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Minimal Invasive Ablative Techniques in the Treatment of Breast Cancer: a Systematic Review

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Minimal Invasive Ablative Techniques in the Treatment of Breast Cancer: a Systematic Review

Abstract

Purpose: Breast conserving surgery is effective for breast cancer treatment but is associated with morbidity in particular high re-excision rates. We performed a systematic review to assess the current evidence for clinical outcomes with minimally invasive ablative techniques in the non-surgical treatment of breast cancer.

Methods: A systematic search of the literature was performed using PubMed and Medline library databases to identify all studies published between 1994 and May 2016. Studies were considered eligible for inclusion if they evaluated the role of ablative techniques in the treatment of breast cancer and included ten patients or more. Studies that failed to fulfil the inclusion criteria were excluded.

Results: We identified 63 studies including 1608 patients whose breast tumours were treated with radiofrequency (RFA), high intensity focused ultrasound (HIFU), cryo-, laser or microwave ablation. Fifty studies reported on the number of patients with complete ablation as found on histopathology and the highest rate of complete ablation was achieved with RFA (87.1%, 491/564) and microwave ablation (83.2%, 89/107). Short-term complications were most often reported with microwave ablation (14.6%, 21/144). Recurrence was reported in 24 patients (4.2%, 24/570) and most often with laser ablation (10.7%, 11/103). The shortest treatment times were observed with RFA (15.6±5.6 minutes) and the longest with HIFU (101.5±46.6 minutes).

Conclusion: Minimally invasive ablative techniques are able to successfully induce coagulative necrosis in breast cancer with a low side effect profile. Adequately powered and prospectively conducted cohort trials are required to confirm complete pathological ablation in all patients.

Keywords: Ablative techniques, radiofrequency ablation (RFA), laser-ablation, cryo ablation, high intensity focused ultrasound (HIFU), microwave ablation, breast cancer.

Introduction

Breast cancer is now diagnosed at an earlier stage due to the wider use of breast cancer screening and use of more advanced imaging modalities including magnetic resonance imaging (MRI). [1, 2] In view of this, more patients are suitable for breast conserving surgery. [3, 4] Although breast conserving surgery is effective, it is associated with high re-excision rates of 20% in the United Kingdom due to its dependence on clear margins and the surgeon's inability to visualize the tumour extent intra-operatively. [5] Furthermore it can be associated with poor cosmetic outcome. [6, 7] There is thus a clinical need to develop non-operative techniques in order to treat patients with both tissue and volume preservation. Potential advantages of a non-operative approach to breast cancer treatment are the ability to image the tumour intra-operatively, reducing the surgical excision rate, reducing treatment cost and thereby potentially improving patients' quality of life. Additional associated potential advantages include reducing the rate of general anaesthesia, reducing the complication rate and severity of these, reducing recovery time and reducing scarring. [5, 8] In addition, adjuvant therapy may be administered faster after ablative treatment, in the absence of a wound requiring healing.

Numerous articles have evaluated novel ablative techniques for the non-operative treatment of breast cancer and it is clinically important to evaluate the evidence in order to

identify the most promising techniques for further clinical evaluation. [9] We performed a systematic review to assess the current evidence on clinical outcomes of minimally invasive ablative techniques for the non-operative treatment of breast cancer.

Methods

Study Selection

A systematic review of the literature was performed using PubMed and Medline library databases to identify all studies published between 1994 and May 2016 that evaluated the role of ablative techniques for the treatment of breast cancer. The MESH terms used were ablative techniques, ablative interventions, ablative therapy, thermal ablation, high intensity focused ultrasound (HIFU), radiofrequency ablation (RFA), laser ablation, cryo-ablation, stereotactic radiotherapy and microwave ablation in combination with breast and cancer. Except for reports in the English language and human subjects, there were no further restrictions. The related articles function was used to broaden the search and identify alternative ablative techniques. References of the articles acquired were also searched by hand. The last search was conducted on June 7th, 2016.

Inclusion Criteria

Studies were considered eligible if they addressed the following: (1) studies performed on human subjects with breast cancer, (2) studies evaluating the role of a minimally invasive ablative technique, (3) studies with ten or more patients included.

Exclusion Criteria

Studies that failed to fulfil the inclusion criteria were excluded. Conference articles, letters, editorials and case reports were excluded from the study. Studies using laser as a surgical scalpel (without ablation), or studies using an ablative technique after surgical excision of the tumour were excluded. In the case of studies with overlapping populations, the most recent study with histopathological outcomes was included. Abstracts of studies that are as yet unpublished (full text not available) were excluded.

Data Extraction

Each study was initially evaluated for either inclusion or exclusion. One reviewer, (M.P) extracted data for all selected studies and a second reviewer (M.A) verified the accuracy of the extracted data. In case of a disagreement the senior author (M.D) made the final decision.

Risk of Bias in Individual Studies

The "Risk of bias" tool presented in the Cochrane Handbook [10] was used to determine the suitability of randomized control trials (RCT). The study quality of cohort studies was assessed according to the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. [11] Seven items of the STROBE statement were considered relevant for quality evaluation. These included clearly reported objectives and inclusion criteria, usage of a standardised technique, standardised histopathology and standardised imaging, patient follow-up and reporting of any withdrawals from the study. Studies with a score of less than four were excluded. Two reviewers (M.P and

M.A) performed the assessment independently. In case of a disagreement, a consensual decision was reached.

Statistical Analysis

All extracted data were tabulated and presented as means, standard deviations (SD) and percentages. Numerators and denominators were provided to address outcomes of included studies.

A meta-analysis was undertaken using a random effect logistic model given the wide variation in complete ablation percentages between studies. Parameter estimation was performed by a maximum-likelihood fit. To check the methodology, a parametric bootstrap technique was used [12] to correct bias using maximum-likelihood estimates. From the bootstrapped solutions, standard errors (s.e.), significance tests and confidence intervals (CI) were calculated. In addition, an analysis of covariance was performed to determine any correlation between the treatment time and treated tumour size.

Results

Selected Studies

A total of 2044 articles published between 1994 and May 2016 were identified from the literature search (*figure 1*). Three additional articles were identified by searching the references of selected articles. After reviewing the title and abstracts, 1930 articles were not deemed relevant and were excluded leaving 114 articles for full text examination. Several studies using techniques such as stereotactic radiotherapy and Gadolinium enhanced RODEO laser ablation were excluded as they did not meet the inclusion criteria (less than ten patients included). A total of 63 articles matched the selection criteria. The 63 articles included 16 feasibility studies [13-28], 12 phase I studies [29-40], nine phase II studies [41-49], three comparative studies [50-52], one retrospective study [53], and four randomised controlled trials [54-56]. In 18 studies the type of study was not reported [8, 57-73]. One article [54] contained the results of four studies of which two were previously published. [39, 41] All four studies (one phase I [39], one phase II [41] and two randomised controlled trials [54]) were included in this systematic review.

