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

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Accelerated Breast Irradiation After Breast-Conserving Surgery for Early Stage Breast Cancer and Breast Brachytherapy as Boost With Whole-Breast Irradiation when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
When using radiotherapy after breast-conserving surgery (BCS) for early stage breast cancer:
   Accelerated whole-breast irradiation (AWBI) may be considered medically necessary for patients who meet the following conditions:
   - Invasive carcinoma of the breast
   - tumors greater than 5 cm in diameter
   - negative lymph nodes
   - technically clear surgical margins, ie, no ink on tumor on invasive carcinoma or ductal carcinoma in situ
   - age at least 50 years old.

Interstitial or balloon brachytherapy may be considered medically necessary for patients undergoing initial treatment for stage 1 or 2 breast cancer when used as local boost irradiation in patients who are also treated with BCS and whole-breast external-beam radiotherapy.

When Policy Topic is not covered
AWBI is considered investigational in all other situations involving treatment of early stage breast cancer after BCS.
Accelerated partial-breast irradiation (APBI), including interstitial APBI, balloon APBI, external-beam APBI, noninvasive brachytherapy using Accuboost®, and intra-operative APBI, is considered investigational.

Noninvasive brachytherapy using Accuboost® for patients undergoing initial treatment for stage 1 or 2 breast cancer when used as local boost irradiation in patients who are also treated with BCS and whole breast external-beam radiotherapy is considered investigational.

**Considerations**
Electronic brachytherapy is considered a type of balloon brachytherapy that can be used to deliver accelerated whole-breast irradiation (AWBI).

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 T1–2 N0 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).

**Description of Procedure or Service**

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **Individuals:**  
  • With node-negative, early-stage breast cancer with clear surgical margins | Interventions of interest are:  
  • Accelerated whole-breast irradiation after breast-conserving surgery | Comparators of interest are:  
  • Standard whole-breast irradiation | Relevant outcomes include:  
  • Overall survival  
  • Disease-specific survival  
  • Change in disease status  
  • Treatment-related morbidity |
| **Individuals:**  
  • With early-stage breast cancer | Interventions of interest are:  
  • Interstitial brachytherapy | Comparators of interest are:  
  • Standard whole-breast irradiation | Relevant outcomes include:  
  • Overall survival  
  • Disease-specific survival  
  • Quality of life  
  • Treatment-related morbidity |
| **Individuals:**  
  • With early-stage breast cancer | Interventions of interest are:  
  • Intraoperative brachytherapy | Comparators of interest are:  
  • Standard whole-breast irradiation | Relevant outcomes include:  
  • Overall survival  
  • Disease-specific survival  
  • Quality of life  
  • Treatment-related morbidity |
Radiotherapy is the standard 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 low risk of recurrence. Accelerated (also called hypofractionated) whole-breast irradiation (AWBI) reduces the number of fractions and the duration of treatment to about 3 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 1 week.

### 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 randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Two randomized noninferiority trials both reported 10-year follow-up data on local recurrence. Both trials found that local recurrence rates with AWBI were no worse than conventional whole-breast irradiation (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 more than 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 1 completed RCT. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The RCT reported 5-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 1 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. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Several RCTs have been published, but they have not demonstrated that outcomes after intraoperative brachytherapy are noninferior to WBI. Results of 2 RCTs (TARGIT-A, ELIOT) comparing intraoperative brachytherapy to 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. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The RCTs only reported outcomes after 3 to 5 years, and 10-year data are required to draw conclusions about the impact of the technology on health outcomes. Moreover, 1 of the 2 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.

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. Relevant outcomes are 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 1 or 2 breast cancer, nonrandomized comparative studies have shown similar outcomes with brachytherapy local boost and with external-beam radiotherapy local boost. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have early-stage breast cancer who receive noninvasive breast brachytherapy, the evidence includes 1 retrospective comparative study. Relevant outcomes are overall survival, 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.

Background

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 5 daily fractions per week over 5 to 6 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 Trialists’ Collaborative Group (EBCTCG) reported that radiotherapy halved the annual recurrence rate after 10 years for women with node-negative disease (n=7287), from 31.0% for those not receiving radiotherapy to 15.6% for those receiving it. 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. However, agreement is not universal.

