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REVIEW ARTICLE

Accelerated Partial Breast Irradiation As a Part of Breast Conservation Therapy

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INTRODUCTION

Historically, the treatment paradigm for early-stage breast cancer has included treatment of the whole breast. Breast conservation therapy (BCT), irradiation of the whole breast following lumpectomy, requires daily treatment for 6 to 6.5 weeks. Although this is a successful and well-tolerated treatment, many patients choose to avoid whole breast irradiation as a result of the time and travel difficulties they are unable to overcome. In response, accelerated partial breast irradiation (APBI) has been investigated as a possible alternative to conventional postlumpectomy treatment. By limiting the volume of breast tissue targeted for treatment, the present data suggests that the radiation dose delivery can be safely accelerated and reduced to a treatment time of 5 days. As a result, APBI has the potential to provide more women with an alternative BCT option. This report reviews the background, concepts supporting APBI, treatment techniques used, available data from single institutional studies, and the details of presently active and planned phase III trials. The compilation of the currently available results supports the national phase III trial (National Surgican Adjuvant Breast and Bowel Project [NSABP] B39/Radiation Therapy Oncology Group [RTOG] 0413), which will begin soon, and practitioners are urged to contribute patients. Both inside and outside the trial, a meticulous quality assurance program is required for optimal results using APBI. The importance of future investigation to establish the limitations of this new treatment approach and to define the role of specific treatment techniques is emphasized.

RATIONALE

The accepted approach to BCT for early-stage breast cancer is the surgical removal of the primary breast lesion followed by whole-breast radiotherapy. Conventional whole-breast irradiation is delivered daily, 5 days per week for 6 to 6.5 weeks. When contemporary surgical and pathologic review principles are applied in conjunction with modern postoperative radiotherapeutic techniques, good to excellent cosmetic results with in-breast control rates exceeding 90% can be expected.[1-4] It should be noted that the prospective randomized studies that originally established the equivalence of conventional BCT and mastectomy also demonstrate that not all women may require postlumpectomy radiation in order to achieve acceptable in-breast disease control. However, there has yet to be a subgroup of women that has been reliably identified who do not benefit from the addition of radiation therapy.[5-8] As a result, standard of care presently dictates that all women should follow through with radiation after breast-conserving surgery to optimize local control rates regardless of age or tumor size.

Despite the equivalence in outcome between traditional BCT and mastectomy, the protracted course of radiotherapy can present a logistical problem for many

patients. This is reflected in the continued high rate of women with early-stage disease that either elect to have a mastectomy or complete their local treatment with lumpectomy alone, thus facing a potentially higher risk of in-breast failure.[9-13] Many of these women face barriers of time and travel depending upon where they live, their distance to a radiotherapy facility, and their expectations of treatment. Some of these patients have made their treatment decisions early in the management of their disease and never reach a radiation oncologist's office for consultation. Therefore, the extent of this problem is likely not well appreciated. However, the variable rates of BCT and the trend towards treatment with lumpectomy alone have shown that this is an established problem.[9-13] If the breast preservation rate is to increase, changes will need to occur to create a more accessible adjuvant treatment that maintains the present standards of excellent local control and cosmetic outcome.

For a major change in the approach to adjuvant radiotherapy to be realized, significant alterations must first occur in the presently accepted treatment paradigm. Management principles have historically focused on treatment of the entire breast, either with surgery or whole-breast radiotherapy. At the inception of BCT, the two basic principles that formed the basis for this approach consisted of the belief that residual microscopic disease following lumpectomy may be present anywhere within the breast and that the management techniques for treatment of the whole breast were widely available and easily applied. However, review of both clinical and pathologic evidence finds that there are scarce data to support the concept that the entire breast requires treatment. In fact, these data suggest that the primary target requiring adjuvant treatment following lumpectomy (with negative surgical margins) is likely limited to a 1 to 2 cm boundary surrounding the lumpectomy cavity edge.[14-23] This potential change in the treatment target provides the opportunity for a possible modification in the treatment paradigm. By reducing this target to less than 50% of the whole breast volume, acceleration of the dose delivery and completion of treatment in less than 5 days becomes feasible. Also, with the advent of new, widely available, radiotherapeutic treatment techniques, the accurate delivery of a conformal APBI dose to a limited target in the breast becomes possible. However, for this new technique of APBI to become an accepted standard of care, questions regarding appropriate application of treatment techniques, proper patient selection criteria, risk of toxicity, and long-term local control equivalence to traditional breast conservation must be answered.

