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

Professional
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DESCRIPTION
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.

Breast Conservation Therapy
Survival after breast-conservation therapy (BCT) is equivalent to survival after mastectomy for patients diagnosed with tumors categorized as stage I or II. BCT is a multimodality treatment that consists of BCS to excise the tumor with adequate margins, followed by whole-breast external-beam radiation therapy 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=7,287), from 31.0% for those not receiving radiotherapy to 15.6% for those receiving it. (1) 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=1,050), 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 42.8% to 51.3% (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, the 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 recent study has raised questions about this recommendation.

Controversy continues on the length of follow-up needed to determine whether APBI is equivalent to whole breast irradiation (for more information, see the recent update to the TEC Assessment on Accelerated Radiotherapy after Breast-Conserving Surgery for Early Stage Breast Cancer) (3); some 10-year data are already available on accelerated whole breast irradiation. However, the issue may be resolved by statistical issues rather than biological ones. 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 for each radiotherapy approach. For example, in the large NSABP-39/RTOG 0413 trial comparing whole breast irradiation versus APBI, the enrollment goal is 4300, which may be achieved around the end of 2012. The length of the trial (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 about 10 years.

Contains Public Information
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. (4-6) A study using data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) tumor registries from 1992 to 2002 examined how many women with early stage (I or II) breast cancer received radiotherapy within 4 months following BCS. (7) 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 Caucasians and 34.0% for African Americans 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 to target the tumor more effectively 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 some of these concerns. Accelerated whole breast irradiation (AWBI) has been used especially 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 the radiation is delivered in fewer fractions at larger doses per fraction to the tumor bed. 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). 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

<table>
<thead>
<tr>
<th>RT Type</th>
<th>Accelerated?</th>
<th>Whole (W) or partial (P) breast</th>
<th>External beam (E) or brachytherapy (B)</th>
<th>Approx duration of treatment</th>
<th>Published RCTs (length of follow-up in yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional whole-breast irradiation</td>
<td>N</td>
<td>W</td>
<td>E</td>
<td>5-6 wks</td>
<td>Multiple; &gt;15 yrs²</td>
</tr>
<tr>
<td>Accelerated whole-breast irradiation</td>
<td>Y</td>
<td>W</td>
<td>E</td>
<td>3 wks</td>
<td>4; 10 yrs</td>
</tr>
<tr>
<td>Interstitial APBI*</td>
<td>Y</td>
<td>P</td>
<td>B</td>
<td>1 wk</td>
<td>2; 5.4 yrs</td>
</tr>
<tr>
<td>Balloon APBI§</td>
<td>Y</td>
<td>P</td>
<td>B</td>
<td>1 wk</td>
<td>0</td>
</tr>
<tr>
<td>External Beam APBI#</td>
<td>Y</td>
<td>P</td>
<td>E</td>
<td>1 wk</td>
<td>0</td>
</tr>
<tr>
<td>Intraoperative APBI†</td>
<td>Y</td>
<td>P</td>
<td>Not applicable</td>
<td>1 day</td>
<td>1; 4 yrs</td>
</tr>
</tbody>
</table>

* 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.

§ Balloon brachytherapy, e.g., Mammosite, entails inserting a balloon into the tumor bed, inflating the balloon, confirming its position radiographically, and then using a remote afterloader to irradiate the targeted area. Some brachytherapy systems combine aspects of interstitial and balloon brachytherapy.

# 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 three-dimensional, conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT).

Intraoperative APBI is performed during breast-conserving surgery, when a single dose of radiation is delivered to the exposed tumor bed. †The authors reported four-year outcomes, but fewer than 20% of participants had longer follow-up; other authors estimate that the median follow-up was about 2 years.

To appreciate the differences among radiotherapy techniques, it is useful to understand attributes of radiation delivery. The goals of cancer radiotherapy are usually to provide the tumor or tumor bed with a high dose of homogeneous radiation (e.g., 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 non-existent. 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 can also be used as an alternative to external beam radiation therapy to deliver boost radiation therapy combined with whole-breast external-beam radiation therapy. Most of the studies of local boost brachytherapy use temporarily implanted needles, wires, or seeds after patients recovered from surgery and completed whole-breast radiation therapy.
Regulatory Status
The various radiotherapy modalities presented in this report have been approved or cleared for marketing by the U.S. Food and Drug Administration (FDA) (for more details, see Appendix in TEC 2013 [3]). All brachytherapy devices have been approved through the 510(k) process and are either balloon brachytherapy or hybrid balloon-interstitial brachytherapy devices. One device can provide either intraoperative or intracavity treatments. The FDA has required a black box warning on each stating 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.”

