

MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	Brachytherapy After Breast-Conserving Surgery, as Boost with Whole Breast Irradiation or Alone as Accelerated Partial Breast Irradiation
Policy Number	6.01.30
Category	Technology Assessment
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Committee Approval Date	04/15/04, 03/17/05, 01/19/06, 11/16/06, 09/20/07, 07/17/08, 07/16/09, 07/15/10, 08/18/11, 08/16/12, 08/15/13, 06/19/14, 08/21/14, 07/16/15, 08/18/16, 08/17/17, 11/15/18, 11/21/19, 1/21/21, 11/18/21, 11/17/22
Current Effective Date	11/17/22
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Product Disclaimer	<ul style="list-style-type: none"> • <i>If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</i> • <i>If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.</i> • <i>If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.</i> • <i>If a Medicare product (including Medicare HMO-Dual Special Needs Program(DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.</i> • <i>If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.</i>

POLICY STATEMENT

- I. Based upon our criteria and assessment of the peer-reviewed literature, accelerated partial breast irradiation (APBI) using either interstitial or balloon brachytherapy of the breast (e.g., the MammoSite Radiation Therapy System) has been medically proven to be effective and, therefore, is considered a **medically appropriate** treatment option for individuals when:
- A. All of the following criteria are met:
 1. BRCA 1 or 2 gene mutation negative women aged 50 years or older; and
 2. Stage T1, N0, estrogen receptor (ER)-positive invasive ductal breast cancer; and
 3. negative margin width two mm or less; and
 4. Tumor size is two cm or less; and
 5. Lymphovascular space invasion (LSVI) is not present. **OR**
 - B. All of the following criteria are met:
 1. Low or intermediate nuclear grade, screening-detected Ductal carcinoma in situ (DCIS); and
 2. Measuring size is 2.5 cm or less; and
 3. Negative margin widths are greater than or equal to three mm.
- II. Based upon our criteria and assessment of the peer-reviewed literature, accelerated partial breast irradiation (APBI) using either interstitial or balloon brachytherapy of the breast (e.g., the MammoSite Radiation Therapy System) as a boost treatment in women who are treated with breast-conserving surgery and whole-breast external beam radiation therapy is considered **not medically necessary**.
- III. Based upon our criteria and assessment of the peer-reviewed literature, intra-operative breast radiotherapy has not been medically proven to be effective and, therefore, is considered **investigational**.

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IV. Based upon our criteria and assessment of the peer-reviewed literature, electronic brachytherapy has not been medically proven to be effective and, therefore, is considered **investigational**.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services.

Refer to Corporate Medical Policy #11.01.15 Medically Necessary Services.

POLICY GUIDELINES

- I. This policy addresses the use of either interstitial or balloon brachytherapy as an alternative to external beam radiation therapy in three settings:
 - A. alone, for accelerated partial breast radiation therapy after breast-conserving surgery;
 - B. in the intra-operative setting; or
 - C. to replace external beam for boost radiation therapy, when combined with whole-breast external-beam radiation therapy and breast-conserving surgery.
- II. Methods other than brachytherapy are also used for partial breast irradiation (PBI), including several types of external beam therapy. They are not addressed in this policy.
- III. At the time of surgery, a cavity evaluation device may be inserted as a placeholder, to simplify insertion of the MammoSite balloon catheter at a later date, when final pathology and staging is known, and a decision regarding the role of brachytherapy in the patient's treatment plan is established.

DESCRIPTION

Survival after breast-conservation therapy (BCT) is equivalent to survival after mastectomy for patients diagnosed with tumors categorized as Stage I or II. BCT is a multi-modality treatment that consists of breast-conserving surgery to excise the tumor with adequate margins, followed by whole-breast external-beam radiation therapy (WB-EBRT), administered as five daily fractions per week over five to six weeks. For those at higher risk of recurrence, local "boost" irradiation, narrowly directed to the tumor bed is often added to whole breast irradiation, to provide a higher dose of radiation at the site where recurrence most frequently occurs. For some patients BCT also includes axillary lymph node dissection or irradiation of the axilla.

