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 has been asked to review the scientific literature on the safety and efficacy of brachytherapy for primary radiation therapy for localized breast cancer. Brachytherapy involves the placement of radioactive sources inside the breast to deliver a relatively high dose of radiation either to gross tumor or to tissue immediately surrounding the site from which the tumor was surgically removed. This is a subset of a relatively new approach to breast cancer radiation therapy known as accelerated partial breast irradiation (APBI).

BACKGROUND

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 2006, there will be an estimated 212,920 new cases of invasive breast cancer in the United States and an estimated 41,000 deaths from this cancer. This represents approximately 31% of all new cancer cases in women and 15% of all cancer deaths in women. In addition to invasive breast cancer, 54,300 new cases of ductal carcinoma in situ (DCIS) breast cancer, a condition also often treated with radiation therapy, will be diagnosed in women in 2006.

The staging system of the American Joint Committee on Cancer defines early stage (Stage I and Stage II) invasive breast cancer as tumors \( \leq 5 \) cm in largest dimension and without distant metastasis or involvement of the fixed axillary or internal mammary lymph nodes (T1-2, N0-1, M0). In the TNM (Tumor Node Metastasis) staging system for breast cancer, stage T1 refers to carcinomas 2.0 cm or less in greatest dimension; stage T2 refers to tumors more than 2.0 cm, but not more than 5.0 cm in greatest dimension; stage T3, to tumors more than 5.0 cm in greatest dimension; and stage T4, to tumors with direct extension to chest wall or skin. Stage N0 refers to tumors without regional lymph node metastasis and N1 to tumors...
with ipsilateral lymph node metastases that are not fixed or grouped. M0 refers to tumors without distant metastases.

Options for surgical management of the primary tumor include breast-conserving surgery (BCS) plus radiation therapy, mastectomy plus reconstruction, and mastectomy alone. Surgical staging of the axilla is usually performed. Survival is equivalent with any of these options as documented in randomized prospective trials and a meta-analysis of the trials (42,000 women).\(^3\)\(^-\)\(^10\) 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.\(^11\)

**Breast Conserving Surgery**

A patient's age should not be a determining factor in the selection of breast-conserving treatment versus mastectomy. A study has shown that treatment with lumpectomy and radiation therapy in women 65 years of age and older produces survival and freedom-from-recurrence rates similar to those of women younger than 65 years of age.\(^12\) It is uncertain whether young women with germ-line mutations or strong family histories are good candidates for breast-conserving therapy. Retrospective studies indicate no difference in local failure rates or overall survival when women with strong family histories are compared to similarly-treated women without such histories.\(^13\)

**Radiation Therapy**

Radiation therapy (as part of breast-conserving local therapy) 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. Two randomized trials conducted in Europe have shown that using boosts from EBR of 10 Gy to 16 Gy reduces the risk of local recurrence from 4.6% to 3.6% at three years (\(p=.044\))\(^14\) and from 7.3% to 4.3% at five years (\(<.0001\)), respectively.\(^15\) The NCI's PDQ on Breast Cancer Treatment cites Wazer et al\(^16\) in concluding that if a boost is used, it can be delivered either by external-beam radiation with electrons or by using an interstitial radioactive implant.\(^17\)

Breast-conserving surgery alone without radiation therapy has been compared with breast-conserving surgery followed by radiation therapy in four prospective randomized trials.\(^4\), \(^10\), \(^18\)\(^-\)\(^20\) All of the trials demonstrated a higher in-breast recurrence rate with breast-conserving surgery alone. All subsets examined benefited from the addition of radiation therapy. A recent meta-analysis pooling data from 42,000 women in 78 randomized trials of radiation therapy versus no radiation therapy clearly demonstrated that radiation
therapy decreases breast cancer specific mortality. Approximately 75% of local recurrences occurred during the first five years of follow-up and large differences in local recurrences translated into significant mortality differences. Among the 7,300 women treated with breast conserving surgery (comparable to those being considered in this review of brachytherapy), radiation therapy was associated with a 19% absolute difference in local recurrence at five years (7% versus 26%) and a 5% absolute reduction in breast cancer mortality (31% versus 36%) and a 5% reduction in total mortality. 21 More recent studies with current surgical and radiation techniques following breast-conserving surgery have decreased local recurrence rates below 3% at five years and 4% at 10 years. 22, 23 This highlights the importance of using concurrent or randomized controls when evaluating new methods of delivering radiation therapy. Recent advances in chemotherapy, hormonal therapy (aromatase inhibitors), and targeted therapy (herceptin), will likely continue to lower local recurrence rates over time.

Despite this strong evidence of the effectiveness of breast-conserving surgery plus radiation, less than half of eligible women in the United States receive such treatment. 24 For some women, fears about local recurrence affect the decision. For others, the fact that radiation therapy is required after partial mastectomy affects the decision about mastectomy versus breast preservation. Many patients maintain a deep-rooted fear of radiation. In some places radiation therapy facilities are not easily accessible. Because the conventional postoperative course of radiation requires daily attendance (Monday to Friday) for five to six weeks, it is often perceived as a major inconvenience. 25-27

**Brachytherapy (BT)**

Brachytherapy, or interstitial implantation of seeds, wires, or other materials that contain radioisotopes, has been used in the treatment of breast cancer since the 1920’s. 28 Brachytherapy was hypothesized to provide more localized delivery of radiation, particularly avoiding irradiation of the skin and intervening tissues when treating deep-seated tumors. This was thought to result in less damage to normal tissue at comparable doses to the tumor site when compared with orthovoltage x-rays. Subsequently, megavoltage machines were developed that produced x-rays of sufficient energy to penetrate more deeply into tissues without energy absorption at or near the surface. Consequently, brachytherapy was used less widely for breast cancer. The use of brachytherapy for breast cancer has 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.

A variety of brachytherapy 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. Older studies of local boost brachytherapy described temporary implantation of the needles, wires, or
seeds after recovery from surgery and completion of whole breast radiation therapy (WBRT). More 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 brachytherapy 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.

