Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Accelerated Breast Irradiation after Breast-Conserving Surgery for Early Stage Breast Cancer and Breast Brachytherapy as Boost with Whole-Breast Irradiation

Description/Background

Radiotherapy is the standard care for patients with breast cancer undergoing breast-conserving surgery (BCS), as it reduces recurrences and lengthens survival. The conventional radiation therapy regimen consists of approximately 25 treatments of 2 Gray (Gy; a measure of absorbed radiation dose) delivered over 5 to 6 weeks. Nonetheless, not all patients undergo radiation therapy following BCS; the duration and logistics of treatment may be barriers for some women. Accelerated radiotherapy approaches have been proposed to make the regimen less burdensome for patients with early-stage breast cancer at low risk of recurrence:

- *Accelerated* (also called hypofractionated) *whole-breast irradiation (AWBI)* reduces the number of fractions and the duration of treatment to about 3 weeks.
- *Accelerated partial-breast irradiation (APBI)* irradiates 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.

BREAST CANCER

Current estimates suggest that over 281,550 new cases of breast cancer of any stage will occur in the United States in 2021. Based on adjusted data from 2014 to 2018, among women, the number of new cases is 128.5 per 100,000 and the number of deaths 20.1 per 100,000.[1]

Breast Conservation Therapy

For patients diagnosed with stage I or II breast tumors, survival after breast-conservation therapy (BCT) is equivalent to survival after mastectomy. BCT is a multimodality treatment that consists of BCS to excise the tumor with adequate margins, followed by whole-breast external-beam radiotherapy (EBRT) administered as 5 daily fractions per week over 5 to 6 weeks. Local boost irradiation to the tumor bed often is added to whole-breast irradiation to provide a higher dose of radiation at the site where recurrence most frequently occurs. For some patients, BCT

also includes axillary lymph node dissection, sentinel lymph node biopsy, or irradiation of the axilla. A number of randomized, controlled trials have demonstrated that the addition of radiotherapy after BCS reduces recurrences and mortality. In an expanded update of an individual-level meta-analysis, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported that radiotherapy halved the annual recurrence rate after 10 years for women with node-negative disease (n=7287), from 31.0% for those not receiving radiotherapy to 15.6% for those receiving it.[2] It also reduced the 15-year risk of breast cancer death from 20.5% to 17.2% (p=0.005). For women with node-positive disease (n=1050), radiotherapy reduced the 1-year recurrence risk from 26.0% to 5.1%. Radiotherapy also reduced the 15-year risk of breast cancer death from 51.3% to 42.8% (p=0.01).

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

Controversy continues on the length of follow-up needed to determine whether APBI is equivalent to WBI (see the 2013 TEC Assessment on accelerated radiotherapy after BCS for early stage breast cancer for details).[5] Because recurrences are relatively rare among low-risk early breast cancer patients, it may take considerable time for there to be enough recurrences to achieve sufficient power to compare 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[6-8] For accelerated whole-breast irradiation (AWBI), some 10-year data are available. However, for newer approaches, the issue may be resolved by statistical issues rather than biological ones.

Currently, most patients diagnosed with stage I or II breast cancer now are offered a choice of BCT or modified radical mastectomy, but BCT is selected less often than expected. Studies have shown that those living furthest from treatment facilities are least likely to select BCT instead of mastectomy and most likely to forgo radiation therapy after BCS.[9-11]

Approaches to Radiotherapy Following Breast-Conservation Treatment

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

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

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

Radiation Type	Accelerated?	Whole or Partial Breast	EBRT or Brachytherapy	Treatment Duration	Published RCTs	Length of Follow-Up
Conventional WBI	No	Whole	EBRT	5-6 wk	Multiple	>15 y
Accelerated WBI	Yes	Whole	EBRT	3 wk	4	10 y
Interstitial APBI[b]	Yes	Partial	Brachytherapy	1 wk	2	5.4 y

Balloon APBI[c]	Yes	Partial	Brachytherapy	1 wk	0	0
EBRT APBI[d]	Yes	Partial	EBRT	1 wk	5	20y
Intraoperative APBI[e]	Yes	Partial	Not applicable	1 d	1	5 y

APBI: accelerated partial-breast irradiation; EBRT: external-beam radiotherapy; RCT: randomized controlled trial; WBI: whole-breast irradiation.
[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 after-loading 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 after-loader to irradiate the targeted area. Some brachytherapy systems combine aspects of interstitial and balloon brachytherapy.
[d] External-beam APBI is delivered in the same way as conventional or accelerated whole-breast radiotherapy but to a smaller area. All three external-beam regimens can use 3-dimensional conformal radiotherapy or intensity-modulated radiotherapy.
[e] Intraoperative APBI is performed during breast-conserving surgery with a single dose of radiation delivered to the exposed tumor bed.

Regulatory Status:

In 2002, the MammoSite® Radiation Therapy System (Proxima Therapeutics; Alpharetta, GA), the first device specifically designed for breast brachytherapy,[11] 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.’’[12]

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

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

Medical Policy Statement

Following breast-conserving surgery (BCS) for early stage breast cancer:

- Accelerated whole breast irradiation, (AWBI) and interstitial or balloon brachytherapy may be considered **established** for patients who meet inclusionary guidelines. These procedures are useful therapeutic options for patients meeting selection criteria.
- Accelerated whole breast irradiation (AWBI) is considered **experimental/investigational** in all other situations involving treatment of early stage breast cancer after BCS.

- Interstitial or balloon brachytherapy may be considered **established** for patients undergoing initial treatment for stage I or II breast cancer when used as local boost irradiation in those who are also treated with BCS and whole-breast external-beam radiotherapy.
- Accelerated partial breast irradiation (APBI) and intra-operative APBI, is established when meeting ASTRO guidelines.
- 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**.