Controversy continues on the length of follow-up needed to determine whether accelerated partial-breast irradiation (APBI) is equivalent to WBI (see the 2013 TEC Assessment 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 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 10 or more years after treatment. For accelerated whole-breast irradiation (AWBI), some 10-year data are available. However, for newer approaches, the issue may be resolved by statistical issues rather than biological ones. For example, in the large NSABP-39/RTOG 0413 trial comparing WBI and APBI (NCT00103181), 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 10 years.

Currently, most patients diagnosed with stage I or II breast cancer are offered a choice of BCT or 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. 8-10

Alternative Radiotherapy Regimens

Given that duration and logistics appear to be barriers to completion of treatment, there has been interest in developing shorter radiotherapy regimens. Two approaches have been explored.

The first method 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 is highlighted below, has allayed most of these concerns. AWBI has been adopted widely in Canada and Europe.

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 4 to 5 days (or 1 day with intraoperative radiotherapy) rather than 5 to 6 weeks, because radiation is delivered to the tumor bed in fewer fractions at larger doses per fraction. Third, radiation dose is intrinsically less uniform within the target volume when APBI uses brachytherapy (ie, the implantation of radioactive material directly in the breast tissue).

The major types of radiotherapy used after BCS are outlined in Table 1. They differ by technique, instrumentation, dose delivery, and possibly 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>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional WBI</td>
<td>No</td>
<td>Whole</td>
<td>EBRT</td>
<td>5-6 wk</td>
<td>Multiple</td>
<td>&gt;15 y</td>
</tr>
<tr>
<td>Accelerated WBI</td>
<td>Yes</td>
<td>Whole</td>
<td>EBRT</td>
<td>3 wk</td>
<td>4</td>
<td>10 y</td>
</tr>
<tr>
<td>Interstitial APBI</td>
<td>Yes</td>
<td>Partial</td>
<td>Brachytherapy</td>
<td>1 wk</td>
<td>2</td>
<td>5.4 y</td>
</tr>
</tbody>
</table>
Balloon APBI<sup>c</sup>  Yes  Partial  Brachytherapy  1 wk  0  0
EBRT APBI<sup>d</sup>  Yes  Partial  EBRT  1 wk  0  0
Intraoperative APBI<sup>e</sup>  Yes  Partial  Not applicable  1 d  1  5 y

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

<sup>a</sup> Noninvasive breast brachytherapy using AccuBoost has been described by the manufacturer as capable of delivering APBI, but no studies for this indication were found.

<sup>b</sup> 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.

<sup>c</sup> Balloon brachytherapy (eg, 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.

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

<sup>e</sup> Intraoperative APBI is performed during breast-conserving surgery with a single dose of radiation delivered to the exposed tumor bed.

To appreciate the differences among radiotherapy techniques, it is useful to understand attributes of radiation delivery. The goals of cancer radiotherapy are to provide the tumor or tumor bed with a high dose of homogeneous radiation (ie, all parts of the tumor cavity receive close to the targeted dose). Areas adjacent to the tumor may be given a lower dose of radiation (eg, 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.

**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.

**Regulatory Status**

In 2002, the MammoSite® Radiation Therapy System (Proxima Therapeutics; Alpharetta, GA), 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 FDA through the 510(k) process. FDA determined that several devices (eg, Axxent® Electronic Brachytherapy System [Xoft; San Jose, CA], Strut-Adjusted Volume Implant [SAVI™] Applicator Kit [Biolucent (now Cianna Medical); Aliso Viejo, CA], Contura® Multi-Lumen Balloon Source Applicator for Brachytherapy [SenoRx; Aliso Viejo, CA], ClearPath™ Adjustable Multi-Catheter...
Source Applicator [North American Scientific; Chatsworth, CA], Intrabeam® System [Carl Zeiss Surgical; Oberkochen, Germany]) 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 FDA regulation, it does not fall under the regulatory purview of the U.S. Nuclear Regulatory Commission. In some states, participation of radiation oncologists in delivering radiation is not required.

**Rationale**
This evidence review was originally created in July 1996 and has been updated regularly with searches of the MEDLINE database. It has been 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. The most recent literature search update covers the period through June 6, 2016.

**Accelerated Whole-Breast Irradiation**
A number of randomized controlled trials (RCTs) have compared accelerated whole-breast radiotherapy (also referred to as accelerated whole-breast irradiation [AWBI]) to 5-week whole-breast radiotherapy. Two prospective noninferiority RCTs directly compared a 5-week to a 3-week regimen. Both trials used noninferiority margins of 5 percentage points for local or locoregional recurrence in the accelerated group at 5 (1-sided $\alpha=0.025$ or $0.05$) or 10 years (1-sided $\alpha=0.025$). Although the trials differed in specific fractionation schedules and patient characteristics, they reported similar ipsilateral local recurrence rates (ie, cancer recurrence in the same breast) across treatment arms.