TREATMENT TECHNIQUE

Several different treatment techniques have been developed for the delivery of APBI. These techniques include multicatheter interstitial brachytherapy, balloon catheter brachytherapy, three-dimensional conformal external beam radiotherapy (3D-CRT) and intraoperative radiotherapy. Each of these techniques is in a different stage of development and acceptance. Although they each have unique advantages and disadvantages, all strive to satisfy the goal of comprehensively irradiating the treatment target and assuring homogeneous dose coverage. Each of the APBI treatment techniques addresses these goals to different degrees and additional investigation is needed to fully understand which technique is most applicable to a given clinical setting. Multicatheter, balloon catheter, and 3D-CRT treatment techniques have centered on postoperative, fractionated dose delivery. Successful treatment schemes reported have been typically 34 Gy in 10 fractions delivered twice a day over 5 days or 32 Gy in eight fractions over 4 days. Alternative fractionation schemes, as well as low-dose rate (LDR) brachytherapy, have also been reported.[24-36] In contrast to this experience, intraoperative radiotherapy offers further acceleration of dose delivery. With this approach, the entire partial breast radiation dose is delivered in one large fraction of 21 Gy at the time of surgical excision.[37-39]

Multicatheter-Based Interstitial APBI

The APBI technique that has been in use the longest, and utilized in the treatment experiences with the most extensive follow-up, is the multicatheter, interstitial brachytherapy approach. This APBI technique was first developed and used as a boost following whole-breast radiotherapy. With this approach, after-loading catheters are placed through the breast tissue surrounding the lumpectomy cavity. Catheters are generally positioned at 1 to 1.5 cm intervals to avoid hot and cold spots. These implants routinely require 14 to $>$ 20 catheters to assure proper dose coverage. The exact number of catheters used is determined by the size and shape of the target, and the configuration of catheters by an understanding of brachytherapy dosimetric guidelines.[40,41] Once the implant geometry is known (through mapping of catheter location), dosimetric planning is completed to determine how to optimally place the radioactive source within the catheters for dose delivery (Fig 1). The majority of patients undergoing this procedure tolerate the presence of these catheters remarkably well, with minimal need for pain medication despite the apparent trauma to the breast. To assure that the goals of target coverage and dose homogeneity are routinely achieved, advances have been necessary to reduce the degree of operator dependence and improve the reproducibility of this procedure.[42,43] With the incorporation of image-guided catheter placement techniques (stereotactic mammography, ultrasound or computed tomography [CT] –guided) and 3D dosimetric planning, the multicatheter approach has evolved into a

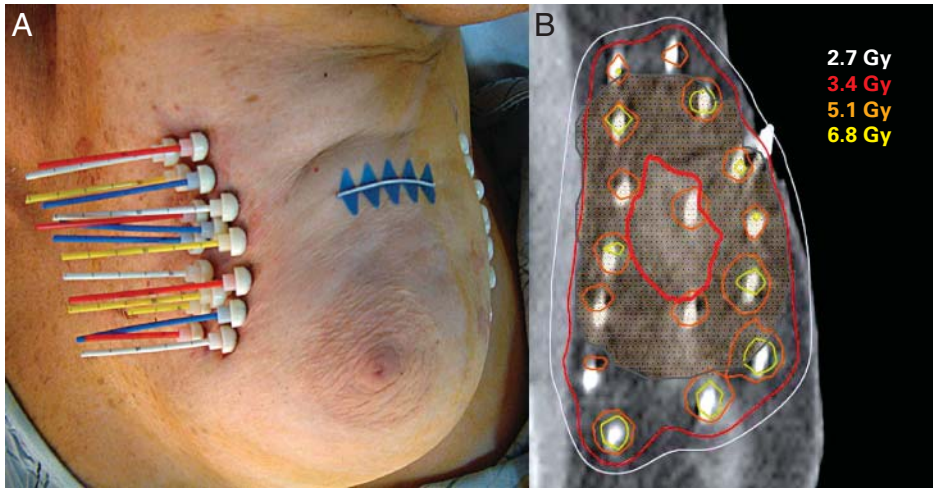

Fig 1. Multicatheter interstitial brachytherapy. External appearance and cross-sectional view of dosimetric target coverage. Lumpectomy cavity is outlined in red and target shaded in orange (target defined as the lumpectomy cavity with 1.5-cm expansion).

reliable technique that is adaptable and can be used for APBI in a variety of treatment situations, regardless of lumpectomy cavity size, shape, or location within the breast. In response to the technical difficulties associated with multicatheter, interstitial brachytherapy, and the general appearance of the breast with catheters in place, alternative methods of dose delivery have now been created that reduce the complexity and invasiveness of APBI.

