



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Radiofrequency Ablation for Breast Cancer

Effective Date 7/15/2011
Next Review Date 7/15/2012
Coverage Policy Number 0449

Table of Contents

Coverage Policy	1
General Background	1
Coding/Billing Information	4
References	4
Policy History	7

Hyperlink to Related Coverage Policies

Brachytherapy for Breast Cancer
 Breast Biopsy Procedures including Sentinel Node Biopsy
 Cryoablation of Breast Lesions
 Prophylactic Mastectomy
 Trastuzumab (Herceptin®)

INSTRUCTIONS FOR USE

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Coverage Policy

CIGNA does not cover radiofrequency ablation for the treatment of breast cancer because it is considered experimental, investigational or unproven.

General Background

Breast cancer is the most common form of cancer among women. In situ breast cancer is confined within the ducts (i.e., ductal carcinoma in situ) or lobules (i.e., lobular carcinoma in situ). Invasive or infiltrating carcinomas start in the ducts or lobules and invade the surrounding fatty tissue.

Treatment of breast cancer depends on the type and stage of cancer, patient's age and comorbidities, and the risks and benefits associated with the various treatment options. Surgical intervention is the primary treatment option for most breast cancers and includes breast-sparing surgery (e.g., lumpectomy, segmental mastectomy, partial mastectomy) and total mastectomy. Surgical treatment may be combined with other therapies, such as chemotherapy, radiation therapy, immunotherapy and/or monoclonal antibody therapy.

The goal of breast-conserving treatment is to remove the malignant tumor and surrounding margin of tissue in the least invasive manner. Radiofrequency ablation (RFA) has been proposed as a less invasive alternative to

surgical excision for breast cancer. RFA is performed by positioning a probe in the tumor using ultrasound guidance or computerized tomography (CT). Prongs, or electrodes, are extruded from the end of the probe and a current is emitted from the tips. The heating destroys the surrounding tissue by thermal coagulation and protein denaturation. Ablation times may vary based on breast size, tumor location, and composition and vascularity of the tissue. With variation in the prong array, a section of three to five centimeters (cm) can be treated. In most studies, general anesthesia has been administered, but in some clinical trials RFA has been successfully performed in an outpatient setting using local anesthesia (Agnese and Burak, 2005; Huston and Simmons, 2005; Fornage, et al., 2004; Burak, 2003; Singletary, et al., 2002).

RFA is generally well tolerated and may provide a better post-procedure cosmetic result compared to more invasive procedures. It has also been associated with minimal reported complications (e.g., minor pain, bruising, low-grade fever and skin burns). The major disadvantage of RFA is the inability to determine if the surrounding margin of tissue is free of viable cancer cells. RFA is not an established treatment modality for breast cancer.

U.S. Food and Drug Administration (FDA)

Ablation systems are approved by the FDA under the 510(k) process as a Class II electrosurgical cutting and coagulation accessory device. An example of this device is the Cool-tip™ RF Ablation System (Valleylab, Boulder, CO). The Cool-tip device is approved for use in “percutaneous, laparoscopic, intraoperative coagulation and ablation of tissue, such as partial or complete ablation of non-resectable liver lesions and osteoma tumors” (FDA, 2006).

Literature Review

There is insufficient evidence in the published peer-reviewed scientific literature to support the effectiveness of RFA for the treatment of breast cancer. Available studies are primarily in the form of case series or retrospective reviews with small, heterogeneous patient populations, short-term follow-up, various tumor sizes, variations in selection criteria and RFA techniques, and do not compare RFA to established minimally invasive procedures. In many studies, viable tumor cells were present following ablation.

Kinoshita et al. (2011) conducted a phase I/II study (n=50) to determine the safety and efficacy of RFA for patients with malignant breast tumors ≤ 3 centimeters (cm) in size. Following RFA, 27 patients underwent total mastectomy and 22 underwent wide local excision. Based on hematoxylin–eosin (H&E) and/or nicotinamide adenine dinucleotide (NADH) diaphorase staining, complete ablation was achieved in 30 patients (61%). NADH diaphorase staining showed no evidence of viable malignant cells in 29 of 38 patients (76.3%). Pathological examination showed complete ablation in 24 of 29 (83%) patients with tumors ≤ 2 cm and in 22 of 24 patients without an extended intraductal component (85%). Adverse events included two cases of skin burns and three cases of muscle burns.

