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

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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
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

Populations	Interventions	Comparators	Outcomes
			• Treatment-related morbidity
Individuals: • With early-stage breast cancer	Interventions of interest are: • Intraoperative radiotherapy	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 of care for patients with breast cancer undergoing breast-conserving surgery because it reduces recurrences and lengthens survival. A 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 breast-conserving surgery; the duration and logistics of treatment may be barriers for some women. Accelerated radiotherapy approaches have been proposed to make the regimen less burdensome for patients with early-stage breast cancer at a low-risk of recurrence. Accelerated (also called hypofractionated) whole-breast irradiation (AWBI) reduces the number of fractions and the duration of treatment to about 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 evidence review is to determine the safety and efficacy of accelerated whole- and partial-breast irradiation and local boost brachytherapy with whole-breast irradiation in individuals with early breast cancer compared with standard whole-breast irradiation.

BACKGROUND

Breast Cancer

Current estimates suggest that 310,720 new cases of breast cancer of any stage will occur in the U.S. in 2024. Based on adjusted data from 2017 to 2021, among women, the number of new cases is 129.4 per 100,000 women per year and the number of deaths is 19.3 per 100,000 women per year.[2,]

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 comprises breast-conserving surgery 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 (RCTs) have demonstrated that the addition of radiotherapy after breast-conserving surgery reduces recurrences and mortality. In an expanded update of an individual patient data meta-analysis, the Early Breast Cancer Trialists' Collaborative Group (2011) reported that radiotherapy halved the annual recurrence rate after 10 years for women with a node-negative disease (n=7287), from 31.0% for those not receiving radiotherapy to 15.6% for those receiving radiotherapy.[3,] It also reduced the 15-year risk of breast cancer death from 20.5% to 17.2% (p=.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=.01).

Consequently, radiotherapy is generally recommended following breast-conserving surgery. A potential exception is for older women at low-risk of recurrence. For example, current National Comprehensive Cancer Network (NCCN) guidelines state that women ages 70 years or older may omit radiotherapy if they are hormone receptor-positive, *HER2*-negative, have T1 tumors, have clinically negative lymph nodes, and plan to take adjuvant endocrine therapy, or if they are 65 years or older with hormone receptor positive and *HER2*-negative tumors (≤3 cm) and have no lymph node metastases.[4,] However, the agreement is not universal.[5,]

Controversy continues on the length of follow-up needed to determine whether accelerated partial-breast irradiation (APBI) is equivalent to WBI (see the TEC Assessment [2013] on accelerated radiotherapy after breast-conserving surgery for early-stage breast cancer for details).[6,] 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.[7,8,9,] For accelerated WBI, some 10-year data are available. However, for newer approaches, the issue may be resolved by statistical issues rather than biologic ones.

Currently, most patients diagnosed with stage I or II breast cancer are offered a choice between BCT and mastectomy but BCT is selected less often than expected. Studies have shown that those living farthest from treatment facilities are least likely to select BCT instead of mastectomy and most likely to forgo radiotherapy after breast-conserving surgery,[10,11,12,] and have recommended the use of multidisciplinary management strategies to eliminate known disparities in rural, minority, and uninsured populations.[13,]

Approaches to Radiotherapy Following Breast-Conservation Treatment

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

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

Table 1. Major Types of Radiotherapy Following Breast-Conserving Surgery[a]

Radiation Type	**Accelerated?**	**Whole or Partial Breast**	**EBRT or Brachytherapy**	**Treatment Duration**
Conventional WBI	No	Whole	EBRT	5-6 wk
Accelerated WBI	Yes	Whole	EBRT	3 wk
Interstitial APBI[b]	Yes	Partial	Brachytherapy	1 wk
Balloon APBI[c]	Yes	Partial	Brachytherapy	1 wk
EBRT APBI[d]	Yes	Partial	EBRT	1 wk
Intraoperative APBI[e]	Yes	Partial	Not applicable	1 d

APBI: accelerated partial-breast irradiation; EBRT: external-beam radiotherapy; WBI: whole-breast irradiation.
[a] Noninvasive breast brachytherapy using AccuBoost has been described by the manufacturer as capable of delivering APBI but no studies for this indication were found.
[b] Interstitial brachytherapy entails placement of multiple hollow needles and catheters to guide placement of the radioactive material by a remote afterloading device. It is more difficult to perform than other types of brachytherapy and has a steep learning curve.
[c] Balloon brachytherapy (e.g., MammoSite) entails inserting a balloon into the tumor bed, inflating the balloon, confirming its position radiographically, and then using a remote afterloader to irradiate the targeted area. Some brachytherapy systems combine aspects of interstitial and balloon brachytherapy.
[d] External-beam APBI is delivered in the same way as conventional or accelerated whole-breast radiotherapy but to a smaller area. All 3 external-beam regimens can use 3-dimensional conformal radiotherapy or intensity-modulated radiotherapy.
[e] Intraoperative APBI is performed during breast-conserving surgery with a single dose of radiation delivered to the exposed tumor bed.

REGULATORY STATUS

In 2002, the MammoSite® Radiation Therapy System (Proxima Therapeutics), the first device specifically designed for breast brachytherapy,[14,] 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."[15,]

Since 2002, several other devices for breast brachytherapy have been cleared for marketing by the FDA through the 510(k) process. The FDA determined that several devices (e.g., Axxent® Electronic Brachytherapy System [Xoft], Strut-Adjusted Volume Implant [SAVI™] Applicator Kit [Biolucent (now Cianna Medical)], Contura® Multi-Lumen Balloon Source Applicator for Brachytherapy [SenoRx], ClearPath™ Adjustable Multi-Catheter Source Applicator [North American Scientific], Intrabeam® System [Carl Zeiss Surgical]) were substantially equivalent to predicate devices. Each includes an FDA-required warning that the safety and effectiveness of the device "as a replacement for whole-breast irradiation in the treatment of breast cancer has not been established." FDA Product Codes: JAD, NEU, PDW, JAQ.

Although the Intrabeam® System (discussed in the Intraoperative Radiotherapy subsection) is subject to the FDA regulation, it does not fall under the regulatory purview of the U.S. Nuclear Regulatory Commission. In some states, the participation of radiation oncologists in delivering radiation is not required.

POLICY

A. When using radiation therapy after breast-conserving (BCS) surgery for early stage breast cancer:
    1. Accelerated whole breast irradiation (AWBI) and accelerated partial breast irradiation (APBI) with external beam radiation, including IMRT, may be considered **medically necessary** for individuals who meet the following conditions:
        a. Invasive carcinoma of the breast
        b. Technically clear surgical margins, i.e., no ink on tumor of invasive carcinoma or ductal carcinoma in situ
        c. Age at least 40 years old

    2. Accelerated whole breast irradiation (AWBI) and accelerated partial breast irradiation (APBI) with external beam radiation, including IMRT 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 individuals undergoing initial treatment for stage I or II breast cancer when used as local boost irradiation in individuals who are also treated with breast-conserving surgery and whole-breast external-beam radiotherapy.

