

## Medical Policy



An independent licensee of the  
Blue Cross Blue Shield Association

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

#### Professional

Original Effective Date: July 1, 2007  
Revision Date(s): June 29, 2010;  
May 27, 2013; December 11, 2013;  
May 28, 2015; January 1, 2016;  
November 24, 2017; January 1, 2018;  
October 12, 2018  
Current Effective Date: October 12, 2018

#### Institutional

Original Effective Date: July 1, 2007  
Revision Date(s): June 29, 2010;  
May 27, 2013; December 11, 2013; May  
28, 2015; January 1, 2016;  
November 24, 2017; January 1, 2018;  
October 12, 2018  
Current Effective Date: October 12, 2018

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

Populations	Interventions	Comparators	Outcomes
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

Populations	Interventions	Comparators	Outcomes
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
Individuals: • With early-stage breast cancer	Interventions of interest are: • External-beam accelerated partial-breast irradiation	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: • Local boost brachytherapy with whole-breast irradiation	Comparators of interest are: • Standard whole-breast irradiation with or without external-beam boost to the tumor bed	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity
Individuals: • With early-stage breast cancer	Interventions of interest are: • Noninvasive breast brachytherapy	Comparators of interest are: • Standard whole-breast irradiation	Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity

## **DESCRIPTION**

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 (Gy; 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.

## **OBJECTIVE**

The objective of this policy is to determine the safety and efficacy of accelerated whole- and partial-breast irradiation and brachytherapy in patients with early-stage breast cancer compared with standard whole-breast irradiation.

## BACKGROUND

### Breast Cancer

Current estimates suggest that over 266,000 new cases of breast cancer of any stage will occur in the United States in 2018. Based on adjusted data from 2011 to 2015, among women, the number of new cases is 126 per 100,000 and the number of deaths 21 per 100,000.<sup>1</sup>

### 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 radiation therapy (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 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 (RCTs) have demonstrated that the addition of radiotherapy after BCS reduces recurrences and mortality. In an expanded update of an individual-level 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.<sup>2</sup> 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, radiation therapy is generally recommended following BCS. A potential exception is for older women at low risk of recurrence. For example, current National Comprehensive Cancer Network (NCCN) guidelines state that women aged 70 or older may omit radiotherapy if they have estrogen-receptor positive, T1 tumors, clinically negative lymph nodes, and plans to take adjuvant endocrine therapy.<sup>3</sup> However, agreement is not universal.<sup>4</sup>

Controversy continues on the length of follow-up needed to determine whether APBI is equivalent to whole-breast irradiation (for more information, see the 2013 TEC Assessment on Accelerated Radiotherapy after Breast-Conserving Surgery for Early Stage Breast Cancer).<sup>5</sup> 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.<sup>6-8</sup> 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 whole-breast irradiation versus APBI (see Table 2), enrollment has reached the revised target of 4214. Trial duration (presumably barring early termination) is determined by the occurrence of a prespecified number (175) of in-breast recurrences. The researchers expect that reaching that number of recurrences will take approximately 10 years.

Currently, most patients diagnosed with stage 1 or 2 breast cancer are offered a choice of BCT or modified radical mastectomy, but BCT is selected less often than expected. Studies have shown that those living furthest from treatment facilities are least likely to select BCT instead of mastectomy and most likely to forgo radiation therapy after BCS.<sup>8-11</sup>

### Alternative Radiotherapy Regimens

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 accelerated partial-breast irradiation (APBI). It differs from conventional whole-breast irradiation 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 in their techniques, instrumentation, dose delivery, and possibly in their outcomes.

**Table 1.** Major Types of Radiation Therapy Following Breast-Conserving Surgery<sup>a</sup>

Radiation Type	Accelerated?	Whole or Partial Breast	EBRT or Brachytherapy	Treatment Duration	Published RCTs	Length of Follow-Up
Conventional WBI	No	Whole	EBRT	5-6 wk	Multiple	>15 y
Accelerated WBI	Yes	Whole	EBRT	3 wk	4	10 y
Interstitial APBI <sup>b</sup>	Yes	Partial	Brachytherapy	1 wk	2	5.4 y
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 Accuboot<sup>®</sup> has been described by the manufacturer as capable of delivering APBI, but no studies on 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<sup>®</sup>, 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 treated with a lower dose of radiation (eg, with whole-breast irradiation) 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 Whole-Breast Irradiation

