



Brachytherapy:

The precise answer for tackling breast cancer



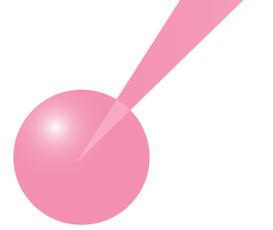
Because life is for living



Table of contents

Executive summary	3
Introduction	4
Management of early stage breast cancer	5
Radiotherapy options in early breast cancer and BCT	6
- Whole Breast Irradiation and Boost	6
- Accelerated Partial Breast Irradiation (APBI)	7
Breast brachytherapy techniques: applying technological advances	8
- Precision radiation delivery	9
- Treatment times and patient acceptability	10
Interstitial multicatheter brachytherapy for boost	11
- Efficacy outcomes	11
- Toxicity outcomes	12
- Cosmetic outcomes	12
Brachytherapy and APBI: evolution in evidence and clinical experience	13
Interstitial multicatheter brachytherapy for APBI	14
- Efficacy outcomes	14
- Toxicity outcomes	16
- Cosmetic outcomes	17
Intracavitary brachytherapy for APBI	18
- Efficacy outcomes	18
- Toxicity outcomes	19
- Cosmetic outcomes	19
Cost-effectiveness	20
Conclusion	21
References	22





Executive summary

Breast cancer survival rates are increasing in the Western world as a result of early detection programs and effective treatment options. In addition to increased efficacy, patients and clinicians are seeking more patient-centered therapy in the form of excellent cosmetic and quality of life outcomes. Mastectomy is increasingly being replaced by breast conservation therapy (BCT; lumpectomy followed by radiation and often chemotherapy and hormone therapy) which offers patients similar efficacy results and the opportunity to keep their breast.

Unfortunately, many women do not undertake, or adhere to, radiation therapy because of the logistical and personal challenges associated with the length of traditional schedules. This White Paper reviews the role of **brachytherapy – high precision, targeted radiotherapy** – in early breast cancer treatment and how it offers an effective and well-tolerated option.

Radiation for breast cancer can be delivered by either **Whole Breast Irradiation** (WBI) or **Accelerated Partial Breast Irradiation** (APBI).

- In the case of WBI, the entire breast is irradiated by external beam radiation (EBRT) over 5–7 weeks. This is followed by an additional **'boost' dose** to the tumor site, which can be delivered by EBRT or brachytherapy.
- APBI is an accelerated form of radiation which delivers a high dose to a portion of the breast over a reduced time frame of 5 days. APBI can be performed using EBRT or brachytherapy.

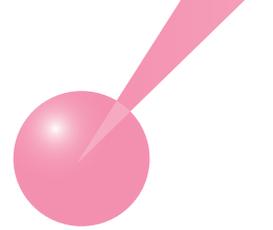
Brachytherapy combines two fundamental aims of radiotherapy: an effective tumor dose whilst sparing the surrounding healthy tissue. Specialized treatment planning programs and image guided delivery systems allow the radiation dose to be placed internally to achieve highly conformal radiotherapy – a tailored radiation dose delivered precisely to the tumor bed whilst sparing surrounding tissues and organs at-risk, therefore minimizing potential side effects.

Currently, there are two brachytherapy techniques utilized. **Interstitial multicatheter brachytherapy** is used for both boost and APBI, whereas **intracavitary brachytherapy** techniques are normally reserved for APBI. Both techniques have demonstrated excellent efficacy, toxicity and cosmesis results.

Clinical experience demonstrate the following key advantages of brachytherapy:

- A **flexible treatment**, proven to work synergistically as a boost following WBI or as the sole method of radiotherapy (APBI).
- **Precision delivery of radiation doses** to the target area via innovative treatment planning and delivery systems ensures **optimal accuracy** and **reduced toxicity**. Targeted precision and reduction in radiation exposure to healthy tissue and organs at risk are benefits of brachytherapy.
- When used as APBI, **treatment times are reduced to 5 days enhancing adherence to treatment and patient acceptance.**
- **Cancer control and long-term survival rates are similar to EBRT** when used as boost or APBI.
- Potential to **optimize healthcare resources**; decreased treatment times can make brachytherapy a very cost-effective treatment option.

Brachytherapy is a precise, effective, state-of-the-art radiotherapy option. It can help improve adherence to critical radiotherapy regimes when used as part of BCT with excellent efficacy, toxicity and cosmesis outcomes. Importantly, it offers patient-centered care, allowing patients to get back to their everyday lives quicker.



Introduction

Breast cancer

Breast cancer is the most common type of cancer in women worldwide, comprising 16% of all female cancers.¹

The incidence rates of breast cancer vary worldwide. Rates are as high as 90 per 100,000 in Western Europe, Australia and New Zealand, 77 per 100,000 in North America and around 70 per 100,000 in Southern Europe, whereas South America, Southern Africa, and Western Asia have more moderate incidence rates, but these are increasing. In fact, a majority (69%) of all breast cancer deaths occur in developing countries, despite the perception that breast cancer is a disease of the Western world.¹

Breast cancer survival rates also show large geographical discrepancies, ranging from 80% or over in North America, Sweden and Japan to around 60% in middle-income countries and below 40% in low-income countries. **The high survival rates in Western countries are largely due to early diagnosis through effective screening programs (self-detection and mammography), and more effective breast cancer treatments.**¹ Early diagnosis of breast cancer allows for a wide range of treatment options.

This paper provides evidence which establishes brachytherapy as a patient-centered treatment option in the management of early breast cancer: an efficacious choice offering good cosmetic outcomes and significant advantages in terms of patient benefits and quality of life.

Brachytherapy

Brachytherapy is a high-precision, targeted radiotherapy, in which the radiation dose is delivered directly to the tumor site from a source placed either within or adjacent to it. Unlike EBRT, in which the radiation is delivered from an external source through healthy tissue ‘from the outside, in’, brachytherapy delivers the radiation dose ‘from the inside, out’.

Brachytherapy has a long heritage in cancer treatment. It was first documented over 100 years ago, with the first report on the use of brachytherapy for the management of breast cancer published in 1929.²⁻⁴ **The past decades have seen significant advances in brachytherapy techniques and technology to the point where brachytherapy is at the forefront of innovation in the field of radiotherapy.**

The developments in brachytherapy techniques mean that the radioactive source can be positioned precisely within the target area. As the source is active over very short distances and the treatment dose is delivered only to the affected tissue, brachytherapy is able to achieve **highly conformal radiotherapy.**^{5,6} This is an important goal of all radiotherapy, allowing for optimal biological and clinical effects on the tumor, while sparing healthy surrounding tissue.

Benefits of brachytherapy ‘from the ‘inside, out’:

- Radiation dose delivered precisely to target tumor area
- Tissue-sparing: minimized radiation dose to normal, healthy tissues
- Excellent efficacy and favorable toxicity and cosmesis profile
- Shorter treatment times
- Potential for lower healthcare costs



Management of early stage breast cancer

Treatment of early breast cancer requires a multi-modal approach with combinations determined not only by stage but patient factors such as age, performance status and acceptance.

Surgical options for early breast cancer

Mastectomy was historically considered the standard treatment. Good cancer control rates are offset by the potential significant physical, psychological and economical effects.⁷

Breast conserving therapy (BCT) involves breast conserving surgery (BCS) in the form of lumpectomy, or partial mastectomy, followed by radiotherapy. BCT provides comparable efficacy to mastectomy, but with **vastly improved cosmetic results and less psycho-emotional trauma**, and is now widely considered a standard of care in early stage breast cancer.