C. Interstitial APBI, balloon APBI, intra-operative APBI and noninvasive brachytherapy using AccuBoost® is considered **experimental / investigational.**

D. Noninvasive brachytherapy using AccuBoost® for individuals undergoing initial treatment for stage I or II breast cancer when used as local boost irradiation in individuals who are also treated with breast conserving surgery and whole-breast external-beam radiotherapy is considered **experimental / investigational**.

POLICY GUIDELINES

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

B. As recommended by the Society of Surgical Oncology and the American Society for Radiation Oncology (ASTRO) in a joint 2014 consensus guideline, technically clear surgical margins can be defined as no ink on tumor of invasive carcinoma or ductal carcinoma in situ.

C. As part of the clinical input process, ASTRO recommended additional criteria that should be satisfied for individuals undergoing AWBI:
    1. Pathologic stage is T1–2N0 and the individual has been treated with breast-conserving surgery.
    2. Individual 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).

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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through May 21, 2024.

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 for early-stage breast cancer.[6,]

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

ACCELERATED WHOLE-BREAST IRRADIATION

Clinical Context and Therapy Purpose

The purpose of accelerated whole-breast irradiation (AWBI) after breast-conserving surgery in individuals 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 following PICO was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is AWBI after breast-conserving surgery. Accelerated whole-breast irradiation provides the same dose to the whole breast in a shorter time than whole-breast irradiation (WBI) 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 has allayed most of these concerns. Accelerated whole-breast irradiation has been adopted widely in Canada and Europe.

Comparators

The comparator of interest is standard WBI.

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs and systematic reviews of RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

REVIEW OF EVIDENCE

Systematic Reviews

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 (N=8189 patients) published prior to October 2014 that compared AWBI with standard fractionation.[16,] 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 Standardization of Breast Radiotherapy (START) A, START B, and NCIC (detailed below).[17,18,19,]

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.[17,18,19,] Both trials used noninferiority margins of 5 percentage points for local or locoregional recurrence in the accelerated group at 5 years (1-sided α=.025[17,] or.05[18,]) or 10 years (1-sided α=.025[19,]). Although the trials differed in specific fractionation schedules and patient characteristics, they reported similar ipsilateral local recurrence rates (i.e., cancer recurrence in the same breast) across treatment arms.

The first RCT evaluating an accelerated whole-breast radiotherapy regimen START B (2008), from the U.K., included women with stage I, II, or III tumors (N=2215) who had clear tumor margins (≥1 mm).[17,] 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 a median follow-up of 6.0 years (interquartile range, 5.0 to 6.2), the 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 versus 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 (i.e., START A, which compared two 5-week whole-breast radiotherapy regimens, and START B). Hopwood et al (2010) examined the patient-reported breast, arm, and shoulder symptoms, as well as body image, over 5 years of follow-up.[20,] 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).[21,] 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.[18,19,] 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).

An RCT by Shaitelman et al (2015), not included in the Valle et al (2017) systematic review, focused on acute and short-term toxicity for conventional WBI versus AWBI.[22,] 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<.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 6 months except that the rate of fatigue (grade ≥2) was significantly lower in the accelerated radiotherapy group (0%) than in the conventional radiotherapy group (6%; p=.01).

In 2020, Brunt et al published 10 year results of the FASTer radiotherapy for breast radiotherapy (FAST) trial.[23,] This multicenter, phase III, RCT enrolled 915 women ≥50 years of age with low-risk invasive breast carcinoma who had undergone breast-conserving surgery with complete microscopic resection and randomly assigned them to 50 Gy in 25 fractions of 2 Gy, 30 Gy in 5 once weekly fractions of 6 Gy, or 28.5 Gy in 5 once weekly fractions of 5.7 Gy. At the time of this analysis, the median follow-up was 9.9 years (interquartile range, 8.3 to 10.1 years). Results revealed that the odds ratios for any moderate/marked physician-assessed breast normal tissue effects (i.e., shrinkage, induration, telangiectasia, edema) were significantly higher for the 30 Gy versus 50 Gy group (2.12; 95% CI, 1.55 to 2.89; p<.001), but not significantly different for the 28.5 Gy versus 50 Gy group (1.22; 95% CI, 0.87 to 1.72; p=.248). Additionally, 11 ipsilateral breast cancer events (50 Gy: 3; 30 Gy: 4; 28.5 Gy: 4) and 96 deaths (50 Gy: 30; 30 Gy: 33; 28.5 Gy: 33) were reported at 10 years of follow-up. These results appear to confirm that a 5-fraction schedule (28.5 Gy in 5 once weekly fractions) is radiobiologically equivalent to the standard 25-fraction schedule with regard to late normal tissue effects.

Brunt et al (2020) also published results from the multicenter, noninferiority, randomized, FAST-Forward trial.[24,] This study enrolled 4096 adults with invasive breast carcinoma following complete microscopic excision of the primary tumor by breast-conserving surgery or mastectomy who were randomly assigned to 3 groups of hypofractionated radiotherapy: 40 Gy in 15 fractions over 3 weeks, 27 Gy in 5 fractions over 1 week, or 26 Gy in 5 fractions over 1 week. At a median follow-up of 71.5 months (interquartile range, 71.3 to 71.7 months), ipsilateral breast tumor relapse occurred in a total of 79 patients (40 Gy: 31; 27 Gy: 27; 26 Gy: 21); the hazard ratio for 27 Gy versus 40 Gy was 0.86 (95% CI, 0.51 to 1.44) and for 26 Gy versus 40 Gy was 0.67 (95% CI, 0.38 to 1.16). The estimated cumulative incidence of ipsilateral breast tumor relapse up to 5

years was 2.1% (95% CI, 1.4 to 3.1) for 40 Gy; 1.7% (95% CI, 1.2 to 2.6) for 27 Gy; and 1.4% (95% CI, 0.9 to 2.2) for 26 Gy. Estimated absolute differences in this outcome were -0.3% (95% CI, -1.0 to 0.9) for 27 Gy versus 40 Gy and -0.7% (95% CI, -1.3 to 0.3) for 26 Gy versus 40 Gy. Moderate or marked physician-assessed normal tissue effects in the breast or chest wall were seen in 9.9% of 40 Gy patients, 15.4% of 27 Gy patients, and 11.9% of 26 Gy patients at 5 years; a significant difference between 40 and 27 Gy (p=.0003) but not between 40 and 26 Gy (p=.17) was observed. These results show that a 1-week course of adjuvant breast radiotherapy delivered in 5 fractions is noninferior to the standard 3-week schedule, with the 26 Gy dose level being similar to 40 Gy in terms of local tumor control and normal tissue effects for up to 5 years.

Observational Studies
Toxicity was evaluated in a large retrospective study of patients with left-sided early-stage breast cancer published by Chan et al (2014, 2015).[25,26,] The study included 2706 patients who received conventional WBI (n=2221) or AWBI (n=485). 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 the 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. Additionally, recent data imply that even more accelerated WBI scheduling may be noninferior to standard 3- or 5-week schedules.