Brachytherapy for breast cancer uses radiate sources placed inside the breast. When used after breast-conserving surgery, brachytherapy is one of several methods of accelerated partial breast irradiation (APBI). APBI differs from WB-EBRT in two ways. First, APBI radiation targets only a segment surrounding the tumor, rather than the entire breast. Second, because the duration of APBI treatment is four to five days, rather than five to six weeks, radiation is delivered in fewer fractions, at larger doses per fraction. APBI brachytherapy is delivered via multi-catheter interstitial brachytherapy, balloon-based applicators, external beam radiotherapy, or intraoperative radiation therapy.

Interstitial breast brachytherapy

Various interstitial brachytherapy techniques have been investigated. They differ in the timing of implantation relative to other components of breast-conserving therapy, the radiation dose rate, the loading technique, the number and volumetric distribution of radioactive sources, and the radioisotopes used. Older forms of local boost irradiation brachytherapy implanted the needles, wires, or seeds for brachytherapy after recovery from surgical tumor excision and WB-EBRT. More recently, the hollow needles and catheters that guide placement of the radioactive material are peri-operatively implanted. This can be done during the initial lumpectomy, if the decision to use brachytherapy has already been made, or at the time of re-excision, if pathologic evaluation of margins shows that additional surgery is necessary. Intraoperative implantation avoids the need for a separate surgical procedure with anesthesia for brachytherapy. Both low-dose rate and high-dose rate techniques have been used. In the low-dose rate technique, radioactive seeds are temporarily implanted in hospitalized patients, to deliver radiation continuously over four days, and are then removed. In the high-dose rate technique, a computer-controlled device loads highly radioactive isotope sources into catheters that have been placed into the tumor bed. The patient is exposed to the radiation therapy for a brief period (15 minutes), then the radioactive sources

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are withdrawn. This type of brachytherapy is typically administered on an outpatient basis as eight fractions, given twice daily over four days. Most brachytherapy for Stage I or II breast cancer uses high dose-rate iridium-192 in the form of wires or needles. Sometimes seeds containing iodine-125 are used in place of iridium-192.

Balloon APBI

Balloon brachytherapy uses a single radioactive source that delivers radiation to a spherical or elliptical target volume with no radiation remaining inside the breast between treatments. The MammoSite Radiation Therapy System (RTS) (Cytec Surgical Products, formerly Proxima Therapeutics) was cleared by the U.S Food and Drug Administration (FDA) for marketing via Section 510(k) in May 2002 as substantially equivalent to other commercially available brachytherapy applicators used with sealed radiation sources. The system consists of a hollow catheter to which an inflatable balloon is attached. It is implanted into the lumpectomy cavity during or shortly after breast-conserving surgery. The balloon is inflated with a sterile solution of contrast media in saline, and its position is confirmed radiographically using computed tomography. A high-dose rate source of iridium-192 is then centrally positioned within the applicator by a remote afterloader. The MammoSite balloon catheter is usually removed on the last day of treatment. The manufacturer has indicated that it may be used to deliver local boost or accelerated partial-breast radiation therapy. The FDA Office of Device Evaluation judged it reasonably likely that the Mammosite RTS would be used in ways outside those specified in the proposed labeling, and that such use could cause harm. Therefore, the FDA required inclusion of the following statement in the Warnings section of the device's labeling: "The safety and effectiveness of the MammoSite RTS as a replacement for whole breast irradiation in the treatment of breast cancer has not been established." In August 2004, the FDA approved a new version of the MammoSite RTS, which offers a thinner catheter shaft and a smaller balloon profile to further minimize intrusion into the lumpectomy cavity during brachytherapy. Many other balloon brachytherapy devices have since been cleared by the FDA through the 510 (k) process as being substantially equivalent to predicate devices (e.g., ClearPath HDR Breast Brachytherapy System (NAS Medical, Chatsworth, CA), the Contura Multi-Lumen Balloon (SenoRx, Inc., Irvine, CA), or the Strut-Adjusted Volume Implant (SAVI) (Cianna Medical, Inc., Aliso Viejo, CA).

