Subject: Focused Microwave Thermotherapy for Breast Cancer	**Original Effective Date: 9/16/20**
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.

RECOMMENDATION

This policy addresses focused microwave thermotherapy as a treatment for breast cancer. Focused microwave thermotherapy has been investigated in a number of settings, including as a treatment for primary breast cancer in conjunction with lumpectomy for early stage breast cancer and as a cytoreductive technique in conjunction with preoperative chemotherapy in locally advanced breast cancer.

Focused microwave thermotherapy is considered experimental, investigational or unproven and not medically necessary as a treatment for breast cancer. There is insufficient evidence in the peer-reviewed literature documenting the safety and efficacy of microwave thermotherapy for the treatment of breast cancer. Published clinical studies have not demonstrated that the use of microwave thermotherapy results in improved health outcomes among individuals with breast cancer. The evidence is insufficient to determine the effects of the technology on health outcomes

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Microwave thermotherapy utilizes focused microwaves for the treatment of primary breast cancer, based on the theory that heat could destroy microscopic carcinoma cells in the breast and reduce cancer recurrence. Microwave thermotherapy exposes the tumor to extremely high temperatures using electromagnetic waves to induce tumor destruction. It uses localized 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 tumor cells, while tissues with lower-water-content such as adipose and breast glandular tissues remain unharmed. Heating the tumor and killing a large percentage or all of the tumor cells before surgery may improve the margins and reduce the possibility of inadvertently seeding viable cancer cells during the surgical procedure, thus reducing local recurrences in the breast. Microwave thermotherapy may reduce the size of the tumor sufficiently to allow a less invasive surgical procedure to be performed. In individuals with locally advanced primary breast cancer, focused microwave thermotherapy may sufficiently reduce the size of the tumor to allow a less invasive surgical procedure to be performed. Furthermore, if a sufficient thermal dose is applied, thermotherapy treatment of early-stage breast cancer may destroy the tumor and completely eliminate the need for any further breast surgery or radiation therapy.

During this procedure, the breast to be treated is compressed between two microwave emitters and a surgical probe is placed within the breast to monitor the temperature of the tissue. When activated, the emitters cover a large volume of breast tissue with microwave energy. In breast cancer, the tumor tissue contains a higher volume of water than the surrounding tissue. The cancerous tissue heats more rapidly and is destroyed while leaving the healthy tissue relatively undisturbed.

However, at this time there is insufficient evidence in the published literature to support the use of focused microwave thermotherapy as a treatment for breast cancer.

Regulatory Status

No microwave thermotherapy device that is indicated for the treatment of breast cancer has received approval for marketing from the U.S. Food and Drug Administration (FDA) has been identified at the present time.

Several microwave ablation systems have received 510(k) approval from the FDA as a class II device for the intended use for coagulation (i.e. ablation of soft tissue). (1, 2) The Microfocus™ APA 1000 System (Celsion, Columbia, MD) is a device that is currently undergoing clinical trials through the FDA investigational device exemption (IDE) process.

SUMMARY OF MEDICAL EVIDENCE

There is limited published clinical trial data regarding focused microwave thermotherapy for the treatment of breast cancer. Additional randomized studies with a larger number of subjects are needed to evaluate the safety and efficacy of these treatments. Further investigation of the use of microwave thermotherapy, both as a preoperative heat-alone treatment to reduce positive margins for early-stage breast cancer and as a preoperative combination heat and chemotherapy treatment to reduce tumor volume for large breast cancer tumors to improve breast conservation are neede (Dooley, et al., 2010; Vargas, et al., 2004; Gardner, et al., 2002).

The key published literature to date, includes case series, a systematic review of feasibility and pilot studies conducted prior to 2010:

Gardner et al. (2002) published on the results of a pilot study of focused microwave phased array thermotherapy in the treatment of 10 patients with primary breast carcinomas beneath the skin ranging from 1 to 8 cm in maximum clinical size. After focused microwave phased array treatment, all patients underwent mastectomy. Eight of 10 patients had a significant tumor response (on the basis of tumor shrinkage measured by ultrasound) or tumor cell kill (on the basis of necrosis and aptosis measurements).