The first RCT evaluating an accelerated whole-breast radiotherapy regimen (Standardisation of Breast Radiotherapy [START] B; 2008), from the U.K., included women with stage I, II or III tumors (N=2215) who had clear tumor margins ($\geq 1$ 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 hospital, type of surgery (8% underwent mastectomy), and plans for 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 and or in ipsilateral axilla or supraclavicular fossa if previously irradiated) at 5 years. At median follow-up of 6.0 years (interquartile range [IQR], 5.0-6.2), estimated 5-year locoregional tumor relapse rate was 2.2% (95% confidence interval [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 (HRs) for 40-Gy AWBI versus conventional whole-breast radiotherapy were not statistically
significant for local or locoregional relapse. There were statistically significant differences between the 2 treatment regimens for distant relapse and overall survival (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 1 year; trial authors speculated that the difference may have been due to chance and might change over longer follow-up.

Subsequent publications provided additional results for both START trials (ie, START A, which compared two 5-week whole-breast radiotherapy regimens, and START B). Hopwood et al (2010) examined patient-reported breast, arm, and shoulder symptoms, as well as body image, over 5 years of follow-up. 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; IQR, 7.5-10.1 years). Locoregional relapse did not differ significantly between the 2 treatment groups: 4.3% (95% CI, 3.2% to 5.9%) for the AWBI group and 5.5% (95% CI, 4.2% to 7.2%) for the standard whole-breast radiotherapy group (HR=0.77; 95% CI, 0.51 to 1.16; p=0.21). However, breast shrinkage, telangiectasia, and breast edema were significantly less common in the AWBI group. These effects were assessed by physician, photographic comparison with baseline, and patient report. Distant relapse (p=0.014), any breast cancer–related event (local, regional, or distant relapse, breast cancer death, contralateral breast cancer; p=0.022), and all-cause mortality (p=0.042) were significantly less common in the AWBI group.

The second RCT assessing a 5- and a 3-week radiotherapy regimen, from Canada, compared AWBI and whole-breast irradiation (WBI) in women with lymph node–negative stage I, II, or III tumors. Intention-to-treat (ITT) analysis was used. 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, without boost radiation. Five-year local recurrence-free survival was 97.2% in the accelerated arm and 96.8% in the conventional arm (absolute 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 (absolute difference, -0.5%; 95% CI, -2.5% to 3.5%). At 5 or 10 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). However, local recurrence at 10 years for patients with high-grade tumors (post hoc analysis) was 4.7% for the conventional WBI arm and 15.6% for the AWBI arm. The absolute difference was -10.9 percentage points (95% CI, -19.1 to -2.8; p=0.01). (The authors did not define “high-grade” tumors. According to the National Cancer Institute website, the most common grading system for breast cancer is the Nottingham grading system. High-grade tumors are those with a score of 8 to 9, which is comprised of the sum of three 3-point scales rating normality of tubule formation, nuclear grade, and mitotic rate.)
At least 2 systematic reviews of RCTs on AWBI that include the 4 RCTs discussed above have been published.\textsuperscript{20,21} Budach et al (2015) stated that the ipsilateral recurrence rates at 10 years ranged from 3.8% to 14.8% after hypofractionated radiotherapy and from 5.2% to 12.1% for conventionally fractionated radiotherapy.\textsuperscript{20} The pooled 10-year recurrence rate was 8.4% in the hypofractionated radiotherapy group and 8.5% in the conventionally fractionated group (p=0.96). A 2010 Cochrane review by James et al rated the studies as low-to-medium quality. Reviewers did not pool study findings, but concluded that unconventional fractional regimens are associated with decreased acute toxicity but not local recurrence or breast appearance.\textsuperscript{21}

Two additional RCTs were published in 2015.\textsuperscript{22,23} In a single-blind trial, Hou et al reported on 80 patients with stage I breast cancer treated with BCS.\textsuperscript{22} Patients were randomized to AWBI (43.2 Gy in 18 fractions over 24 days, n=40) or conventional WBI (45 Gy in 25 fractions over 44 days, n=40). Both groups received tumor bed boosts, 50.4 Gy in the accelerated group and 59 Gy in the conventional group. Primary end points were OS and locoregional recurrence. The 2-year survival rate was 100% in both groups and there was no locoregional recurrence. Moreover, there were no statistically significant differences in adverse events between the 2 groups.