Study Characteristics

In total, 63 studies with 1608 patients and 1627 breast cancers, were included in the systematic review. The characteristics of the studies are summarized per technique in *table's 1a-e*. Radiofrequency ablation (RFA) was used in 27 studies (657 patients) [13-17, 26, 27, 29-32, 42-48, 51, 64-71], in which a needle electrode is percutaneously inserted under ultrasound

(US) guidance to deliver an alternating current that generates ionic agitation, localised tissue heating and cell death. [32, 46, 74] Twelve studies used high intensity focused ultrasound (HIFU) (227 patients) [8, 23, 24, 38, 52, 55-60, 72], a completely non-invasive ablative technique in which a focused US beam propagates through tissue as a high frequency pressure wave causing the temperature to rise, leading to protein denaturation and coagulative necrosis. [55, 75-77] Ten studies used cryo-ablation (269 patients) [19-22, 35-37, 49, 61, 73], in which a probe is inserted into the tumour under US guidance. The ablation process involves two phases: freezing and thawing with four mechanisms destroying the tumour cells: direct damage by intracellular ice formation and osmotic dehydration and indirect damage due to ischemia and immunologic response. [36, 78] Seven studies used laser-ablation (231 patients) [18, 28, 33, 34, 50, 62, 63], in which lesions are ablated due to direct heating with low-power laser light energy delivered percutaneously via thin optical fibres. Upon absorption in the tissue, heat is produced, inducing lethal thermal injury. Six studies used microwave ablation (144 patients) [25, 39-41, 54], which uses localised heating caused by water molecules which move within tissues, and externally applied focused microwaves to cause tissue necrosis. This technique can heat and damage high-water-content tumour cells, whilst tissues with lower-water-content such as adipose and breast glandular tissues remain unharmed. [41, 79] One study [53] compared cryo-ablation with RFA (80 patients).

All but two studies treated patients with malignant breast tumours, one study treated newly diagnosed breast cancer and breast recurrences [21] and one treated breast recurrences

only. [43]. For image guidance of the ablative techniques, US was used by all five ablative techniques in 44 studies [13-20, 22, 24-27, 29-36, 39, 40, 42-51, 53, 55, 56, 64-71], magnetic resonance imaging (MRI) in 11 studies using HIFU and cryo-ablation. [8, 23, 37, 38, 52, 57-61, 72]Two cryo-ablation studies [21, 73] and one laser ablation study [28] used computer tomography (CT) in combination with US and two laser ablation studies [62, 63] used stereotactic guidance. In three microwave studies the imaging modality is not known. [41, 54] The ablative treatments were performed by the surgeon in six studies [25, 26, 35, 48, 56, 62], radiologist in four studies [15, 31, 45, 64], a combination of both in one study [40] and 52 studies did not report on who performed the treatment.

There are some important differences between the ablative techniques. The benefit of HIFU is that insertion of a probe is not required as this technique is completely non-invasive and scar less. Cryo-ablation and microwave ablation require the insertion of a single probe and RFA and laser ablation require the insertion of multiple probes. Furthermore, cryo-ablation is the only to use freezing rather than heat to cause tumour necrosis.

Quality Assessment

Seven items of the STROBE statement [11] were used for quality assessment of the included cohort studies (*table 2a).* All studies included specified study objectives and all but eight [28, 33, 37, 39, 50, 51, 60, 61] had clear inclusion criteria. A standardised technique was used in all but five studies [23, 26, 27, 36, 57], all but seven studies reported standardised

histopathology [19, 23, 33, 38, 52, 58, 60] and standard imaging was performed in 30 studies [8, 16, 17, 21-24, 26-28, 31, 32, 34, 37, 38, 40, 46, 47, 50, 52, 53, 57-60, 66-68, 72, 73]. Patient follow-up, in the case of no surgical excision or after surgical excision of breast cancer was undertaken in 17 studies [21, 22, 24, 28, 30, 31, 33, 34, 42, 44, 52, 60, 66-68, 70, 73], however, 14 studies [17, 18, 26, 27, 40, 45-47, 49, 50, 53, 62, 63, 72] reported follow-up only until delayed surgical excision. In four studies [16, 32, 65, 69], a group of patients underwent immediate surgical excision of the tumour and the remaining patients were followed up until surgical excision. In five studies [21, 24, 49, 59, 63], patients withdrew from the study during or after treatment and in another six studies [15, 26, 44, 48, 49, 72] patients withdrew before the start of the treatment. The overall STROBE score ranged from four to seven (mean 5.4±0.9).

For the four included RCTs [54-56], the Cochrane checklist [10] was used (t*able 2b*). All studies had unspecified sequence generations (selection bias) and allocated concealment (selection bias). All studies did not perform a power calculation or any blinding of the participants or personnel (performance bias) or outcome assessment (detection bias, patient-reported outcomes and mortality). The second study by Dooley *et al.* [54] included incomplete data addresses (attrition bias; short- and longer-term outcomes missing) and all studies were free of selective reporting (selection bias) or other biases.

Outcomes

Histopathology

Post-treatment surgical excision of tumours was performed in 52 studies (1339 patients) in which immediate surgical excision was performed in 16 studies (387 patients, most often with RFA) [13-15, 18, 25, 26, 29, 35, 42-45, 48, 51, 64, 71], delayed surgical excision in 33 studies (853 patients) [8, 17, 19, 20, 22, 27, 28, 33, 34, 36-41, 46, 47, 49, 50, 52-59, 61-63, 67, 70, 72] and a combination of immediate and delayed surgical excision in three studies (99 patients) [16, 65, 69]. A combination of follow-up and immediate or delayed surgical excision was performed in two studies (49 patients).[32, 33] Follow-up with imaging alone or imaging and core biopsies was performed in nine studies (220 patients) [21, 23, 24, 30, 31, 60, 66, 68, 73]. Reasons for performing a treat and resect study or a follow-up study were often not reported. Follow-up was performed in studies with patients unsuitable or not willing to have surgical excision. Immediate surgical excision was performed to determine the true zone of necrosis and delayed surgical excision was performed to determine the degenerative changes over time.

Delayed surgical excision was performed within a week of treatment in four studies [19, 33, 50, 72] (most often following laser ablation), within two weeks of treatment in ten studies [8, 20, 27, 34, 36, 38, 55, 56, 58, 59] (most often following HIFU), within three weeks of treatment in eight studies [17, 28, 39, 41, 46, 47, 54, 62] (most often following RFA), within four weeks of treatment in four studies [37, 40, 49, 67] and longer than four weeks of

treatment in six studies [22, 52, 53, 61, 63, 70]. In two studies the timing of surgical excision in relation to treatment was not reported [54, 57]. In the three combination studies [16, 65, 69] (all RFA studies), delayed surgical excision was performed after a longer period ranging from 1-40 months.

Complete ablation on histopathology was reported in 50 studies. Considering RFA, in 87.1±12.8% (491/564) of all patients who underwent surgical excision, complete ablation of the tumour was achieved [13-17, 26, 27, 29, 32, 42-48, 51, 53, 64, 65, 67, 69-71] (table 1a). For laser ablation, 52.2±29.2% (48/92) of all patients had complete ablation post-treatment [18, 34, 63] (table 1b) and for cryo-ablation, complete ablation was achieved in 74.1±28.9% (186/251) of all patients [19, 20, 22, 35-37, 49, 53, 61] (table 1c). With HIFU, complete ablation was achieved in 47.6±29.9% (60/126) of all patients [8, 38, 52, 55, 57-59] (table 1d) and in microwave ablation 83.2±11.6% (89/107) of patients obtained complete ablation [25, 41, 54] (table 1e).

Using a random effect logistic model given the wide-variation in complete ablation rates between studies, the probabilities of success to achieve complete pathological response for the five ablative techniques with 95% CI were calculated. The highest estimate was for RFA (0.87 (0.82, 0.91)), followed by microwave ablation (0.81 (0.70, 0.93)), cryo-ablation (0.75 (0.70, 0.85)), laser ablation (0.71 (0.67, 0.82)) and HIFU (0.71 (0.67, 0.79)) (*figure 2)*.