Brachytherapy also can be used as an alternative to EBRT to deliver boost radiation therapy 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<sup>®</sup> Radiation Therapy System (Proxima Therapeutics; Alpharetta, GA), the first device specifically designed for breast brachytherapy,<sup>12</sup> 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.”<sup>13</sup>

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<sup>®</sup> Electronic Brachytherapy System [Xoft], Strut-Adjusted Volume Implant [SAVI<sup>™</sup>] Applicator Kit [Biolument (now Cianna Medical)], -Contura<sup>®</sup> Multi-Lumen Balloon Source Applicator for Brachytherapy [SenoRx], ClearPath<sup>™</sup> Adjustable Multi-Catheter Source Applicator [North American Scientific], Intrabeam<sup>®</sup> 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 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.

## **POLICY**

- A. When using radiation therapy after breast-conserving (BCS) surgery for early stage breast cancer:
1. Accelerated whole breast irradiation may be considered **medically necessary** for patients who meet the following conditions:
    - a) Invasive carcinoma of the breast
    - b) Technically clear surgical margins, ie, no ink on tumor of invasive carcinoma or ductal carcinoma in situ
    - c) Age at least 50 years old.
  2. Accelerated whole breast irradiation is considered **experimental / investigational** in all other situations involving treatment of early stage breast cancer after breast-conserving surgery.
- B. Interstitial or balloon brachytherapy may be considered **medically necessary** for patients undergoing initial treatment for stage I or II breast cancer when used as local boost irradiation in patients who are also treated with breast-conserving surgery and whole-breast external-beam radiotherapy.
- C. Accelerated partial breast irradiation (APBI), including interstitial APBI, balloon APBI, intraoperative APBI, external beam APBI, and noninvasive brachytherapy using Accuboot®, is considered **experimental / investigational**.
- D. Noninvasive brachytherapy using Accuboot® for patients undergoing initial treatment for stage I or II breast cancer when used as local boost irradiation in patients who are also treated with BCS and whole-breast external-beam radiotherapy is considered **experimental / investigational**.

## **Policy Guidelines**

1. Electronic brachytherapy is considered a type of balloon brachytherapy that can be used to deliver accelerated partial-breast irradiation (APBI).
2. 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](http://www.redjournal.org/article/S0360-3016(13)03315-4/pdf)).

3. As part of the clinical input process, ASTRO recommended additional criteria that should be satisfied for patients undergoing AWBI:
  - a. Pathologic stage is T1–2N0 and the patient has been treated with breast-conserving surgery.
  - b. Patient has not been treated with systemic chemotherapy.
  - c. 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 ( $\pm 7\%$ ) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

## **RATIONALE**

The most recent literature search update covers the period through May 7, 2018.

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.<sup>5</sup>

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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 accelerated whole-breast irradiation (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 PICOTS were used to select literature to inform this review.

### Patients

The relevant population of interest is patients who have node-negative, early-stage breast cancer with clear surgical margins.

### Interventions

The therapy being considered is AWBI after BCS.

### 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.

### Timing

Patients with early-stage breast cancer should be followed for 10 years to evaluate OS and disease-related survival.

### Setting

WBI is administered in an outpatient oncology setting.

### Systematic Reviews

A number of RCTs and systematic reviews of RCTs have compared AWBI (also referred to as accelerated whole-breast radiotherapy) with conventional 5-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.<sup>14</sup> 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, START B, and NCIC (detailed below).<sup>15-17</sup>

### Randomized Controlled Trials

Two of the RCTs included in the systematic review were noninferiority trials that directly compared a 5-week with a 3-week regimen.<sup>15-17</sup> Both trials used noninferiority margins of 5 percentage points for local or locoregional recurrence in the accelerated group at 5 (1-sided  $\alpha=0.025^{15}$  or  $0.05^{16}$ ) or 10 years (1-sided  $\alpha=0.025^{17}$ ). 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 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).<sup>15</sup> 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 5 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 1 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 (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.<sup>18</sup> 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).<sup>19</sup> Locoregional recurrence did not differ significantly between the 2 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.<sup>16,17</sup> 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 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).