ACCELERATED PARTIAL-BREAST IRRADIATION

Clinical Context and Therapy Purpose
The purpose of accelerated partial-breast irradiation (APBI) in individuals who have early-stage breast cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

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

Interventions
The therapies being considered are interstitial brachytherapy alone, intraoperative radiotherapy (IORT) alone, and external-beam APBI. APBI 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 IORT) rather than 5 to 6 weeks, because radiation is delivered to the tumor bed in fewer fractions at larger doses per fraction. Third, the radiation dose is intrinsically less uniform within the target volume when APBI uses brachytherapy (i.e., the implantation of radioactive material directly in the breast tissue).

Comparators
The comparator of interest is standard WBI.

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs and systematic reviews of RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

REVIEW OF EVIDENCE

Systematic Reviews
A number of RCTs and nonrandomized comparative studies have evaluated interstitial, external-beam, or intraoperative APBI compared with conventional WBI. Several meta-analyses of these studies have evaluated evidence on APBI compared to WBI, with various methods grouped in the same review.[27,28,29,30,31,32,33,34,] Conclusions cannot be drawn from these meta-analyses because analyses of the methods varied and methods were not evaluated individually. The review authors were generally consistent in concluding that additional data from RCTs are needed. In 2020, Viani et al published a systematic review and updated meta-analysis of partial- versus WBI for early breast cancer that included a subgroup analysis assessing the potential effectiveness of APBI technique - IORT, brachytherapy, or external beam radiotherapy (EBRT).[35,] Results revealed no significant difference in local recurrence with APBI and WBI when using brachytherapy (p=.051), EBRT (p=.25), or mixed techniques (p=.89) at 5 years; however, a significant increase in local recurrence was noted with IORT use (p=.014). At 7 and 10 years follow-up, the difference in local recurrence within the IORT subgroup disappeared. Additionally, an analysis of overall mortality revealed no difference at 5, 7, and 10 years of follow-up for any subgroup. Korzets et al (2019) revealed similar results from a subgroup analysis of APBI modality within a systematic review and meta-analysis that evaluated toxicity and clinical outcomes of partial- versus WBI for early-stage breast cancer.[36,] These authors concluded that the highest risk of local recurrence was seen with IORT, whereas when EBRT was used the odds for local recurrence

were equivalent to WBI. The IORT studies included a larger number of patients with high-grade disease and nodal involvement, which may partially explain the increased local recurrence rate with this modality.

INTERSTITIAL BRACHYTHERAPY

Randomized Controlled Trials

GEC-ESTRO was a European multicenter noninferiority RCT with 5-year results (Table 2). Primary results were published in 2016, late-side effects in 2017, and quality of life in 2018.[37,38,39,] The primary study endpoint 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 (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=.02).

Ten-year outcomes of the GEC-ESTRO trial were published by Strnad et al in 2023.[40,] At a median follow-up of 10.36 years, rates of local recurrence were 1.58% (95% CI, 1.99 to 5.03) in the WBI group and 3.51% (95% CI, 1.99 to 5.03) in the APBI group (Table 3). Significantly fewer treatment-related grade 3 late adverse effects were observed in the APBI group (1%) compared to the WBI group (4%). No grade 4 adverse events or treatment-related deaths were reported. Additional publications with detailed analyses of late adverse effects (e.g., cosmesis) and quality of life outcomes are planned by the investigators.

Table 2. Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
GEC-ESTRO[37,38,39,40,]	EU	16	2004-2009	1328 patients ≥40 y with breast-conserving surgery 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 to 2.0 Gy over 5 wk

APBI: accelerated partial breast irradiation; EU: European Union; Gy: gray; WBI: whole-breast irradiation.

Table 3. Summary of Key Randomized Controlled Trial 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[37,38,39,40,					
5-year Outcomes					
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)
Difference (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	.11	.080	.12	.94
10-year Outcomes					
n	772	772	688	688	NR
WBI	9 (1.58)	89.5%	3%	121/313 (34)	NR
APBI	21 (3.51)	90.5%	1%	188/446 (45)	NR
Difference (95% CI)	1.93% (-0.018 to 3.87)	0.95% (-2.66 to 4.56)	2% (NR)	NR	NR
p	.074	.50	.70	NR	NR

APBI: accelerated partial breast irradiation; CI: confidence interval; NR: not reported; NS: nonsignificant; SD: standard deviation; WBI: whole-breast irradiation.

Major limitations in relevance and design and conduct are shown in Tables 4 and 5, respectively. 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. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
GEC-ESTRO[37,38,39,40,				1. Overall survival was not a primary outcome	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
GEC-ESTRO[37,38,39,40,]		1-3. Not blinded				1. No prespecified noninferiority analysis on survival outcomes

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] 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).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] 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

Kim et al (2023) reported 5-year survival outcomes in 223 patients with early-stage breast cancer prospectively enrolled in a single-center registry.[41,] Patients were treated with breast-conserving surgery and individualized applicator-based brachytherapy administered via a Strut Adjusted Volume Implant (SAVI) device. After a median follow-up of 63 months, recurrence was reported in 19 (8.5%) patients with ipsilateral breast tumor recurrence occurring in 17 (7.6%). Rates of 5-year ispilateral breast tumor-free survival, disease-free survival, and OS were 92.2%, 91.1%, and 97.8%, respectively. Significantly higher rates of 5-year ispilateral breast tumor-free survival were noted in postmenopausal women (93.6% vs. 66.4%; p=.04), patients with body mass index <30 kg/m^2 (97.5% vs. 88.1%; p=.02), and endocrine therapy adherence in postmenopausal women (97.5% vs. 88.6%; p=.02). Eight (3.6%) developed a grade 2 or higher treatment-related complication within 9 months of brachytherapy completion.

Ajkay et al (2015) reported retrospectively on 5-year adverse events in patients with early-stage breast cancer treated at a single-center.[42,] Of 417 patients who received breast-conserving surgery 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 to 50.4 Gy in 25 to 28 fractions with 10 to 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<.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<.001) and fat necrosis (40% vs. 24%; p<.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 was small. Ten-year follow-up data published in 2023 reported a nonsignificant 1.93% difference in the cumulative incidence of local recurrence between groups. At least 1 additional trial to confirm these findings is needed.

INTRAOPERATIVE RADIOTHERAPY

Systematic Reviews

Ravani et al (2024) conducted a meta-analysis of patient-level data from RCTs that compared partial breast irradiation, IORT, and WHI in patients with early-stage breast cancer who underwent breast-conserving surgery.[43,] A total of 11 trials were included (N=15,460), and the trials had a median follow-up of 9 years. About half of the included patients (49.6%) received WBI, while 35% received partial breast irradiation, and 15.3% received IORT. Patients who received IORT had a higher risk of recurrence (HR, 1.46; 95% CI, 1.23 to 1.72; p<.01) compared to WBI with similar risk of OS (p=.81) and disease-free survival (p=.31). The authors concluded that IORT was inferior to WBI.