Local boost irradiation when combined with whole-breast radiotherapy but *without* surgical excision is considered **experimental/investigational**. There is a lack of published data to validate the efficacy of brachytherapy without surgical excision of the tumor.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:

Following breast-conserving surgery for early stage breast cancer:

- Accelerated whole breast irradiation (AWBI) may be considered appropriate for both I and II stages of breast cancer.
- Accelerated partial breast irradiation (APBI) may be considered appropriate when all of the following criteria are met:
    - Age 45 or greater for invasive breast cancer and greater than age 50 for DCIS
    - Tumor less than or equal to 3 cm with pathologically negative surgical margins
    - Lymph nodes are negative show only immune histochemical involvement.
- Intraoperative radiation therapy is appropriate when all the following criteria are met:
    - Age 50 or greater
    - Tumor equal to or less than 3 cm with grossly uninvolved surgical margins
    - Lymph nodes are grossly negative and negative on intraoperative frozen section if performed.
- Interstitial or balloon brachytherapy may be considered **established** for patients undergoing initial treatment for stage I or II breast cancer when used as local boost irradiation in patients who are also treated with breast-conserving surgery and whole-breast external-beam radiotherapy.

Table 2. Stages of Breast Cancer (American Cancer Society)

Stage	Category	Description
0	Tis, NO, MO	• This is ductal carcinoma in situ (DCIS), a pre-cancer of the breast. Many consider DCIS the earliest form of breast cancer. In DCIS, cancer cells are still within a duct and have not yet invaded deeper into the surrounding fatty breast tissue. • Paget disease of the nipple (without an underlying tumor mass) is also stage 0. • In all cases the cancer has not spread to lymph nodes or distant sites.
1A	T1, NO, MO	The tumor is 2 cm (about ¾ of an inch) or less across (T1) and has not

		spread to lymph nodes (NO) or distant sites (MO).
IIA	T0 or T1, N1 (but not N1mi), MO	• The tumor is 2 cm or less across (or is not found) (T1 or T0) and either: ✓ It has spread to 1 to 3 axillary lymph nodes, with the cancer in the lymph nodes larger than 2 mm across (N1a), or ✓ It has spread to 1 to 3 axillary lymph nodes and to internal mammary lymph nodes (found on sentinel lymph node biopsy) (N1c). • The cancer has not spread to distant sites (MO).
1B	T0 or T1, N1mi, MO	• The tumor is 2 cm or less across (or is not found) (T0 or T1) with micrometastases in 1 to 3 axillary lymph nodes (the cancer in the underarm lymph nodes is greater than 0.2 mm across and/or more than 200 cells but is not larger than 2 mm) (N1mi). • The cancer has not spread to distant sites (MO).
IIB	T2, N1, MO	• The tumor is larger than 2 cm but no larger than 5 cm; small groups of breast cancer cells—larger than 0.2 mm but not larger than 2 mm—are found in the lymph nodes, or
		• The tumor is larger than 2 cm but no larger than 5 cm; cancer has spread to 1 to 3 axillary lymph nodes near the breastbone, or
	T3, NO, MO	• The tumor is larger than 5 cm but has not spread to the axillary lymph nodes.
IIIA	T0 to T2, N2, MO	• The tumor is not more than 5 cm across (or cannot be found). It has spread to 4 to 9 axillary lymph nodes, or it has enlarged the internal mammary lymph nodes. The cancer hasn't spread to distant sites
	T3, N1 or N2, MO	• The tumor is larger than 5 cm across but does not grow into the chest wall or skin. It has spread to 1 to 9 axillary nodes, or to internal mammary nodes. The cancer hasn't spread to distant sites.
IIIB	T4, NO to N2, MO	• The tumor has grown into the chest wall or skin and one of the following applies: ✓ It has not spread to the lymph node ✓ It has spread to 1 to 3 axillary lymph nodes and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy ✓ It has spread to 4 to 9 axillary lymph nodes, or it has enlarged the internal mammary lymph nodes. • The cancer hasn't spread to distant sites. • Inflammatory breast cancer is classified as T4d and is at least stage IIIB. If it has spread to many nearby lymph nodes it could be stage IIIC, and if it has spread to distant lymph nodes or organs it would be stage IV.
IIIC	Any T, N3, MO	• The tumor is any size (or can't be found), and one of the following applies: ✓ Cancer has spread to 10 or more axillary lymph nodes. ✓ Cancer has spread to the lymph nodes under the collar bone. ✓ Cancer has spread to the lymph nodes above the collar bone. ✓ Cancer involves axillary lymph nodes and has enlarged the internal mammary lymph nodes. ✓ Cancer has spread to 4 or more axillary lymph nodes, and tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy • The cancer hasn't spread to distant sites.
IV	Any T, any N, M1	• The cancer can be any size and may or may not have spread nearby lymph nodes. • It has spread to distant organs or to lymph nodes far from the breast. • The most common sites of spread are the bones, liver, brain, or lungs.

Exclusions:

- Accelerated whole breast irradiation for patients not meeting the above inclusions.
- Interstitial or balloon brachytherapy in all other situations not specified under the inclusions.
- 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.
- Local boost irradiation when combined with whole-breast radiotherapy but *without* surgical excision.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

19294	19296	19297	19298	77261	77262
77263	77280	77285	77290	77295	77316
77317	77318	77778			

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

This policy, which addresses accelerated breast irradiation following breast-conserving surgery (BCS) for early stage breast cancer, is based on several TEC Assessments, the most recent of which was released in 2013.[5]

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse

events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

ACCELERATED WHOLE-BREAST IRRADIATION

Clinical Context and Therapy Purpose

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

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

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

Populations

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

Interventions

The therapy being considered is AWBI after BCS. AWBI provides the same dose to the whole breast in a shorter time than 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.

AWBI is administered in an outpatient oncology setting.

Comparators

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

Outcomes

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

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

Study Selection Criteria

To assess efficacy outcomes, we included comparative controlled prospective trials, with a preference for randomized controlled trials (RCTs) and systematic reviews of RCTs.