Vargas et al. (2004) reported a dose-finding study in 25 subjects, performed as part of an Investigational Device Exemption (IDE) trial. Study subjects underwent microwave thermotherapy at various doses before undergoing surgical resection of breast cancer to determine whether the use of thermotherapy before breast conserving surgery (BCS) could potentially reduce the incidence of positive surgical margins, and thus the need for re-excision. The authors concluded that thermotherapy causes tumor necrosis and can be performed safely with minimal morbidity. The degree of tumor necrosis is a function of the thermal dose. Future studies will evaluate the impact of high doses of thermotherapy on margin status and complete tumor ablation.

Preoperative Focused-Microwave Thermotherapy

Two small studies with early, intermediate outcomes were noted. However these studies provide insufficient data due to the limited numbers of patients and duration. Longer follow-up of clinical outcomes are required to evaluate the clinical benefit of therapy:

> Vargas et al. (2007) reported on a study of 15 patients who received preoperative focused microwave thermotherapy (FMT) in combination with neoadjuvant anthracycline-based chemotherapy for invasive (T2, T3) breast cancer. Compared with 13 patients who received only the anthracycline-based regimen, there was greater (88% verses 59%) tumor volume reduction in the experimental group.
>
> Dooley et al. (2008) reported on a randomized study of preoperative focused-microwave thermotherapy for early-stage breast cancer. In this study, 34 patients received thermotherapy before surgery and 41 received only surgery. Positive margins were found in 10% (4 of 41 controls) compared with 0% (0 of 34) in the experimental group (p=0.13).

Dooley et al. (2010) reviewed results of four clinical studies evaluating focused microwave thermotherapy for preoperative treatment of invasive breast cancer.

- In the initial phase I study, 8 of 10 (80%) participants receiving one low dose of focused microwave thermotherapy prior to mastectomy had a partial tumor response. Partial tumor response was identified by ultrasound measurements of tumor volume reduction or by pathologic cell kill.
- In the phase II study, the focused microwave thermotherapy dose was increased to stimulate 100% pathologic tumor cell kill for invasive carcinoma prior to BCS.
- In a randomized trial comprised of participants with early-stage invasive breast cancer. In this study, 34 patients received thermotherapy before surgery and 41 received only surgery. Positive margins were found in 10% (4 of 41 controls) compared with 0% (0 of 34) in the experimental group (p=0.13). These studies provide insufficient data to change the coverage statement. Studies involving larger numbers of patients with longer follow-up of clinical outcomes are needed.
- In a randomized trial of participants with large breast tumors, the median reduction of tumor volume based on ultrasound measurements was 88.4% (n=14) for those who received focused microwave thermotherapy and chemotherapy, as compared with 58.8% (n=10) reduction in those who received chemotherapy alone. Study limitations include small numbers of participants.
- The authors concluded that wide-field adaptive phased-array FMT can be safely administered in a preoperative setting, and data from randomized studies suggest both a reduction in positive tumor margins as a heat-alone treatment for early-stage breast cancer and a reduction in tumor volume when used in combination with anthracycline-based chemotherapy for patients with large breast cancer tumors; larger randomized studies are required to verify these conclusions.

Systematic Review/Meta-Analysis

Outcomes Comparison of Types of Minimally Invasive Breast Cancer Treatment

Mauri et al. (2017) published a 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). The review found the following results:

- 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).

The study concluded that techniques are technically successful, but efficacy remains suboptimal.

Comparison of Breast Cancer Treatment with and without Thermotherapy

Datta et al. (2016) performed a systematic review of 34 studies (n=2100) divided locally recurrent breast cancer subjects into single- and double-arm groups. Subjects were 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%. The authors concluded that treatment is more effective when thermotherapy is added to radiation therapy for breast cancer patients.

Minimally Invasive Treatment to Destroy Breast Cancer

Zhou et al. (2010) conducted a systematic review of minimally-invasive thermal treatment for small breast cancers. All studies were feasibility or pilot studies. The 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).

