

# THE CURRENT STATUS OF ACCELERATED PARTIAL BREAST RADIATION THERAPY

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## ABSTRACT

This article is designed to be an update on the current status of Accelerated Partial Breast Irradiation (APBI). It has been shown that breast-conserving therapy (lumpectomy plus radiation therapy) is equivalent to mastectomy in terms of long term overall survival, disease free survival, and distant recurrence.

This review discusses the history of breast brachytherapy including the goals of treatment and the background development of this option for accelerated breast radiation therapy. In addition, partial breast radiation therapy options are covered including multi-planar interstitial implants, balloon catheter implant, and external beam 3-D conformal APBI. Both background data and current data for APBI are also reviewed.

The potential benefits of partial breast radiation and potential complications are also discussed in this update on APBI. Appropriate APBI patient selection and current guidelines for treatment as published by the American Society of Breast Surgeons (ASBS) and the American Brachytherapy Society are reviewed as well. APBI seems to be an acceptable option for definitive breast radiation therapy for patients who desire breast conservation.

**Key words:** breast cancer, breast radiation therapy, breast conservation, breast brachytherapy

## AKSELERE PARŞİYEL MEME RADYOTERAPİSİNİN GÜNCEL DURUMU

### ÖZET

Bu yazı Akselere Parsiyel Meme Radyoterapisinin (APMR) güncel durumunu anlatmak için hazırlanmıştır. Meme koruyucu cerrahi (lumpektomi + radyoterapi) ve mastektominin uzun dönem sağkalım, hastaliksız sağkalım ve uzak metastaz sonuçlarının benzer olduğu gösterilmiştir. Bu derleme meme brakiterapisinin tarihini, tedavi hedeflerini akselere meme radyoterapisinin arka planındaki gelişmeleri tartışmaktadır.

Ek olarak, parşiyel meme radyoterapisi seçeneklerinden çok boyutlu interstisyel implantlar, balon katater implantları ve eksternal üç boyutlu APMR'den de bahsedilmiştir. APMR için hem güncel hem de geçmiş bilgiler gözden geçirilmiştir.

Parsiyel meme radyoterapisinin muhtemel faydaları ve komplikasyonları APMR'nin bu güncellemesinde tartışılmıştır. APMR için uygun hasta seçimi, Amerikan Brakiterapi Derneđi ve Amerikan Meme Cerrahları Derneđi tarafından bildirilen güncel tedavi kılavuzları gözden geçirilmiştir. APMR meme koruyucu cerrahi isteyen hastaların radyoterapisi için kabul edilebilir bir seçenek gibi gözükmektedir.

**Anahtar sözcükler:** meme kanseri, meme radyoterapisi, meme korunması, meme brakiterapisi

It is well established that breast-conserving surgery (lumpectomy), with the addition of whole breast radiation, is equivalent to mastectomy in terms of long term overall survival, disease free survival, and distant recurrence (1). Whole breast irradiation (WBI) reduces the incidence of in-breast tumor recurrence (IBTR) by 60% to 70% when compared to lumpectomy alone (Figure 1). The benefit of the addition of WBI is to reduce loco-regional recurrence in the same quadrant as the primary tumor. However, it has not been shown that WBI reduces the risk of recurrence in other quadrants of the breast away from the site of the primary tumor, so called elsewhere failures (Figure 2).

The primary objective of this review is to discuss the current status of accelerated partial breast irradiation (APBI) in the treatment of breast cancer. APBI is a means to deliver localized, targeted radiotherapy to

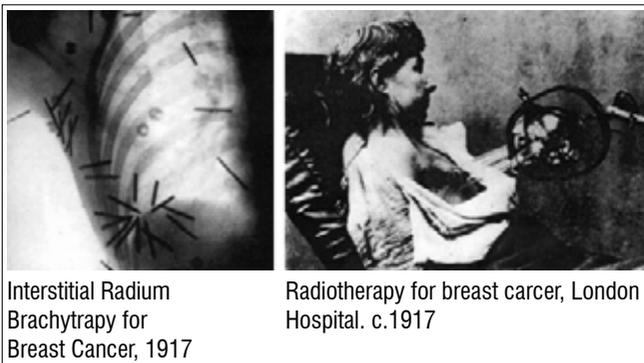
Figure 1. Randomized trials comparing lumpectomy alone vs lumpectomy plus RT -Impact of Radiation-

Trial	% of patients with Recurrence		% Reduction Recurrence (CS vs CS + RT)
	CS Alone	CS + RT	
NSABP B-06	36	12	67
Ontario	35	11	69
Milan	24	6	75
Scottish	25	6	76
English	35	13	63
Uppsala-Orebro	24	9	63