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

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

Systematic Reviews

A number of randomized controlled trials (RCTs) have compared accelerated whole-breast radiotherapy (also referred to as accelerated whole-breast irradiation [AWBI]) to 5-week whole-breast radiotherapy. A systematic review and meta-analysis by Valle et al (2017) included 13 trials (total n=8189 patients) published prior to October 2014 that compared AWBI with standard fractionation.[15] 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).[16-18]

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.[16-18] Both trials used noninferiority margins of 5 percentage points for local or locoregional recurrence in the accelerated group at 5 (1-sided α=0.025[16] or 0.05[17]) or 10 years (1-sided α=0.025[18]). 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 (Standardizations of Breast Radiotherapy [START] B; 2008), from the U.K., included women with stage I, II, or III tumors (N=2215) who had clear tumor margins (≥1 mm).[16] Approximately 75% of the women have negative lymph nodes, and approximately 42% had a radiation boost to the tumor bed. Randomization was stratified for hospital, type of surgery (8% underwent mastectomy), and plans for tumor bed boost. Systemic therapy, primarily tamoxifen, was used by some patients and appears to be fairly evenly distributed across treatment groups. Treatment arms compared a total dose of 40 Gy in 15 fractions over 3 weeks to 50 Gy in 25 fractions over 5 weeks. The primary efficacy outcome was locoregional relapse (relapse in ipsilateral breast or chest wall and or in ipsilateral axilla or supraclavicular fossa if previously irradiated) at 5 years. At median follow-up of 6.0 years (interquartile range [IQR], 5.0-6.2), estimated 5-year locoregional tumor relapse rate was 2.2% (95% confidence interval [CI], 1.3% to 3.1%) in the 40 Gy group and 3.3% (95% CI, 2.2% to 4.5%) in the 50 Gy group, for an absolute difference of -0.7% (95% CI, -1.7% to 0.9%). Hazard ratios (HRs) for 40 Gy accelerated whole-breast radiotherapy versus conventional whole-breast radiotherapy were not statistically significant (using the log-rank test) for local or local-regional relapse. There were statistically significant differences between the 2 treatment regimens for distant relapse and overall survival (OS), with relapse less frequent and survival longer for the 40 Gy accelerated whole-breast irradiation (AWBI) group. This unexpected difference between treatment arms began to appear at about 1 year; trial authors speculated that the difference may have been due to chance and may have changed with 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 patient- reported breast, arm, and shoulder symptoms, as well as body

image, over 5 years of follow-up.[19] There was no evidence that providing radiotherapy in fewer, larger fractions increased the incidence of these adverse events or adversely affected body image. Haviland et al (2013) reported 10-year relapse, survival, and adverse event outcomes (median follow-up, 9.9 years [IQR, 7.5-10.1 years]).[20] Locoregional relapse did not differ significantly between the 2 treatment groups: 4.3% (95% CI, 3.2 to 5.9) for the AWBI group and 5.5% (95% CI, 4.2 to 7.2) for the standard whole-breast radiotherapy group (HR=0.77 [95% CI,0.51 to 1.16]; p=0.21). However, breast shrinkage, telangiectasia, and breast edema were significantly less common in the AWBI group. These effects were assessed by physician, photographic comparison with baseline, and patient report. Distant relapse (p=0.014), any breast-cancer-related event (local, regional, or distant relapse, breast cancer death, contralateral breast cancer; p=0.022), and all-cause mortality (p=0.042) were significantly less common in the AWBI group.

The second RCT assessing a 5- and 3-week radiotherapy regimen, from Canada, compared AWBI versus whole-breast irradiation (WBI) in women with lymph node–negative stage I, II, or III tumors.[17,18] Treatment arms included a hypofractionated ration group (n=622), who were treated with a total dose of 42.5 Gy in 16 fractions over 3 weeks, and a standard irradiation group (n=612), who were treated with 50 Gy in 25 fractions over 5 weeks without boost radiation. Five-year local recurrence-free survival was 97.2% in the accelerated arm and 96.8% in the conventional arm (absolute difference: 0.4% [95% CI, -1.5% to 2.4%). Ten-year local recurrence was 6.7% for the conventional arm and 6.7% for the conventional arm (absolute difference: -0.5% [95% CI, -2.5% to 3.5%). At 5 or 10 years, local recurrence rates with AWBI were no worse than conventional WBI, when applying a noninferiority margin of 5%. In prespecified subgroup analyses, treatment effects were similar by age, tumor size, estrogen-receptor status, and chemotherapy use (48% had no systemic therapy).

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

In 2020, Brunt et al published 10 year results of the FASTer radiotherapy for breast radiotherapy (FAST) trial.[22] This multicenter, phase III, RCT enrolled 915 women ≥50 years of age with low-risk invasive breast carcinoma who had undergone BCS 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, 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<0.001), but not significantly different for the 28.5 Gy versus 50 Gy group (1.22; 95% CI, 0.87 to 1.72; p=0.248). 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, non-inferiority, randomized, FAST-Forward trial.[23] This study enrolled 4096 adults with invasive breast carcinoma following complete microscopic excision of the primary tumor by BCS 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=0.0003) but not between 40 and 26 Gy (p=0.17) was observed. These results show that a 1-week course of adjuvant breast radiotherapy delivered in 5 fractions is non-inferior 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 rates were also evaluated in a large 2014 retrospective study of patients with left-sided early-stage breast cancer published by Chan et al.[24,25] The study included 2706 patients who received conventional WBI (n=2221) or (n=485) AWBI. Cardiotoxic chemotherapy regimens were similar between groups. At a median follow-up of 14.2 years, there was no statistical difference in cardiac hospitalization or cardiac mortality, breast cancer mortality, or overall mortality. Results were similar for 2628 patients with right-sided tumors. This study was not designed to capture outcomes of moderate or mild cardiac toxicity.