In 2002, the FDA approved an interstitial 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 brachytherapy over the past four years. However, there are many uncertainties about outcomes with the device that are underappreciated. The patient characteristics required for balloon-based brachytherapy are more selective than those for traditional interstitial brachytherapy. 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 interstitial brachytherapy. 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 catheter compared with 15 or more entry sites and 15 or more exit sites for interstitial brachytherapy. Comparative trials are needed to assess patient satisfaction and cosmetic outcomes with the two techniques.

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 – 5 to 15 minutes – and then the radioactive source is withdrawn. HDR brachytherapy 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.
Current interest in brachytherapy is partly based on the observation that the majority of ipsilateral breast recurrences after breast-conserving surgery with radiation therapy occur at or near the tumor bed, with only a small proportion of recurrences located in distant regions of the affected breast.\textsuperscript{19, 29-31} In addition, in trials of breast-conserving surgery 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. Together these findings suggest that the major benefit of external beam radiation therapy is related to radiation of the tumor bed. In the United States breast conserving surgery is usually tylectomy, a form of segmental mastectomy that achieves less generous margins than quadrantectomy and results in better cosmetic outcome, adjuvant radiotherapy to the tumor bed could compensate for less extensive surgery.

The advantages of primary brachytherapy 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 an apparent lower incidence of adverse effects. 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 can result in areas of underdosage or overdosage resulting in inadequate treatment or worse cosmetic outcomes; (3) higher dose inhomogeneity causing adverse effects; and (4) 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.

\textbf{Technology Assessment (TA)}

\textbf{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.

The Axxent Electronic Brachytherapy System (Xoft Inc., Fremont, CA) received FDA 510K clearance on December 22, 2005. The same black box warning was noted: “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.

**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) 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 1966 through May 2006. The bibliographies of systematic reviews and key articles were manually searched for additional references. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. The initial search identified 453 articles. 47 articles were reviewed in full.

Clinical studies of interstitial brachytherapy as the primary form of radiation therapy have included one randomized clinical trial,\(^\text{32}\) five cohort studies with controls\(^\text{33-45}\) (Table 1) and at least 16 retrospective and prospective case series involving women with stage I and II tumors (Table 2).\(^\text{32, 40, 41, 46-65}\) Many of the studies have multiple publications describing the cohorts. In addition, the search identified 10 case series evaluating the MammoSite balloon brachytherapy system.\(^\text{61, 66-76}\) No studies were identified that directly compared the balloon technique to whole breast irradiation.

Meaningful comparisons between published series are difficult because of the large variation in patient selection criteria, the varying technical methods, variability and brevity of follow-up times, and addition of hormonal or other therapies. Cohort effects due to changes in surgical technique and adjuvant chemotherapy also confound comparisons. Unfortunately, many of the reported studies of brachytherapy have not separated outcomes for patients based on tumor stage or other important prognostic factors. Furthermore, the one randomized trial\(^\text{32}\) was too small (and reported outcomes after a median follow-up of
only two and a half years) to have enough power to definitively answer questions about the efficacy of brachytherapy.

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. Series reporting overall survival are most numerous; however, differences in overall survival between series may often be explained by patient selection factors. In addition, because many women with breast cancer are older at the time of diagnosis, comorbid conditions often affect overall survival. Breast cancer-specific survival is also useful, but requires long follow-up given the long natural history of early stage breast cancer. Long-term disease-free survival is probably the most useful outcome. Local control is an important intermediate outcome both because local control appears to predict long-term mortality and because the primary goal of breast-conserving surgery with radiation is to preserve the breast: most patients with recurrent local disease are treated with mastectomy.

Because breast preservation is a key goal of therapy, adverse effects and cosmetic outcomes are also of high importance. Adverse effects include breast edema, erythema, fibrosis, hyperpigmentation, hypopigmentation, telangectasias, breast pain, delayed wound healing, local infection, abscess formation, fat necrosis, and fibrosis. These are usually evaluated using the Common Toxicity Criteria with grading ranging from 0: no observable radiation effects to 3: severe radiation effects. Cosmetic outcomes are usually measured using the Harvard criteria: a four-point scale (excellent, good, fair, poor) based on visual comparison of the treated and untreated breast by the examining physician.

Level of Evidence: 2, 3, 4, 5

TA Criterion 2 is met.

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

*Interstitial brachytherapy*

Table 1 summarizes data from one published randomized clinical trial and five cohort comparisons of brachytherapy as monotherapy versus whole breast irradiation alone. Table 2 reports data from 16 case series of brachytherapy monotherapy without controls.

The only randomized clinical trial comparing primary brachytherapy to whole breast irradiation after breast-conserving surgery was published in 2002. Polgar and colleagues reported on 126 patients randomized to
receive 50 Gy whole breast irradiation (n = 63) or brachytherapy alone (n = 63); the latter consisted of either 7 x 5.2 Gy HDR-brachytherapy using Ir-192 (n = 46) or 50-Gy wide-field electron irradiation (n = 17). 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). These selection criteria limit the study to women at very low risk for local recurrence. Not surprisingly, after a median follow-up of 30 months, the locoregional tumor control was 100% in both arms. The 3-year probability of cancer-specific and relapse-free survival was 98.1% and 98.4% in the whole breast irradiation group and 100% and 94.4% in the brachytherapy group, respectively (P = NS). The overall cosmetic outcomes were not reported, however the incidence of fat necrosis was higher in the brachytherapy group (16%) than in the whole breast irradiation group (9%, p=0.22). There was no significant difference between the two treatment arms regarding the incidence of radiation side effects. They conclude that long-term results of phase III trials are required to determine the equivalence of brachytherapy alone, compared with whole breast irradiation in the management of selected patients with early breast cancer. The median follow-up in this study is too short for meaningful comparison to the historical literature on whole breast irradiation, but the results appear promising.

