Review

Minimally-invasive thermal ablation of early-stage breast cancer: A systemic review

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Accepted 13 September 2010

Abstract

Background: Minimally-invasive thermal ablation techniques provide an effective approach for local destruction of solid tumor. A novel application is the use for treatment of early-stage breast carcinoma.

Methods: A broad search was conducted in Pubmed, Embase and the Cochrane databases between January 1990 and December 2009. Clinical results of the relevant articles were collected and analyzed.

Results: The analyzed studies were almost all feasibility or pilot studies using different energy sources, patients, tumor characteristics and ablation settings. They were conducted in research settings for the assessment of technical safety and feasibility, and none of those was used alone in clinical practice. Despite many methodological differences, complete tumor ablation could be achieved in 76e100% of breast cancer patients treated with radiofrequency ablation, 13e76% in laser ablation, 0e8% in microwave ablation, 36e83% in cryoablation, and 20e100% in high-intensity focused ultrasound ablation.

Conclusion: Minimally-invasive thermal ablation is a promising new tool for local destruction of small carcinomas of the breast. Large randomized control studies are required to assess the long-term advantages of minimally-invasive thermal ablation techniques compared to the current breast conserving therapies.

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Keywords: Thermal ablation; Ablative interventions; Radiofrequency; Laser; Cryoablation; Microwave; High-intensity focused ultrasound; Breast, Neoplasms; Humans

Introduction

Breast cancer is the most frequently occurring female cancer, and the leading cause of mortality from cancer in women. There were an estimated 1.15 million new breast cancer cases in 2002.1 Radical mastectomy has been accepted as an appropriate therapy for breast cancer for a long time. The move from mastectomy to breast conservation therapy has not affected the long-term survival rates of patients in the past decades. Today, breast conservation surgery is performed increasingly often in patients with early-stage breast cancer.

In the context of this background, non-surgical minimally-invasive thermal ablation techniques have been explored with the intention of achieving equivalent efficacy to that achieved with breast conservation therapy, but with improved cosmesis. Using either percutaneous or extracorporeal approach, local tumor destruction occurs while destructive energy is transmitted into a breast lesion, and all the targeted breast cancer cells are completely destroyed, instead of local tumor removal. They employ various kinds of physical energy to raise the temperature between 56 and 100 °C, or to drop the temperature to a freezing point in a targeted tumor, and thus induce complete destruction.2 Due to differences in energy sources and their delivery, these thermal techniques can be classified into five categories as follow: radiofrequency ablation (RFA), laser ablation (LA), microwave ablation (MWA), cryoablation, and

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high-intensity focused ultrasound (HIFU) ablation. Each method has unique characteristics for breast tissue ablation. A summary comparing the varied methods is shown in Table 1.

Compared with surgical procedure, the main advantages of minimally-invasive thermal therapies are less invasive with no incision, less scarring, cheap, less pain and short recovery time. These result in an associated reduction in mortality, morbidity, hospital stay, cost and improved quality of life for cancer patients. The purpose of this paper is to review the published experiences in the clinical use of thermal ablation techniques for patients with early-stage breast cancer, and to compare the clinical results of recent studies in this application.

Materials and methods

This is a systematic review of published clinical experiences using minimally-invasive thermal ablation techniques for the treatment of breast cancer. A literature search was undertaken for all clinical studies involved in minimally-invasive thermal ablation of breast cancer. Articles were selected from the Medline, Embase and the Cochrane databases between January 1990 and December 2009. Study designs included retrospective, match-paired analysis, prospective non-randomized and randomized trials. If more than one trial contained overlapping patients from the same institution, the most recent publication was included.

Two sets of key words were used for the search strategy. One was for the ablative interventions, including radiofrequency, laser, cryoablation, microwave, high-intensity focused ultrasound, catheter ablation, ablative therapy, thermal ablation and ablation techniques. The other set was for breast cancer, and the key words used were humans, female, breast, breast neoplasms/pathology, and breast neoplasms/surgery. For the purpose of the study, we defined the thermal ablation techniques as the locally interventional treatment for human breast cancer.