Section Summary: Accelerated Whole-Breast Irradiation

The overall body of evidence on AWBI compared to conventional whole-breast irradiation has indicated that local recurrence rates with accelerated whole-breast radiotherapy are no worse than conventional WBI, when applying a noninferiority margin of 5%. Canadian and U.K. noninferiority trials have reported 10-year follow-up data. Thus, conclusions apply to patients meeting eligibility criteria of these trials, including having early-stage invasive breast cancer, clear surgical margins, and negative lymph nodes. In addition, consistent with national guidelines, these conclusions apply to tumors greater than 5 cm in diameter and women at least 50 years old. Based on 14-year retrospective data, severe cardiac toxicity with AWBI for left-sided breast cancers may not be increased compared with conventional WBI. Additionally, recent data imply that even more accelerated WBI scheduling may be non-inferior to standard 3- or 5-week schedules.

ACCELERATED PARTIAL-BREAST IRRADIATION

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

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

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

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

Interventions
The therapies being considered are interstitial brachytherapy alone, intraoperative brachytherapy alone, and external-beam APBI. 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 intraoperative radiotherapy) rather than 5 to 6 weeks, because radiation is delivered to the tumor bed in fewer fractions at larger doses per fraction. Third, 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).

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

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

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

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

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

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

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

Systematic Reviews

A number of RCTs and nonrandomized comparative studies have evaluated interstitial, external-beam, or intraoperative APBI compared with conventional WBI. Several meta-analyses have evaluated evidence on APBI, with various methods grouped in the same review.[26-30] Conclusions cannot be drawn from these meta-analyses because methods varied and were not evaluated individually. The review authors were consistent in concluding that additional data from RCTs are needed. In 2020, Viani et al published a systematic review and update meta-analysis of partial- versus whole-breast radiotherapy for early breast cancer that included a subgroup analysis assessing the potential effectiveness of APBI technique - intraoperative radiotherapy (IORT), brachytherapy, or EBRT.[31] Results revealed no significant difference in local recurrence with APBI and WBI when using brachytherapy (p=0.051), EBRT (p=0.25), or mixed techniques (p=0.89) at 5 years; however, a significant increase in local recurrence was noted with IORT use (p=0.014). 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.[32] 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.[33-35] The primary study end point was the first incidence of local ipsilateral breast cancer recurrence within the 5-year observation period and the noninferiority margin was a 3% difference. At 5 years, the associated cumulative incidence of local recurrence was 0.92% (95% CI, 0.12% to 1.73%) in the conventional WBI group and 1.44% (95% CI, 0.51% to 2.38%) in the APBI group (Table 3). The difference between groups was within the noninferiority margin. There was no grade 4 skin toxicity. Grade 2 and 3 skin toxicity was 10.7% with WBI and 6.9% with APBI (p=0.02).

Table 2. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
GEC-ESTRO[33-35]	EU	16	2004-2009	1328 patients ≥40 y with BCS for stage 0-IIa breast cancer, lesions ≤3 cm in diameter, clear margins ≥2 mm in any direction, and no lymph or blood vessel invasion	655 patients given APBI using interstitial brachytherapy	673 patients given WBI at 50 Gy in daily fractions of 1.8-2.0 Gy over 5 wk

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

Table 3. Summary of Key RCT Results

Study	Local Recurrence, n (%)	Overall Survival	Grade 2 to 3 Late Skin Toxicity	Excellent-to-Good Cosmetic Results, n (%)	Global Health Status (SD)
GEC-ESTRO[33-35]					
n	1184	1184	1184	1007	537
WBI	5 (0.92)	95.5%	5.7%	408 (90)	66.0 (21.8)
APBI	9 (1.44)	97.27%	3.2%	503 (93)	66.2 (22.2)
Diff (95% CI)	0.52% (-0.72% to 1.75%)	1.72% (-0.44% to 3.88%)			-0.2 (-4.0 to 3.6)
p	*NS*	0.11	0.080	0.12	0.94

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

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

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
GEC-ESTRO[33-35]				1. Overall survival was not a primary outcome	1. Only followed for 5 y

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

Table 5. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
GEC-ESTRO[33-35]		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 limitations 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

Ajkay et al (2015) reported retrospectively on 5-year adverse events in patients with early-stage breast cancer treated at a single center.[36] Of 417 patients who received BCS and radiotherapy, 271 received brachytherapy (34 Gy in 10 fractions; 90% MammoSite, 9% Contura, 1% strut-adjusted volume implant) and 146 received WBI using 3-dimensional conformal radiotherapy (45-50.4 Gy in 25-28 fractions with 10-16 Gy boost). Median follow-up was 4.8 years in the brachytherapy group and 4.1 years in the WBI group. The estimated 5-year overall incidence of any adverse event was greater in the brachytherapy group (72%) than in the WBI group (52%; p<0.001). For prespecified adverse events of interest, estimated 5-year incidences of infectious skin complications, abscess, telangiectasia, and breast pain were similar between groups. Estimated 5-year incidences of seroma (47% vs. 19%, p<0.001) and fat necrosis (40% vs. 24%, p<0.001) were greater in the brachytherapy group, respectively.

Section Summary: Interstitial Brachytherapy

The 2015 GEC-ESTRO RCT reported 5-year follow-up data and found that interstitial brachytherapy was noninferior to WBI on rates of local breast cancer recurrence, when applying a noninferiority margin of 3%. Ten-year follow-up data are needed and at least 1 additional trial confirming these findings.

