Clinical Policy Title: Microwave thermotherapy for breast cancer

Clinical Policy Number: CCP.1397

Effective Date: September 1, 2018
Initial Review Date: July 3, 2018
Most Recent Review Date: November 6, 2018
Next Review Date: November 2019

Related policies:
- CCP.1208 Stem cell transplant for breast cancer
- CCP.1254 Prophylactic mastectomy
- CCP.1284 Breast reconstruction following breast cancer surgery

Policy contains:
- Breast cancer.
- Focused microwave phase array thermotherapy.
- Microwave thermotherapy.

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of microwave thermotherapy for breast cancer and all other cancers to be investigational/experimental and, therefore, not medically necessary.

Limitations:

None.

Alternative covered services:

Chemotherapy.
Hormone therapy.
Lumpectomy.
Mastectomy.
Radiation therapy.
Stem cell transplant.
Targeted therapy.

**Background**

Breast cancer is the most commonly diagnosed cancer in the United States. A total of 266,120 new cases will be diagnosed among American females in 2018, a number that exceeds that of any other female cancer. About 80 percent of female breast cancers are classified as invasive, and the other 20 percent as *in situ*. Both invasive and *in situ* breast cancer incidence rates in the United States are largely unchanged from 2003 to 2015, the latest year for which data is available (Noone, 2018).

While female breast cancer mortality rates have declined in recent years, 40,920 deaths are expected in 2018, the most common cause of female cancer mortality other than lung and bronchus cancer. This pattern has persisted despite a variety of treatment options, and new options are being sought. One option is microwave thermotherapy, also known as focused microwave phase array thermotherapy, which is also intended for some other cancers.

Thermotherapy works on the principle that heat applied to the organ in question (in this case, the breast), generates antitumor activity. Typically, thermotherapy raises the temperature of the breast to between 40° C and 43° C. The treatment produces cytotoxic effects yielding the denaturation of cytoplasmic/membrane tumor proteins, decreases blood flow to impair oxygen and nutrient supply of the tumor, and activates heat shock proteins that help destroy breast tumors.

The breast is compressed between two microwave applicators with fans that help cool the skin’s surface. Five sensors are attached to the skin, and monitor skin temperature during treatment. Two additional sensors are inserted in the breast, one to monitor breast temperature, and the other to direct microwave energy into the cancerous tissue (Gardner, 2002).

Thermotherapy for breast cancer patients can be rendered in several ways. These include a microwave applicator, a Sigma 60 applicator, or a radiant system for whole-body hyperthermia. These treatments typically take one hour. Other types of thermotherapy can be given when heating is induced by far-infrared radiation, which heats the blood under the skin, and gradually heats the entire body (Alphandery, 2014).

Thermotherapy is not used as monotherapy, as it is unable to effectively treat breast cancer. Instead, it is typically combined with other commonly used treatments:

1. Breast cancer treatments with radiation therapy are limited in some cases by the inability to eradicate the cancer entirely, while not exceeding doses that can cause life-threatening
conditions. In these cases (often advanced breast cancer), thermotherapy can be employed after radiation.

2. In cases of metastatic breast cancer treated with chemotherapy, combining chemotherapy with thermotherapy can increase the effectiveness of treatment.

3. Targeted treatment of breast cancer can be conducted together with hyperthermia. In this scenario, heating the organ can ensure delivery of the antitumor drugs specifically at the tumor location, enabling the release of the drugs specifically to the tumors.

4. Combining thermotherapy with cryotherapy can potentially enable the reduction of the size of large breast tumors (Alphandery, 2014).

Thermotherapy to treat breast cancer has been used for about two decades. One of the earlier studies found that with sufficient skin cooling, the technology was observed to be safe and efficacious, with significant tumor size reduction or tumor cell kill documented in eight of 10 women, five to 18 days after treatment (Gardner, 2002).

Searches

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on May 22, 2018. Search terms were: “thermotherapy breast cancer,” “hyperthermia breast cancer,” “ablation breast cancer,” and “focused microwave phase array thermotherapy.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

The National Comprehensive Cancer Network guideline for breast cancer treatment does not address the use of focused microwave thermotherapy as a treatment option (National Comprehensive Cancer
The American Society of Breast Surgeons issued a consensus guideline in 2017 on transcutaneous and percutaneous methods of treating breast cancer. The Society stated that while these treatments are being investigated, they are not approved by the U.S. Food and Drug Administration, and should not be performed, except in clinical trials (American Society of Breast Surgeons, 2017).

Results of trials starting in the 1990s produced mixed results on whether adding thermotherapy to radiation therapy increases response or survival. A meta-analysis of five randomized trials was published in 1996 by the United Kingdom Medical Research Council, European Society for Hyperthermic Oncology, Dutch Hyperthermic Group, and Princess Margaret Hospital/Ontario Cancer Institute. A total of 306 women with superficial localized breast cancer were randomized to radiation therapy, with and without thermotherapy. The complete response rate for the combination therapy group was significantly greater (59 versus 41 percent, \( P < .001 \)), but no difference was observed in survival, the median of which was 18 months (Vernon, 1996).

Minimally invasive thermal ablation, of which microwave thermotherapy is one type, has been used on breast cancer patients, and results have been reported in the literature. One systematic review determined that minimally invasive thermal treatment to destroy small breast cancers was promising, despite the fact that all studies were feasibility or pilot studies, and the percentage of patients achieving complete tumor ablation using microwave ablation was just zero to eight (Zhou, 2010).

