

## BRACHYTHERAPY AS PRIMARY RADIATION THERAPY FOLLOWING BREAST-CONSERVING SURGERY FOR STAGE I OR II BREAST CANCER

### A Technology Assessment

#### INTRODUCTION

The California Technology Assessment Forum (CTAF) has been asked to update its review of the scientific literature on the safety and efficacy of brachytherapy (BT) for primary radiation therapy for localized breast cancer. BT is a subset of a relatively new approach to breast cancer radiation therapy known as accelerated partial breast irradiation (APBI). The goal of APBI is to reduce the length of time required for radiation therapy following breast conserving surgery from the five to six weeks required for standard external beam radiation therapy to one week or less while preserving the life-saving benefits of radiation therapy. On June 21, 2006 the Forum discussed BT and concluded that the technology was promising, but the data were insufficient to conclude that BT was equivalent to external beam therapy. A high level of evidence was thought to be required because early stage breast cancer is a common, but potentially life-threatening disease with two well studied and effective therapeutic options: mastectomy or breast conserving surgery (BCS) with whole breast irradiation (WBI). In August 2007, the Blue Cross Blue Shield Association Technology Evaluation Center similarly concluded that the evidence on APBI is insufficient to permit conclusions on the effect of the technology on net health outcomes. Due to significant interest from the provider community and the availability of new, long-term follow-up data, CTAF is updating its prior review.

#### BACKGROUND

##### Breast Cancer

Cancer of the breast is the most common form of cancer in women. Every American woman is estimated to have a one in nine chance of developing breast cancer at some time during her life. In 2008, there will be an estimated 184,450 new cases of invasive breast cancer in the United States and an estimated 40,930 deaths from this cancer.<sup>1</sup> In addition to invasive breast cancer, 67,770 new cases of breast carcinoma *in situ*, a condition also often treated with radiation therapy, will be diagnosed in women in 2006.

##### Radiation Therapy

Radiation therapy (as part of breast-conserving local therapy) usually consists of postoperative external-beam radiation (EBR) to the entire breast with doses of 45 Gy to 50 Gy, in 1.8 Gy to 2.0 Gy daily fractions

over a five-week period. A further radiation boost is commonly given to the tumor bed. Large randomized trials with more than 15 years of follow-up have demonstrated that treatment of breast cancer with BCS plus radiation therapy has equivalent outcomes to mastectomy.<sup>2-9</sup> Selection of a local therapeutic approach depends on the location and size of the lesion, analysis of the mammogram, breast size, and the patient's attitude toward preserving the breast. The presence of multi-focal disease in the breast or a history of collagen vascular disease are relative contraindications to breast-conserving therapy.<sup>10</sup>

Despite the strong evidence of the effectiveness of BCS plus WBI, many eligible women in the United States opt for mastectomy.<sup>11</sup> For some women, fears about local recurrence affect the decision. For others, fears about the radiation therapy that is required after partial mastectomy affects their decision-making. Finally, the conventional postoperative course of radiation requires daily attendance (Monday to Friday) for five to six weeks and is perceived as a major inconvenience.<sup>12-14</sup> This last concern may disproportionately affect patients with limited economic means or patients who have to travel large distances to reach a center offering radiation therapy.

### Brachytherapy (BT)

BT, the interstitial implantation of seeds, wires, or other materials that contain radioisotopes, has been used in the treatment of breast cancer since the 1920's.<sup>15</sup> BT delivers localized radiation to the tumor bed, avoiding irradiation of the skin and intervening normal tissues. However, newer technology delivered x-rays with sufficient energy to penetrate more deeply into tissues without energy absorption at or near the surface and external beam radiation therapy became the standard of care. The use of BT for breast cancer declined even further since linear accelerators that generate electrons for EBR became widely available. At present electron beams are used most frequently both for irradiation of the whole breast and for local boost to the tumor bed.

Current interest in BT is based on the observation that the majority of ipsilateral breast recurrences after BCS with radiation therapy occur at or near the tumor bed (~70%), with only a small proportion of recurrences located in distant regions of the affected breast (often called else-where breast failures if more than 2 cm from the surgical site).<sup>16-19</sup> In addition, in trials of BCS without radiation therapy, the majority of recurrences occurred at or near the tumor bed, suggesting that multicentric disease is not a common cause of recurrence. Factors that increase the likelihood of local recurrence include younger age, lobular histology, positive surgical margins, extensive intraductal component, vascular invasion, and positive lymph nodes.<sup>20</sup>

<sup>21</sup> The 2005 Consensus Statement of the American Society of Breast Surgeons recommends that outside of

clinical trials, the use of APBI should be limited to women at low risk for elsewhere breast failures using the following criteria: age 45 years old or greater; invasive ductal carcinoma or ductal carcinoma in situ; total tumor size (invasive and DCIS) less than or equal to 3 cm in size; negative microscopic surgical margins of excision; and axillary lymph nodes/sentinel lymph node negative.<sup>22</sup> Presumably, this reflects the lack of confidence in the equivalence of APBI to WBI in patients at higher risk for local recurrence.

