MEDICAL POLICY	Breast Surgery: Radiofrequency Ablation of Breast Tumors
Effective Date: 4/1/2022  4/1/2022 Medical Officer Date	Medical Policy Number: 67 Technology Assessment Committee Approved Date: 2/07; 6/09 Medical Policy Committee Approved Date: 8/11; 5/13; 6/14; 9/15; 4/16; 5/17; 1/18; 1/19; 12/19; 2/2021; 3/2022

See Policy CPT CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

Radiofrequency ablation of breast tumors is considered **not medically necessary and is not covered**, including but not limited to the treatment of malignant breast cancer and breast fibroadenomas.

Link to Policy Summary

CPT CODES

All Lines of Business	
Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be **denied as not covered.**	
19499	Unlisted procedure, breast

DESCRIPTION

Early-stage primary breast tumors are typically treated surgically by way of lumpectomy or mastectomy, depending on a number of factors unique to each patient. Surgical excision may be preoperatively treated using systematic therapy regimens (hormonal and/or chemotherapy) and likely followed by post-operative radiation treatment.[1]

Fibroadenomas are common benign breast tumors, which may present as a palpable round mass. They typically tend to shrink after menopause. The current treatment is observation.[1] However, if they continue to grow or change the shape of the breast, surgical excision is an option.

Radiofrequency ablation (RFA) of breast tumors is currently being investigated either as an alternative to excision, or as a pre- or post-operative adjunct to surgery. RFA is based on the local production of heat through the application of electric alternating current flowing from the tip of an uninsulated electrode. The tissue heats resistively in the area that is in contact with the electrode tip, and the heat is transferred conductively to more distant tissues.[2]

One limitation of RFA is that as soon as the treatment is initiated, the region surrounding the target lesion becomes highly echogenic, completely obscuring the tumor, making it difficult to monitor and control the ablation procedure. More importantly, the amount of pain associated with high temperatures elicited during RFA is not trivial, requiring carefully designed and applied anesthesia if general anesthesia has been avoided.[2] Furthermore, RFA can cause burning of the skin or damage to muscle, possibly limiting use in patients with tumors near the skin or chest wall.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of microwave thermotherapy as a treatment for breast cancer. Below is a summary of the available evidence identified through January 2022.

Systematic Reviews

In 2010, Zhao and Wu published the results of a systematic review of minimally invasive ablation techniques for the treatment of early-stage breast cancer, including nine small case series (n=5-34

patients) on RFA for small breast tumors (0.5-7.0cm diameter).[3] In most studies, tumor resection was performed immediately after RFA or up to four weeks post-RFA. Complete ablation rates of 76% to 100% were reported. Complication rates typically ranged from 0-7%, but one study reported muscle burns in 23% of patients. The reviewers conceded that the included studies were almost all feasibility or pilot studies using different energy sources, patients, tumor characteristics and ablation settings; and they were conducted in research settings and not in clinical practice. The reviewers concluded that RFA for breast tumors was feasible but further studies with longer follow-up on survival rates and tumor recurrence were needed.

In 2010 Soukup et al., published the results of a systematic review that included 17 studies that evaluated RFA of breast lesions.[4] The reviewers concluded that RFA is emerging as a promising treatment, but comparison between studies was challenging due to the heterogeneity of treatment protocols between groups. Although minimal adverse effects and complications have been reported, the reviewers noted that incomplete tumor ablation remained a concern. In addition, the reviewers indicated that further studies are required to delineate suitable patients populations for successful RFA intervention (e.g., tumors <2 cm in diameter and at least 1 cm away from skin and chest wall). Regarding the use of RFA for benign breast tumors, the reviewers concluded that further research was required, since they were unable to identify any studies that evaluated the potential role of RFA in benign breast disease.

In 2016, Chen et al. reported results from a meta-analysis of clinical trials assessing the safety and efficacy of RFA for breast cancer, including 15 nonrandomized trials.[5] Of the 15 trials, eight studies reported that the tumor size was <2 cm in diameter, five studies reported <3 cm, and the remaining two studies reported <5 cm tumor diameter. Pooled analyses from 11 studies indicated a complete ablation rate of 89% (95% CI: 85-93%). Pooled analyses from five studies reported no local recurrence at a maximum follow-up of 76 months, however, one case of relapse and three cases of recurrence outside the ablation zone were observed in various studies. Pooled estimates from seven studies showed an incidence of skin burn was 4%. The reviewers concluded that large-scale, well-performed trials were needed, since included studies were limited by small sample size, lack of randomization and heterogeneity in patient selection.