Electronic brachytherapy.

Electronic brachytherapy is x-ray radiotherapy that does not utilize a radioactive isotope or require a high-dose rate (HDR) afterloader. It can be applied directly to the excised tumor bed, or to deliver intracavitary or interstitial radiation to surgical margins following lumpectomy for breast cancer. The FDA approved the Axxent Electronic Radiotherapy device (Xoft) in December of 2005 via Section 510(k) as substantially equivalent to the MammoSite and other brachytherapy systems. It is comprised of three components: the controller (a mobile platform responsible for overall operation of the device), a balloon applicator and an x-ray source. A breast surgeon implants the balloon applicator into the lumpectomy cavity, then balloon is inflated with sterile saline. Radiation is delivered by a disposable micro-miniature x-ray source located at the end of a flexible cable, which is comparable in dosage strength to iridium-192. Given that the Axxent device utilizes low energy x-ray, it does not require the heavily shielded treatment rooms necessary for the delivery of isotope-based HDR brachytherapy. Treatments are given in 10 fractions, twice per day for five days.

IORT

IORT is delivered directly to exposed tissues during lumpectomy, allowing a patient to receive all required radiation in a single fraction. It may allow higher radiation doses by excluding nearby radiation dose-sensitive tissues and may replace post-operative WB-EBRT for early breast cancer. IORT is marketed to help patients avoid three to six weeks of daily hospital visits, be more efficient for those that do not live close to a radiation facility who may elect total mastectomy vs. breast conservation, and also substantially reduce the heavy workload of radiotherapy departments. IORT techniques include electron beam IORT (EIORT), high-dose rate brachytherapy based IORT, and low-energy x-ray IORT.

RATIONALE

Implanting the guides used to insert radioisotopes for brachytherapy is a surgical procedure and, therefore, is not subject to government regulation. As iodine-125 seeds were marketed prior to enactment of the 1976 Medical Device Regulation Act, also known as the Medical Device Amendments, they were cleared by the FDA for marketing on a "grandfathered"

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basis. Subsequent radioactive isotope implants, including iridium-192, received Section 510(k) approval from the FDA as substantially equivalent to the radioactive iodine seeds.

Interstitial, multi-catheter APBI

Several single-institution, non-randomized studies using the multicatheter technique have shown low local recurrence rates that are comparable to standard external beam radiation therapy.

Balloon APBI

Initial published results of the MammoSite Patient Registry addressed the cosmetic results and early toxicity rates of 1,403 women with early stage breast cancer. Cosmetic results at 12 months were comparable to those reported with whole-breast radiation therapy. A good/excellent result was identified at the last follow-up visit in 95% of patients (1,030 of 1,084 patients) who had a cosmetic assessment. Early toxicity rates (infections, radiation recall) appeared to be acceptable. An infection in the treated breast developed in 8.1% (92 of 1,140 patients). A radiation recall reaction was reported in 3.4% (15 of 442 patients) who had this information recorded. At the time of publication, one local recurrence (0.1%) was reported, which was a new primary cancer. Of 158 ductal carcinoma in situ (DCIS) patients, two to 24 months follow-up of 104 patients showed 94% had an excellent or good cosmetic result and 5% had fair or poor results (Jeruss, 2006). Lowest toxicity was obtained in patients with the greatest device-to-skin distance. Long-term follow-up data regarding patient satisfaction, cosmesis and efficacy are needed. Data continue to accrue from uncontrolled studies on the use of Mammosite balloon brachytherapy. The longest follow-up fund was five years in a study of 36 patients, with no local recurrences reported. Based on development of recurrences beyond five years, longer follow-up is needed, as well as controlled trials.

