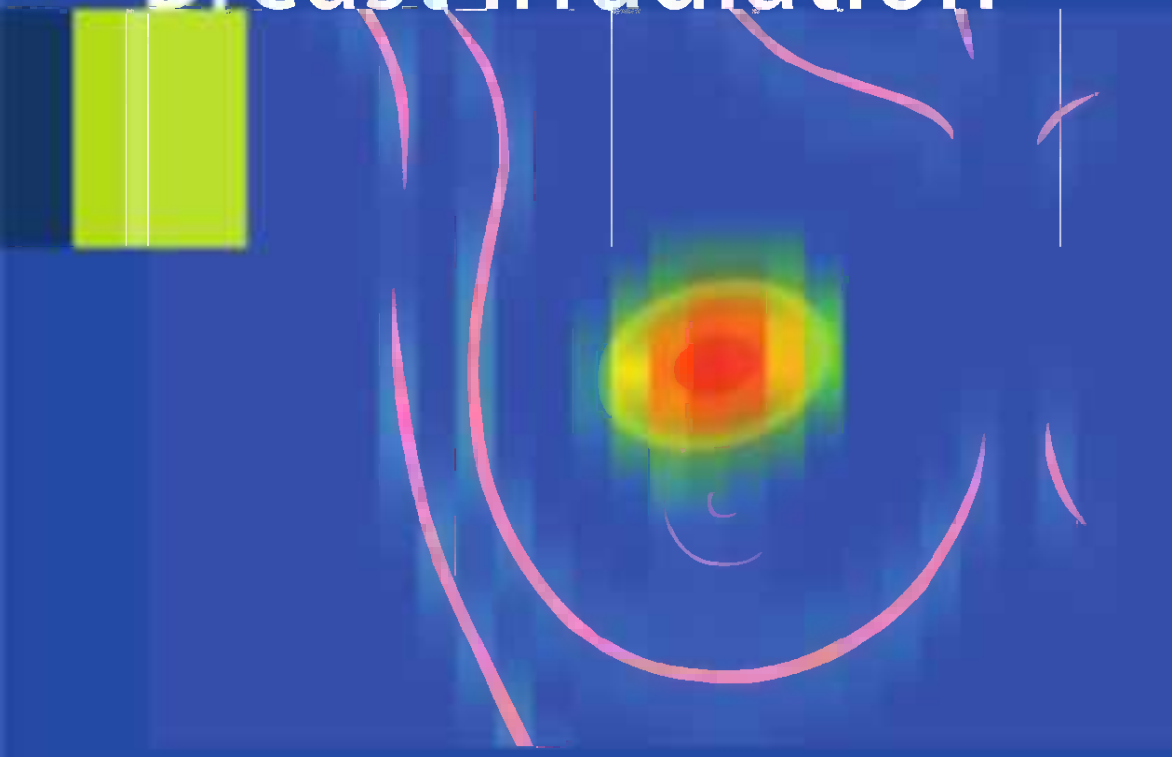
David E. Wazer · Douglas W. Arthur
Frank A. Vicini *Editors*

Accelerated Partial Breast Irradiation



Techniques and Clinical Implementation

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Techniques and Clinical Implementation

With 125 Figures and 42 Tables

Springer

David E. Wazer
Department of Radiation Oncology
Tufts-New England Medical Center
Tufts University School of Medicine
750 Washington Street
Boston, MA 02111
USA

Douglas W. Arthur
Department of Radiation Oncology
Virginia Commonwealth University Medical Center
Medical College Virginia Campus
401 College St
Richmond, VA 23298-0058
USA

Frank A. Vicini
Department of Radiation Oncology
William Beaumont Hospital
3577 W. Thirteen Mile Road, Ste. 210
Royal Oak, MI 48073
USA

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Contents

List of Contributors

Douglas W. Arthur
Department of Radiation Oncology,
Virginia Commonwealth University
Medical Center,
Medical College Virginia Campus,
401 College Street
Richmond, VA 23298 USA