Both English and non-English literatures were adopted, but non-English literatures should have an English abstract available. Relevant articles selected in peer-review journals, including non-English papers with English abstracts, were assessed in detail. If the articles were appropriate, they were then included in the reference lists of the review. A data form was specifically designed to collect all relevant information in the articles used for the review. They included the parameters analyzed, the type of analysis conducted and the results obtained. Data analysis was performed after data collection was fully finished.

Results

Initial literature search revealed 135 possible papers. However, using the selection criteria quoted in the methodology, only 38 studies fulfilled the inclusion criteria. The analysis involved 38 clinical studies published from 1994...
to 2009, and 844 patients with breast cancer underwent minimally-invasive thermal ablation. Thirty-four clinical studies were prospective in design, and received the approval of institute ethic committees. Thermal ablation was usually indicated in patients with small, well-localized breast cancer, which was diagnosed with imaging modalities and histologically confirmed by biopsy. The methods used for the identification of breast cancer were based not only on clinical examination (palpation), but also on mammography, ultrasound, and MRI. Either needle or core biopsy was performed to confirm the pathological diagnosis of breast cancer before ablation procedure. The majority of the tumors analyzed in the studies were in the early stage, and the breast lesions ranged from 0.5 to 2.0 cm in size, with a demarcated margin. The ablation procedure was usually guided by either ultrasound or MR imaging.

Two types of clinical studies have been performed to support thermal ablation as a local therapy of breast cancer. The first type of the studies is designed to investigate the ability of thermal ablation to adequately destroy a targeted breast cancer. They are phase I and II clinical trials for assessing the feasibility and safety of thermal ablation. The ablated tumor was removed immediately or 1–4 weeks after thermal ablation, and histopathologic examinations were performed to evaluate tumor viability. Most forms of thermal ablation are currently at this stage until now. The second type of the clinical studies focuses on identifying what happens to breast tumors after ablation in terms of survival benefit and local appearance, in combination with chemotherapy, radiation, endocrine and biological therapies. In addition to oncological assessments, follow-up radiological examinations were performed to detect tumor response and recurrence. Clinical studies for long-term follow-up results are still underway.

Radiofrequency ablation

Radiofrequency ablation (RFA) has been widely used to ablate liver tumors for a long time in clinical practice. The first study of RFA in human breast cancer was performed in 1999 by Jeffrey et al., and complete ablation was found in 4 of 5 enrolled patients, with no complications.3

Subsequently, several investigators reported feasibility studies of RFA for small breast cancer.4–11 The tumor was removed immediately or 1–4 weeks after RF ablation, and tumor viability was evaluated on histopathologic examinations. The results of these studies are summarized in Table 2, and the rates of complete coagulation necrosis ranged from 76 to 100% in this series. Thus, preliminary experiences of RFA for small breast cancer, followed by surgical excision, were encouraging.

Several pilot studies were performed to investigate the effectiveness of RFA for treatment of breast cancer in elderly patients, and all patients were followed up after the ablation, without any surgical excision. Susini et al.12 reported the first short-term result of RFA in three elderly patients with inoperable breast cancer, and no evidence of local recurrence was found by MRI and core-needle biopsy after 18 months of follow-up. RFA was also performed after hormone therapy in four elderly inoperable patients, and there was no breast recurrence in three patients who received breast radiation with a mean follow-up of 29.4 months.13 Oura et al.14 performed RFA, followed by breast radiation therapy in 52 patients, and reported no breast recurrence with a mean follow-up of 15 months. Breast cosmetic results after RF ablation was excellent in 43 patients (83%), good in 5 (12%), and fair in 3 (6%). Thus, based on these early results, this technique is promising as a local treatment for small breast cancer. However, the follow-up periods are too short to allow investigation of tumor recurrence and survival rates, and the long-term cosmetic appearance of the ablated area of the breast is still unknown.