Electronic APBI

Current literature regarding the use of electronic brachytherapy for the treatment of breast cancer is limited. The FDA required a black box warning stating, "The safety and effectiveness of the Axxent Electronic Brachytherapy System as a replacement for whole breast irradiation in the treatment of breast cancer has not been established."

The American Brachytherapy Society published a consensus statement for electronic brachytherapy in 2018 stating that, "In light of a randomized trial in breast showing higher rates of recurrence and the lack of prospective data with mature follow up with other sites, as well as concerns regarding dosimetry, it is not recommended that [electronic brachytherapy] be utilized for accelerated partial breast irradiation, nonmelanomatous skin cancers, or vaginal cuff brachytherapy outside prospective clinical trials at this time.

The National Comprehensive Cancer Network (NCCN) Breast Cancer guidelines (v4.2022) reports that studies of APBI suggest that rates of local control in selected low-risk patients with early-stage breast cancer are comparable to those treated with standard WB-EBRT. However, compared to standard WBRT, several studies document an inferior cosmetic outcome with external beam delivery methods of APBI and that follow-up is limited, and studies are ongoing. Patients are encouraged to participate in clinical trial.

The American Society for Radiation Oncology (ASTRO) developed a Consensus Statement of Accelerated Partial Breast Irradiation in 2016 to provide recommendations on appropriate candidates for APBI outside of a clinical trial. The task force proposed three patient groups; 1) a "suitable" group for whom APBI outside a clinical trial is acceptable; 2) a "cautionary" group for whom caution and concern should be applied when considering APBI outside of a clinical trial; and 3) an "unsuitable" group, for whom APBI outside of a clinical trial is not generally considered warranted. Patients who choose treatment with APBI should be informed that whole breast irradiation is an established treatment with a much longer track record that has documented long-term effectiveness and safety. The suitable group selection criteria include the following: women 50 years or older, stage T1 breast cancer, negative margins by at least two mm, and in DCIS if screen-detected, is low to intermediate nuclear grade, size less than or equal to 2.5 cm, and resected with margins negative at greater than or equal to three mm. Electron beam IORT should be restricted to women with invasive cancer who are considered "suitable" for PBI while low-energy x-ray IORT for PBI should be used within the context of a prospective

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registry or clinical trial. Patients should be counseled that the risk of ipsilateral breast tumor recurrence was higher with IORT.

NCCN guidelines accept the updated 2016 version of the ASTRO APBI guideline.

The American Society of Breast Surgeons, in its Consensus Statement of Accelerated Partial Breast Irradiation (revised June 2018), reached the following conclusions:

1. Outside of multi-institutional studies and institutional protocols, patients should be carefully selected for APBI and properly informed of the benefits and risks of this type of radiation treatment. The American Society of Breast Surgeons recommends the following selection criteria when considering patients for treatment with APBI, as a sole form of radiation therapy, in lieu of whole breast irradiation:
 - a. Patient is age 45 years or older;
 - b. Tumor is invasive ductal carcinoma or ductal carcinoma in situ;
 - c. Total tumor size (invasive and DCIS) less than or equal to three cm in size;
 - d. There is no tumor on ink for invasive tumors and invasive tumors with associated DCIS; tumor is greater than two mm for DCIS
 - e. Sentinel lymph node is negative;
 - f. If multifocal disease is present, the combined area of tumor is less than or equal to three cm;
 - g. Estrogen receptor positive or estrogen receptor negative tumor;
 - h. If lymphovascular invasion is present, it must be focal;
 - i. Patient has not been treated with APBI, if there is a BRCA genetic mutation or other genetic mutation that confers an increased risk of breast cancer;
 - j. There is no evidence to support use of APBI in male patients;
 - k. Patients with a history of ipsilateral breast cancer treated with radiation should only be treated with APBI as part of specific clinical trial;
 - l. There should be no contraindication to APBI in patients with history of contralateral breast cancer.
2. Patient selection and counseling should be performed in a multidisciplinary fashion with collaboration between the treating surgeon and the treating radiation oncologist.
3. It is preferred that all patients treated are part of a clinical trial or registry.
4. All patients should be monitored regularly to identify adverse events as well as local recurrences.
5. The published dataset for APBI supports the recommendations summarized above. Continuous, long-term, outcomes-based monitoring of APBI is desirable. The American Society of Breast Surgeons maintains an ongoing Mammosite Registry (registration completed in 2004) collecting data on 1440 patients treated via the Mammosite balloon catheter technique. As is the case with all cancer treatments, participation in multi-institutional clinical studies, including NSABP/RTOG B39, or in single-site protocols, or as part of data-gathering registries, is desirable, if available.
6. These recommendations are intended as a guide for patient treatment, but individual treatment decisions could allow for treatment outside of the parameters listed above with appropriate discussion with the patient.

