# Accelerated Breast Irradiation and Brachytherapy Boost After Breast-Conserving Surgery for Early-Stage Breast Cancer

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## Policy Statement

### Whole Breast

Accelerated (hypofractionated) whole-breast irradiation (AWBI) after breast conserving surgery (BCS) may be considered medically necessary for patients who meet all of the following conditions:

- Invasive carcinoma of the breast
- Tumors less than or equal to 5 cm in diameter
- Negative lymph nodes
- Technically clear surgical margins, i.e., no ink on tumor or invasive carcinoma or ductal carcinoma in situ
- Age at least 50 years old

AWBI is considered investigational in all other situations involving treatment of early-stage breast cancer after BCS.

### Partial Breast

Accelerated partial-breast irradiation (APBI), including interstitial APBI and balloon APBI, may be considered medically necessary for the treatment of early stage breast cancer in low risk patients when all of the following criteria are met:

- Age greater than or equal to 50
- Tumor size less than or equal to 2 cm
- Node-negative
- Resected with margins negative at greater than or equal to 2 mm
- Stage Tis (in situ) or T1 (local only, no spread)
- Estrogen Receptor (ER) status positive
- Unicentric

Local boost irradiation using interstitial or balloon brachytherapy may be considered medically necessary for patients who meet all of the following conditions:

- Patient is undergoing initial treatment for stage I or II breast cancer
- Patient is also treated with both BCS and whole-breast external-beam radiotherapy

Ductal carcinoma in situ (DCIS) early stage breast cancer treatment using APBI, including either interstitial or balloon APBI, may be considered medically necessary when all of the following criteria are met:

- Detected by breast cancer screening
- Low to intermediate nuclear grade
- Size less than or equal to 2.5 cm
- Resected with margins negative at greater than or equal to 3 mm

Intraoperative APBI (commonly known as IORT or Intraoperative Radiation Therapy) is considered investigational.

Other uses of APBI including external-beam APBI, and noninvasive brachytherapy using AccuBoost, are considered investigational.

Noninvasive brachytherapy using AccuBoost for patients undergoing initial treatment for stage I or II breast cancer when used as local boost irradiation in those who are also treated with BCS and whole-breast external-beam radiotherapy is considered investigational.
Policy Guidelines

Brachytherapy delivers a higher dose of radiation to a smaller area of the breast over a shorter period of time compared to traditional (external beam) radiation therapy. Giving higher doses in a shorter time period is also called hypofractionation or accelerated treatment because the total dose is divided into a smaller number of fractions (each at a higher dose) compared to standard. Brachytherapy is sometimes referred to as accelerated partial breast irradiation (APBI).

Standard brachytherapy usually involves the use of radioactive seeds placed inside a tube. Interstitial tubes get placed directly into tissue; balloons are placed inside the cavity left from tumor removal. They can be used as a “boost” to standard radiation therapy, or as the primary type of radiation.

Electronic brachytherapy is considered a type of balloon brachytherapy that can be used to deliver accelerated partial-breast irradiation (APBI).

Intraoperative Radiation Therapy (IORT) is a type of accelerated radiation therapy given in the operating room (OR) after lumpectomy (see Blue Shield of California Medical Policy: Intraoperative Radiotherapy).

As recommended by the Society of Surgical Oncology and the American Society for Radiation Oncology (ASTRO), technically clear surgical margins can be defined as no ink on tumor of invasive carcinoma or ductal carcinoma in situ (http://www.redjournal.org/article/S0360-3016(13)03315-4/pdf).

As part of the clinical input process, ASTRO recommended additional criteria that should be satisfied for patients undergoing AWBI:

1. Pathologic stage is T1-2N0 and the patient has been treated with breast-conserving surgery.
2. Patient has not been treated with systemic chemotherapy.
3. Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose (±7%) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

Coding

There are CPT codes for placement of radiotherapy afterloading catheters:

- **19296**: Placement of radiotherapy afterloading expandable catheter (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

The following specific CPT radiology codes exist for application of brachytherapy radiation sources:

- **77770**: Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 1 channel
- **77771**: Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 2-12 channels
- **77772**: Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; over 12 channels

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The following CPT category III code is specific to high-dose electronic brachytherapy:

- **0395T**: High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed

**Description**

Radiotherapy is the standard of care for patients with breast cancer undergoing breast-conserving surgery (BCS) because it reduces recurrences and lengthens survival. The conventional radiotherapy regimen consists of approximately 25 treatments of 2 gray (a measure of absorbed radiation dose) delivered over 5 to 6 weeks. Nonetheless, not all patients undergo radiotherapy following BCS; the duration and logistics of treatment may be barriers for some women. Accelerated radiotherapy approaches have been proposed to make the regimen less burdensome for patients with early-stage breast cancer at a low-risk of recurrence. Accelerated (also called hypofractionated) whole-breast irradiation (AWBI) reduces the number of fractions and the duration of treatment to about three weeks. Accelerated partial-breast irradiation (APBI) targets a limited part of the breast in and close to the tumor cavity. By reducing the area irradiated, fewer treatments are needed, and the total treatment takes about one week.

**Related Policies**

- N/A

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

In 2002, the MammoSite® Radiation Therapy System (Proxima Therapeutics), the first device specifically designed for breast brachytherapy, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. Its intended use is “to provide brachytherapy when the physician chooses to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer.”

Since 2002, several other devices for breast brachytherapy have been cleared for marketing by the FDA through the 510(k) process. The FDA determined that several devices (e.g., Axxent® Electronic Brachytherapy System [Xoft], Strut-Adjusted Volume Implant [SAVI™] Applicator Kit [Biolucent (now Cianna Medical)], Contura® Multi-Lumen Balloon Source Applicator for Brachytherapy [SonoRx], ClearPath™ Adjustable Multi-Catheter Source Applicator [North American Scientific], Intrabeam® System [Carl Zeiss Surgical]) were substantially equivalent to predicate devices. Each includes an FDA-required warning that the safety and effectiveness of the device “as a replacement for whole-breast irradiation in the treatment of breast cancer has not been established.”
Although the Intrabeam® System (discussed in the Intraoperative Brachytherapy subsection) is subject to the FDA regulation, it does not fall under the regulatory purview of the U.S. Nuclear Regulatory Commission. In some states, the participation of radiation oncologists in delivering radiation is not required.

**Rationale**

**Background**

**Breast Cancer**

Current estimates suggest that over 266000 new cases of breast cancer of any stage will occur in the U.S. in 2018. Based on adjusted data from 2011 to 2015, among women, the number of new cases is 126 per 100000 and the number of deaths 21 per 100000.1

**Breast Conservation Therapy**

For patients diagnosed with stage I or II breast tumors, survival after breast conservation therapy (BCT) is equivalent to survival after mastectomy. BCT is a multimodality treatment that initially comprised breast-conserving surgery (BCS) to excise the tumor with adequate margins, followed by whole-breast external-beam radiotherapy (EBRT) administered as five daily fractions per week over five to six weeks. Local boost irradiation to the tumor bed often is added to whole-breast irradiation (WBI) 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, sentinel lymph node biopsy, or irradiation of the axilla. A number of randomized controlled trials have demonstrated that the addition of radiotherapy after BCS reduces recurrences and mortality. In an expanded update of an individual patient data meta-analysis, the Early Breast Cancer Trialsists' Collaborative Group (2011) reported that radiotherapy halved the annual recurrence rate after 10 years for women with a node-negative disease (n=7287), from 31.0% for those not receiving radiotherapy to 15.6% for those receiving it.2 It also reduced the 15-year risk of breast cancer death from 20.5% to 17.2% (p=0.005). For women with node-positive disease (n=1050), radiotherapy reduced the 1-year recurrence risk from 26.0% to 5.1%. Radiotherapy also reduced the 15-year risk of breast cancer death from 51.3% to 42.8% (p=0.01).