A variety of BT techniques have been developed, differing in the timing of implantation relative to other components of breast conserving therapy, the dose rate, the loading technique, and the radioisotopes used. Recently, investigators have used perioperative implantation of the hollow needles and catheters that guide placement of the radioactive material. This can be done during the initial lumpectomy if the decision to use BT has already been made, or at the time of a re-excision if the lumpectomy specimen has positive surgical margins. Intraoperative implantation avoids the need for a separate surgical procedure with anesthesia for brachytherapy. Depending on the technique used it may require 15-20 catheters to assure the target area of the breast is covered with an even dose of radiation. Once the catheters are placed, computer-assisted dosimetry is performed to determine where and how much radiation will be delivered.

Both low-dose-rate (LDR) and high-dose-rate (HDR) techniques have been used, with HDR techniques increasing in popularity. In the LDR technique, temporarily implanted radioactive seeds deliver radiation therapy continuously over a course of four to five days and then are removed. This treatment is generally given as an inpatient. The patient is confined to an isolated hospital room with limited visitation. In the HDR technique, a computer-controlled device pushes a highly radioactive isotope into a catheter that has been placed in the tumor bed. The patient is exposed to the radiation therapy for a brief period – five to 15 minutes – and then the radioactive source is withdrawn. HDR BT is typically administered on an outpatient basis in fractions given twice daily over four to five days. After the treatment session is finished, the catheters are disconnected and the patient is free to go until the next treatment session. Following the last treatment session, the catheters are easily removed in the clinic and the treatment area is cleaned and dressed.

In 2002, the Food and Drug Administration (FDA) approved a balloon catheter device (Mammosite) that is inserted into the lumpectomy cavity so that the surrounding tissue conforms to the balloon's surface. The balloon device is much easier to use than interstitial catheters resulting in an explosion of interest in and use of BT over the past six years. However, the patient characteristics required for balloon-based BT are more selective than those for traditional interstitial brachytherapy (IB). The distance from the edge of the lumpectomy site to the skin and to the chest wall must be at least 5 mm to avoid significant toxicities and a

10 mm margin is preferable. Women with smaller breasts or superficial tumors will be better served by IB. Furthermore, the need for an elliptical incision and possible removal of additional breast tissue to accommodate the spherical device may impact cosmetic outcomes. On the other hand, there is usually only one entry site for the balloon catheter compared with 15 or more entry sites and 15 or more exit sites for IB. Comparative trials are needed to assess patient satisfaction and cosmetic outcomes with the two techniques.

The potential advantages of primary BT include: (1) the procedure is performed over four to five days on an outpatient basis if the HDR technique is used and (2) the relative sparing of surrounding normal tissue, resulting in lower incidence of adverse effects including less cardiac toxicity. The disadvantages include: (1) the placement of catheters or a balloon for four to five days may increase the risk of local infection; (2) the energy levels involved and the potential for placement errors may result in areas of underdosage or overdosage resulting in inadequate treatment or worse cosmetic outcomes; (3) the energy levels mean that the effect dose is confined to the tumor bed with an additional margin of about 2 cm, such that locally advanced disease extending beyond this margin may not be adequately treated.

### Technology Assessment (TA)

**TA Criterion 1:           The technology must have the appropriate regulatory approval.**

Iodine-125 radioisotope seeds became available and were marketed prior to the 1976 enactment of the Medical Devices Amendments. Subsequent radioactive isotope seeds (such as iridium-192) have received FDA 510(k) approval as being substantially equivalent to the I-125 seeds.

The MammoSite™ Radiation Therapy System (RTS) (Proxima Therapeutics, Inc., Alpharetta, GA) received FDA 510K clearance on May 24, 2002. The intended use of the MammoSite Radiation Therapy System is to provide brachytherapy when the physician chooses to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer. The FDA notes “Although the indication for use is not identical to the predicate devices, the intended use is the same and the difference does not introduce any new questions about safety or effectiveness”. At the time of approval the FDA noted: “The safety and effectiveness of the MammoSite RTS as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.” This is a black box warning.

While the original FDA clearance included a “black box warning” this warning has not been included on subsequent clearances in 2003 and 2004.

The MammoSite® Cavity Evaluation Device (Hologic, Inc., Melville, NY) received FDA 510(k) clearance on May 9, 2008. Per the FDA, the MammoSite Cavity Evaluation Device (CED) may be used to assess the lumpectomy cavity and aid in the selection of the appropriate MammoSite Radiation Therapy System (RTS) applicator. It may be used during surgery to assess skin spacing and conformance. The CED may also be left in the lumpectomy cavity as a placeholder until it is exchanged for the MammoSite RTS applicator.