Following lumpectomy, two different radiotherapy treatment options are available: whole breast irradiation (WBI) and accelerated partial breast irradiation (APBI) (Figure 1).

Radiotherapy: standard of care in BCT

Multiple studies confirm the efficacy of radiation therapy in reducing local tumor recurrence rates, particularly in the area of the tumor bed where studies suggest 60–100% of local recurrences typically occur.^{9,10}

In the USA it is estimated that 15–30% of women undergoing BCS do not follow through with adjunct radiotherapy. The length of the conventional radiation treatment schedule is undoubtedly a deterrent for many women. The decision to have radiation therapy is also influenced by logistical issues such as distance from a treatment center and lack of transportation, and issues such as lack of an adequate support system, age and ambulatory status. These factors are particularly relevant for patients of a lower socioeconomic status, whose uptake of radiotherapy is well below average.¹²

Modern, well-tolerated treatment modalities including brachytherapy, have the potential to make BCT more attractive and accessible to increasing numbers of women.

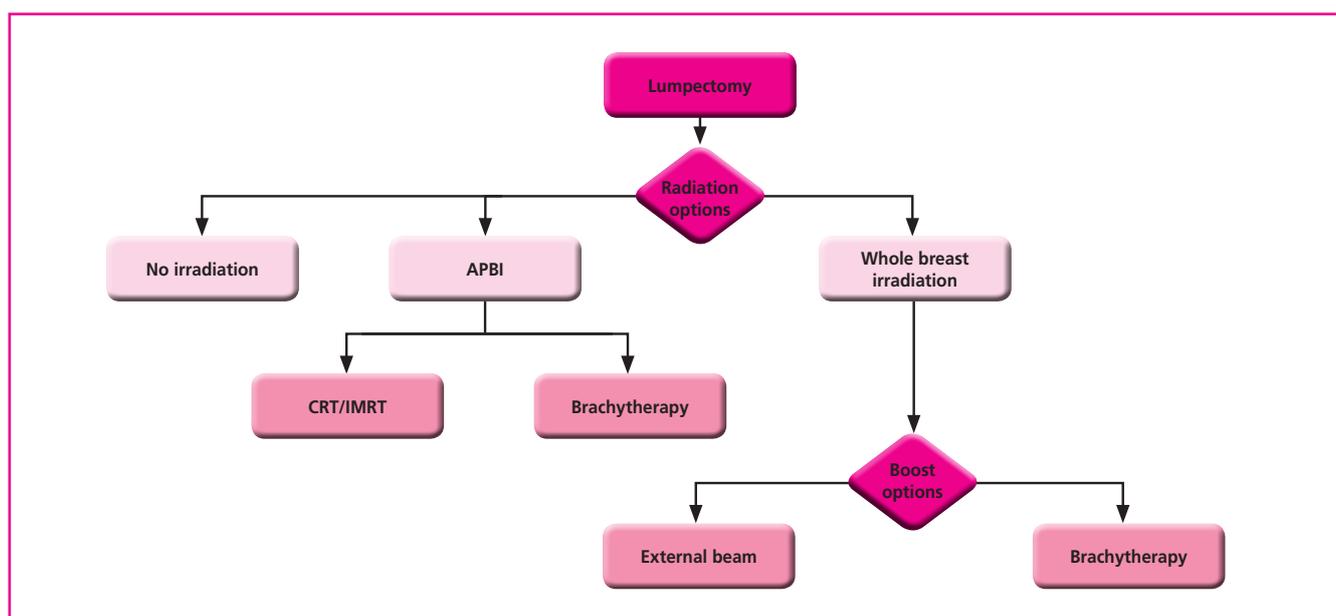


Figure 1. Radiotherapy options in early stage breast cancer
APBI: Accelerated Partial Breast Irradiation; CRT: Conformal Radiation Therapy;
IMRT: Intensity Modulation Radiation Therapy



Radiotherapy options in early breast cancer and BCT

Whole Breast Irradiation: a homogenous dose to the entire breast

Traditional BCT involves surgical removal of the tumor mass plus a margin followed by irradiation of the whole breast, **so-called whole breast irradiation or WBI**. A total radiation dose of 45–50 Gy (Gray) is divided into smaller doses (fractions) and delivered daily for 5–7 weeks via EBRT.^{13,14} WBI has been shown to be effective in reducing local recurrence rates.¹⁵

Radiation ‘boost’ dose: an additional, targeted dose to the tumor bed

Based on evidence which suggests ipsilateral (same side) recurrence occurs at the site of the tumor bed in a large majority of cases, an additional radiation ‘boost’ of between 10–25 Gy is often added to the radiation prescription following WBI. The effectiveness of this additional dose in preventing local recurrence has been demonstrated in trials with up to 10-year follow-up.¹⁶

Several ‘boost versus no boost’ studies have demonstrated the value of an additional radiation dose when added to traditional WBI treatment, in the form of either EBRT or brachytherapy (Figure 2). Five and 10-year results clearly show the benefit of a boost dose in terms of reducing local recurrence rates.

‘Boost’ radiotherapy can be in the form of EBRT (electrons/photons) or brachytherapy.

When used as boost, brachytherapy delivers high doses to a smaller treatment volume over a short treatment period. This results in more precise dose delivery to the target area, together with greater sparing of the skin and surrounding healthy tissues from unnecessary radiation. The treatment schedule for the boost dose is shortened to 1–2 days when utilizing brachytherapy.¹⁴

Ideal candidates for boost radiation include those patients under 50, with close, microscopically positive or unknown surgical margins, and an extensive intraductal component (EIC).¹³

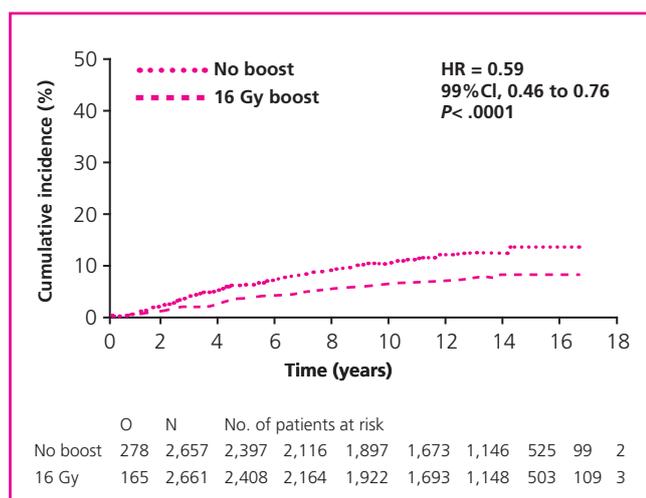
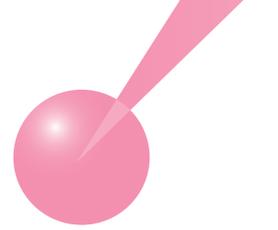


Figure 2. Cumulative incidence of recurrence of tumor as first event in the ipsilateral breast following WBI or WBI + boost^{16†}
HR: hazard ratio; O: occurrences; N: number of patients at risk;
CI: confidence interval



Accelerated Partial Breast Irradiation (APBI): definitive radiotherapy to the tumor site

In the past decade, an accelerated form of radiation to a portion of the breast, APBI, has been gaining interest among patients and clinicians. Recommendations from professional organisations for patients that are considered suitable and most likely to benefit from APBI have been developed (see page 13). APBI builds on the rationale that irradiating the entire breast may not be entirely necessary to achieve the same efficacy results when the tumor bed and surrounding margin has the highest likelihood of tumor recurrence.¹⁸ **APBI techniques deliver high dose radiation in a short timeframe with a small number of treatment sessions.** Treatment is generally initiated shortly after BCS and is typically completed in 5 days, allowing patients to get back to their everyday life quick. Currently, APBI is administered using brachytherapy, as well as newer forms of 3D conformal external radiation (3D CRT).^{14,19}

Brachytherapy, the ability to deliver high doses of radiation directly to the tumor site, is ideally suited to precision treatment options like boost and APBI, and is becoming an increasingly important part of BCT.