When looking at complete ablation rates of RFA studies that followed patients up with core needle biopsy (CNB) and imaging but without surgical excision, complete ablation was achieved in 98.0±4.0% (100/102) [30, 32, 66, 68], in follow-up studies using cryo-ablation 100% (6/6) of patients had complete ablation [21] and in follow-up studies using HIFU 89.1±14.8% (41/46) of patients had complete ablation. [23, 24]

Follow-up:

Follow-up was performed in all [21, 23, 24, 30, 31, 60, 66, 68, 73] or in a cohort of patients [32, 33] in eleven studies. Follow-up was performed with MRI (n=3), US (n=1) and cytology (n=1) in RFA studies [30-32, 66, 68] with a mean follow-up period of 28.1±15.6 months; with CT (n=1) and MRI (n=2) in cryo-ablation studies [21, 73] with a follow-up of 18.7±5.8 months; with MRI (n=3), US (n=2), SPECT (n=1) and core biopsies (n=1) in HIFU studies [23, 24, 60] with a mean follow-up period of 29.7±22.0 months and with US (n=1), CT (n=1) and core biopsies (n=1) in laser ablation studies with a mean follow-up of 20.5±0 months.[33]

Treat and resect studies also undertook patient follow-up. RFA studies used MRI (n=6), US (n=4), mammography (n=2) or CT (n=1) for follow-up up to one month after surgical excision, laser ablation studies used MRI (n=2), US (n=1), CT (n=1) and mammography (n=1) for follow-up up to two weeks after surgical excision and every three months thereafter, cryo-ablation studies used MRI (n=3) or US (n=1) for follow-up up to one month after surgical excision, HIFU studies used MRI (n=5) for follow-up up to three weeks

after surgical excision, and microwave ablation studies used MRI (n=1) or US (n=1) up to three weeks prior to surgical excision.

Margins:

Fifteen studies reported on treating an additional margin of normal breast tissue around the tumour. Six RFA studies treated a margin of 5mm (n=3) [29, 42, 44] or more than 5mm (n=3). [13, 27, 45] One laser ablation study treated an additional 5mm of normal breast tissue. [62] Two cryo-ablation studies treated an additional margin of 5-10 mm of normal tissue. [35, 37] Six HIFU studies treated a margin of 5 mm (n=3) [8, 38, 52] or 15-20 mm (n=3).[24, 55, 56]

Axillary lymph nodes:

The type of axillary treatment was reported in 40 studies. Axillary treatment was performed prior to ablative treatment (n=17), after ablative treatment (n=2), along with surgical excision (n=14), or the timing was not specified (n=7). Sentinel lymph node biopsy (SLNB) in immediate surgical excision studies was often performed just prior to the ablative treatment, which was then followed by surgical excision of the tumour. For delayed surgical excision, SLNB was often performed along with surgical excision of the tumour or prior to the ablative treatment in order to perform an axillary clearance (if necessary) simultaneously with the surgical excision. For follow-up studies, SLNB was performed prior to ablative treatment. In the case of clinically or radiologically positive nodes or positive nodes after SLNB, an

axillary node clearance was performed instead or after involved nodes were removed during SLNB.

A total of 187 positive nodes were found in the ablative studies, 103 with RFA, 20 with cryo-ablation, 17 with laser and microwave ablation and 15 with HIFU and the combined study (RFA and cryo ablation).

Local Recurrence:

Local recurrence was reported in 24 patients from nine studies (24/570, 4.2%). Most local recurrences were reported with laser ablation (10.7%, 11/103) [33, 34] at a mean follow-up time of 20.5±0 months, and RFA (3.1%, 9/291) [31, 42, 64, 69] at a mean follow-up time of 30.8±16.9 months. No local recurrences were reported with microwave ablation, (0/144) one case of local recurrence was reported with cryo-ablation (1.4%, 1/74) [73] at a mean follow-up time of 16.9±2.0 months and three cases with HIFU (2.9%, 3/102) [24, 60] at a mean follow-up time of 21.4±19.3 months.

Recurrences were documented in two studies (n=3) who performed immediate surgical excision [42, 64], one study (n=2) with delayed surgical excision [34], one study (n=3) with combined immediate and delayed surgical excision [69], one study with combined delayed surgical excision (n=8) and follow-up (n=1) [33] and three studies (n=7) who performed follow-up only [24, 31, 60, 73].

Post-Treatment Short-Term Complications

Complications were reported in 9.0% of all patients (123/1258). The most common complications were skin burns (3.5%, 44/1258), pectoralis major muscle damage (1.1%, 14/1258), seroma (0.6%, 8/1258), skin necrosis (0.6%, 7/1258) and ecchymosis (0.6%, 7/1258). Other reported complications were blistering (0.5%, 6/1258), hematoma (0.4%, 5/1258), coagulative changes to the skin (0.4%, 5/1258), nipple retraction (0.3%, 4/1258), pneumothorax (0.2%, 3/1258), flap necrosis (0.2%, 3/1258), fever (0.2%, 3/1258), infection (0.2%, 2/1258), skin puckering (0.2%, 2/1258), skin retraction (0.2%, 2/1258) and single cases (0.1%, 1/1258) of overreaction of the ablated zone, fistula, white lumps on treated area, haemorrhage, arterial bleeding, tumour rupture and abscess. All complications were device related rather than cancer specific complications, and thus far, only one of the nine studies [21, 23, 24, 30, 32, 60, 66, 68, 73] without surgical excision of the ablated tumour post-treatment, documented longer-term complications, one patient (0.1%, 1/1258) with skin retraction which turned into skin ulceration at 12 months follow-up.

With RFA, 10.5% of patients developed post-treatment complications (58/555) of which 23 were skin burns [14-16, 26, 27, 29-32, 42, 47, 48, 66, 67], 12 muscle burns [14, 15, 48], five cases of blistering [51], four of coagulative changes to the skin [51], three were cases of ecchymosis [27, 46], three cases of nipple retraction, [31] two case of pneumothorax [15, 64], two incidences of skin puckering [44], two infections [42, 44] and single cases of overreaction [30] and fistula [47] (table 1a). With cryo-ablation 10.9% of patients (20/183)

developed a complication, these were skin necrosis (n=5) [61], haematoma (n=5) [22, 73], ecchymosis (n=4) [22], skin retraction (n=2) [73], seroma (n=2) [19, 20], arterial bleeding (n=1) [20] and skin ulceration (n=1). [73] Several patients also developed skin burns and mastitis (number unreported) [37] (table 1c). With laser ablation 6.3% of patients (12/191) developed complications, which included skin burns (n=7) [18, 33, 63], necrosis (n=2) [34], haemorrhage (n=1) [28], pneumothorax (n=1) [18] and rupture of the tumour (n=1) [33] (table 1b). With HIFU complications occurred in 6.5% of patients (12/185) which included skin burns (n=8) [8, 23, 38, 55, 57, 60], fever (n=3) [56] and white lumps at the treatment site (n=1) [72] (table 1d). Microwave ablation resulted in the most complications (14.6%, 21/144), which included skin burns (n=6) [41, 54], seroma (n=6) [54], flap necrosis (n=3) [39], muscle burns (n=2) [25], blistering(n=1) [39], coagulative changes to the skin (n=1), [25] abscess (n=1) [25, 54] and nipple retraction (n=1) [54] (table 1e).