Laser ablation

The term laser ablation (LA) also refers to as laser photocoagulation or laser interstitial thermal therapy. Almost all studies on laser ablation were designed to investigate

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The results of feasibility studies using radiofrequency ablation for breast cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
</tr>
<tr>
<td>Jeffrey3</td>
<td>5</td>
</tr>
<tr>
<td>Izzo4</td>
<td>26</td>
</tr>
<tr>
<td>Burak5</td>
<td>10</td>
</tr>
<tr>
<td>Hayashi6</td>
<td>22</td>
</tr>
<tr>
<td>Fornage7</td>
<td>21</td>
</tr>
<tr>
<td>Earashi8</td>
<td>24</td>
</tr>
<tr>
<td>Imoto9</td>
<td>30</td>
</tr>
<tr>
<td>Medina-Franco10</td>
<td>25</td>
</tr>
<tr>
<td>Manenti11</td>
<td>34</td>
</tr>
</tbody>
</table>
the safety and feasibility of LA for the treatment of breast cancer. Surgical resection was followed 0–70 days after LA, followed by histopathologic examinations to determine the extent of coagulation necrosis in the targeted tumor. The results of these studies are summarized in Table 3. Although four studies did not mention the complete ablation rate, tissue damage was clearly seen in 90–100% of ablated breast cancer.15–18 Three studies showed that complete ablation of the breast cancer was achieved in 13–70% of the patients with T1–T3 tumors.19–21 Apart from small skin burns, a gaseous rupture of the tumor was noted as a serious complication of LA.17

The largest clinical experience with LA for breast cancer was reported by Dowlatshahi et al.19 Fifty-four patients were enrolled in this study, and the results showed that the complete ablation rate was 70%, whereas 96% complete ablation was observed in the most recent series of 28 patients. In addition, he reported a 70-year-old woman who underwent LA for a 7 mm low-grade invasive breast cancer without surgery. The patient was placed on tamoxifen (20 mg/day), and followed up closely at 3- to 6-month intervals. There was no evidence of recurrence 3 years after LA.22 Based on promising results in the feasibility study, Esser et al.23 followed up 7 patients who underwent LA. Among them, three were stage IV patients, and LA was intended for palliative treatment. The remaining 4 patients were diagnosed as stage I–III breast cancer, and LA was used as an alternative to surgery in the primary treatment. The results showed that local tumor control was achieved in five patients, and disease-free survival was 19–60 months in three patients with stage I–III breast cancer.

**Microwave ablation**

Clinical experiences of using microwave ablation (MWA) for breast cancer are limited. Gardner et al.24 reported the first pilot study in which 10 patients with biopsy-proven invasive breast cancer underwent focused microwave ablation, followed by mastectomy. Histopathologic examinations showed that tumor necrosis was noted in 4 of 10 specimens and apoptosis in 6, but no complete ablation was observed. Complications included skin burn in 1 patient and skin flap necrosis in 3 after mastectomy.

The same group also published another article focusing on sentinel lymph node mapping after thermal ablation.25 The sentinel lymph node was found in 19 (91%) of 21 patients, and axillary metastases were detected in 9 (42%) of 21 patients. Finally, this group reported a prospective, non-randomized dose-escalation study.26 Twenty-five women with invasive breast cancers underwent MWA, and H&E staining showed pathological necrosis in 17 patients (68%), including 2 patients with complete ablation. Complications mentioned were mild pain during treatment, skin burn, and short-lived erythema of the skin.

**Cryoablation**

Cryoablation is an alternative technique that uses extreme cold to freeze a targeted tumor in the form of an “ice-ball”. A typical cryoablation session involves a freeze—thaw—freeze cycle. The argon and helium gases are alternately delivered to achieve extra- and intra-cellular ice-crystal formation and tissue osmosis. This process causes protein denaturation, rupture of cell membranes and cellular death.