In 28 patients with early breast cancer, Tsuda et al. (2011) conducted a prospective case series to evaluate the rate of complete ablation correlated to tumor size. Tumor sizes ranged from 0.6–5.0 cm (mean 2.21 cm) and invasive size ranged from 0–5.0 cm (mean 1.44 cm). Based on H&E staining, 100% ablation was found in 16 tumors (57%) compared to 22 tumors (79%) based on NADH diaphorase staining. The specificity and sensitivity of NADH diaphorase staining results reporting complete or incomplete ablation compared to H&E results reporting complete or incomplete ablation were 100% (16 of 16) and 50% (6 of 12), respectively. Based on H&E, the rate of complete ablation was significantly higher in a patient with a tumor size of ≤ 1.0 cm compared to a tumor size > 1.0 cm (p=0.0037), tumor size ≤ 1.5 cm compared to tumors > 1.5 cm (p=0.0034) and in tumors without extensive intraductal component (EIC) compared to tumors with EIC (p=0.0022). Following RFA, patients underwent surgical resection.”

Using magnetic resonance imaging (MRI) and vacuum-assisted core needle biopsy, Yamamoto et al. (2011) conducted a case series (n=29) to evaluate the safety and effectiveness of RFA on women with malignant breast tumors ≤ 2.0 cm. Three to four weeks following RFA, MRI and histological examinations were performed. MRI in all patients showed clearly ablated zones with no hypervascularity. H&E revealed no remarkable changes in 26 of 29 specimens which were diagnosed as viable tumor tissue. NADH diaphorase staining showed no viable tumor tissue in 24 of 26 patients. One patient received a grade 2 burn at the site of the ground pad, one received a grade 3 burn on the treated breast, and one patient had an overreaction of the ablated zone similar to chronic granulomatous mastitis with no evidence of cancer cells. Patients with viable cells following RFA underwent salvage surgery and/or radiotherapy. At a median follow-up of 17 months (range 2–41 months), all patients were alive without recurrence.

Zhao and Wu (2010) conducted a systematic review of the literature to evaluate minimally-invasive thermal ablation, including radiofrequency ablation, for the treatment of breast cancer. Twelve studies utilizing radiofrequency ablation met inclusion criteria. Nine studies (n=5-34) were feasibility studies and reported complete coagulation necrosis in 76%–100% of patients who then underwent surgical excision. Three pilot studies (n=3–52) with short-term follow-ups (n=15–29.4 months) reported no breast cancer recurrence following RFA. Some patients were also treated with hormone or radiation therapy following RFA. The authors noted that long-term follow-ups of tumor regression and survival rates are unknown.

To investigate the effectiveness of RFA for tumor recurrence, Garbay et al. (2008) conducted a phase II study including ten patients with 1.0–2.2 cm ipsilateral breast tumor recurrence (nine were invasive ductal carcinoma). In two cases, needle placement was difficult because of the density of recurrent tumor following radiation therapy. Following RFA, nicotinamide adenine dinucleotide (NADH)-diaphorase histological staining revealed no viable cells. Hematoxylin-eosin (H&E) staining revealed unaltered tumor cells in three patients and the study was stopped because RFA was considered not “sufficiently effective” for the treatment of recurrence.

Medina-Franco et al. (2008) conducted a phase II study to evaluate the safety and efficacy of RFA in 25 women with 0.9–3.8 cm malignant breast tumors. Following RFA, tumor resection was performed with a wide local excision (n=15) or mastectomy (n=10). No viable malignant cells were seen in 19 cases using NADH-diaphorase staining. A significant difference was seen in complete necrosis based on tumor size. Complete necrosis was seen in 13 of 14 (92.8%) tumors < 2 cm in size compared to six of 11 (55%) tumors > 2 cm (p<0.05). Two patients that had tumors > 2 cm, axillary metastasis and incomplete RFA developed distant metastases. Three patients had superficial skin burns following therapy. The authors noted that “a lumpectomy, despite its limitations primarily from its cosmetic viewpoint is still a time-tested standard of care and is a relatively easy operation. Therefore, rigorous research will be needed to evaluate ablative therapies before they can replace lumpectomy.”

Earashi et al. (2007) conducted a two-series study to assess tissue destruction following RFA. Surgical resection was performed immediately following RFA in the first series and delayed mammotome excision was performed following RFA in the second series. The first case series included 17 women with tumors < 3.0 cm (0.5–2.4 cm) in diameter. Invasive ductal carcinoma was present in 14 patients and noninvasive in three patients. Using the classification of response criteria, 15 patients had Grade 1a (mild response) H&E response, two were Grade 2 (marked response) and none were Grade 3 (complete response). The second case series involved seven women with well-localized invasive ductal carcinoma, with tumors < 2.0 cm (0.7–2.0 cm). Results of the H&E staining following RFA varied from complete necrosis to normal-appearing cells, with more noticeable degenerative changes in the specimens from the second series of patients. In the second group, four H&E responses were Grade 2 and three were Grade 3, reflecting greater degenerative changes in patients who had delayed excision following RFA. However, the authors noted that the degenerative changes could have been due to adjuvant chemotherapy and the length of time that it takes for the disappearance of all tumor cells following RFA is unknown. The NADH-diaphorase staining revealed no viable tumor cells in any of the patients.