MammoSite Radiation Therapy System for APBI

The first alternative method for APBI developed using brachytherapy was the MammoSite Radiation Therapy System (RTS; Proxima Therapeutics Inc, Alpharetta, GA). The MammoSite RTS is a balloon catheter treatment device designed to simplify the brachytherapy procedure, while improving the reproducibility of dosimetric coverage of the target (Fig 2). Building on the experience reported with multicatheter brachytherapy, the research and development of this device focused on the ability to reproduce the target coverage and dosimetry achieved with published multicatheter brachytherapy techniques. The MammoSite RTS balloon is composed of a 15-cm double lumen catheter that is 6 mm in diameter. The catheter is located centrally within a distally located balloon that is placed into the lumpectomy cavity and inflated with sterile water. To accommodate the variation in lumpectomy cavity size, two balloon sizes are available, inflating to a sphere of 4 to 5 cm or 5 to 6 cm in diameter. The device is placed in the lumpectomy cavity either during or following breast-conserving surgery. After inflation, balloon catheter placement is evaluated to assure balloon symmetry, an overlying skin distance of > 5 mm, and lumpectomy cavity conformance with the balloon surface. Final approval for treatment follows a review of dosimetric

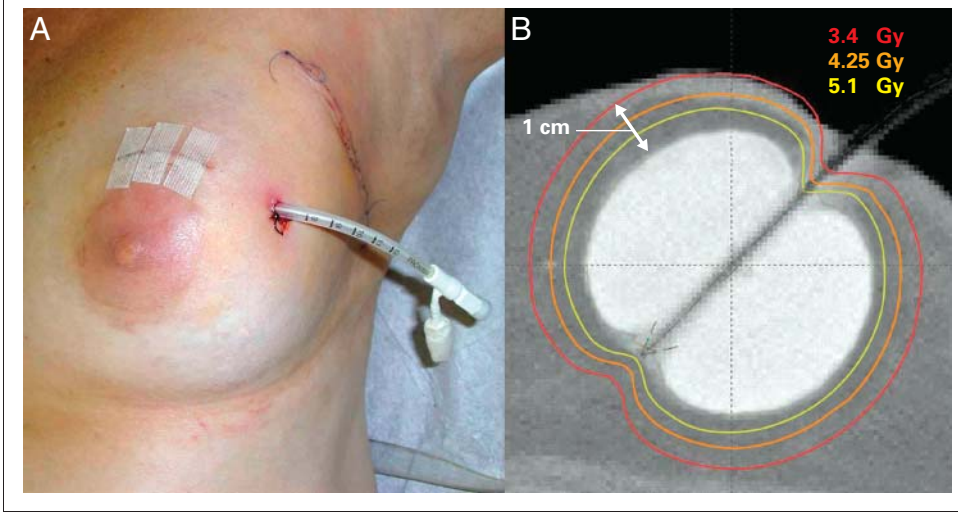

Fig 2. MammoSite radiation therapy system. External appearance and sagittal view of balloon with dosimetric target coverage. Target is defined as tissue within 1 cm of balloon surface.

planning to assure target coverage and acceptable dose homogeneity.[44] Treatment is delivered with a single, centralized, high-dose rate source to a circumferential 1-cm distance from the surface of the balloon. The MammoSite RTS was cleared by the US Food and Drug Administration (US FDA) in May 2002 based on results from an initial phase I/II trial (43 patients treated at eight institutions) designed to test the safety and performance of the device. Follow-up data reported at 1 month and again at 21 and 29 months report little or no toxicity.[45-47] It is estimated that greater than 4,000 balloons have been used for APBI since US FDA clearance, thus reflecting the improvements in patient comfort and relative simplicity of treatment offered by this device. Although additional reports of acute toxicity are available, further analysis of the 1,500-patient MammoSite RTS registry trial (managed by the American Society of Breast Surgeons) and long-term follow-up are necessary before definitive statements can be made.[48-50]