Intraoperative Brachytherapy

Randomized Controlled Trials

One RCT, reported by Vaidya et al (2010, 2014) compared intraoperative radiotherapy (IORT) with WBI in 2232 women.[37-38] Radiotherapy was delivered to the tumor bed using the Intrabeam® device, which provides a point source of 50 kV energy x-rays at the center of a spherical applicator, for 20 to 45 minutes. It was specifically developed for IORT. The TARGIT-A (Risk-adapted Targeted Intraoperative Radiotherapy) trial was a noninferiority trial with 28 centers in 9 countries and a sample size of 3451. (In 2010, the trial was extended for 2 more years to allow accrual in sub-protocols.) An ITT approach was used. Patients were not blinded to treatment choice. As anticipated in advance, 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. The most recent article reported 5-year results, defined as results for patients with 5-years of follow-up or “if they were seen the year before database lock.”[38] Median follow-up for all patients was 2 years and 5 months (IQR, 12-52 months), and 1222 patients (35%) had a median follow-up of 5 years. Estimated 5-year risks for ipsilateral local recurrence were 3.3% (95% CI, 2.1 to 5.1) in the TARGIT group and 1.3% (95% CI, 0.7 to 2.5; p=0.042) in the whole-breast radiotherapy group. Mortality was similar between the 2 groups (2.6% TARGIT vs. 1.9%; p=0.56). However, there were significantly fewer non-breast cancer deaths in the TARGIT group than in the whole-breast radiotherapy group (1.4% [95% CI, 0.8 to 2.5] vs. 3.5% [95% CI, 2.3 to 5.2]; p<0.001), with fewer deaths from cardiovascular causes and other cancers in the TARGIT group. In the group that received IORT plus whole-breast radiotherapy, the mortality rate was higher at 8% (95% CI, 3.7 to 17.5), but the percentage of women with local recurrences (0.9%; 95% CI, 0.1 to 6.1) was similar to those who received only IORT. Noninferiority was established for the whole intraoperative cohort and for those who received IORT alone, but not for those patients who underwent both types of radiotherapy. There was no significant difference between the IORT and WBI groups in predefined 6-month wound-related complications. However, grade 3 or 4 radiotherapy-related skin complications were more common in the WBI group (13/1730 vs. 4/1731; p=0.029). 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."[39]

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.[40] 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 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 overall survival. 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.[41] The 2013 ELIOT trial compared IORT plus ELIOT to WBI.[42] With a sample size of 1305 patients and median follow-up of 5.8 years (IQR, 4.1-7.7 years), 35 (4.4%) patients in the intraoperative group and 4 (0.4%) patients in the WBI group developed ipsilateral breast tumor recurrences (HR=9.3; 95% CI, 3.3 to 26.3; p<0.001). There was no statistically significant difference in 5-year OS. For women with data on adverse skin events (IORT=464, WBI=412), there were significantly fewer events among women who received IORT (p<0.001). This was an equivalence trial with a prespecified limit of 7.5% for local recurrence in the IORT group only. Therefore, although the criterion for equivalence was satisfied, ipsilateral breast recurrence rate was significantly higher in the IORT group. A subsequent review of the ELIOT trial noted that, of 69 women who had 4 or more positive lymph nodes, those randomized to

WBI (n=38) received concurrent axillary radiation; for those randomized to ELIOT (n=31), axillary irradiation was delayed 6 to 12 weeks.[9] These reviewers also characterized ELIOT data as “still early” 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.[46.] 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 Brachytherapy
Several RCTs have been published, but they have not demonstrated that outcomes after intraoperative brachytherapy are noninferior to WBI. Five-year results from the TARGIT-A RCT showed increased ipsilateral local recurrence with APBI compared with whole-breast radiotherapy. In a parallel study to TARGIT-A, delayed IORT was also associated with an increase in local recurrence rates at 5 years as compared to EBRT. In another RCT that used a different technology (ELIOT), recurrence rate with IORT was statistically greater than that with WBI.

External-Beam APBI

Randomized Controlled Trials
Rodriguez et al (2013), reported on 102 patients were randomized to WBI, with or without a boost to the tumor bed, or APBI.[47] The primary end point was local recurrence within 5 years. In this noninferiority trial, the sample size was calculated to detect a 10% difference between treatment arms, with a power of 80% and a significance level of 0.05. The APBI group was significantly younger than the WBI group (mean age [SD], 67.1 years vs. 70.1 years; p=0.009). After a median follow-up of 5 years, there were no recurrences in either group, nor was there a statistically significant difference in survival. Investigators noted that the sample size may have been insufficient to detect a true difference in local control. Ninety percent (46/51) of APBI patients had acute skin effects, mostly grade 1; all patients in the WBI group had acute skin effects, and most were grade 2. Grade 1 and 2 late effects were reported with some changes in the relative positions of the treatment groups over time. Li et al (2021) reported long-term results of this trial (median, 10.3 years).[48] 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 RAPID trial (Randomized Trial of Accelerated Partial Breast Irradiation).[49] The sample size was 2135, and median follow-up was 3 years. Most patients were older than 50 years and had estrogen receptor–positive tumors less than 1.5 cm in diameter. An interim article reported on cosmetic and toxicity results. An accelerated regimen was used for WBI, and 21% of these patients received a boost to the tumor bed. APBI patients were more likely than WBI patients to have adverse cosmesis at 3 years, whether reported by physicians (p<0.001), nurses (p<0.001), or patients (p<0.05). As for late toxicities, 1.4% of APBI patients had a grade 3 adverse event versus none of the WBI patients. Telangiectasia and breast induration were more common among APBI patients (p<0.001). 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 published longer term results from RAPID.[50] Results from this analysis revealed similar ipsilateral breast tumor recurrence rates at 8 year between the groups (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.[51] 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=0.057). 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).[52] 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 comparing APBI to WBI after breast-conserving surgery for early-stage breast cancer that enrolled the largest number of patients (n=4216) and provided the longest follow-up reported to date.[53] 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 versus 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=0.02); 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. Tables 6 and 7 detail key characteristics and results of the RCTs in this section.

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.[54] 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.