In a second, non-randomized study, Polgar et al compared 45 patients receiving primary interstitial brachytherapy to 80 patients treated with whole breast irradiation during the same time period who met the criteria for brachytherapy (node negative non-lobular invasive tumors ≤ 2 cm in diameter with negative margins and no extensive intraductal component). There were no significant differences between the two groups, although there were modest differences in patient age, ER status, and chemotherapy received. Median follow-up was approximately six and three-quarter years in both groups. Cosmetic results favored the brachytherapy group (84% vs. 68% good/excellent results). Five-year local recurrence rates also favored the brachytherapy group (4.4% vs. 4.7% for whole breast irradiation alone vs. 5.7% for whole breast radiation plus local boost). The fact that the patients receiving whole breast irradiation plus boost had higher recurrence rates suggests that these patients had more aggressive tumors to begin with as randomized trials have demonstrated that local boost decreases local recurrence rates. This once again illustrates that randomization is necessary to ensure that groups are comparable.

In their 2003 report, Vicini and colleagues update their prior results on this use of primary brachytherapy in women with Stage I or II breast cancer undergoing breast-conserving surgery at the William Beaumont Hospital. The women in the series were required to be at least 40 years old with stage I or II infiltrating ductal carcinomas less than 3 cm in diameter with negative surgical margins of at least 2 mm and to have no lymph node involvement. Women were excluded if they had extensive intraductal component, infiltrating lobular histology, DCIS or lobular carcinoma in situ (LCIS). The investigators
compared 199 consecutive women treated with brachytherapy between 1993 and 2001 to 199 historical controls treated with whole breast irradiation between 1980 and 1997 matched for age, tumor size and histology, surgical margins, estrogen receptor status, and use of tamoxifen. The patient characteristics were similar except that median follow-up was significantly longer in the whole breast irradiation group (8.9 years versus 5.0 years, p<.001). Cohort effects due to the whole breast irradiation group being treated on average four years earlier than the brachytherapy group may also explain the other differences: the whole breast irradiation group received less adjuvant chemotherapy (4% vs. 13%, p=.01) and had fewer re-excisions (11% vs. 42%, p<.001). No statistically significant differences were noted in the five-year actuarial rates of ipsilateral breast treatment failure or locoregional failure between patients receiving whole breast irradiation and brachytherapy patients (1% v 1%, P =.65 and 1% v 1%, P =.54, respectively). In addition, there were no statistically significant differences noted in rates of disease-free survival (91% v 87%, P =.30) or overall survival (93% v 87%, P =.23). The whole breast irradiation group did have significantly greater incidence of contralateral breast cancer (4% vs. 1%, p=.03) suggesting either that they were a higher risk group in spite of matching or that the adjuvant therapy that they received was not as efficacious as that given to patients in the brachytherapy group. Cosmetic outcomes were initially reported as good or excellent in 90% of the brachytherapy group and 83% of the whole breast irradiation group. Chen et al\textsuperscript{34} reported on the long term adverse events and cosmetic outcomes at a median follow-up of 6.4 years among women in this study who received brachytherapy. They reported these results at less than six months of follow-up (n=165 patients), at two years (n=128 patients), and greater than five years (n=79 patients). The majority of adverse outcomes were mild (Grade 1/3) and tended to decrease with time. These included breast pain (27% to 14% to 9%), breast swelling (51% to 12% to 7%), erythema and hyperpigmentation. Fibrosis increased from 23% at six months to 53% at two years and 52% at five years, with 5% Grade 2 fibrosis and 1% Grade 3. Fat necrosis also increased with time from 1% at six months to 11% at five years. The majority of patients with the percentage of excellent results increasing from 10% at six months to 33% at five years. The investigators concluded that treatment of breast cancer using an interstitial implant to deliver radiation to the tumor bed alone over four to five days seems to produce five-year results equivalent to those achieved with conventional external radiation therapy (ERT). However, they also noted “extended follow-up will be required to determine the long-term efficacy of this treatment approach.”

The results from this carefully controlled trial are encouraging. The 5-year ipsilateral recurrence rate of 1% in both groups was much lower than the 7% rate reported in the radiation arms of randomized trials of radiation therapy in patients treated with breast conserving surgery.\textsuperscript{21} The remarkably good outcomes in both groups in the William Beaumont series likely reflect the strict inclusion and exclusion criteria used to select
patients for brachytherapy. While encouraging, it also highlights the limited group to whom these results can be generalized. These results clearly will not apply to all women who desire breast-conserving surgery. There were also no statistically significant differences in disease-free or overall survival between the whole breast and brachytherapy groups. However, there were statistically significant differences between groups in the five-year contralateral breast cancer rate, in the percentage who received adjuvant chemotherapy, and in the percentage receiving re-excision. These differences likely reflect the difficulty in using historical controls, even if they are carefully matched. There was also a trend towards worse disease-free and overall survival in the brachytherapy group. These data suggest that brachytherapy as accelerated partial breast irradiation may be as effective as whole breast irradiation in appropriate patients, but also highlight the need for large randomized controlled trials to have confidence in the equivalence of long-term outcomes.

In their 2000 non-randomized comparative trial, King and colleagues\textsuperscript{37} compared outcomes for 144 women with Stage Tis, T1 or T2 tumors ≤4cm with negative surgical margins and no positive lymph nodes. Important prognostic variables were not evenly distributed: the whole breast irradiation group (n=94) was six years younger (p=0.002), more often premenopausal (27% vs 12%, p=0.03) and had more T2 tumors (16% vs. 8%, p=0.17). No statistically significant differences were noted in the six-year rates of locoregional failure between whole breast irradiation (2%) and brachytherapy patients (1%) or disease-free survival (92% v 88%). Cosmetic outcomes were judged good or excellent in 75% of the brachytherapy group and 84% of the whole breast irradiation group.