A more recent RCT by Shaitelman et al (2015) focused on acute and short-term toxicity for conventional WBI vs AWBI.<sup>20</sup> 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 six6 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 was also evaluated in a large retrospective study of patients with left-sided early-stage breast cancer published by Chan et al (2014, 2015).<sup>21,22</sup> 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 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: Accelerated Whole-Breast Irradiation*

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 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 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 interstitial brachytherapy or intraoperative brachytherapy or external-beam accelerated partial-breast irradiation (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 with interstitial brachytherapy or intraoperative brachytherapy or APBI improve the net health outcome in patients who have early-stage breast cancer?

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

#### Patients

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

#### Interventions

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

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.

Timing

Patients with early-stage breast cancer should be followed for 10 years to evaluate OS and disease-related survival.

Setting

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

Interstitial Brachytherapy

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 have evaluated evidence on APBI, with various methods grouped in the same review.<sup>23,24</sup> Conclusions cannot be drawn from these meta-analyses because methods varied and need to be evaluated individually.

Randomized Controlled Trials

GEC-ESTRO was a European multicenter noninferiority RCT with 5-year results (see Table 2). Primary results were published in 2016, late-side effects in 2017, and quality of life in 2018.<sup>25-27</sup> The primary study end point was the first incidence of local ipsilateral breast cancer recurrence within the 5-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

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
GEC-ESTRO <sup>25-27</sup>	EU	16		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	655 patients given APBI using interstitial brachytherapy	673 patients given WBI at 50 Gy in daily fractions of 1.8-2.0 Gy over 5 wk

APBI: accelerated partial breast irradiation; BCS: breast conserving therapy; RCT: randomized controlled trial; WBI: whole-breast irradiation.

**Table 3.** Summary of Key RCT Results

Study	Local Recurrence, n (%)	Overall Survival	Grade 2 to 3 Late Skin Toxicity	Excellent-to-Good Cosmetic Results, n (%)	Global Health Status (SD)
GEC-ESTRO <sup>25-27</sup>					
n	1184	1184	1184	1007	537
WBI	5 (0.92)	95.5%	5.7%	408 (90)	66.0 (21.8)
APBI	9 (1.44)	97.27%	3.2%	503 (93)	66.2 (22.2)
Diff (95% CI)	0.52% (-0.72% to 1.75%)	1.72% (-0.44% to 3.88%)			-0.2 (-4.0 to 3.6)
p	NS	0.11	0.080	0.12	0.94

APBI: accelerated partial breast irradiation; CI: confidence interval; Diff: difference; HR: hazard ratio; RCT: randomized controlled trial; RRWBI: whole-breast irradiation.

Major gaps in relevance and design and conduct are shown in Tables 4 and 5 is to display notable gaps 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 Gaps

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
GEC-ESTRO <sup>25-27</sup>				1. Overall survival was not a primary outcome	1. Only followed for 5 y

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

<sup>a</sup> 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.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> 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.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 5.** Study Design and Conduct Gaps

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
GEC-ESTRO <sup>25-27</sup>		1-3. Not blinded				1. No prespecified noninferiority analysis on survival outcomes

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

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> 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).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> 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.<sup>28</sup> 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 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 3% noninferiority margin. The number of events at 5 years is small. Ten-year follow-up data are needed and at least 1 additional trial confirming these findings.

### Intraoperative Brachytherapy

One RCT, reported by Vaidya et al (2010, 2014) compared intraoperative radiotherapy (IORT) with WBI in 2232 women.<sup>29,30</sup> 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 (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."<sup>30</sup> 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 received only 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 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.<sup>31</sup> The ELIOT trial, reported by Veronesi et al (2013), compared IORT plus ELIOT with WBI.<sup>32</sup> 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 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 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.<sup>8</sup> 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*

Several RCTs have been published but 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

Two RCTs have compared EBRT APBI with WBI (using 3-dimensional conformal radiotherapy). In the first, Rodriguez et al (2013) reported on 102 patients randomized to WBI, with or without a boost to the tumor bed, or APBI.<sup>33</sup> 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 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.

The second RCT, reported by Olivotto et al (2013), was the multicenter Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) trial.<sup>34</sup> The sample size was 2135, and the 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 vs 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, one of the 2 trials reported higher rates of adverse cosmetic outcomes and grade 3 toxicities in the external-beam APBI group than in the WBI group.

**Brachytherapy with Local Boost**

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 PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The therapy being considered is local boost brachytherapy with WBI.

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.

Timing

Patients with early-stage breast cancer should be followed for 10 years to evaluate OS and disease-related survival.