Consequently, radiotherapy is generally recommended following BCS. A potential exception is for older women at low-risk of recurrence. For example, current National Comprehensive Cancer Network guidelines state that women ages 70 or older may omit radiotherapy if they are estrogen receptor-positive, have T1 tumors, have clinically negative lymph nodes, and plan to take adjuvant endocrine therapy.3 However, the agreement is not universal.4

Controversy continues on the length of follow-up needed to determine whether accelerated partial-breast irradiation (APBI) is equivalent to WBI (see the Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment [2013] on accelerated radiotherapy after BCS for early-stage breast cancer for details). Because recurrences are relatively rare among low-risk early breast cancer patients, it may take a considerable time for enough recurrences to occur to provide sufficient power for comparing recurrence rates across radiotherapy approaches. Additionally, radiation-induced adverse cardiovascular effects and radiation-induced non-breast cancers tend to occur ten or more years after treatment.5,7,8 For accelerated WBI, some ten-year data are available. However, for newer approaches, the issue may be resolved by statistical issues rather than biologic ones. For example, in the large NSABP-39/RTOG 0413 trial comparing WBI with APBI (NC00103181), enrollment has reached the revised target of 4216. Trial duration (barring early termination) is determined by the occurrence of a prespecified number (175) of in-breast recurrences. Researchers expect that reaching that number of recurrences will take approximately ten years.

Currently, most patients diagnosed with stage I or II breast cancer are offered a choice between BCT and mastectomy but BCT is selected less often than expected. Studies have shown that those living farthest from treatment facilities are least likely to select BCT instead of mastectomy and most likely to forgo radiotherapy after BCS.9,10,11
Approaches to Radiotherapy Following Breast-Conservation Treatment

The goals of cancer radiotherapy are to deliver a high dose of homogeneous radiation (i.e., all parts of the tumor cavity receive close to the targeted dose) to the tumor or tumor bed. Areas adjacent to the tumor may be given a lower dose of radiation (e.g., with WBI) to treat any unobserved cancerous lesions. Radiation outside the treatment area should be minimal or nonexistent. The goal is to target the tumor or adjacent areas at risk of harboring unseen cancer with an optimum dose while avoiding healthy tissues.

Table 1 outlines the major types of radiotherapy used after BCS. They differ by technique, instrumentation, dose delivery, and possible outcomes.

<table>
<thead>
<tr>
<th>Radiation Type</th>
<th>Accelerated?</th>
<th>Whole or Partial Breast</th>
<th>EBRT or Brachytherapy</th>
<th>Treatment Duration</th>
<th>Published RCTs</th>
<th>Length of Follow-Up</th>
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<td>Conventional WBI</td>
<td>No</td>
<td>Whole EBRT</td>
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<td>Multiple</td>
<td>&gt;15 y</td>
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<td>Whole EBRT</td>
<td></td>
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<td>4</td>
<td>10 y</td>
</tr>
<tr>
<td>Interstitial APBi b</td>
<td>Yes</td>
<td>Partial Brachytherapy</td>
<td></td>
<td>1 wk</td>
<td>2</td>
<td>5.4 y</td>
</tr>
<tr>
<td>Balloon APBi c</td>
<td>Yes</td>
<td>Partial Brachytherapy</td>
<td></td>
<td>1 wk</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>EBRT APBi d</td>
<td>Yes</td>
<td>Partial EBRT</td>
<td></td>
<td>1 wk</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Intraoperative APBi e</td>
<td>Yes</td>
<td>Partial Not applicable</td>
<td></td>
<td>1 d</td>
<td>1</td>
<td>5 y</td>
</tr>
</tbody>
</table>

APBi: accelerated partial-breast irradiation; EBRT: external-beam radiotherapy; RCT: randomized controlled trial; WBI: whole-breast irradiation.

Noninvasive breast brachytherapy using AccuBoost has been described by the manufacturer as capable of delivering APBi but no studies for this indication were found.

b Interstitial brachytherapy entails placement of multiple hollow needles and catheters to guide placement of the radioactive material by a remote afterloading device. It is more difficult to perform than other types of brachytherapy and has a steep learning curve.

c Balloon brachytherapy (e.g., MammoSite) entails inserting a balloon into the tumor bed, inflating the balloon, confirming its position radiographically, and then using a remote afterloader to irradiate the targeted area. Some brachytherapy systems combine aspects of interstitial and balloon brachytherapy.

d External-beam APBi is delivered in the same way as conventional or accelerated whole-breast radiotherapy but to a smaller area. All three external-beam regimens can use 3-dimensional conformal radiotherapy or intensity-modulated radiotherapy.

e Intraoperative APBi is performed during breast-conserving surgery with a single dose of radiation delivered to the exposed tumor bed.

Accelerated Whole Breast Irradiation

One approach to reducing radiotherapy treatment time is to provide the same dose to the whole breast in a shorter time by increasing the dose provided per treatment (hypofractionation). This approach was initially avoided out of concern that increasing doses might induce more severe adverse events from radiation exposure, thus tipping the balance between benefits and harms. More recent research, some of which are highlighted below, has allayed most of these concerns. Accelerated whole-breast irradiation has been adopted widely in Canada and Europe.

Accelerated Partial Breast Radiation

The second approach to reducing radiotherapy treatment time is APBi. It differs from conventional WBI in several ways. First, the radiation only targets the segment of the breast surrounding the area where the tumor was removed, rather than the entire breast. This approach was based in part on the finding that recurrences are more likely to occur close to the tumor site rather than elsewhere in the breast. Second, the duration of treatment is four to five days (or one day with intraoperative radiotherapy) rather than five to six weeks, because radiation is delivered to the tumor bed in fewer fractions at larger doses per fraction. Third, the radiation dose is intrinsically less uniform within the target volume when APBi uses brachytherapy (i.e., the implantation of radioactive material directly in the breast tissue).
Several methods to deliver APBI are available, including Interstitial brachytherapy, intraoperative brachytherapy, and external-beam APBI irradiation.

**Brachytherapy Boost With WBI**

Brachytherapy also can be used as an alternative to EBRT to deliver boost radiotherapy combined with whole-breast EBRT. Most studies of local boost brachytherapy use temporarily implanted needles, wires, or seeds after patients have recovered from surgery and completed whole-breast radiotherapy.

**Noninvasive Breast Brachytherapy**

Noninvasive breast brachytherapy (Accuboost), has been used for local boost around the tumor bed. The AccuBoost system provides image-guided radiotherapy before each treatment to ensure that radiation is directed at the treatment target. The breast is placed between mammography paddles, where images are taken and radiation is delivered using a distinct applicator. The paddles prevent motion during treatment. Radiation is delivered from one side of the breast to the other or from the top of the breast to the bottom. This is proposed to reduce radiation exposure to adjacent tissues, including the heart and lung.\(^\text{12}\) No long-term studies are available to confirm this.

**Literature Review**

This review was informed by several TEC Assessments, the most recent of which was released in 2013, on accelerated breast irradiation following breast-conserving surgery (BCS) for early-stage breast cancer.\(^\text{5}\).

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Accelerated Whole-Breast Irradiation**

**Clinical Context and Therapy Purpose**

The purpose of AWBI after BCS in patients who have node-negative, early-stage breast cancer with clear surgical margins is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does AWBI after BCS improve the net health outcome in patients who have node-negative, early-stage breast cancer with clear surgical margins?