Finally, Fentiman et al reported on 27 women with tumors ≤4 cm treated with brachytherapy and compared their outcomes with 221 women who were treated with whole breast irradiation and brachytherapy boost.\textsuperscript{35, 36} After six years median follow-up, the local recurrence rate was high (37%). Compared with historical controls there was significantly lower disease free survival (60% vs. 88%, p<0.003). The incidence of distant metastases and overall survival were similar in the two groups. The authors concluded that LDR brachytherapy was not an effective means of achieving local control in patients with operable breast cancer. However, they used an outdated approach to brachytherapy with nine rigid needles that is considered technically inadequate by today’s standards. The study also highlights the need for careful patient selection when considering brachytherapy. Patients with large tumors or positive surgical margins are no longer considered appropriate candidates for brachytherapy.

The study of Ott et al\textsuperscript{39} was included for completeness, but the investigators only reported on the incidence of fat necrosis. Other cosmetic results and clinical outcomes hopefully will be reported in future publications.

Table 2 summarizes the outcomes reported from 16 small case series with a total of 909 patients treated with primary brachytherapy after breast-conserving surgery.\textsuperscript{32, 53, 58, 60, 63} Patient inclusion criteria were
initially quite broad, but more recently have been limited to smaller (< 2-3 cm), node negative, non-lobular
tumors with negative surgical margins and no EIC. The more stringent criteria correspond to series with
lower recurrence rates, but this would be expected as they are lower risk cancers by definition. Median
follow-up ranged from 0.9 to 7.6 years. The five-year rates of local recurrence, often extrapolated from much
shorter follow-up, ranged from 0 to 24%: the remarkably higher recurrence rates occurred in series that
allowed larger tumors with as many as nine positive lymph nodes51 or used non-standard, and arguably
poor brachytherapy technique.80, 81 In one of the case series with longer follow-up,32 Polgar et al reported a
five-year disease free survival rate of 86%. Survival data were rarely reported by the studies. Cosmetic
outcomes were good or excellent in 50%-100% of the patients. Again, the outlier for poor outcomes used a
non-standard approach.80 A number of different dose rate approaches were used including low dose rate
(LDR), medium dose rate (MDR), high dose rate (HDR) and pulsed dose rate (PDR). The total tissue
dosages ranged from 20-60 Gy. Given the wide range of inclusion criteria, technical approaches, and follow-
up time it is impossible to directly compare these results to each other or to historical outcomes.

Balloon brachytherapy (MammoSite)

Table 3 describes the initial 10 case series with the MammoSite brachytherapy system, a HDR balloon-
based system using a standard dosing regimen of 34 Gy in 10 equal fractions over five days. There are no
randomized trials and no direct comparative trials with whole breast irradiation. The series all began
enrollment recently, so must reflect current thinking on the appropriate patient characteristics for
brachytherapy: older women with small, node-negative, non-lobular breast cancers, negative surgical
margins, and no extensive intraductal component. Except for the series of Keisch et al,70, 71 follow-up in
these series was very short, often less than one year. Hence, it is not surprising that no local recurrences
were described in these studies. Most of the publications focused on procedure related adverse events and
cosmetic outcomes. The studies reported between 84% and 97% of the cosmetic outcomes were rated
good or excellent by providers. These were unblinded assessments, so there could be some bias in these
results. Infection and abscess formation was a commonly reported adverse event with rates ranging from
5%73 to as high as 19%.76 Because of the high observed infection rate, some investigators now use
intravenous antibiotic therapy before catheter implantation and 10 days of oral antibiotics after implantation.
Most investigators did not describe whether or not they routinely used antibiotic prophylaxis. Moderate to
severe skin toxicity was seen in up to 9% of patients, usually as a result of the balloon-to-skin distance
being less than the recommended 5-10 mm. Seroma formation occurred in 9% to 50% of patients, so that
many providers now routinely place a drain in the lumpectomy cavity, a procedure that is not usually
performed after standard lumpectomy. Finally, device failure because of catheter leakage or balloon rupture
occurred in 1% to 13% of cases. Usually the device could be replaced without complication. It is also worth
noting that between 10% and 29% of patients thought to be suitable candidates, later had their MammoSite balloons removed because of insufficient balloon-to-skin distance, poor conformance of the balloon to the lumpectomy cavity, positive surgical margins, positive lymph nodes, other histopathological exclusion criteria, or patient discomfort. Many surgeons no longer insert the device at the time of lumpectomy in order to verify the final pathology results prior to implanting the device.

Summary

In general, published data suggest that interstitial brachytherapy can now be performed with acceptably low morbidity rates and low local recurrence rates. The local recurrence rates reported in the studies of interstitial brachytherapy reporting median follow-ups of three to five years (1% to 8%) are much lower than those reported by randomized clinical trials for patients treated with breast conserving surgery without radiation (24% to 37%). These large differences are unlikely to be completely due to selection bias (lower risk patients in the trials of brachytherapy) and improvements in non-radiotherapy treatment modalities. Thus TA criterion 3 is met for interstitial brachytherapy. However, the data for balloon brachytherapy are not yet mature. Data on three to five year recurrence rates have not yet been published for cohorts of patients treated with balloon brachytherapy. Thus TA criterion 3 is not met for balloon brachytherapy.