Table 6. Summary of Key RCT Characteristics-External Beam APBI vs. WBI

Trial	Countries	Sites	Dates	Participants	Interventions	
Polgar et al (2021)[54,]	Hungary	1	1998-2004	Low risk invasive breast carcinoma with negative margins after BCS	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)[53]	U.S., Canada,	154	2005-2013	Over age 18, lumpectomy for stage	APBI: 34 Gy with brachytherapy or	WBI: 50 Gy per day in

	Ireland, Israel			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	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	25 total fractions spread over 5 weeks N=2109
Livi et al (2015)[51] Meattini et al (2020)[52]	Italy	1	2005-2013	Over age 40, maximum tumor size 25mm	APBI: 30 GY to the tumor bed in five daily fractions N=260	WBI: 50 Gy in 25 fractions, followed by a boost on the tumor bed of 10 Gy in five fractions N=260
Olivotto et al (2013)[44] Whelan et al (2019)[45]	Canada, Australia, New Zealand	33	2006-2011	Invasive ductal carcinoma or DCIS treated with BCS 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 4-5 daily fractions after WBI was based on criteria such as young age or close margins N=1065
Rodriguez et al (2013)[43] Li et al (2021)[48]	Spain	1	NR	Invasive ductal carcinoma; age 60 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

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

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

Study	Local Recurrence	Overall Survival	Toxicity
Polgar et al (2021)[54,]	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: 9.4%
WBI	7.9%	59.7%	Skin: 11.8% Fibrosis: 9.4%
Vicini et al (2019)[48]	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)[46]	Ipsilateral tumor recurrence at	Number of deaths at 5	Acute skin toxicity (≥grade

Meattini et al (2020)[52]	5 years	years	2) at 5 years
N	520		520
APBI	1.5%	1	37.7%
WBI	1.4%	7	2%
Olivotto et al (2013)[44] Whelan et al (2019)[45]	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)[43]; Li et al (2021)[49]			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

RCT: randomized controlled trial; APBI: accelerated partial breast irradiation; WBI: whole breast irradiation; Gy: Grays; N: sample size; BCS: breast-conserving surgery; DCIS: ductal carcinoma in situ. CTCAE: Common Terminology Criteria for Adverse Events

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

Table 8. Relevance Limitations-External Beam APBI vs. WBI

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Polgar et al (2021)[54.]		3. 69% of patients received high-dose brachytherapy, 33% of patients received EBRT		3. Not reported	
Vicini et al (2019)[48]	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 ABPI technique (either single-entry or multi-catheter)			
Livi et al (2015)[46]; Meattini et al (2020)[52]				1.Overall survival NR	
Olivotto et al (2013)[44] Whelan et al (2019)[45]				1.Too few events for efficacy analysis of the primary outcome (local recurrence)	
Rodriguez et al					

(2013)[43]; Li et al (2021)[48]						

APBI: accelerated partial breast irradiation; NR: not reported; NCT: national clinical trial; WBI: whole breast irradiation.
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 9. Study Design and Conduct Limitations-External Beam APBI vs. WBI

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Polgar et al (2021)[54.]		1,2	1. Protocol not registered			
Vicini et al (2019)[48]		1,2				
Livi et al (2015)[46]; Meattini et al (2020)[52]						
Olivotto et al (2013)[44] Whelan et al (2019)[45]		1		1.335/2135 (15.7%) completed 5-year assessment		
Rodriguez et al (2013)[43]; Li et al (2021)[48]			1.Protocol not registered	1.Toxicity outcomes reported on 70/102 patients (68.6%)	3.May have been underpowered to detect difference in local recurrence rates	Trial terminated early due to cosmesis benefit

APBI: accelerated partial breast irradiation; NCT: national clinical trial; WBI: whole breast irradiation
The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[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 APBI

RCTs have reported outcomes from 5 to 10 years. Results from the trial with the largest number of patients and longest duration of follow-up 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. Moreover, one of

the trials reported higher rates of adverse cosmetic outcomes and grade 3 toxicities in the external-beam APBI group than in the WBI group.

LOCAL BOOST BRACHYTHERAPY

Clinical Context and Therapy Purpose

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

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

The following **PICOS** was used to select literature to inform this review.

Populations

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

Interventions

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

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

Comparators

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

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

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

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

Systematic Reviews

A 1996 TEC Assessment that concluded that net health outcome with a local boost using brachytherapy were equivalent to outcomes with EBRT with local boost in women who received BCS plus WBI as initial treatment for stage I or II breast cancer.[55] No RCTs were identified. However, there were 7 nonrandomized studies comparing 2 types of local boost radiotherapy: brachytherapy (n=2033) and EBRT (n=1557); all patients also received BCS and WBI. The combination of brachytherapy with local boost, BCS, and WBI prevented local tumor recurrence and salvage mastectomy in 95% to 97% of patients at 5 years and 88% to 92% of patients at 10 years. Five-year survival in the 5 studies reporting this outcome ranged from 83% to 96%. Data from uncontrolled studies reported similar rates of local control and 5-year survival.

Section Summary: Local Boost Brachytherapy

For women undergoing BCS plus WBI as initial treatment for stage I or II breast cancer, nonrandomized comparative studies have shown similar outcomes with brachytherapy with local boost and with EBRT with local boost.

NONINVASIVE BREAST BRACHYTHERAPY

Clinical Context and Therapy Purpose

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

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

The following **PICOs** was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is noninvasive breast brachytherapy.

AccuBoost for image-guided breast irradiation, also called noninvasive breast brachytherapy, has been used for local boost around the tumor bed. The AccuBoost system provides image-guided radiotherapy before each treatment to ensure that radiation is directed at the treatment target. The breast is placed between mammography paddles, where images are taken and radiation is delivered using a distinct applicator. The paddles prevent motion during treatment. Radiation is delivered from 1 side of the breast to the other or from the top of the breast to the bottom of the breast. This is proposed to reduce radiation exposure to adjacent tissues, including the heart and lung.[50] No long-term studies are available to confirm this.

Noninvasive breast brachytherapy is administered in an outpatient oncology setting.