The following PICOs were used to select literature to inform this review.
Patients
The relevant population of interest are patients who have node-negative, early-stage breast cancer with clear surgical margins.

Interventions
The therapy being considered is AWBI after BCS.

AWBI is administered in an outpatient oncology setting.

Comparators
The following therapy is currently being used to make decisions: standard whole-breast irradiation (WBI).

Outcomes
The general outcomes of interest are overall survival (OS), disease-related survival, local recurrence, and treatment-related adverse events.

Patients with early-stage breast cancer should be followed for ten years to evaluate OS and disease-related survival.

Study Selection Criteria
To assess efficacy outcomes, we included comparative controlled prospective trials, with a preference for RCTs and systematic reviews of RCTs.

In the absence of such trials, we included comparative observational studies, with a preference for prospective studies.

To assess long-term outcomes and adverse effects, we included single-arm studies that captured longer periods of follow-up and/or larger populations.

Systematic Reviews
A number of RCTs and systematic reviews of RCTs have compared AWBI (also referred to as accelerated whole-breast radiotherapy) with conventional five-week WBI. A systematic review and meta-analysis by Valle et al (2017) included 13 trials (total n=8189 patients) published prior to October 2014 that compared AWBI with standard fractionation. No differences were observed in local recurrence (7 trials; relative risk [RR], 0.97; 95% confidence interval [CI], 0.78 to 1.19), locoregional failure (8 trials; RR=0.86; 95% CI, 0.63 to 1.16), or survival (4 trials; RR=1.00; 95% CI, 0.85 to 1.17). There was less acute toxicity with AWBI (5 trials; RR=0.36; 95% CI, 0.21 to 0.62), and no difference in late cosmesis (RR=0.95; 95% CI, 0.81 to 1.12). The largest trials included in the meta-analysis were the Standardisation of Breast Radiotherapy (START) A, STARTB, and NCIC (detailed below).

Randomized Controlled Trials
Two of the RCTs included in the systematic review were noninferiority trials that directly compared a five-week with a three-week regimen. Both trials used noninferiority margins of 5 percentage points for local or locoregional recurrence in the accelerated group at 5 years (1-sided α=0.02516, or 0.0517) or 10 years (1-sided α=0.02518). Although the trials differed in specific fractionation schedules and patient characteristics, they reported similar ipsilateral local recurrence rates (i.e., cancer recurrence in the same breast) across treatment arms.

The first RCT evaluating an accelerated whole-breast radiotherapy regimen START B (2008), from the U.K., included women with stage I, II or III tumors (n=2215) who had clear tumor margins (≥1 mm). Approximately 75% of the women had negative lymph nodes, and approximately 42% had a radiation boost to the tumor bed. Randomization was stratified for the hospital, type of surgery (8% underwent mastectomy), and plans for a tumor bed boost. Systemic therapy, primarily tamoxifen, was used by some patients and appeared to be evenly distributed across...
treatment groups. Treatment arms compared a total dose of 40 gray (Gy) in 15 fractions over 3 weeks with 50 Gy in 25 fractions over 5 weeks. The primary efficacy outcome was locoregional relapse (relapse in ipsilateral breast or chest wall or in the ipsilateral axilla or supraclavicular fossa if previously irradiated) at five years. At median follow-up of 6.0 years (interquartile range, 5.0-6.2), estimated 5-year locoregional tumor relapse rate was 2.2% (95% CI, 1.3% to 3.1%) in the 40-Gy group and 3.3% (95% CI, 2.2% to 4.5%) in the 50-Gy group, for an absolute difference of -0.7% (95% CI, -1.7% to 0.9%). Hazard ratios for 40-Gy AWBI vs conventional WBI were not statistically significant for local or locoregional relapse. There were statistically significant differences between the 2 treatment regimens for distant relapse and OS, with relapse less frequent and survival longer for the 40-Gy AWBI group. This unexpected difference between treatment arms began to appear at about one year; trialists speculated that the difference might have been due to chance and might change over longer follow-up.

Subsequent publications provided additional results for both START trials (i.e., START A, which compared two, five-week whole-breast radiotherapy regimens, and START B). Hopwood et al (2010) examined the patient-reported breast, arm, and shoulder symptoms, as well as body image, over 5 years of follow-up.19, There was no evidence that providing radiotherapy in fewer, larger fractions increased the incidence of these adverse events or adversely affected body image. Haviland et al (2013) reported 10-year relapse, survival, and adverse event outcomes (median follow-up, 9.9 years).20, Locoregional recurrence did not differ significantly between the two treatment groups: 4.3% for the AWBI group and 5.5% for the standard WBI group. However, breast shrinkage, telangiectasia, and breast edema were significantly less common in the AWBI group. These effects were assessed by a physician, photographic comparison with baseline, and patient report.

The second RCT assessing a 5- and a 3-week radiotherapy regimen compared AWBI with WBI in women who had lymph node-negative stage I, II, or III tumors.17,18, Treatment arms included a hypofractionated-radiation group (n=622), who were treated with a total dose of 42.5 Gy in 16 fractions over 3 weeks, and a standard irradiation group (n=612), who were treated with 50 Gy in 25 fractions over 5 weeks. Five-year local recurrence-free survival was 97.2% in the accelerated arm and 96.8% in the conventional arm (difference, 0.4%; 95% CI, -1.5% to 2.4%). Ten-year local recurrence was 6.2% for the accelerated arm and 6.7% for the conventional arm (difference, -0.5% 95% CI, -2.5% to 3.5%). At five or ten years, local recurrence rates with AWBI were no worse than with conventional WBI, when applying a noninferiority margin of 5%. In prespecified subgroup analyses, treatment effects were similar by age, tumor size, estrogen receptor status, and chemotherapy use (48% had no systemic therapy).

An RCT by Shaitelman et al (2015) published after the Valle et al (2017) systematic review focused on acute and short-term toxicity for conventional WBI vs AWBI.21, This unblinded trial included 287 patients with stage 0 to III breast cancer treated with breast-conserving therapy who had negative tumor margins. Patients were randomized to conventional radiotherapy at 50 Gy in 25 fractions (n=149) or AWBI at 42 Gy in 16 fractions (n=138). The rate of grade 2 or higher acute toxic events was 47% in the AWBI group and 78% in the conventional WBI group (p <0.001). A total of 271 (94%) of 287 patients were available for an assessment at 6 months. There were no significant between-group differences in toxic effects at six months except that the rate of fatigue (grade ≥2) was significantly lower in the accelerated radiotherapy group (0%) than in the conventional radiotherapy group (6%; p =0.01).

**Observational Studies**

Toxicity was evaluated in a large retrospective study of patients with left-sided early-stage breast cancer published by Chan et al (2014, 2015).22,23, The study included 2706 patients who received conventional WBI (n=2221) or AWBI (n=485) AWBI. Cardiotoxic chemotherapy regimens were similar between groups. At a median follow-up of 14.2 years, there were no statistical differences in cardiac hospitalization or cardiac mortality, breast cancer mortality, or overall mortality. Results were similar for 2628 patients with right-sided tumors. This study was not designed to capture outcomes of moderate or mild cardiac toxicity.
Section Summary: AWBI
The overall body of evidence on AWBI compared with conventional WBI has indicated that local recurrence rates with AWBI are no worse than conventional WBI when applying a noninferiority margin of 5%. Canadian and U.K. noninferiority trials have reported ten-year follow-up data. Thus, conclusions apply to patients meeting eligibility criteria of these trials, including having early-stage invasive breast cancer, clear surgical margins, and negative lymph nodes. In addition, consistent with national guidelines, these conclusions apply to tumors less than or equal to 5 cm in diameter and women at least 50 years old. Based on 14-year retrospective data, severe cardiac toxicity with AWBI for left-sided breast cancers may not be increased compared with conventional WBI.