3D Conformal External Beam APBI

Although APBI is still dominated by brachytherapy approaches, recent investigation into treatment delivery with conformal external beam fields is well underway. This APBI technique is attractive to both physician and patient alike because it is (1) noninvasive, (2) delivers a homogeneous dose with decreased procedural trauma to the breast, and (3) offers a potential reduction in normal breast tissue toxicity (Fig 3). The feasibility of this approach is dependent on several technologic advances including CT-based planning, 3D treatment planning systems, and sophisticated linear accelerators permitting treatment delivery with highly conformal dose distributions. Two institutions have published phase I/II trials, one treating patients in the prone position and the other in the supine position.[51-54] Challenges with this treatment approach are different then those confronted with brachytherapy. Since it requires multiple field angles to conform the dose to the target in the breast, the technique can significantly increase the integral dose received by surrounding normal structures. The long-term effect of delivering these lower doses to an increased volume of normal tissue in a population with a long life expectancy is uncertain. In response to these concerns, early investigators have set conservative normal tissue dose limitations to guide field orientation and design.[55] Unfortunately, these constraints limit the number of cases that can be treated with an external beam approach to those with small target sizes and specific locations within the breast. To increase the number of patients eligible, the maximum-dose limitations for the adjacent normal tissue structures will need to be better defined so that target sizes can be safely increased, allowing this technique to be more universally applied. Further investigation is also needed to fully understand the impact of breathing motion and set-up error on treatment accuracy, with the possible development of methods for correction.

Intraoperative APBI

Outside the United States, intraoperative radiotherapy has been the primary focus of investigation for the delivery of APBI (Table 1). All of the adjuvant radiation is delivered at the time of surgery (quadrantectomy/lumpectomy), thus maximally accelerating dose delivery and patient convenience. The University College of London (London, United Kingdom) has investigated the use of low energy x-rays (maximum energy, 50 kv) delivered by a portable, spherical, radiation-generating device that is placed into the lumpectomy cavity following tumor resection.[38,39] The prescribed dose is given in one 5- to 20-Gy fraction at a depth of 1 and 2 cm, respectively. The European Institute of Oncology (Milan, Italy) has used intraoperative electrons (generated by a mobile linear accelerator) delivering 21 Gy in one fraction (immediately following quadrantectomy) for their APBI technique. In this approach, the breast is surgically manipulated to assure

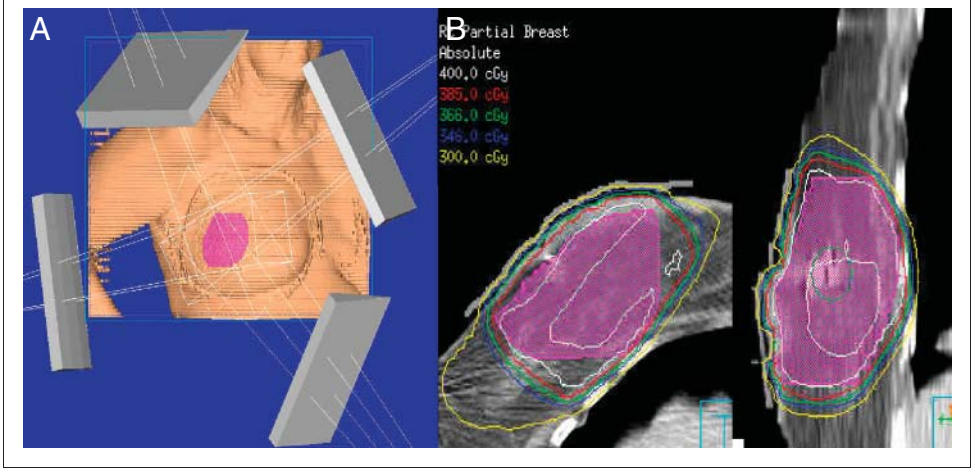

Fig 3. Three-dimensional conformal external beam radiotherapy. Four-field beam arrangement and conformal, homogeneous dose coverage of the target. Target is shaded in purple.