POLICY
Following 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; tumor >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.

C. Accelerated partial breast irradiation (APBI), including interstitial APBI, external beam APBI, and intra-operative APBI, is considered experimental / investigational.

D. 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.

RATIONALE
The use of brachytherapy as boost with breast irradiation is considered medically necessary and is not discussed further in this policy.

Accelerated Whole-Breast Irradiation
Four randomized, controlled trials (RCTs) compared accelerated whole-breast radiotherapy to 5-week whole-breast radiotherapy, as well as a fifth, older, nonrandomized study. (9-14) Two of the studies are particularly useful, as they directly compare a 5-week to a 3-week regimen. They are both prospectively designed noninferiority trials. Both trials accepted a maximum loss of efficacy of 5 percentage points in local or local-regional recurrence in the accelerated group at 5
or 10 years (one-sided $\alpha=0.025$ or 0.05). Although the studies differ in the specific fractionation schedules and patient characteristics, they report no difference in local recurrence rates (i.e., recurrence of the cancer in the same breast) across treatment arms.

One study from the United Kingdom includes women with grade 1–3 tumors. (10) 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 (about 15% had a 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. The 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 hazard ratios 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. The absolute difference in local-regional relapse rates after 5 years was $-0.7\%$ (95% CI: $-1.7\%, \ 0.9\%$). There were statistically significant differences in the two treatment regimens for distant relapse and overall survival (OS), with relapse more frequent and survival longer for the 40 Gy accelerated whole breast irradiation (AWBI). This unexpected difference between treatment arms began to appear at about 1 year. The authors speculate that it could be due to chance and might change with longer follow-up. An article on patient-reported breast, arm, and shoulder symptoms, as well as body image, over 5 years of follow-up for both Standardisation of Breast Radiotherapy (START) trials was published in March 2010. (15) At 5 years’ follow-up, there is no evidence that providing radiotherapy in fewer, larger fractions increases these adverse events. The 6-year follow-up period on this trial is too short to reach firm conclusions; follow-up continues.

The second RCT from Canadian researchers compared AWBI versus whole-breast irradiation. (11,12) Of 2,429 eligible patients, 51% agreed to participate in the trial. Intention-to-treat (ITT) analysis was used. The 10-year local recurrence was 6.2% for the 42.5 Gy arm AWBI arm and 6.7% for the conventional 50 Gy whole-breast irradiation (absolute difference: $-0.5\%$, 95% CI: $-2.5\%, \ 3.5\%$). Local recurrence rates with accelerated whole breast radiotherapy were not worse than conventional whole breast irradiation, when applying a noninferiority margin of 5%. In “exploratory” 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 was 4.7% for the conventional whole breast irradiation arm and 15.6% for the 42.5 Gy AWBI arm. The

A Cochrane review on “Fraction Size in Radiation Treatment for Breast Conservation in Early Breast Cancer” (16) conducted a systematic review based on the four randomized, controlled trials described above. They concluded the following:

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.
The overall body of evidence on AWBI compared to conventional whole-breast irradiation suggests local recurrence rates with accelerated whole breast radiotherapy were not worse than conventional whole breast irradiation in patients meeting the criteria of the Canadian trial, when applying a noninferiority margin of 5%. Longer follow-up is needed for the United Kingdom trial.

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 vary in women with other disease characteristics. The 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 for the trial included “invasive disease or ductal carcinoma in situ 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.” In the trial, lymph node status was determined by axillary dissection, but recent reports suggest that sentinel lymph node biopsy is likely to be as effective. (e.g., see 17) Forty-one percent of the women took tamoxifen, despite the fact that 71% were estrogen-receptor positive.

Patients selecting this accelerated whole breast radiotherapy should be told that while the 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 of the existing trials could uncover additional concerns. Some potential adverse events, such as cardiac ischemia, may take longer to become evident. This regimen has been widely used outside the U.S. without substantial reports of major adverse events. Potential patients should be carefully selected and given full information, while the results of longer follow-up for the START B trial are awaited.