Minimally-Invasive Thermal ablation of Early-Stage Breast Cancer

Zao and Wu (2010) published a systematic review of minimally invasive thermal ablation of early-stage breast cancer (searching in Pubmed, Embase and the Cochrane databases between January 1990 and December 2009). Clinical results of the relevant articles were collected and analyzed. 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 76-100% of breast cancer patients treated with radiofrequency ablation, 13-76% in laser ablation, 0-8% in microwave ablation, 36-83% in cryoablation, and 20-100% in high-intensity focused ultrasound ablation.

The authors concluded that 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.

Randomized Clinical Trials

The following clinical trials are ongoing with the first update posted in 2003 and the last updated posted in 2013. There is no estimated date of completion for these trials:

Microwave Thermotherapy in Treating Women With Stage I or Stage II Breast Cancer

Randomized phase II trial to compare the effectiveness of microwave thermotherapy before surgery to that of surgery alone in treating women who have stage I or stage II breast cancer.

A total of 222 female patients with early-stage primary breast cancer will be randomized (ratio 1:1) either to thermotherapy (at one of two different doses) plus surgery or surgery alone. The primary endpoints include reduction of tumor cells at surgical margins and reduction of second incision rates due to unclean surgical margins. No additional study details are available at the time of this writing. ClinicalTrials.gov Identifier: NCT00036998

Combination Chemotherapy With or Without Microwave Thermotherapy Before Surgery in Treating Women With Locally Advanced Breast Cancer

A total of 228 female patients with locally advanced primary breast cancer will be randomized (ratio 1:1) either to chemotherapy plus thermotherapy or chemotherapy alone. The primary endpoints include downsizing from mastectomy to partial mastectomy, and determining the percentage of patients with ≥85% pathological cell death. Trials are ongoing, but are no longer recruiting new patients. This study is ongoing, but not actively recruiting participants. ClinicalTrials.gov Identifier: NCT00036985

http://www.clinicaltrials.gov Trial 10200201. Breast Cancer Trial. Combination chemotherapy with or without microwave thermotherapy before surgery in treating women with locally advanced breast cancer

The American Society of Breast Surgeons

A consensus guideline on transcutaneous and percutaneous methods of treating breast cancer was published in 2017. 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).

The American College of Radiology (ACR)

The 2012 ACR updated in 2016, states there is insufficient evidence to support the use of other imaging modalities such as thermography, breast specific gamma imaging (BSGI), positron emission mammography (PEM), or optical imaging for breast cancer screening.

National Comprehensive Cancer Network (NCCN)

The NCCN Breast Cancer guideline (1.2020 — January 15, 2020) does not address microwave thermotherapy. The guideline addresses hyperthermia treatment (e.g., breast cancer of the chest wall).

- The 2019 Clinical Practice Guidelines in Oncology document for the treatment of breast cancer does not address the use of focused microwave thermotherapy as a treatment option.
- The NCCN guideline for breast cancer treatment (2017) does not address the use of focused microwave thermotherapy as a treatment option (NCCN, 2017).

National Cancer Institute (NCI)

NCI Breast Cancer Treatment (PDQ) Health Professional Version (updated November 12, 2019) does not mention microwave thermotherapy.

DEFINITIONS

Ablation refers to destroying tumors without removing them. *Microwave ablation (MWA)* is a technique to destroy tumors and soft tissue using microwave energy to create thermal coagulation and localized tissue necrosis. A small probe is placed into the tumor and the probe sends out microwave energy.

CODING INFORMATION

THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
19499	Unlisted procedure, breast [when specified as focused microwave thermotherapy]

HCPCS	Description
	N/A

ICD-10	Description: [For dates of service on or after 10/01/2015]
	Any/All

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Clinical Trials

Breast Cancer Trial.

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- Combination chemotherapy with or without microwave thermotherapy before surgery in treating women with locally advanced breast cancer. Available at: http://www.clinicaltrials.gov. Trial 10200201.

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Systematic review and Meta-analysis

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Peer Review: Policy reviewed by AMR practicing physician board-certified in Oncology/Hematology. Date: Sep 8 2020

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August 2020: New Policy