Radiation therapy 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. This approach has been commonly used in Canada and Europe.
• 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. Several approaches can be used to deliver APBI, including interstitial brachytherapy, balloon brachytherapy, external beam radiotherapy, or intraoperative radiotherapy (which occurs on only 1 day).

The critical question is whether these three approaches are equivalent in outcomes and adverse events to the conventional radiation therapy regimen.

Accelerated Whole Breast Irradiation
The overall body of evidence on AWBI compared with conventional whole-breast irradiation suggests that local recurrence rates with AWBI are not worse than with conventional whole-breast irradiation in patients meeting criteria of the Canadian trial, with a noninferiority margin of 5%. Patient selection is important, and at this point, only patients similar to those in the Canadian trial should be considered for this therapy. Thus, AWBI may be considered medically necessary for these patients with clinical characteristics noted in the medically necessary policy statement. Outcomes could differ in women with other disease characteristics.

Brachytherapy Boost with Whole-Breast Irradiation
For patients treated with whole-breast external-beam radiation and BCS, local boost irradiation via interstitial or balloon brachytherapy is likely to result in equivalent outcomes compared with local boost given by external-beam. This is based on results from nonrandomized comparative studies, a TEC Assessment, and specialty society guidelines. As a result, interstitial or balloon brachytherapy may be considered medically necessary for these patients when used as local boost irradiation.

Accelerated Partial Breast Irradiation
Overall, the body of evidence on interstitial accelerated partial-breast irradiation (APBI) compared with conventional whole-breast irradiation is weak; evidence is extremely weak (ie, no randomized studies) for balloon brachytherapy. The strongest published evidence is on intraoperative radiotherapy. Five-year results of one randomized controlled trial (TARGIT-A) showed increased ipsilateral local recurrence with APBI compared with whole-breast radiotherapy. In another randomized controlled trial that used a different technology (ELIOT), recurrence rate with intraoperative radiation therapy was statistically greater than with whole-breast irradiation. It is becoming increasingly clear that each type of APBI should be judged on its own merits, and studies comparing different APBI techniques to each other, as well as to whole-breast irradiation, are needed. A number of large RCTs are underway. However, based on current evidence, APBI is considered investigational for treatment of early stage breast cancer after BCS, except when interstitial or balloon brachytherapy is used as local boost with whole-breast external-beam radiation after BCS, as described above.

Noninvasive Breast Brachytherapy
Evidence for noninvasive breast brachytherapy using Accuboost® to provide boost radiation to the tumor bed is very weak; therefore this technique is considered investigational.
Background
Breast Conservation Therapy
For patients diagnosed with stage 1 or 2 breast tumors, survival after breast-conservation therapy (BCT) is equivalent to survival after mastectomy. BCT is a multimodality treatment that initially comprised breast-conserving surgery (BCS) to excise the tumor with adequate margins, followed by whole-breast external-beam radiation therapy (EBRT) administered as 5 daily fractions per week over 5 to 6 weeks. Local boost irradiation to the tumor bed often is added to whole-breast irradiation to provide a higher dose of radiation at the site where recurrence most frequently occurs. For some patients, BCT also includes axillary lymph node dissection, sentinel lymph node biopsy, or irradiation of the axilla. A number of randomized controlled trials (RCTs) have demonstrated that the addition of radiotherapy after BCS reduces recurrences and mortality. In an expanded update of an individual-level meta-analysis, the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) reported that radiotherapy halved the annual recurrence rate after 10 years for women with node-negative disease (n=7287), from 31.0% for those not receiving radiotherapy to 15.6% for those receiving it. It also reduced the 15-year risk of breast cancer death from 20.5% to 17.2% (p=0.005). For women with node-positive disease (n=1050), radiotherapy reduced the 1-year recurrence risk from 26.0% to 5.1%. Radiotherapy also reduced the 15-year risk of breast cancer death from 51.3% to 42.8% (p=0.01).

Consequently, radiation therapy is generally recommended following BCS. A potential exception is for older women at low risk of recurrence. For example, current National Comprehensive Cancer Network (NCCN) guidelines state that women aged 70 or older may omit radiotherapy if they have estrogen-receptor positive, T1 tumors, clinically negative lymph nodes, and plans to take adjuvant endocrine therapy.(2) However, a 2012 study has raised questions about this recommendation.(3)

Controversy continues on the length of follow-up needed to determine whether APBI is equivalent to whole-breast irradiation (for more information, see the 2013 TEC Assessment on Accelerated Radiotherapy after Breast-Conserving Surgery for Early Stage Breast Cancer).(4) 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.(5-7) For accelerated whole-breast irradiation (AWBI), some 10-year data are available. However, for newer approaches, the issue may be resolved by statistical issues rather than biological ones. For example, in the large NSABP-39/RTOG 0413 trial comparing whole-breast irradiation versus APBI (see Table 2), enrollment has reached the revised target of 4214. Trial duration (presumably barring early termination) is determined by the occurrence of a prespecified number (175) of in-breast recurrences. The researchers expect that reaching that number of recurrences will take approximately 10 years.

Currently, most patients diagnosed with stage 1 or 2 breast cancer are offered a choice of BCT or modified radical mastectomy, but BCT is selected less often than expected. Studies have shown that those living furthest from treatment facilities are least likely to select BCT instead of mastectomy and most likely to forgo radiation therapy after BCS.(8-10) A study using data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results tumor registries from
1992 to 2002 examined how many women with early stage (1 or 2) breast cancer received radiotherapy within 4 months following BCS.(11) After adjusting for age, they found that in 2002, 30.8% of Caucasian women and 44.7% of African-American women had not received radiotherapy. Furthermore, these rates had increased from 24.7% for Caucasian and 34.0% for African-American women in 1992.

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

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

The second approach to reducing radiotherapy treatment time is accelerated partial-breast irradiation (APBI). It differs from conventional whole-breast irradiation in several ways. First, the radiation only targets the segment of the breast surrounding the area where the tumor was removed, rather than the entire breast. This approach was based in part on the finding that recurrences are more likely to occur close to the tumor site rather than elsewhere in the breast. Second, the duration of treatment is 4 to 5 days (or 1 day with intraoperative radiotherapy) rather than 5 to 6 weeks, because radiation is delivered to the tumor bed in fewer fractions at larger doses per fraction. Third, radiation dose is intrinsically less uniform within the target volume when APBI uses brachytherapy (ie, the implantation of radioactive material directly in the breast tissue).