Rationale for APBI:

- Recent studies estimate that between 60–100% of ipsilateral recurrences following BCT develop at the primary tumor site or periphery^{4,20}
- The radiated area is small, and the dose is delivered in a small number of fractions which reduces side effects and may limit late toxicities²¹
- Radiation to healthy breast tissue is reduced, allowing for additional radiotherapy dosing in the case of recurrence²¹
- APBI can be completed within 5 days following surgery, allowing systemic therapy, if warranted, to begin in a timely manner⁸
- Shortened treatment times reduce the opportunity for tumor repopulation¹⁴
- A short treatment schedule of days increases adherence to treatment and improves quality of life¹⁴



Breast brachytherapy techniques: applying technical advances

Breast brachytherapy devices aim to achieve conformal dose coverage of the tumor site, high dose homogeneity, and a rapid dose fall-off outside the target area which translates into excellent efficacy and toxicity outcomes.¹³

An iridium source is temporarily placed directly into the target tissue using specially designed catheters at either a high dose rate (HDR: a high dose over a short time), pulse dose rate (PDR: a high dose over a series of short pulses) or low dose rate (LDR: a lower dose over a longer period).¹⁴

Low dose rate brachytherapy was historically used for boost brachytherapy following WBI. As techniques have advanced, HDR brachytherapy has become more prevalent and is now incorporated into treatment guidelines for both boost treatment following WBI, and APBI.²²

Imaging and treatment planning

Pre-planning is critical to accurately localize the tumor bed and map the target treatment area, also known as the planning treatment volume (PTV). Localization methods include computed tomography (CT), ultrasound and magnetic resonance imaging (MRI), as well as implanted surgical markers (titanium clips), often in combination with CT.^{15,23}

Brachytherapy software programs follow dosimetric guidelines to produce 3D images of the target volume, organs and tissues at risk and applicator placement. Placement technique includes some form of image-guidance such as CT or ultrasound to enable real-time monitoring and adjustments to catheter placement.¹⁵

Brachytherapy devices in breast cancer

Breast brachytherapy is currently divided into two categories: interstitial multicatheter brachytherapy and intracavitary brachytherapy. Both deliver the radiation dose to the tumor site with high precision in a pre-determined number of fractions. Boost radiation using brachytherapy typically uses the interstitial multicatheter approach, whereas in APBI either technique can be used. This depends on treatment center resources and capabilities and patient, radiation oncologist and surgeon preference.²⁴

Interstitial multicatheter brachytherapy: building on a strong heritage

The first brachytherapy modality used in breast cancer, it has the longest period of follow-up.¹² First used as boost therapy following WBI over 20 years ago, it has a large body of evidence and experience to support its efficacy and cosmetic outcomes.¹⁴ Modern interstitial techniques use 3D planning and imaging to define the PTV. Multiple, specially designed catheters are then inserted in the breast to cover the PTV with high conformity and accuracy (Figure 3). Once correct placement is verified, the radioactive source is delivered to the internal catheters via a remote afterloading device.^{8,12} The entire procedure is normally carried out in an outpatient setting, and the catheters are removed following delivery of the last fraction.⁸

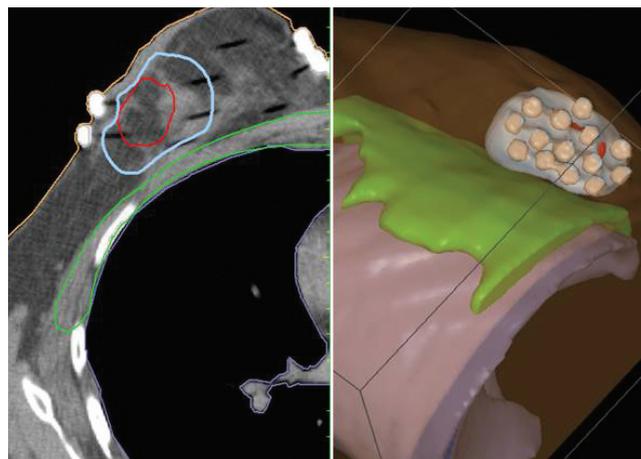


Figure 3. Interstitial multicatheter brachytherapy imaging and planning

Intracavitary brachytherapy: single or multi-channel devices

Intracavitary devices (e.g. MammoSite®, SAVI®, Contura®) were developed with a view to matching the high conformity achieved with interstitial multicatheter brachytherapy using a simplified delivery process via a single catheter (Figure 4).¹⁹ The applicator contains a single channel or multiple channels, which is inserted into the tumor cavity via a single puncture site. After insertion, placement is verified to conform to the treatment volume, and an HDR source is delivered to the catheter using a remote afterloader.^{8,12}



After treatment, which typically occurs in an outpatient setting and involves 4–5 daily sessions, the device is removed.

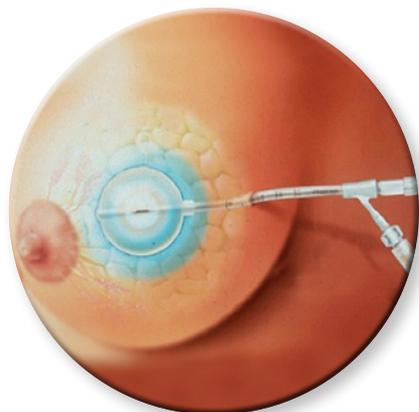


Figure 4. Intracavitary balloon brachytherapy*
*Courtesy of HOLOGIC, Inc. and affiliates

In both treatment types the catheters or intracavitary devices can be inserted into the tumor cavity during surgery and the radioactive source will be applied later. Alternatively, they can be inserted, using image guided technology, during a separate procedure following lumpectomy.²²

Precision radiation delivery

Brachytherapy, by the very nature of its technique, allows a tailored radiation dose to be delivered very precisely to the target area, while minimizing unwanted exposure of the surrounding healthy tissues and organs. A comparative study of the dosimetric properties of brachytherapy and EBRT in breast cancer considered the percentage of the total dose received by non-target tissue; specifically the organs at risk such as the heart and lung. **The highly targeted and conformal dosing provided by brachytherapy meant the organs at risk received far less of the total dose** (Figure 5). The authors found that the exposure to at risk tissue and organs such as the heart and lung were consistently lower for APBI using brachytherapy.

A meta-analysis of toxicity and survival data from WBI studies, including those with over 20 years of follow-up, demonstrated a significant increase in mortality from all causes other than breast cancer. Vascular events were the most common cause of death.²⁵ Recent studies have confirmed a link between radiation exposure of the left ventricle and left ventricular defects, in patients with left-sided breast cancer.³⁴ These results emphasize the importance of limiting the treatment volume to avoid radiation exposure to vital organs and subsequent toxicity – one of the most important principles of brachytherapy.