Wang et al (2021) conducted a systematic review and meta-analysis to compare the efficacy and safety of IORT to WBI in patients with early-stage breast cancer receiving breast-conserving surgery.[44,] A total of 10 RCTs representing 5698 patients were included for analysis. The IORT group was associated with a significantly higher risk of local recurrence (RR, 2.11; 95% CI, 1.13 to 3.94; p=.019). Pooled analyses did not find any statistically significant differences in OS, recurrence-free survival, distant metastasis-free survival, and cancer-specific survival between groups. While the risk of skin toxicity was significantly lower in the IORT group compared to the WBI group (RR, 0.28; 95% CI, 0.16 to 0.49; p<.0001), the incidence of fat toxicity, scar calcification, and edema were 3.1, 1.3, and 2.4 times higher than that in the WBI group, respectively. The authors concluded that IORT is not a better alternative to WBI.

Randomized Controlled Trials

One RCT, reported by Vaidya et al (2010, 2014) compared IORT with WBI in 2232 women.[45,46,] 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 with 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 EBRT as well, because of unfavorable pathologic features determined after surgery (e.g., lobular carcinoma). The predefined noninferiority margin was an absolute difference of 2.5% between groups for pathologically confirmed, ipsilateral local recurrence. In 2013, a study report 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."[46,] Median follow-up for all patients was 2 years and 5 months (interquartile range, 12 to 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=.042) in the WBI group. Mortality was similar between the 2 groups (2.6% with TARGIT vs. 1.9% with WBI; p=.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<.001), with fewer deaths from cardiovascular causes and other cancers in the TARGIT group. In the group that received IORT plus WBI, the mortality rate was higher at 8% (95% CI, 3.7% to 17.5%), but the percentage of women with local recurrences (0.9%; 95% CI, 0.1% to 6.1%) was similar for those who only received IORT. Noninferiority was established for the whole intraoperative cohort and for those who received IORT alone but not for patients who underwent both types of radiotherapy. There was no significant difference between the IORT and WBI groups in predefined 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=.029). In 2016, the full final report of the TARGIT-A trial was published concluding that "for patients with breast cancer (women who are aged ≥45 years with hormone-sensitive invasive ductal carcinoma that is up to 3.5 cm in size), targeted IORT concurrent with lumpectomy within a risk-adapted approach is as effective as, safer than, and less expensive than postoperative EBRT."[47,]

In a parallel study to TARGIT-A, Vaidya and colleagues (2020) randomly assigned 1153 patients who had undergone breast cancer excision to either conventional fractionated whole breast EBRT over 3 to 6 weeks or to undergo a further operation to deliver delayed radiotherapy (as a single dose via Intrabeam) to the wound by reopening the original incision.[48,] Results at 5 years revealed local recurrence rates of 3.96% for delayed IORT versus 1.05% for EBRT, a difference of 2.9% with an upper 90% CI of 4.4, which crossed the noninferiority margin of 2.5%. Of note, at a median follow-up of 9 years, there were no significant differences between the 2 treatment approaches with regard to local recurrence-free survival, invasive local recurrence-free survival, mastectomy-free survival, distant disease-free survival, breast cancer mortality, and OS. The authors concluded that the results of this trial clearly show that the preferred timing of IORT use is during the initial surgical excision of breast cancer setting, not in the delayed setting; however, if immediate IORT is not possible the data from this trial may assist clinicians and patients who want to avoid a prolonged postoperative EBRT course.

Another form of IORT, called electron intraoperative radiotherapy (ELIOT), uses electrons.[49,] The ELIOT trial, reported by Veronesi et al (2013), compared IORT plus ELIOT with WBI.[50,] With a sample size of 1305 patients and median follow-up of 5.8 years (interquartile range, 4.1 to 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<.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<.001). This was an equivalence trial with a prespecified limit of 7.5% for local recurrence in the IORT group only. Therefore, although the criterion for equivalence was satisfied, the ipsilateral breast recurrence rate was significantly higher in the IORT group. A subsequent review of ELIOT trial data by Silverstein et al (2014) noted that, of 69 women who had 4 or more positive lymph nodes, those randomized to WBI (n=38) received concurrent axillary radiation; for those randomized to ELIOT (n=31), axillary irradiation was delayed 6 to 12

weeks.[8,] These reviewers also characterized ELIOT data as premature and noted that long-term results are needed to assess net health benefit. Orrechia et al (2021) reported 15-year results of the ELIOT trial that confirmed the 5-year findings.[51,] After a median follow-up of 12.4 years (interquartile range, 9.7 to 14.7 years), ipsilateral breast tumor recurrence had occurred in 70 patients (11%) in the IORT group 16 patients (2%) in the WBI group (hazard ratio, 4.62; 95% CI, 2.68 to 7.95; p<.0001). Fifteen-year OS was 83.4% in the IORT group and 82.4% in the WBI group. The authors concluded that low risk patients may be appropriate for IORT since the higher rate of ipsilateral breast cancer recurrence in the ELIOT trial did not lead to an increase in OS.

Section Summary: Intraoperative Radiotherapy
Randomized controlled trials have not demonstrated that outcomes after IORT are noninferior to WBI. Five-year results from the TARGIT-A RCT showed increased ipsilateral local recurrence with APBI compared with WBI. In a parallel study to TARGIT-A, delayed IORT was also associated with an increase in local recurrence rates at 5 years compared to EBRT. 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 ACCELERATED PARTIAL-BREAST IRRADIATION

Randomized Controlled Trials

Tables 6 and 7 detail key characteristics and results of the RCTs summarized in this section.

Rodriguez et al (2013) reported on 102 patients randomized to WBI, with or without a boost to the tumor bed, or APBI.[52,] The primary endpoint 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=.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. Li et al (2021) reported long-term results of this trial (median, 10.3 years).[53,] Rates of recurrence (4%) and disease-free survival (84%) were the same in both groups. Estimated 12-year OS was also similar between groups (81.8±7.4% APBI vs. 89.9±4.3% WBI; p>.05). Grade 1 and 2 fibrosis was numerically more common the ABPI group (n=10) than the WBI group (n=4; p=.18).

Olivotto et al (2013) reported interim results of the multicenter Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) trial.[54,] 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 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<.001), nurses (p<.001), or patients (p<.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<.001). Although the primary outcome was ipsilateral local breast tumor recurrence, there were too few events to trigger an efficacy analysis. In 2019, Whelan et al (2019) published longer term results from RAPID.[55,] Results from this analysis revealed similar ipsilateral breast tumor recurrence rates between the groups at 8 years (hazard ratio, 1.27; 90% CI, 0.84 to 1.91) and no difference in OS (hazard ratio, 1.18; 95% CI, 0.84 to 1.64).

In Livi et al (2015), 520 patients with early breast cancer were randomized to APBI using intensity-modulated radiotherapy or WBI.[56,] The local recurrence rate at 5 years was 1.5% (3 cases) in the APBI group. There were 7 deaths in the WBI group and 1 in the APBI group (p=.057). The 5-year OS was 96.6% for the WBI group and 99.4% for the APBI group. Long-term results (mean, 10.5 years; range, 1.4 to 14.8 years) were published by Meattini et al (2020).[57,] The 10-year cumulative ipsilateral breast tumor recurrence rate was 2.5% with APBI and 3.7% with WBI (hazard ratio, 1.56; 95% CI, 0.55 to 4.37; p=.40). A similar number of deaths occurred in both groups (24 ABPI vs. 25 WBI) and the 10-year point estimate for OS was the same in both groups (91.9%; hazard ratio, 0.95; 95% CI, 0.50 to 1.79; p=.86).

