatment

Histopathology was discussed in all nine studies (*Table 2*). The absence of tumour or residual tumour after treatment was reported for 95·8 per cent of patients (160 of 167). In six studies[6,7,15,16,18,19] (68·9 per cent, 115 of 167 patients) the histopathology results were based on specimens from surgical removal of the tumour by lumpectomy or mastectomy after HIFU. Core needle biopsies were obtained in two studies[17,20] (27·5 per cent, 46 of 167 patients), and a combination of core needle biopsies and surgical removal was used in the remaining study[9] (3·6 per cent, 6 of 167 patients). In five[6,7,16,18,19] of seven studies, patients underwent surgery 1–3 weeks after the HIFU treatment and in one study[9] patients underwent surgery after 3–11 months; the final study[15] did not specify the time of surgery after HIFU treatment. In five studies[6,7,15,16,20] haematoxylin and eosin was used for histopathological staining, whereas the other four[9,17–19] did not report the type of staining used.

To get a clear view of the percentage of complete ablation and residual tumour, histopathology findings were divided into three groups: complete ablation, less than 10 per cent residual tumour, and residual tumour between 10 and 90 per cent. Complete ablation is a primary outcome and therefore reported as a separate group. Thus an incomplete ablation indicates an incomplete treatment. The threshold of 10 per cent residual tumour was used in four studies[6,16,18,19].

One study[7] recorded complete necrosis of the tumours in all patients. In total, complete ablation or no residual tumour was found in 46·2 per cent (55 of 119; range 17–100 per cent) of all patients who underwent surgical excision after HIFU treatment. Weighted summary proportion analysis showed that an estimated 30 (95 per cent c.i. 18 to 43) per cent of patients had no residual disease after HIFU treatment (*Fig. 2*). The I^2 statistic of 47·2 per cent confirms the heterogeneity among studies. The study[7] that reported 100 per cent ablation was excluded from this analysis.

Residual tumour of less than 10 per cent was found in 29·4 per cent of patients (35 of 119; range 0–53 per cent)[6,15,16,18,19]. These histopathology results were obtained within the first 3 weeks after HIFU treatment. Residual tumour between 10 and 90 per cent was found in 22·7 per cent (27 of 119; range 0–60 per cent)[6,15,16,18,19]. Surgical resection of the tumour was performed between 1 and 3 weeks after surgery, and in one study[15] no time of resection was mentioned. One study[9] reported the number of patients with complete ablation, but the percentage of residual tumour in the remaining patients (2 of 119; 1·7 per cent, 0–33 per cent) was not mentioned.

In the three studies[9,17,20] that used core needle biopsies, no residual disease was found in 90 per cent of patients (43 of 48; 79–100 per cent). Residual disease was found in the other five patients, but no quantitative statements were made. The core biopsies were performed after 2 weeks[20], 6 months[17] and 2–20 months[9].

One study[20] reported partial fibrosis in the core biopsies of all 18 patients after 3 months; complete fibrosis was visible in all biopsies from 14 patients after 6 and 12 months.

Two studies[6,16] determined the percentage of tumour located in the treated area. The whole tumour was located in the treated area in 83 per cent of patients (33 of 40; range 58–93 per cent), between 90 and 99 per cent of the tumour was located in the treated area in 10 per cent (4 of 40; range 7–17 per cent), and less than 70 per cent of the tumour was located in the treated area in 8 per cent (3 of 40; range 0–25 per cent).

One study[7] measured the ablated margin around the tumour, which was mean(s.d.) 1·80(0·58) cm. The ablated margin around the tumour was stated as 0·5 cm in three studies[6,15,18], 1·0 cm in one study[9], and 1·5–2·0 cm in two reports[7,20].