TA Criterion 3 is met for interstitial brachytherapy

TA Criterion 3 is not met for balloon brachytherapy
Table 1: Comparative Studies of Primary Interstitial Brachytherapy to the Tumor Bed Alone Compared to Whole Breast External Beam Radiation Therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Study subjects</th>
<th>BT isotope</th>
<th>BT Method</th>
<th>Dose (Gy)</th>
<th>Excellent/Good Cosmetic result</th>
<th>5 yr local recurrence rate (%)</th>
<th>5 yr disease free survival (%)</th>
<th>5 yr overall survival (%)</th>
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<tr>
<td>Chen 2006</td>
<td>HC</td>
<td>Stage I/II T&lt;3 cm, N0, No EIC, negative margins. breast-conserving surgery with AD</td>
<td>Ir-192</td>
<td>LDR/HDR</td>
<td>34-50</td>
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<td>Vicini 2003</td>
<td></td>
<td>120 LDR 50 Gy, 54 HDR 34 Gy</td>
<td>Ir-192</td>
<td>LDR/HDR</td>
<td>60</td>
<td>83</td>
<td>1</td>
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<td>Vicini 2001</td>
<td></td>
<td>Historical controls matched for age, T size, histology, N status, ER status, use of tamoxifen, but from more than 13 yrs earlier</td>
<td>Ir-192</td>
<td>LDR/HDR</td>
<td>50</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Baglan 2001</td>
<td></td>
<td>Historical controls matched for age, T size, histology, N status, ER status, use of tamoxifen, but from more than 13 yrs earlier</td>
<td>Ir-192</td>
<td>LDR/HDR</td>
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<td>Historical controls matched for age, T size, histology, N status, ER status, use of tamoxifen, but from more than 13 yrs earlier</td>
<td>Ir-192</td>
<td>LDR/HDR</td>
<td>50</td>
<td>NR</td>
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<td>Historical controls matched for age, T size, histology, N status, ER status, use of tamoxifen, but from more than 13 yrs earlier</td>
<td>Ir-192</td>
<td>LDR/HDR</td>
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<td>Ir-192</td>
<td>LDR/HDR</td>
<td>50</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Ott 2005</td>
<td>CC</td>
<td>BCS between 2/2000 and 3/2002</td>
<td>Ir-192</td>
<td>HDR</td>
<td>30-36</td>
<td>84</td>
<td>4.4</td>
<td>80</td>
<td>78</td>
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<tr>
<td>– BT</td>
<td>33</td>
<td>NR</td>
<td>32-50</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>– WBRT</td>
<td>30</td>
<td>50</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>– WBRT w/BT boost</td>
<td>22</td>
<td>50+12</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Polgar 2004</td>
<td>CC</td>
<td>T1N0, non-lobular. Negative margins, no EIC.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>46-52</td>
<td>68</td>
<td>4.7</td>
<td>73</td>
<td>78</td>
</tr>
<tr>
<td>– BT</td>
<td>45</td>
<td>6.8</td>
<td>46-52</td>
<td>68</td>
<td>4.7</td>
<td>73</td>
<td>78</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>– WBRT</td>
<td>44</td>
<td>6.9</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>– WBRT w/BT boost</td>
<td>36</td>
<td>6.9</td>
<td>50+12</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Polgar 2002</td>
<td>RCT</td>
<td>Stage I, T1 N0 breast-conserving surgery, clear margins, no LCIS, no DCIS, no EIC</td>
<td>Ir-192</td>
<td>HDR</td>
<td>30-36</td>
<td>2.5</td>
<td>94</td>
<td>94</td>
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<tr>
<td>– BT</td>
<td>63</td>
<td>6.8</td>
<td>46/53 received BT, the remainder EBR</td>
<td>Ir-192</td>
<td>HDR</td>
<td>30-36</td>
<td>2.5</td>
<td>94</td>
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<tr>
<td>– WBRT</td>
<td>63</td>
<td>6.9</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>King 2000</td>
<td>CC</td>
<td>Tis T1 T2 ≤4 cm, negative margins, ≥3 positive nodes</td>
<td>Ir-192</td>
<td>HDR</td>
<td>45</td>
<td>75</td>
<td>8</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>– Ir-192 BT</td>
<td>50</td>
<td>6.2</td>
<td>25 HDR, 25 LDR</td>
<td>Ir-192</td>
<td>HDR</td>
<td>45</td>
<td>75</td>
<td>8</td>
<td>88</td>
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<tr>
<td>– WBRT w/BT boost</td>
<td>94</td>
<td>6.2</td>
<td>59</td>
<td>84</td>
<td>5</td>
<td>92</td>
<td>92</td>
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<tr>
<td>Fentiman 1996</td>
<td>HC</td>
<td>T≤4 cm, N0, EIC allowed, positive margins. breast-conserving surgery with AD</td>
<td>Ir-192</td>
<td>LDR</td>
<td>55</td>
<td>83</td>
<td>37</td>
<td>60</td>
<td>85</td>
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<tr>
<td>Fentiman 1992</td>
<td></td>
<td>45 Gy WBRT, 20 Gy Ir-192 boost</td>
<td>Ir-192</td>
<td>LDR</td>
<td>55</td>
<td>83</td>
<td>37</td>
<td>60</td>
<td>85</td>
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Legend:
- BT: Brachytherapy
- BCS: Breast conserving surgery
- N: Node
- PDR: Pulsed Dose Rate
- WBRT: Whole breast radiation therapy
- LCIS: Lobular carcinoma in situ
- ER: Estrogen receptor
- EIC: Extensive intra ductal carcinoma
- DCIS: Ductal carcinoma in situ
- RCT: Randomized clinical trial
- LDR: Low dose rate
- AD: Axillary node dissection
- HDR: High dose rate
- T: Tumor
- CC: Concurrent controls
- NR: Not reported
<table>
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<tr>
<th>Reference</th>
<th>Study design</th>
<th>N</th>
<th>Median follow-up (yr)</th>
<th>BT isotope</th>
<th>BT method</th>
<th>Dose (Gy)</th>
<th>Excellent/Good Cosmetic result</th>
<th>5 yr local recurrence rate (%)</th>
<th>5 yr disease free survival (%)</th>
<th>5 yr overall survival (%)</th>
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<tbody>
<tr>
<td>Kuske 2006</td>
<td>CS</td>
<td>33</td>
<td>2.9 T&lt;3 cm, ≤3 axillary nodes with no extracapsular extension, non-lobular. Negative margins, no EIC.</td>
<td>NR</td>
<td>HDR</td>
<td>34</td>
<td>96</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Wazer 2006</td>
<td>CS</td>
<td>75</td>
<td>6.1 Stage I/II breast-conserving surgery then HDR BT. Stage T1 T2, N0 N1, ≤3 axillary nodes, ≥1 mm margin. No lobular cancer or DCIS.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>34</td>
<td>91</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Perera 2005</td>
<td>CS</td>
<td>39</td>
<td>7.6 T1 T2 N0, EIC allowed. breast-conserving surgery, 13 intra-breast-conserving surgery implant, 26 outpt implantation</td>
<td>Ir-192</td>
<td>HDR</td>
<td>37.2</td>
<td>NR</td>
<td>16</td>
<td>NR</td>
<td>NR</td>
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<td>Das 2004</td>
<td>CS</td>
<td>50</td>
<td>- T1, T2&lt;3 cm, non-lobular, negative nodes, negative margins, no EIC.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>32</td>
<td>36</td>
<td>98</td>
<td>0</td>
<td>100</td>
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<tr>
<td>Fentiman 2004</td>
<td>CS</td>
<td>49</td>