**Accelerated Partial-Breast Irradiation**

There are three RCTs on interstitial, external-beam, or intraoperative accelerated partial-breast irradiation (APBI) compared to conventional whole-breast irradiation, as well as 7 nonrandomized comparative studies. (18-34) These studies evaluated interstitial, external, or intraoperative brachytherapy; no published comparative studies were found that assessed balloon brachytherapy. For the first, accrual was stopped before reaching the goal specified to evaluate differences in local recurrence, to allow patients to participate in another trial. (18-20) The randomization process was unclear, patients deemed “technically unsuitable” for interstitial brachytherapy were given external-beam APBI; and the patient characteristics and outcomes for each type of APBI were not reported separately. Finally, the sample size of 126 was relatively small, and longest follow-up reported was 66 months. Similar local and regional failure rates were found in the treatment arms.

The second RCT on APBI was reported in 1990 and 1993, and many changes in the care of breast cancer have occurred since. (21,22) The study was weakened by the fact that the 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 the initial work-up for nodal involvement was limited. The follow-up was 65 months; and the sample size, 708.
The third randomized trial compared intraoperative to external-beam accelerated partial-breast irradiation. (23) It is a noninferiority trial with 28 centers in 9 countries and a sample size of 2,232. An ITT approach was used; 89% of the intraoperative group and 92% of the external radiotherapy group completed treatment. Patients were not blinded to treatment choice. As anticipated in advance, 14% of those in the intraoperative arm received external beam radiotherapy as well, because of unfavorable pathologic features determined after surgery, e.g., lobular carcinoma. The pre-defined noninferiority margin was an absolute difference of 2.5% between groups for pathologically confirmed, ipsilateral local recurrence. After 4 years, wound seroma needing more than three aspirations was significantly more common in the intraoperative group than in the external radiotherapy group (2.1% vs. 0.8%, respectively; p=0.012). Conversely, Radiation Therapy Oncology Group (RTOG) toxicity grade of 3 or 4 was more common in the external radiotherapy group than in the intraoperative group (2.1% vs. 0.5%, respectively; p=0.002). The 4-year local recurrence rates in the ipsilateral breast were 1.20% (95% CI: 0.53%, 2.71%) in the intraoperative radiotherapy arm vs. 0.95% (95% CI: 0.39%, 2.31%) in the external radiotherapy arm (difference between groups=0.25%, 95% CI: -1.04%, 1.54%; log-rank test, p=0.41). Local recurrence rates after 4 years with intraoperative radiotherapy were not worse than with external irradiation, when applying a noninferiority margin of 2.5%. Fortunately for the patients, the recurrence rates are low: 6 in the intraoperative group versus 5 in the external radiotherapy group. But these small numbers make it more difficult to detect real differences between arms, if they exist. Also, while the results are interesting, the follow-up of 4 years is insufficient to reach a conclusion on the comparative benefits and adverse events of these two treatments.

A number of reviews and editorials discussed the preliminary results of the TARGIT-A trial (35-38). 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” (35), a number of concerns have been expressed. They include the following:

- If IORT is performed during the surgery to excise the tumor, the definitive pathology is not available when the radiotherapy is performed. Therefore, a subset of patients must also undergo whole breast external beam radiotherapy following surgery. The article reports that 14% of patients in the IORT arm also received whole breast external beam radiotherapy. When only those who received IORT during initial surgery are considered, 21% received whole breast external beam radiotherapy. There are limited data suggesting that breast symptoms and pain following treatment may be greater for patients receiving both IORT and whole breast external radiotherapy compared with IORT alone and that patients’ satisfaction is greater for whole breast external radiotherapy or IORT alone compared to the combined treatment (39). Therefore, IORT may result in harm for a subset of patients who receive both IORT and whole breast external radiotherapy.
- Whether the radiation dose and type is actually equivalent to the standard radiation therapy regimen. Of particular concern is the rapid drop in dose with distance from the applicator and whether any residual disease will eradicated. Some argue that the TARGIT-A trial alleviates this concern, while others do not.
• The length of follow-up is insufficient to determine long-term toxicity and efficacy, particularly since only 19% of the participants in the TARGIT-A trial completed 4 years of follow-up. The median follow-up is not reported but appears to be around 2 years.