The major types of radiotherapy used after BCS are outlined in Table 1. They differ in their techniques, instrumentation, dose delivery, and possibly in their outcomes.

| Table 1. Major Types of Radiation Therapy Following Breast-Conserving Surgery^a |
|-----------------|-----------------|-------------------|------------------|----------------------|
| **RT Type**     | Accelerated?    | Whole or Partial  | EBRT or Brachytherapy | Approximate Duration of Treatment | Published RCTs (length of follow-up in yrs) |
| Conventional whole-breast irradiation | No | Whole | EBRT | 5-6 wks | Multiple; >15 yrs |
| Accelerated whole-breast irradiation | Yes | Whole | EBRT | 3 wks | 4; 10 yrs |
| Interstitial APBI^b | Yes | Partial | Brachytherapy | 1 wk | 2; 5.4 yrs |
| Balloon APBI^c | Yes | Partial | Brachytherapy | 1 wk | 0 |
| External Beam APBI^d | Yes | Partial | EBRT | 1 wk | 0 |
| Intraoperative APBI^e | Yes | Partial | Not applicable | 1 day | 1; 5 yrs |

*APBI: accelerated partial breast irradiation; EBRT: external-beam radiation therapy; RCT: randomized controlled trial

^a Noninvasive breast brachytherapy using Accuboost™ has been described by the manufacturer as capable of delivering APBI, but no studies on 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, eg, MammoSite®, entails inserting a balloon into the tumor bed, inflating the balloon, confirming its position radiographically, and then using a remote afterloader to irradiate the targeted area. Some brachytherapy systems combine aspects of interstitial and balloon brachytherapy.

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 radiation therapy or intensity-modulated radiation therapy.

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

To appreciate the differences among radiotherapy techniques, it is useful to understand attributes of radiation delivery. The goals of cancer radiotherapy are to provide the tumor or tumor bed with a high dose of homogeneous radiation (i.e., all parts of the tumor cavity receive close to the targeted dose). Areas adjacent to the tumor may be treated with a lower dose of radiation (e.g., with whole-breast irradiation) to treat any unobserved cancerous lesions. Radiation outside the treatment area should be minimal or nonexistent. The goal is to target the tumor or adjacent areas at risk of harboring unseen cancer with an optimum dose, while avoiding healthy tissues.

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

Regulatory Status
The MammoSite® Radiation Therapy System (Proxima Therapeutics; Alpharetta, GA), the first device specifically designed for breast brachytherapy,(12) was FDA-cleared under a 510(k) premarket notification in 2002. Its intended use is “to provide brachytherapy when the physician chooses to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer.”(13)

Since 2002, several other devices for breast brachytherapy have been FDA-cleared for marketing through the 510(k) process as substantially equivalent to predicate 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]). 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 further below; see Intraoperative Brachytherapy) is subject to FDA regulation, it does not fall under the regulatory purview of the U.S. Nuclear Regulatory Commission. In some states, participation of radiation oncologists in delivering radiation is not required.
POLICY
When using radiation therapy after breast-conserving surgery for early stage breast cancer:

A. Accelerated whole breast irradiation may be considered medically necessary for patients who meet the following conditions:
   1. Invasive carcinoma of the breast. 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.
   2. Negative lymph nodes
   3. Technically clear surgical margins

B. Accelerated whole breast irradiation is considered experimental / investigational in all other situations involving treatment of early stage breast cancer after breast-conserving surgery.

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

D. 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.

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.

Policy Guidelines
Electronic brachytherapy is considered a type of balloon brachytherapy that can be used to deliver APBI.

RATIONALE
The most recent literature search update covered the period through November 3, 2014.(4)

Accelerated Whole-Breast Irradiation
Four randomized controlled trials (RCTs) and 1 nonrandomized study compared accelerated whole-breast radiotherapy to 5-week whole-breast radiotherapy.(14-19) Two RCTs directly compared a 5-week to a 3-week regimen.(15,17,18) Both were prospective noninferiority trials with noninferiority margins of 5 percentage points for local or local-regional recurrence in the
accelerated group at 5 (1-sided α=0.025(15) 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 (Standardisation of Breast Radiotherapy [START] B; 2008), from the U.K., included women with stage 1-3 tumors (N=2215).(15) Approximately 75% of the women had negative lymph nodes, and approximately 42% had a radiation boost to the tumor bed. Randomization was stratified for hospital, type of surgery (8% underwent mastectomy), and plans for tumor bed boost. Systemic therapy, primarily tamoxifen, was used by some patients and appeared to be evenly distributed across treatment groups. Treatment arms compared a total dose of 40 Gy in 15 fractions over 3 weeks to 50 Gy in 25 fractions over 5 weeks. The primary efficacy outcome was local-regional 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 local-regional 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.(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 [IQR, 7.5-10.1]).(21) Local-regional 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, from Canada, compared AWBI versus whole-breast irradiation in women with lymph node-negative stage 1-3 tumors.(17,18) Of 2429 eligible patients, 51% agreed to participate in the trial. Intention-to-treat (ITT) analysis was used. Treatment arms compared a total dose of 42.5 Gy in 16 fractions over 3 weeks to 50 Gy in 25 fractions over 5 weeks. Boost radiation was not used. Five-year local recurrence-free survival was 97.2% in the accelerated arm and 96.8% in the conventional arm (absolute difference: 0.4% [95% CI, -1.5% to 2.4%]). Ten-year local recurrence was 6.2% for the accelerated arm and 6.7% for the conventional arm.
(absolute difference: -0.5% [95% CI, -2.5% to 3.5%). At 5 or 10 years, local recurrence rates with AWBI were not 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). However, local recurrence at 10 years for patients with high-grade tumors (post hoc analysis[22]) was 4.7% for the conventional WBI arm and 15.6% for the AWBI arm. The absolute difference was -10.9 percentage points (95% CI, -19.1 to -2.8; test for interaction, p=0.01).

