Brachytherapy in the Treatment of Breast Cancer

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Introduction

Breast brachytherapy has been in use for most of the 20th century. In the 1920s, Keynes used interstitial radium needles to implant the entire breast, and frequently, the peripheral lymph nodes, to treat cancer of the breast.[1] With the advent of megavoltage radiation, external-beam radiation therapy (EBRT) was used to treat the whole breast, with brachytherapy being utilized as a boost for unresected tumors. The high total doses resulted in poor cosmetic results, and therefore, the trend was to perform lumpectomy followed by EBRT and lower doses of brachytherapy.[2,3]

Published reports, however, showed that lumpectomy (with biopsy-negative margins) followed by EBRT without an interstitial boost was as effective as mastectomy.[4] This raised the question of whether boosts were necessary. In addition to these reports, the widespread availability of the less invasive electron-beam boost led to a decline in the role of brachytherapy boost in treating primary breast cancers.

Whole-breast EBRT involves a 6-week course of fractionated treatments. In contrast, brachytherapy can be completed in a 4- to 5-day treatment course.[5-7] This feature has renewed interest in breast brachytherapy as a sole treatment modality after lumpectomy. The American Brachytherapy Society (ABS) recognizes that EBRT is the standard radiation modality used in the treatment of breast cancer. Brachytherapy is an alternative that is being investigated for specific circumstances.

The ABS Guidelines for Brachytherapy

Breast brachytherapy techniques vary widely, and few radiation oncologists have extensive experience in this realm. Because limited guidelines exist for the clinical use of this therapy,[8] the ABS formed a panel to issue guidelines specifically for the use of brachytherapy in breast carcinoma.

The ABS panel consisted of selected ABS members with expertise in breast brachytherapy. The panel performed a literature review, and supplemented with their clinical experience and biomathematical modeling, formulated specific recommendations and directions for future investigations in breast brachytherapy. Technical details were also included to benefit readers who may not be able to find such details in standard textbooks.

Recommendations were made by consensus and supported by evidence in the literature whenever possible. The ABS’s categories of consensus are similar to those used by the National Comprehensive Cancer Network.[9] Unless specifically noted, these recommendations generally reflect a category 2 consensus. Definitions of categories 1 through 3 are as follows:

**Category 1:** There is uniform panel consensus based on high-level evidence that the recommendation is appropriate.

**Category 2:** There is panel consensus based on lower-level evidence, including nonpublished clinical experience, that the recommendation is appropriate. There is no major disagreement among panel members.

**Category 3:** There is major disagreement among panel members that the recommendation is
appropriate.

The initial report was revised due to additional comments of external experts who were not members of the panel. These reviewers are listed in the acknowledgments below. The Board of Directors of the ABS approved the final document.

General Considerations Regarding Technique

Clinical Target Volume

The ABS recommends precise definition and meticulous delineation of the clinical target volume. There are various methods of identifying this parameter, including the use of surgical clips, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, nonionic radio-opaque contrast material, and/or direct visualization at the time of surgery.[8,10-12] Patients should be seen by both a surgeon and radiation oncologist before treatment.

The optimum volume to be treated by breast brachytherapy is controversial; treating too small a volume would result in high recurrence rates.[13,14] The ABS currently recommends a 2-cm margin around the lumpectomy cavity. This results in the irradiation of a large volume, but reduces local recurrence. Only controlled clinical trials will be able to demonstrate whether it is possible to treat a smaller volume and still obtain good local control.

The clinical target volume is defined as the volume encompassed by an irregularly shaped surface approximately 2 cm outside of the excision cavity, unless extending the margin would go beyond the breast tissue.[8] If the skin restricts the superficial margin, then the superficial target margin is redefined as 0.5 cm below the skin surface. Similarly, if the chest wall restricts the deep margin, the new deep-target margin boundary would be redefined as the surface of the chest wall.

The margin can be modified under special circumstances, depending on the tumor size and extent of surgical resection (consensus category 3). For brachytherapy, the clinical target volume is the same as the planning-target volume. In order to guarantee adequate coverage, the treated volume is ideally larger than the target volume.[8]

Treatment Planes

The ABS recommends using a minimum of two planes, unless the amount of breast tissue limits the target volume to less than a 2-cm thickness. For a larger target volume (> 2.5- to 3-cm thickness), additional planes should be considered.

Optimized values of interplanar spacing for a range of biplanar implant sizes are available.[15-17] Within a given plane, the separation between catheters is 1.0 to 1.5 cm. Ideally, the catheters should extend 1 to 2 cm beyond the edge of the clinical target volume. Coverage of the target volume along the length of the catheters is determined by the length of the active sources or dwell positions along each catheter. They should also extend 1 to 2 cm beyond the target volume.