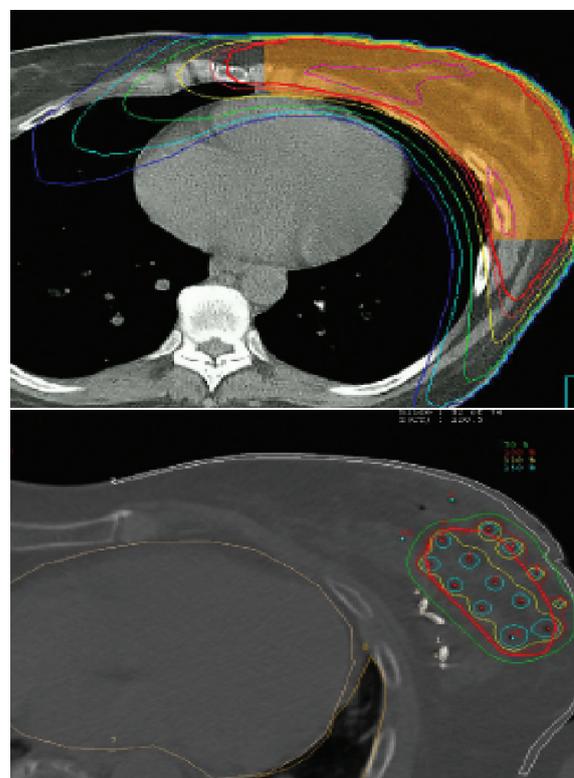


Figure 5. Example of dose distribution of EBRT WBI (top) and APBI using multicatheter interstitial brachytherapy (bottom)^{25†}



Treatment times and patient acceptability

The principles of breast brachytherapy allow for precise, high dose delivery which results in shortened treatment times (Table 1). When applied in the boost setting alongside WBI, the use of modern HDR brachytherapy techniques can reduce the time required to deliver the boost dose to a matter of days. As APBI, good efficacy and toxicity results with brachytherapy increase the likelihood of patient acceptance of the treatment, and adherence to a much shortened schedule meaning more women can opt for BCT and complete the radiotherapy regimen in a shorter, more convenient time frame. This is particularly important for ensuring compliance with the full radiation schedule.

For many patients, putting the physical and psychological trauma of treatment behind them is of paramount importance. The shorter treatment and reduced disruption of brachytherapy are therefore an extremely attractive option.

Radiation modality	Typical treatment time
EBRT	WBI: 6–7 weeks + boost: 1–2 weeks ¹⁴
3D Conformal radiation/IMRT	WBI: 3–5 weeks ²⁷ APBI: 5 days ²⁸
Helical tomotherapy	APBI: 5 days ²⁸
Brachytherapy	Boost: 1–2 days (interstitial)²² APBI: 5 days (interstitial or intracavitary)²²

Table 1. Typical treatment times for breast conserving radiotherapy
IMRT: intensity modulated radiation therapy

With the rapid advancement of highly targeted and conformal radiation and imaging modalities, sophisticated brachytherapy devices and application techniques have emerged. This places brachytherapy in an ideal situation to meet the growing demand for effective, patient-centered treatment options.

The following sections of this paper outline in turn the different settings where brachytherapy is utilized, covering essential elements such as efficacy, toxicity and cosmesis for each.

Key benefits of brachytherapy in breast cancer:

- A flexible treatment, proven to work synergistically as a boost following WBI or as the sole method of radiotherapy following lumpectomy (APBI), in the form of either interstitial multicatheter or intracavitary techniques
- Cancer control and long-term survival rates are similar to EBRT when used as boost or APBI
- Highly targeted radiation doses delivered directly to the tumor bed spare surrounding healthy breast tissue and skin, as well as underlying structures such as the chest wall, heart and lungs
- Excellent cosmetic results, at least similar to EBRT
- Significantly reduced treatment times for both boost and APBI treatment. When used as APBI, treatment times are reduced to 5 days, enhancing adherence to treatment and patient acceptance
- Potential to optimize healthcare resources; decreased treatment times can be more cost-effective.



Interstitial multicatheter brachytherapy for boost after WBI

When used to deliver the boost dose to the tumor bed, brachytherapy offers the practical advantages of delivering high doses to a smaller treatment volume, and reduced doses to the skin and surrounding healthy structures.¹³

Following completion of a WBI radiation schedule using EBRT, a 1–2 day course of interstitial brachytherapy can provide an additional boost dose of radiation to the tumor bed.^{14,16} **Brachytherapy boost has the benefit of comparable efficacy to EBRT boost, as well as tissue sparing and a short treatment schedule.**

Published studies demonstrate interstitial multicatheter brachytherapy consistently provides excellent efficacy when used as a boost, with local control rates comparable to those for EBRT boost therapy.¹⁶ As the treatment volume is limited to the tumor bed and a small margin using interstitial multicatheter brachytherapy, there is less healthy tissue irradiated offering demonstrated benefits in terms of early and late toxicities.²⁵

“In addition to external beam boost modalities, multicatheter brachytherapy remains a treatment option to deliver an additional dose to the tumor bed after Breast Conserving Therapy and Whole Breast Irradiation.¹³”

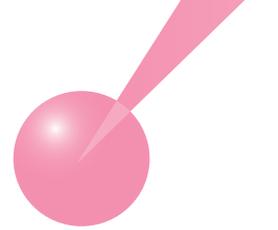
Efficacy outcomes

Recurrence rates of <10% after 5 and 10 years' follow-up are typically reported for interstitial multicatheter boost brachytherapy which compare favorably with EBRT boost therapy. These treatment responses are maintained long-term with local tumor control and overall survival comparable between both boost options (Table 2).

Study	EBRT			Brachytherapy		
	n	10 yr DFS (%)	Recurrence rates* (%)	n	10 yr DFS (%)	Recurrence rates** (%)
Mansfield, 1995	416	78	19	654	76	12
Perez, 1996	490	79	6	129	80	7
Touboul, 1995	160	85	15	169	86	8
Bartelink, 2007	1653	-	4.7**	225	-	2.5#
Polgar, 2002	52	94*	-	52	91.4**	-
Knauerhase, 2008	181	-	10.5	75	-	5.9

Table 2. Recurrence and survival rates for patients treated with EBRT or interstitial multicatheter brachytherapy boost^{10,16, 29-32}
*: Ipsilateral breast tumor recurrence (IBTR); **: local (ipsilateral breast) recurrence; DFS: disease free survival; #: 5-year survival

A retrospective comparison of 438 patients who received interstitial multicatheter brachytherapy boost WBI and 214 patients who received EBRT boost treatment showed no significant difference in local tumor control or overall survival rates between the two modalities. Seven year local recurrence-free rates of 93.7% for brachytherapy and 93.9% for EBRT (p=0.53), and overall survival rates of 81.4% and 83.1%, respectively were reported (p=0.77).³³



A further differentiating factor is brachytherapy's tissue-sparing advantages. The radiation is delivered directly to where it is needed: the tumor bed area; sparing surrounding healthy tissues and organs such as the heart and lungs (see page 9).