Vicini et al (2019) completed a phase 3, equivalence, multicenter, RCT that compared APBI to WBI after breast-conserving surgery for early-stage breast cancer that enrolled 4216 patients.[58,] Results revealed that, at a median follow-up of 10.2 years, ABPI did not meet the criteria for equivalence to WBI with regard to controlling ipsilateral breast tumor recurrence (hazard ratio, 1.22; 90% CI, 0.94 to 1.58); however, the absolute difference in the 10-year cumulative incidence of ipsilateral recurrence was <1% (4.6% APBI vs. 3.9% WBI). Significantly more evaluable patients in the APBI group had recurrence-free interval events than patients in the WBI group (hazard ratio, 1.33; 95% CI, 1.04 to 1.69; p=.02); distant disease-free survival, OS, and disease-free survival were not different between the groups. The trial had broad eligibility criteria, but was not designed to test equivalence in patient subgroups or outcomes from varying APBI techniques.

Polgar et al (2021) reported 20-year results of an RCT that compared APBI with either EBRT or high-dose interstitial brachytherapy (n=128) and WBI (n=130) in patients with early-stage breast cancer who had undergone breast-conserving surgery.[59,] Patient accrual was stopped early and the study did not have sufficient power for the difference that was seen in the primary outcome (ipsilateral breast tumor recurrence). Median follow-up was 17 years (range, 1.5 to 21.2 years). Tumor recurrence rates were similar with APBI and WBI (9.6% vs. 7.9%, respectively; p=.59). Overall survival at 20 years was also similar between groups (59.5% vs. 59.7%, respectively; p=.90). Similar rates of grade 2 to 3 skin toxicity (p=.32) and fibrosis (p=.16) were reported in both groups.

Meduri et al (2023) reported 5-year outcomes of the IRMA trial.[60,] The IRMA trial randomly assigned women with early-stage breast cancer to breast-conserving surgery and WBI (n=1657) or twice-daily external-beam APBI (n=1602). At a median follow-up of 5.6 years, significantly higher rates of adverse cosmesis were reported in the APBI group (14% vs. 9.8%; p=.012) compared to WBI. Grade 3 late soft tissue (2.8% APBI vs. 1% WBI; p<.0001) and bone toxicities (1.1% APBI vs. 0% WBI) were significantly higher in the APBI arm. No significant differences in late skin or lung toxicities were observed. Five-year OS was 97.4% with APBI compared to 97.2%

with WBI. The investigators plan to publish primary endpoint results (i.e., ipsilateral breast tumor recurrence) in a future study.

Table 6. Summary of Key Randomized Controlled Trial Characteristics-External Beam Accelerated Partial-Breast Irradiation versus Whole-Breast Irradiation

Trial	Countries	Sites	Dates	Participants	Interventions	
Meduri et al (2023)[60,]	Italy	35	2007-2019	Age 49 years or older, with stage I-IIA breast cancer; tumor size <3 cm in diameter; with negative margins after breast-conserving therapy and a clinical target volume <30% of whole breast volume	APBI: 38.5 Gy total in 10 fractions (3.85 Gy/fraction), twice-daily for 5 consecutive days N=1602	WBI: 50.0 Gy in 25 fractions over 5 weeks N=1657
Polgar et al (2021)[59,]	Hungary	1	1998-2004	Low risk invasive breast carcinoma with negative margins after breast-conserving therapy	APBI: 5.2 Gy fractions given twice daily for 7 fractions with brachytherapy or 50 Gy total dose fractions over 5 weeks with EBRT N=128	WBI: 50 Gy given in 25 fractions over 5 weeks N=130
Vicini et al (2019)[58,]	U.S., Canada, Ireland, Israel	154	2005-2013	Over age 18 years, lumpectomy for stage 0 cancer or stage I or II invasive adenocarcinoma of the breast with no distant metastases, life expectancy of at least 10 y; surgical resection margins needed to be cancer free	APBI: 34 Gy with brachytherapy or 38.5 Gy with EBRT in 10 fractions given twice daily, at least 6 hours apart, on 5 treatment days within an 8-day period N=2107	WBI: 50 Gy per day in 25 total fractions spread over 5 weeks N=2109
Livi it al (2015)[56,]; Meattini et al (2020)[57,]	Italy	1	2005-2013	Over age 40 years, maximum tumor size 25 mm	APBI: 30 Gy to the tumour bed in 5 daily fractions N=260	WBI: 50 Gy in 25 fractions, followed by a boost on the tumour bed of 10 Gy in 5 fractions N=260

Trial	Countries	Sites	Dates	Participants	Interventions	
Olivotto et al (2013)[54,]; Whelan et al (2019)[55,]	Canada, Australia, New Zealand	33	2006-2011	Invasive ductal carcinoma or DCIS treated with breast-conserving therapy with microscopically clear margins and negative axillary nodes by sentinel node biopsy, or axillary dissection for those with invasive disease, or by clinical examination for those with DCIS alone	APBI: 38.5 Gy in 10 fractions treated twice daily over 5 to 8 days with a minimum interfraction interval of 6 hours N=1070	WBI: 42.5 Gy in 16 fractions or 50 Gy in 25 fractions. Boost irradiation of 10 Gy in 4 to 5 daily fractions after WBI was based on criteria such as young age or close margins N=1065
Rodriguez et al (2013)[52,]; Li et al (2021)[53,]	Spain	1	NR	Invasive ductal carcinoma; age 60 years or older; unifocal tumor; primary tumor size ≤30 mm	37.5 Gy in 3.75 Gy per fraction delivered twice daily N=51	WBI: 48 Gy in daily fractions of 2 Gy, with or without additional 10 Gy to the tumor bed N=51

APBI: accelerated partial breast irradiation; DCIS: ductal carcinoma in situ; EBRT: external beam radiotherapy; Gy: gray; NR: not reported; WBI: whole breast irradiation.