IORT

RCTs have compared IORT with WB-EBRT. Vaidya et al. (2010,2014) summarized The Risk-adapted Targeted Intraoperative Radiotherapy (TARGIT-A) trial that evaluated IORT compared with WB-EBRT in a non-inferiority study with a predefined noninferiority margin of 2.5% between groups for pathologically confirmed ipsilateral local recurrence. 5-year ipsilateral local recurrence (median follow up of 29 months, 18% met 5 year follow up mark) were 3.3% (95% CI, 2.1% to 5.1%) in the TARGIT group and 1.3% (95% CI, 0.7% to 2.5%; p=.042) in the WB-EBRT group. Mortality was similar between the 2 groups (2.6% with TARGIT vs 1.9% with WB-EBRT; p=.56) and there were fewer non-breast cancer deaths in the TARGIT group (1.4%; 95% CI, 0.8% to 2.5%) than in the WB-EBRT group (3.5%; 95% CI, 2.3% to 5.2%; p<.001). Due to post-operative discovery of predefined factors (e.g., lobular carcinoma), the addition of external beam WB-EBRT was provided to 14% of patients. In the group that received IORT plus WB-EBRT, the mortality rate was higher at 8% (95% CI, 3.7% to 17.5%), but the percentage of women with local recurrences (0.9%; 95% CI, 0.1% to

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6.1%) was similar for those who only received IORT. There was no significant difference between the IORT and WB-EBRT groups in predefined 6-month wound-related complications. However, grade 3 or 4 radiotherapy-related skin complications were more common in the WB-EBRT group (13/1730 vs 4/1731; p=.029). In 2016, the full final report of the TARGIT-A trial was published concluding that "for patients with breast cancer (women who are aged ≥ 45 years with hormone-sensitive invasive ductal carcinoma that is up to 3.5 cm in size), targeted IORT concurrent with lumpectomy within a risk-adapted approach is as effective as, safer than, and less expensive than postoperative EBRT. Responses to this trial have been controversial with several authors ((Cuzick 2014), Haviland et al (2014), Silverstein et al (2014)) questioning the statistical analysis.

Valente, et al (2021), in the TARGIT-R multi-institutional retrospective registry, recently reported notably different outcomes on 5 year results of patients who underwent lumpectomy and IORT between 2007 and 2013 to measure ipsilateral breast tumor recurrence in those who received primary IORT (at the time of lumpectomy, 72%), delayed IORT (after lumpectomy, 3%), intended boost (8%), and unintended boost (primary IORT followed by WB-EBRT, 17%). Tumor recurrence occurred in 8% for the primary IORT group, 1.7% for the unintended boost group. No recurrences were identified in the delayed IORT or intended-boost groups. Authors conclude that given the local recurrence rate difference between this and the TARGIT-A trial, more information is needed to optimize patient selection and outcomes in the future.