Treated Tumour Sizes

Considering the size of treated tumours, microwave ablation was used to treat the largest tumours, with a mean tumour diameter of 2.7±1.1 cm (six studies) [25, 39-41, 54]. HIFU was used to treat tumours of 2.1±0.9 cm (seven studies) [8, 23, 24, 38, 52, 55, 72], and cryo-ablation was used to treat tumours with a mean size of 1.6±0.7 cm (eight studies) [19, 21, 22, 35-37, 49, 61]. The smallest tumours were treated with laser-ablation (1.2±0.2 cm, three studies) [34, 62, 63] and RFA (1.5±0.4 cm, 17 studies), [13, 15, 29, 30, 42, 44-48, 51, 65-69, 71] Only mean sizes were included in this analysis (table's 1a-e).

Total Treatment Duration

Considering treatment duration, RFA had the shortest mean treatment time of 15.6±5.6 minutes (20 studies) [13-15, 29-31, 42-46, 48, 51, 53, 64-68, 70]. Laser ablation had a mean treatment time of 25.7±6.1 minutes (two studies) [18, 34] and microwave ablation had a mean treatment time of 19.0±18.2 minutes (four studies) [25, 39, 40, 54]. Cryo-ablation had a much longer mean treatment time of 50.3±58.4 minutes (seven studies) [19, 21, 35-37, 61, 73] and HIFU the longest mean treatment time of 101.5±46.6 minutes (four studies). [8, 52, 57, 72] Only mean treatment times were included in this analysis (tables 1a-e).

An analysis of covariance's initially showed a significant increase in treatment time with tumour size. Correcting for tumour size, showed that microwave ablation was the quickest technique, followed by RFA, laser ablation, cryo-ablation and HIFU. A purpose written Fortran program and RFA as a baseline showed the following estimates (95% CI): MW 0.32 (0.15, 0.68), RFA 1.0 (1.0, 1.0), laser ablation 1.27 (0.76, 2.11), cryo-ablation 2.58 (1.69, 3.96) and HIFU 5.03 (3.15, 8.02). Unfortunately, on replacing tumour sizes by rank size, no significant relationship between the treatment time and tumour size was found. The apparent strong dependence of treatment time on tumour size was shown to be spurious, and driven by outlying studies with large tumour sizes and long treatment times.

Cosmetic Outcome:

Cosmetic outcome was reported in nine studies using RFA, HIFU and cryo-ablation. Seven studies [30, 32, 42, 53, 66, 67, 70] using RFA reported an excellent cosmesis in 85.3% of

patients (168/197), good cosmesis in 9.6% (19/197), acceptable cosmesis in 0.5% (1/197), fair cosmesis in 2.5% (5/197), poor cosmesis in 1.5% (3/197) and cosmesis was unknown in 0.5% (1/197). Cosmesis was collected using a 1-4 point scaling system (n=4), a 1-10 point scaling system (n=1) or it was not reported (n=2). The cosmesis was evaluated by the consultant (n=3), the patient (n=2) or this was not reported (n=2) and it was evaluated four weeks after treatment (n=2), one year after treatment (n=1), at one, three and six months after treatment (n=1) or not reported (n=3). No surgical excision was performed in three studies [30, 32, 66] and delayed surgical excision was performed in three studies [53, 67, 70] and the cosmesis in these six studies was evaluated prior to surgical excision. In one study, [42] immediate surgical excision was performed and cosmesis was evaluated after surgical excision (excellent (12), good (3) cosmesis).

With HIFU [24, 38], 59.3% of patients (16/27) graded their cosmetic outcome as good and 7.4% (2/27) as acceptable and cosmesis was unknown in nine patients (9/27, 33.3%). One follow-up study [24] evaluated the cosmesis using a 1-5 point scale at the last follow-up and cosmetic evaluation was undertaken by the consultant. The other study [38] performed delayed surgical excision and did not report on the methods used to evaluate cosmesis. With cryo-ablation [53], excellent cosmesis was reported in 92.5% (37/40) of patients, good cosmesis in 5.0% (2/40) and acceptable in 2.5% (1/40). This study performed delayed surgical excision and the cosmesis was evaluated by the consultant after four weeks, using a 1-4 point scaling system.

Discussion

The trials conducted to date demonstrate feasibility and potential benefits for minimally invasive ablative treatment of breast cancer. However, ablative techniques are generally being evaluated in small, often uncontrolled studies that are unlikely to change clinical practice or provide the basis for phase III trials. The trials in this systematic review also included four RCTs but none of these carried out adequate sample size calculations. Therefore a deficiency of this systematic review is the limited quality of published studies in this field.

The most important outcome measures are completeness of ablation, complication rate and tumour recurrence. In terms of complete ablation, the best outcomes are reported with RFA (87.1%, 491/564), microwave ablation (83.2%, 89/107) and cryo-ablation (74.1%, 186/251). Limitations exist in the comprehensive recording of reported histopathological outcomes. The most reliable way to determine cell death (especially immediately post-surgical excision) is with nicotinamide adenine dinucleotide (NADH) staining. However this type of staining was not always used. [16] With respect to radio-pathological correlation, more concordance with imaging was observed with NADH assessment of necrosis compared to haematoxylin and eosin (H&E).

The histopathology results in almost all studies described the number of patients with complete ablation. In patients with partial ablation, the percentage of viable tumour seen within the ablated zone, was only reported in three studies [57, 58, 61]. Several studies used

biopsies of the ablated zone to evaluate completion of tumour ablation. With respect to percentages of complete ablation and mean tumour size, no direct comparison can be made because of study heterogeneity. Rate of complete ablation cannot be controlled for lesion size, since lesion size was not consistently reported in each study.

The most common complications were skin burns which occurred in 3.5% of patients (44/1258, most in RFA) and damage to the pectoralis major muscle which was reported in 1.1% of patients (14/1258, most in RFA). With respect to treatment related complications laser ablation (6.3%, 12/191) and HIFU (6.5%, 12/185) have the fewest complications and most complications were reported with microwave-ablation (14.6%, 21/144). However, complications may be under-reported since some such as pain, oedema and erythema are not consistently reported in all studies. Some studies only report severe complications and others report all complications. Furthermore, not all studies evaluated the level of pain during and after treatment. Skin burns were the most serious complication described, and likely causation was not described in most studies, however in some studies the burn may have been caused by a short lump-skin distance or therapy was performed immediately after biopsies were taken. Only one longer-term complication was reported in the nine studies, without surgical excision of the ablated tumour post-treatment. All other studies included only short-term complications up until surgical excision. Large prospective trials with long-term follow-up of at least five years are required to determine the long-term complications.

Local recurrence occurred following 11 laser, nine RFA, three HIFU and one cryo-ablation treatment, however only 22 studies looked at the recurrence rates, including all nine follow-up studies. With respect to cosmesis, patients treated with cryo-ablation and RFA seem to have a better cosmesis post-treatment compared to pre-treatment than patients treated with HIFU. However, HIFU is a completely non-invasive technique which requires no incision whilst all the other techniques do require a small incision. Therefore HIFU is expected to achieve a better cosmesis. In addition, the only complications reported with HIFU were skin burns, whilst all other ablative techniques reported complications related to the insertion of the needle or probe.