A 2010 Cochrane review entitled “Fraction Size in Radiation Treatment for Breast Conservation in Early Breast Cancer”(23) included a systematic review based on the 4 RCTs described above. The authors concluded:

“We have evidence from four low to medium quality randomised trials that using unconventional fractionation regimens (greater than 2 Gy per fraction) does not affect local recurrence, is associated with decreased acute toxicity and does not seem to affect breast appearance or late toxicity for selected women treated with breast conserving surgery.”

A large retrospective study compared cardiac toxicity in patients with left-sided, early stage breast cancer who received conventional versus accelerated whole breast radiation therapy.(24,25) Chan et al (2014) in Canada reviewed medical database records of 2706 patients who received conventional (n=2221) or accelerated (n=485) whole breast irradiation. Cardiotoxic chemotherapy regimens were similar between groups. At 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.

Several authors have examined AWBI in patients with ductal carcinoma in situ (prospective cohort studies(26) and retrospective reviews(27,28) [total N=2152]). With median follow-up of 9 years, one retrospective study reported estimated 10-year local recurrence-free survival of 89% in 638 patients who received AWPI and 86% in 971 patients who received conventional whole breast irradiation (log rank test, p=0.03).(27) This result requires replication in prospective, randomized trials before deviation from patient selection criteria derived from the Canadian study (described above) can be considered.

Section Summary
The overall body of evidence on AWBI compared with conventional whole-breast irradiation indicates that local recurrence rates with accelerated whole-breast radiotherapy were not worse than conventional whole-breast irradiation in patients meeting criteria of the Canadian trial, when applying a noninferiority margin of 5%. Longer follow-up is needed for the U.K. trial. Based on 14-year retrospective data, severe cardiac toxicity with AWBI for left-sided breast cancers may not be increased compared with conventional WBI.

Patient selection is key, and at this point, only patients similar to those in the Canadian trial should be considered for this therapy. Outcomes could differ in women with other disease characteristics. Patients in this trial all had invasive carcinoma of the breast with negative lymph nodes and surgical margins, and they did not have a radiotherapy boost to the tumor site. Exclusion criteria included “invasive disease or ductal carcinoma in situ (DCIS) involving the
margins of excision, tumors that were larger than 5 cm in diameter, and a breast width of more than 25 cm at the posterior border of the medial and lateral tangential beams, which could increase the heterogeneity of the radiation dose to the breast.” Lymph node status was determined by axillary dissection, but subsequent reports suggested that sentinel lymph node biopsy is likely to be as effective (e.g., see James et al [2010][23]). Despite the fact that 71% of women were estrogen-receptor positive, only 41% took tamoxifen.

Patients selecting accelerated whole-breast radiotherapy should be told that although current evidence on this radiotherapy regimen is strong, it is not as strong as that for conventional whole-breast irradiation. Additional RCTs or longer follow-up could uncover additional concerns. Some potential adverse events, such as cardiac ischemia, may take longer to become evident. This accelerated whole-breast regimen has been widely used outside the United States without substantial reports of major adverse events. Potential patients should be carefully selected and given full information.

Accelerated Partial-Breast Irradiation
Six RCTs(29-38) and 9 nonrandomized comparative studies(39-50) evaluated interstitial, external-beam, or intraoperative accelerated partial-breast irradiation (APBI) compared with conventional whole-breast irradiation. Several of these studies were included in a 2014 meta-analysis by Kong et al that compared APBI (various methods) with whole-breast irradiation.(51) Literature was searched through June 2012, and 11 comparative studies were included (4 RCTs, 2 retrospective and 5 prospective cohort studies). APBI methods included interstitial brachytherapy (5 studies), balloon brachytherapy (3 studies), intraoperative radiotherapy (1 study), external beam radiation therapy (1 study), and multiple techniques (1 study). Median follow-up was 5 years (range, 5 months to 12 years). A small risk of publication bias was detected. Fixed effects meta-analysis of 10 studies (total N=4995) showed greater odds of local recurrence in patients who received APBI compared with patients who received whole-breast irradiation (pooled OR=1.54 [95% CI, 1.15 to 2.06]; p=0.004; I²=0%). Meta-analysis of 5 studies (total N not reported) showed greater odds of axillary failure in patients who received APBI (pooled OR=2.52 [95% CI, 1.72 to 3.68]; p<0.001; I² not reported). Meta-analyses of other outcomes showed no statistical differences in odds of distant metastases, overall survival, and disease-free survival. Given the heterogeneity of APBI methods, comparative efficacy of which is currently unknown, and follow-up durations across studies, clinically informative conclusions that can be drawn from these results are limited.

Interstitial Brachytherapy
For a 2007 RCT, accrual was stopped before reaching the goal specified to evaluate differences in local recurrence, to allow patients to enroll in another trial.(31,32) The randomization process was unclear; patients deemed “technically unsuitable” for interstitial brachytherapy were given EBRT APBI; and patient characteristics and outcomes for each type of APBI were not reported separately. Finally, the sample size of 126 was relatively small, and longest reported follow-up was 66 months. Similar local and regional failure rates were found across treatment arms.

Ajkay et al (2014) reported a retrospective study of 5-year adverse events in patients with early stage breast cancer who were treated at a single U.S. center.(52) Of 417 patients who received BCS and radiation therapy, 271 received intracavitary brachytherapy (34 Gy in 10 fractions; 90% MammoSite®, 9% Contura®, 1% strut-adjusted volume implant [SAVI]) and 146 received whole
breast irradiation using 3-dimensional conformal radiotherapy (3D-CRT; 45-50.4 Gy in 25-28 fractions with 10-16 Gy boost). Median follow-up was 4.8 years in the brachytherapy group and 4.1 years in the whole-breast irradiation group. Estimated 5-year overall incidence of any adverse event was greater in the brachytherapy group compared with the whole breast irradiation group (72% vs 52%; log rank test for all comparisons, p<0.001). For prespecified adverse events of interest, estimated 5-year incidence of infectious skin complications, abscess, telangiectasia, and breast pain was similar between groups. Estimated 5-year incidence of seroma (47% vs 19%, p<0.001) and fat necrosis (40% vs 24%, p<0.001) was greater in the brachytherapy group.