To allow for this, skin entry and exit points should extend 2 to 4 cm beyond the edge of the target volume. This will allow a "dead space" of 1 to 2 cm from the last radioactive sources to the skin, which minimizes the risk of skin hyperpigmentation and telangiectasia.[8] To minimize the risk of a high dose to the ribs, a minimum distance of 0.5 cm between catheters in the deep plane and the ribs is suggested.

If a wide separation between catheters or planes is noted, or if a peripheral edge at the clinical target volume is not covered by the prescription isodose curve, it is preferable to insert additional catheters to avoid underdosage. Similarly, if the target volume is thicker on one side, additional crossing catheters may be required to adequately cover the thicker side. A less desirable alternative would be a higher weighting (increased dwell times) on the thicker side. However, this may lead to
problematic local high-dose regions surrounding these catheters.

Catheter Concerns

The ABS deems the use of rigid templates as optional. The advantage of templates is that they effect precise geometric source distributions. However, this strategy may produce coverage problems in cases of curved, irregularly shaped target volumes. The freehand technique, especially with an open wound, permits catheter placement that conforms to the shape of the lumpectomy cavity. Nonetheless, this may result in less uniform isodose distributions.

The ABS recommends the appropriate use of dose optimization in high-dose-rate therapy. However, optimization should not be used to compensate for inadequate or improper catheter placement. It is preferable to have too many catheters implanted rather than too few. Since the catheters are commonly left in place for 1 to 2 weeks when brachytherapy is used as a sole modality, the ABS recommends appropriate catheter care to reduce the risk of infection and minimize discomfort.[8] The ABS recommends adequate treatment planning to ensure dose coverage and dose homogeneity within the clinical target volume. These characteristics define the quality of a breast implant. Iridium-192 is the most commonly used isotope for both low-dose-rate and high-dose-rate breast brachytherapy. The ABS recommends the following procedures for calibration and quality assurance of high-dose-rate units as specified by the device manufacturer, license conditions, and national professional organizations.[16-21] The ABS also recommends in-house calibration of low-dose-rate sources as specified by the American Association of Physicists in Medicine (AAPM).[18,22]

For large numbers of brachytherapy sources, it is recommended that at least 10% of sources be checked for consistency with the manufacturer’s stated value. Tolerance levels for possible discrepancies and specifications for well counters used for this purpose are available in the literature. The AAPM recommendation should also be followed for source-activity specification and dose-calculation formalism.[22]

High-Dose-Rate Implants

Due to the flexibility of dwell-time optimization, a high dose rate can provide greater dose homogeneity than a low dose rate. For high-dose-rate implants, it is possible to optimize dose homogeneity by requiring that a uniform dose be delivered in the plane midway between and parallel to the implant planes. To achieve this with biplanar implants, the separation between the ideally positioned catheter planes can be calculated as the target thickness divided by the square root of 2.[16] Dwell times in this case will assume a Manchester-type configuration,[23] with longer dwell times near the edges of the implanted planes. Foreknowledge of the optimal interplanar separation will provide the clinician with a concrete physics-based plan of action with which to begin the procedure. Although the actual centering and dimensions of the implant will deviate from the ideal, small deviations are not expected to have a great impact on the clinical effectiveness of the treatment.[16]

For any given set of dose constraints, dwell-time optimization programs can often yield a wide disparity in dwell times between neighboring dwell positions. This, in turn, can lead to intense local hot spots. Dwell times should be examined before treatment to avoid such extreme variations.

Non-CT-Based Treatment

For non-CT-based treatment planning, the ABS recommends that either orthogonal or two variable-angle films of the implanted breast with dummy seeds in each catheter be obtained for dosimetry calculations. Additional film, with planes parallel and perpendicular to the implant plane, should be produced to aid in visualization of the target dimensions and to determine the relationship with the chest wall and position of clips. These films are used to define the clinical target volume and produce computer-generated isodose curves.

Commonly obtained calculation planes are the central transverse, extreme transverse, coronal, and sagittal planes. The coronal and sagittal planes are orthogonal to the central transverse plane and to each other, but may not correspond to the strict anatomic definition of "coronal" and "sagittal."
the purpose of breast brachytherapy, these calculation planes are defined as follows:[8]:

**Central Transverse Plane:** The plane through the geometric center of the implant, slicing perpendicularly through the catheters.