Accelerated Partial-Breast Irradiation
Clinical Context and Therapy Purpose
The purpose of APBI in patients who have early-stage breast cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does APBI improve the net health outcome in patients who have early-stage breast cancer?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are patients who have early-stage breast cancer.

Interventions
The therapies being considered are interstitial brachytherapy alone, intraoperative brachytherapy alone, and external-beam APBI.

Interstitial brachytherapy, intraoperative brachytherapy, and external-beam APBI irradiation are administered in an outpatient oncology setting.

Comparators
The following therapy is currently being used to make decisions about early-stage breast cancer: standard WBI.

Outcomes
The general outcomes of interest are OS, disease-related survival, local recurrence, and treatment-related adverse events.

Patients with early-stage breast cancer should be followed for ten years to evaluate OS and disease-related survival.

Study Selection Criteria
To assess efficacy outcomes, we included comparative controlled prospective trials, with a preference for RCTs and systematic reviews of RCTs.

In the absence of such trials, we included comparative observational studies, with a preference for prospective studies.

To assess long-term outcomes and adverse effects, we included single-arm studies that captured longer periods of follow-up and/or larger populations.

Systematic Reviews
A number of RCTs and nonrandomized comparative studies have evaluated interstitial, external-beam, or intraoperative APBI compared with conventional WBI. Several meta-analyses of these
studies have evaluated evidence on APBI compared to WBI, with various methods grouped in the same review. Conclusions cannot be drawn from these meta-analyses because analyses the methods varied and were not evaluated individually. The review authors were consistent in concluding that additional data from RCTs are needed.

**Interstitial Brachytherapy Randomized Controlled Trials**

GEC-ESTRO was a European multicenter noninferiority RCT with five-year results (see Table 2). Primary results were published in 2016, late-side effects in 2017, and quality of life in 2018. The primary study endpoint was the first incidence of local ipsilateral breast cancer recurrence within the five-year observation period and the noninferiority margin was a 3% difference. At 5 years, the associated cumulative incidence of local recurrence was 0.92% (95% CI, 0.12% to 1.73%) in the conventional WBI group and 1.44% (95% CI, 0.51% to 2.38%) in the APBI group (see Table 3). The difference between groups was within the noninferiority margin. There was no grade 4 skin toxicity. Grade 2 and 3 skin toxicity was 10.7% with WBI and 6.9% with APBI (p=0.02).

### Table 2. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
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<tr>
<td>GEC-ESTRO 28,29,30</td>
<td>EU</td>
<td>16</td>
<td></td>
<td>1328 patients ≥40 y with BCS for stage 0-IIa breast cancer, lesions ≤3 cm in diameter, clear margins ≥2 mm in any direction, and no lymph or blood vessel invasion</td>
<td>655 patients given APBI using interstitial brachytherapy</td>
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<table>
<thead>
<tr>
<th>Active</th>
<th>Comparator</th>
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<td>655 patients given APBI at 50 Gy in daily fractions of 1.8-2.0 Gy over 5 wk</td>
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APBI: accelerated partial breast irradiation; BCS: breast-conserving therapy; Gy: gray; RCT: randomized controlled trial; WBI: whole-breast irradiation.

### Table 3. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Local Recurrence, n (%)</th>
<th>Overall Survival</th>
<th>Grade 2 to 3 Late Skin Toxicity</th>
<th>Excellent-to-Good Cosmetic Results, n (%)</th>
<th>Global Health Status (SD)</th>
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<td>GEC-ESTRO 28-30</td>
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<td>1184</td>
<td>1184</td>
<td>1184</td>
<td>1007</td>
</tr>
<tr>
<td>WBI</td>
<td>5 (0.92)</td>
<td>95.5%</td>
<td>5.7%</td>
<td>408 (90)</td>
<td>66.0 (21.8)</td>
</tr>
<tr>
<td>APBI</td>
<td>9 (1.44)</td>
<td>97.27%</td>
<td>3.2%</td>
<td>503 (93)</td>
<td>66.2 (22.2)</td>
</tr>
<tr>
<td>Diff (95% CI)</td>
<td>0.52%</td>
<td>1.72%</td>
<td>(-0.44% to 3.88%)</td>
<td>-0.2</td>
<td>(-4.0 to 3.6)</td>
</tr>
</tbody>
</table>

| p | NS | 0.11 | 0.080 | 0.12 | 0.94 |

APBI: accelerated partial breast irradiation; CI: confidence interval; Diff: difference; RCT: randomized controlled trial; RRWBI: whole-breast irradiation; SD: standard deviation.

Major limitations in relevance and design and conduct are shown in Tables 4 and 5 is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

### Table 4. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC-ESTRO 28,29,30</td>
<td></td>
<td></td>
<td></td>
<td>1. Overall survival was not a primary outcome</td>
<td>1. Only followed for 5 y</td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

### Table 5. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC-ESTRO 28,29,30</td>
<td>1-3. Not blinded</td>
<td>1. No prespecified noninferiority analysis on survival outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

- **Allocation key:** 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
- **Blinding key:** 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
- **Selective Reporting key:** 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
- **Data Completeness key:** 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
- **Power key:** 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
- **Statistical key:** 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or \( p \) values not reported; 4. Comparative treatment effects not calculated.

### Nonrandomized Studies

Ajkay et al (2015) reported retrospectively on 5-year adverse events in patients with early-stage breast cancer treated at a single-center. Of 417 patients who received BCS and radiotherapy, 271 received brachytherapy (34 Gy in 10 fractions; 90% MammoSite, 9% Contura, 1% strut-adjusted volume implant) and 146 received WBI using 3-dimensional conformal radiotherapy (45-50.4 Gy in 25-28 fractions with 10-16 Gy boost). Median follow-up was 4.8 years in the brachytherapy group and 4.1 years in the WBI group. The estimated 5-year overall incidence of any adverse event was greater in the brachytherapy group (72%) than in the WBI group (52%; \( p<0.001 \)). For prespecified adverse events of interest, estimated five-year incidences of infectious skin complications, abscess, telangiectasia, and breast pain were similar between groups. Estimated 5-year incidences of seroma (47% vs 19%, \( p<0.001 \)) and fat necrosis (40% vs 24%, \( p<0.001 \)) were greater in the brachytherapy group, respectively.

### Section Summary: Intersitial Brachytherapy

The 2015 GEC-ESTRO RCT reported 5-year follow-up data and found that interstitial brachytherapy was noninferior to WBI on rates of local breast cancer recurrence when applying a 3% noninferiority margin. The number of events at five years was small. Ten-year follow-up data and at least one additional trial confirming these findings are needed.