Complications after high-intensity focused ultrasound treatment

Complications were described in seven studies (*Table 1*, *Fig. 3*)[6,7,9,15,17,18,20]. Pain was reported in 40·1 per cent of

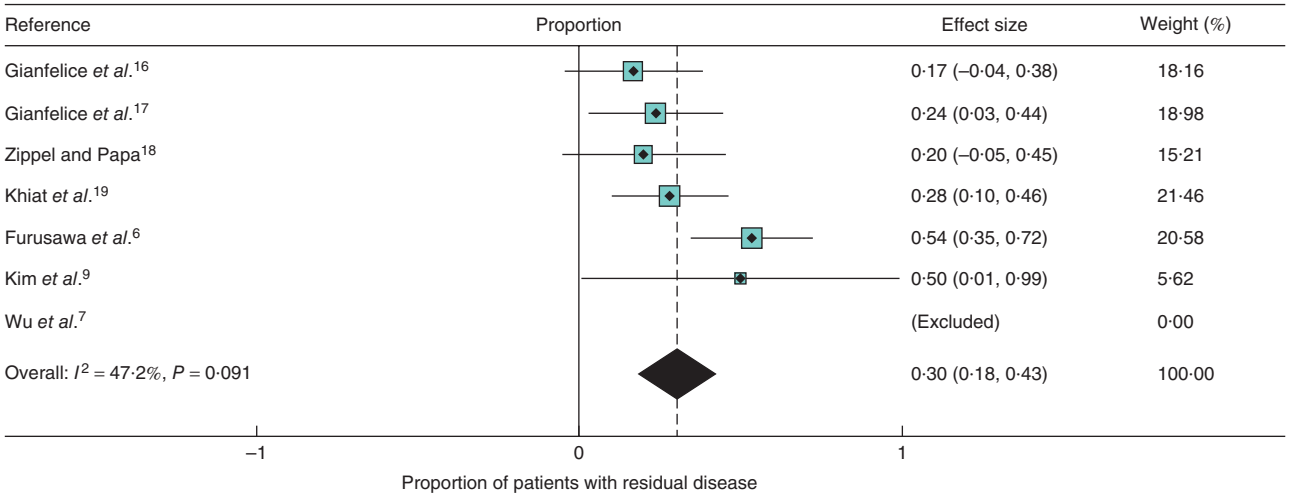

Fig. 2 Forest plot showing random-effects analysis of patients with residual disease after high-intensity focused ultrasound ablation. Effect sizes are shown with 95 per cent c.i.

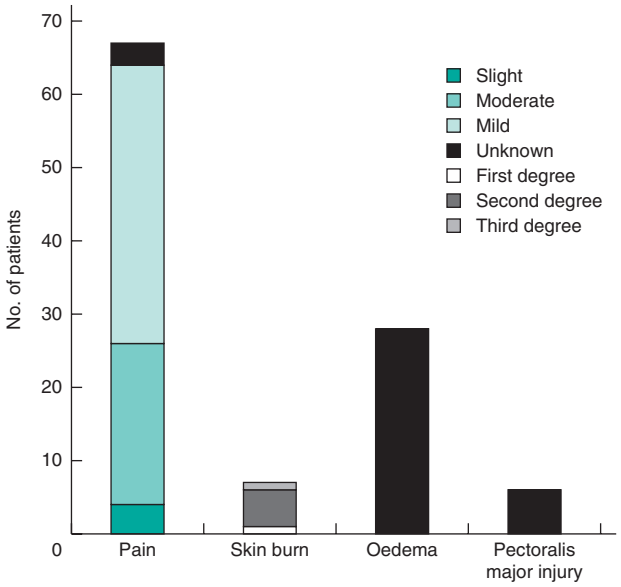

Fig. 3 Complications after high-intensity focused ultrasound ablation

patients (67 of 167), and was slight in 6 per cent, moderate in 33 per cent, mild in 57 per cent and unknown in 4 per cent of these 67 patients. Skin burns occurred in 4·2 per cent (7 of 167), with one superficial, five second-degree and one third-degree burns. Oedema of the lump was noted in three studies[7,9,20] and occurred in at least 16·8 per cent of patients (28 of 167). In one study[7] oedema was noted, but the number of patients was not reported. The oedema disappeared within 2 weeks of treatment. Pectoralis major injuries were reported in one study[9] and occurred in six patients (6 of 167, 3·6 per cent). Other complications were claustrophobia (1 of 167, 0·6 per cent), redness of the skin (1 of 167, 0·6 per cent) and tenderness of the breast (1 of 167, 0·6 per cent).