The Axxent Electronic Brachytherapy System (Xoft Inc., Fremont, CA) received FDA 510K clearance on December 22, 2005 and February 29, 2008. The same black box warning was noted on both clearances: “The safety and effectiveness of the Axxent Electronic Brachytherapy System as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.

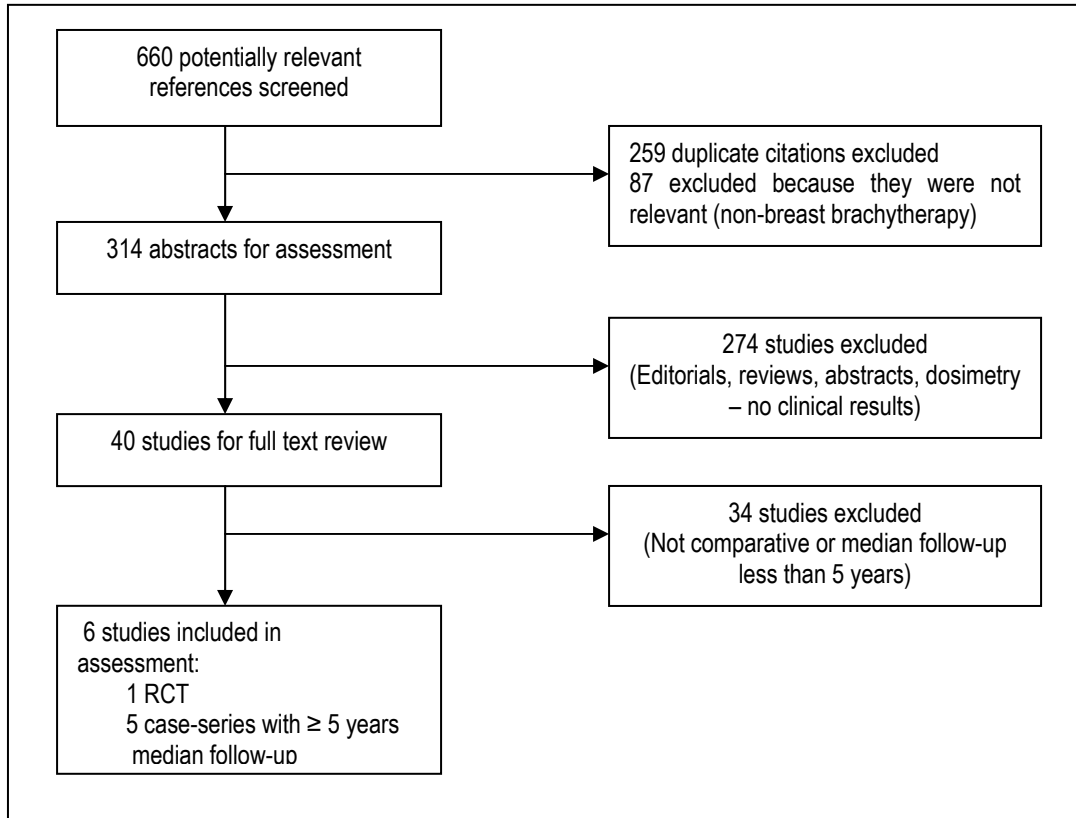
The SenoRad Multi-Lumen Balloon Source Applicator for Brachytherapy (SenoRx, Inc., Aliso Viejo, CA) received FDA 510(k) clearance on October 22, 2007 and on May 2, 2008. A black box warning is also noted: The safety and effectiveness of the SenoRad Multi-Lumen Balloon Source Applicator for Brachytherapy as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.

TA Criterion 1 is met.

TA Criterion 2:           The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE), and Embase were searched using the key words brachytherapy or MammoSite or accelerated partial breast irradiation. These were cross-referenced with the keywords breast neoplasms and human. The search was performed for the period from May 2006 through September 2008 to update the prior systematic review. The bibliographies of review articles and other key references were manually searched for additional references and the manufacturers were contacted for reference lists. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. Full details of the search terms are included in Appendix 1. Figure 1 describes the search results. In brief, a total of 660 references were reviewed (316 from Embase, 240 from PubMed, 16 from the combined Cochrane databases, and 88 provided by the Cytoc Corporation). We included studies published since the last review in June 2006 if they reported breast cancer recurrence rates in case-series with at least five years median follow-up or comparative trials between BT and EBR therapy.

Figure 1: Selection of studies for inclusion in review



New clinical studies of BT as the primary form of radiation therapy included an updated report on the Hungarian randomized clinical trial<sup>23</sup> and five case series involving women with early stage breast cancer. Meaningful comparisons between the published series are difficult because of the variation in patient selection criteria, the varying technical methods, and differences in the proportion of patients receiving adjuvant hormonal and chemotherapy. Cohort effects due to changes in surgical technique and adjuvant chemotherapy also may bias comparisons. Most of the reported studies of BT were too small to separately report outcomes for patients based on tumor stage or other important prognostic factors.