### Intraoperative Brachytherapy

#### Randomized Controlled Trials

One RCT, reported by Vaidya et al (2010, 2014) compared intraoperative radiotherapy (IORT) with WBI in 2232 women. Radiotherapy was delivered to the tumor bed using the Intrabeam device, which provides a point source of 50 kV energy x-rays at the center of a spherical applicator, for 20 to 45 minutes. It was specifically developed for IORT. The Risk-adapted Targeted Intraoperative Radiotherapy (TARGIT-A) trial was a noninferiority study at 28 centers in 9 countries and a sample size of 3451. In 2010, the trial was extended for 2 more years to allow accrual in subprotocols. An intention-to-treat approach was used. Patients were not blinded to treatment.
choice. As anticipated, 14% of those in the IORT arm received external-beam radiotherapy (EBRT) as well, because of unfavorable pathologic features determined after surgery (e.g., lobular carcinoma). The predefined noninferiority margin was an absolute difference of 2.5% between groups for pathologically confirmed, ipsilateral local recurrence. The most recent report (2013) provided 5-year results, defined as results for patients with 5 years of follow-up or "if they were seen the year before database lock." Median follow-up for all patients was 2 years and 5 months (interquartile range, 12-52 months), and 1222 (35%) patients had a median follow-up of 5 years. Estimated 5-year risks for ipsilateral local recurrence 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=0.042) in the WBI group. Mortality was similar between the 2 groups (2.6% with TARGIT vs 1.9% with WBI; p=0.56). However, there were significantly fewer non-breast cancer deaths in the TARGIT group (1.4%; 95% CI, 0.8% to 2.5%) than in the WBI group (3.5%; 95% CI, 2.3% to 5.2% p<0.001), with fewer deaths from cardiovascular causes and other cancers in the TARGIT group. In the group that received IORT plus WBI, 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 6.1%) was similar for those who only received IORT. Noninferiority was established for the whole intraoperative cohort and for those who received IORT alone but not for patients who underwent both types of radiotherapy. There was no significant difference between the IORT and WBI groups in predefined six-month wound-related complications. However, grade 3 or 4 radiotherapy-related skin complications were more common in the WBI group (13/1730 vs 4/1731; p=0.029). Five- and 10-year follow-ups for the entire TARGIT-A cohort have yet to be accrued.

Another form of IORT, called electron intraoperative radiotherapy (ELIOT), uses electrons.34 The ELIOT trial, reported by Veronesi et al (2013), compared IORT plus ELIOT with WBI.35 With a sample size of 1305 patients and median follow-up of 5.8 years (interquartile range, 4.1-7.7 years), 35 (4.4%) patients in the intraoperative group and 4 (0.4%) patients in the WBI group developed ipsilateral breast tumor recurrences (hazard ratio, 9.3; 95% CI, 3.3 to 26.3; p<0.001). There was no statistically significant difference in five-year OS. For women with data on adverse skin events (IORT=464, WBI=412), there were significantly fewer events among women who received IORT (p<0.001). This was an equivalence trial with a prespecified limit of 7.5% for local recurrence in the IORT group only. Therefore, although the criterion for equivalence was satisfied, the ipsilateral breast recurrence rate was significantly higher in the IORT group. A subsequent review of ELIOT trial data by Silverstein et al (2014) noted that, of 69 women who had 4 or more positive lymph nodes, those randomized to WBI (n=38) received concurrent axillary radiation; for those randomized to ELIOT (n=31), axillary irradiation was delayed 6 to 12 weeks.8 These reviewers also characterized ELIOT data as premature and noted that long-term results are needed to assess net health benefit.

Section Summary: Intraoperative Brachytherapy

RCTs have not demonstrated that outcomes after intraoperative brachytherapy are noninferior to WBI. Five-year results from the TARGIT-A RCT showed increased ipsilateral local recurrence with APBI compared with WBI. In another RCT that used a related but different technology (ELIOT), the recurrence rate with IORT was statistically greater than that with WBI.
External-Beam APBI
Randomized Controlled Trials

Three RCTs have compared EBRT APBI with WBI using 3-dimensional conformal radiotherapy (Tables 6 and 7).

Rodriguez et al (2013) reported on 102 patients randomized to WBI, with or without a boost to the tumor bed, or APBI. The primary endpoint was local recurrence within five years. In this noninferiority trial, the sample size was calculated to detect a 10% difference between treatment arms, with a power of 80% at a significance level of 0.05. The APBI group was significantly younger than the WBI group (mean age, 67.1 years vs 70.1 years; \( p=0.009 \)). After a median follow-up of five years, there were no recurrences in either group nor was there a statistically significant difference in survival. Investigators noted that the sample size might have been insufficient to detect a true difference in local control. Ninety percent (46/51) of APBI patients had acute skin effects, mostly grade 1; all patients in the WBI group had acute skin effects, and most were grade 2. Grade 1 and 2 late effects were reported with some changes in the relative positions of the treatment groups over time.

Olivotto et al (2013) reported results of the multicenter Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) trial (\( p<0.001 \)), nurses (\( p<0.001 \)), or patients (\( p<0.05 \)). As for late toxicities, 1.4% of APBI patients had a grade 3 adverse event vs none of the WBI patients. Telangiectasia and breast induration were more common among APBI patients (\( p<0.001 \)). Although the primary outcome was ipsilateral local breast tumor recurrence, there were too few events to trigger an efficacy analysis.

In Livi et al (2015), 520 patients with early breast cancer were randomized to APBI using intensity-modulated radiotherapy or WBI (\( p=0.057 \)). The 5-year OS was 96.6% for the WBI group and 99.4% for the APBI group. Longer-term results (median 9.2 years, range 3.8 to 12.1 years) were reported in Becherini et al (2019) but only for the 22 patients in the APBI arm. There were no local recurrences occurrence, distant metastasis, or breast cancer-related deaths, and 10-year OS was 90.9%.

NSABP B-39/RTOG 0413 is the largest and longest-term RCT to compare APBI to WBI (n=4216). Results have not yet been fully published but are available in abstract form from a December 2018 conference presentation. As of July 2018, the median follow-up was 10.2 years. APBI did not meet the criteria for equivalence to WBI in controlling local recurrence based on the upper limit of the hazard ratio CI, but the absolute difference in the ten-year rate of EBTR was <1% (4.8% APBI vs 4.1% WBI). The study authors noted that the trial population was heterogeneous and analyses of outcomes by risk categories are ongoing.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livi et al (2015)(^{38})</td>
<td>Italy</td>
<td>1</td>
<td>2005-2013</td>
<td>Over age 40, maximum tumor size 25mm</td>
<td>APBI: 30 Gy to the tumour bed in five daily fractions, N=260</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WBI: 50 Gy in 25 fractions, followed by a boost on the tumour bed of 10 Gy in five fractions, N=260</td>
</tr>
<tr>
<td>Olivotto et al (2013)(^{37})</td>
<td>Canada, Australia, New Zealand</td>
<td>33</td>
<td>2006-2011</td>
<td>invasive ductal carcinoma or DCIS treated with BCS with microscopically</td>
<td>APBI: 38.5 Gy in 10 fractions treated twice daily over 5 to</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WBI: 42.5 Gy in 16 fractions or 50 Gy in 25 fractions. Boost irradiation of 10</td>
</tr>
</tbody>
</table>
clear margins and negative axillary nodes by sentinel node biopsy, or axillary dissection for those with invasive disease, or by clinical examination for those with DCIS alone.

Table 7. Summary of Key RCT Results-External Beam APBI vs WBI

<table>
<thead>
<tr>
<th>Study</th>
<th>Local Recurrence</th>
<th>Overall Survival</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livi et al (2015)</td>
<td>Ipsilateral tumor recurrence at 5 years</td>
<td>Number of deaths at 5 years</td>
<td>Acute skin toxicity (≥ grade 2) at 5 years</td>
</tr>
<tr>
<td>N</td>
<td>520</td>
<td>1</td>
<td>37.7%</td>
</tr>
<tr>
<td>APBI</td>
<td>1.5%</td>
<td>1</td>
<td>37.7%</td>
</tr>
<tr>
<td>WBI</td>
<td>1.4%</td>
<td>7</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olivotto et al (2013)</td>
<td>Grade 2 or 3 toxicity at 3 years</td>
<td>Grade 2 or 3 toxicity at 3 years</td>
<td>Grade 2 or 3 toxicity at 3 years</td>
<td></td>
</tr>
<tr>
<td>NC00282035</td>
<td>N</td>
<td>1070</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>APBI</td>
<td>No significant differences between groups in recurrence rates at 5 years (data NR)</td>
<td>No significant differences between groups in 5-year survival rates (data NR)</td>
<td>Acute: 46/51 (90.2%) 4 years: 16% all grade 1</td>
<td></td>
</tr>
<tr>
<td>WBI</td>
<td>Acute: 51/51 (100%) 4 years: 11% all grade 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; APBI: accelerated partial breast irradiation; WBI: whole breast irradiation; Gy: gray; N: sample size; BCS: breast-conserving surgery; DCIS: ductal carcinoma in situ.