While the Intrabeam device is subject to FDA regulation, it does not fall under the regulatory purview of the US Nuclear Regulatory Commission. In some states, the participation of radiation oncologists in delivering radiation is not required. There is another form of intraoperative radiotherapy using electrons, called ELIOT (40). An RCT has completed accrual, and initial results are awaited. Other IORT modalities are also being researched, e.g., using the Xoft® Axxent® eBx™ system (NCT01644669; see ClinicalTrials.gov).

The other 8 nonrandomized, comparative studies were all 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. (24-34)

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. The mean age was 74.8 years (SD=5.5). They found that the use of brachytherapy rose 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 patients, even after adjusting for imbalanced covariates (HR, 1.87; 95% CI: 1.36, 2.58; p<0.001). This finding held true when all WBI patients were compared to all brachytherapy patients using multivariable analysis (HR, 2.19; 95% CI: 1.84, 2.61; p<0.001). Variables in the multivariable analysis significantly associated with subsequent mastectomy besides brachytherapy included age 75-79 (p=0.01), axillary lymph node involvement (p=0.004), and living in the South (p=0.005). The cause of the mastectomies, e.g., recurrence or treatment complications, could not be determined from the claims data. Breast brachytherapy was also associated with a higher risk of postoperative complications, both infectious and noninfectious (27.56% [95% CI: 26.51%, 28.63%] vs. 16.92% for WBI patients [95% CI: 16.67%, 17.18%]; p<0.001).

Overall, the body of evidence on interstitial APBI compared to conventional whole-breast irradiation is weak; and it is extremely weak (i.e., no comparative studies) for balloon brachytherapy and external-beam APBI. The strongest published evidence is on intraoperative radiotherapy, but the follow-up is insufficient at this time. 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 the 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 should also be presented to women who meet the criteria for the Canadian trial, as well as the critical importance of completing radiotherapy for the majority of patients undergoing BCS.
A large, multicenter RCT of APBI versus whole-breast irradiation was initiated in 2005 to compare APBI to whole-breast irradiation. It is led by the National Surgical Adjuvant Breast and Bowel Project and the Radiation Therapy Oncology Group and referred to as NSABP B-39/RTOG 0413 (available online at: www.rtog.org). Patients are randomized to whole-breast irradiation (total dose: 60-66.6 Gy) or APBI (total dose: 34-38.5 Gy). Within the APBI group, the participant’s physician may choose whether to use interstitial brachytherapy, Mammosite balloon brachytherapy, or external beam radiotherapy using 3-dimensional, conformal radiation therapy (3D-CRT). The initial target sample size of 3,000 was increased to 4,300 in 2007. The accrual targets for the women with a lower risk of recurrence were met by the end of 2006; only women in the higher risk groups are still being recruited. As of May 16, 2012, 4,217 patients had been accrued. The estimated completion date is June 1, 2015. There are another 6 RCTs on the use of APBI versus whole breast irradiation underway, as well as two trials comparing two forms of APBI (available online at: www.clinicaltrials.gov; see Appendix I). There is also a study on using ABI as a boost with whole breast irradiation and 3 randomized trials comparing standard whole breast irradiation and AWBI. It appears that the first randomized trial that compares recurrence for APBI and whole breast irradiation will be completed in November 2014. The study is being conducted by the University of Erlangen-Nurnberg Medical School and has 1,300 participants.

In a review of the APBI trials currently underway, Mannino and Yarnold (note Yarnold is a lead author on the START A and B trials) raise several concerns regarding variations across the trials. (42) The extent of the 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 respiration motion. Studies of APBI usually distinguish between “same site relapse,” i.e., 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 a recurrence), or that earlier studies have shown that radiotherapy is not effective on these tumors in any case. Mannino and Yarnold challenge each of these points in turn, although they also conclude that the results of the trials currently underway will provide level-I evidence for or against APBI.

Use as Local Boost Radiotherapy
This section is based on a 1996 TEC Assessment that concluded net health outcomes after brachytherapy for local boost were equivalent to outcomes after external beam radiation therapy for local boost in women given BCS plus whole-breast radiation therapy as initial treatment for stage I or stage II breast cancer. In 7 nonrandomized comparisons (total N=2,022), the rate of local control at 5 years after treatment was 88-98% for those given brachytherapy for local boost, compared to 91-99% for those given external-beam radiation therapy.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
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. 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. There was near-unanimous support for the policy statement regarding accelerated whole-breast irradiation (AWBI). The input was mixed regarding accelerated partial-breast irradiation (APBI); those agreeing with the conclusion noted the need to define the risks and benefits of this approach in patient subgroups and noted that current data are inconclusive concerning the effectiveness of APBI compared to whole-breast irradiation.