Table 1. Accelerated Partial Breast Irradiation Studies (intraoperative)

Institution	No. of Cases	Surgery	Dose	Radiation Source	Type of Radiation/Energy
University College of London[38,39]	25 (pilot trial)	Lumpectomy (per institution)	5 Gy × 1*; 5 Gy at 1 cm; 20 Gy at 0.2 cm	Miniature electron beam-driven x-ray source†	Low energy x-rays, 50 kV
European Institute of Oncology[37]	237	Quadrantectomy	21 Gy × 1*	Mobile linear accelerator	3, 5, 7, or 9 MeV electrons

*Dose utilized in randomized trial
†Photon radiosurgery system (Photoelectron Corporation, North Billerica, MA).

that all targeted tissue is within the electron field boundaries, while nontargeted normal tissue is either outside the limits of the electron field or shielded.[37] Phase I/II results are promising and both institutions are presently conducting phase III randomized trials. Although the advantages of intraoperative treatment are clear, this approach raises some important concerns. As all adjuvant radiotherapy treatment is completed before the availability of the final microscopic margin and axillary nodal status, this information cannot be incorporated as a part of the selection criteria or in the determination of the target extent. Quality assurance guidelines related to target delineation and dose coverage also appear difficult to derive and the late effects on breast tissue as a result of a very large single dose are uncertain at this time. The phase III trials now being conducted will be helpful in addressing these questions.

PATIENT SELECTION

In addition to target delineation and dose coverage, one of the key components contributing to the successful application of APBI appears to be case selection. Patients with a significant risk of harboring microscopic disease within the breast, but located outside the stated treatment target (1 to 2 cm beyond the lumpectomy cavity), are not optimal candidates for APBI. The discussion begins when attempting to determine the appropriate criteria to be used in the proper selection of patients for APBI. Early treatment experiences were highly selective. In response to the increased interest in APBI, two societies have endorsed conservative patient selection criteria with the goal of providing guidance and general consistency in selection of eligible patients.[56,57] The American Brachytherapy Society patient selection criteria include: patients $\geq$ 45 years of age, invasive ductal carcinoma only, tumor size of $\leq$ 3cm, negative resection margins (defined as "no tumor on ink"), and a negative axillary nodal status. Although similar in concept, the patient selection criteria endorsed by the American Society of Breast Surgeons includes: patients $\geq$ 50 years of age, invasive ductal carcinoma or ductal carcinoma-in-situ, tumor size of $\leq$ 2cm, negative resection margins (defined as at least 2 mm in all directions), and a negative axillary nodal status. In reviewing the literature, it appears that the need to obtain a negative surgical margin and the restriction to smaller tumors are the only two criteria that have been consistently applied within the successful APBI trials. An extensive intraductal component, limited positive nodal status, infiltrating lobular histology, ductal carcinoma-in-situ, and young age have been inconsistently used as exclusion criteria in these successful early treatment experiences. These clinicopathologic features have presently been adopted as exclusion criteria by the American Brachytherapy Society and American Society of Breast Surgeons to maintain a conservative approach until more definitive data are available.

TOXICITY

Reports of treatment toxicity with APBI are predominantly found in the multicatheter, interstitial brachytherapy experiences. Whether this is technique related or due to limited follow-up in the other techniques is not known. In all of the treatment approaches described, the toxicity observed has been limited to the breast tissue and overlying skin. Although target volumes are typically small, the intensity of dose delivery can be problematic depending on the total dose, homogeneity of the dose, and the potential interaction between dose delivered to the skin and the subsequent delivery of chemotherapy. When presently accepted dose schemes and dose homogeneity are used, there appears to be a low risk of toxicity.[24,36,58] In an investigation of total dose, Massachusetts General Hospital (Boston, MA) described a treatment experience employing a dose-escalation scheme using low-dose rate implantation.[30] They reported an increased rate of performing biopsies during follow-up (usually done because of changes on examination or mammography due to fat necrosis) and an increasing proportion of patients with moderate or severe fibrosis that paralleled the increase in dose. Patients received dose levels of 50 Gy (19 patients), 55 Gy (15 patients), or 60 Gy (12 patients), and these dose levels corresponded with biopsy rates of 11%, 20%, and 25%, and fibrosis development rates of 0, 7%, and 25%, respectively.