Thomas A. Buchholz
Department of Radiation Oncology,
The University of Texas
M. D. Anderson Cancer Center,
1515 Holcombe Blvd., Unit 1202,
Houston, TX 77030, USA

Peter Y. Chen
Department of Radiation Oncology,
William Beaumont Hospital,
3601 W. 13 Mile Road,
Royal Oak, MI 48073, USA

Laurie W. Cuttino
Department of Radiation Oncology,
Virginia Commonwealth University,
Richmond, VA 23298, USA

Rupak Das
Department of Human Oncology,
University of Wisconsin,
K4/B100 Clinical Sciences Center,
Madison, WI 53792, USA

Gregory K. Edmundson
Cytyc Surgical Products,
P.O. Box 944, Rough and Ready,
CA 95975, USA

Neal S. Goldstein
Department of Anatomic Pathology,
William Beaumont Hospital,
3601 West Thirteen Mile Road,
Royal Oak, MI 48073, USA

Yasmin Hasan
William Beaumont Hospital,
3601 West Thirteen Mile Road,
Royal Oak, MI 48073-6769, USA

Shruti Jolly
Department of Radiation Oncology,
William Beaumont Hospital,
3601 West Thirteen Mile Road,
Royal Oak, MI 48073, USA

Martin E. Keisch
Mt. Sinai Medical Center,
4300 Alton Road, Blum Bldg,
Miami Beach, FL 33140, USA

Joseph R. Kelley
Department of Radiation Oncology,
Virginia Commonwealth University
Medical Center,
Medical College Virginia Campus,
401 College Street
Richmond, VA 23298 USA

Larry L. Kestin
Department of Radiation Oncology,
William Beaumont Hospital,
3601 West Thirteen Mile Road,
Royal Oak, MI 48073, USA

Henry M. Kuerer
Department of Surgical Oncology,
The University of Texas,
M. D. Anderson Cancer Center,
Box 444, 1515 Holcombe Boulevard,
Houston, TX 77030, USA

Robert R. Kuske Jr.
Arizona Oncology Services,
8994 E Desert Cove Avenue, Ste. 100,
Scottsdale, AZ 85260, USA

Tibor Major
Department of Radiotherapy,
National Institute of Oncology,
Ráth Gy. u. 7-9.,
Budapest 1122, Hungary

Peter Niehoff
Department of Radiation Oncology,
University Hospital Schleswig-Holstein
Campus Kiel, Arnold-Heller Str. 9,
24105 Kiel, Germany

Oliver J. Ott
Department of Radiation Oncology,
University Hospital Erlangen,
Universitätsstr. 27,
91054 Erlangen, Germany

Rakesh R. Patel
Department of Human Oncology,
University of Wisconsin,
600 Highland Avenue K4/B100,
Madison, WI 53792, USA

Csaba Polgár
Department of Radiotherapy,
National Institute of Oncology,
Ráth Gy. u. 7-9.,
Budapest 1122, Hungary

Simon N. Powell
Department of Radiation Oncology,
Washington University School of Medicine,
4511 Forest Park,
St. Louis, MO 63108, USA

Mark J. Rivard
Department of Radiation Oncology,
Tufts-New England Medical Center,
750 Washington Street,
Boston, MA 02111, USA

Vratislav Strnad
Department of Radiation Oncology,
University Hospital Erlangen,
Universitätsstr. 27,
91054 Erlangen, Germany

Eric A. Strom
Department of Radiation Oncology,
The University of Texas
M. D. Anderson Cancer Center,
1515 Holcombe Blvd.,
Houston, TX 77030, USA

Alphonse G. Taghian
Department of Radiation Oncology,
Massachusetts General Hospital,
Harvard Medical School,
55 Fruit Street,
Boston, MA 02114, USA

Bruce Thomadsen
Departments of Medical Physics and
Human Oncology,
University of Wisconsin,
1530 Medical Sciences Center,
Madison, WI 53706, USA