The other newer RCT, published in 2015 by Shaitelman et al focused on acute and short-term toxicity for conventional versus accelerated whole-breast radiotherapy.\textsuperscript{23} 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 accelerated radiotherapy at 42 Gy in 16 fractions (n=138). The rate of grade 2 or higher acute toxic events was 47% in the accelerated radiotherapy group and 78% in the conventional radiotherapy group (p<0.001). A total of 271 (94%) of 287 patients were available for an assessment of 6-month toxic effects. There were no significant between-group differences in toxic effects at 6 months except that the rate fatigue (grade $\geq$2) was significantly lower in the accelerated radiotherapy group (0%) than in the conventional radiotherapy group (6%; p=0.01).

Toxicity rates were also evaluated in a large 2014 retrospective study of patients with left-sided early-stage breast cancer published by Chan et al.\textsuperscript{24,25} The study included 2706 patients who received conventional WBI (n=2221) or (n=485) AWBI. Cardiotoxic chemotherapy regimens were similar between groups. At a median follow-up of 14.2 years, there was no statistical difference 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: Accelerated Whole-Breast Irradiation**

The overall body of evidence on AWBI compared with conventional WBI has indicated that local recurrence rates with accelerated whole-breast radiotherapy are no worse than conventional WBI, when applying a noninferiority margin of 5%.
Canadian and U.K. noninferiority trials have reported 10-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 greater than 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
A number of RCTs and nonrandomized comparative studies have evaluated interstitial, external-beam, or intraoperative accelerated partial-breast irradiation (APBI) compared with conventional WBI. Several meta-analyses have evaluated evidence on APBI, with various methods grouped in same review. Conclusions cannot be drawn from these meta-analyses because methods vary and need to be evaluated individually. This evidence is reviewed next.

Interstitial Brachytherapy
In 2016, Strnad et al published findings of the GEC-ESTRO multicenter noninferiority RCT. The trial included patients ages 40 and older with stage 0 to II breast cancer and lesions of 3 cm or less in diameter. Patients had undergone BCS with clear margins of at least 2 mm in any direction and no lymph or blood vessel invasion. Patients were randomized to conventional WBI at 50 Gy in daily fractions of 1.8 to 2.0 Gy over 5 weeks (n=551) or APBI using interstitial brachytherapy (n=633). The primary study end point was the first event of local ipsilateral breast cancer recurrence within the 5-year observation period and the noninferiority margin was a difference of 3%. At 5 years, 5 of 551 women in the conventional WBI group and 9 of 633 women in the APBI group had a local recurrence. 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 (risk difference, 0.52%; 95% CI, -0.72% to 1.75%). The difference between groups was within the noninferiority margin. OS was not a primary end point and there was no prespecified noninferiority analysis on survival outcomes. However, trialists reported that, at the time of data analysis, 32 (6%) of 551 patients in the conventional WBI group and 27 (4%) of 633 in the APBI group had died. Trial limitations included outcomes data only being available up to 5 years, survival not being a primary end point, and the absolute number of women with local recurrences being small.

For a 2007 RCT, accrual was stopped before reaching the goal specified to evaluate differences in local recurrence, to allow patients to enroll in another trial. The randomization process was unclear; patients deemed “technically unsuitable” for interstitial brachytherapy were given external-beam radiotherapy (EBRT) APBI; and patient characteristics and outcomes for each type of APBI were not reported separately. Finally, the sample size (N=126) was relatively small; and longest reported follow-up was 66 months. Similar local and regional failure rates were found across treatment arms.
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 intracavitary brachytherapy (34 Gy in 10 fractions; 90% MammoSite, 9% Contura, 1% strut-adjusted volume implant [SAVI]) and 146 received WBI using 3-dimensional conformal radiotherapy (3D-CRT; 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. 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 5-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: Interstitial 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 noninferiority margin of 3%. Ten-year follow-up data are needed and at least 1 additional trial confirming these findings.