Toxicity outcomes

Excellent efficacy rates for interstitial multicatheter boost brachytherapy are coupled with low toxicity rates and high 'excellent to good' cosmetic results.³⁵

Fibrosis

Fibrosis is a common side effect associated with breast conservation treatment. It can be difficult to differentiate surgical fibrosis from an acute or late toxicity of radiation therapy.³⁶ In either case, it can have an impact on cosmetic outcome, although it does tend to improve over time.

A 'boost versus no boost' study found that the incidence of severe fibrosis increased as the radiation dose increased, with up to 14.4% of 5,569 patients reporting severe fibrosis at 10-year follow-up; this figure however, included both EBRT boost and brachytherapy, and so can be attributed more to the dose than to how the radiotherapy was administered.³⁷

Cosmetic outcomes

Excellent to good cosmetic results of 88% for interstitial multicatheter brachytherapy as boost have been reported, which are superior to those of EBRT boost (70%).¹⁵

The effect of tissue sparing achieved with brachytherapy, including its use in the boost setting, help to reduce the likelihood and severity of side effects which translates into good cosmetic outcomes and patient satisfaction.

Key efficacy and safety outcomes with interstitial multicatheter brachytherapy for boost:

- Local recurrence and survival rates compare favorably with EBRT boost
- Treatment time for boost therapy can be decreased to 1–2 days using brachytherapy
- Precision placement of the source inside the target treatment area means less toxicity/damage to surrounding healthy breast tissue, skin and other organs
- The incidence of acute and late toxicities is low, with good cosmetic outcomes



Brachytherapy and APBI: evolution in evidence and clinical experience

The past decade has seen significant growth in the interest and use of brachytherapy in APBI, mostly due to the fact it effectively addresses some of the biggest patient concerns with respect to radiotherapy: treatment times, convenience and patient acceptance.³⁸

Many centers in the US, and other regions, now offer it as a standard treatment option. This spurred the American Brachytherapy Society (ABS) and the American Society for Therapeutic Radiation and Oncology (ASTRO) to develop treatment guidelines which recommend APBI as a definitive radiotherapy source following lumpectomy. In Europe, recommendations of the Groupe Européen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) Breast Cancer Working Group identify a subgroup of patients with low-risk breast cancer for whom treatment with APBI is considered acceptable outside of clinical trials (Table 3).

Ongoing research will help to determine further the patient subsets which will benefit most from the treatment, and which APBI technique will be most beneficial.^{19,40}

The number of published studies with APBI continues to grow. Early APBI studies showed poor efficacy results, largely due to improper patient selection and poor treatment technique.³⁹ Although both interstitial multicatheter and intracavitary techniques are used for APBI, there is a much broader base of evidence and experience with the interstitial multicatheter brachytherapy technique. Collectively, the **evidence from more recent, well designed studies provides strong support for APBI with brachytherapy. Efficacy and toxicity data show comparable rates to WBI. The benefits of APBI include a reduced treatment schedule of up to 5 days** which aids treatment compliance. **However, several authors agree that two critical components for good outcomes are appropriate – patient selection and adequate brachytherapy quality assurance.^{17,39}**

APBI with brachytherapy involves irradiating a small area of the breast typically restricting dose to the tumor bed and a small margin. Compared to WBI, which uses a homogenous dose extending over the entire breast, APBI allows healthy tissue and adjacent vital organs to be spared from unnecessary radiation.

The need for localization of target volume, optimal dose homogeneity and precision delivery to target tissue is a standard goal of APBI.³⁹

The following sections of this paper outline the two most widely used brachytherapy techniques for APBI delivery (interstitial multicatheter and intracavitary) in more detail.

Characteristic	GEC-ESTRO	ABS	ASTRO
Patient age (years)	≥50	≥50	≥60
Histology	IDC and favorable subtypes	IDC	IDC or other favorable subtypes**
Tumor size	≤30 mm	≤3cm	≤2cm
Tumor stage	T1–2	T1–T2	T1
Surgical margins	Negative (≥2mm)	Negative at surgical margin	Negative by at least 2mm
Lymph node status	pN0 (by SLNB or ALND)	Negative (by sentinel lymph node or axillary dissection)	pN0 (i-, i+) (nodal surgery SLNB or ALND)

Table 3. Good* candidates for APBI following BCS according to current treatment guidelines^{4,12,40} *ASTRO guidelines use the term 'suitable'; **Favorable subtypes include mucinous, tubular, and colloid; SLNB; sentinel lymph node biopsy; ALND: axillary lymph node dissection (at least 6 nodes pathologically examined); IDC: invasive ductal carcinoma; pN0: no affected lymph nodes on pathology



Interstitial multicatheter brachytherapy for APBI

Interstitial multicatheter brachytherapy remains the technology with the largest evidence and experience base for APBI.

The interstitial multicatheter brachytherapy procedure delivers a high dose of radiation over a period of 5 days. As with boost brachytherapy, pre-planning software using 3D imaging is critical to determine treatment volume which normally includes the tumor bed plus a 1–2cm margin.²² This precise technique means interstitial multicatheter brachytherapy delivers excellent conformity with greater tissue sparing, reduced side effects and excellent cosmetic outcomes.

Optimizing dose distribution and sparing of healthy tissue in APBI

In a study comparing dosimetry of 4 different APBI methods, interstitial multicatheter brachytherapy was found to have the highest dose conformity of all methods including 3D CRT. The study considered the percentage of the breast which received 100% of the total dose V100 using interstitial multicatheter brachytherapy, 3D CRT and helical tomotherapy (a form of EBRT in which the radiation is directed at the tumor site in a spiral or helical formation) in both the supine and prone position. The V100 was lowest with brachytherapy at 12% and highest with the least conformal external beam technique, 3D CRT, at 26%. The study also noted that in order to achieve optimal PTV coverage, a much larger portion of normal tissue is required to receive radiation exposure with the external beam methods. Brachytherapy has the benefit of reducing the radiation risk to normal tissue.²⁸

Efficacy outcomes

APBI using interstitial multicatheter brachytherapy provides exceptional long-term tumor control and survival rates, comparable to WBI and APBI using 3D CRT.

Long-term efficacy outcomes

Interstitial multicatheter brachytherapy efficacy results are supported by a large set of evidence including studies with over 12-years of follow-up. These studies consistently report low rates of both local and more distant recurrence (Table 4).

Study	Patients (n)	Median follow-up (months)	IBFR (%)	EFR (%)
Vicini, 2003	199	65	2.5	1.5
King, 2000	160	84	2.5	1.2
Lawenda, 2003	48	23	0	0
Arthur, 2003	44	42	0	0
Johansen, 2002	43	34	2.3	NR
Wazer, 2002	33	33	3.0	3.0
Polgar, 2004	164	46	3.7	3.0
Polgar, 2010	45	133	8.9	8.9
Antonucci, 2008	199	115	5.0	1.5
Strnad, 2010	274	63	2.9	2.9

Table 4. Efficacy results of trials using interstitial multicatheter brachytherapy for APBI^{17,39,41-48}
IBFR: ipsilateral breast failure rate; EFR: elsewhere failure rate

Treatment responses are maintained long-term, with excellent outcomes seen with more than 10 years follow-up. A study reported a 5, 10 and 12-year actualized local recurrence rate (LR) of 4.4%, 9.3% and 9.3% respectively. At 12 years, the disease-free survival rate was 75.3%, while distant metastasis-free survival, cancer-specific survival, and overall survival rates were 83.8%, 91.1%, and 88.9%, respectively.⁴¹

Efficacy outcomes versus WBI

Long-term results also demonstrate **equivalence to WBI** as shown by outcomes from a matched-pair institutional study comparing interstitial multicatheter brachytherapy



with WBI (no boost) in carefully selected patients with early stage disease. Patients treated with LDR or HDR brachytherapy as APBI were matched against patients undergoing WBI. **Ten-year results indicate the difference in local recurrence rates was not statistically different between the two groups:** LR= 5% for the APBI group versus 4% for WBI, $p=0.48$ (Figure 6)⁴⁸ demonstrating that reducing the overall target treatment volume does not negatively impact efficacy outcomes.