Jayant S. Vaidya
Department of Surgery and Molecular
Oncology,
University of Dundee, Level 6,
Ninewells Hospital and Medical School,
Dundee DD1 9SY, UK

Frank A. Vicini
Department of Radiation Oncology,
William Beaumont Hospital,
3577 W. Thirteen Mile Road, Ste. 210,
Royal Oak, MI 48073, USA

David E. Wazer
Department of Radiation Oncology,
Tufts-New England Medical Center,
Tufts University School of Medicine,
750 Washington Street,
Boston, MA 02111, USA

Chapter

1 Accelerated Partial Breast Irradiation: History, Rationale, and Controversies

Thomas A. Buchholz
and Eric A. Strom

Contents

1.1 Introduction

Results from two decades of study have conclusively shown that radiation therapy has an important role in ensuring local control for patients with early-stage breast cancer who are treated with breast-conserving surgery. When breast-conservation therapy was first explored as an alternative to mastectomy, many trials investigated whether surgical resection of the tumor-bearing region of the breast was sufficient, or whether adjuvant irradiation of the entire breast would be required to improve patient outcome. These trials showed that whole-breast irradiation significantly reduced the risk of ipsilateral tumor recurrence after resection of the tumor and the tissue immediately surrounding the tumor (Fisher et al. 2002a; Veronesi et al. 2001; Vinh-Hung and Verschraegen 2004).

On the basis of the results of these phase III trials, whole-breast irradiation became a standard component of breast-conservation therapy. Subsequently, two randomized trials investigated whether the addition of a tumor-bed boost following whole-breast irradiation offered further benefit (Bartelink et al. 2002; Romestaing et al. 1997). Both of these studies demonstrated a small but statistically significant reduction in ipsilateral breast tumor recurrence. Correspondingly, the available medical evidence to date

suggests that the optimal radiation treatment schedule should include 5 weeks of daily therapy directed to the ipsilateral breast followed by 1 to 1.5 weeks of additional daily therapy directed to the tumor-bed region. A single randomized study has suggested that a 16-fraction course of whole-breast irradiation might also be considered for selected elderly patients with stage I disease (Whelan et al. 2002).

The studies investigating radiation and breast-conservation therapy proved to be one of the more significant advances in the local–regional management of breast cancer. It is now accepted that whole-breast irradiation after breast-conserving surgery decreases the risk of local recurrence to very low levels that are comparable to those achieved with mastectomy. Correspondingly, there is consensus that nearly all patients with early-stage breast cancer should be offered the option of being treated with a breast-conserving approach. An equally positive finding of these studies is that the radiation component of breast-conservation therapy is associated with a very low rate of toxicity to normal tissue and that modern local–regional treatment has little impact on the long-term quality of life for breast cancer survivors. Finally, with optimal surgical and radiation treatment the long-term aesthetic outcomes associated with this approach are excellent (Taylor et al. 1995; Wazer et al. 1992).

However, despite its many positive benefits, radiation therapy is also associated with some disadvantages, the foremost of which is perhaps the fact that it is a relatively complex and expensive treatment. Radiation treatments require physical resources, such as linear accelerators, simulators, and treatment planning systems, in addition to significant personnel resources, such as specialty-trained physicians, physicists, dosimetrists, and therapists. This level of expertise is not available in every city and the level varies from country to country. A second major downside of radiation therapy is that the treatments are inconvenient. As mentioned, standard whole-breast irradiation in the United States is typically administered over 6–7 weeks and treatments are preceded by 2 or 3 days of treatment planning. The 5-day-a-week treatment schedule may require patients to miss work and can lead to other significant life-style disruptions. These factors are particularly relevant for patients who do not live in close proximity to a radiation treatment facility. Standard whole-breast treatment may require such individuals to temporarily relocate, which might cause financial burdens such as temporary lodging expenses and the costs of missing work. Furthermore, such relocation may mean separating patients from their family, friends, and other supporters.