The first breast cancer patient treated with cryoablation was presented in 1997 by Rabin et al.27 Until now, almost all clinical trials of using cryoablation for breast cancer are both pilot and feasibility studies.28–32 as shown in Table 4. All patients receive surgical excision 5 days to 6 weeks after cryoablation. Complete ablation of the tumor, which is confirmed by histopathologic examinations, ranges from 36% to 83%. Twenty-nine women with early-stage breast cancer were treated with cryoablation in a multi-institutional study, followed by surgical resection 1–4 weeks later.28 The results showed that cryoablation successfully destroyed 100% of cancers in all patients with tumor leas

![Table 3](image)

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Tumor size (cm)</th>
<th>Histological staining</th>
<th>Complete ablation</th>
<th>Complication</th>
<th>Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harries15</td>
<td>44</td>
<td>1.0–5.0 (Mean: unknown)</td>
<td>HE staining</td>
<td>Unclear, but ablation seen in 91% tumors</td>
<td>Nil</td>
</tr>
<tr>
<td>Mumtaz16</td>
<td>20</td>
<td>0.4–3.3 (Mean: 2.0)</td>
<td>HE, NADH staining</td>
<td>Unclear, but ablation seen in 90% tumors</td>
<td>Nil</td>
</tr>
<tr>
<td>Akimov17</td>
<td>28</td>
<td>1.0–6.0 (Mean:3.0)</td>
<td>HE staining</td>
<td>Unclear, but ablation seen in all tumors</td>
<td>Gaseous rupture of tumor (4%), skin burn (7%)</td>
</tr>
<tr>
<td>Bloom18</td>
<td>40</td>
<td>0.5–2.3 (Mean:0.95)</td>
<td>HE staining</td>
<td>Unclear, but ablation seen in all tumors</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Dowlatshahi19</td>
<td>54</td>
<td>0.5–2.2 (Mean:1.2)</td>
<td>HE staining</td>
<td>70%</td>
<td>Skin burns (4%)</td>
</tr>
<tr>
<td>Korourian20</td>
<td>29</td>
<td>1.8–4.0 (Mean: 2.6)</td>
<td>HE staining, PCNA immunohistochemistry</td>
<td>76%</td>
<td>Skin burn (7%)</td>
</tr>
<tr>
<td>Haraldsdottir21</td>
<td>24</td>
<td>0.5–3.5 (Mean:1.4)</td>
<td>HE staining</td>
<td>13%</td>
<td>Skin burn (8%)</td>
</tr>
<tr>
<td>van Esser23</td>
<td>14</td>
<td>0.8–3.7 (Mean: 1.7)</td>
<td>HE, NADH staining</td>
<td>50%</td>
<td>Skin burn (7%), pneumothorax (7%)</td>
</tr>
</tbody>
</table>
than 1 cm. For tumors >1.5 cm, cryoablation was not reliable with this technique in terms of complete ablation.

Similar results were observed in cryoablation when breast lesion was less than 15 mm, and complete ablation was achieved in 24 (83%) of 29 patients with small breast cancer. Cryoablation was also performed under MRI guidance in two studies, but complete ablation achieved was low, ranging from 36% (4/13) to 52% (13/25) in patients with invasive breast cancer. Cyrotherapy seems more successful in treating invasive than in situ disease. Roubidoux et al. reported their clinical experience with cryoablation for small breast cancers. With ultrasound guidance, seven of nine treated patients had no residual disease, which was confirmed by histopathologic examinations.

**High-intensity focused ultrasound ablation**

Of all of the minimally-invasive therapies, high-intensity focused ultrasound (HIFU) ablation is the only non-invasive approach proposed to date. It employs extracorporeal ultrasound energy to ablate the conformal confluent volume of a targeted tumor at depth, without any needle insertion.