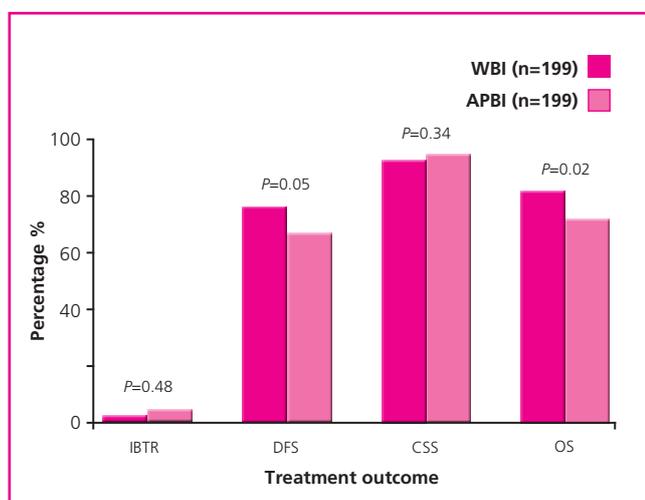


Figure 6. Ten year actuarial results (95% CI) from a matched-pair analysis of patients treated with WBI and APBI (Adapted from Antonucci *et al*, 2008)³⁹
CI: confidence interval; IBTR: ipsilateral breast tumor recurrence; DFS: disease-free survival; CSS: cause-free survival; OS: overall survival

No significant difference in local recurrence or cancer-specific survival rates between APBI, WBI and WBI plus boost has been shown (Table 5).⁴⁷

The study presented in Table 5 also considered differences in elsewhere breast failure (EBF) rates, defined as local recurrence located at least 2cm from the tumor margin, which is a topic of some debate in the literature. A theoretical disadvantage associated with the use of APBI is the possibility of higher rates of regional failure (primarily axillary failure) based upon the fact that unlike WBI, APBI does not irradiate the entire breast. This study determined no significant difference in 7-year actuarial EBF rates between the APBI group (9.0%) and the control group (8.3%, $p=0.80$).⁴⁷ Additional long-term data, including results of Phase III trials, is needed to draw any conclusions on the relationship between APBI and EBF.

Event	APBI (n=45)	WBI (n=44)	WBI + boost (n=36)
Local recurrence (%)*	3(6.7)	5(11.4)	3(8.3)
TR/MM (%)	0(0)	1(2.3)	2(5.6)
EBF (%)	3(6.7)	4(9.1)	1(2.8)
Relapse-free survival (%)#	79.8	73.5	77.7
Cancer-specific survival (%)#	93.3	92.9	93.9

Table 5. Seven year treatment outcome results: APBI versus WBI with or without boost (Adapted from Polgar *et al*, 2004)⁴⁷
*: crude data; #: actuarial data; TR: true recurrence; MM: marginal miss; EBF: elsewhere breast failure

Efficacy outcomes versus 3D CRT and IMRT

The efficacy of 3D CRT and intensity modulated radiation therapy (IMRT) when applied in APBI is less well established than is the case for brachytherapy. The average follow-up reported in the ASTRO consensus follow-up is 1 year, compared to 5 years for brachytherapy (335 versus 7,133 patient years respectively).⁴⁰ Longer-term results have been reported in a prospective study of 52 patients treated with APBI in the form of 3D CRT, with 4-year local recurrence rates of 6%. The results achieved with brachytherapy, over similar or longer follow up (Table 4) thus compare favorably.⁴⁹

The results of long-term studies confirm that interstitial multicatheter brachytherapy can be used with reproducibility of clinical results, delivering outcomes in terms of local recurrence and cancer survival rates, which is comparable to that achieved with WBI (with or without boost) but with treatment delivered over a considerably shorter timeframe, and compares favorably with other modalities used to administer APBI, such as 3D CRT. Further differences in terms of toxicity, etc., are explored in the following sections.



Toxicity outcomes

Interstitial multicatheter brachytherapy used as APBI is associated with a low risk of acute and late toxicity. Side effects are generally limited to effects on breast tissue and overlying skin.

Minimizing exposure to chest structures

Recent studies have determined the **amount of radiation delivered to non-target tissue and organs is significantly less using interstitial multicatheter brachytherapy than other forms of radiotherapy.**

Results show that APBI (utilising interstitial multicatheter brachytherapy) dose parameters for the heart are superior to WBI by a factor of 4, followed by the lungs and the skin where APBI leads by a factor of 3 and 2, respectively.²⁵

Skin toxicity

The skin must be considered when comparing the side effect profiles of both brachytherapy and EBRT. In the case of WBI using EBRT, the skin is considered part of the target volume and therefore receives the whole treatment dose. APBI using interstitial multicatheter brachytherapy reduces the target volume so the skin can be spared effectively.²⁵

Long-term data suggest that **skin toxicity is limited** with only 1.8% reported any skin changes (all Grade 1) in a 5-year follow-up,³⁹ and only about 4% of patients experiencing \geq Grade 2 toxicity over 12-years' follow-up. (Figure 7).⁴¹

Fibrosis

The **dose reductions resulting from the use of interstitial multicatheter brachytherapy have clinical relevance in terms of reducing fibrosis.** Earlier studies, which used both LDR and HDR interstitial multicatheter brachytherapy as APBI, identify LDR brachytherapy as causing higher rates of fibrosis compared to HDR brachytherapy, with rates of Grade 3 or 4 fibrosis documented in 12% and 3% of patients, respectively.⁵⁰

A recent long-term study of HDR interstitial multicatheter brachytherapy for APBI identified Grade 3 fibrosis in only one patient in a study population followed up to 12 years (Figure 7).⁴¹

Fat necrosis

Fat necrosis is a benign inflammation of the breast which can occur following breast conserving treatment. Although its exact cause is unknown, evidence suggests that radiotherapy following breast conserving surgery has a role in the pathogenesis of fat necrosis.⁵¹

A randomised study of 258 patients undergoing WBI or interstitial multicatheter brachytherapy as APBI found no significant difference in incidence of fat necrosis for WBI using EBRT (31.9%) and interstitial multicatheter brachytherapy (36.5%).⁵¹

Results of a recent 5-year study showed fat necrosis in a minority of patients (5.1%) and was associated with no or only minor symptoms.³⁹ A further recent study found modest rates of fat necrosis following interstitial multicatheter brachytherapy at 12-year follow-up. Almost two-thirds experienced no fat necrosis, and 98% experienced \leq Grade 2 toxicity. Only one patient required surgical intervention for Grade 4 fat necrosis (Figure 7).⁴¹