<td>6.3 Age &gt; 70, T≥4 cm, N1 up to 9, positive margins in 43%</td>
<td>Cs-137</td>
<td>MDR</td>
<td>45</td>
<td>81</td>
<td>42</td>
<td>18</td>
<td>NR</td>
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<tr>
<td>Ott 2004</td>
<td>CS</td>
<td>69</td>
<td>2.0 T1, T2≤3 cm, negative margins ≥ 2 mm, node negative, ER+/PR+, no high grade, no EIC</td>
<td>Ir-192</td>
<td>HDR/PDR</td>
<td>32</td>
<td>50</td>
<td>NR</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Polgar 2004</td>
<td>CS</td>
<td>45</td>
<td>6.6 Stage I, T1&lt;2 cm, N0 breast-conserving surgery, clear margins, no LCIS, no DCIS, no EIC</td>
<td>Ir-192</td>
<td>HDR</td>
<td>36.4</td>
<td>98</td>
<td>7</td>
<td>86</td>
<td>100</td>
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<td>Arthur 2003</td>
<td>CS</td>
<td>31</td>
<td>3.5 T&lt;4 cm, N1, no EIC, negative margins, ≤3 nodes positive.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>32</td>
<td>90</td>
<td>0</td>
<td>NR</td>
<td>100</td>
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<tr>
<td>Lawenda 2003</td>
<td>CS</td>
<td>48</td>
<td>1.9 Age ≥18. DCIS or T1N0 &lt; 2 cm. Negative margins. No EIC. No lymphatic or vascular invasion.</td>
<td>Ir-192</td>
<td>LDR</td>
<td>50-60</td>
<td>96</td>
<td>0</td>
<td>100%</td>
<td>NR</td>
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<tr>
<td>Krishnan 2001</td>
<td>CS</td>
<td>24</td>
<td>4 Stage 1, &gt; 60 years old</td>
<td>Ir-192</td>
<td>LDR</td>
<td>20</td>
<td>100</td>
<td>0</td>
<td>NR</td>
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<td>Samuel 1999</td>
<td>CS</td>
<td>11</td>
<td>5.6</td>
<td></td>
<td>LDR</td>
<td>46-55</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
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<td>Cionini 1995</td>
<td>CS</td>
<td>115</td>
<td>4.2</td>
<td></td>
<td>LDR</td>
<td>50-60</td>
<td>NR</td>
<td>6</td>
<td>NR</td>
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<td>Clarke 1994</td>
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<td>45</td>
<td>1.5</td>
<td></td>
<td>HDR</td>
<td>32-40</td>
<td>NR</td>
<td>16</td>
<td>NR</td>
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<td>Jewell 1987</td>
<td>CS</td>
<td>107</td>
<td>4.3</td>
<td></td>
<td>LDR</td>
<td>NR</td>
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<th>Reference</th>
<th>Study design</th>
<th>N</th>
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<th>Study subjects</th>
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<th>BT Method</th>
<th>Dose (Gy)</th>
<th>Excellent/Good Cosmetic result</th>
<th>5 yr local recurrence rate (%)</th>
<th>5 yr disease free survival (%)</th>
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<tr>
<td>Dickler 2005&lt;sup&gt;6&lt;/sup&gt;</td>
<td>CS</td>
<td>30</td>
<td>13</td>
<td>Inc/Exc not described. DCIS + IDC, N1 allowed.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>34</td>
<td>93</td>
<td>NR</td>
<td>NR</td>
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<td>DiFronzo 2005&lt;sup&gt;57&lt;/sup&gt;</td>
<td>CS</td>
<td>40</td>
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<td>Age ≥ 45, invasive ductal carcinoma ≤ 2 cm, negative lymph nodes, no EIC, ≥ 5mm lumpectomy to skin distance.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>34</td>
<td>97</td>
<td>NR</td>
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<td>Harper 2005&lt;sup&gt;59&lt;/sup&gt;</td>
<td>CS</td>
<td>37</td>
<td>0.6</td>
<td>DCIS or invasive carcinoma ≤ 3 cm with “appropriate” tumor-skin and tumor chest wall distance, ≤ 3 positive nodes, at least 5 mm balloon-skin distance once inflated.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>34</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Keisch 2005&lt;sup&gt;70&lt;/sup&gt;</td>
<td>CS</td>
<td>43</td>
<td>2.5</td>
<td>IDC T1N0M0, age &gt;45. Negative margins., No EIC, ≥ 5mm lumpectomy to skin distance once inflated.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>34</td>
<td>84</td>
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<tr>
<td>Keisch 2003&lt;sup&gt;71&lt;/sup&gt;</td>
<td>CS</td>
<td>19</td>
<td>1.0</td>
<td>Node negative DCIS or ductal carcinoma ≤ 2 cm, at least 5 mm balloon-skin distance.</td>
<td>Ir-192</td>
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<td>34</td>
<td>90</td>
<td>NR</td>
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<td>Stolier 2005&lt;sup&gt;73&lt;/sup&gt;</td>
<td>CS</td>
<td>1419</td>
<td>NR</td>
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<td>Ir-192</td>
<td>HDR</td>
<td>34</td>
<td>90-95</td>
<td>NR</td>
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<tr>
<td>Vicini 2005&lt;sup&gt;14&lt;/sup&gt;</td>
<td>CS</td>
<td>19</td>
<td>NR</td>
<td>Age ≥ 45, invasive ductal carcinoma ≤ 2 cm, negative lymph nodes, no EIC or lobular cancer, ≥ 5mm lumpectomy to skin distance.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>34</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Dowlatshahi 2004&lt;sup&gt;68&lt;/sup&gt;</td>
<td>CS</td>
<td>112</td>
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<td>Age≥40, Tis./1/2, N0/I.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>34</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Richards 2004&lt;sup&gt;72&lt;/sup&gt;</td>
<td>CS</td>
<td>28</td>
<td>0.9</td>
<td>Age ≥ 45, invasive ductal carcinoma ≤ 2 cm, ≤ 3 lymph nodes, ≥ 2 mm negative margins, no EIC, ≥ 5mm lumpectomy to skin distance.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>34</td>
<td>86</td>
<td>0</td>
<td>16</td>
<td>NR</td>
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<td>Shah 2004&lt;sup&gt;41&lt;/sup&gt;</td>
<td>CS</td>
<td>28</td>
<td>1.6</td>
<td>IDC≤ 2 cm, N0, , ≥ 2 mm negative margins, no EIC, ≥ 5mm lumpectomy to skin distance.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>34</td>
<td>93</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
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<td>Zannis 2003&lt;sup&gt;76&lt;/sup&gt;</td>
<td>CS</td>
<td>21</td>
<td>NR</td>
<td>Age ≥45, IDC≤3 cm, N0, , ≥ 2 mm negative margins, no EIC, ≥ 5mm lumpectomy to skin distance.</td>
<td>Ir-192</td>
<td>HDR</td>
<td>34</td>
<td>NR</td>
<td>NR</td>
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**BT:** Brachytherapy, **BCS:** Breast conserving surgery, **N:** Node, **WBRT:** Whole breast radiation therapy, **LCIS:** Lobular carcinoma in situ, **ER:** Estrogen receptor, **EBR:** External beam radiation therapy, **DCIS:** Ductal carcinoma in situ, **RCT:** Randomized clinical trial, **LDR:** Low dose rate, **EID:** Extensive intraductal disease, **CC:** Concurrent controls, **HDR:** High dose rate, **AD:** Axillary node dissection, **HC:** Historical controls, **NR:** Not reported, **T:** Tumor, **CS:** Case series
TA Criterion 4: The technology must be as beneficial as any established alternatives.