The first HIFU-treated case was reported by Hübner et al. Table 5 shows a summary about clinical results of breast cancer. Wu et al. undertook a randomized clinical trial phase I and II using ultrasound-guided HIFU for the treatment of breast cancer. Twenty-two patients underwent ultrasound-guided HIFU treatment. The cosmetic result was judged to be good to excellent by 94% of patients. Gianfelice et al. reported the initial use of MRI-guided HIFU ablation for patients with invasive breast cancer, and complete ablation was observed by histopathologic analysis in 4 (24%) of 17 patients. Similar results were also found in another feasibility study, with complete ablation in 2 (20%) of 10 patients with infiltrating breast cancer. Using MRI-guided HIFU, Furusawa et al. found that 15 (53.5%) of 28 evaluable patients with breast cancer had 100% necrosis of the ablated tumor, 10 (35.8%) had 95–97%, and 3 (10.7%) had less than 95% necrosis. Gianfelice et al. followed up 24 patients treated with MRI-guided HIFU device for 13–39 months (mean: 20.2 months), including 10 patients undergoing a second HIFU due to residual tumor cells. Core biopsy showed 19 of 24 patients (79%) had negative biopsy results after 1 or 2 HIFU sessions.

Recently, Wu et al. reported long-term survival data from a prospective phase III clinical trial. Twenty-two patients with breast cancer underwent ultrasound-guided HIFU ablation with conservative intent for the primary lesion, followed by chemotherapy, radiation therapy and tamoxifen therapy. The five-year disease-free survival and recurrence-free survival rates were 95% and 89%, respectively. The cosmetic result was judged to be good to excellent by 94% of patients. Gianfelice et al. reported follow-up results (3–26 months; mean, 14 months) in 21 patients undergoing MRI-guided HIFU treatment. One case had local recurrence, but no evidence of recurrence was detected through MRI in the remaining 20 (95%) patients.

**Table 4**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Tumor size (cm)</th>
<th>Image guidance</th>
<th>Histological staining</th>
<th>Complete ablation</th>
<th>Complication</th>
<th>Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabel32</td>
<td>29</td>
<td>1.0–5.0 (Mean unknown)</td>
<td>Ultrasound</td>
<td>HE staining</td>
<td>Unclear, but 100% seen in patients with a tumor &lt; 1.0 cm</td>
<td>None mentioned</td>
</tr>
<tr>
<td>Morin29</td>
<td>25</td>
<td>1.2–6.0 (Mean: 2.98)</td>
<td>MRI</td>
<td>HE staining</td>
<td>52%</td>
<td>Skin burn at probe entry site</td>
</tr>
<tr>
<td>Roubidoux30</td>
<td>9</td>
<td>0.8–1.8 (Mean: 1.2)</td>
<td>Ultrasound</td>
<td>HE staining</td>
<td>78%</td>
<td>Nil</td>
</tr>
<tr>
<td>Pfleiderer31</td>
<td>29</td>
<td>0.5–1.5 (Mean: 1.2)</td>
<td>Ultrasound</td>
<td>HE staining</td>
<td>83%</td>
<td>Nil</td>
</tr>
<tr>
<td>Pusztaszeri32</td>
<td>11</td>
<td>0.5–2.5 (Mean: 1.3)</td>
<td>MRI</td>
<td>HE staining</td>
<td>36%</td>
<td>Skin ulceration and necrosis (45%)</td>
</tr>
</tbody>
</table>

**Table 5**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Tumor size (cm)</th>
<th>Image guidance</th>
<th>Histological staining</th>
<th>Complete ablation</th>
<th>Complication</th>
<th>Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gianfelice33</td>
<td>17</td>
<td>&lt;3.5 (Mean: unknown)</td>
<td>MRI</td>
<td>HE staining</td>
<td>24%</td>
<td>None mentioned</td>
</tr>
<tr>
<td>Zippel34</td>
<td>10</td>
<td>&lt;3.0 (Mean: 2.2)</td>
<td>MRI</td>
<td>HE staining</td>
<td>20%</td>
<td>Skin burn (10%)</td>
</tr>
<tr>
<td>Gianfelice35</td>
<td>24</td>
<td>0.6–2.5 (Mean: 1.51)</td>
<td>MRI</td>
<td>HE staining (core biopsy)</td>
<td>58.3% (1 session)</td>
<td>Skin burn (4%)</td>
</tr>
<tr>
<td>Furusawa36</td>
<td>30</td>
<td>0.5–2.5 (Mean: 1.3)</td>
<td>MRI</td>
<td>HE staining</td>
<td>53.5%</td>
<td>Skin burn (3%)</td>
</tr>
<tr>
<td>Wu37</td>
<td>23</td>
<td>2.0–4.7 (Mean: 3.1)</td>
<td>Ultrasound</td>
<td>HE, NADH staining</td>
<td>100%</td>
<td>Skin burn (4%), moderate pain (17%)</td>
</tr>
</tbody>
</table>
Discussion