Summary
The overall body of evidence on accelerated whole-breast irradiation (AWBI) compared to conventional whole-breast irradiation suggests local recurrence rates with accelerated whole breast radiotherapy were not worse than conventional whole breast irradiation in patients meeting the criteria of the Canadian trial, when applying 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, accelerated whole-breast irradiation may be considered medically necessary for these patients with clinical characteristics noted in the medically necessary policy statement. Outcomes could vary in women with other disease characteristics.

For patients treated with whole breast external beam radiation and breast-conserving surgery, local boost irradiation via interstitial or balloon brachytherapy is likely to result in equivalent outcomes compared to local boost given by external beam. This is based on results on 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.

Overall, the body of evidence on interstitial APBI compared to conventional whole-breast irradiation is weak; and it is extremely weak (i.e., no comparative studies) for balloon brachytherapy and external-beam APBI. The strongest published evidence is on intraoperative radiotherapy, but the follow-up is insufficient at this time. 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. Thus, these techniques are considered investigational. Fortunately, a number of large randomized, controlled trials are underway to provide additional data.

According to the National Comprehensive Cancer Network (NCCN) guidelines, “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. Follow-up, however, is limited and studies are on-going. 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 below). 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 the NCCN guidelines do not specify the duration of treatment, the latter is presumably an accelerated whole-breast irradiation regimen. A boost to the tumor bed is recommended for higher risk whole breast radiotherapy patients, i.e., those who are younger than 50 years-old and have positive axillary nodes, lymphovascular invasion, or close margins.
The American Society of Breast Surgeons and the American Society for Radiation Oncology (ASTRO) have issued guidelines for the selection of patients for APBI, which are summarized in Table 2. (43) According to the authors, the impetus for this guideline was the increased use of APBI outside of clinical trials, even as the results of those trials are awaited. The authors cite estimates that more than 32,000 women have already been treated with the MammoSite,® a mechanism for delivering APBI. The statement says that the guidelines are based on the results of a systematic review, which is not described in much detail, and expert opinion.

**Table 2. Professional medical society criteria for performing APBI**

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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient factors</td>
<td>Age</td>
<td>≥ 60 y</td>
<td>50-59 y</td>
<td>&lt; 50 y</td>
<td>≥ 45 y</td>
</tr>
<tr>
<td></td>
<td>BRCA ½ Mutation</td>
<td>Not present</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Pathologic factors</td>
<td>Tumor size</td>
<td>≤ 2 cm</td>
<td>2.1-3.0 cm</td>
<td>&gt; 3 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T stage</td>
<td>T1</td>
<td>T0 or T2</td>
<td>T3-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Margins</td>
<td>Negative ≥ 2 mm</td>
<td>Close (&lt;2 mm)</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade</td>
<td>Any</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LVSI</td>
<td>No</td>
<td>Limited / focal</td>
<td>Extensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ER status</td>
<td>Positive</td>
<td>Negative*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multicentricity</td>
<td>Unicentric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multicentricity</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>Invasive ductal carcinoma or DCIS</td>
</tr>
<tr>
<td></td>
<td>Histology</td>
<td>Invasive ductal or other favorable subtypes</td>
<td>Invasive lobular</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pure DCIS</td>
<td>Not allowed</td>
<td>≤ 3 cm</td>
<td>&gt;3 cm</td>
<td>≤ 3 cm</td>
</tr>
<tr>
<td></td>
<td>EIC</td>
<td>Not allowed</td>
<td>≤ 3 cm</td>
<td>&gt;3 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Associated LCIS</td>
<td>Allowed</td>
<td></td>
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<tr>
<td></td>
<td>N stage</td>
<td>pNO (i, i')</td>
<td>pN1, pN2, pN3</td>
<td>SN pNO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nodal surgery</td>
<td>SN Bx, ALND</td>
<td>None performed</td>
<td></td>
<td></td>
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<tr>
<td>Treatment factors</td>
<td>Neoadjuvant therapy</td>
<td>Not allowed</td>
<td>If used</td>
<td></td>
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</tr>
</tbody>
</table>

*Gray shading = not reported

*Strongly encouraged to enroll in NSABP B-39/RTOG 04-13 trial.