Relevance and study design limitations are summarized in Tables 8 and 9. The studies were limited by a lack of long-term follow-up data, small sample size, and incomplete follow-up data.

Table 8. Relevance Limitations-External Beam APBI vs WBI

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olivotto et al (2013)</td>
<td></td>
<td>1. Too few events for efficacy analysis of the primary outcome (local recurrence)</td>
<td>1, 2. 5 years follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rodriguez et al (2013)</td>
<td></td>
<td></td>
<td>1, 2. 5 years follow-up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APBI: accelerated partial breast irradiation; NR: not reported; NCT: national clinical trial; WBI: whole breast irradiation.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
Accelerated Breast Irradiation and Brachytherapy Boost After Breast-Conserving Surgery for Early-Stage Breast Cancer

Section Summary: External-Beam APBI

Two RCTs have reported outcomes to three to five years. A third trial reported 10-year results but only for the 22 patients in the APBI arm. Ten-year comparative data are required to draw conclusions about the impact of technology on health outcomes. Moreover, one of the trials reported higher rates of adverse cosmetic outcomes and grade 3 toxicities in the external-beam APBI group than in the WBI group.

Local Boost Brachytherapy

Clinical Context and Therapy Purpose

The purpose of local boost brachytherapy with WBI in patients who have early-stage breast cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does local boost brachytherapy with WBI improve the net health outcome in patients who have early-stage breast cancer?

The following PICOs were used to select literature to inform this review.
Patients
The relevant population of interest are patients who have early-stage breast cancer.

Interventions
The therapy being considered is local boost brachytherapy with WBI.

Brachytherapy can be used as an alternative to EBRT to deliver boost radiotherapy combined with whole-breast irradiation.

Local boost brachytherapy with WBI is administered in an outpatient oncology setting. Most studies of local boost brachytherapy use temporarily implanted needles, wires, or seeds after patients have recovered from surgery and completed whole-breast radiotherapy.

Comparators
The following therapy is currently being used to make decisions about early-stage breast cancer: standard WBI with or without an external-beam boost to the tumor bed.

Outcomes
The general outcomes of interest are OS, disease-related survival, local recurrence, and treatment-related adverse events.

Patients with early-stage breast cancer should be followed for ten years to evaluate OS and disease-related survival.

Study Selection Criteria
To assess efficacy outcomes, we included comparative controlled prospective trials, with a preference for RCTs and systematic reviews of RCTs.

In the absence of such trials, we included comparative observational studies, with a preference for prospective studies.

To assess long-term outcomes and adverse effects, we included single-arm studies that captured longer periods of follow-up and/or larger populations.

Systematic Reviews
A TEC Assessment (1996) concluded that net health outcomes with a local boost using brachytherapy were equivalent to outcomes of local boost using EBRT in women who received BCS plus WBI as initial treatment for stage I or II breast cancer.41, No RCTs were identified. However, there were 7 nonrandomized studies comparing 2 types of local boost radiotherapy: brachytherapy (n=2033) and EBRT (n=1557); all patients also received BCS and WBI. The combination of brachytherapy with local boost, BCS, and WBI prevented local tumor recurrence and salvage mastectomy in 95% to 97% of patients at 5 years and 88% to 92% of patients at 10 years. Five-year survival in the 5 studies reporting this outcome ranged from 83% to 96%. Data from uncontrolled studies reported similar rates of local control and five-year survival.

Section Summary: Local Boost Brachytherapy
For women undergoing BCS plus WBI as initial treatment for stage I or II breast cancer, nonrandomized comparative studies have shown similar outcomes with local boost using brachytherapy and local boost using EBRT.
Noninvasive Breast Brachytherapy

Clinical Context and Therapy Purpose
The purpose of noninvasive breast brachytherapy in patients who have early-stage breast cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does noninvasive breast brachytherapy improve the net health outcome in patients who early-stage breast cancer?

The following PICO(s) were used to select literature to inform this review.

Patients
The relevant population of interest are patients who have early-stage breast cancer.

Interventions
The therapy being considered is noninvasive breast brachytherapy.

AccuBoost for image-guided breast irradiation, also called noninvasive breast brachytherapy, has been used for local boost around the tumor bed. The AccuBoost system provides image-guided radiotherapy before each treatment to ensure that radiation is directed at the treatment target. The breast is placed between mammography paddles, where images are taken and radiation is delivered using a distinct applicator. The paddles prevent motion during treatment. Radiation is delivered from 1 side of the breast to the other or from the top of the breast to the bottom. This is proposed to reduce radiation exposure to adjacent tissues, including the heart and lung.12 No long-term studies are available to confirm this.

Noninvasive breast brachytherapy is administered in an outpatient oncology setting.

Comparators
The following therapy is currently being used to make decisions about early-stage breast cancer: standard WBI.

Outcomes
The general outcomes of interest are OS, disease-related survival, local recurrence, and treatment-related adverse events.

Patients with early-stage breast cancer should be followed for ten years to evaluate OS and disease-related survival.

Study Selection Criteria
To assess efficacy outcomes, we included comparative controlled prospective trials, with a preference for RCTs and systematic reviews of RCTs.

In the absence of such trials, we included comparative observational studies, with a preference for prospective studies.

To assess long-term outcomes and adverse effects, we included single-arm studies that captured longer periods of follow-up and/or larger populations.

Systematic Reviews and RCTs
No systematic reviews or RCTs of noninvasive breast brachytherapy for patients with early-stage breast cancer were identified.
Nonrandomized Studies
One comparative study on noninvasive breast brachytherapy was identified. This matched retrospective study by Leonard et al (2013) assessed patients receiving the boost dose using AccuBoost or electron beams (a type of EBRT). Each of the 47 AccuBoost patients was compared with 2 controls matched on age, stage, chemotherapy use, fractionation, and when possible, breast size, comorbidities, and smoking status. Main differences between the two treatment groups were in radiation doses received and the timing of radiotherapy administration. The percentage of patients with a WBI dose (accompanying the boost dose) of 50 to 50.4 Gy was 68% in the AccuBoost group and 37% in the electron-treated group (p<0.001). Also, a greater proportion of patients in the electron-treated group received the boost dose after WBI, rather than during WBI or starting before and ending during WBI (99% for the electron-treated group vs 6% for the AccuBoost group). Approximately 60% of patients had stage I breast cancer, and approximately 25%, ductal carcinoma in situ. With a median follow-up of 13.6 months, skin and subcutaneous tissue toxicity incidence occurred less often among patients treated with AccuBoost than among those treated with an electron beam (p=0.046). Locoregional control rates were 99% or greater in both groups. Study limitations included the between-group differences in dose and timing of boost, as well as selection bias and the study's retrospective design.

Section Summary: Noninvasive Breast Brachytherapy
One nonrandomized comparative study was identified. The comparative study was a retrospective matched comparison of noninvasive breast brachytherapy or EBRT to provide boost radiation to the tumor bed. The study was subject to selection bias, relatively short follow-up, and use of a retrospective design.