The most important health outcome of breast cancer treatment is survival. Most authorities agree that the long natural history of breast cancer means that 10- to 15-year follow-up is required for meaningful survival data.<sup>24</sup> However, local control is an important intermediate outcome both because local control appears to predict long-term mortality<sup>25</sup> and because the primary goal of BCS with radiation is to prevent local recurrences and to preserve the breast: most patients with recurrent local disease are treated with mastectomy. The majority of local recurrences occur within the first five years, although additional

recurrences continue to accrue through at least fifteen years of follow-up.<sup>25</sup> A minimum of five to seven years follow-up should be required to adequately evaluate differences in local recurrence rates. Because local recurrence rates vary significantly by patient age, tumor histology, nodal status, and adjuvant therapy, comparative studies need to be closely matched on these characteristics or be randomized. As, noted above, most organizations promoting the use of APBI, recommend limiting the eligible patients to women with tumors less than or equal to 3 cm, negative surgical margins, negative lymph nodes, and ductal (not lobular) histology.<sup>22</sup>

Breast preservation is a key goal of therapy. Thus cosmetic outcomes are also of high importance. If local recurrence rates were equivalent, but cosmetic outcomes were significantly worse, BT would not be considered equivalent to WBI. Adverse effects include breast edema, erythema, fibrosis, hyperpigmentation, hypopigmentation, telangiectasias, breast pain, delayed wound healing, local infection, abscess formation, fat necrosis, and fibrosis. These are usually evaluated using the Common Toxicity Criteria<sup>26</sup> with grading ranging from 0: no observable radiation effects to 3: severe radiation effects. Cosmetic outcomes are usually measured using the Harvard criteria<sup>27</sup>: a four-point scale (excellent, good, fair, poor) based on visual comparison of the treated and untreated breast by the examining physician.

For the purposes of this review, we will focus on local recurrence rates at five years as the primary outcome with cosmetic outcomes being an important secondary outcome if local recurrence rates are found to be equivalent. Given the relatively low local recurrence rates expected in the low risk groups eligible for BT, large sample sizes will be needed to detect the potential for a 30-40% higher rate of local recurrence in women treated with partial breast irradiation (PBI) rather than WBI.

Level of Evidence: 2, 3, 4, 5

TA Criterion 2 is met.

TA Criterion 3: The technology must improve the net health outcomes.

*Randomized controlled trials (Table 1)*

The only randomized clinical trial comparing primary BT to WBI after BCS was published in 2007.<sup>23</sup> Polgar and colleagues randomized 258 patients with early stage breast cancer to receive 50 Gy WBI (n = 130) or PBI primarily with BT (n = 128); the latter consisted of either 7 x 5.2 Gy HDR-brachytherapy using Ir-192 (n = 88, 69%) or 50-Gy limited-field electron beam irradiation for those patients randomized to brachytherapy who were “technically unsuitable” for interstitial implantation (n = 40, 31%).

They limited their participants to women with stage 1, T1, N0 cancers with clear surgical margins after breast-conserving surgery and excluded women with extensive intraductal component (EIC), lobular histology, or high grade disease. These selection criteria limit the study to women at very low risk for local recurrence. Recruitment into the trial was stopped at less than half the planned sample size (n=570 planned), because a larger multi-center European trial began to accrue patients (the Groupe Europeen de Curietherapie – European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) Phase III APBI trial). Median follow-up at the time of the report was 66 months. The five year local recurrence rates were not significantly different (4.7% for patients in the PBI arm compared with 3.4% for patients in the whole breast irradiation arm, p=0.50). The difference was almost entirely due to the rate of elsewhere failures in the ipsilateral breast being 82% higher in the PBI arm (3.1% versus 1.7%), although this may be due to chance given the relatively small numbers in the study. The 5-year probability of overall survival and disease-free survival were 94.6% and 88.3% in the PBI arm and 91.8% and 90.3% in the whole breast irradiation arm (P = NS). Women in the PBI arm had better cosmetic outcomes (excellent or good 77.6% versus 62.9%, p=0.009). The investigators concluded that their results suggested that PBI gave similar results to WBI, but the long-term results of ongoing phase III trials are required to determine the role of APBI in patients with early breast cancer.

The overall quality of the randomized trial was good. Given the nature of the intervention, the investigators were not able to blind patients or study staff to the intervention. Lack of blinding may have biased the relatively subjective assessment of cosmetic outcomes, but should have had little impact on the primary outcome, local recurrence, as it is a more objective outcome. The major flaw in the trial is the fact that 31% of patients randomized to the PBI arm were found not to be candidates for BT and thus received five weeks of external beam partial breast radiation therapy instead of APBI. This leaves the door open for selection bias during the post-randomization determination of therapy. Additionally, it limits the ability to directly compare the results of BT to WBI as it is no longer a randomized comparison. Indeed, the investigators did not report the local recurrence rate data or other survival data in the BT subgroup. Finally, the trial was underpowered to detect a potentially meaningful difference in the local recurrence rates between the two groups.