**Extreme Transverse Planes:** Located 1 cm proximal from each edge of the clinical target volume, and parallel to the central transverse plane.

**Coronal Plane:** The plane midway between the two implant planes (or between any two, if there are more), and parallel to them. Note that this need not be coronal in strict anatomic terms.

**Sagittal Plane:** The plane perpendicular to the other two planes and passing through the implant center. Note that this need not be sagittal in strict anatomic terms.

It should be recognized that each isodose plot provides only two-dimensional (2D) information that is relevant to its corresponding calculation plane.

**Image-Based Treatment Planning**

The ABS considers image-based treatment planning to be ideal due to the additional information that can be obtained. If image-based planning is available, isodose plots on all CT cuts or a representative selection of CT cuts should be generated. If possible, three-dimensional (3D) images of the target and relevant isodose surfaces should be examined.

A dose-volume histogram of the clinical target volume provides useful information and should be used whenever available to aid in the assessment of dose coverage and homogeneity.[24] A dose-volume histogram of the skin can be useful for predicting cosmesis.

The plan evaluation should include an assessment of target volume coverage, including a determination or estimate of the fraction of the target volume that is receiving the prescription dose ($V_{100}$). If 3D planning is available, the percentage volume of target contained within various isodose surfaces (e.g., $V_{90}$, $V_{100}$, $V_{150}$, $V_{200}$) should be obtained and correlated with the outcome. There was no consensus (category 3) regarding the acceptable value for $V_{100}$. However, it was felt that one should be concerned if the $V_{100}$ is significantly less than 90%. The actual volume of the target volume (in cubic centimeters) should be obtained and recorded.

Several schemes have been put forward to plan and evaluate interstitial iridium-192 implants and to assess dose homogeneity within an implant.[25-29] For 2D planning, the isodose plots of the central reference plane can be used to determine the mean central dose (or dose rate) of a measurement that is geometrically identical to the basal dose (or dose rate) of the Paris System.[25]

**Dose-Homogeneity Index**

The International Commission on Radiation Units and Measurement defines the dose homogeneity index as the ratio of the minimum target dose to the mean central dose.[30] The Radiation Therapy Oncology Group (RTOG) defines the dose homogeneity index as the ratio of the prescribed dose to the mean central dose.[8] The ABS recommends the use of the RTOG definition, since its value is dependent on the choice of the prescription isodose line. The maximum dose to skin for brachytherapy as a boost is typically kept below 50% of the implant dose. For implant only, the ABS suggests keeping the skin dose limited to the prescribed dose.

**Brachytherapy as the Sole Modality for Subclinical Disease**

For more than a century, the management of breast cancer was based on the premise that the entire breast should be treated. The published literature, however, indicates that the vast majority of recurrences occur in the vicinity of the surgical excision site—both with and without whole-breast irradiation.[31-36]
Remote relapse rates are approximately 0% to 3.5% in trials with lumpectomy alone or lumpectomy and breast irradiation.[31-37] These published trials did not exclude patients with biologically significant multicentric breast disease. Therefore, it has been hypothesized that the primary benefit of breast irradiation following tumor excision exists in its effects on the breast tissue immediately surrounding the lumpectomy cavity.

Numerous clinical trials have been undertaken to evaluate the treatment of breast cancer by brachytherapy alone (Table 1).[5,8,10,38-43] Whereas most of the early results are comparable to standard breast conservation, some reported results are not. These differences emphasize the importance of patient selection and treatment approach.

The ABS recognizes that EBRT is the standard radiation modality used in the treatment of breast cancer. At the present time, the use of brachytherapy as a sole modality should be considered investigational and should be performed in the context of a controlled clinical trial. The ABS acknowledges the significant increase in the use of brachytherapy as the sole treatment in the management of early-stage breast cancer after lumpectomy. In view of promising early results, the ABS encourages the enrollment of these patients in clinical trial protocols in order to address the issues raised in this report.

The ABS recommends the routine use of dose-volume histograms and the dose homogeneity index (as defined by the RTOG) as tools to ensure reproducible brachytherapy and to allow interinstitutional comparison. To demonstrate that a 4- to 5-day brachytherapy regimen is an acceptable alternative to the standard 6 weeks of EBRT, the ABS recommends adherence to these guidelines. If accelerated treatment using brachytherapy yields comparable local control and cosmetic outcome, it would likely improve the quality of life for women with breast cancer. Just as importantly, it would also extend the option of breast conservation to more women.