Summary of Evidence
Accelerated Whole-Breast Irradiation
For individuals who have node-negative, early-stage breast cancer with clear surgical margins who receive AWBI after BCS, the evidence includes RCTs and systematic reviews. The relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. Two randomized noninferiority trials both reported ten-year follow-up data on local recurrence. Both trials found that local recurrence rates with AWBI were no worse than conventional WBI when applying a noninferiority margin of 5%. Conclusions apply to patients meeting eligibility criteria of the RCTs trials, including having early-stage invasive breast cancer, clear surgical margins, and negative lymph nodes. In addition, consistent with national guidelines, these conclusions apply to tumors less than or equal to 5 cm in diameter and women at least 50 years old. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Accelerated Partial-Breast Irradiation
For individuals who have early-stage breast cancer who receive interstitial brachytherapy, the evidence includes an RCT. The relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. The RCT reported five-year follow-up data and found that interstitial brachytherapy was noninferior to WBI for rates of local breast cancer recurrence when applying a noninferiority margin of 3%. Ten-year follow-up data are needed on local recurrence as well as at least one additional trial confirming these findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have early-stage breast cancer who receive intraoperative brachytherapy, the evidence includes RCTs. The relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. Several RCTs have been published but collectively they have not demonstrated that outcomes after intraoperative brachytherapy are noninferior to WBI. Results of two RCTs (TARGIT-A, ELIOT) comparing intraoperative brachytherapy with WBI found higher rates of local recurrence with intraoperative brachytherapy than with WBI. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals who have early-stage breast cancer who receive external-beam APBI, the evidence includes RCTs. The relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. The RCTs have reported outcomes out to three to five years, and ten-year data are required to draw conclusions about the impact of the technology on health outcomes. Moreover, one of the two trials reported higher rates of adverse cosmesis and grade 3 toxicities in the external-beam APBI group compared with the WBI group. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Local Boost Brachytherapy**

For individuals who have early-stage breast cancer who receive local boost brachytherapy with WBI, the evidence includes nonrandomized studies and a systematic review. The relevant outcomes are OS overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. A TEC Assessment concluded that, for women undergoing BCS plus WBI as initial treatment for stage I or II breast cancer, nonrandomized comparative studies have shown similar outcomes with brachytherapy local boost and with EBRT local boost. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Noninvasive Breast Brachytherapy**

For individuals who have early-stage breast cancer who receive noninvasive breast brachytherapy, the evidence includes a retrospective comparative study. The relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. The retrospective study was a matched comparison of noninvasive breast brachytherapy or electron beam radiotherapy to provide boost radiation to the tumor bed. The study was subject to selection bias, relatively short follow-up, and use of a retrospective design. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

**Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

**2017 Input**

In response to requests from Blue Cross Blue Shield Association, input was received from 1 physician specialty society and 4 academic medical centers in 2017. Input was limited to the policy statement on accelerated whole-breast irradiation. Three of four academic medical centers and the physician specialty society agreed with the statement as a whole. Reviewers suggested other eligibility criteria but there was no consensus on specific criteria.

**2011 Input**

In response to requests from Blue Cross Blue Shield Association, input was received from 1 physician specialty society and 4 academic medical centers in 2011. There was near-unanimous support for the policy statement on accelerated whole-breast irradiation. Input was mixed on accelerated partial-breast irradiation; those agreeing with the conclusion noted the need to define the risks and benefits of this approach in patient subgroups and noted that current data are inconclusive on the effectiveness of accelerated partial-breast irradiation compared with whole-breast irradiation.
Practice Guidelines and Position Statements
National Comprehensive Cancer Network

Current NCCN guidelines (v.1.2019) on breast cancer state:

“Preliminary studies of APBI [accelerated partial-breast irradiation] suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard whole breast RT [radiotherapy]. However, compared to standard whole breast radiation, several recent studies documented an inferior cosmetic outcome with APBI. Follow-up is limited and studies are ongoing. Patients are encouraged to participate in clinical trials. The NCCN panel accepts the updated 2016 version of the ASTRO [American Society for Radiation Oncology] APBI guideline” (see Table 10).

For whole-breast radiotherapy, the NCCN recommends a conventional whole-breast irradiation regimen or a total dose of 45 to 50.4 gray in 25 to 28 fractions or 40 to 42.5 gray in 15 to 16 fractions, with hypofractionation preferred. The latter is presumably an accelerated whole-breast irradiation regimen. A boost to the tumor bed is recommended for higher-risk patients receiving whole-breast radiotherapy (i.e., those who are <50 years old with a high-grade disease).

American Society for Radiation Oncology et al
The ASTRO (2017), American Society of Breast Surgeons (2011), and the American Brachytherapy Society (2018) have issued various consensus statements for the selection of patients for APBI (summarized in Table 10). Recommendations were based on systematic reviews, which are not described in detail, and expert opinion.

Table 10. Professional Medical Society Criteria for Performing APBI

<table>
<thead>
<tr>
<th>Factor</th>
<th>ASTRO “Suitable”</th>
<th>ASTRO “Cautionary”</th>
<th>ASTRO “Unsuitable”</th>
<th>ASBS</th>
<th>ABS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>≥50 y</td>
<td>40-49 y</td>
<td>&lt;40 y</td>
<td>≥45 y</td>
<td>≥45 y</td>
</tr>
<tr>
<td>BRCA1 and BRCA2 variants</td>
<td>Not present</td>
<td>NR</td>
<td>Present</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Pathologic factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>≤2 cm</td>
<td>2.1-3.0 cm</td>
<td>&gt;3 cm</td>
<td>≤3 cm</td>
<td>≤3 cm</td>
</tr>
<tr>
<td>Tumor stage</td>
<td>Tis or T1</td>
<td>T0 or T2</td>
<td>T3-4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Margins</td>
<td>≥2 mm</td>
<td>Close (&lt;2 mm)</td>
<td>Positive</td>
<td>Microscopically negative</td>
<td>Negative (no tumor on ink for invasive ≥2 mm for DCIS)</td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>LVSI</td>
<td>No</td>
<td>Limited/focal</td>
<td>Extensive</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>ER status</td>
<td>Positive</td>
<td>Negativea</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Unicentric</td>
<td>NR</td>
<td>Present</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Clinically unifocal; total size, ≤2.0 cm</td>
<td>Clinically unifocal; size, 2.1-3.0 cm</td>
<td>Clinically multifocal or microscopically multifocal; size, ≥3 cm</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Histology</td>
<td>Invasive ductal or other favorable subtypesab</td>
<td>Invasive lobular</td>
<td>NR</td>
<td>Invasive ductal carcinoma or DCIS</td>
<td>All invasive subtypes and DCIS</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>Not allowed</td>
<td>≤3 cm if “suitable” criteria not fully met</td>
<td>&gt;3 cm</td>
<td>≤3 cm</td>
<td>≤3 cm</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Not allowed</td>
<td>≤3 cm</td>
<td>&gt;3 cm</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nodal factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal stage</td>
<td>pN0 (i, i)</td>
<td>NR</td>
<td>pN1, pN2, pN3</td>
<td>SN pN0</td>
<td>pN0c</td>
</tr>
</tbody>
</table>

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Accelerated Breast Irradiation and Brachytherapy Boost After Breast-Conserving Surgery for Early-Stage Breast Cancer

The ASTRO (2018) updated its guidelines on fractionation for whole-breast irradiation. The consensus-based guidelines conclude that accelerated whole-breast irradiation may be used for any age and any stage provided the intent is to treat the whole breast without any additional field, and with any chemotherapy.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 11.