Khatri et al. (2007) conducted a phase II trial to assess the efficacy and safety of RFA in the treatment of small invasive breast cancer. Fifteen women with 0.8–1.5 cm tumors were ablated under general anesthesia. RFA was followed by immediate surgical excision. One patient had infiltrating lobular carcinoma and 14 patients had infiltrating ductal carcinoma with associated ductal carcinoma in situ in six of the patients. The H&E staining reflected complete ablation of tumors in all but one patient in whom the whole tumor was missed. NADH staining on 14 patients revealed no viable malignant cells in 13 of the patients (92.8%).

Oura et al. (2007) performed RFA on 52 women with small (i.e., under 2.0 cm), localized breast tumors (ductal carcinoma in situ, invasive ductal carcinoma, invasive lobular carcinoma and tubal carcinoma). Postoperatively, cytological assessment revealed 30 patients with degenerative cancer cells, and 22 patients with no cancer cells and/or degenerative material. MRI revealed no residual tumors, and ultrasound demonstrated 30 visible tumors, 22 nonvisible tumors, and no vascular flow into any tumors. Following RFA, patients received adjuvant radiotherapy and chemotherapy. With an average 15-month follow-up (range, 6–30 months), no in-breast, loco-regional, or distant recurrences were detected. Cosmesis was graded as excellent in 43 patients.

In a systematic review, van der Ploeg et al. (2007) identified over 150 articles on RFA for breast cancer. Only six phase II studies with an equal level of evidence met inclusion criteria for analysis and comparison. The studies

were comprised of small patient populations (n=5–26) and involved tumors less than or equal to 3.0 cm, with the exception of one study that included five patients with 4–7 cm tumors. Surgical excision was performed immediately after or between weeks one and three following RFA. H&E was used to assess tumor margins, and NADH-diaphorase staining was used to assess cell viability. Complete tumor ablation was reported in 80–100% of cases. The authors stated that the studies were difficult to compare because of variations in selection criteria, RFA technique, time interval between RFA and surgical excision of the tumor, heterogeneity of breast size, tumor location, and composition and vascularity of the breasts. They also explained that more research is “clearly needed” to determine target temperature and duration of RFA, as well as shape, size and design of electrodes. Due to technical limitations, only small breast lesions are candidates for RFA. Additional research is needed to establish effects on surrounding tissue, recurrence rates, optimal technique and long-term effects.

Earlier studies reporting on RFA for the treatment of breast cancers included various tumor sizes: 2.0 cm or less (n=21) (Fornage, et al., 2004), 0.8-1.6 cm (n=10) (Burak, et al., 2003), less than 3.0 cm (n=23) (Hayashi, et al., 2003) and 0.7-3.0 cm (n=26) (Izzo, et al., 2001). In all studies viable cancer cells were found in patients following RFA. One study reported that three tumors had incomplete ablation of the index tumor (Hayashi, et al., 2003). RFA long-term outcomes are unknown and patient selection criteria have not been established.

Professional Societies/Organizations

The National Cancer Institute (2011), National Comprehensive Cancer Network® (2011), and American Cancer Society (2011) do not discuss radiofrequency ablation (RFA) as a treatment option for breast cancer.

Summary

There is insufficient evidence in the published, peer-reviewed scientific literature to support radiofrequency ablation (RFA) for the treatment of breast cancer. Limitations of the studies include small, heterogeneous patient populations, short-term follow-ups, and lack of comparison of RFA to established breast-conserving therapies. There are limited and variable outcome data on loco-regional and distant recurrence rates, as well as disease-free survival rates. Well-designed, prospective, randomized clinical trials are needed to determine the long-term outcomes and the effectiveness of RFA for the treatment of breast cancer.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered when used to report radiofrequency ablation for breast cancer:

CPT* Codes	Description
19499	Unlisted procedure, breast

ICD-9-CM Diagnosis Codes	Description
174.0-174.9	Malignant neoplasm of female breast
175.0-175.9	Malignant neoplasm of male breast
198.81	Secondary malignant neoplasm of other specified sites; breast
233.0	Carcinoma in situ of breast
238.3	Neoplasm of uncertain behavior of breast
239.3	Neoplasm of unspecified nature of breast

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	07/15/2008	0449	Radiofrequency Ablation for Breast Cancer

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