Breast cancer recurrence after high-intensity focused ultrasound treatment

Recurrence of the tumour was found in two patients in one study[20] (2 of 167 patients overall, 1·2 per cent; 2 of 28 with follow-up, 7 per cent). Both had modified radical mastectomy followed by chemotherapy; one patient died from metastatic disease 44 months after HIFU ablation.

Cosmetic outcome after high-intensity focused ultrasound treatment

In two studies[18,20] a cosmetic outcome analysis was performed after HIFU treatment. A good to excellent cosmetic result was achieved in 25 of 27 patients and an acceptable result in two patients.

High-intensity focused ultrasound treatment time

Five studies[6,7,9,15,20] reported the treatment times for HIFU; the median duration ranged between 78 and 171 min for a lesion between 1·3 and 3·4 cm in size.

Discussion

The studies included in this systematic review demonstrate that HIFU treatment has been shown in small series to

induce coagulative necrosis in breast cancers. No residual tumour was found at histopathology in 46·2 per cent of patients. However, residual tumour of less than 10 per cent was found in 29·4 per cent, and between 10 and 90 per cent in 22·7 per cent. The volume of residual tumour was not mentioned in 1·7 per cent of patients[6,15,16,18,19]. Recurrence was reported in two patients, in whom an increase in tumour size was seen after an initial reduction on ultrasonography. The percentage of residual tumour after HIFU treatment varied between the studies. In previous studies[21,22] tumour cells that showed normal cellular structure after staining with haematoxylin and eosin were found not to be viable on subsequent reduced nicotinamide adenine dinucleotide staining and electron microscopy. Therefore, the percentage of residual tumour might be lower than reported here.

Failure to achieve complete ablation of the lesion may be related to accuracy of targeting the treatment area or to failure of the technique. Problems in targeting can be due to problems in the imaging process itself, or to movement of the patient during HIFU treatment. In many of the reviewed studies, it is unclear whether the whole tumour was actually located within the treated field, whether complete necrosis was achieved, and subsequently what part any difficulties in targeting may have played in the failure to achieve full ablation. Such data were reported in only two[6,16] of the nine studies. The remaining studies recorded only the percentage of patients in whom complete ablation of the tumour was achieved. It is therefore not evident whether this represents a failure of the HIFU treatment itself or in actually locating the lesion. It is possible that, with improved targeting of the lesion, the efficacy of HIFU treatment could potentially be higher than described here. Surprisingly, ultrasound-guided HIFU treatment[7,9,20] gave better results than MRI-guided ablation[6,15–19]. Although only three studies described HIFU performed under ultrasound guidance, two[7,20] of these had an efficacy of 100 per cent and the third[9] an efficacy of 67 per cent; however, the latter investigation included only six patients. It is likely that patients are selected for ultrasound treatment and so patient selection may partially be responsible for this observation.

The extra margin of normal tissue ablated around the target tumour in the included studies varied from 0·5 to 1·5–2·0 cm. The two studies[7,20] with a margin of between 1·5 and 2·0 cm are the only two to report complete necrosis of the lesion in all patients, and both used ultrasound-guided HIFU therapy. The only other ultrasound-guided study[9] applied a margin of 1·0 cm and achieved complete ablation in four of six patients. In the MRI-based studies[6,15–19], the margins treated around the lesion were between 0 and 1·0 cm, and complete ablation was obtained in fewer instances. This wider treated margin of surrounding tissue could explain the high rates of complete ablation achieved in studies that used ultrasound guidance.

Post-treatment MRI images showed an absence of contrast enhancement and a thin rim enhancement at the periphery of the treated area in 31 of 38 patients, indicative of coagulative necrosis[7,9,17,20]. A positive correlation between the percentage of residual tumour and the ISI, MDF and PEI was observed on MRI after HIFU treatment[16,19], and this could be used to determine the extent of residual lesion.