In 2016, Peek et al. published the results of a systematic review that assessed clinical outcomes of minimally invasive ablative techniques for breast cancer, including RFA, high intensity focused ultrasound (HIFU), cryoablation, laser ablation, or microwave ablation.[6] RFA was used in 27 studies in a total of 657 patients (26 case series with 14-52 patients and one nonrandomized comparative study). Mean follow-up period of RFA was 28.1 ± 15.6 months. Of all the techniques reviewed, the highest rate of complete ablation was achieved with RFA (87.1 %, 491/564 patients. Short-term complication rate was 10.5% (58/555), the most frequent of which were skin burns (23), muscle burns (12) and blistering (5). RFA recurrence rate of 3.1% (9 patients out of 291) was reported at a mean follow-up time of 30.8 ± 16.9 months. The reviewers concluded that RFA demonstrated the most promise of any minimally invasive technique for the non-surgical treatment of breast cancer, but there are no RCTs that have evaluated this technique. The reviewers conceded that more RCTs comparing ablative techniques with surgical excision or with each other are needed with larger sample sizes to accurately evaluate differences between the techniques.

In 2017, Mauri et al. published the results of a systematic review that evaluated the technical success, technique efficacy, and complications of minimally invasive percutaneous ablation procedures of breast cancer, including 23 studies on RFA (N=577 lesions).[7] Only one comparative study was identified for RFA, and this study is described in detailed below.[8] Other techniques evaluated in the review included microwaves, laser, cryoablation and high-intensity focused ultrasound (HIFU). Of all the techniques assessed, RFA had the highest technical success rate at 96% (95%CI 93-97%) and the second highest technique efficacy at 82% (95%CI 74-88%). Major and minor complication rates for RFA were lower than those of HIFU at 6% (95% CI 4–9%) and 8% (95% CI 5-13%), respectively. The reviewers concluded that while minimally invasive techniques may offer several advantages, that large, multicenter, RCTs comparing these approaches breast-conserving surgery are needed.

Randomized Controlled Trials (RCTs)

In 2018, Garcia-Tejedor and colleagues published results from a randomized phase 2 clinical trial evaluating RFA followed by surgical excision versus lumpectomy for the treatment of early stage breast cancer.[9] In total, 40 women with invasive ductal carcinoma of the breast were randomly assigned to review RFA or lumpectomy alone (control group). Outcomes of interest included margin status at surgery, tumor cell viability after RFA (with NADH and CK18 staining), cosmetic results, adverse advents, and local recurrences. Median follow-up was 25 months (range, 1-83 months). Investigators reported that NADH and CK18 staining demonstrated absence of tumor cell viability after RFA with at least of one the two staining techniques. Surgical margins were positive in 4 of the 20 RFA patients (p = 0.02). Limitations included the comparably higher rates of adverse events among RFA patients (8 of 20 vs. 1 of 20) and local infection (3 of 20 participants). Moreover, staining technique interpretations are subjective measures. The study was also under-powered as the target sample size for the main outcome was not reached. Larger RCTs with longer follow-up periods measuring clinical endpoints are needed to validate the authors' conclusion that RFA is effective for local tumor control.

Non-Comparative Studies

In 2007 Oura et al. published the results of a nonrandomized case series that included 52 individuals with small breast tumors (<2.0cm diameter) were treated by RFA followed by radiation therapy and chemotherapy.[10] Three weeks post-procedure, cytological evaluation indicated complete destruction of cancer cells. At a mean of 15-months post-procedure (6-30 months), no recurrence was reported. Limitations of this study include lack of a comparator group, specifically standard surgical excision, and short-term follow-up.

In 2011, Kinoshita et al. published the results of a phase 1/2 study that evaluated the use of RFA as pre-operative therapy for early breast carcinomas, including 49 patients with tumors ≤ 3cm in diameter.[11] Complete ablation was achieved in 30 patients (61%) by hematoxylin-eosin staining and/or nicotinamide adenine dinucleotide (NADH) diaphorase staining. Of the 29 treated patients with breast carcinomas ≤ 2 cm in diameter, complete ablation was achieved in 24 patients (83%). RFA-related adverse events were observed in five cases: two with skin burn and three with muscle burns.

In 2012, Wilson et al. reported the results of a case series of 73 patients with invasive breast cancer who underwent lumpectomy followed immediately by RFA to the lumpectomy bed, also known as excision followed by RFA (eRFA).[12] The average breast tumor size was 1.0±0.54 cm (range: 0.2-2.6 cm) and

median follow-up was 55 ± 21 months. Sixteen out of 19 (84 %) of patients with close or positive margins were spared of re-excision as a result of being treated with RFA. Disease-free survival was 100%, 92%, and 86% at one, three, and five years, respectively. One patient (1.3 %) developed an in-site recurrence and three developed recurrences elsewhere. However, less promising results were reported in a smaller but more recent case series of 20 patients who received eRFA, where the treatment protocol only spared 31% of patients from undergoing a re-excision surgical procedure.[13]

In 2013, Manenti et al. published the results of a nonrandomized study comparing RFA to cryoablation in women with early breast cancer.[8] Eighty women (40 who had undergone cryoablation and 40 who had undergone RFA) were retrospectively evaluated. All patients underwent surgical resection of the tumor with 30-45 days after RFA. MRI at four weeks post-ablation indicated that two patients in the RFA group and three patients in the cryoablation group had residual disease. No local recurrence was reported in either group. This study was limited by the fact that the study population was small and highly selected for low-grade tumors in elderly patients, indicating a lack of generalizability of results.