Intraoperative Brachytherapy
One RCT compared intraoperative radiotherapy (IORT) to whole-breast irradiation in 2232 women.(34,35) 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 subprotocols.) 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.”(35) 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 nonbreast 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. Overall, there were 12 more local recurrences but 14 fewer deaths in the TARGIT group than in the whole-breast radiotherapy 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 whole-breast radiotherapy groups in predefined 6-month wound-related complications. However, grade 3 or 4 radiotherapy-related skin complications were more common in the whole-breast radiotherapy group (13/1730 vs 4/1731; p=0.029). Five- and 10-year follow-up for the entire TARGIT-A cohort has yet to be accrued.

A number of reviews and editorials discussed results of the TARGIT-A trial.(5,6,53-59) While recognizing the potential benefits of intraoperative radiotherapy, including convenience, “excellent delineation of the tumour bed under visual control, very good dose homogeneity, and high sparing of normal tissue,”(53) a number of concerns have been expressed. They include the following:
• If IORT is performed during the surgery to excise the tumor, definitive pathology is unavailable when radiotherapy is performed. Therefore, a subset of patients must also undergo whole-breast EBRT following surgery. In the trial, 14% of patients in the IORT arm also received whole-breast EBRT. When only those who received IORT during initial surgery (rather than during repeat surgery to clear positive margins) were considered, 21% received whole-breast EBRT. Limited data suggest that breast symptoms and pain after treatment may be greater for patients receiving both IORT and whole-breast external radiotherapy compared with those receiving IORT alone and that patient satisfaction is greater with whole-breast external radiotherapy or IORT alone compared with combined treatment. Therefore, IORT may result in harm for a subset of patients who receive both IORT and whole-breast external radiotherapy.

• Whether radiation dose and type is actually equivalent to the standard radiation therapy regimen is unknown. Of particular concern is the rapid drop in dose with distance from the applicator and whether any residual disease will be eradicated. Some argue that the TARGIT-A trial alleviates this concern, but others disagree.

• Because 93% of tumors included in the TARGIT trial were estrogen-receptor positive, and estrogen-receptor positive tumors tend to recur later, longer follow-up is needed. Further, because cardiovascular adverse events may occur more than 7-10 years after completion of radiation treatment, 10-year results are needed to assess net health benefit.

• Claims that IORT may improve overall survival due to fewer non-breast cancer deaths may be premature due to short median follow-up (2.4 years) in TARGIT-A. Studies suggest that the latency period for radiation-induced non-breast cancers is 15-20 years from breast treatment.

A 2014 Cochrane review on partial breast irradiation for early breast cancer included the 3 RCTs discussed above plus a fourth RCT that compared conventional (not accelerated) whole breast irradiation to conventional partial breast irradiation by a variety of techniques. The overall quality of evidence was considered low to very low, and conclusions could not be reached.

Another form of intraoperative radiotherapy, called electron intraoperative radiotherapy (ELIOT), uses electrons. The 2013 ELIOT trial compared intraoperative radiotherapy with ELIOT to whole-breast irradiation. With a sample size of 1305 patients and median follow-up of 5.8 years (IQR, 4.1-7.7), 35 patients in the intraoperative group (4.4%) and 4 patients in the whole-breast irradiation group (0.4%) developed ipsilateral breast tumor recurrences (HR=9.3 [95% CI, 3.3 to 26.3]; log-rank test, p<0.001). There was no statistically significant difference in 5-year overall survival. For women with data on adverse skin events (intraoperative radiotherapy=464; whole-breast irradiation=412), there were significantly fewer events among women who received intraoperative radiotherapy (p<0.001). This was an equivalence trial with a prespecified equivalence limit for local recurrence in the intraoperative radiotherapy group only of 7.5%. Therefore, although the criterion for equivalence was satisfied, ipsilateral breast recurrence rate was significantly higher in the intraoperative radiotherapy group. A subsequent review of the ELIOT trial noted that, of 69 women who had 4 or more positive lymph nodes, those randomized to whole breast irradiation (n=38) received concurrent axillary radiation; for those randomized to ELIOT (n=31), axillary irradiation was delayed 6 to 12 weeks. These reviewers also characterized ELIOT data as “still early” and noted that long-term results are needed to assess net health benefit.
All 8 nonrandomized, comparative studies included in the 2013 TEC Assessment were flawed, due to potential baseline differences in treatment groups, lack of multivariable analyses to account for them, inclusion of patients who did not meet eligibility criteria, variations in treatment within arms, and generally small sample sizes and insufficient follow-up.(39-49)

Other IORT modalities are being researched, e.g., electronic brachytherapy using the Xoft® Axxent® eBx™ system (NCT01644669; see Ongoing and Unpublished Clinical Trials). Use of the Xoft® Axxent® eBx™ system is not limited to intraoperative radiotherapy of the breast; it is also used in breast balloon brachytherapy and to treat other organs. Few studies have evaluated electronic brachytherapy devices (balloon and radiation source); no comparative studies were found. The purported advantage of using Axxent® is to eliminate the need for heavy shielding, as required when using a high-dose rate afterloader unit. (For more information on the Intrabeam® device and the Xoft® Axxent® eBx™ system, see Cox and Swanson.)(63)

External-Beam APBI
Two RCTs compared EBRT APBI to whole-breast radiotherapy using 3D-CRT. In the first, 102 patients were randomized to either whole-breast irradiation, with or without a boost to the tumor bed, or APBI.(37) 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% and a significance level of 0.05. The APBI group was significantly younger than the whole-breast irradiation group (mean age [SD], 67.1 [6.1] years vs 70.1 [5.2] years; p=0.009). After 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) APBI patients had acute skin effects, mostly grade 1; all patients in the whole-breast irradiation group had acute skin effects, and most were grade 2. Grade 1 and 2 late effects were reported with some changes in the relative positions of the treatment groups over time.