Setting

Local boost brachytherapy with WBI is administered in an outpatient oncology setting.

Systematic Reviews

A TEC Assessment (1996) concluded that net health outcomes with brachytherapy with local boost were equivalent to outcomes with EBRT with a local boost in women who received BCS plus WBI as initial treatment for stage I or II breast cancer.<sup>35</sup> 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**

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 PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The therapy being considered is noninvasive breast brachytherapy.

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.

Timing

Patients with early-stage breast cancer should be followed for 10 years to evaluate OS and disease-related survival.

Setting

WBI is administered in an outpatient oncology setting.

Nonrandomized Studies

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.<sup>36</sup> No long-term studies are available to confirm this.

Only 1 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).<sup>37</sup> 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 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 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*

No RCTs and a nonrandomized comparative study were identified. The comparative study was 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. 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 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. 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 collectively they have not demonstrated that outcomes after intraoperative brachytherapy are noninferior to WBI. Results of 2 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. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The RCTs have reported outcomes out to 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 I or II 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 a 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.

### **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, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2017. Input was limited to the policy statement on accelerated whole-breast irradiation). 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 criteria.

### 2011 Input

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 regarding AWBI. The input was mixed regarding 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 concerning 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.1.2018) on breast cancer state<sup>3</sup>:

“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 2).

For whole-breast radiotherapy, 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 (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 (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 6).<sup>38-40</sup> Recommendations were based on systematic reviews, which are not described in detail, and expert opinion.

**Table 6.** Professional Medical Society Criteria for Performing APBI

Factor	ASTRO “Suitable”	ASTRO “Cautionary”	ASTRO “Unsuitable”	ASBS	ABS
Patient factors					
Age	≥50 y	40-49 y	<40 y	≥45 y ≥50 y for DCIS	≥45 y
BRCA1 and BRCA2 variants	Not present	NR	Present	NR	NR
Pathologic factors					

Factor	ASTRO "Suitable"	ASTRO "Cautionary"	ASTRO "Unsuitable"	ASBS	ABS
Tumor size	≤2 cm	2.1-3.0 cm	>3 cm	≤3 cm	≤3 cm
Tumor stage	Tis or T1	T0 or T2	T3-4	NR	
Margins	Negative ≥2 mm	Close (<2 mm)	Positive	Microscopically negative	Negative (no tumor on ink for invasive ≥2 mm for DCIS)
Grade	Any	NR	NR	NR	NR
LVSI	No	Limited/focal	Extensive	NR	NR
ER status	Positive	Negative <sup>a</sup>	NR	NR	Positive or negative
Multicentricity	Unicentric	NR	Present	NR	NR
Multifocality	Clinically unifocal; total size, ≤2.0 cm	Clinically unifocal; size, 2.1-3.0 cm	Clinically multifocal or microscopically multifocal; size, ≥3 cm	NR	NR
Histology	Invasive ductal or other favorable subtypes <sup>b</sup>	Invasive lobular	NR	Invasive ductal carcinoma or DCIS	All invasive subtypes and DCIS
Pure DCIS	Not allowed	≤3 cm if "suitable" criteria not fully met	>3 cm	≤3 cm	≤3 cm
EIC	Not allowed	≤3 cm	>3 cm	NR	NR
Associated LCIS	Allowed	NR	NR	NR	NR
Nodal factors					
Nodal stage	pN0 (i <sup>-</sup> , i <sup>+</sup> )	NR	pN1, pN2, pN3	SN pN0	pN0 <sup>c</sup>
Nodal surgery	SNB, ALND	NR	None performed	NR	NR
Treatment factors					
Neoadjuvant therapy	Not allowed	NR	If used	NR	NR

ABS: American Brachytherapy Society; ALND: axillary lymph node dissection; ASBS: American Society of Breast Surgeons; ASTRO: American Society for Radiation Oncology; DCIS: ductal carcinoma in situ; EIC: extensive intraductal component; ER: estrogen receptor; LCIS: lobular carcinoma in situ; LVSI: lymphovascular space invasion; NR: not reported; SN: sentinel node; SNB sentinel node biopsy.

<sup>a</sup> Strongly encouraged to enroll in NSABP B-39/RTOG 04-13 trial.

<sup>b</sup> Allowed if screen-detected, low to intermediate nuclear grade, ≤2.5 cm size, and resected with margins negative at ≥3 mm.