Comparators

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

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

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

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

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

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

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

Nonrandomized Studies
One comparative study on noninvasive breast brachytherapy. This 2013 matched retrospective study assessed patients receiving the boost dose using AccuBoost or electron beams (a type of EBRT).[57] Each of 47 AccuBoost patients was compared with 2 controls matched on age, stage, chemotherapy use, fractionation, and when possible, breast size, comorbidities, and smoking status. Main differences between the 2 treatment groups were in radiation doses received and timing of radiotherapy administration. The percentage of patients with a WBI dose (accompanying the boost dose) of 50 to 50.4 Gy was 68% in the AccuBoost group and 37% in the electron-treated group ($p<0.001$). Also, a greater proportion of patients in the electron-treated group received the boost dose after WBI, rather than during WBI or starting before and ending during WBI (99% for the electron-treated group vs. 6% for the AccuBoost group). Approximately 60% of patients had stage I breast cancer, and approximately 25%, ductal carcinoma in situ. With median follow-up of 13.6 months, skin and subcutaneous tissue toxicity occurred less often among patients treated with AccuBoost than among those treated with electron beam ($p=0.046$). Locoregional control rates were 99% or greater in both groups. Study limitations included the between-group differences in dose and timing of boost, as well as selection bias and the study's retrospective design.

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

SUMMARY OF EVIDENCE

Accelerated Whole-Breast Irradiation

For individuals who have node-negative, early-stage breast cancer with clear surgical margins who receive accelerated whole-breast irradiation (AWBI) after breast-conserving surgery (BCS), the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Two randomized noninferiority trials both reported 10-year follow-up data on local recurrence. Both trials found that local recurrence rates with AWBI were no worse than conventional whole-breast irradiation (WBI), when applying a noninferiority margin of 5%. Conclusions apply to patients meeting eligibility criteria of the RCTs trials, including having early-stage invasive breast cancer, clear surgical margins, and negative lymph nodes. In addition, consistent with national guidelines, these conclusions apply to tumors more than 5 cm in diameter and women at least 50 years old. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Accelerated Partial-Breast Irradiation

For individuals who have early-stage breast cancer who receive interstitial brachytherapy, the evidence includes 1 completed RCT. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The RCT reported 5-year follow-up data and found that interstitial brachytherapy was noninferior to WBI for rates of local breast cancer recurrence, when applying a noninferiority margin of 3%. Ten-year follow-up data are needed on local recurrence as well as at least 1 additional trial confirming these findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have early-stage breast cancer who receive intraoperative brachytherapy, the evidence includes RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Several RCTs have been published, but they have not demonstrated that outcomes after intraoperative brachytherapy are noninferior to WBI. Results of 2 RCTs (TARGIT-A, ELIOT) comparing intraoperative brachytherapy to WBI found higher rates of local recurrence with intraoperative brachytherapy than with WBI. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have early-stage breast cancer who receive external-beam accelerated partial-breast irradiation (APBI), the evidence includes RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity The RCTs only reported outcomes from 5 to 10 years. Results from the trial with the largest number of patients and longest duration of follow-up 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. Moreover, one of the trials reported higher rates of adverse cosmetic outcomes and grade 3 toxicities in the external-beam APBI group than in the WBI group. The evidence is insufficient to determine the effects of the technology on health outcomes.

Local Boost Brachytherapy

For individuals who have early-stage breast cancer who receive local boost brachytherapy with WBI, the evidence includes nonrandomized studies and a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. A TEC Assessment concluded that, for women undergoing BCS plus WBI as initial treatment for stage 1 or 2 breast cancer, nonrandomized comparative studies have shown similar outcomes with brachytherapy local boost and with external-beam radiotherapy local boost. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Noninvasive Breast Brachytherapy

For individuals who have early-stage breast cancer who receive noninvasive breast brachytherapy, the evidence includes 1 retrospective comparative study. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The retrospective study was a matched comparison of noninvasive breast brachytherapy or electron-beam radiotherapy to provide boost radiation to the tumor bed. The study was subject to selection bias, relatively short follow-up, and use of a retrospective design. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 10.

Table 10. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
WBI vs. APBI with or without tumor bed boost in DCIS			
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	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 Brachytherapy			
NCT01343459	Intra-operative electron boost and hypofractionated whole-breast irradiation during breast-conserving treatment (BCT) (HIOB)	1300	May 2022
NCT01644669	Safety and efficacy study of the Xoft® Axxent® eBx™ IORT system	1200	Dec 2029
External-beam APBI			
NCT01247233	Standard or hypofractionated radiotherapy vs. 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)			
NCT00892814	Partial breast vs. whole breast irradiation in elderly women operated on for early breast cancer	882	May 2026
NCT01185145	Accelerated partial breast radiotherapy with either mammosite or intensity modulated radiotherapy (APBI)	291	Aug 2024
Unpublished			

NCT01803958	Breast cancer with low risk of local recurrence: partial and accelerated radiation with three-dimensional conformal radiotherapy (3DCRT) vs. standard radiotherapy after conserving surgery (Phase III study) (IRMA)	3302	Jan 2019

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

SUPPLEMENTAL INFORMATION

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

2017 Input

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 no specialty society-level response(s) including physicians with academic medical center affiliation; 1 physician-level responses identified through a specialty society; 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

Clinical input was sought to help determine whether the use of AWBI and accelerated partial breast irradiation (ABPI) for individuals with early-stage breast cancer 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 no specialty society-level response(s) including physicians with academic medical center affiliation; 1 physician-level responses identified through a specialty society; 4 physician-level responses identified through an academic medical center.

For individuals who have early-stage breast cancer 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. There was near unanimous support for the policy statement on AWBI. Input was mixed on APBI; those agreeing with the conclusion noted the need to define the risks and benefits of this approach in patient subgroups and noted that current data are inconclusive on the effectiveness of APBI compared with whole-breast irradiation.

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) guidelines (version 4.2021) on breast cancer state:[4]

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

For whole-breast radiotherapy, NCCN recommends a dose of 46 to 50 gray in 40 to 42.5 gray in 15 to 16 fractions. Based on convenience and the data from the START trials, the short course of radiation therapy is the NCCN preferred option in patients given radiation treatment to the breast only. A boost to the tumor bed is recommended for higher risk patients receiving whole-breast radiotherapy (i.e., those who are <50 years old, high-grade disease or patients with focally positive margins) in order to reduce local relapse.

American Society for Radiation Oncology et al

ASTRO (2017), 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 11).[58-60] Recommendations were based on systematic reviews, which are not described in detail, and expert opinion.