The results from the randomized clinical trial of Polgar and colleagues\textsuperscript{32} are encouraging. There have been no local recurrences in either arm and the disease free survival rates (94\% and 98\%) are better than those reported in comparable clinical trials of radiation therapy.\textsuperscript{14, 15, 21, 77, 83} However, the median follow-up time is only two and one-half years and the number of participants (63 in each arm) too small to draw any meaningful conclusions.

Some of the studies with controls\textsuperscript{35, 37, 41, 45} have longer follow-up (median six years), but only a total of 321 participants received brachytherapy. The best of these studies\textsuperscript{45} had matched controls and a very low rate of local recurrence (1\%) with a median follow-up of five years. However, there was a trend towards better disease free survival at five years for whole breast irradiation (91\%) compared with brachytherapy (87\%). Furthermore, Fentiman and colleagues\textsuperscript{35, 36} reported significantly worse disease free survival at five years for brachytherapy group (60\%) compared with whole breast irradiation (88\%, \textit{p}<0.003), albeit with patient selection and brachytherapy techniques not considered appropriate by today’s standards. As noted above under TA Criterion 3, there are problems with the control groups in each of these studies, which limit confidence in the generalizability of the findings. As a whole, the data suggest that interstitial brachytherapy may be equivalent to whole breast irradiation, but randomized comparisons using current technologies and appropriate patient selection are needed. The data on the MammoSite device are much more limited and no conclusions can be drawn.

Additionally, a randomized controlled study by Magee and colleagues reported on 708 women with localized breast cancer treated with breast-conserving surgery and then randomized to either local radiation to the tumor bed or whole breast irradiation.\textsuperscript{84} After a median eight years of follow-up the local recurrence rate was significantly higher in the group randomized to local radiation therapy (25\%) compared to the group randomized to whole breast irradiation (13\%, \textit{p}<0.0001). The technology used in the study would not now be considered optimal, but the results do call into question the hypothesis that accelerated partial breast irradiation is necessarily equivalent to whole breast irradiation. Randomized trials are necessary to ensure that we do not offer women an inferior alternative to current standards.

\textit{Modeling}

One cost-effectiveness analysis\textsuperscript{85} done from a societal perspective compared eight different approaches to radiation therapy including accelerated partial breast irradiation (using interstitial brachytherapy, the MammoSite balloon and intensity modulated radiation therapy) and whole breast irradiation using a variety of techniques. Whole breast irradiation techniques were the most cost effective because the increased
technical costs associated with accelerated partial breast irradiation more than offset patient costs from lost wages and travel to and from the home to the clinic. The model was fairly simplistic as it assumed equal efficacy, toxicity, and quality of life for all eight techniques and focused only on a 60 year old woman with Stage I breast cancer. Any increase in adverse outcomes or decrease in effectiveness associated with accelerated partial breast irradiation would only magnify the differences. Once more detailed data on effectiveness and toxicity are available, more sophisticated analyses could be done. Until that time, these results should be considered preliminary at best.

**Ongoing randomized trials**

The literature search identified five ongoing randomized clinical trials\textsuperscript{30, 32, 86-89} of accelerated partial breast irradiation. The three trials with brachytherapy arms plan to randomize 4,740 women.\textsuperscript{32, 86-88} All three 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\textsuperscript{87}. The investigators plan to randomize 3,000 women to partial breast irradiation with interstitial implants, MammoSite balloon, 3D conformal radiation therapy or to standard whole breast irradiation at 45 to 50 Gy with a 10 Gy boost. According to the investigators, this is the fastest accruing breast cancer clinical trial in history.