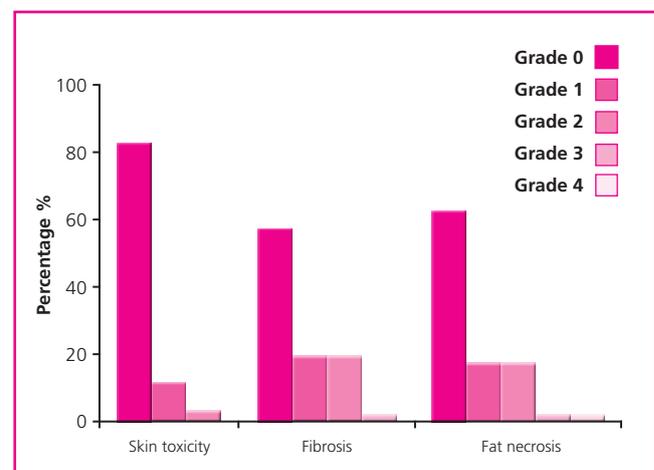


Figure 7. Twelve year skin toxicity, fibrosis and fat necrosis results using interstitial multicatheter brachytherapy as APBI (Adapted from Polgar *et al*, 2010)⁴¹

Infection and breast pain

Most studies report that infection and breast pain are directly related to trauma caused by breast conserving surgery and invasive brachytherapy techniques. Both infection and pain are generally mild and tend to occur predominantly within the first month of treatment and progressively improve with time.^{50,52}



Cosmetic outcomes

Various large scale studies have reported over 90% 'excellent to good' long-term cosmesis results for interstitial multicatheter brachytherapy.^{41,52}

Many of the toxicities associated with BCT are related to radiation of the entire breast. **APBI, through interstitial multicatheter brachytherapy, limits toxicities related to radiation leading to better cosmetic outcomes⁵²** (Table 6).

Study	Patients (n)	Technique	Median follow-up (years)	5-year LR (%)	Excellent to good cosmesis (%)
Antonucci, 2009	199	LDR/HDR	9.6	2.2	99
Polgar, 2009	128	HDR/EBI	6.8	4.7	77 (HDR:81, EBI:68)
King, 2000	51	LDR/HDR	6.25	3.9*	75
Strnad, 2010	274	PDR/HDR	5.25	2.9*	90
Polgar, 2010	45	HDR	11.1	4.4	78
All patients	697	HDR	5.25–11.1	2.2–4.7	75–99

Table 6. Results of APBI studies (interstitial multicatheter brachytherapy) with extended (≥5 years) follow-up^{13,39,41,43,48}

*Crude rate; LR: local recurrence (actuarial rate unless otherwise specified); HDR: high dose rate; LDR: low dose rate; PDR: pulsed dose rate; EBI: external beam irradiation

The appearance over time of late toxicities such as fibrosis is known to have a negative effect on cosmesis.⁵³ Nevertheless, **several long-term studies on interstitial multicatheter brachytherapy show impressive cosmetic outcomes which are significantly better than those achieved with WBI.** Five-year results of a randomized comparative study between interstitial multicatheter brachytherapy as APBI and WBI demonstrated significantly better cosmetic outcomes with carefully designed HDR multicatheter implants compared with WBI (81.2% vs. 62% excellent to good cosmesis).¹⁸ **A more recent study reported only one case of Grade 3 fibrosis among 274 patients and overall cosmetic results were good to excellent in 90% of patients.**³⁹

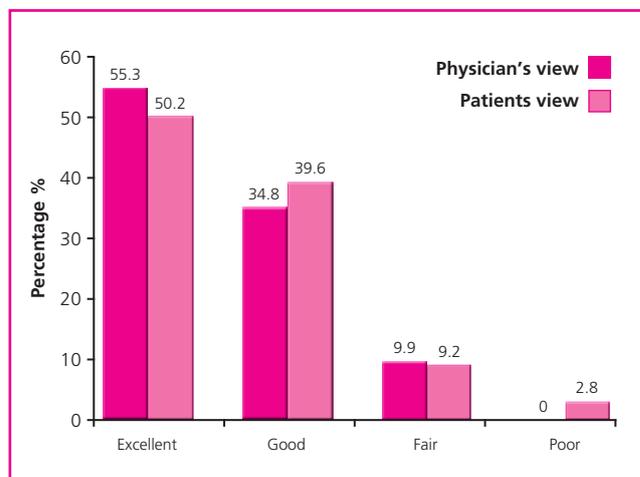


Figure 8. Cosmetic evaluation of interstitial multicatheter brachytherapy (Adapted from Strnad *et al*, 2010)³⁹

As research indicates, cosmetic outcome can have an impact on patient satisfaction with treatment and overall quality of life. The consistent and impressive cosmesis results achieved with brachytherapy help to establish it as truly patient-centered care.

Key efficacy and safety outcomes with interstitial multicatheter brachytherapy for APBI:

- Excellent long-term tumor control and survival rates which compare favorably with 3D CRT
- Excellent conformity.
- Precision treatment means less toxicity/damage to surrounding healthy breast tissue, skin and other organs at risk, such as the heart and lungs than with 3D CRT
- The incidence of acute and late toxicities are low, with good cosmetic outcomes



Intracavitary brachytherapy for APBI

First approved for use in APBI in 2002, clinical evidence for balloon catheters and related devices is emerging, further demonstrating the value of brachytherapy for APBI.

A ‘balloon’ applicator is essentially a single or multichannel device with an inflatable balloon at the end which is expanded with saline solution following insertion, to comfortably fill the tumor cavity. Pre-planning using ultrasound or CT imaging to help identify the tumor bed is essential to create an accurate picture of the treatment volume and ensure proper placement of the single applicator within the tumor cavity, as even small placement errors can have a large impact on results.

The two critical factors for achieving efficacy and optimal cosmetic outcomes are balloon cavity conformance and skin-to-balloon surface distance. The former is essential in order to achieve good dose homogeneity. The latter is important to control the maximum dose received by the skin. Evidence suggests a minimum ‘balloon to skin ratio’ is 5mm, but 7mm is desirable for reduced toxicity outcomes.^{54,55}

A number of small scale studies have considered the dosimetry parameters of balloon brachytherapy devices. Balloon brachytherapy was found to provide good coverage of the PTV, similar to interstitial multicatheter brachytherapy and 3D CRT, and less radiation exposure to non-target structures such as the lungs and heart compared to 3D CRT.⁵⁴⁻⁵⁶

Efficacy outcomes

Despite data currently being less extensive due to follow-up times being shorter than interstitial multicatheter brachytherapy, early efficacy and safety reports show promising results for intracavitary brachytherapy. Longer term follow-up data is emerging.

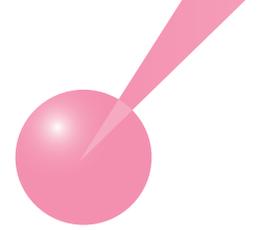
Results from studies with up to 5 years follow-up depict local recurrence rates of between 0 and 5.7% for the study period. These preliminary results suggest **efficacy similar to WBI and APBI using interstitial multicatheter brachytherapy** in the same time period (Table 7).