In 2014, Klimberg et al. published the results of a prospective phase II trial that evaluated the use of RFA after breast lumpectomy added to extend intraoperative margins (ABLATE 1), thereby potentially reducing the need for re-excision and to potentially preclude the need for radiation.[14] Standard lumpectomy was performed on 100 women with breast cancer and then the RFA probe was deployed into the walls of the lumpectomy cavity at 100 °C for 15 minutes (eRFA). Of the 100 women who received (eRFA), 23 patients received adjuvant XRT after eRFA for unfavorable disease including positive nodes. Overall, 22 women had margins that were ≤ 2 mm (making them candidates for re-excision) and nine women proceeded to mastectomy. With a mean follow-up of 62 ± 24 months (median of 68 months), there were a total of seven recurrences and one contralateral recurrence in the 77 women treated with eRFA. Five-year disease-free survival and overall survival for eRFA was 88% and 93%, respectively. Limitations include the fact that this was a small, single-institution nonrandomized pilot study, and therefore the results lack generalizability.

Several additional studies have published on the use of RFA as a potential adjunctive treatment prior to excision for patients with small primary breast tumors (<3.0cm diameter). These studies include small, uncontrolled pilot studies that included between 21 and 30 patients.[15-17] RFA was typically performed immediately (<2 weeks) prior to surgery. Overall, complete necrosis was reported in 86-100% of the excised tumors, with low complication rates (0-4%). However, none of the studies reported on whether pre-surgical RFA altered surgical or other treatment decisions. Follow-up of these studies did not extend beyond a few weeks post-surgery.

Evidence Summary

There is insufficient evidence that RFA is a safe or effective treatment for breast tumors, whether used as an alternative or an adjunct to standard breast conserving surgery. The body of evidence consists primarily of non-comparative case series with small, heterogeneous patient populations, short-term follow-up, various tumor sizes, and variations in selection criteria and RFA techniques. A number of systematic reviews have been published on these non-comparative studies that yield to the same limitations of the studies they have included. In many studies, complete ablation was not achieved, as viable tumor cells were present following treatment with RFA. Long-term improvements in health outcomes have not been demonstrated and studies comparing RFA to other minimally invasive therapy

techniques or to breast conserving surgery are lacking. Comparative studies, with long-term follow-up and adequately sized patient populations, should focus on whether RFA can provide local control and survival rates comparable with conventional breast-conserving treatment.

CLINICAL PRACTICE GUIDELINES

American Society of Breast Surgeons (ASBS)

The 2018 ASBS published a consensus guideline on the use of transcutaneous and percutaneous ablation for the treatment of benign and malignant tumors of the breast.[18] This guideline was evidence-based, but was not based on a systematic review of the evidence. The committee recommended the following for percutaneous treatment of benign and malignant breast tumors:

> "Indications for percutaneous or transcutaneous ablative treatment of malignant tumors of the breast: At this time, there are no FDA approved percutaneous or transcutaneous ablative treatments for breast cancer. At the present time, cryoablation is approved for treatment of soft tissue malignancies. However, there is emerging data from clinical trials utilizing percutaneous ablative therapies for patients with early stage breast cancer without surgical excision. Techniques being evaluated include ablation by focused ultrasound, laser, cryotherapy, microwave, and radiofrequency. Percutaneous excision by vacuum-assistance is also being Investigated."

Neither the National Comprehensive Cancer Network (NCCN) nor the American Society of Clinical Oncology guidelines address radiofrequency ablation (RFA) as a treatment option for breast cancer.

CENTERS FOR MEDICARE & MEDICAID

As of 2/16/2022, no Centers for Medicare & Medicaid (CMS) coverage guidance was identified which addresses radiofrequency ablation for the treatment of breast tumors.

POLICY SUMMARY

There is insufficient evidence that RFA is a safe or effective treatment for malignant breast tumors, whether used as an alternative or an adjunct to standard breast conserving surgery. Long-term improvements in health outcomes have not been demonstrated and studies comparing RFA to other minimally invasive therapy techniques or to breast conserving surgery are lacking. Comparative studies, with long-term follow-up and adequately sized patient populations, should focus on whether RFA can provide local control and survival rates comparable with conventional breast conserving treatment. In addition, there is a paucity of evidence on the safety and effectiveness of RFA as a treatment for benign breast tumors such as fibroadenomas. Furthermore, current clinical practice guidelines recommend against the use of RFA for malignant breast tumors, but recommend RFA for fibroadenomas, despite the lack of evidence.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

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