**Intraoperative Brachytherapy**
One RCT 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 TARGIT-A (Risk-adapted Targeted Intraoperative Radiotherapy) 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 ITT approach was used. Patients were not blinded to treatment choice. As anticipated, 14% of those in the IORT arm received EBRT as well, because of unfavorable pathologic features determined after surgery (eg, 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 (IQR, 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 whole-breast radiotherapy; 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 whole-breast radiotherapy, 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 to those who received only IORT. Noninferiority was established for the whole intraoperative cohort and for those
who received IORT alone, but not for those patients who underwent both types of radiotherapy. There was no significant difference between the IORT and WBI groups in predefined 6-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. The 2013 ELIOT trial compared IORT plus ELIOT to WBI. With a sample size of 1305 patients and median follow-up of 5.8 years (IQR, 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 (HR=9.3; 95% CI, 3.3 to 26.3; p<0.001). There was no statistically significant difference in 5-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, ipsilateral breast recurrence rate was significantly higher in the IORT group. A subsequent review of the ELIOT trial 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. These reviewers also characterized ELIOT data as “still early” and noted that long-term results are needed to assess net health benefit.

**Section Summary: Intraoperative Brachytherapy**

Several RCTs have been published, but they 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 whole-breast radiotherapy. In another RCT that used a different technology (ELIOT), recurrence rate with IORT was statistically greater than that with WBI.

**External-Beam APBI**

Two RCTs compared EBRT APBI with WBI using 3D-CRT. In the first (2013), 102 patients were randomized to WBI, with or without a boost to the tumor bed, or APBI. The primary end point was local recurrence within 5 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 5 years, there were no recurrences in either group, nor was there a statistically significant difference in survival. Investigators noted that the sample size may 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.
The second RCT (2013) was the multicenter randomized RAPID (Randomized Trial of Accelerated Partial Breast Irradiation) trial. The sample size was 2135, and median follow-up was 3 years. Most patients were older than 50 years and had estrogen receptor–positive tumors less than 1.5 cm in diameter. This interim report provided on cosmetic and toxicity results. An accelerated regimen was used for WBI, and 21% of these patients received a boost to the tumor bed. APBI patients were more likely than WBI patients to have adverse cosmesis at 3 years, whether reported by physicians (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 versus none of the WBI patients. Telangiectasia and breast induration were more common among APBI patients (p<0.001).

**Section Summary: External-Beam APBI**
Two RCTs have been published, but have only reported outcomes to 3 to 5 years; 10-year data are required to draw conclusions about the impact of the technology on health outcomes. Moreover, 1 of the 2 trials reported higher rates of adverse cosmetic outcomes and grade 3 toxicities in the external-beam APBI group compared with the WBI group.

**Brachytherapy With Local Boost**
A 1996 TEC Assessment concluded that net health outcomes with brachytherapy with local boost were equivalent to outcomes with EBRT with local boost in women who received BCS plus WBI as initial treatment for stage I or II breast cancer. 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 5-year survival.

**Section Summary: Brachytherapy With Local Boost**
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 with local boost and with EBRT with local boost.

**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. No long-term studies are available to confirm this.
There is only 1 comparative study on noninvasive breast brachytherapy. This 2013 matched retrospective study assessed patients receiving the boost dose using AccuBoost or electron beams (a type of EBRT). Each of 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 2 treatment groups were in radiation doses received and 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 median follow-up of 13.6 months, skin and subcutaneous tissue toxicity occurred less often among patients treated with AccuBoost than among those treated with 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**

No RCTs and only 1 nonrandomized comparative study were identified. The comparative study was retrospective 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.

**Summary of Evidence**

**Accelerated Whole-Breast Irradiation**

For individuals who have node-negative, early-stage breast cancer with clear surgical margins who receive accelerated whole-breast irradiation (AWBI) after breast-conserving surgery (BCS), the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Two randomized noninferiority trials both reported 10-year follow-up data on local recurrence. Both trials found that local recurrence rates with AWBI were no worse than conventional whole-breast irradiation (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 more than 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 1 completed RCT. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The RCT reported 5-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 1 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. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Several RCTs have been published, but they have not demonstrated that outcomes after intraoperative brachytherapy are noninferior to WBI. Results of 2 RCTs (TARGIT-A, ELIOT) comparing intraoperative brachytherapy to 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 accelerated partial-breast irradiation (APBI), the evidence includes RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The RCTs only reported outcomes after 3 to 5 years, and 10-year data are required to draw conclusions about the impact of the technology on health outcomes. Moreover, 1 of the 2 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.