Study	Patients (n)	Median follow-up (months)	Local recurrence (%)
Vicini, 2008	1440	30	1.0
Dragun, 2007	70	26	5.7
Niehoff and Ballerdini, 2006	90	24	2.2
Voth, 2006	55	24	3.6
Chao, 2007	80	36	2.5
Goyal, 2010	70	51.5	1.4

Table 7. Rates of local recurrence from trials of intracavitary balloon brachytherapy utilizing the MammoSite® applicator⁵⁷⁻⁶²

Early experience with modified catheters is recently available. Contura®, a multi-lumen, single applicator device has demonstrated good dosimetry parameters when used in a study of 100 patients. One patient (1%) developed a tumor bed recurrence at median follow-up of 4 months (range 0.2–13 months).⁶³ Another device, the Strut-Adjusted Volume Implant (SAVI®) is a single entry applicator with peripheral struts that also shown excellent dosimetry and a low recurrence rate of 1% at 21 months median follow-up.⁶⁴

The available data for intracavitary brachytherapy demonstrate this method is highly suitable in terms of cancer control for appropriate patients. Further data will provide additional information on long-term efficacy and cosmesis outcomes, and further determine which patient subsets will benefit most from the treatment.⁵⁴



Limiting radiation exposure to healthy structures

A small sub-set study of 15 patients with invasive ductal carcinoma compared the levels of radiation to the heart and ipsilateral lung between EBRT and intracavitary balloon brachytherapy. This study assigned low values for incidental radiation received by the heart and ipsilateral lung using the balloon applicator. The volume of heart and lung irradiated to clinically significant levels was significantly lower with the balloon applicator than using simulated WBI (EBRT) fields of the same data sets. The authors also noted that treatment parameters and patient specific characteristics such as proximity of the catheter to the chest wall, and patient breast size, could affect incidental radiation.⁶⁵

Toxicity and cosmetic outcomes

As with efficacy outcomes, evidence is currently being compiled for extensive long-term data but reports indicate good toxicity outcomes with few complications and excellent cosmetic results.⁵⁷

A study of 1,440 patients undergoing APBI with intracavitary balloon brachytherapy identified infection in 9.5% of patients, fat necrosis in 2.0% and seromas in 23.9% of patients at 4-year follow-up. Symptomatic seromas occurred in 10.6% of cases.⁶⁶ Seroma appears to be the most frequent complication of intracavitary balloon brachytherapy with nearly a third of patients reporting seroma in some studies.⁶⁷

Data released from published clinical trials with an average follow-up of 16 months report few non-target tissue complications, and a high incidence of good to excellent cosmesis (Table 8), with rates over 90% in some cases.

Study	Patients (n)	Average follow-up (months)	Good to excellent cosmesis (%)
Dragun, 2007	100	24	21–69
Benitez, 2006	100	9.5	98
Jeruss, 2006	158	12	88
Sadeghi, 2006	67	13	96

Table 8. Clinical results of cosmetic outcomes using intracavitary balloon brachytherapy^{57,58,67-69}

It is well documented in the literature that an appropriate distance from the inflatable balloon to the skin, or ‘skin bridge’, is a critical determinant of a good cosmetic outcome in intracavitary balloon brachytherapy. A skin bridge of 7mm or greater has been associated with lower toxicities and good cosmesis.^{57,67}

A recent report highlighted more than 7 years of experience with 176 patients treated with intracavitary balloon brachytherapy. Good/excellent cosmetic results were seen in 94% of patients during 31-month median follow-up. They also report that the procedure is very well accepted by all patients.⁷⁰

As results of published studies substantiate comparable local control and survival rates between the various treatment options for BCT, long-term toxicities and cosmetic outcome become important differentiating considerations for both surgeons and patients.



Brachytherapy in early stage breast cancer: cost-effectiveness

Given that the different treatment options for breast conservation treatment are generally considered to provide similar efficacy, other factors such as costs to patients, providers and the healthcare system become especially relevant.

The increasing pressure on healthcare budgets emphasizes the need to make the best use of available resources. **Reducing treatment duration and the need for repeated or extended hospital visits and inpatient treatment all help to lower the initial costs of therapy and reduce pressure on healthcare staff and facilities. Breast brachytherapy as APBI offers shorter treatment time of up to 5 days and in most cases can be administered in the outpatient setting.**

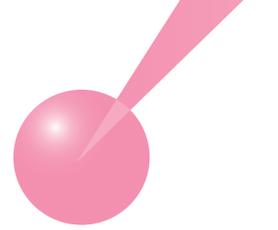
The inherent costs of the different radiotherapy techniques differ significantly. **Brachytherapy requires low investment and maintenance costs which make it an attractive, cost-effective option.**⁶ Furthermore, brachytherapy can maximize the use of existing facilities and resources in some centers. Most radiotherapy centers possess an HDR afterloading machine for other conditions such as prostate or cervical cancer, which could ultimately result in efficiencies and cost savings within healthcare centers.⁶

Brachytherapy and breast boost: cost-saving

Boost brachytherapy can be considered a cost-saving modality when recurrence rates are factored into the equation.

APBI with brachytherapy

The cost-effectiveness of APBI has not yet been adequately examined, but given the prevalence of breast cancer and the increasing popularity of this treatment option, results from such an analysis may have broad implications.⁷² The accelerated dosage schedule and resultant shortened treatment times of APBI mean it boasts real personal savings to patients in terms of travel and work-related costs.



Conclusion

When used as part of breast conserving treatment, breast brachytherapy provides high precision, targeted radiotherapy with proven efficacy over short treatment times.

The sophisticated and advanced technologies for imaging, treatment planning and treatment delivery allow precise, conformal delivery of irradiation, and reduced unnecessary exposure of healthy tissues and organs to radiation. These principles of brachytherapy have resulted in excellent patient outcomes, as demonstrated by extensive clinical experience and research, particularly in the case of interstitial multicatheter brachytherapy, with accumulating evidence for intracavitary balloon and strut device brachytherapy.

Whether used synergistically with EBRT as part of Whole Breast Irradiation (WBI) or as a definitive Accelerated Partial Breast Irradiation (APBI) treatment, breast brachytherapy has produced good efficacy, toxicity and cosmesis results comparable to EBRT. Importantly, radiation exposure to organs at risk such as the heart and lungs, has been shown to be greatly reduced with brachytherapy compared to EBRT, which can significantly impact acute and long-term toxicity, adverse events, and cosmesis.

Brachytherapy is a patient-centered modality – its short treatment times enable plans to be individualized, adapted to each patient's needs and preferences, and allow a quick return to everyday life, all of which increases its acceptability to patients. This is a particularly attractive and valuable consideration for early breast cancer treatment. Given the unfortunate number of women choosing to avoid radiation therapy due to logistical challenges, brachytherapy is an obvious option to make radiotherapy more accessible and attractive to increasing numbers of women.

Brachytherapy remains at the forefront of radiation technology. As experience and evidence accumulate, and new technologies emerge, breast brachytherapy is likely to further advance the standards of breast cancer care. In doing so, the costs to patients, healthcare providers and the healthcare system will diminish, and the benefits increase.

Brachytherapy is an important treatment option for patients with early breast cancer, offering them the confidence of an effective treatment, favorable adverse event and tolerability profiles and the comfort of an excellent cosmetic outcome and good quality of life.



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For further information on brachytherapy for breast cancer, consult the following resources:

Speak to colleagues who have successfully integrated brachytherapy into their practice

ESTRO (European Society for Therapeutic Radiology and Oncology)
www.estro.org

ASTRO (American Society for Therapeutic Radiology and Oncology)
www.astro.org

GEC-ESTRO (Groupe Européen de Curiethérapie and the European Society for Therapeutic Radiology and Oncology)
www.estro.org/about/Pages/GEC-ESTRO.aspx

ABS (American Brachytherapy Society)
www.americanbrachytherapy.org

NCCN (National Comprehensive Cancer Network)
www.nccn.org



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