Analysis of mean treatment duration, demonstrated that RFA (15.6±5.6 minutes), laser (25.7±6.1 minutes) and microwave ablation (19.0±18.2 minutes) have the shortest treatment time. Analysis of covariance was difficult due to inconsistent methods of reporting tumour sizes and treatment times. After replacing tumour sizes by their ranks, no significant relationship was found. Clearly, the choice of ablative technique in individual studies was based on access or availability of the technique rather than a conscious selection based on which ablative technique has the shortest treatment times or showed highest complete ablation rates.

The limitation of this study is that only four RCTs [54-56] and one retrospective analysis comparing two techniques [53] were included and therefore a comparative meta-analysis could not be performed. The RCTs compared HIFU and microwave ablation with

breast conserving surgery [54-56] or microwave ablation with neo-adjuvant chemotherapy with chemotherapy alone [54]. When considering histopathology, treatment time and complications, RFA demonstrated the most promise of any minimally invasive technique for the non-surgical treatment of breast cancer, but RFA is not included in the RCTs. More RCTs comparing ablative techniques with surgical excision or with each other (including RFA) are needed with sample size calculations to accurately evaluate differences between the techniques. However, initially adequately powered cohort trials should be conducted to confirm complete pathological ablation in all patients is feasible. This can be obtained by first developing a predictive tool for assessing complete ablation within treat and resect studies, by imaging the tumour post-treatment prior to surgical excision and verifying the extent of ablation on imaging with histopathological correlation. And secondly by using this predictive tool in follow-up studies to determine the amount of complete ablation. Once efficacy to achieve complete pathological ablation is confirmed, RCTs comparing the most promising ablative technique to surgical excision can be conducted to determine long-term treatment related and cancer specific complications.

Another limitation is that the cohort studies included, have considerable heterogeneity. It is therefore not possible to perform a quantitative comparison between the studies. Compared to breast surgery, these techniques have the advantage of intra-operative imaging to improve accuracy during the treatment. Other potential benefits are the low and less severe complication rates, minimal invasiveness of the techniques resulting in a short hospital stay

and recovery time which might lead to a reduction in treatment cost compared to breast surgery. [8, 9, 80] Also adjuvant therapy may be administered faster after ablative treatment, in the absence of a wound requiring healing. All the trials treated patients with invasive breast cancer or breast recurrences, for the treatment of ductal carcinoma in-situ the challenge is the lack of reliable imaging tools for real-time treatment planning and assessment of response to treatment. However, the disadvantage of these techniques is axillary staging as surgery is still required in patients with early breast cancer to perform SLNB.

Conclusion

Minimally invasive ablative techniques are able to successfully induce coagulative necrosis with a low side-effect profile but complete ablation is not achieved consistently. The best response in terms of complete ablation was reported following RFA and the fewest complications were reported following HIFU treatment. Adequately powered and prospectively conducted cohort trials are required to confirm complete pathological ablation is achievable in all patients and to develop a predictive tool for assessing complete ablation. Once this is confirmed, RCTs comparing the most promising ablative technique to surgical excision can be conducted to determine long-term treatment related and cancer specific complications.

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Authors MP, MA, AN and MD have special interest in the HIFU technique. MD has some prior experience with RFA and laser ablation. None of the other ablative techniques mentioned in the manuscript have been used by the authors.

Declaration of Interest

The authors report no conflicts of interest.

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Figures and Tables

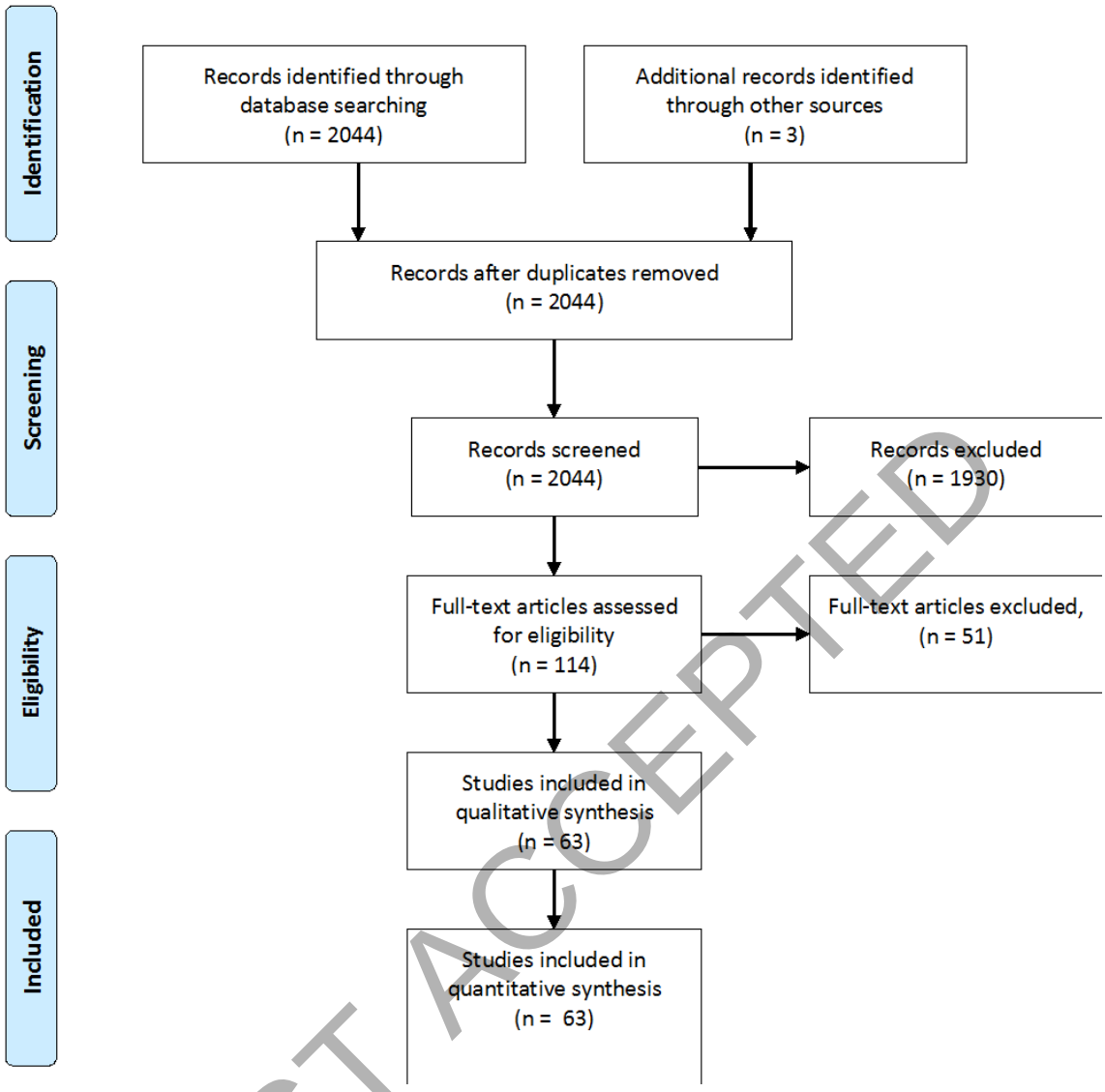
Figure 1. PRISMA 2009 Flow Diagram

Figure 2. Probabilities of success to achieve complete pathological response with 95% confidence intervals calculated using a random logistic effect model.

Table 1. Study characteristics and outcomes for (a) radio-frequency, (b) laser, (c) cryo, (d) high intensity focused ultrasound and (e) microwave ablation.

Table 2. Quality assessment (Yes/No) for (a) cohort studies and (b) randomized controlled trials.