These downsides of radiation have been proven to have consequences. First, some women elect to forgo breast-conservation therapy and to be treated with mastectomy in order to avoid the need for radiation treatments. In fact, a number of studies have found an inverse relationship between the use of breast-conservation therapy and the distance from a patient's home to the nearest radiation facility (Athas et al. 2000). Furthermore, the regions of the country with the lowest density of radiation treatment facilities have the lowest rates of breast-conserving treatments (Farrow et al. 1992). An even more serious consequence that can result from the inconvenience of the radiation treatment schedule is that some patients treated with breast-conservation therapy elect to forgo the radiation component of their treatment. Recent pattern-of-care studies have indicated that approximately 20% of patients with early-stage invasive breast cancer treated in the United States do not receive radiation as a component of breast-conservation therapy (Nattinger et al. 2000). This option has been proven to place these patients at higher risk of tumor recurrence and possibly a higher risk of death.

The magnitude of the problem posed by the time required to administer radiation treatments is much greater outside the United States. The shortage of radiation treatment facilities in many countries makes the traditional scheduling of breast treatments impractical. In these countries, there can be extended delays in starting radiation therapy due to patient backlogs, and in other countries, the scheduling of radiation and the shortage of facilities have hindered the use of breast-conservation therapy.

One strategy to overcome some of these issues is to accelerate the course of radiation treatments. Although this may seem an intuitive solution, there are biological reasons why the 5- to 6-week treatment course for whole-breast radiation was originally developed. In brief, this schedule was thought to optimize the therapeutic ratio (defined as the probability of achieving tumor control versus the probability of causing normal-tissue injury). Decreasing the radiation treatment schedule to less than 5 weeks would require increasing the daily dose per fraction, and this increase, unfortunately, has a greater effect on the probability of normal-tissue injury than tumor control. A second important determinant of normal-tissue injury in addition to fraction size is the volume of normal tissue that is irradiated. Therefore, it was rational to hypothesize that an optimal therapeutic ratio could be maintained with an accelerated radiation schedule if the volume of normal tissue included in the irradiated volume was minimized.

This rationale, along with the clinical desire to shorten the radiation course, led to the investigation of accelerated partial breast irradiation (APBI). In this strategy, radiation is delivered only to the tumor bed region of the breast plus an arbitrarily defined margin. To date, APBI has been delivered with a variety of techniques, including single-fraction intraoperative electron or orthovoltage treatment, low-dose-rate interstitial brachytherapy (temporary implantation of radioactive sources), high-dose-rate interstitial brachytherapy, high-dose-rate brachytherapy delivered with a balloon catheter system (MammoSite; Proxima Therapeutics, Alpharetta, GA), and three-dimensional conformal external beam radiation treatment. Although these strategies differ with respect to many key variables, such as the dose of radiation delivered and the volume of breast tissue treated, they all share the common characteristic of attempting to shorten the treatment schedule from 6 to 7 weeks to a course that lasts 1 week or less.

1.2 History of APBI

Over the past 5 years, APBI has generated a great degree of enthusiasm among both cancer care providers and breast cancer patients. However, the first investigations of APBI as an alternative to conventional whole-breast irradiation began some time ago and were abandoned because of lack of efficacy. The first two trials investigating APBI were conducted in the United Kingdom in the early 1990s. Investigators at Guy's Hospital, London, conducted a relatively small phase I/II trial in which a low-dose-rate brachytherapy implant directed to the tumor bed region was used as the sole radiation component of breast-conservation therapy (Fentiman et al. 1996). After a median follow-up of 6 years, local in-breast relapse had developed in ten patients (37%). This rate is similar to that predicted for treatment with lumpectomy without any radiation. A much larger phase III clinical trial comparing whole-breast external beam irradiation to APBI was conducted at the Christie Hospital (Manchester, UK) during this same period (Magee et al. 1998). The APBI approach used in this trial was a fractionated external beam approach

that utilized a single electron field. It should be recognized that the targeting of the APBI to the region at greatest risk in this trial was relatively crude by today's standards. Since this study, a number of improvements in imagining and treatment planning have been developed. In the Christie Hospital trial, APBI proved to be an inferior treatment to whole-breast irradiation. The 8-year actuarial local recurrence rate was 25% for those treated with partial-breast therapy and 13% for those receiving whole-breast treatment (Magee et al. 1998). These discouraging results led to a reluctance to pursue further the concept of APBI for some time.