<sup>c</sup> Lymphovascular space invasion is considered a contraindication for accelerated partial-breast irradiation.

ASTRO updated its guidelines on fractionation for whole-breast irradiation in 2018.<sup>41</sup> 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.

### ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 7.

**Table 7.** Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>WBI vs APBI with or without tumor bed boost in DCIS</b>			
NCT00470236	Radiation Doses and Fractionation Schedules in Non-low Risk Ductal Carcinoma In Situ (DCIS) of the Breast (TROG)	1600	Nov 2024
<b>Intraoperative brachytherapy</b>			
NCT01343459	Intra-Operative Electron Boost and Hypofractionated Whole-Breast Irradiation During Breast-conserving Treatment (BCT) (HIOB)	1000	Mar 2021
NCT01644669	Safety and Efficacy Study of the Xofigo® Axxent® eBx™ IORT System	1000	Dec 2024
<b>External-beam APBI</b>			
NCT01803958	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)	3302	Jun 2018 (Ongoing)
NCT01247233	Standard or Hypofractionated Radiotherapy Versus Accelerated Partial Breast Irradiation (APBI) for Breast Cancer (SHARE)	2796	Oct 2024
NCT01185132	Intensity Modulated Radiotherapy (IMRT) vs. 3D-conformal Accelerated Partial Breast Irradiation (APBI) for Early Stage Breast Cancer After Lumpectomy (2009-APBI)	660	Jul 2028
<b>APBI (multimodality)</b>			
NCT00103181	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)	4216	Apr 2020
NCT00282035	Randomized Trial of Accelerated Partial Breast Irradiation (RAPID)	2128	Dec 2020
NCT00892814	Partial Breast Versus Whole Breast Irradiation in Elderly Women Operated on for Early Breast Cancer	628	May 2022
NCT01185145	Accelerated Partial Breast Radiotherapy With Either Mammosite or Intensity Modulated Radiotherapy (APBI)	291	Aug 2024

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

## **CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

### CPT

- 19294 Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with partial mastectomy (List separately in addition to code for primary procedure)
- 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
77299	Unlisted procedure, therapeutic radiology clinical treatment planning
77316	Brachytherapy isodose plan; simple (calculation[s] made from 1 to 4 sources, or remote afterloading brachytherapy, 1 channel), includes basic dosimetry calculation(s)
77317	Brachytherapy isodose plan; intermediate (calculation[s] made from 5 to 10 sources, or remote afterloading brachytherapy, 2-12 channels), includes basic dosimetry calculation(s)
77318	Brachytherapy isodose plan; complex (calculation[s] made from over 10 sources, or remote afterloading brachytherapy, over 12 channels), includes basic dosimetry calculation(s)
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
77778	Interstitial radiation source application, complex, includes supervision, handling, loading of radiation source, when performed
0395T	High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed
C1717	Brachytherapy source, nonstranded, high dose rate iridium-192, per source
C9726	Placement and removal (if performed) of applicator into breast for intraoperative radiation therapy, add-on to primary breast procedure
Q3001	Radioelements for brachytherapy, any type, each

- There are CPT codes for placement of radiotherapy afterloading catheters: 19296, 19297, 19298.
- Specific CPT radiology codes exist for application of brachytherapy radiation sources: 77770, 77771, 77772.
- There is a CPT category III code specific to high-dose electronic brachytherapy: 0395T.

### ICD-10 Diagnoses

C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.111	Malignant neoplasm of central portion of right female breast

- C50.112 Malignant neoplasm of central portion of left female breast
- C50.211 Malignant neoplasm of upper-inner quadrant of right female breast
- C50.212 Malignant neoplasm of upper-inner quadrant of left female breast
- C50.311 Malignant neoplasm of lower-inner quadrant of right female breast
- C50.312 Malignant neoplasm of lower-inner quadrant of left female breast
- C50.411 Malignant neoplasm of upper-outer quadrant of right female breast
- C50.412 Malignant neoplasm of upper-outer quadrant of left female breast
- C50.511 Malignant neoplasm of lower-outer quadrant of right female breast
- C50.512 Malignant neoplasm of lower-outer quadrant of left female breast
- C50.611 Malignant neoplasm of axillary tail of right female breast
- C50.612 Malignant neoplasm of axillary tail of left female breast
- C50.811 Malignant neoplasm of overlapping sites of right female breast
- C50.812 Malignant neoplasm of overlapping sites of left female breast