#### *Case series (Table 2)*

Five manuscripts published since the last review report data on 416 patients in case series with a median follow-up of at least five years.<sup>28-32</sup> Two of them <sup>28, 32</sup> are updates to trials described in the prior CTAF review.<sup>33, 34</sup> Only one small trial presents data on the Mammosite Balloon Catheter (n=36),<sup>29</sup> although the full

registry from which this sample is drawn has recruited over 1400 patients.<sup>35</sup>

As in the prior review, the actuarial rate of local recurrence at five years was low; ranging from 0 to 6.1%. The recurrence rate tracks with the inclusion criteria of the studies. The studies including only very low risk patients with node negative disease had recurrence rates of 0 to 1.8%, while those that allowed enrollment of patients with node positive disease had recurrence rates of 4 to 6.1% even though the majority of patients were node negative. Similar findings were reported in an analysis of 273 women treated with HDR BT at the University of Wisconsin: the five year risk for local recurrence was estimated to be 2.2% for those at low risk versus 6.4% for those at “high-risk” even though they still would be eligible for randomization in the National Surgical Adjuvant Breast and Bowel B-39 trial comparing APBI to WBI in women with early breast cancer.<sup>36</sup> The correlation of case mix with recurrence rates makes it impossible to compare case series data for BT to prior case series data for WBI with any confidence.

All five of the series divided the local recurrence into those close to the tumor bed (true recurrences) and those at a distance from the tumor bed (elsewhere failures). Ten of the 18 recurrences (56%) observed in these case series were elsewhere failures. A concern raised by some radiation oncologists is that whole breast irradiation may be treating some of these “elsewhere” tumors and that PBI, by not irradiating the entire breast, may be less effective. One of the investigators performed clonal analysis on all of the recurrences and determined that two of the three elsewhere failures were clonally related to the original tumor and thus represented local disease that was inadequately treated by PBI.<sup>32</sup>

### Summary

In general, published data suggest that IB can now be performed with acceptably low morbidity rates and low local recurrence rates when used in women at low risk for local recurrence. The local recurrence rates reported in the studies of IB reporting median follow-ups of five years (0% to 6.1% in the new series) are much lower than those reported by randomized clinical trials for patients treated with BCS without radiation (24% to 37%). These large differences are unlikely to be completely due to selection bias (lower risk patients in the trials of BT) and improvements in non-radiotherapy treatment modalities. Thus, TA criterion 3 is met for IB. However, the data for balloon BT are not yet mature. Data on five year recurrence rates only has been published for one small cohort of 36 patients treated with balloon BT. Thus, TA criterion 3 is not met for balloon BT.

**TA Criterion 3 is met for interstitial brachytherapy**

**TA Criterion 3 is not met for balloon brachytherapy**

Table 1: Comparative Studies of Primary Brachytherapy to the Tumor Bed alone Compared to Whole Breast External Beam Radiation Therapy Published since May 2006

Reference	Study design	N	Median Follow-up (yr)	Study subjects	BT isotope	BT Method	Dose (Gy)	Excellent/Good Cosmetic result	5 yr local recurrence rate (%)	5 yr disease free survival (%)	5 yr overall survival (%)
Polgar 2007 <sup>23</sup>	RCT		5.5	Stage I, T1 N0 BCS, clear margins, no Grade 3, no lobular histology, no DCIS, no EIC.							
- Ir-192 BT (69%) or PBI using EBR (31%)		128		127/128 received PBI, the other opted for mastectomy. 40 were "technically unsuitable" for BT and received 50 Gy electron beam irradiation in 25 treatments over 5 weeks.	Ir-192	HDR	36.4	77.6	4.7	88.3	94.6
- WBRT		130		129/130 received WBRT, the other found to have metastatic disease before WBRT			50	62.9	3.4	90.3	91.8

BT	Brachytherapy	DCIS	Ductal carcinoma in situ	EBR	External beam radiation therapy
T	Tumor	EIC	Extensive intraductal component	HDR	High dose rate
N	Node	PBI	Partial breast irradiation	WBRT	Whole breast radiation therapy

Table 2: Uncontrolled Studies of Primary Brachytherapy to the Tumor Bed Published since May 2006