PRISMA 2009 Flow Diagram



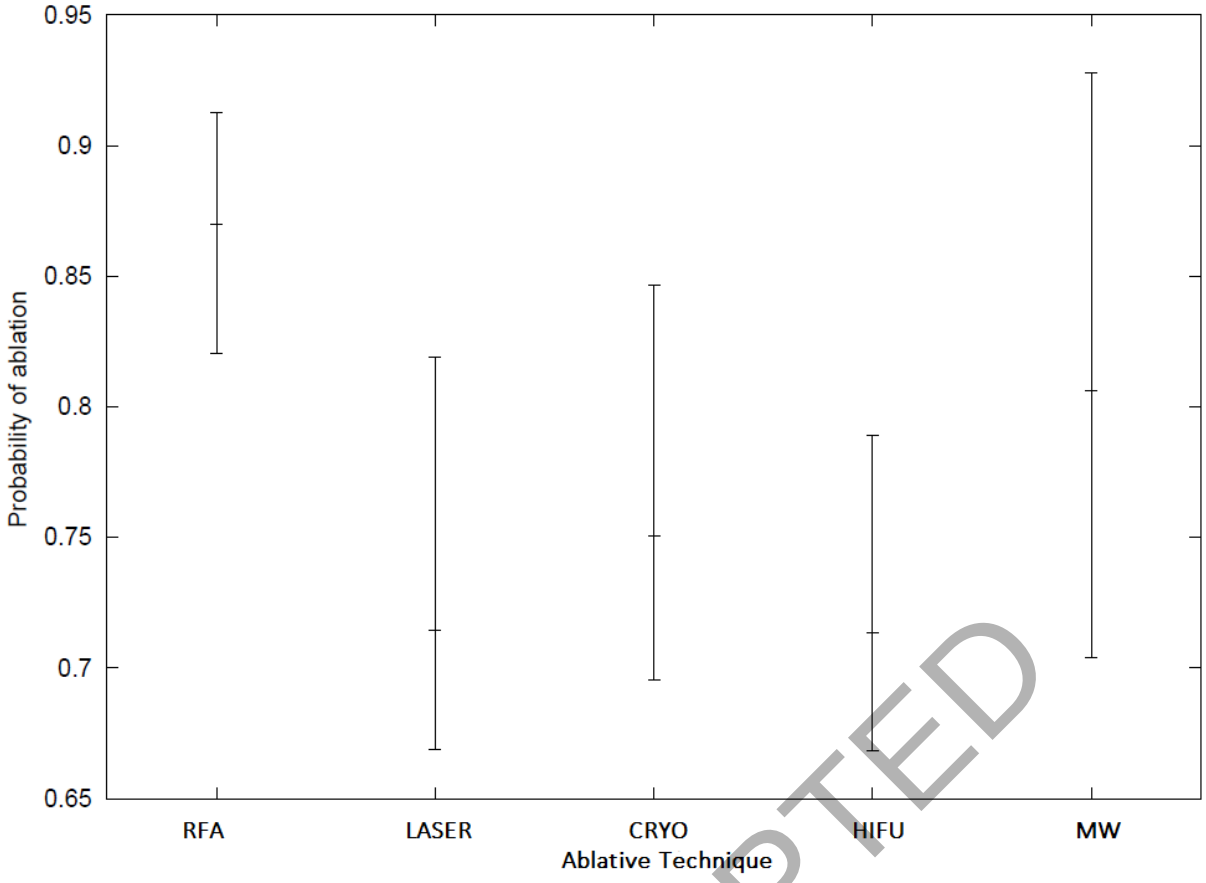


Table 1a: Study characteristics and outcomes for radiofrequency ablation (RFA)

Study	N	Size lesion (cm)*	Age (years)*	Electrode+	CA	Resection*	Complications	Treatment time (min)*
Izzo (2001)	26	1.8 (0.7-3.0)	57 (37-78) [1]	LeVeen	96% (NADH)	Immediately	Skin burn (1)	15.4 (6.4 - 24.9)
Burak (2003)	10	1.2 (0.8-1.6)	53.7 (37-67)	RadioTherapeutics	90% (H&E)	16.1 (8-24) D	Ecchymosis	13.8 (7-21)
Hayashi (2003)	22	0.9 (0.5-2.6) [1]	73 (60-80) [1]	StarBurst	86% (NADH, H&E)	1-2 wk	Skin burn (1), Ecchymosis (2)	15 (15-20.5) [1]
Singletary (2003)	29	<2.0	-	RITA Model 500 / Starburst	86% (NADH, H&E)	Immediately	Skin burn (1)	30-45
Fornage (2004)	20 (21)	1.2±0.3 (0.6-2.0)	56±11 (38-80)	StarBurst	100% (NADH)	Immediately		21.2 (18.9-29)
Noguchi (2006)	10	1.1 (0.5-2.0)	54 (33-70)	StarBurst	100% (NADH)	Immediately	-	18 (17-19.5)
Earashi (2007)	17+7	1.1 (0.5-2.4) and 1.1 (0.7-2.0)	55 (33-78) and 44 (29-55)	StarBurst	100% (NADH)	Immediately (n=17), delayed (n=7) by mammotome 91 (30-202) D[1]	-	18 (17-21.5)
Khatri (2007)	15	1.28 (0.8-1.5)	63 (39-83)	Cool-Tip	93% (NADH)	Immediately	Skin puckering (2), infection (1)	21 (7-36)
Oura	52	1.3	55 (37-	Cool-Tip	100%	Follow-up	Skin burn (1)	12 (5-25)

Study	N	Size lesion (cm)*	Age (years)*	Electrode+	CA	Resection*	Complications	Treatment time (min)*
(2007)		(0.5-2.0)	83)		(CNB)	15 (6-30) M		
Garbay (2008)	10	1.4 (1.0-2.2) [1]	50 (44-70) [1]	LeVeen	75% (NADH, n=8), 70% (H&E, n=10)	Immediately	-	10.7 (5.3 - 16.0)
Medina-Franco (2008)	25	2.1 (0.9-3.8)	55.3 (42-89)	Elektrotom	76% (NADH)	Immediately	Skin burn (3), skin infection (1), recurrence (2)	11 (9-15)
Imoto (2009)	30	1.7 (0.9-2.4) [1]	38-76	LeVeen	92% (NADH), 87% (H&E)	Immediately	Skin burn (2, incl skin necrosis(1)), pectoralis major burn (7)	18 (4-42)
Manenti (2009)	34	1.9±0.6 (1.7-2.0)	53±5 (49-62)	Cool-Tip	97% (NADH)	4 wk	Skin burn (1)	27±3.7 (25-35)
Nagashima (2009)	17	1.1 (0.6-1.8)	61.8 (47-71)	Cool-Tip	100% (Imaging)	Follow-up 19M (12-28) [1]	-	9.6 (6.5-17)
Motoyoshi (2010)	2x17	1.5 (0.5-2.1) and 1.2 (0.5-2.0)	55 (33-78) [1] and 45 (22-59) [1]	StarBurst	100% (NADH, n=33), 64.7% (H&E, n=34)	Immediately, delayed 30-202 D	Recurrence(3)	-
Wiksell (2010)	31	1.1±0.3 (0.6-1.5)	63.6±8.9 (46-83)	NeoDynamics AB	84% (H&E)	Immediately	Skin burn (1), muscle burn (2), pneumothorax (1)	9.5±1.2 (6.5-11)
Hung	2x1	1.4±0.	60±12	LeVeen and	90%	Immediatel	Blistering	28±6 vs