Table 7. Summary of Key Randomized Controlled Trial Results-External Beam Accelerated Partial-Breast Irradiation versus Whole-Breast Irradiation

Study	Local Recurrence	OS	Toxicity
Meduri et al (2023)[60,]	*Ipsilateral tumor recurrence at 5 years*	*5-year OS*	*Grade ≥3 late toxicity*
N		3225	3225
APBI	NR	97.17%	Skin: 0.5% Soft Tissue: 2.8% (p<.0001) Lung: 0.1% Bone: 1.1% (p<.0001)
WBI	NR	97.44%	Skin: 0.4% Soft Tissue: 1.0% Lung: 0.2% Bone: 0.0%

Study	Local Recurrence	OS	Toxicity
Polgar et al (2021)[59,]	*Ipsilateral tumor recurrence at 20 years*	*20-year OS*	*Grade 2-3 late toxicity*
N	258		
APBI	9.6%	59.5%	Skin: 13.6% Fibrosis: 14.4%
WBI	7.9%	59.7%	Skin: 11.8% Fibrosis: 9.4%
Vicini et al (2019)[58,]	*Ipsilateral tumor recurrence (first recurrence)*	*10-year point-estimate*	*CTCAE toxicity grade*
N	4025		4109
ABPI	4%	90.6%	Grade 1: 40% Grade 2: 44% Grade 3: 10%
WBI	3%	91.3%	Grade 1: 31% Grade 2: 59% Grade 3: 7%
Livi it al (2015)[56,]; Meattini et al (2020)[57,]	*Ipsilateral tumor recurrence at 10 years*	*Number of deaths at 10 years*	*Acute skin toxicity (≥grade 2) at 10 years*
N	520	--	520
APBI	2.7%	24	0%
WBI	3.5%	25	2.7%
Olivotto et al (2013)[54,]; Whelan et al (2019)[55,]	*Ipsilateral tumor recurrence at 8 years*	*Deaths*	*Grade 2 or 3 toxicity at 3 years*
N	--	140	1070
APBI	3%	76	1.4%
WBI	2.8%	64	0%
Rodriguez et al (2013)[52,]; Li et al (2021)[53,]		*12-year OS*	*Acute and late toxicity*
N	102	102	Acute: 102; 4 years: 70
APBI	4%	81.8%	Acute: 46/51 (90.2%); 4 years: 16%, all grade 1
WBI	4%	89.9%	Acute: 51/51 (100%); 4 years: 11%, all grade 1

APBI: accelerated partial breast irradiation; CTCAE: Common Terminology Criteria for Adverse Events; N: sample size; NR: not reported; OS: overall survival; WBI: whole breast irradiation.
Relevance and study design and conduct limitations are summarized in Tables 8 and 9, respectively.

Table 8. Study Relevance Limitations-External Beam Accelerated Partial-Breast Irradiation versus Whole-Breast Irradiation

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Meduri et al (2023)[60,]				1. Primary endpoint (ipsilateral breast tumor recurrence) NR	1. 5-year outcomes
Polgar et al (2021)[59,]		3. 69% of patients received high-dose brachytherapy, 33% of patients received EBRT			
Vicini et al (2019)[58,]	4. Absence of *HER2* data for enrolled patients with invasive breast cancer	3. 73% of patients had 3DCRT as their APBI technique; 27% underwent brachytherapy as the APBI technique (either single-entry or multi-catheter)			
Livi et al (2015)[56,]; Meattini et al (2020)[57,]				1. Overall survival NR	
Olivotto et al (2013)[54,]; Whelan et al (2019) [55,]				1. Too few events for efficacy analysis of the primary outcome (local recurrence)	
Rodriguez et al (2013)[52,]; Li et al (2021)[53,]					

3DCRT: 3 dimensional conformal radiotherapy; APBI: accelerated partial breast irradiation; EBRT: external beam radiotherapy; *HER2*: human epidermal growth factor receptor 2; NR: not reported.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 9. Study Design and Conduct Limitations-External Beam Accelerated Partial-Breast Irradiation versus Whole-Breast Irradiation

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Meduri et al (2023)[60,]		1, 2. Not blinded to treatment assignment and outcome assessment				
Polgar et al (2021)[59,]		1, 2. Not blinded to treatment assignment and outcome assessment	1. Protocol not registered			
Vicini et al (2019)[58,]		1, 2. Not blinded to treatment assignment and outcome assessment				
Livi it al (2015)[56,]; Meattini et al (2020)[57,]						
Olivotto et al (2013)[54,]; Whelan et al (2019) [55,]		1. Not blinded to treatment assignment		1. 335/2135 (15.7%) completed 5-year assessment		
Rodriguez et al (2013)[52,]; Li et al (2021)[53,]			1. Protocol not registered	1. Toxicity outcomes reported in 70/102 patients (68.6%)	3. May have been underpowered to detect difference in local recurrence rates	Trial terminated early due to cosmesis benefit

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] 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).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] 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.

Section Summary: External-Beam Accelerated Partial-Breast Irradiation

Randomized controlled trials have reported outcomes from 5 to 20 years. Results from the trial with the largest number of patients reveal that external-beam APBI did not meet the criteria for equivalence to WBI with regard to controlling tumor recurrence; however, the absolute difference in the 10-year cumulative incidence of ipsilateral recurrence was low and survival was not different between groups. Other RCTs found no significant differences between external beam ABPI and WBI regarding local recurrence or survival, including the trial with the longest follow-up (20 years). Moreover, 2 of the trials reported higher rates of adverse cosmetic outcomes and grade 3 toxicities in the external-beam APBI group than in the WBI group.

LOCAL BOOST BRACHYTHERAPY

Clinical Context and Therapy Purpose

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

The following PICO was used to select literature to inform this review.

Populations

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

Interventions

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

Comparators

The comparator of interest is standard WBI with or without an external-beam boost to the tumor bed.

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs and systematic reviews of RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

REVIEW OF EVIDENCE

Systematic Reviews
A TEC Assessment (1996) concluded that net health outcomes with a local boost using brachytherapy were equivalent to outcomes of local boost using EBRT in women who received breast-conserving surgery plus WBI as initial treatment for stage I or II breast cancer.[61,] 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 breast-conserving surgery and WBI. The combination of brachytherapy with local boost, breast-conserving surgery, 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: Local Boost Brachytherapy
For women undergoing breast-conserving surgery plus WBI as initial treatment for stage I or II breast cancer, nonrandomized comparative studies have shown similar outcomes with local boost using brachytherapy and local boost using EBRT.

NONINVASIVE BREAST BRACHYTHERAPY

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

The following PICO was used to select literature to inform this review.

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

Interventions

The therapy being considered is noninvasive breast brachytherapy. AccuBoost for image-guided breast irradiation, also called noninvasive breast brachytherapy, has been used for local boost around the tumor bed. The AccuBoost system provides image-guided radiotherapy before each treatment to ensure that radiation is directed at the treatment target. The breast is placed between mammography paddles, where images are taken and radiation is delivered using a distinct applicator. The paddles prevent motion during treatment. Radiation is delivered from 1 side of the breast to the other or from the top of the breast to the bottom. This is proposed to reduce radiation exposure to adjacent tissues, including the heart and lung.[62,] No long-term studies are available to confirm this potential benefit.

Comparators

The comparator of interest is standard WBI.

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs and systematic reviews of RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Review of Evidence

No systematic reviews or RCTs of noninvasive breast brachytherapy for patients with early-stage breast cancer were identified.

Nonrandomized Studies

One comparative study on noninvasive breast brachytherapy was identified. This matched retrospective study by Leonard et al (2013) assessed patients receiving the boost dose using AccuBoost or electron beams (a type of EBRT).[63,] 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. The main differences between the 2 treatment groups were in radiation doses received and the timing of radiotherapy administration. The percentage of patients with a WBI dose (accompanying the boost dose) of 50 to 50.4 Gy was 68% in the AccuBoost group and 37% in the electron-treated group ($p<.001$). 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% had 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=.046). Locoregional control rates were 99% or greater in both groups. Study limitations included the between-group differences in dose and timing of boost, as well as selection bias and the study's retrospective design.