Reference	Study design	N	Median follow-up (yr)	Study subjects	BT isotope	BT method	Dose (Gy)	Excellent/Good Cosmetic result (%)	5 yr local recurrence rate (%)	5 yr disease free survival (%)	5 yr overall survival (%)
Benitez 2007 <sup>29</sup>	CS	36	5.5	T1N0 invasive ductal carcinoma ≤ 2 cm, age ≥ 45 years, no EIC, final margins negative, cavity size ≥ 3 cm, minimum balloon to skin distance 5 mm. Only 43/70 original patients were successfully treated with MS and 36 followed for 5.5 years (3 other died, 2 in hospice, 2 lost to FU).	Ir-192	HDR MS	34	83	0	NR	NR
Kaufman 2007 <sup>31</sup>	CS	32	NR	T1-2, ≤ 3 axillary nodes, non-lobular histology, negative surgical margins.	Ir-192	HDR IB	34	89	6.1	NR	NR
Vicini 2007 <sup>32</sup> Chen 2006 <sup>33</sup>	CS	199	8.0	T1/2N0 Invasive ductal carcinoma < 3 cm, negative surgical margins ≥ 2 mm, age > 40 years, negative lymph nodes. No EIC.	Ir-192	LDR/HDR IB	34-50	99	1.8	97	87
Arthur 2008 <sup>28</sup> Kuske 2006 <sup>34</sup>	CS	99	7	T1/2 < 3 cm, ≤ 3 axillary nodes, non-lobular histology, negative surgical margins	NR	LDR/HDR IB	34-45	91	4	87	93
Johansson 2008 <sup>30</sup>	CS	50	7.2	T1/2, ≤ 3 axillary nodes, negative surgical margins	Ir-192	PDR IB	56.8	51 by patient 56 by nurse	4	88	88

BT	Brachytherapy	CS	Case series	T	Tumor
N	Node	EIC	Extensive Intraductal Component	MS	Mammosite Balloon Catheter
HDR	High dose rate	NR	Not reported		

TA Criterion 4:           The technology must be as beneficial as any established alternatives.

Only one comparative trial has been published since the last review. The updated results from the randomized clinical trial of PBI by Polgar and colleagues<sup>23</sup> are encouraging. The actuarial five-year local recurrence rates were low in both arms (4.7% and 3.4%) and they were statistically equivalent. They are similar to the 2 to 4% 5-year rates seen in the WBI arms of randomized trials of patients with similar low risk characteristics.<sup>17, 37</sup> However the recurrence rate was 38% higher in the PBI arm and primarily was due to elsewhere failures that may have been treated if whole breast irradiation had been used. More importantly, the study was underpowered as it was stopped early and it did not truly evaluate BT as 31% of the patients randomized to the PBI arm received external beam therapy and not BT. As noted under TA Criterion 3, cosmetic outcomes were better in the PBI arm, particularly for the women receiving BT (81.2% good to excellent).

#### *Ongoing randomized trials*

The literature search identified five ongoing randomized clinical trials<sup>18, 38-42</sup> of APBI. The three trials with BT arms plan to randomize more than 5,000 women.<sup>38-41</sup> All five are actively recruiting patients. The largest ongoing trial is co-sponsored by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Radiation Therapy Oncology Group (RTOG) in North America<sup>39</sup>. The investigators plan to randomize 4,300 women to PBI with interstitial implants, Mammosite balloon, 3-D conformal radiation therapy or to standard WBI at 45 to 50 Gy with a 10 Gy boost. In addition to standard breast cancer recurrence outcomes, they are measuring quality of life (QOL) related to cosmesis, fatigue, treatment-related symptoms, and perceived convenience of care. Acute and late toxicities between PBI and WBI will also be compared. According to the investigators, this is the fastest accruing breast cancer clinical trial in history.

#### *Summary*

Larger phase III trials with longer follow-up are needed to assess the long term efficacy of BT compared with standard therapy. The one randomized trial comparing BT to WBI had low recurrence rates in both arms, but it was underpowered to detect important differences in recurrence rates. Initial data suggest that cosmetic outcomes are similar and may be better with BT. There are five large, ongoing randomized trials of APBI, three of which are evaluating BT. It is not yet clear that primary BT is equivalent to standard therapy with WBI after BCS.

TA Criterion 4 is not met.

TA Criterion 5:           The improvement must be attainable outside the investigational setting.

The published data represent BT used primarily in investigational settings with considerable expertise in BT. Additionally, most radiation oncologists do not have extensive experience in breast BT as most training programs, particularly in the United States, do not teach IB. However many clinical centers, particularly in Europe, are represented in the literature. Since the approval of the MammoSite device, many sites in the United States have also begun using BT. The MammoSite balloon is technically less demanding, but can only be used in a highly select group of women with breast cancer. Given the limited experience of most radiation oncologists with breast BT, close adherence to the American Brachytherapy Society guidelines<sup>43</sup> would be recommended if BT is used. Given that equivalence in local recurrence outcomes has not yet been proven in the investigational setting, TA criterion 5 is not met.

TA Criterion 5 is not met.