With the successful completion of the RTOG 95-17 phase II brachytherapy trial, the ABS recommends the initiation of a randomized clinical trial comparing brachytherapy alone to whole-breast EBRT. An accelerated (4- to 5-day) brachytherapy treatment course can be an attractive alternative to 6 weeks of EBRT, especially in the following groups:

- patients living a long distance from radiation oncology treatment facilities
- patients who lack transportation
- professional women whose schedules will not accommodate a 6-week course of therapy
- elderly, frail patients in poor health who may not be able to travel for a prolonged course of daily treatment
- women with large breasts who may have unacceptable toxicity with EBRT.

**Patient Selection Criteria**

Patients who are not acceptable candidates for breast-conserving therapy should not be considered for brachytherapy alone.[13,31,44-46] The ABS recommends that to be considered for treatment with brachytherapy as a sole modality, patients should have T1/2, N0 histologically confirmed, unifocal, invasive ductal carcinoma of the breast, with a lesion < 3 cm, treated with lumpectomy and axillary dissection.

The ideal patient has negative surgical margins of excision. However, patients with close, but negative, inked histologic margins of lumpectomy or reexcision specimen are appropriate candidates.
Margins are generally considered positive if a tumor exists at the inked resection margin; margins are deemed close, but negative, if the tumor exists within 2 mm of the inked margin; and margins are considered negative if the tumor is at least 2 mm from the inked edge.[8,47-49]

Special Circumstances: The treatment of node-positive patients is controversial. Some panel members feel that patients with less than four positive axillary nodes with no extracapsular extension (with at least eight sampled axillary lymph nodes), or a negative sentinel node, could also be considered for brachytherapy as the sole modality (category 3). Patients must have negative postlumpectomy or postreexcision mammography if they had presented with malignancy-associated microcalcifications. There should be no remaining suspicious microcalcifications in the breast before brachytherapy.[32]

Insufficient evidence exists regarding the use of brachytherapy in patients with invasive lobular histology. Some panel members expressed concern about biologically significant multicentricity and multifocality with this histology (category 3).[6,50] Treatment of patients with ductal carcinoma in situ (DCIS) by this modality is also controversial, but considered acceptable by the panel as long as the other selection criteria are met. Specifically, small, unifocal DCIS that is excised with clear margins appears to have recurrence rates and patterns of failure that are similar to those of invasive cancer (category 3).[51]

Patients with collagen-vascular diseases, Paget’s disease of the nipple, or significant skin involvement are poor candidates for breast-conservation therapy. Moreover, patients with a breast that is technically unsuitable for brachytherapy should not be considered for such treatment.

Dose of Sole-Modality Brachytherapy

The ABS recognizes that an optimal dose has not been established, and that the following range of doses may be appropriate:

Low Dose Rate: The ABS recommends a dose range of 45 to 50 Gy to the clinical target volume.[7,8,10] Traditionally, the dose has been administered at about 10 Gy/d, at a rate of 30 to 70 cGy/h.[52]

High Dose Rate: The ABS recommends a total dose of 34 Gy in 10 fractions to the clinical target volume.[8,10,53] Treatments of 3.4 Gy are generally administered at two fractions per day, separated by at least 6 hours. This dose, which was originally derived using the linear quadratic model to determine the biological equivalence of a 45-Gy low dose rate,[54] was used in the phase II RTOG trial.[8] However, since the actual alpha/beta ratio of breast tissues and tumors is not known, it should be realized that these doses may not be exactly bioequivalent to the corresponding doses of the low dose rate.

Pulsed Dose Rate: The pulsed dose rate is rarely used in the United States. That said, doses used for this schedule are similar to those employed for the low dose rate.

Despite the common use of a brachytherapy boost following EBRT to the whole breast, its necessity remains controversial. A randomized trial from Lyon, France, addressing this issue demonstrated a small but statistically significant improvement in local control with the addition of a boost.[55] Another randomized trial from Nice, France, showed improvement in local control, but this difference was not statistically significant.[56] Results are awaited from the European Organization for Research and Treatment of Cancer (EORTC) randomized trial consisting of approximately 5,500 patients. Other studies have not shown any improvement with a brachytherapy boost.[48]

If a boost is deemed necessary, either EBRT or brachytherapy can deliver the desired dose.[57-61] Acceptable local control and cosmetic results have been reported (Table 2).[52,57-59,62-69] The cost and time required (for both the patient and physician) for these two boosting techniques differ greatly. In addition, brachytherapy adds the risk of an invasive procedure with an outcome that is highly dependent upon the expertise of the physician/physicist team.[10,58] Therefore,
Brachytherapy should be used selectively as a boosting technique.