Table 11. Professional Medical Society Criteria for Performing APBI

Factor	ASTRO "Suitable"	ASTRO "Cautionary"	ASTRO "Unsuitable"	ASBS	ABS
Patient factors					
Age	≥50 y	40-49 y; ≥50 y if patient has at least 1 of the pathologic factors and does not have any"unsuitable" factors	<40 y; 40-49 y and do not meet the criteria for cautionary	≥45 y for all tumor types	≥45 y
BRCA 1 and BRCA 2 variants	Not present	NR	Present	Patients should not be treated if they have a BRCA genetic mutation	NR
Pathologic factors					
Tumor size	≤2 cm	2.1-3.0 cm	>3 cm	≤3 cm	≤3 cm
Tumor stage	Tis or T1	T0 or T2	T3-4	Tis, T1, T2 (≤3cm)	
Margins	Negative ≥2 mm	Close (<2 mm)	Positive	No tumor on ink for invasive	Negative (no tumor

				tumors or tumors involved with DCIS; ≥2 mm for DCIS	on ink for invasive ≥2 mm for DCIS
Grade	Any	NR	NR	NR	NR
LVSI	No	Limited/focal	Extensive	Allowed as long as it is focal	NR
ER status	Positive	Negative[a]	NR	Positive or negative	Positive or negative
Multicentricity Multifocality	Unicentric Clinically unifocal; total size, ≤2.0 cm	NR Clinically unifocal; size, 2.1-3.0 cm	Present Clinically multifocal or microscopically multifocal; size, ≥3 cm	NR Multifocal disease is allowed as long as the combined area of tumor is ≤3cm	NR NR
Histology	Invasive ductal or other favorable subtypes [b]	Invasive lobular	NR	All invasive subtypes; DCIS	All invasive subtypes and DCIS
Pure DCIS	Not allowed	≤3 cm if "suitable" criteria not fully met	>3 cm	≤3 cm	≤3 cm
EIC	Not allowed	≤3 cm	>3 cm	NR	NR
Associated LCIS	Allowed	NR	NR	NR	NR
Nodal Factors					
Nodal Stage/status	pN0 (i^-, i^+)	NR	pN1, pN2, pN3	Negative	Negative
Nodal Surgery	SNB, ALND	NR	None performed	NR	NR
Treatment Factors					
Neoadjuvant Therapy	Not allowed	NR	If used	NR	NR

ABS: American Brachytherapy Society; ALND: axillary lymph node dissection; APBI: accelerated partial-breast irradiation; 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] Strongly encouraged to enroll in NSABP B-39/RTOG 04-13 trial.
[b] Allowed if screen-detected, low to intermediate nuclear grade, ≤2.5 cm size, and resected with margins negative at ≥3 mm.
[c] Lymphovascular space invasion is considered a contraindication for accelerated partial-breast irradiation.

The ASTRO (2018) updated its guidelines on fractionation for whole-breast irradiation.[61] The consensus-based guidelines conclude that accelerated whole-breast irradiation may be used for any age and any stage provided the intent is to treat the whole breast without any additional field, and with any chemotherapy.

Government Regulations

National:

There is no national coverage determination on this topic. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Local:

Wisconsin Physicians Service Insurance Corporation has a local coverage determination on brachytherapy (L30320); however it is not specific for treatment of the breast. Policy was retired 6/1/15 and not replaced.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Brachytherapy for Prostate Cancer
- Brachytherapy of the Femoropopliteal Arterial System after Percutaneous Transluminal Angioplasty (PTA)
- Electronic Brachytherapy
- Intraoperative Radiation Therapy

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2022, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
6/25/02	6/25/02	6/25/02	Joint policy established
7/20/05	7/20/05	7/28/05	Updated policy; added references to "MammoSite" RT system and accelerated partial breast irradiation.
5/1/07	2/9/07	2/9/07	Routine maintenance; policy retired.
7/1/12	4/10/12	5/18/12	Policy taken out of retirement to address breast brachytherapy done without prior breast conserving surgery (BSC). Brachytherapy of the breast alone (without prior BCS) is experimental and investigational.
9/1/13	6/19/13	6/26/13	Routine maintenance/code update. Policy updated to mirror BCBSA, including title change. Policy statement and criteria for accelerated whole breast radiation changed from "negative surgical margins" to "technically clear surgical margins." Added APBI to the exclusions. Added procedure codes 77261-77263; 77280-77295; 77326-77328 and 0182T.
1/1/14	10/17/13	10/25/13	Removed 0182T from policy as it does not apply to this topic.
9/1/15	6/16/15	7/16/15	Routine maintenance. Routine updated of rationale and references. Deleted codes 77326-8; added codes 77316-8 effective 1/1/15
9/1/16	6/21/16	6/21/16	Routine maintenance. Updated references.
9/1/17	6/20/17	6/20/17	Routine maintenance. References updated. Deleted codes 77776, 77777 and 77787, no longer valid.

5/1/18	2/20/18	2/20/18	Changes made to policy statement to align with ASTRO guidelines. Changes to inclusion/exclusion criteria for alignment. Added code 19294 as established. Added table depicting stages of breast cancer.
5/1/19	2/19/19		Routine policy maintenance. No changes in policy status.
5/1/20	2/18/20		Rationale updated, references # 26, 27, 29, 30, and 38-40 added. Outdated references removed. No change in policy status.
5/1/21	2/16/21		Updated rationale, references # 22, 23, 39 and 48 added. NCCN/ASTRO guidelines section updated.
5/1/22	2/15/22		Updated rationale, references 46, 48, 52 and 54 added. No changes in policy status.

Next Review Date: 1st Qtr. 2023

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ACCELERATED BREAST IRRADIATION AFTER BREAST-CONSERVING SURGERY FOR EARLY STAGE BREAST CANCER AND BREAST BRACHYTHERAPY AS BOOST WITH WHOLE-BREAST IRRADIATION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.