Table 11. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBI vs APBI with or without tumor bed boost in DCIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC10470236 Radiation Doses and Fractionation Schedules in Non-low Risk Ductal Carcinoma In Situ (DCIS) of the Breast (TROG)</td>
<td>1600</td>
<td>Nov 2024</td>
<td></td>
</tr>
<tr>
<td>Intraoperative brachytherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC101343459 Intra-Operative Electron Boost and Hypofractionated Whole- Breast Irradiation During Breast-conserving Treatment (BCT) (HIOB)</td>
<td>1000</td>
<td>Mar 2021</td>
<td></td>
</tr>
<tr>
<td>NC101644669 Safety and Efficacy Study of the Xoft® Axxent® eBx™ IORT System</td>
<td>1000</td>
<td>Dec 2024</td>
<td></td>
</tr>
<tr>
<td>External-beam APBI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC101803958 Breast Cancer With Low Risk Of Local Recurrence: Partial and Accelerated Radiation With Three-Dimensional Conformal Radiotherapy (3DCRT) vs Standard Radiotherapy After Conserving Surgery (Phase III Study) (IRMA)</td>
<td>3302</td>
<td>Jan 2019 (unpublished)</td>
<td></td>
</tr>
<tr>
<td>NC101247233 Standard or Hypofractionated Radiotherapy Versus Accelerated Partial Breast Irradiation (APBI) for Breast Cancer (SHARE)</td>
<td>2796</td>
<td>Oct 2024</td>
<td></td>
</tr>
<tr>
<td>NC101185132 Intensity Modulated Radiotherapy (IMRT) vs 3D-conformal Accelerated Partial Breast Irradiation (APBI) for Early Stage Breast Cancer After Lumpectomy (2009-APBI)</td>
<td>660</td>
<td>Jul 2028</td>
<td></td>
</tr>
<tr>
<td>APBI (multimodality)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC1010892814 Partial Breast Versus Whole Breast Irradiation in Elderly Women Operated on for Early Breast Cancer</td>
<td>628</td>
<td>May 2022</td>
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<tr>
<td>NC101185145 Accelerated Partial Breast Radiotherapy With Either Mammosite or Intensity Modulated Radiotherapy (APBI)</td>
<td>291</td>
<td>Aug 2024</td>
<td></td>
</tr>
</tbody>
</table>
References

16. Starl Trials’ Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early...
8.01.13 Accelerated Breast Irradiation and Brachytherapy Boost After Breast-Conserving Surgery for Early-Stage Breast Cancer

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**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Tumor classification
  - Past medical and/or surgical treatment and response
- Operative report(s) or procedure report(s)
- Pathology report(s)
- Radiation treatment plan including: type of brachytherapy, therapy schedule, and number of treatments

**Post Service**
- Daily radiation treatment records

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0395T</td>
<td>High dose rate electronic brachytherapy, interstitial or intracavity treatment, per fraction, includes basic dosimetry, when performed</td>
</tr>
<tr>
<td></td>
<td>19294</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>19296</td>
<td>Placement of radiotherapy afterloading expandable catheter (single or multichannel) into the breast for interstitial radionuclide application following partial mastectomy, includes imaging guidance; on date separate from partial mastectomy</td>
</tr>
<tr>
<td></td>
<td>19297</td>
<td>Placement of radiotherapy afterloading expandable catheter (single or multichannel) into the breast for interstitial radionuclide application following partial mastectomy, includes imaging guidance; concurrent with partial mastectomy (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>19298</td>
<td>Placement of radiotherapy after loading brachytherapy catheters (multiple tube and button type) into the breast for interstitial radionuclide application following (at the time of or subsequent to) partial mastectomy, includes imaging guidance</td>
</tr>
<tr>
<td></td>
<td>77261</td>
<td>Therapeutic radiology treatment planning; simple</td>
</tr>
<tr>
<td></td>
<td>77262</td>
<td>Therapeutic radiology treatment planning; intermediate</td>
</tr>
<tr>
<td></td>
<td>77263</td>
<td>Therapeutic radiology treatment planning; complex</td>
</tr>
<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>---------------</td>
<td>------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>77280</td>
<td>Therapeutic radiology simulation-aided field setting; simple</td>
</tr>
<tr>
<td></td>
<td>77285</td>
<td>Therapeutic radiology simulation-aided field setting; intermediate</td>
</tr>
<tr>
<td></td>
<td>77290</td>
<td>Therapeutic radiology simulation-aided field setting; complex</td>
</tr>
<tr>
<td></td>
<td>77295</td>
<td>3-dimensional radiotherapy plan, including dose-volume histograms</td>
</tr>
<tr>
<td></td>
<td>77316</td>
<td>Brachytherapy isodose plan; simple (calculation[s] made from 1 to 4 sources, or remote afterloading brachytherapy, 1 channel), includes basic dosimetry calculation(s)</td>
</tr>
<tr>
<td></td>
<td>77317</td>
<td>Brachytherapy isodose plan; intermediate (calculation[s] made from 5 to 10 sources, or remote afterloading brachytherapy, 2-12 channels), includes basic dosimetry calculation(s)</td>
</tr>
<tr>
<td></td>
<td>77318</td>
<td>Brachytherapy isodose plan; complex (calculation[s] made from over 10 sources, or remote afterloading brachytherapy, over 12 channels), includes basic dosimetry calculation(s)</td>
</tr>
<tr>
<td></td>
<td>77770</td>
<td>Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 1 channel</td>
</tr>
<tr>
<td></td>
<td>77771</td>
<td>Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 2-12 channels</td>
</tr>
<tr>
<td></td>
<td>77772</td>
<td>Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; over 12 channels</td>
</tr>
<tr>
<td></td>
<td>77778</td>
<td>Interstitial radiation source application, complex, includes supervision, handling, loading of radiation source, when performed</td>
</tr>
<tr>
<td></td>
<td>77799</td>
<td>Unlisted procedure, clinical brachytherapy</td>
</tr>
</tbody>
</table>

**HCPCS**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1717</td>
<td>Brachytherapy source, nonstranded, high dose rate iridium-192, per source</td>
</tr>
<tr>
<td>C9726</td>
<td>Placement and removal (if performed) of applicator into breast for intraoperative radiation therapy, add-on to primary breast procedure</td>
</tr>
<tr>
<td>Q3001</td>
<td>Radioelements for brachytherapy, any type, each</td>
</tr>
</tbody>
</table>

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/30/2015</td>
<td>Policy title change from Brachytherapy for Oncologic Indications</td>
</tr>
<tr>
<td></td>
<td>Policy revision with position change</td>
</tr>
<tr>
<td></td>
<td>BCBSA Medical Policy adoption</td>
</tr>
<tr>
<td>09/30/2015</td>
<td>Coding update</td>
</tr>
<tr>
<td>01/01/2016</td>
<td>Coding update</td>
</tr>
<tr>
<td>04/01/2017</td>
<td>Policy title change from Accelerated Breast Irradiation After Breast-Conserving Surgery for Early Stage Breast Cancer and Breast Brachytherapy as Boost With Whole-Breast Irradiation</td>
</tr>
<tr>
<td></td>
<td>Policy revision with position change</td>
</tr>
<tr>
<td>01/01/2018</td>
<td>Coding update</td>
</tr>
<tr>
<td>03/01/2018</td>
<td>Policy statement clarification</td>
</tr>
<tr>
<td>09/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>10/01/2019</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>04/01/2020</td>
<td>Administrative update. Policy statement and guidelines updated.</td>
</tr>
</tbody>
</table>
Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member’s illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.