The second RCT was the multicenter randomized RAPID trial (Randomized Trial of Accelerated Partial Breast Irradiation).(38) The sample size was 2135, and median follow-up was 3 years. Most patients were older than 50 years and had estrogen-receptive-positive tumors less than 1.5 cm in diameter. An interim article reported on cosmetic and toxicity results. An accelerated regimen was used for whole-breast irradiation, and 21% of these patients received a boost to the tumor bed. APBI patients were more likely than whole-breast irradiation 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 whole-breast irradiation patients. Telangiectasia and breast induration were more common among APBI patients (p<0.001).

One RCT was reported in 1990 and 1993, and many changes in the care of patients with breast cancer have occurred since then.(29,30) The study was weakened by the fact that initial groups were potentially unbalanced, and nodal status was based on clinical exam, among other factors. Recurrence was higher for the “limited field” treatment arm (analogous to partial-breast irradiation) than for the “wide field” arm (analogous to whole-breast irradiation), but some of the “excess” recurrences in the limited field arm were axillary. This may be accounted for by the fact that the axillary area was included in the wide field radiotherapy but not in the limited field, and
initial work-up for nodal involvement was limited. The follow-up was 65 months; and the sample size was 708.

Smith et al (2012) analyzed Medicare data on 92,735 women, 67 years or older diagnosed with breast cancer between 2003 and 2007, who underwent lumpectomy followed by radiation therapy.(64) The mean age (SD) was 74.8 (5.5) years. Use of brachytherapy increased from 3.5% in 2003-2004 to 12.5% in 2007 (p<0.001 for trend). Brachytherapy patients were more likely to undergo a subsequent mastectomy than matched whole-breast irradiation (WBI) patients, even after adjusting for imbalanced covariates (HR=1.87 [95% CI, 1.36 to 2.58]; p<0.001). This finding held true when all WBI patients were compared with all brachytherapy patients using multivariable analysis (HR=2.19 [95% CI, 1.84 to 2.61]; p<0.001). Covariates that were significantly associated with subsequent mastectomy (besides brachytherapy) included age 75 to 79 (p=0.01), axillary lymph node involvement (p=0.004), and living in the South (p=0.005). The cause of the mastectomies, eg, recurrence or treatment complications, could not be determined from the claims data. Breast brachytherapy also was associated with a higher risk of postoperative complications, both infectious and noninfectious (27.56% [95% CI, 26.51% to 28.63%] vs 16.92% for WBI patients [95% CI, 16.67% to 17.18%], p<0.001).

Czechura et al (2013) evaluated the frequency of APBI versus whole-breast irradiation in the National Cancer Data Base from 2003 to 2010.(65) The use of brachytherapy accounted for 3.4% of cases in 2003, 12.8% (p<0.001) in 2008, and 12.4% in 2010. The largest percentage point increase by type of APBI was for brachytherapy (from 2.0% to 8.9%) followed by 3D-CRT (from 0.8% to 2.2%) and intensity-modulated radiation therapy (IMRT) (from 0.7% to 1.3%). Mean age was 58.7 years for whole-breast irradiation patients versus 61.6 years for APBI patients. Patients with managed care were most likely to use APBI (46.3% of all APBI), compared with 12.2% for private payers and 6.9% for Medicare. APBI was used most often in the southeastern U.S. Considering invasive cancers, 43.6% of APBI patients met the ASTRO (American Society for Radiation Oncology) “suitable” guidelines; 47.0%, the “cautionary” guidelines; and 9.2%, the “unsuitable” guidelines.

Section Summary
Overall, the body of evidence on interstitial APBI compared with conventional whole-breast irradiation is weak; and it is extremely weak (i.e., no randomized studies) for balloon brachytherapy. One small RCT compared EBRT APBI to whole-breast radiotherapy, and a second larger RCT reported on cosmesis and toxicity after a median of 3 years. The strongest published evidence is on intraoperative radiotherapy (the TARGIT trial); 5-year results showed increased ipsilateral local recurrence with APBI compared with whole-breast radiotherapy, although a prespecified noninferiority criterion for this outcome was satisfied.

Similarly, 5-year results of the ELIOT trial met a prespecified equivalence criterion; however, recurrence rate for intraoperative radiotherapy patients was statistically greater than for whole-breast irradiation patients. Furthermore, it is becoming increasingly clear that each type of APBI should be judged on its own merits, and studies comparing different APBI techniques to each other, as well as to whole-breast irradiation, are needed. Fortunately, a number of large RCTs are underway.
Given the current level of evidence, it is important for patients to be aware of the uncertainty regarding the outcomes of this approach. This information should include failure rates for specific devices (e.g., explantation for Mammosite®, incomplete expansion of the catheters for some of the hybrid devices), as well as the uncertainty regarding their comparative effectiveness. The intermediate alternative provided by AWBI also should be presented to women who meet criteria for the Canadian trial, as well as the critical importance of completing radiotherapy for the majority of patients undergoing BCS.

**Use as Local Boost Radiotherapy**

A 1996 TEC Assessment concluded that net health outcome with brachytherapy local boost were equivalent to outcomes with EBRT local boost in women who received BCS plus whole-breast radiation therapy as initial treatment for stage 1 or stage 2 breast cancer.(66) In 7 nonrandomized comparisons (total N=2022), the 5-year local control rate was 88%-98% for those who received brachytherapy local boost, compared with 91%-99% for those who received EBRT local boost.

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.(67) No long-term studies are available to confirm this. There is only 1 comparative study for this use, a matched retrospective study of patients receiving the boost dose using Accuboost® or electron beams (a type of EBRT).(68) 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 dose received and timing of radiotherapy administration. The percentage of patients with a whole-breast irradiation 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 whole-breast irradiation, rather than during whole-breast irradiation or starting before and ending during whole-breast irradiation (99% for the electron-treated group vs 6% for the Accuboost® group). Approximately 60% of patients had stage 1 breast cancer, and approximately one quarter, DCIS. With median follow-up of 13.6 months, skin/subcutaneous tissue toxicity occurred less often among patients treated with Accuboost® than among those treated with electron beam (p=0.046). Local-regional control rates were 99% or greater in both groups. Study limitations included the between-group differences in whole-breast radiation dose and timing of boost, as well as selection bias and the study’s retrospective design.