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

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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
Clinical input was sought to help determine whether the use of accelerated whole breast irradiation (AWBI) for individuals with node-negative, early-stage breast cancer with clear surgical margins would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 5 respondents, including 1 physician-level responses identified through a specialty society and 4 physician-level responses identified through an academic medical center.

For individuals who have node-negative, early-stage breast cancer with clear surgical margins who receive AWBI, clinical input supports this use provides a clinically meaningful improvement in net health outcome and indicates this use is consistent with generally accepted medical practice. Input was limited to the policy statement on 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 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 on AWBI. Input was mixed on accelerated partial-breast irradiation; those agreeing with the conclusion noted the need to define the risks and benefits of this approach in patient subgroups and noted that current data are inconclusive on the effectiveness of accelerated partial-breast irradiation compared with whole-breast irradiation.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network (NCCN) guidelines (v.2.2024)[4,] on breast cancer state that "APBI/PBI [accelerated partial breast irradiation / partial breast irradiation] offers comparable local control to WBRT [whole breast radiotherapy] in selected low-risk patients with early-stage breast cancer. However, the optimal external beam-APBI/PBI technique/fractionation for minimizing long-term cosmesis effects has not been determined. Patients are encouraged to participate in clinical trials. The NCCN Panel recommends APBI/PBI for any patient who is BRCA negative and meets the 2016 ASTRO criteria" (see Table 10 below)." The NCCN guideline has not been updated to reflect the 2023 ASTRO criteria.

For whole-breast radiotherapy, the NCCN recommends a hypofractionated dose of 40 to 42.5 Gy in 15 to 16 fractions, and in selected cases, 46 to 50 Gy in 23 to 25 fractions. Ultra-hypofractionated whole-breast radiotherapy of 28.5 Gy delivered as 5 once-weekly fractions may be considered in select patients aged >50 years following breast-conserving surgery with pTis/T1/T2/N0 based on data from the FAST-Forward trial. A boost to the tumor bed is recommended in patients at higher risk of recurrence, typically delivered as 10 to 16 Gy in 4 to 8 fractions.

American Society for Radiation Oncology et al
The American Society for Radiation Oncology (ASTRO, 2023), American Society of Breast Surgeons (2018), and the American Brachytherapy Society (2018) have issued various consensus statements for the selection of patients for APBI (summarized in Table 10). [64,65,66,] Recommendations were based on systematic reviews, which are not described in detail, and expert opinion.

Table 10. Professional Medical Society Criteria for Performing Accelerated Partial-Breast Irradiation

Factor	ASTRO "Suitable" (2016)	ASTRO "Cautionary" (2016)	ASTRO "Unsuitable" (2016)	ASTRO Recommended (2023)	ASTRO Conditionally Recommended (2023)	ASTRO Conditionally Not Recommended (2023)	ASTRO Not Recommended (2023)	ASBS	ABS
Patient factors									
Age	≥50 y	40 to 49 y; ≥50 y if	<40 y; 40 to 49 y and do	≥40 y	NR	NR	<40 y	≥45 y for all	≥45 y

Factor	ASTRO "Suitable" (2016)	ASTRO "Cautionary" (2016)	ASTRO "Unsuitable" (2016)	ASTRO Recommended (2023)	ASTRO Conditionally Recommended (2023)	ASTRO Conditionally Not Recommended (2023)	ASTRO Not Recommended (2023)	ASBS	ABS
		patient has at least 1 of the pathologic factors and does not have any "unsuitable" factors	not meet the criteria for cautionary					tumor types	
BRCA1 and *BRCA2* variants	Not present	NR	Present	NR	NR	NR	Present	Patients should not be treated if they have a *BRCA* genetic mutation	NR
Pathologic factors									
Tumor size	≤2 cm	2.1 to 3.0 cm	>3 cm	≤2 cm	>2 to ≤3 cm	NR	NR	≤3 cm	≤3 cm
Tumor stage	Tis or T1	T0 or T2	T3-4	NR	NR	NR	NR	Tis, T1, T2 (≤3 cm)	
Margins	Negative ≥2 mm	Close (<2 mm)	Positive	NR	NR	NR	Positive	No tumor on ink for invasive tumors or tumors involved with DCIS; ≥2 mm for DCIS	Negative (no tumor on ink for invasive ≥2 mm for

Factor	ASTRO "Suitable" (2016)	ASTRO "Cautionary" (2016)	ASTRO "Unsuitable" (2016)	ASTRO Recommended (2023)	ASTRO Conditionally Recommended (2023)	ASTRO Conditionally Not Recommended (2023)	ASTRO Not Recommended (2023)	ASBS	ABS
									DCIS)
Grade	Any	NR	NR	1 or 2	3	NR	NR	NR	NR
LVSI	No	Limited/focal	Extensive	NR	NR	Yes	NR	Allowed as long as it is focal	Not present
ER status	Positive	Negative	NR	Positive	Negative	*HER2* positive and not receiving anti-*HER2* therapy	NR	Positive or negative	Positive or negative
Multicentricity	Unicentric	NR	Present	NR	NR	NR	NR	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	NR	NR	Multifocal disease is allowed as long as the combined area of tumor is ≤3 cm	NR
Histology	Invasive ductal or other favorable subtypes	Invasive lobular	NR	Invasive	Invasive	Invasive lobular	NR	All invasive subtypes; DCIS	All invasive subtypes and DCIS

Factor	ASTRO "Suitable" (2016)	ASTRO "Cautionary" (2016)	ASTRO "Unsuitable" (2016)	ASTRO Recommended (2023)	ASTRO Conditionally Recommended (2023)	ASTRO Conditionally Not Recommended (2023)	ASTRO Not Recommended (2023)	ASBS	ABS
Pure DCIS	Not allowed[a]	≤3 cm if "suitable" criteria not fully met	>3 cm	NR	NR	NR	NR	≤3 cm	≤3 cm
EIC	Not allowed	≤3 cm	>3 cm	NR	NR	NR	NR	NR	NR
Associated LCIS	Allowed	NR	NR	NR	NR	NR	NR	NR	NR
Nodal factors				NR	NR	NR	NR		
Nodal stage/status	pN0 (i^-, i^+)	NR	pN1, pN2, pN3	NR	NR	NR	Positive	Negative	Negative
Nodal surgery	SNB, ALND	NR	None performed	NR	NR	NR	NR	NR	NR
Treatment factors									
Neoadjuvant therapy	Not allowed	NR	If used	NR	NR	NR	NR	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.
[a] Allowed if screen-detected, low to intermediate nuclear grade, ≤2.5 cm size, and resected with margins negative at ≥3 mm.

The ASTRO (2018) updated its guidelines on fractionation for whole-breast irradiation.[67,] The consensus-based guidelines conclude that AWBI 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 11.