## CONCLUSION

The goal of radiation therapy after breast conserving therapy is primarily to prevent local recurrences. One small randomized, controlled trial has been published assessing the effectiveness and morbidity of primary BT after BCS for Stage I breast cancer compared to WBI after BCS. The results were promising, but the small number of participants did not permit any firm conclusions. Five additional new publications presented data on cases series each with a median follow-up of at least five years. Local recurrence rates in those studies ranged from 0% to 6.1%. It is not yet clear that local BT after BCS will have rates of local recurrence and disease-free survival that are equivalent to those obtained by the standard therapy of WBI after BCS. An important question to address will be how close is close enough. In the NSABP-B21 trial evaluating tamoxifen and WBI for women with T1 tumors  $\leq$  1 cm, tumor-free margins, and negative lymph nodes, the five year local recurrence rate was 2% for the combined arm, 4% for those who received WBI without tamoxifen, and 10.5% in those who received tamoxifen without WBI. Would a five-year local recurrence rate of 3% for BT plus tamoxifen be acceptable evidence for equivalence if included in this trial?

The consensus in the field appears to be that APBI, including BT, is a promising alternative to WBI, but that randomized clinical trials are needed in order to definitively establish equivalence and to better define the appropriate population to whom this form of radiation therapy should be offered. The American Society of

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Breast Surgeons supports the use of APBI, including BT, in research studies and in patients at very low risk for local recurrence. Other organizations are more conservative. For instance, the 2008 National Comprehensive Cancer Network guidelines state that PBI “should be performed only as part of a prospective trial. PBI can be delivered with brachytherapy or external beam radiation using 3-D conformal radiation or IMRT. If not trial eligible, PBI should be reserved for patients with a low risk of recurrence.” Fortunately, there are five ongoing randomized clinical trials of APBI that should provide more definitive data in the near future. The ongoing NSABP B-39/RTOG 0413 randomized trial completed accrual in its low risk strata more rapidly than anticipated. Until these studies demonstrate that APBI gives equivalent cancer and cosmetic outcomes, whole breast radiation therapy (WBRT) should remain the standard method for treating early stage breast cancer with radiation.

#### **DRAFT RECOMMENDATION**

It is recommended that the use of breast brachytherapy does not meet Technology Assessment Criterion 4 or 5 for safety, effectiveness and improvement in health outcomes when used as primary radiation therapy following breast conserving surgery for localized breast cancer.

October 15, 2008

## RECOMMENDATIONS OF OTHERS

### Blue Cross Blue Shield Association (BCBSA)

In 2007, the BCBSA Technology Evaluation Center (TEC) determined that accelerated partial breast irradiation as the sole radiation treatment after breast-conserving surgery for early stage breast cancer does not meet TEC criteria.

### Centers for Medicare and Medicaid Services (CMS)

No specific mention of a National Coverage Decision regarding this technology was found. The California CMS contractor has a retired coverage decisions regarding the use of APBI.

### California Radiological Society (CRS)

CRS has been invited to provide an opinion regarding this technology and will be represented at the meeting by the radiation oncology societies.

### American Society for Therapeutic Radiology and Oncology (ASTRO)

ASTRO will have representatives attending the meeting and has been invited to provide an opinion statement.

### American Cancer Society (ACS)

The ACS Detailed Guide: Breast Cancer, Radiation Therapy, revised on September 4, 2008 is available at

[http://www.cancer.org/docroot/CRI/content/CRI\\_2\\_4\\_4X\\_Radiation\\_Therapy\\_5.asp?sitearea=](http://www.cancer.org/docroot/CRI/content/CRI_2_4_4X_Radiation_Therapy_5.asp?sitearea=).

The guide notes in part that: "While these methods (Brachytherapy and Interstitial Brachytherapy) are sometimes used as ways to add a boost of radiation to the tumor site (along with external radiation to the whole breast), they are also being studied in clinical trials as the only source of radiation for women who have had a lumpectomy. In this sense they can also be considered forms of *accelerated partial breast irradiation*. Early results have been promising, but long-term results are not yet available, and it's not yet clear if irradiating only the area around the cancer will reduce the chances of the cancer coming back as much as giving radiation to the whole breast. The results of studies now being done will probably be needed before more doctors recommend accelerated partial breast irradiation as a standard treatment option.

Association of Northern California Oncologists (ANCO)

ANCO referenced the NCCN Breast Cancer Guidelines and also urged CTAF to seek input from any and all radiation oncology organizations.

Medical Oncology Association of Southern California (MOASC)

MOASC has been invited to provide an opinion and participate at the meeting.

American College of Radiation Oncology (ACRO)

ACRO has submitted an opinion on the use of this technology and will have a representative at the meeting.

American Brachytherapy Society (ABS)

ABS has published a statement from the American Brachytherapy Society Breast Brachytherapy Task Group dated February, 2007 and available at [http://www.americanbrachytherapy.org/resources/abs\\_breast\\_brachytherapy\\_taskgroup.pdf](http://www.americanbrachytherapy.org/resources/abs_breast_brachytherapy_taskgroup.pdf).