**Key:** DCIS, ductal carcinoma in situ; EIC, extensive intraductal component; ER status, estrogen receptor status; LCIS, lobular carcinoma in situ; LVSI, lymphovascular space invasion; N stage, nodal stage; T stage, tumor stage. **Sources:** 43-45
Several studies have tried to assess the validity of these recommendations, by comparing recurrence rates retrospectively for patients that meet the criteria for one or more of these categories. Beitsch et al. used data from the American Society of Breast Surgeons MammoSite® Registry. (46) The database does not contain data on all of the elements in the recommendations (multifocality, multicentricity, presence of lymph-vascular space invasion, histology of invasive cancer, BRCA 1 or 2 mutation, and type of nodal surgery performed). Of the total of 1,449 patients in the Registry study, 1,025 (70.7%) could be grouped into the Consensus Statement categories. Of these, 176 fell in the unsuitable category (73.9% were under 50 years-old; 21.6% had positive nodes; 10.2% had more than 2 characteristics that put them in this category; 7.4% had positive margins; 5.1% had extensive intraductal component greater than 3 cm; and 3.4% had tumors greater than 3 cm). The 5-year actuarial rate of ipsilateral breast tumor recurrence was 5.25% in this group (7 patients; 2 at lumpectomy site and 5 elsewhere); 4.04% in the suitable or cautionary categories (24 of 849 patients; 8 recurrences at the lumpectomy site and 16 elsewhere). This difference was not statistically significant (p=0.3223). There were no other statistically significant differences between these two groups for any of the other outcomes reported either: regional nodal failure, distant metastases, disease-free survival, cause-specific survival, and overall survival. Another study that appears to be using the data on the same patients but was able to assign them to all three consensus statement categories (suitable, cautionary, and unsuitable) reached the similar conclusions. (47) A third study compared 199 patients at a single institution who underwent APBI with 199 matched controls who received whole breast irradiation. (48) When each group was stratified into the three categories in the ASTRO consensus statement, there was no statistically significant difference in the 10-year, ipsilateral breast recurrence rates across categories. There did appear to be a statistically significant difference across the categories for the patients treated with APBI, with no patients in the suitable group having distant metastases at 10 years versus 7.1% of the cautionary group and 11.2% of the unsuitable group (p=0.018); this statistically significant trend was not repeated in the patients receiving whole breast irradiation. Similarly, a statistically significant difference in regional nodal failure at 10 years was evident among all patients (0% for the suitable group; 0.7% for the cautionary group; and 4.0% for the unsuitable group); but not for either the APBI or whole breast irradiation group. The authors state that little evidence was available for the consensus panel in deciding which patients were not suitable and called for further research. The generalizability of the findings is open to question, however, because of the small number of events upon which these calculations are based, as well as missing data elements in the MammoSite® registry that are included in the consensus statement categorization. One researcher was an author on all three articles.

ASTRO released guidelines on fractionation for whole breast irradiation in 2010. (49) They rely on the Canadian trial (11,12), START A (14) and START B, (10) and the Owen/Yarnold trial (9,13). They conclude 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 aged 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 it is recommended to use HF-WBI when receiving a tumor boost.
CODING

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

CPT
19296 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
19297 Placement of radiotherapy afterloading expandable catheter (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)
19298 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
77785 Remote afterloading high dose rate radionuclide brachytherapy; 1 channel
77786 Remote afterloading high dose rate radionuclide brachytherapy; 2-12 channels
77787 Remote afterloading high dose rate radionuclide brachytherapy; over 12 channels

DIAGNOSIS

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 Diagnosis (Effective October 1, 2014)
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

Contains Public Information
C50.612  Malignant neoplasm of axillary tail of left female breast
C50.811  Malignant neoplasm of overlapping sites of right female breast
C50.812  Malignant neoplasm of overlapping sites of left female breast

REVISIONS

06-29-2010  In Coding Section:
- Updated wording for the following CPT Codes:  19296, 19297.
- Added CPT Codes: 77785, 77786, 77787 (effective 01/01/09).