**Section Summary**

For women undergoing breast-conserving surgery plus whole-breast irradiation as initial treatment for stage 1 or stage 2 breast cancer, nonrandomized comparative studies have shown similar outcomes with brachytherapy local boost and with EBRT (external beam radiation therapy) local boost.
One matched retrospective study of 141 patients who received noninvasive breast brachytherapy with Accuboost® or electron beam irradiation (a type of EBRT) to provide boost radiation to the tumor bed had a median follow-up of 14 months. This evidence is insufficient to form any conclusion about Accuboost®.

**Ongoing and Unpublished Clinical Trials**

A search of online site ClinicalTrials.gov found 12 ongoing comparative trials (10 randomized, 2 nonrandomized) of APBI (see Table 2). No comparative trials of accelerated whole breast irradiation or Accuboost® were identified.

Additionally, GEC-ESTRO (Groupe Européen de Curietherapie-European Society for Therapeutic Radiology and Oncology) is sponsoring a phase 3 multicenter trial to compare interstitial brachytherapy alone versus EBRT after BCS in patients with low risk invasive carcinoma or low risk DCIS.(69) This trial is not listed at ClinicalTrials.gov or the European Union Clinical Trials Register. Expected enrollment is 1170 patients, and 10-year follow-up is planned.

In 2009, Mannino and Yarnold (note Yarnold is a lead author on the START A and B trials) reviewed current ongoing APBI trials and raised several concerns regarding cross-trial variations.(70) The extent of initial BCS can vary substantially across studies, as well as the definition of the targeted tumor cavity. A larger margin is usually drawn around the tumor cavity for 3D-CRT, for example, because of the need to allow for variations in set-up and respiratory motion. Studies of APBI usually distinguish between “same site relapse,” ie, close to the irradiated area and “elsewhere relapse,” yet it is unclear whether what constitutes the same site varies across studies. The percentage of relapses occurring “elsewhere” in the ipsilateral breast in studies of whole-breast radiotherapy following BCS range from 18% to 42%; these studies may include some patients at higher risk of recurrence. Proponents of APBI have sometimes asserted that “elsewhere” tumors are rare, that they are mostly new primary tumors (rather than recurrence), or that earlier studies have shown that radiotherapy is not effective for these tumors in any case. Mannino and Yarnold challenged each of these points in turn, although they also concluded that results of trials currently underway will provide level-1 evidence for or against APBI.

**Table 2. Ongoing Comparative Trials of Accelerated Partial Breast Irradiation Listed at ClinicalTrials.gov**

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Title</th>
<th>Phase</th>
<th>Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00470236</td>
<td>Radiation Doses and Fractionation Schedules in Non-low Risk Ductal Carcinoma In Situ (DCIS) of the Breast (TROG)</td>
<td>3</td>
<td>1600</td>
<td>Nov 2024</td>
</tr>
<tr>
<td>NCT01343459</td>
<td>Intra-Operative Electron Boost and Hypofractionated Whole-Breast Irradiation During Breast-conserving Treatment (BCT) (HIOB)</td>
<td>3</td>
<td>1000</td>
<td>Mar 2021</td>
</tr>
<tr>
<td>NCT01644669</td>
<td>Safety and Efficacy Study of the Xoft® Axxent® eBx™ IORT System</td>
<td>4</td>
<td>1000</td>
<td>Dec 2024</td>
</tr>
<tr>
<td>NCT Number</td>
<td>Title</td>
<td>Phase</td>
<td>Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>-------</td>
<td>------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>NCT01185132</td>
<td>Intensity Modulated Radiotherapy (IMRT) vs 3D-conformal Accelerated Partial Breast Irradiation (APBI) for Early Stage Breast Cancer After Lumpectomy (2009-APBI)</td>
<td>3</td>
<td>660</td>
<td>Jul 2028</td>
</tr>
<tr>
<td>NCT01247233</td>
<td>Standard or Hypofractionated Radiotherapy vs Accelerated Partial Breast Irradiation (APBI) for Breast Cancer (SHARE)</td>
<td>3</td>
<td>2796</td>
<td>Oct 2024</td>
</tr>
<tr>
<td>NCT01803958</td>
<td>Breast Cancer With Low Risk Of Local Recurrence: Partial and Accelerated Radiation With 3D-Conformal Radiotherapy (EDCRT) vs Standard Radiotherapy After Conserving Surgery (Phase III Study) (IRMA)</td>
<td>NR</td>
<td>3302</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02104895</td>
<td>Accelerated Partial Breast Irradiation Using Intensity Modulated Radiotherapy vs Whole Breast Irradiation</td>
<td>3</td>
<td>520</td>
<td>Feb 2014</td>
</tr>
<tr>
<td>NCT00103181</td>
<td>Radiation Therapy (WBI vs PBI) in Treatment Women Who Have Undergone Surgery For Ductal Carcinoma In Situ or Stage I or Stage II Breast Cancer (RTOG 0413/NSABP B39)</td>
<td>3</td>
<td>4216</td>
<td>June 2016</td>
</tr>
<tr>
<td>NCT00282035</td>
<td>Randomized Trial of Accelerated Partial Breast Irradiation (RAPID)</td>
<td>3</td>
<td>2128</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT00892814</td>
<td>Partial Breast vs Whole Breast Irradiation in Elderly Women Operated on for Early Breast Cancer</td>
<td>2</td>
<td>628</td>
<td>May 2022</td>
</tr>
<tr>
<td>NCT00185744</td>
<td>Accelerated Partial Breast Irradiation Following Lumpectomy for Breast Cancer</td>
<td>NR</td>
<td>400</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>NCT01185145</td>
<td>Accelerated Partial Breast Radiotherapy With Either Mammosite or Intensity Modulated Radiotherapy (APBI)</td>
<td>2</td>
<td>291</td>
<td>Aug 2024</td>
</tr>
</tbody>
</table>

DCIS: ductal carcinoma in situ; NR: not reported; PBI: partial breast irradiation; WBI: whole breast irradiation.

a Expected.
b Estimated.
c Accelerated interstitial or balloon PBI, or 3-dimensional conformal accelerated PBI.
d 3-dimensional conformal accelerated PBI.
e PBI mode of delivery unspecified.
f Intraoperative radiotherapy, balloon APBI, or stereotactic APBI.
g Nonrandomized.