American Society of Breast Surgeons

The American Society of Breast Surgeons has been invited to participate at the meeting and provide an opinion statement. A Consensus Statement for Accelerated Partial Breast Irradiation is available at [www.breastsurgeons.org](http://www.breastsurgeons.org). The Society also has a MammoSite Patient Registry. ([www.breastsurgeons.org/MammoSitePatientRegistry.htm](http://www.breastsurgeons.org/MammoSitePatientRegistry.htm))

**ABBREVIATIONS USED IN THIS ASSESSMENT**

CTAF	California Technology Assessment Forum
BT	Brachytherapy
APBI	Accelerated partial breast irradiation
BCS	Breast conserving surgery
WBI	Whole breast irradiation
EBR	External beam radiation
LDR	Low dose rate
HDR	High dose rate
IB	Interstitial brachytherapy
FDA	Food and Drug Administration
DARE	Database of Abstracts of Reviews of Effects
PBI	Partial breast irradiation
EIC:	Extensive Intraductal Component
GEC-ESTRO	Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology
NR	Not reported
DCIS:	Ductal Carcinoma in situ
N	Node
T	Tumor
MS	Mammosite Balloon Catheter
NSABP	National Surgical Adjuvant Breast and Bowel Project
RTOG	Radiation Therapy Oncology Group
QOL	Quality of life
WBRT	Whole breast radiation therapy

## Appendix 1: Detailed search criteria

Pubmed Search

Search	Most Recent Queries	Result
<a href="#">#8</a>	Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 Limits: Publication Date from 2006 to 2008	<a href="#">240</a>
<a href="#">#7</a>	Search #1 OR #2 OR #3 OR #4 OR #5 OR #6	<a href="#">849</a>
<a href="#">#6</a>	Search PARTIAL[TI] AND BREAST[TI] AND (IRRADIAT*[TI] OR RADIAT*[TI] OR RADIOTHERAP*[TI])	<a href="#">176</a>
<a href="#">#5</a>	Search ACCELERATED AND BREAST NEOPLASMS/RADIOTHERAPY	<a href="#">183</a>
<a href="#">#4</a>	Search BRACHYTHERAPY OR APBI OR PBI OR PBRT AND BREAST	<a href="#">693</a>
<a href="#">#3</a>	Search PARTIAL BREAST IRRADIAT* OR PARTIAL BREAST RADIAT* OR PARTIAL BREAST RADIOTHERAP*	<a href="#">259</a>
<a href="#">#2</a>	Search MAMMOSITE	<a href="#">90</a>
<a href="#">#1</a>	Search ACCELERATED AND PARTIAL AND BREAST	<a href="#">171</a>

Embase Search

No.	Query	Results
#1	accelerated:ti,ab AND 'breast tumor'/exp/dm_rt	244
#2	mammosite	141
#3	'partial breast' AND (irradiat* OR radiat* OR radiotherap*)	327
#4	('partial irradiation' OR 'partial radiation' OR 'partial radiotherapy') AND 'breast tumor'/exp/dm_rt	7
#5	('brachytherapy'/exp OR apbi:ti,ab OR pbi:ti,ab OR pbrt:ti,ab) AND 'breast tumor'/exp	1,047
#6	#1 OR #2 OR #3 OR #4 OR #5	1,241
#7	#1 OR #2 OR #3 OR #4 OR #5 AND [2006-2008]/py	351
#8	#1 OR #2 OR #3 OR #4 OR #5 AND [english]/lim AND [2006- 2008]/py	316

Cochrane Search:

### Current Search History

ID	Search	Hits	Edit	Delete
#1	<a href="#">(mammosite)</a>	4	<a href="#">edit</a>	<a href="#">delete</a>
#2	<a href="#">(partial next breast) and (irradiat* or radiat* or radiotherap*)</a>	20	<a href="#">edit</a>	<a href="#">delete</a>
#3	<a href="#">(brachytherapy or apbi or pbi or pbrt ) and (breast):ti,ab,kw</a>	37	<a href="#">edit</a>	<a href="#">delete</a>
#4	<a href="#">(accelerated) and (breast):ti,ab,kw and (irradiat* or radiat* or radiotherap*)</a>	25	<a href="#">edit</a>	<a href="#">delete</a>
#5	<a href="#">(#1 OR #2 OR #3 OR #4)</a>	60	<a href="#">edit</a>	<a href="#">delete</a>
#6	<a href="#">(#5), from 2006 to 2008</a>	16	<a href="#">edit</a>	<a href="#">delete</a>

### Search Results

Show Results in:

**Cochrane Reviews [3]** | Other Reviews [0] | [Clinical Trials \[10\]](#) | Methods Studies [0] | [Technology Assessments \[2\]](#) | [Economic Evaluations \[1\]](#) | Cochrane Groups [0]

[Eit Search](#)

## Appendix 2: Case series and other studies excluded because of short follow-up or no brachytherapy

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