CS: Lumpectomy

**Figure 2.** Incidence of else-where failures outside of the quadrant of the primary tumor in randomized trials comparing lumpectomy with or without postoperative irradiation

Trial	Surgery alone		Surgery plus RT		
	Median f/u (mo)	N	%	N	%
NSABP-B06	125	17/636	2.7	24/629	3.8
Milan	39	4/273	1,5	0/294	0
Uppsala-Orebro	64	7/197	3.5	-	-
Ontario	43	15/421	3.5	4/416	1.0



**Figure 3.** Historical Perspective

the breast using an interstitial catheter or catheters. The treatments are designed to give a uniform dose of radiotherapy to the breast in an accelerated fashion. The goal is to provide radiation to the lumpectomy cavity with an additional 1 to 2 cm margin in a homogeneous manner, while providing minimal radiation to the normal and uninvolved breast tissue. Also, the objective is to provide a comparable tumoricidal radiation dose as conventional whole breast irradiation. APBI hopes to optimize cosmesis of the breast while at the same time trying to avoid some of the toxicity of WBI to the skin as well as fibrosis and fat necrosis to the tissue. Some of the potential benefits of APBI include: decreasing treatment time of WBI being 6 to 7 weeks down to 5 days for APBI, consistent and reproducible radiation dosing, and decreasing radiation dosing to the heart and lungs.

Although only recently has APBI been offered as monotherapy in providing radiation treatment to the breast for well-selected patients with early stage breast cancer, the concept is certainly not new. Interstitial breast brachytherapy was performed as early as 1917 at the London Hospital in England using radium implants (Figure 3). There was renewed interest in APBI when Dr. Robert Kuske performed partial breast radiation treatment as monotherapy in 1991 in New Orleans (2,3). Shortly thereafter, several other institutions began to offer APBI for early stage breast cancer under protocol utilizing multi-planar, interstitial radiation implants. The data has been reported from these radiation centers showing both very good local control with low IBTR rates and excellent cos-

**Figure 4.** Early multiplanar APBI single institution data

Author	PT#	Med f/u (mos)	Dose-Gy	Tot. Dose	%LR	Cosmesis
Kuske	26	75	4x8	32	<2	75%
Clarke	45	18	10x2, 7x4, 6x6	20, 28, 36	8.8	95%
Polgar	72	21	5.2x7, 4.3x7	36.4, 30.3	2.8	98%
Pecera	39	20	3.72x10	37.2	2.6	-
Vicini	54	>36	4x8, 3.4x10	32, 34	0	>90%
RTOG 95-17	68	-	3.4x10	34	-	-
Wazer	30	24	3.4x10	34	-	-
Total	334					

metic outcomes (Figure 4). An early multi-center trial, RTOG 95-17, which accrued 100 patients from 1997 to 2000, was recently updated. The median follow-up was 6.14 years for the 66 high dose rate (HDR) patients with an IBTR rate of 3% at 5 years (4).

As a result of the early promising data for multi-planar APBI, Proxima Therapeutics, Inc., originally developed a new product the MammoSite Catheter (5). The device is now produced by Hologic, Inc. (6), and is a balloon catheter implant to provide APBI directly at the lumpectomy site. The prescription 100% radiation dose is targeted to a margin 1 cm around the entire lumpectomy cavity. The FDA cleared the MammoSite device for use in May of 2002, based upon the data from the initial 43 patients who were treated with APBI. These data were recently updated by Dr. Benitez et al. (7). There has been no IBTR with good to excellent cosmesis in 83% of the patients. The median follow-up for these patients in this study at the time of data being reported was 5.5 years.

After this initial study for FDA clearance, data was gathered in a prospective database for multi-institutional reporting of data of early MammoSite APBI patients. The American Society of Breast Surgeons (ASBS) currently manages this data set with recently updated data published by Dr. Vicini et al. (8). The ASBS Registry Study is the largest series of MammoSite APBI patient data, which has been published to date, with a total of 1449 cases. In this database, 93% of the patients had good/excellent cosmetic outcome at 4 years of follow-up, and the 3-year actuarial rate of IBTR was 1.79%. The second largest data set available for MammoSite APBI is a multi-institutional retrospective study published by Dr. Cuttino et al. (9). In this paper, from between 2000 and 2004, 483 patients were treated with APBI with a median follow-up of 24 months. A total of 6 patients (1.2%) had an IBTR with good/excellent cosmetic outcome in 91% of patients. The two largest single institution studies on MammoSite RTS, with prospective databases, show similar results to the larger multi-institution studies. Dr. Prestidge et al. published data on 234 patients with a median follow-up of