**Clinical Input Received 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.
2011 Input
In response to requests, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2011. There was near-unanimous support for the policy statement regarding AWBI. The input was mixed regarding APBI; those agreeing with the conclusion noted the need to define the risks and benefits of this approach in patient subgroups and noted that current data are inconclusive concerning the effectiveness of APBI compared with whole-breast irradiation.

Summary
Accelerated Whole Breast Irradiation
The overall body of evidence on AWBI compared with conventional whole-breast irradiation suggests that local recurrence rates with AWBI are not worse than with conventional whole-breast irradiation in patients meeting criteria of the Canadian trial, with a noninferiority margin of 5%. Patient selection is important, and at this point, only patients similar to those in the Canadian trial should be considered for this therapy. Thus, AWBI may be considered medically necessary for these patients with clinical characteristics noted in the medically necessary policy statement. Outcomes could differ in women with other disease characteristics.

Brachytherapy Boost With Whole-Breast Irradiation
For patients treated with whole-breast EBRT and BCS, local boost irradiation via interstitial or balloon brachytherapy is likely to result in equivalent outcomes compared with local boost given by EBRT. This is based on results from nonrandomized comparative studies, a TEC Assessment, and specialty society guidelines. As a result, interstitial or balloon brachytherapy may be considered medically necessary for these patients when used as local boost irradiation.

Accelerated Partial Breast Irradiation
Overall, the body of evidence on interstitial accelerated partial-breast irradiation (APBI) compared with conventional whole-breast irradiation is weak; evidence is extremely weak (ie, no randomized studies) for balloon brachytherapy. The strongest published evidence is on intraoperative radiotherapy. Five-year results of one randomized controlled trial (TARGIT-A) showed increased ipsilateral local recurrence with APBI compared with whole-breast radiotherapy. In another randomized controlled trial that used a different technology (ELIOT), recurrence rate with intraoperative radiation therapy was statistically greater than with whole-breast irradiation. It is becoming increasingly clear that each type of APBI should be judged on its own merits, and studies comparing different APBI techniques to each other, as well as to whole-breast irradiation, are needed. A number of large RCTs are underway. However, based on current evidence, APBI is considered investigational for treatment of early stage breast cancer after BCS, except when interstitial or balloon brachytherapy is used as local boost with whole-breast external-beam radiation after BCS, as described above.

Noninvasive Breast Brachytherapy
Evidence for noninvasive breast brachytherapy using Accuboost® to provide boost radiation to the tumor bed is very weak; therefore this technique is considered investigational.

Practice Guidelines and Position Statements
According to current National Comprehensive Cancer Network (NCCN) guidelines (version 3.2014),(2) “Preliminary studies of APBI suggest rates of local control in selected patients with
early stage breast cancer may be comparable to those treated with standard whole breast RT [radiotherapy]. However, compared with standard whole breast radiation, several recent studies documented an inferior cosmetic outcome with APBI. Follow-up is limited and studies are ongoing. Patients are encouraged to participate in clinical trials. If not trial eligible, per the consensus statement from the American Society for Radiation Oncology (ASTRO), patients who may be suitable are..[see ASTRO Criteria: Suitable in Table 3]” For whole-breast radiotherapy, NCCN recommends either a conventional whole-breast irradiation regimen or a total dose of 42.5 Gy with 2.66 Gy per fraction, which equals 16 fractions. Although NCCN guidelines do not specify the duration of treatment, the latter is presumably an AWBI regimen. A boost to the tumor bed is recommended for higher risk patients receiving whole-breast radiotherapy, ie, those who are younger than 50 years old with high-grade disease. The American College of Radiology has ACR Appropriateness Criteria® for conservative surgery and radiation for stage 1 and 2 breast carcinoma, last reviewed in 2011. The document provides appropriateness criteria for the use of radiotherapy after breast conserving surgery for specific cases.

The American Society of Breast Surgeons (ASBS), ASTRO, and the American Brachytherapy Society (ABS) have issued consensus statements for the selection of patients for APBI (summarized in Table 2). According to statement authors, the impetus for the publications was the increased use of APBI outside of clinical trials, even as results of those trials were awaited. The authors estimated that more than 32,000 women have already been treated with MammoSite®, a mechanism for delivering APBI. The statements are based on systematic reviews, which are not described in detail, and expert opinion. Several authors have questioned the validity of ASTRO consensus statement categories based on retrospective studies that showed inconsistent associations between ASTRO category and recurrence rates and no association between ASTRO category and survival outcomes.(50,71-73)