Table 11. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
WBI versus APBI with or without tumor bed boost			
NCT04669873	Clinical Trial, Randomized, Open Label, With an Active Comparator to Assess the Efficacy and Safety of Using Accelerated Partial Irradiation Versus Standard or Hypofractionated Irradiation of the Entire Breast in Patients With Initial Breast Cancer After Conservative Surgery (LAPIDARY)	36	Dec 2026
NCT00470236	Radiation Doses and Fractionation Schedules in Non-low Risk Ductal Carcinoma In Situ (DCIS) of the Breast (TROG)	1608	Jun 2024
Intraoperative Radiotherapy			
NCT06375798	Clinical Study of Breast Conserving Surgery Combined With Intraoperative Radiotherapy for Early Breast Cancer	620	Nov 2026
NCT03838419	Intraoperative Electron Radiotherapy for Low-risk Early Breast Cancer (COSMOPOLITAN)	202	May 2030
NCT01644669[a]	Safety and Efficacy Study of the Xoft® Axxent® eBx™ IORT System	1200	Dec 2029
External-beam APBI			
NCT06185205	Accelerated Super-Hypofractionated Breast Brachytherapy - ASHBY Trial	60	Jan 2033
NCT01247233	Standard or Hypofractionated Radiotherapy Versus Accelerated Partial Breast Irradiation (APBI) for Breast Cancer (SHARE)	1006	Oct 2025
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
APBI (multimodality)			
NCT05914831	Ultra-hypofractionated for Whole Breast Irradiation (WBI) Compared to Partial Breast Irradiation (PBI): A Single-Institution Prospective Phase 2 Trial	100	May 2033
NCT00892814	Partial Breast Versus Whole Breast Irradiation in Elderly Women Operated on for Early Breast Cancer	882	Mar 2026

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01185145	Accelerated Partial Breast Radiotherapy With Either Mammosite or Intensity Modulated Radiotherapy (APBI)	291	Aug 2024
NCT05472792	Comparison of Adjuvant Monotherapy With Endocrine Therapy or Accelerated Partial Breast Irradiation Following Lumpectomy for Low Risk Breast Cancer Patients Over 65 (CAMERAN) (CAMERAN)	90	May 2032
NCT00185744	Accelerated Partial Breast Irradiation Following Lumpectomy for Breast Cancer	400	Mar 2029
NCT04852887	A Phase III Clinical Trial Evaluating De-Escalation of Breast Radiation for Conservative Treatment of Stage I, Hormone Sensitive, HER-2 Negative, Oncotype Recurrence Score Less Than or Equal to 18 Breast Cancer	1670	Jul 2041

[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
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
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)

CPT/HCPCS	
77318	Brachytherapy isodose plan; complex (calculation[s] made from over 10 sources, or remote afterloading brachytherapy, over 12 channels), includes basic dosimetry calculation(s)
77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
77385	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
77386	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
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

REVISIONS	
06-29-2010	In Coding Section: ▪ Updated wording for the following CPT Codes: 19296, 19297. ▪ Added CPT Codes: 77785, 77786, 77787 (effective 01/01/09).
05-27-2013	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".
	Updated the Description section.
	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:

REVISIONS	
	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 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."
	Updated the Rationale section.
	Updated the Reference section.
12-11-2013	In Coding section: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*
05-28-2015	Updated Description section.
	In Policy section: ▪ In Item B, added "involving treatment of early stage breast cancer after breast-conserving surgery," to read "Accelerated whole breast irradiation is considered experimental/investigational in all other situations involving treatment of early stage breast cancer after breast-conserving surgery." ▪ In Item D, added "balloon APBI" and "noninvasive brachytherapy using Accuboost®," to read, "Accelerated partial breast irradiation (APBI), including interstitial APBI, balloon APBI, external beam APBI, noninvasive brachytherapy using Accuboost®, and intra-operative APBI, is considered experimental/investigational." ▪ Added Item E, "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 experimental/investigational." ▪ Added Policy Guidelines, "Electronic brachytherapy is considered a type of balloon brachytherapy that can be used to deliver APBI."
	Updated Rationale section.
	In Coding section: ▪ Added HCPCS code 0182T. ▪ Updated ICD-10 effective date to October 1, 2015.
	Updated References section.
01-01-2016	In Coding section: ▪ Added CPT codes 77770, 77771, 77772, and 0395T. ▪ Removed CPT codes 77785, 77786, 77787, 0182T.
11-24-2017	Updated Description section.
	In Policy section: ▪ In Item A 1, removed "Exclude disease involving the margins of excision; tumors >5 cm in diameter; breast width >25 cm at posterior border of medial and lateral tangential beams" to read, "Invasive carcinoma of the breast." ▪ Removed Item A 2, "Negative lymph nodes." ▪ 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, i.e., no ink on tumor on invasive carcinoma or ductal carcinoma in situ" ▪ Added new Item A 3, "Age at least 50 years old." ▪ 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)." ▪ Added new Policy Guidelines 2 and 3.
	Updated Rationale section.

REVISIONS	
	In Coding section: ▪ Added coding bullets.
	Updated References section.
01-01-2018	In Coding section: ▪ Added CPT code: 19294. ▪ Removed ICD-9 codes.
10-12-2018	Updated Description section.
	In Policy Guidelines: ▪ 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)."
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes: 77261, 77262, 77263, 77280, 77285, 77290, 77293, 77295, 77299, 77316, 77317, 77318, 77778. ▪ Added HCPCS codes: C1717, C9726, Q3001.
	Updated References section.
02-01-2021	Updated Description section
	Updated Rationale section
	Updated Reference section
09-17-2021	Updated Description section
	Updated Rationale section
	Updated Reference section
11-22-2022	Updated Description Section
	Updated Policy Section ▪ Section A1 Added "and accelerated partial breast irradiation(APBI) with external beam radiation, including IMRT" to statement ▪ Section A1c changed age from 50 to 40. "Age at least 40 years old" ▪ Section C Removed: "external beam APBI" now reads "Interstitial APBI, balloon APBI, intra-operative APBI, and noninvasive brachytherapy using Accuboost® is considered experimental / investigational."
	Updated Policy Guideline Section ▪ Section B Added "in a joint 2014 consensus guideline" and removed hyperlink "(http://www.redjournal.org/article/S0360-3016(13)03315-4/pdf)."
	Updated Rationale Section
	Updated Coding Section ▪ Removed Coding Bullets o There are CPT codes for placement of radiotherapy after loading catheters: 19296, 19297, 19298. o Specific CPT radiology codes exist for application of brachytherapy radiation sources: 77770, 77771, 77772. o There is a CPT category III code specific to high-dose electronic brachytherapy: 0395T. ▪ Removed 77299 ▪ Added C79.81 ▪ Converted ICD-10 codes to range (C50.011-C50.929) to include all codes within range
	Updated References Section
09-12-2023	Updated Description Section

REVISIONS	
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Codes
	Updated Reference Section
08-27-2024	Updated Description Section
	Updated Policy Section ▪ Section A2: Added "and accelerated partial breast irradiation (APBI) with external beam radiation, including IMRT" to Accelerated whole breast irradiation (AWBI) is considered experimental / investigational in all other situations involving treatment of early stage breast cancer after breast-conserving surgery.
	Updated Rationale Section
	Updated Coding Section ▪ Added 77338, 77385, and 77386
	Updated Reference Section

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