**Figure 5.** ABS and ASBS patient selection criteria

	<b>ABS Recommendations<sup>1</sup> (updated February 2007)</b>	<b>ASBS Recommendations<sup>2</sup> (updated December 2005)</b>
Age	≥50	≥45
Diagnosis	Infiltrating ductal carcinoma	Invasive ductal carcinoma or DCIS
Tumor size	≤ 3 cm	≤ 3 cm
Surgical Margins	Negative microscopic surgical margins of excision	Negative microscopic surgical margins of excision
Nodal Status	NØ	NØ

<sup>1</sup> American Brachytherapy Society, Breast Brachytherapy task group, February 2007.  
<sup>2</sup> Consensus statement for a accelerated partial irradiation. American Society of Breast surgeons, 2005.

21 months (10). The IBTR was 0.8% and good/excellent cosmetic outcomes were 94%. Likewise, Dr Soran et al., with a median follow-up to 11 months in 108 patients, found an IBTR of 0.0% and a good/excellent cosmetic outcome in 95% of patients (11).

Published infection rates for MammoSite APBI range from 3.6% to 14.3% and are well within the range of prior published data from lumpectomy plus WBI for breast conservation (12). In addition, MammoSite infection rates also fall within published data for seroma following BCT, consisting of lumpectomy plus WBI, and ranging from 9 to 40%. Other complications such as skin toxicities: telengectasia, moist desquamation, and hyperpigmentation occur rarely in appropriately treated patients.

Accelerated partial breast radiation is not for all patients with invasive breast cancer. There are established guidelines for which patients are appropriate to offer APBI to as set forth by both the American Society of Breast Surgeons (ASBS) and the American Brachytherapy Society (ABS) (Figure 5).

A randomized phase 3 trial, NSABP B-39/ RTOG 0413, of conventional whole breast irradiation (WBI) versus APBI for women with stage 0, 1, or 2 breast cancer was activated in March of 2005. The accrual goal for this study is 4300 patients. The patients are randomized after lumpectomy into the arm of WBI or APBI with MammoSite RTS, multi-planar interstitial implant, or 3-D conformal APBI with external beam tangents. If a patient is randomized to APBI, they are eligible for any one of the stated choices to receive that treatment. The eligibility criteria are very broad when compared to either the ASBS or ABS patient selection guidelines (Figure 6).

**Figure 6.** NSABP B-39/RTOG 0413 - Phase III Study

- Eligible patients:
  - Stage 0, 1, II Breast Canser
  - Tumor size ≤ 3.0 cm
  - DCIS or invasive carcinoma by histoyogy
  - Negative margins
  - Node negative & node positive (1-3 positive)
  - Women aged 18 or older
  - ER-positive or ER-negative
  - EIC permitted
  - Invasive Lobular permitted

Outside of multi-planar interstitial APBI, MammoSite RTS, and external beam 3-D conformal APBI; there have recently been developed several other APBI delivery devices. These include: Contura by SenoRx (13), ClearPath by North American Scientific (14), SAVI by Cianna Medical (15), and the Axxent Electronic Brachytherapy System by Xoft (16). We await more data from patients treated with these newer devices.

At this point, although patients with pure DCIS have been treated with APBI and are being treated with APBI, there is not a significant amount of data, which has been published in regards to those patients. Patients with DCIS are appropriate for APBI under ASBS guidelines and are eligible to participate in the NSABP B-39/ RTOG 0413 study. The two largest data sets for DCIS have fairly recently published their most current results. The largest series is a subset analysis from the ASBS Registry Study, which includes a total of 194 patients treated with APBI (17). The median follow-up for these patients was 21 months with an IBTR of 0.9%. The patients with pure DCIS represented 13% of the cases within the ASBS Registry Trial. The second largest DCIS series is a multi-institutional prospective study presented by Streeter et al. (18). A total of 100 patients were treated with a median follow-up of 15 months. The good/excellent cosmetic outcome was 95%, and 3% of patients had an IBTR.

Accelerated Partial Breast Irradiation (APBI) appears to be an acceptable option for definitive radiation treatment for patients who desire breast conservation. It is imperative that the patients are well and appropriately chosen based upon current published guidelines as defined by ASBS or ABS. It is also important to put patients on open trials for APBI when they are available. The current data available shows excellent results in terms of both local control and cosmesis. It is crucial that these patients continue to be followed long term to monitor if these results persist over time. The results of NSABP B-39/ RTOG 0413 and long-term data are eagerly awaited.

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