Study	N	Size lesion (cm)*	Age (years) *	Electrode+	CA	Resection*	Complications	Treatment time (min)*
(2011)	0	3 vs 1.3±0.3	vs 57±9	Cool-Tip	and 89% (H&E, NADH)	y	(5), coagulative changes to skin (n=4)	12±0
Kinoshita (2011)	49	1.7 (0.5-3.0)	61 (36-82) [1]	Cool-Tip	61% (H&E and NADH)	Immediately	Skin burn (2), muscle burn (3)	8.7 (3-18)
Ohtani (2011)	41	1.3 (0.6-3.5) [1]	59 (38-92) [1]	Cool-Tip	87.8% (H&E, NADH)	Immediate (n=9), delayed 1-2 M (n=32)	Skin burn (1)	9 (6-15)[1]
Tsuda (2011)	28	2.2±1.3 (0.6-5.0)	59.1 (36-82)	Cool-Tip	79% (NADH)	Immediately	-	-
Yamamoto (2011)	29 (30)	1.3 (0.5-1.9)	55.9 (38-78)	Cool-Tip	92% (NADH, n=26)	Follow-up 17 (2-41) M	Skin burn (3), overreaction (1)	11.4 (6-20)
Noguchi (2012)	19	1.3 (0.5-2.0) [1]	45 (22-59) [1]	StarBurst	100% (NADH, n=18)	30 (24-202)D [1]	-	15
Palussiere (2012)	21	2.0[1]	79 (70-88) [1]	LeVeen	-	Follow-up 49.6 (17-77)M [1]	Skin burn (4), nipple retraction (3), recurrence (3)	11 (4-19)
Vilar (2012)	14	1.8 (1.0-2.5)	56 (37-71)	LeVeen	50% (H&E)	3 wk	skin burn (1), fistula (1)	-
Manenti (2013)	40	-	73±5 (64-82)	Miras PTV	92.5% (H&E, NADH)	34 (30-45) D	-	27 (24-35)
Yoshinaga (2013)	6+8	1.2 (0.6-	67 (45-82) [1]	Cool-Tip	100% (n=7), 100% (NADH,	Immediate (n=6), follow-up 39.9 M	Skin burn (1)	9.6 (4.8-14.7) [1]

Study	N	Size lesion (cm)*	Age (years) *	Electrode[+]	CA	Resection*	Complications	Treatment time (min)*
		2.0) [1]			n=5)	(n=8) [1]		
Schassburger (2014)	18	1.0 (0.6-1.5) [1]	67 (46-84) [1]	NeoDynamics	89% (CK8)	14.5 (6-22) D[1]	-	10 (8-14) [1]
Waaijer (2014)	15	1.1 (0.4-1.7) [1]	63 (50-76) [1]	CelonProSurge	77% (n=13)	Immediately	Pneumothorax (1), recurrence (1)	13±0.2 (6-26)

CA = complete ablation, d= days, H&E = haematoxylin and eosin, m= months, min = minutes, N = number of patients, NADH = nicotinamide adenine dinucleotide, wk = weeks, yr = years.

* Values are Mean±SD (range), unless indicated otherwise by [1] in which case it is medium (range).

[+] Cool-Tip RF Needle Electrode (Radionics, Burlington, MA); Elektrotom 106 HiTT, (Berchtold, Germany); LeVeen needle electrode (RadioTherapeutics Corporation, Mountain View, CA); Miras PTV (University Hospital Policlinico Tor Vergata, Rome, Italy and INVATEC ITALIA, Roncadelle, Brescia, Italy); Unknown model type (NeoDynamics AB, Sweden); StarBurst radioprobe (RITA Medical Systems, Mountain View, California); bipolar radiofrequency ablation system was used (CelonProSurge150-T20, Olympus Winter & Ibe GmbH, Hamburg, Germany).

Table 1b: Study characteristics and outcomes for laser ablation

Study	N	Size (cm)*	Age (yr)*	Device [+]	CA	Complications	Resection*	Time (min)*
Harries (1994)	44	-	-	Diomed	-	Haemorrhage (1)	1-34 D	3.3-12.5
Mumtaz (1996)	20 (27)	2.0 (0.4-3.3) [1]	57 (34-79) [1]	Diomed	-	-	5 (1-15) D [1]	5.0-8.3
Akimov (1998)	28+7	3.0 (1.0-6.0) [1]	53 (38-78) [1]	Nd:YAG	-	Gaseous rupture of the tumour (1), skin burn (4), recurrence (9)	Delayed (n=28) 1-11 D, follow-up (n=7) 20.5 (5-64) M	-
Bloom (2001)	40	0.95 (0.5-2.3)	60 (42-80)	Diomed	-	-	14.5 (0-70) D	-
Dowlatshahi (2002)	54	1.3 (0.5-2.3)	60 (42-80)	Diomed	70%	Skin burn (2)	1-8 wk	25- 30
Haraldsdottir (2008)	24	1.4 (0.5-3.5)	61 (39-84)	Diomed	12.5% (H&E)	Skin necrosis (2), recurrence (2)	12 (4-23) D	30
Van Esser (2009)	14	1.7 (0.8-3.7) [1]	54.5 (35-85) [1]	Nd:YAG	50% (NADH)	Skin burn (1), pneumothorax (1)	Immediately	21.4 (15-30)

CA = complete ablation, d= days, H&E = haematoxylin and eosin, m= months, min = minutes, N = number of patients, NADH = nicotinamide adenine dinucleotide, wk = weeks, yr = years.

* Values are Mean±SD (range), unless indicated otherwise by [1] in which case it is medium (range).

[+] Diomed, (Cambridge, UK); Nd:YAG laser (Polar Ltd., Russia)

Table 1c: Study characteristics and outcomes of cryo-ablation

Study	N	Size (cm)*	Age (years)*	Device type [+]	CA	Complications	Resection*	Time (min)*
Pfleiderer (2002)	15 (16)	2.2±0.93 (0.9-4.0)	60.3±9.4 (38-80)	CryoHit	31.3%	Seroma (1)	1-5 D	52.4±7.1 (41-64)
Tafra (2003)	24	1.2±0.4 (0.7-2.0)	61 (41-78)	Visica	-	-	Immediately	15.8±7.6 (14[1])
Sabel (2004)	29	1.2±0.5 (0.6-2.0)	52.5 (34-77)[1]	Visica	85% (H&E, n=27)	-	14 (6-30) D	30
Morin (2004)	25	3.0 (1.2-6.0)	61.0 (41-77)	CryoHit	52%	Minimal skin burn (?) and mastitis (?)	4 wk	180
Pfleiderer (2005)	30	1.2 (0.5-1.5)[1]	61.5 (48-80)[1]	CryoHit	83% (H&E)	Arterial bleeding (1), seroma (1)	11±9.2 D	40-75
Pusztaszeri (2007)	11	1.3 (0.5-2.5)	63 (52-78)	CryoHit	20% (H&E)	Skin ulceration and/or necrosis (5)	4-5 wk	20
Littrup (2009)	11 (18_4 LN)	1.7±1.2 (0.5-5.8)	62.5	Endocare	100% (CNB, n=6)	-	Follow-up 22.8 M	24.7 (14-33)
Manenti (2011)	15	0.8±0.4 (4-1.2)	73±5 (64-82)	IceRod®	93.3% (H&E)	Subcutaneous haematoma (2), ecchymosis (4)	34 (30-45) D	-
Manenti	40	-	73±5	IceRod®	95% (H&E,	-	34 (30-45) D	-

Study	N	Size (cm)*	Age (years)*	Device type [+]	CA	Complications	Resection*	Time (min)*
(2013)			(64-82)		NADH)			
Luigi Cazatto (2015)	23	1.4 (0.5-2.8)[1]	85 (56-96)[1]	IceSphere and IceRod®	-	Haematoma (3), skin burn to imflammation to skin retraction (1), haematoma to skin retraction (1), skin retraction to ulceration (1), recurrence (n=1)	Follow-up 14.6 M[1]	29.4
Simmons (2016)	86 (87)	1.2±0.3 (0.5-1.9)	61.1±9.3 (42-81)	Visica	75.9 % (H&E)	-	<4 wk	-

CA = complete ablation, d= days, H&E = haematoxylin and eosin, m= months, min = minutes, N = number of patients, NADH = nicotinamide adenine dinucleotide, wk = weeks, yr = years.