## REVISIONS

06-29-2010	<p>In Coding Section:</p> <ul style="list-style-type: none"> <li>▪ Updated wording for the following CPT Codes: 19296, 19297.</li> <li>▪ Added CPT Codes: 77785, 77786, 77787 (effective 01/01/09).</li> </ul>
05-27-2013	<p>In the Medical Policy Title section: Revised the following medical policy title: "High Dose Rate (HCR) Breast Brachytherapy with HDR Radioactive Source via MammoSite Catheter".</p> <p>Updated the Description section.</p> <p>In the Policy section: Revised the following medical policy language: "A. Brachytherapy used as accelerated partial breast irradiation (local boost irradiation) is a medically appropriate treatment option in women with stage 0, I, or II breast cancer who are also treated with breast conserving surgery and whole breast radiation therapy. B. Brachytherapy as the sole form of breast irradiation after breast-conserving surgery for early stage breast cancer (Stage 0, I, or II – based on size only – over 2 cm) is considered investigational. It may be considered as a medically appropriate treatment option in limited circumstances for patients in whom whole breast external beam irradiation is not feasible, although this is not the current standard of care. These patients fall into one of the two categories:</p> <ol style="list-style-type: none"> <li>1. Patients with anatomic difficulties (e.g. large, pendulous breasts) that prevent delivery of traditional whole breast external beam radiation without compromising large sections of the lung; or</li> <li>2. Patients with infirmities (e.g. arthritis, severe pulmonary disease, multiple medical problems) that make the tolerance of a 6-7 week course of radiotherapy difficult or impossible."</li> </ol> <p>Updated the Rationale section.</p> <p>Updated the Reference section.</p>
12-11-2013	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added ICD-10 Diagnosis (<i>Effective October 1, 2014</i>)</li> </ul>
05-28-2015	<p>Updated Description section.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ In Item B, added "involving treatment of early stage breast cancer after breast-conserving surgery," to read "Accelerated whole breast irradiation is considered</li> </ul>

	<p>experimental/investigational in all other situations involving treatment of early stage breast cancer after breast-conserving surgery."</p> <ul style="list-style-type: none"> <li>▪ In Item D, added "balloon APBI" and "noninvasive brachytherapy using Accuboot®," to read, "Accelerated partial breast irradiation (APBI), including interstitial APBI, balloon APBI, external beam APBI, noninvasive brachytherapy using Accuboot®, and intra-operative APBI, is considered experimental/investigational."</li> <li>▪ Added Item E, "Noninvasive brachytherapy using Accuboot® 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 experimental/investigational."</li> <li>▪ Added Policy Guidelines, "Electronic brachytherapy is considered a type of balloon brachytherapy that can be used to deliver APBI."</li> </ul>
	Updated Rationale section.
	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added HCPCS code 0182T.</li> <li>▪ Updated ICD-10 effective date to October 1, 2015.</li> </ul>
	Updated References section.
01-01-2016	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added CPT codes 77770, 77771, 77772, and 0395T.</li> <li>▪ Removed CPT codes 77785, 77786, 77787, 0182T.</li> </ul>
11-24-2017	Updated Description section.
	<p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ In Item A 1, removed "Exclude disease involving the margins of excision; tumors &gt;5 cm in diameter; breast width &gt;25 cm at posterior border of medial and lateral tangential beams" to read, "Invasive carcinoma of the breast."</li> <li>▪ Removed Item A 2, "Negative lymph nodes."</li> <li>▪ Previous Item A 3 is new Item A 2, with addition of ", i.e., no ink on tumor on invasive carcinoma or ductal carcinoma in situ" to read, "Technically clear surgical margins, ie, no ink on tumor on invasive carcinoma or ductal carcinoma in situ"</li> <li>▪ Added new Item A 3, "Age at least 50 years old."</li> <li>▪ In Policy Guidelines 1, removed "APBI" and added "accelerated whole-breast irradiation (AWBI)" to read, "Electronic brachytherapy is considered a type of balloon brachytherapy that can be used to deliver accelerated whole-breast irradiation (AWBI)."</li> <li>▪ Added new Policy Guidelines 2 and 3.</li> </ul>
	Updated Rationale section.
	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added coding bullets.</li> </ul>
	Updated References section.
01-01-2018	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added CPT code: 19294.</li> <li>▪ Removed ICD-9 codes.</li> </ul>
10-12-2018	Updated Description section.
	<p>In Policy Guidelines:</p> <ul style="list-style-type: none"> <li>▪ In Policy Guidelines #1, removed "whole" and added "partial" to read, "Electronic brachytherapy is considered a type of balloon brachytherapy that can be used to deliver accelerated partial-breast irradiation (APBI)."</li> </ul>
	Updated Rationale section.
	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added CPT codes: 77261, 77262, 77263, 77280, 77285, 77290, 77293, 77295, 77299, 77316, 77317, 77318, 77778.</li> <li>▪ Added HCPCS codes: C1717, C9726, Q3001.</li> </ul>