An additional factor that appears to be important to the risk of normal breast tissue complications is the volume of implantation and the volume of increased dose heterogeneity ("hot spots") within the implanted volume. In the study from Tufts-New England Medical Center (Boston, MA),

Table 2. Accelerated Partial Breast Irradiation Studies (interstitial Experience)

Institution	No. of Cases	Median Follow-Up (months)	5-Year Actuarial Recurrence Rate Total (%)	5-Year Elsewhere Failure Rate (%)
William Beaumont Hospital[24]				
Total	199	65	1	0.6
Low dose rate protocol	120	82	0.9	0
High dose rate protocol	79	52	2.1	2.1
Ochsner Clinic[25]	160	84	2.5*	1.2*
Virginia Commonwealth University[26]	44	42	0	0
RTOG 95-17[27]	99	44	3	—
University of Kansas[28]	25	47	0	—
University of Pisa, Italy[29]	90	27	4.4	—
Massachusetts General Hospital[30]	48	23	0	—
Tufts/Brown Universities[31]	33	58	6*	6*
University of Wisconsin[32]	50	—	—	—
Guy's Hospital[33]	27	72	37	—
Guy's Hospital II[34]	50	60	18	4
London Regional Cancer Center[35]	39	91	16.2	10
National Institute of Oncology, Hungary phase I/II trial[36,61]	45	80	6.7*	6.7*
National Institute of Oncology, Hungary phase III trial[36,62]	119	30	2.5*	1.7*

Abbreviation: RTOG, Radiation Therapy Oncology Group.
*Crude rate.

patients with grade 3 or 4 complications, fibrosis, and fat necrosis had mean treatment volumes that were much larger than those in patients with grade 2 or lower complications.[31,59] This correlation held true whether the volume was defined by the 3.4 Gy per fraction isodose surface (234 and 148 cc in the two groups, respectively), the 5.1 Gy per fraction isodose surface (69 and 36 cc), or the 6.8 Gy per fraction isodose surface (21 and 11 cc).

A comparison of toxicity between the early experience with the MammoSite RTS and multicatheter brachytherapy was presented recently by Tufts-New England Medical Center and Virginia Commonwealth University (Richmond, VA).[60] Initial evaluation found a higher risk of subcutaneous fibrosis and fat necrosis with intersititial brachytherapy as compared with MammoSite RTS treatment (32% and 12% *v* 10.7% and 7.1%, respectively). On further analysis, there was a significant correlation between receiving chemotherapy and suboptimal outcome. Due to the disproportionate number of patients treated with a combination of interstitial brachytherapy and adriamycin, an analysis of chemotherapy-naïve patients was performed, showing no difference in outcome between MammoSite RTS and interstitial brachytherapy.

The interaction between chemotherapy and APBI is also described in the Virginia Commonwealth University multicatheter brachytherapy experience.[26] Acute recall reactions involving the treated skin were noted in six (43%) of 14 patients, who were subsequently treated with doxorubicin. In this experience, the subsequent development of grade 2 or higher fibrosis was predominant in patients treated with LDR brachytherapy when doxorubicin was given (five of six patients), compared to LDR brachytherapy alone (one of seven patients). It was concluded that the variable patient position during the LDR treatment delivery (avoided with high dose rate treatment delivery) resulted in a collapse of the implant structure, change in dose distribution, and the potential for an immeasurable amount of increased dose delivered. In this situation, chemotherapy appeared to potentiate the risk of soft tissue complications when combined with this suboptimal dosimetry.

INTEGRATION WITH CHEMOTHERAPY

One of the potentially attractive aspects of APBI is the ability to complete adjuvant radiotherapy within a short amount of time following lumpectomy, so as not to delay the initiation of systemic treatment when indicated. Simultaneous delivery of the intense dose fractionation scheme with chemotherapy has not been performed due to concerns of increased toxicity. With proper coordination, patients should be able to initiate APBI within 1 to 2 weeks postlumpectomy, allowing chemotherapy to be initiated within 4 to 5 weeks following lumpectomy (since a 2-week interval between the completion of APBI and the start of chemotherapy is the present practice). Communication and coordination between involved physicians is necessary for successful and timely treatment delivery. Waiting until after chemotherapy delivery is complete is possible, but would require surgical clip placement to provide a method of target definition. Additionally, the delay would exclude the MammoSite RTS as a treatment option as it is unlikely that the lumpectomy cavity would be appropriate, or even exist, for balloon placement.