* Values are Mean±SD (range), unless indicated otherwise by [1] in which case it is medium (range).

[+] CryoHit (Galil Medical, Yokneam, Israel); Endocare, (Irvine, California); IceRod® and IceSphere models (Galil Medical, Yokneam, Israel); Visica Cryoablation System (Sanarus Medical, Inc., Pleasanton, CA).

Table 1d: Study characteristics and outcomes for high intensity focused ultrasound (HIFU)

Study	n	Size (cm)*	Age (years)*	Guidance and device [+]	CA	Resection*	Complications	Time (min)*
Gianfelice (2003)	12	2.8 (0.1-8.8) cm^3	60±9.6 (45-74)	MRI, ExAblate 2000	17% (H&E)	Delayed (unknown time)	Skin burn (2)	80 (35-133)
Gianfelice (2003)	17	2.5 (0.1-8.8) cm^3	61.2±8.9 (48-76)	MRI, ExAblate 2000	24% (H&E)	3-21 D	-	-
Gianfelice (2003)	24	1.5 (0.6-2.5)	74.2 (53-92)	MRI, ExAblate 2000	79%	Follow-up 20.2 M (12-39)	Skin burn (1)	-
Wu (2003)	23	3.1±0.8 (2.0-4.7)	46.5±1.7	US, JC HAIFU	100% (H&E)	1-2 wk	Skin burn (1)	78 (45-150) [1]
Wu (2005)	22	3.4 (2.0-4.8)	48.6(36-68)	US, JC HAIFU	100% (H&E)	Follow-up 54.8 M (36-72) [1]	Recurrence (2)	132 (60-180) [1]
Zippel (2005)	10	2.2	56 (45-72)	MRI, ExAblate 2000	20%	7-10 D	Skin burn (1)	Max 240
Khiat (2006)	25 (26)	3.3 (0.1-11.2) cm^3	61.3±11 (45-87)	MRI, ExAblate 2000	31% (8/26)	3-21 D	-	-
Furusawa (2006)	28	1.3 (0.5-2.5)	56.9 (41-79)	MRI, ExAblate 2000	53.5% (H&E)	5-23 D	Skin burn (1)	140 (76-231)
Furusawa (2007)	21	1.5 (0.5-5.0) [1]	54 (34-72) [1]	MRI, ExAblate 2000	-	Follow-up 14 M (3-26)	Skin burn (2), recurrence (1)	-

Study	n	Size (cm)*	Age (years)*	Guidance and device [+]	CA	Resection*	Complications	Time (min)*
Cavallo-Marincola (2013)	10	1.2	-	MRI, Exablate 2100	60%	24-35 D	-	140 (80-180)
Merckel (2016)	10	2.0±0.6	54.8±12.5	MRI, Sonalleve	-	5.0±2.2 D	White lumps (1)	46±17 (12-75)
Guan (2016)	25	(2.1-4.8)	48 (22-63)	US, JC HAIFU	-	1-2 wk	Fever (3)	66 (40-132)[1]

CA = complete ablation, d= days, H&E = haematoxylin and eosin, m= months, min = minutes, N = number of patients, NADH = nicotinamide adenine dinucleotide, wk = weeks, yr = years.

* Values are mean ± SD (range), unless indicated otherwise by [1] in which case it is medium (range).

[+] JC HAIFU (Chongqing Haifu Tech Co., Ltd., China); ExAblate 2000; InSightec-TxSonics, Haifa, Israel and Dallas, Tex); Sonalleve (Philips heathcare, Finland);

Table 1e: Study characteristics and outcomes for microwave ablation

Study	N	Size (cm)*	Age (years)*	Device[+]	CA	Complications	Resection*	Time (min)*
Gardner (2002)	10	4.3 (1-8)	58.5 (47-82)	Medifocus 1000 APA	-	Flap necrosis (3), blister (1)	5-27 D	34.7 (12-40)
Vargas (2004)	25	1.76 (0.7-2.8)	57.2	Medifocus 1000 APA	68% (H&E)	Skin burn (3)	17 (6-38) D	-
Dooley (2010)	41	1.6 (0.7-2.73)	58.0	Medifocus 1000 APA	85.3% (H&E)	Skin burn (3), nipple retraction (1), seroma (6), abscess (1)	19.6 (7-60) D	-
Dooley (2010)	15	3.65 (2.0-7.8)	45.1 (26-72)	Medifocus 1000 APA	-	Skin burn (5 treatments)	Delayed (unknown)	34.8
Zhou (2012)	41	2.0±0.5 (1.0-3.0)	55.5±11.4 (38-78)	-	90% (NADH)	Skin injury (1), pectoralis major injury (2)	Immediate	4.48±2.03 (3-10)
Zhou (2014)	12	2.89±0.44	54 (34-61)[1]	-	-	-	>3 wk	2.15 (1.3-3)

CA = complete ablation, d= days, H&E = haematoxylin and eosin, m= months, min = minutes, N = number of patients, NADH = nicotinamide adenine dinucleotide, wk = weeks, yr = years.

* Values are Mean±SD (range), unless indicated otherwise by [1] in which case it is medium (range).

[+] Medifocus-1000 APA (Celsion Corporation, Columbia, MD)

Table 2: Quality assessment (Yes/No) for (a) cohort studies and (b) randomized controlled trials.

(a)	Objective	Incl. criteria	Standardised			Follow-up	With-drawals
			Technique	Histopathology	Imaging		
Radiofrequency ablation	27/0	26/1	25/2	27/0	11/3 (13 -)	12/15	0/27
Cryo-ablation	10/0	8/2	9/1	9/1	4/1 (5 -)	3/7	2/8
Laser ablation	7/0	4/3	7/0	6/1	3/2 (2 -)	3/4	1/6
HIFU	10/0	9/1	8/2	5/5	10/0	3/7	3/7
Microwave ablation	4/0	3/1	4/0	4/0	1/0 (3 -)	0/4	0/4
Combined technique	1/0	1/0	1/0	1/0	1/0	0/1	0/1

Study quality was assessed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.
- no data available to answer

(b)	Adequate sequence generation	Power analysis	Concealed allocation	Blinding	Incomplete data addresses	Free of other bias	Free selective reporting
HIFU	U	0/2	U	0/2	0/2	2/0	2/0
Microwave ablation	U	0/2	U	0/2	1/1	2/0	2/0

U = unspecified
Study quality was assessed according to the “Risk Bias Tool” in the Cochrane Handbook.