Minimally-invasive ablation approaches have been shown to be technically feasible for the treatment of primary breast cancer. Among them, RFA seems the most promising technique in terms of safety and complete ablation rates. HIFU is a newer technique that works in a non-invasive way with no skin incision to be made. All of the approaches have much potential for further clinical investigation and technical improvements. However, in order to demonstrate that thermal ablation has similar efficacy to breast conservation treatment, large-scale, multi-center randomized clinical trials are needed to determine the future role of these novel approaches for the treatment of breast cancer.

Minimally-invasive ablative techniques may offer complete ablation of breast cancer, with less psychological morbidity, better cosmetic results, and shorter hospital stay. Until now, thermal ablation of early-stage breast cancer have been conducted in research settings for the assessment of technical safety and feasibility, and none of those described herein have been used alone in clinical practice. In addition, thermal ablation has a number of problems that remain to be resolved, as follows: (a) lack of ability to precisely determine tumor size; (b) determination of 100% tumor cell killing; (c) ability to follow local recurrence; and (d) cosmetic outcome. Not until these issues have been resolved, and the results from prospective, randomized clinical trials worldwide become available, can minimally-invasive ablative techniques be considered as candidates for conventional therapy for widespread clinical application.

As shown in the tables, the incidence of complications induced by thermal ablation is not low in the early stage of technical devolvement. The major complication is minor skin burn, which usually occurs in 3–10% treated patients. Skin necrosis, followed by ulceration, is observed in 5 patients treated with cryoablation. The main reason for both skin complications is that the targeted breast lesion is too close to the skin, resulting in therapeutic energy deposited on the overlying skin. This has been avoided while patients with a breast lesion lying within 1 cm of the overlying skin are excluded in the subsequent RFA studies. Serious complications are observed in 2 patients treated with laser ablation, including one with pneumothorax due to the mis-insertion of probes and the other with tumor rupture caused by tissue vaporization and cavitation. Four patients experience moderate local pain after HIFU ablation in the diseased breast, and are given 3–5 days prescription for oral analgesics.

There are several weaknesses encountered in thermal ablation for breast cancer. Successful thermal ablation is a function of appropriate patient selection, and the breast lesion close to the skin and chest wall, as well as the multiple lesions, should be excluded from thermal ablation. As pathological samples are not obtainable for assessing the tumor-free margins of the ablated tissue after thermal ablation, the lack of pathologic method directly to examine tumor margins is still a major argument against this thermal approach for breast cancer. Recently, innovative techniques for the detection of residual disease, such as PET/CT scan and near-infrared fluorescence optical imaging, have been examined in the fields of breast imaging, and preliminary results are very encouraging. Finally, determination of the status of the sentinel nodes in breast cancer is important in breast conserving therapy. As lymph drainage may be disturbed after local tumor ablation, it is reliable to perform the sentinel node biopsy before the ablation. This invasive procedure may reduce the minimally-invasiveness of thermal ablation, but it should be essential to perform such a relatively minor procedure that allows the detection of lymph node metastasis that otherwise would not be amenable to this form of therapy.

However, some of minimally-invasive thermal therapies can already be offered as option for the treatment of some carefully selected breast cancers. Thermal ablation may also be performed as a local treatment to eradicate small primary tumors or any residual tumor that persists after the completion of systemic therapy. Finally, they can be used as a salvage method to treat local recurrence after breast conservation therapy.

Conflict of interest statement

All authors confirm that there are no financial and personal relationships with other people or organisations that could inappropriately influence (bias) their review work.

References


**Further reading**