05-27-2013  In the Medical Policy Title section:
Revised the following medical policy title:
"High Dose Rate (HCR) Breast Brachytherapy with HDR Radioactive Source via
MammoSite Catheter".

Updated the Description section.

In the Policy section:
Revised the following medical policy language:
"A. Brachytherapy used as accelerated partial breast irradiation (local boost irradiation) is a medically appropriate treatment option in women with stage 0, I, or II breast cancer who are also treated with breast conserving surgery and whole breast radiation therapy.
B. Brachytherapy as the sole form of breast irradiation after breast-conserving surgery for early stage breast cancer (Stage 0, I, or II – based on size only – over 2 cm) is considered investigational. It may be considered as a medically appropriate treatment option in limited circumstances for patients in whom whole breast external beam irradiation is not feasible, although this is not the current standard of care. These patients fall into one of the two categories:
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)

REFERENCES


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).
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).

Appendix I. Ongoing Randomized Trials on "Partial Breast Irradiation"
Source: Clinicaltrials.gov

Ongoing Research on Accelerated Whole Breast Irradiation
Randomized, controlled trials currently underway (www.clinicaltrials.gov) comparing the accelerated and conventional whole-breast irradiation regimens, including ones by the following sponsors:

- Radiation Therapy Oncology Group (RTOG), n=2,312; NCT01349322. This trial includes boost to tumor area.
- UNICANCER, n=2,796; NCT01247233. This is a three-arm trial comparing conventional WBI, accelerated WBI, and APBI.
- Danish Breast Cancer Cooperative Group, n=976; NCT00909818. The primary endpoint is late radiation morbidity at 3 years.
- Chinese Academy of Medical Sciences, n=630; NCT01413269. This trial includes boost to tumor area.
- M.D. Anderson Cancer Center, n=200; NCT01266642. Primary outcome is adverse cosmetic effects at 3 years.

Ongoing Research on APBI
As discussed above, a large, multicenter randomized controlled trial of APBI versus whole-breast irradiation was initiated in 2005 to compare APBI to whole-breast irradiation. It is led by the National Surgical Adjuvant Breast and Bowel Project and the Radiation Therapy Oncology Group and referred to as NSABP B-39/RTOG 0413 (see www.rtog.org). Eligible patients have stage 0, 1, or II unifocal breast cancer resected by lumpectomy with a tumor size no larger than 3.0 cm and no more than 3 histologically positive nodes. Participants are stratified by disease stage, menopausal status, hormone receptor status, and intent (or not) to receive chemotherapy. Patients are randomized to whole-breast irradiation (total dose 60–66.6 Gy) or APBI (total dose 34–38.5 Gy). Within the APBI group, the participant’s physician may choose whether to use interstitial brachytherapy, MammoSite™ balloon brachytherapy, or external-beam radiotherapy using 3D-CRT. The endpoints include overall survival, recurrence-free survival, distant disease-free survival, quality of life, and acute and late toxicity.

The initial target sample size of 3,000 was increased to 4,300 in 2007. The accrual targets for the women with a lower risk of recurrence were met by the end of 2006; only women in the higher risk groups are still being recruited. As of May 16, 2012, 4,217 patients had been accrued. The estimated completion date is June 1, 2015.

There are a number of randomized, controlled trials on the use of APBI currently underway (www.clinicaltrials.gov) comparing whole-breast irradiation to

1) intraoperative radiation therapy (University Hospital London Hospitals, n=2,232; NCT00983684);
2) interstitial or balloon brachytherapy or 3D-CRT (NSABP B 39/RTOG 0413, n=4,300; NCT00103181);
3) interstitial brachytherapy (GEC-ESTRO, n=1,300; NCT00402519); and
4) 3D-CRT (Ontario Clinical Oncology Group, n=2,128; NCT00282035); (UNICANCER, France, n=2,796; NCT01247233. This is a three-arm trial comparing conventional WBI, accelerated WBI, and APBI.).

There are also two RCT between APBI modalities:
1) IMRT versus 3D-CRT APBI (Rocky Mountain Cancer Centers, n=660; NCT01185132)
2) 3D-CRT APBI versus interstitial brachytherapy (All Ireland Cooperative Oncology Research Group, n=75; NCT00802711)

Additional comparative studies on APBI techniques, especially randomized controlled trials, will be useful as well.