The electron intraoperative radiotherapy (ELIOT) trial reported by Veronesi, et al. (2013) compared individuals treated with ELIOT vs. individuals treated with WB-EBRT. They evaluated 1305 patients with a median follow up of 5.8 years. 35 (4.4%) individuals in the ELIOT group and 4 (0.4%) individuals in the WB-EBRT group developed ipsilateral breast tumor recurrences (hazard ratio, 9.3; 95%CI, 3.3 to 26.3; p<.001) There was no statistically significant difference in 5-year overall survival. Adverse skin events were fewer in individuals who had received IORT. The ELIOT trial has also been criticized by several authors. Silverstein, et al. (2014) noted that of the individuals with 4 or more positive lymph nodes, those in the WB-EBRT group (n=38) received concurrent axillary radiation, while those in the IORT group were delayed by 6-12 weeks.

15-year results of the ELIOT trial were published by Orrechia, et al. (2021) and noted that at a median of 12.4 years of follow up, 11% (n=70) of the IORT group experienced ipsilateral breast tumor recurrence versus 2% (n=16) 16 in the WB-EBRT group. Fifteen-year overall survival was 83.4% and 82.4%, respectively. The authors concluded that even though there was a higher rate of recurrence in the IORT group, long term results did not lead to an increase in overall survival.

The existing literature has not demonstrated that intraoperative radiotherapy is superior to whole breast irradiation after breast conserving surgery.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
19294	Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with partial mastectomy (list separately in addition to code for primary procedure)

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Code	Description
19296	Placement of radiotherapy afterloading expandable (single or multichannel) into the breast for interstitial radioelement application following partial mastectomy, includes imaging guidance; on date separate from partial mastectomy
19297	Placement of radiotherapy afterloading expandable catheter (single or multichannel) into the breast for interstitial radioelement application following partial mastectomy, includes imaging guidance; concurrent with partial mastectomy (list separately in addition to code for primary procedure)
19298	Placement of radiotherapy after loading brachytherapy catheters (multiple tube and button type) into the breast for interstitial radioelement application following (at the time of or subsequent to) partial mastectomy, includes imaging guidance
77316	Brachytherapy isodose plan; simple (calculation[s] made from 1 to 4 sources, or remote afterloading brachytherapy, 1 channel), includes basic dosimetry calculation(s)
77317	Brachytherapy isodose plan; intermediate (calculation[s] made from 5 to 10 sources, or remote afterloading brachytherapy, 2-12 channels), includes basic dosimetry calculation(s)
77318	Brachytherapy isodose plan; complex (calculation[s] made from over 10 sources, or remote afterloading brachytherapy, over 12 channels), includes basic dosimetry calculation(s)
77424 (E/I)	Intraoperative radiation treatment delivery, x-ray, single treatment session
77425 (E/I)	Intraoperative radiation treatment delivery, electrons, single treatment session
0394T (E/I)	High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed
0395T (E/I)	High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed

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HCPSC Codes

Code	Description
A9527	Iodine I-125, sodium iodide solution, therapeutic, per millicurie
C1717	Brachytherapy source, non-stranded, high dose rate iridium-192, per source
C2634	Brachytherapy source, non-stranded, high activity, iodine 125, greater than 1.01 mCi (NIST), per source
C9726	Placement and removal (if performed) of applicator into breast for intraoperative radiation therapy, add-on to primary breast procedure
Q3001	Radioelements for brachytherapy, any type, each

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ICD10 Codes

Code	Description
C50.011- C50.922	Malignant neoplasm of the breast (code range)
C79.81	Secondary malignant neoplasm of breast
D05.00-D05.92	Carcinoma in situ of the breast (code range)
Z85.3	Personal history of malignant neoplasm of breast

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*Key Article

KEY WORDS

Accelerated partial breast irradiation; APBI, Axxent, Electronic brachytherapy, Interstitial brachytherapy, MammoSite

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based on our review, brachytherapy after breast conserving surgery is not addressed in National or Regional Medicare coverage determinations or policies.