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. Relevant outcomes are 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 1 or 2 breast cancer, nonrandomized comparative studies have shown similar outcomes with brachytherapy local boost and with external-beam radiotherapy local boost. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have early-stage breast cancer who receive noninvasive breast brachytherapy, the evidence includes 1 retrospective comparative study. Relevant outcomes are overall survival, 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.

2016
In response to requests, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2016. Input was limited to the policy statement on accelerated whole-breast irradiation (AWBI). Three of 4 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 criterion.

2011
In response to requests, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2011. There was near-unanimous support for the policy statement on AWBI. The input was mixed on accelerated partial-breast irradiation (APBI); 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 APBI compared with whole-breast irradiation.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network (NCCN) guidelines (v.2. 2016) 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. If not trial eligible, per the consensus statement from the American Society for Radiation Oncology (ASTRO), patients who may be suitable for APBI are ... [see ASTRO Criteria ‘Suitable’ in Table 2].”

For whole-breast radiotherapy, NCCN recommends a conventional whole-breast irradiation regimen or a total dose of 42.5 gray (Gy) with 2.66 Gy per fraction (16
fractions). Although NCCN guidelines do not specify the duration of treatment, the latter is presumably an accelerated whole-breast irradiation (AWBI) regimen. A boost to the tumor bed is recommended for higher risk patients receiving whole-breast radiotherapy (ie, those who are <50 years old with high-grade disease).

American Society for Radiation Oncology et al
ASTRO, American Society of Breast Surgeons, and the American Brachytherapy Society have issued various consensus statements for the selection of patients for APBI (summarized in Table 2).41-44 Statement authors estimated that more than 32,000 women have already been treated with MammoSite, a mechanism for delivering APBI. Recommendations were based on systematic reviews, which are not described in detail, and expert opinion. Several authors have questioned the validity of ASTRO consensus statement categories based on retrospective studies that showed inconsistent associations between ASTRO category and recurrence rates and no association between ASTRO category and survival outcomes.

Table 2. Professional Medical Society Criteria for Performing APBI45-48

<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>≥60 y</td>
<td>50-59 y</td>
<td>&lt;50 y</td>
<td>≥45 y</td>
<td>≥50 y</td>
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<tr>
<td><strong>BRCA1 and BRCA2 variants</strong></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>
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<tr>
<td>Tumor stage</td>
<td>T1</td>
<td>T0 or T2</td>
<td>T3-4</td>
<td>NR</td>
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<tr>
<td>Margins</td>
<td>Negative ≥2 mm</td>
<td>Close (&lt;2 mm)</td>
<td>Positive</td>
<td>Microscopically negative</td>
<td>Negative</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>Negative&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>Positive or negative</td>
<td></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 subtypes</td>
<td>Invasive lobular</td>
<td>NR</td>
<td>Invasive ductal carcinoma or DCIS</td>
<td>All invasive subtypes and DCIS</td>
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<tr>
<td>Pure DCIS</td>
<td>Not allowed</td>
<td>≤3 cm</td>
<td>&gt;3 cm</td>
<td>≤3 cm</td>
<td>≤3 cm</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
<td>≤3 cm</td>
<td>&gt;3 cm</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Allowed</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></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&lt;sup&gt;-&lt;/sup&gt;, i&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>NR</td>
<td>pN1, pN2, pN3</td>
<td>SN pN0</td>
<td>pN0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Factor | ASTRO “Suitable” | ASTRO “Cautionary” | ASTRO “Unsuitable” | ASBS | ABS
---|---|---|---|---|---
Nodal surgery | SN Bx, ALND | NR | None performed | NR | NR
Treatment factors | Not allowed | NR | If used | NR | NR


a Strongly encouraged to enroll in NSABP B-39/RTOG 04-13 trial.
b Lymphovascular space invasion is considered a contraindication for accelerated partial-breast irradiation.

ASTRO released guidelines on fractionation for WBI in 2011. Guidelines were based on the Canadian trial, Startup A, and START B, and a third RCT. Guideline authors concluded that “Data are sufficient to support the use of HF-WBI [hypofractionated or accelerated, whole-breast irradiation] for patients with early breast cancer who meet all of the aforementioned criteria,” including age 50 years or older, disease stage pT1-2 pN0, no chemotherapy, and treatment with radiation dose homogeneity within ±7% in the central axis plane. The task force did not agree on whether HF-WBI is recommended for tumor boost.

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

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, 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 3.