In summary, the authors of the two best studies\textsuperscript{40, 45} comparing brachytherapy to whole breast irradiation both conclude that the results are promising, but that phase III trials with longer follow-up are needed to assess the long term efficacy of brachytherapy compared with standard therapy. One of the four comparative studies reported significantly worse outcomes with brachytherapy.\textsuperscript{35} Finally, the only large randomized clinical trial comparing partial breast irradiation alone (using external beam radiation) to whole breast irradiation found significantly higher local recurrence rates with local therapy.\textsuperscript{84} The one randomized trial comparing brachytherapy to whole breast irradiation had no local recurrences in either arm, but it was small with short follow-up and disease free survival was higher in the whole breast irradiation arm. There are three large, ongoing randomized trials of brachytherapy including one large trial recruiting patients in the United States. It is not yet clear that primary brachytherapy is equivalent to standard therapy with whole breast irradiation after breast-conserving surgery. If there was consensus regarding the equivalence of brachytherapy to whole breast irradiation, then the ongoing clinical trials would not still be accruing patients.

TA Criterion 4 is not met.

**TA Criterion 5:** The improvement must be attainable outside the investigational setting.
The published data represent brachytherapy used primarily in investigational settings with considerable expertise in brachytherapy. Additionally, most radiation oncologists do not have extensive experience in breast brachytherapy as most training programs, particularly in the United States, do not teach interstitial breast brachytherapy. 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 brachytherapy. The MammoSite balloon is technically less demanding, but cannot be used in many women. Given the limited experience of most radiation oncologists with breast brachytherapy, close adherence to the American Brachytherapy Society guidelines\textsuperscript{90} is advisable. However, given that the improvements have not yet been proven in the investigational setting, TA criterion 5 is not met.

**TA Criterion 5 is not met.**

**CONCLUSION**

One small prospective randomized, controlled trial has been published assessing the effectiveness and morbidity of primary brachytherapy after breast-conserving surgery for Stage I breast cancer compared to whole breast irradiation after breast-conserving surgery. The results were promising, but the small number of participants and short follow-up do not permit any firm conclusions. Five cohort studies with controls have been reported, but are too small and short to establish equivalence with existing alternatives. One of these studies reported significantly worse outcomes with brachytherapy. One large clinical trial compared local external beam radiation to whole breast irradiation and reported significantly higher rates of local recurrence in the group randomized to local radiation therapy. It is not yet clear that local brachytherapy after breast-conserving surgery results in rates of local recurrence and disease-free survival that are equivalent to those obtained by the standard therapy of whole breast irradiation after breast-conserving surgery.

In early 2005, the American Society of Breast Surgeons Consensus Statement on accelerated partial breast irradiation, including brachytherapy, stated “The published data on APBI are not extensive or definitive; it is preferable that APBI be performed as part of ongoing investigative protocols.”\textsuperscript{67} Although they are now permissive on their updated statement, they support restricting the technology to patients at least 50 years of age with node negative DCIS or invasive ductal carcinoma ≤2.0 cm and negative surgical margins. These selection criteria are even more restrictive than the Vicini case series at the William Beaumont Hospital or the ongoing NSABP B-39/RTOG 0413 randomized trial. The consensus in the field appears to be that accelerated partial breast irradiation, including brachytherapy, is a promising alternative to whole breast irradiation, 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.
Fortunately, there are five ongoing randomized clinical trials of accelerated partial breast irradiation which should provide more definitive data in the future.

**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.

*The California Technology Assessment Forum voted unanimously in favor of this recommendation.*

June 21, 2006
RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

In October 2002, the BCBSA TEC found that accelerated partial breast irradiation using brachytherapy as the sole radiation treatment after breast-conserving surgery for early stage breast cancer did not meet TEC criteria.

Centers for Medicare and Medicaid Services (CMS)

No specific mention of a National Coverage Decision regarding this technology was found. Several individual state CMS contractors have coverage decisions regarding the use of APBI. In California, the National Health Insurance Company has a decision as of January 1, 2005 noting the following:

“APBI after breast-conserving surgery for early stage breast cancer may be considered as a medically appropriate treatment option only when all of the following strict selection criteria are met:

Age: Equal to or greater than 50 years old,
Diagnosis: Invasive ductal carcinoma,
Size of tumor: Less than or equal to 2cm,
Margin status: Negative - at least 2 mm in all directions,
Nodal status: Negative axillary lymph node dissection or sentinel lymph node evaluation.

California Radiological Society (CRS)

CRS is in agreement with the other radiological societies.

American Society for Therapeutic Radiology and Oncology (ASTRO)

ASTRO representatives provided testimony in favor of the use of this technology.

American Cancer Society (ACS)

ACS does not have a specific opinion on the use of this technology. A representative will not be able to attend.

Association of Northern California Oncologists (ANCO)

ANCO representation provided support for the use of this technology.
Medical Oncology Association of Southern California (MOASC)

MOASC supports the use of this technology.

American College of Radiation Oncology (ACRO)

ACRO representative provided testimony in support of this technology.

American Brachytherapy Society (ABS)

The ABS was contacted for opinion however a response was not received.

American Society of Breast Surgeons (ASBS)

The ASBS representative provided testimony in support of the use of this technology.
**ABBREVIATIONS USED IN THIS ASSESSMENT:**

*Common Abbreviations Used Throughout the Review*

- **BT:** Brachytherapy
- **EBR:** External beam radiation
- **WBRT:** Whole breast radiation therapy
- **DCIS:** Ductal Carcinoma in situ
- **LCIS:** Lobular Carcinoma in situ
- **LDR:** Low dose rate
- **HDR:** High dose rate
- **PDR:** Pulsed dose rate
- **MDR:** Medium dose rate
- **BCS:** Breast conserving surgery
- **APBI:** Accelerated partial breast irradiation
- **EIC:** Extensive Intraductal Component
- **ERT:** External Radiation Therapy
REFERENCES


81. Vicini F, Edmundson G, Arthur D. In regard to Poti et al.: Partial breast irradiation with interstitial (60)co brachytherapy results in frequent grade 3 or 4 toxicity: Evidence based on a 12-year follow-