A positive correlation was found between the ISI on MRI after HIFU treatment and the percentage of residual tumour tissue after HIFU treatment[16,19]. Before the HIFU treatment, strong enhancement of the whole tumour lesion was observed on dynamic contrast-enhanced MRI. After treatment, no enhancement was seen when complete necrosis was achieved. When residual tumour was left behind, post-treatment MRI scans showed nodular enhancement at the periphery of the treated area. However, some benign processes such as oedema, fibrosis, necrosis and inflammation can mimic malignant contrast enhancement, and so the time interval between treatment and the imaging procedure, as well as the shape of the enhancement curves, must be taken into account. Malignant tissues continue to show an irregular border, rapid enhancement and an early distinct washout phase after HIFU ablation[19]. The histopathology and MRI results after HIFU treatment were compared directly in three studies[7,17,20]. Two studies[7,20] with complete ablation demonstrated on histopathology also showed complete ablation on MRI. However, in the other study[17], MRI gave one false-positive and two-false negative results when compared with histology. This suggests that MRI is a fairly accurate predictor of complete ablation following HIFU treatment.

To treat breast cancer with HIFU ablation, histopathology of the tumours must be established before therapy for definitive diagnosis. Surgical resection after HIFU treatment may not provide definitive diagnostic or prognostic factors for the determination of adjuvant systemic therapies. Some prognostic factors (such as presence or absence of lymphovascular invasion) cannot be assessed reliably on the limited sampling of a core biopsy sample. This may potentially limit the value of this technique in the setting of breast cancer treatment until improvements in imaging and genomic evaluations allow collection of prognostic factors comparable to those identified by histopathology. When only limited examination with small biopsies is performed, it is not possible to conclude whether complete or incomplete ablation has been achieved after HIFU therapy.

The most common complications during and after treatment are pain (40·1 per cent), skin burns (4·2 per cent), oedema (at least 16·8 per cent) and pectoralis major injury (3·6 per cent). These are relatively mild problems compared with the possible complications of breast surgery (infection, bleeding, incomplete wound healing). The most significant concern regarding HIFU treatment of malignant lesions is inadequate treatment of the breast cancer, although recurrence was described in only two patients[20]. However, follow-up was reported in only two studies[9,20], so this number is likely to be higher overall among all patients with HIFU-treated breast cancer.

The cosmetic result after HIFU treatment was good to excellent in 25 of 27 patients asked and acceptable in the other two[18,20]. However, the cosmetic outcome of HIFU could not be assessed in the majority of the studies because HIFU treatment was mostly followed by surgical resection.

Lesion resorption is a long process and can take 6 months after HIFU treatment[17,20]. This could prove a challenge during follow-up and may also have a psychological impact on patients, who might believe that they still have a lesion or even recurrence[7]. Therefore, it is important to inform patients that lumps may remain palpable for some time. Furthermore, HIFU treatment might also prove challenging for interpretation of breast imaging, if radiologists are not made aware that this treatment has been carried out.

The treatment times for HIFU therapy are a major disadvantage of the technique. The mean duration for a lesion with dimensions between 1·3 and 3·4 cm ranged from 78 to 171 min. To make this treatment a viable alternative not only for patients clinically unfit for surgery, it is imperative that treatment times be reduced.

All cohort studies reviewed were performed in different ways, and varied in outcome measures and consistency of reporting of results; the results could not, therefore, be compared directly in a quantitative analysis. There are significant variations in, for example, the times of further imaging and subsequent biopsies as well as the lesions included in the studies, the mode of HIFU treatment, different MRI devices and MRI sequences. Heterogeneity was also found in the width of the surrounding tissue treated, the ablation dose and the frequency of treatment. Inclusion criteria differed in terms of the distance between the lesion and the skin, chest wall and nipple. Finally, the median number of patients per study was 16·7, and two studies[9,18] included ten or fewer patients. Strict standardization within the setting of clinical trials is needed to compare HIFU with breast surgery, and to compare MRI-guided *versus* ultrasound-guided HIFU.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Imaging findings and outcomes (PDF document)

Editor's comments

The incidence of breast cancer is increasing and many of the newly diagnosed tumours are small. Several innovative methods for tumour removal or destruction are being developed. High-intensity focused ultrasound (HIFU) ablation is one of these, and would, in theory, allow for treatment as an outpatient. However, as is shown in this systematic review, unsolved issues remain, such as finding an imaging modality that predicts the percentage of complete ablation accurately. Until then, HIFU ablation for breast cancer should be regarded as experimental, and only be performed within the setting of a clinical trial.

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