Updated References section.
-----------------------------

## REFERENCES

1. National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Female Breast Cancer. n.d.; <https://seer.cancer.gov/statfacts/html/breast.html>. Accessed July 10, 2018.
2. Early Breast Cancer Trialists' Collaborative Group, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. Nov 12 2011;378(9804):1707-1716. PMID 22019144
3. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: breast cancer, version 1.2018. [https://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf). Accessed June 27, 2018.
4. Albert JM, Pan IW, Shih YC, et al. Effectiveness of radiation for prevention of mastectomy in older breast cancer patients treated with conservative surgery. *Cancer*. Oct 1 2012;118(19):4642-4651. PMID 22890779
5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Accelerated radiotherapy after breast-conserving surgery for early stage breast cancer. *TEC Assessments*. 2013;Volume 27:Tab 6.
6. Kaidar-Person O, Yarnold J, Offersen BV, et al. Is current evidence about intraoperative partial breast irradiation sufficient for broad implementation in clinical practice? *Eur J Surg Oncol*. Jul 2014;40(7):791-793. PMID 24721228
7. Silverstein MJ, Fastner G, Maluta S, et al. Intraoperative radiation therapy: a critical analysis of the ELIOT and TARGIT trials. Part 2-TARGIT. *Ann Surg Oncol*. Nov 2014;21(12):3793-3799. PMID 25138079
8. Silverstein MJ, Fastner G, Maluta S, et al. Intraoperative radiation therapy: a critical analysis of the ELIOT and TARGIT trials. Part 1-ELIOT. *Ann Surg Oncol*. Nov 2014;21(12):3787-3792. PMID 25160734
9. Athas WF, Adams-Cameron M, Hunt WC, et al. Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. *J Natl Cancer Inst*. Feb 2 2000;92(3):269-271. PMID 10655446
10. Farrow DC, Hunt WC, Samet JM. Geographic variation in the treatment of localized breast cancer. *N Engl J Med*. Apr 23 1992;326(17):1097-1101. PMID 1552910
11. Nattinger AB, Kneusel RT, Hoffmann RG, et al. Relationship of distance from a radiotherapy facility and initial breast cancer treatment. *J Natl Cancer Inst*. Sep 5 2001;93(17):1344-1346. PMID 11535710
12. Berliner E. Adopting medical technology. *Med Decis Making*. Nov 2014;34(8):948-950. PMID 25224365
13. Food and Drug Administration. 510(K) summary of safety and effectiveness: MammoSite™ Radiation Therapy System. 2002; <https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pmn&id=K011690>. Accessed July 10, 2018.
14. Valle LF, Agarwal S, Bickel KE, et al. Hypofractionated whole breast radiotherapy in breast conservation for early-stage breast cancer: a systematic review and meta-analysis of randomized trials. *Breast Cancer Res Treat*. Apr 2017;162(3):409-417. PMID 28160158
15. Start Trialists' Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet*. Mar 29 2008;371(9618):1098-1107. PMID 18355913

16. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst.* Aug 7 2002;94(15):1143-1150. PMID 12165639
17. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med.* Feb 11 2010;362(6):513-520. PMID 20147717
18. Hopwood P, Haviland JS, Sumo G, et al. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol.* Mar 2010;11(3):231-240. PMID 20138809
19. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* Oct 2013;14(11):1086-1094. PMID 24055415
20. Shaitelman SF, Schlembach PJ, Arzu I, et al. Acute and short-term toxic effects of conventionally fractionated vs hypofractionated whole-breast irradiation: a randomized clinical trial. *JAMA Oncol.* Oct 2015;1(7):931-941. PMID 26247543
21. Chan EK, Woods R, McBride ML, et al. Adjuvant hypofractionated versus conventional whole breast radiation therapy for early-stage breast cancer: long-term hospital-related morbidity from cardiac causes. *Int J Radiat Oncol Biol Phys.* Mar 15 2014;88(4):786-792. PMID 24606848
22. Chan EK, Woods R, Virani S, et al. Long-term mortality from cardiac causes after adjuvant hypofractionated vs. conventional radiotherapy for localized left-sided breast cancer. *Radiother Oncol.* Jan 2015;114(1):73-78. PMID 25227961
23. Kong L, Cheng J, Ding X, et al. Efficacy and safety of accelerated partial breast irradiation after breast-conserving surgery: a meta-analysis of published comparative studies. *Breast J.* Mar-Apr 2014;20(2):116-124. PMID 24372818
24. Marta GN, Macedo CR, Carvalho Hde A, et al. Accelerated partial irradiation for breast cancer: systematic review and meta-analysis of 8653 women in eight randomized trials. *Radiother Oncol.* Jan 2015;114(1):42-49. PMID 25480094
25. Strnad V, Ott OJ, Hildebrandt G, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet.* Jan 16 2016;387(10015):229-238. PMID 26494415
26. Polgar C, Ott OJ, Hildebrandt G, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol.* Feb 2017;18(2):259-268. PMID 28094198
27. Schafer R, Strnad V, Polgar C, et al. Quality-of-life results for accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation in early breast cancer after breast-conserving surgery (GEC-ESTRO): 5-year results of a randomised, phase 3 trial. *Lancet Oncol.* Jun 2018;19(6):834-844. PMID 29695348
28. Ajkay N, Collett AE, Bloomquist EV, et al. A comparison of complication rates in early-stage breast cancer patients treated with brachytherapy versus whole-breast irradiation. *Ann Surg Oncol.* Apr 2015;22(4):1140-1145. PMID 25319575
29. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet.* Jul 10 2010;376(9735):91-102. PMID 20570343
30. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet.* Feb 15 2014;383(9917):603-613. PMID 24224997
31. Veronesi U, Orecchia R, Luini A, et al. Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. *Breast Cancer Res Treat.* Nov 2010;124(1):141-151. PMID 20711810

32. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol*. Dec 2013;14(13):1269-1277. PMID 24225155
33. Rodriguez N, Sanz X, Dengra J, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys*. Dec 1 2013;87(5):1051-1057. PMID 24161420
34. Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *J Clin Oncol*. Nov 10 2013;31(32):4038-4045. PMID 23835717
35. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Brachytherapy in breast-conserving initial treatment of stage I or II breast cancer. *TEC Assessments*. 1996;Volume 11:Tab 7.
36. Hamid S, Rocchio K, Arthur D, et al. A multi-institutional study of feasibility, implementation, and early clinical results with noninvasive breast brachytherapy for tumor bed boost. *Int J Radiat Oncol Biol Phys*. Aug 1 2012;83(5):1374-1380. PMID 22209153
37. Leonard KL, Hepel JT, Styczynski JR, et al. Breast boost using noninvasive image-guided breast brachytherapy vs. external beam: a 2:1 matched-pair analysis. *Clin Breast Cancer*. Dec 2013;13(6):455-459. PMID 24099648
38. Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO Evidence-Based Consensus Statement. *Pract Radiat Oncol*. Mar - Apr 2017;7(2):73-79. PMID 27866865
39. American Society of Breast Surgeons. Consensus statements: accelerated partial breast irradiation. Revised. 2011 <https://www.breastsurgeons.org/about/statements/>. Accessed June 27, 2018.
40. Shah C, Vicini F, Shaitelman SF, et al. The American Brachytherapy Society consensus statement for accelerated partial-breast irradiation. *Brachytherapy*. Jan - Feb 2018;17(1):154-170. PMID 29074088
41. Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol*. May - Jun 2018;8(3):145-152. PMID 29545124

### Other References

1. Blue Cross and Blue Shield of Kansas Radiology Liaison Committee, February 28, 2007 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-01-07); January 2014; January 2015; April 2016; July 2017; January 2018.
2. Blue Cross and Blue Shield of Kansas Medical Advisory Committee meeting, April 19, 2007 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-01-07.
3. Blue Cross and Blue Shield of Kansas Oncology Liaison Committee, August 2017.