Studies of thermotherapy have followed. Results have typically found that adding thermotherapy to radiation therapy have been effective in controlling superficial recurrences in breast cancer, which often metastasize, although it is not yet the standard of care in treatment of recurrences (Zagar, 2010).

Microwave thermotherapy also showed potential as an effective preoperative treatment of breast cancer. Prior to breast-conserving surgery, none of the 34 patients had positive tumor margins after microwave thermotherapy and subsequent breast-conserving surgery, compared with four of 41 (9.8 percent) of patients only undergoing breast-conserving surgery only \( (P = .13) \) (Dooley, 2010).

Only a small number of systematic reviews of microwave thermotherapy for breast cancer exist; these articles are summarized below. A major limitation of these studies is that virtually none of the included randomized controlled trials (other than the early clinical trials), making judgment on effectiveness and safety of thermotherapy elusive compared to other breast cancer treatments.

A systematic review of 34 studies (n=2100) divided locally recurrent breast cancer subjects into single- and double-arm groups. In the eight two-arm studies, a complete response was achieved in 60.2 percent of patients with radiation therapy and thermotherapy, compared to just 38.1 percent of those with radiation therapy only \( (P < .0001) \). The 63.4 percent complete response for single-arm studies was comparable to that in two-arm studies. Authors conclude that treatment is more effective when thermotherapy is added to radiation therapy for breast cancer patients (Datta, 2016).
Microwave thermotherapy has been compared with other techniques for minimally invasive ablation for breast cancer. One review of 45 studies (n=1156) included radiofrequency, microwaves, laser, cryoablation, and high-intensity focused ultrasound. Differences between techniques were not significant for technical success ($P=.449$), major complications ($P = .181$) or minor complications ($P = .762$), but significant for technique efficacy ($P = .009$). Results indicate these techniques are technically successful, but efficacy remains suboptimal (Mauri, 2017).

Thermotherapy has been used concurrently with radiation therapy for breast cancer. In a randomized trial of 57 patients with high-risk breast cancer, both medial and lateral sides were irradiated, and the control (lateral) side of some subjects also received thermotherapy. After an average follow up of 79 months, insignificant differences between the two groups were observed in ≥grade 2 toxicity ($P = .38$) with no significant link between number of hyperthermia sessions and toxicity ($P = .09$). Simultaneous radiation and thermotherapy was deemed to be feasible and well tolerated (Varma, 2012).

Microwave thermotherapy has also been used for tumors other than breast cancer. Probably the most studied of these is bladder cancer. A systematic review of 22 studies showed that the recurrence rate was 59 percent lower after microwave-induced hyperthermia with intravesical chemotherapy (mitomycin C), as opposed to mitomycin C alone (Lammers, 2011). A meta-analysis of 24 studies two years later found the same 59 percent superior rate, in a relatively short time after treatment (Colombo, 2013). Literature reviews also include microwave thermotherapy, including lung/bronchus, pancreatic, and nasopharyngeal cancers.

**Policy updates:**

None.

**Summary of clinical evidence:**

<table>
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<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tr>
<td>Mauri (2017)</td>
<td><strong>Key points:</strong></td>
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</table>
| Outcomes comparison of types of minimally invasive breast cancer treatment. | - Systematic review of 45 studies (n=1,156), including radiofrequency (n=577), microwaves (n=78), laser (n=227), cryoablation (n=156), and high-intensity focused ultrasound (n=129).
- Pooled technical success was 96 % (microwave = 93%).
- Pooled technique efficacy was 75% (67 – 81), not reported for microwaves.
- Differences between techniques were not significant for technical success ($P = .449$), major complications ($P = .181$) or minor complications ($P = .762$), but significant for technique efficacy ($P = .009$).
- Techniques are technically successful, but efficacy remains suboptimal. |
| Datta (2016)   | **Key points:**                   |
Comparison of breast cancer treatment with and without thermotherapy

- Systematic review of 34 studies (n=2100) of locally recurrent breast cancer subjects.
- Subjects divided into single-arm (only combination therapy) and double-arm (randomized to radiation therapy only and radiation plus thermotherapy) studies.
- In the eight two-arm studies, complete response achieved in 60.2% of patients with both treatments versus 38.1% of those with radiation therapy only ($P < .0001$).
- In the 26 one-arm studies, the 63.4% complete response was comparable to that in two-arm studies (60.2%).
- Acute and late grade 3/4 toxicities with combination therapy were 14.4 and 5.2%.

Zagar (2010)

Efficacy of adding thermotherapy to radiation in treating breast cancer.

Key points:
- Literature review of combined use of hyperthermia and radiotherapy in superficial recurrences of breast cancer.
- Adding hyperthermia to radiotherapy show greater response rate in Phase III trials.
- Combination therapy is not yet the standard of care in treatment of recurrences.

Zhou (2010)

Minimally invasive treatment to destroy breast cancer

Key points:
- Systematic review of minimally-invasive thermal treatment for small breast cancers.
- All studies were feasibility or pilot studies.
- Complete tumor ablation could be achieved in 76 – 100% of patients after radiofrequency ablation, greater than laser ablation (13 – 76), microwave ablation (0 – 8), cryoablation (36-83), and high-intensity focused ultrasound ablation (20 – 100).
- Study concluded minimally-invasive thermal treatment for small breast cancers was promising.

References

Professional society guidelines/other:


**Peer-reviewed references:**


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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