Table 3. 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>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>
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<tr>
<td>NCT00470236</td>
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<tr>
<td>NCT01343459</td>
<td>Intra-Operative Electron Boost and Hypofractionated Whole-Breast Irradiation During Breast-conserving Treatment (BCT) (HIOB)</td>
<td>1000</td>
<td>Mar 2021</td>
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<tr>
<td>Intraoperative brachytherapy</td>
<td>Safety and Efficacy Study of the Xoft® Axxent® eBx™ IORT System</td>
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<td>Dec 2024</td>
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<tr>
<td>NCT01644669</td>
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</tr>
<tr>
<td>External-beam APBI</td>
<td>Breast Cancer With Low Risk Of Local Recurrence: Partial and Accelerated Radiation With Three-Dimensional Conformal Radiotherapy (3DCRT) Vs. Standard Radiotherapy After Conserving Surgery</td>
<td>3302</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT01803958</td>
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</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>NCT01247233</td>
<td>Standard or Hypofractionated Radiotherapy Versus Accelerated Partial Breast Irradiation (APBI) for Breast Cancer (SHARE)</td>
<td>2796</td>
<td>Oct 2024</td>
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<tr>
<td>NCT01185132</td>
<td>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>
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<tr>
<td>NCT00103181</td>
<td>Radiation Therapy (WBI Versus PBI) in Treating Women Who Have Undergone Surgery For Ductal Carcinoma In Situ or Stage I or Stage II Breast Cancer (RTOG 0413/NSABP B39)</td>
<td>4216</td>
<td>Apr 2020</td>
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<tr>
<td>NCT00282035</td>
<td>Randomized Trial of Accelerated Partial Breast Irradiation (RAPID)</td>
<td>2128</td>
<td>Dec 2020</td>
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<tr>
<td>NCT00892814</td>
<td>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>NCT01185145</td>
<td>Accelerated Partial Breast Radiotherapy With Either Mammosite or Intensity Modulated Radiotherapy (APBI)</td>
<td>291</td>
<td>Aug 2024</td>
</tr>
</tbody>
</table>

APBI: accelerated partial-breast irradiation; DCIS: ductal carcinoma in situ; NCT: national clinical trial; WBI: whole-breast irradiation.

References


Billing Coding/Physician Documentation Information

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 afterloading 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

77261 Therapeutic radiology treatment planning; simple

77262 Therapeutic radiology treatment planning; intermediate

77263 Therapeutic radiology treatment planning; complex

77280 Therapeutic radiology simulation-aided field setting; simple

77285 Therapeutic radiology simulation-aided field setting; intermediate

77290 Therapeutic radiology simulation-aided field setting; complex

77293 Respiratory motion management simulation (List separately in addition to code for primary procedure)

77295 3-dimensional radiotherapy plan, including dose-volume histograms

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)
Brachytherapy isodose plan; complex (calculation[s] made from over 10 sources, or remote afterloading brachytherapy, over 12 channels), includes basic dosimetry calculation(s)

Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 1 channel

Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 2-12 channels

Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; over 12 channels

Brachytherapy source, nonstranded, high dose rate iridium-192, per source

Placement and removal (if performed) of applicator into breast for intraoperative radiation therapy, add-on to primary breast procedure

Radioelements for brachytherapy, any type, each

**ICD-10 Codes**

**C50.011-C50.929** Malignant neoplasm male and female breast code range

Secondary malignant neoplasm of breast

**Coding**

There are CPT codes for placement of radiotherapy afterloading catheters (19296, 19297, 19298)

Specific CPT radiology codes exist for application of brachytherapy radiation sources (codes 77770-77772).

There is a CPT category III code specific to high-dose electronic brachytherapy:

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

Codes 77776, 77777, 77778, 77785, 77786, 77787 and 0182T were deleted effective 1/1/2016.

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

2/1/16 New Policy. Medically necessary when criteria met.

2/1/17 No policy statement changes.

3/1/17 Breast width criterion was removed from the first medically necessary statement. Based on review of clinical input, the following additional
changes were made to the policy statement on accelerated whole-breast irradiation: a bullet point was added to state age of at least 50 years; there was clarification to the meaning of ‘technically clear surgical margins’ in both this policy statement as well as the Policy Guidelines section; and “exclude disease involving the margins of excision” was removed from this policy statement. The policy title was shortened to “Accelerated Breast Irradiation and Brachytherapy Boost After Breast-Conserving Surgery for Early-Stage Breast Cancer”.

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