### Table 3. Professional Medical Society Criteria for Performing APBI (74-77)

<table>
<thead>
<tr>
<th>Factor</th>
<th>ASTRO &quot;Suitable&quot;</th>
<th>ASTRO &quot;Cautionary&quot;</th>
<th>ASTRO &quot;Unsuitable&quot;</th>
<th>ASBS</th>
<th>ABS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>≥60 y</td>
<td>50-59 y</td>
<td>&lt; 50 y</td>
<td></td>
<td>≥ 50 y</td>
</tr>
<tr>
<td>BRCA ½ Mutation</td>
<td>Not present</td>
<td>NR</td>
<td>Present</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Pathologic factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>≤ 2 cm</td>
<td>2.1-3.0 cm</td>
<td>&gt; 3 cm</td>
<td>≤ 3 cm</td>
<td>≤ 3 cm</td>
</tr>
<tr>
<td>Tumor stage</td>
<td>T1</td>
<td>T0 or T2</td>
<td>T3-4</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Margins</td>
<td>Negative ≥ 2 mm</td>
<td>Close (&lt;2 mm)</td>
<td>Positive</td>
<td>Microscopically negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>LVSI</td>
<td>No</td>
<td>Limited/focal</td>
<td>Extensive</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>ER status</td>
<td>Positive</td>
<td>Negative²</td>
<td>NR</td>
<td>Positive or negative</td>
<td></td>
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<tr>
<td>Multicentricity</td>
<td>Unicentric</td>
<td>NR</td>
<td>Present</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Clinically unifocal, total size ≤ 2.0 cm</td>
<td>Clinically unifocal, total size: 2.1-3.0 cm</td>
<td>Clinically multifocal or microscopically multifocal, total size ≥ 3 cm</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Factor</td>
<td>ASTRO &quot;Suitable&quot;</td>
<td>ASTRO &quot;Cautionary&quot;</td>
<td>ASTRO &quot;Unsuitable&quot;</td>
<td>ASBS</td>
<td>ABS</td>
</tr>
<tr>
<td>-------------------</td>
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<td>------</td>
<td>----------------</td>
</tr>
<tr>
<td>Histology</td>
<td>Invasive ductal or other favorable subtypes</td>
<td>Invasive lobular</td>
<td>NR</td>
<td>Invasive ductal carcinoma or DCIS</td>
<td>All invasive subtypes and DCIS</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>Not allowed</td>
<td>≤ 3 cm</td>
<td>&gt; 3 cm</td>
<td>≤ 3 cm</td>
<td>≤ 3 cm</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
<td>≤ 3 cm</td>
<td>&gt;3 cm</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Allowed</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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</tbody>
</table>

**Nodal factors**

<table>
<thead>
<tr>
<th>Nodal stage</th>
<th>pNO (i, i')</th>
<th>NR</th>
<th>pN1, pN2, pN3</th>
<th>SN pNO</th>
<th>pNO&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal surgery</td>
<td>SN Bx, ALND</td>
<td>NR</td>
<td>None performed</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Treatment factors**

| Neoadjuvant therapy | Not allowed | NR | If used | NR | NR |

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

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

<sup>b</sup> Lymphovascular space invasion is considered a contraindication for APBI.

ASTRO released guidelines on fractionation for whole-breast irradiation in 2010.(78) Guidelines are based on the Canadian trial,(17,18) START A(16) and START B(15), and a third RCT.(14,19) Guideline authors concluded that “Data are sufficient to support the use of HF-WBI [hypofractionated or accelerated, whole breast irradiation] for patients with early breast cancer who meet all of the aforementioned criteria,” including age 50 years or older, disease stage pT1-2 pN0, no chemotherapy, and treatment with radiation dose homogeneity within ±7% in the central axis plane. The task force did not agree on whether HF-WBI is recommended for tumor boost.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>19296</td>
<td>Placement of radiotherapy afterloading expandable catheter (single or multichannel) into the breast for interstitial radionuclide application following partial mastectomy, includes imaging guidance; on date separate from partial mastectomy</td>
</tr>
<tr>
<td>19297</td>
<td>Placement of radiotherapy afterloading expandable catheter(s) single or multichannel) into the breast for interstitial radionuclide application following partial mastectomy, includes imaging guidance; concurrent with partial mastectomy (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>
Placement of radiotherapy afterloading brachytherapy catheters (multiple tube and button type) into the breast for interstitial radionuclide application following (at the time of or subsequent to) partial mastectomy, includes imaging guidance

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

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

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

High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed

ICD-9 Diagnoses
These diagnoses are otherwise subject to medical policy as stated above
174.0 Malignant neoplasm of female breast; Nipple and areola
174.1 Malignant neoplasm of female breast; Central portion
174.2 Malignant neoplasm of female breast; Upper-inner quadrant
174.3 Malignant neoplasm of female breast; Lower-inner quadrant
174.4 Malignant neoplasm of female breast; Upper-outer quadrant
174.5 Malignant neoplasm of female breast; Lower-outer quadrant
174.6 Malignant neoplasm of female breast; Axillary tail
174.8 Malignant neoplasm of female breast; Other specified sites of female breast

ICD-10 Diagnoses (Effective October 1, 2015)
C50.011 Malignant neoplasm of nipple and areola, right female breast
C50.012 Malignant neoplasm of nipple and areola, left female breast
C50.111 Malignant neoplasm of central portion of right female breast
C50.112 Malignant neoplasm of central portion of left female breast
C50.211 Malignant neoplasm of upper-inner quadrant of right female breast
C50.212 Malignant neoplasm of upper-inner quadrant of left female breast
C50.311 Malignant neoplasm of lower-inner quadrant of right female breast
C50.312 Malignant neoplasm of lower-inner quadrant of left female breast
C50.411 Malignant neoplasm of upper-outer quadrant of right female breast
C50.412 Malignant neoplasm of upper-outer quadrant of left female breast
C50.511 Malignant neoplasm of lower-outer quadrant of right female breast
C50.512 Malignant neoplasm of lower-outer quadrant of left female breast
C50.611 Malignant neoplasm of axillary tail of right female breast
C50.612 Malignant neoplasm of axillary tail of left female breast
C50.811 Malignant neoplasm of overlapping sites of right female breast
C50.812 Malignant neoplasm of overlapping sites of left female breast

REVISED
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:

Contains Public Information
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:

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.
REFERENCES


58. Kuske RR, Young SS. Breast brachytherapy versus whole-breast irradiation: reported differences may be statistically significant but clinically trivial. Int J Radiat Oncol Biol Phys. Feb 1 2014;88(2):266-268. PMID 24411598
64. Smith GL, Xu Y, Buchholz TA, et al. Association between treatment with brachytherapy vs whole-breast irradiation and subsequent mastectomy, complications, and survival among
older women with invasive breast cancer. JAMA. May 2 2012;307(17):1827-1837. PMID 22550197


66. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Brachytherapy in breast-conserving initial treatment of stage I or II breast cancer. TEC Assessments 1996; Volume 11, Tab 7.


Other References
1. Blue Cross and Blue Shield of Kansas Radiology Liaison Committee, February 28, 2007 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-01-07); January 2014; January 2015.
2. Blue Cross and Blue Shield of Kansas Medical Advisory Committee meeting, April 19, 2007 (see Blue Cross and Blue Shield of Kansas Newsletter, Blue Shield Report. MAC-01-07).