TREATMENT EXPERIENCE

The number of published APBI experiences continues to increase yearly. The majority of the patients treated with

Table 3. Accelerated Partial Breast Irradiation Studies (MammoSite Radiation Therapy System experience)

Institution	No. of Cases	Follow-Up (months)	Local Recurrence (%)	Good/Excellent Cosmetic Results (%)	Infection (%)
Multi-institutional trial[45-47]	43	29	0	84	3.7
MammoSite™ Registry Trial[48]	106	NR	0	90	6
Tufts-New England Medical Center, Virginia Commonwealth University[60]	28	19	0	93	NR
St. Vincent's Comprehensive Cancer Center[50]	32	11	0	86	16
Breast Care Center of the Southwest[63]	21	NR	NR	NR	NR
Rush University Medical Center[49]	112	NR	0	80	6

Abbreviation: NR, not reported.

the longest follow-up in these reports have been treated with multicatheter interstitial technique. The published interstitial brachytherapy experiences are summarized in Table 2. Collectively, this represents an experience of hundreds of patients with in-breast failure rates that are less than 5%, and with good to excellent cosmetic outcome reported in the majority (cosmetic data not shown). In three of these reports,[33-35] unacceptable in-breast disease control rates were observed. These higher rates of in-breast failure appear to be directly related to the lack of patient selection criteria and/or treatment quality assurance. As an example, in the earlier experience at Guy's Hospital (London, United Kingdom),[33,34] microscopic margin assessment was not employed and it is unclear as to how many patients included would have even been eligible for standard BCT by modern standards. Additionally, the authors from Guy's Hospital themselves have introduced questions regarding the quality assurance of the treatment delivered; specifically the methods used for target delineation and the ability to confirm dosimetric coverage of the target.[33] At the London Regional Cancer Center (London, United Kingdom), dosimetric coverage of an appropriately delineated target is questioned, as the target appears to have been limited to the seroma cavity only, without the immediately surrounding normal breast tissue at risk included.[35,62] These publications further validate that the success of APBI is realized through proper patient selection and quality assurance of treatment delivery.

The published experience using the MammoSite RTS is tabulated in Table 3. The original experience of 43 patients that lead to US FDA clearance of the device is reported with the longest follow-up, but as expected, the follow-up interval of 1 year or less in the other publications is relatively limited. Results are encouraging, but additional follow-up is necessary in order to make any definitive conclusions. Infection rates associated with the MammoSite device appear to be in line with those reported from other surgical procedures. The isolated infection rate of 16% reported out of St. Vincent's Comprehensive Cancer Center (New York, NY) may have been related to the initial catheter care applied at the introduction of this device into clinical use.[50] The rate of infection is expected to decrease with additional experience. A large patient registry database, managed by the American Society of Breast Surgeons, has recently completed accrual. This registry includes 1,500 MammoSite RTS patients. Information collected on registered patients includes a wide spectrum of clinical, pathologic, treatment, and follow-up data points. When analyzed, this database will prove to be valuable in guiding the proper use of this novel brachytherapy device.

The limited APBI treatment experience with external beam radiotherapy is presented in Table 4. The two experiences reported out of Europe both have applied electron beam radiation but have reported striking differences in disease control rates.[36,64] In review of these publications, it appears that there is a difference in patient selection and quality assurance that may account for the difference in outcome. In the Christie Hospital/Holt Radium Institute (Manchester, UK) experience, microscopic margin assessment was not included and there was no assurance of

Table 4. Accelerated Partial Breast Irradiation Studies (external beam radiotherapy)

Institution	No. of Cases	Follow-Up (months)	Fractionation Scheme	Local Recurrence (%)	Good/Excellent Cosmetic Result (%)
William Beaumont Hospital[51]	9	8 (median)	3.4 or 3.85 Gy × 10 bid	0	100
William Beaumont Hospital[52]	31	10 (median)	3.4 or 3.85 Gy × 10 bid	0	100
New York University/Keck School of Medicine[54]	47	18	6 Gy × 5 for 10 days	0	100
Christie Hospital/Holt Radium Institute[64]	353	96 (mean)	5-5.31 Gy × 8 for 10 days	25	NS*

Abbreviation: NS, not stated.
*Partial breast irradiation patients had a greater incidence of fibrosis, telengiectasias, and fat necrosis.