**Benefits of Brachytherapy Boost**

Brachytherapy can deliver a higher dose to the clinical target volume with a lower dose to the skin, and as a result, it has the potential for an improved cosmetic result.[57,70] Situations in which a higher dose may be required because of a larger tumor burden include[57-59,61]:

- close, positive, or unknown margins
- an extensive intraductal component (category 3)
- a younger patient.

In addition, brachytherapy has been considered potentially advantageous over EBRT when the location/shape of the clinical target volume allows brachytherapy to provide better coverage while reducing the surrounding normal tissue dose. Examples include deep tumors in a large breast or a clinical target volume of irregular thickness.[57-59,61]

The brachytherapy boost can be administered before or after EBRT. There is generally a 1- to 2-week gap between the EBRT and brachytherapy. The ABS does not favor one method of sequencing over the other. The ABS recommends defining the clinical target volume for boost as it would be defined with brachytherapy alone.

Publications showing inferior cosmetic outcomes after brachytherapy boost have lacked the necessary attention to technical details such as dose homogeneity.[63,66,68,69,71] Recent experiences have demonstrated equivalent or superior results to electron-beam boosting despite the higher doses. Various low-dose-rate boost doses and high-dose-rate fractionation schemes have been used.

**Dose of Brachytherapy After Whole-Breast EBRT**

Following 45 to 50 Gy of EBRT to the whole breast, doses for brachytherapy are as follows:

- **Low Dose Rate:** The ABS recommends a total dose of 10 to 20 Gy (at 30 to 70 cGy/h) prescribed to the clinical target volume depending on the surgical margins and EBRT dose.

- **High Dose Rate:** Data on the use of a high dose rate as a boost are limited. The ABS recommends that a dose-fractionation scheme be used that yields early and late effects approximately equivalent to those of a 10- to 20-Gy low dose rate. Examples of fractionation schemes that have been used are included in Table 2.

- **Pulsed Dose Rate:** The pulsed dose rate is rarely used in the United States. Doses are similar to those used for the low-dose rate.[72]

Biomathematical models are often used to estimate equivalent high-dose-rate regimens.[53,54] For example, linear quadratic modeling has suggested[73] that a high-dose-rate regimen of 5 fractions of 310 cGy per fraction should approximate the early and late effects of a 20-Gy low dose rate delivered at 0.5 Gy/h.

The actual alpha/beta ratio of breast tissues and tumors is not known. Nevertheless, such estimates can now be useful in reinforcing the clinician’s judgment, and may one day be improved when more reliable values of the model parameters for breast tissue become known. Although biomathematical models[53,54] can be used to estimate the appropriate dose, there is no standardized high-dose-rate fractionation schedule that can be recommended.
Brachytherapy for Recurrence After Breast Conservation

Literature is sparse on the use of brachytherapy to treat recurrence after breast-conservation therapy. Maulard et al.[74] treated 15 patients with tumorectomy and 30 Gy of perioperative low-dose-rate brachytherapy (with catheters being placed at the time of surgery). They reported a local recurrence in four patients (26%), an overall 5-year survival rate of 61%, and a disease-free survival rate of 33%.

The 30-Gy dose that Maulard et al used was lower than the usual 40 to 50 Gy used by radiation oncologists to treat microscopic disease. It is possible that the investigators could have achieved greater local control if they had administered a higher dose (40 to 50 Gy) following tumorectomy.[75] Maulard et al also treated 23 patients with larger tumors using brachytherapy alone (without tumorectomy) at 60 to 70 Gy in two implants, achieving an overall survival of 50%.[74]

The ABS feels that mastectomy remains the treatment standard for local recurrence after breast-conservation therapy. Due to the paucity of published data, the ABS cannot make a firm recommendation on the use of brachytherapy in recurrent breast cancers.

However, brachytherapy may provide a viable option for women with a strong desire for breast conservation, assuming appropriate selection and treatment techniques are exercised. The ABS believes that complete excision should precede brachytherapy.

The clinical target volume should be defined as previously detailed in these recommendations. Factors to be considered include time to recurrence, late effects from prior radiation, and a strong desire on the part of the patient to preserve her breast. After adequate excision of the recurrence, management should proceed as outlined in the section entitled, "Brachytherapy as the Sole Modality for Subclinical Disease."

Conclusions

These guidelines have been established for the use of brachytherapy in the treatment of breast cancer; they will be modified as further clinical results become available. Practitioners and cooperative groups are encouraged to use these guidelines to formulate their treatment and dose-reporting policies. However, the responsibility for medical decisions ultimately rests with the treating radiation oncologist.

References:


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