Table 5. Prospective Randomized Trials of Accelerated Partial Breast Irradiation

Institution/Trial	Trial Design	No. of Cases	Control Arm	Experimental Arm	Status
NSABP B 39/RTOG 0413	Equivalence	3,000	50-50.4 Gy WB +/− 10-16 Gy boost	(1) Interstitial brachytherapy, or (2) MammoSite, or (3) 3D-CRT	Not yet activated
National Institute of Oncology, Hungary[36]	Noninferiority	570	50 Gy WB	(1) Interstitial brachytherapy (5.2 Gy × 7), or (2) electrons (50 Gy)	255 enrolled
European Brachytherapy Breast Cancer GEC-ESTRO Working Group	Noninferiority, nonirrelevant, 3% difference	1,170	50-50.4 Gy WB + 10 Gy boost	Brachytherapy only; 32 Gy. 8 fractions HDR; 30.3 Gy, 7 fractions HDR; 50 Gy PDR	Activated May 2004
European Institute of Oncology[37]	Equivalence	824	50 Gy WB + 10 Gy boost	Intraoperative, single-fraction EBRT, 21 Gy × 1	587 patients enrolled
University College of London[38]	Equivalence	1,600	WBRT (per center) + boost	Intraoperative, single-fraction EBRT, 5 Gy × 1	110 enrolled
Christie Hospital/Holt Radium Institute[64]	NS	708	40 Gy in 15 fractions WB (no boost)	5-5.31 Gy × 8 (10 days)	Completed

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; RTOG, Radiation Therapy Oncology Group; WB, whole breast; 3D-CRT, three-dimensional conformal external beam radiotherapy; GEC-ESTRO, Groupe Europeen de Curietherapie–European Society for Therapeutic Radiology and Oncology; HDR, high-dose rate; PDR, pulsed dose rate; EBRT, external beam radiation therapy; NS, not stated; WBRT, whole-breast radiation therapy.

accurate target delineation with proven dose coverage.[64] These essential components were included in the experience from the National Institute of Oncology, Hungary.[36] The need for proper patient selection and quality assurance to ensure success cannot be overstated. The experience in the United States is limited, and the data reported are yet to have the follow-up needed to generate strong conclusions. However, the experience to date has been positive, with little to no acute toxicity. In the two experiences listed in Table 4, multiple photon fields are arranged to deliver a conformal, homogeneous dose distribution.[51-54] The complex field arrangements have produced concerns regarding the feasibility of this approach as it applies to a multi-institutional study with the varying types of planning and treatment equipment available. In response to this concern, a RTOG phase I/II trial was conducted to investigate this question (RTOG 03-19).[55] As a result of the interest in this technique, the necessary number of patients was enrolled in less than a year and results are forthcoming.

ONGOING STUDIES AND FUTURE DIRECTIONS

Continued studies are necessary to address questions regarding patient selection criteria, details of treatment technique, and to help determine which APBI approach is best applied for each clinical setting. With the continued reporting of the initial trials and the initiation of additional single and multi-institutional phase I/II trials and phase III prospective randomized trials, these questions will be appropriately addressed and further define the role of APBI in the management of early-stage breast cancer.

Descriptions of the activated and proposed phase III trials from the United States and Europe are presented in Table 5. The European trials are accruing well and the United States phase III trial is anticipated to be open in early 2005. This trial will be a combined effort between the NSABP and RTOG. The protocol has been designed to address many of the questions regarding patient selection and technique application. The accrual goal of this trial will be 3,000 patients. Randomization will be between standard whole-breast radiotherapy and APBI. Patients will be randomly assigned postoperatively so that the pathologic information is available, and a postlumpectomy CT scan will be necessary to ensure partial breast treatment can be executed. The physician will have the option of using any of the three acceptable APBI techniques—multicatheter interstitial brachytherapy, MammoSite RTS brachytherapy, or 3D-CRT. Additionally, an extensive quality assurance program will be the hallmark of this protocol and has been developed to guarantee that with each of the treatment approaches used, both whole and partial breast, the intended target is clearly defined and appropriately covered with the prescribed dose.

Although APBI is now offered in many facilities as an alternative to whole-breast irradiation, this approach has not been fully established as an equivalent to conventional whole-breast irradiation due to the paucity of long-term results (in a disease with an extended risk of local recurrence) and, more importantly, to the absence of data from phase III studies. Practitioners are urged to contribute patients to the national phase III trial (NSABP B39/RTOG 0413), which will open soon. Both inside and outside the trial, however, a meticulous quality assurance program is required for optimal results using APBI.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for

drugs or devices used in a study if they are not being evaluated as part of the investigation. Honoraria: Douglas W. Arthur, Proxima Therapeutics; Frank A. Vicini, Proxima Therapeutics. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

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