In the late 1990s, interest in APBI was renewed. Investigators hoped that the high local recurrence rates noted in the early studies could be avoided with more stringent patient selection criteria, more uniform definitions of target volumes, a greater ability to define the target due to improved imaging and treatment planning, and more uniform dose prescriptions. In addition, in the first APBI trials, many important pathological factors that were subsequently found to be associated with local–regional recurrence were not evaluated systematically. Specifically, these studies included patients with unassessed or positive surgical margins and patients who did not undergo axillary lymph node evaluation. Finally, the presence or absence of invasion of the lymphovascular space and/or an extensive intraductal component were not analyzed.

In the United States, the first studies of APBI investigated treatment delivered with an interstitial implant (usually a double-plane implant) with the targeted region typically being the tumor bed plus a margin of 2.0–2.5 cm. Eligibility was limited to patients with tumors less than 4 cm in size with no more than three positive lymph nodes who were treated with a breast-conserving surgery that achieved negative surgical margins. Unlike previous experiences, these initial studies showed 3- to 5-year breast recurrence rates ranging from 1% to 5% (King et al. 2000; Vicini et al. 2003a). The short-term efficacy of the interstitial implant approach was also confirmed in many European centers. One of the leading European centers investigating APBI has been the National Institute of Oncology in Hungary. Investigators from this institution completed a phase I/II trial with encouraging results and have begun a follow-up phase III trial (Polgar et al. 2004). On the basis of the initial favorable data from approaches utilizing multicatheter implants, the Radiation Therapy Oncology Group (RTOG) conducted a multicenter phase II trial investigating a double-plane brachytherapy approach to APBI. Again, after a relatively short median follow-up period, the short-term in-breast recurrence rate and the normal-tissue toxicity rate were both excellent (Kuske et al. 2004).

The double-plane interstitial breast brachytherapy approach to APBI, however, has not been widely adopted in the United States. The treatment technique requires a specialized skill set, and the procedure and its planning require a significant amount of time. More recent technological advances, such as the use of template-guided approaches, have improved the reproducibility and convenience of interstitial brachytherapy, but even with these improvements brachytherapy remains a less popular option for APBI in the United States.

The initial therapeutic success of interstitial brachytherapy, coupled with its lack of widespread adoption, led to the development of a number of other methods of delivering APBI. In Italy and the United Kingdom, single-fraction intraoperative electron-beam or orthovoltage treatments have been studied in phase II trials, and both of these approaches are now being tested in phase III studies (Vaidya et al. 2004; Veronesi et al. 2003). In the United States, alternatives to double-plane interstitial implants have also

been developed. At William Beaumont University (Vicini et al. 2003b) and New York University (Formenti et al. 2004) a conformal three-dimensional external-beam approach to APBI has been studied in pilot trials that were followed by a phase II RTOG study, which proved the feasibility of this approach in a multicenter setting. Another approach developed in the United States that has proven to be the most popular method of APBI has been the use of the MammoSite delivery device to deliver fractionated high-dose rate brachytherapy. The MammoSite is a balloon catheter that can be inserted into the tumor bed in a relatively straightforward fashion. After initial studies, the Food and Drug Administration approved the MammoSite applicator as a treatment-delivery device. It has been estimated that this device has been used in over 3000 patients.

Arguably, the use of APBI has outpaced the clinical data proving that it is an appropriate alternative to whole-breast treatment. The most mature data to date concerning the safety and efficacy of APBI have been derived from studies investigating the double-plane brachytherapy approach; however, as mentioned, this approach represents a relatively small percentage of the current APBI practice pattern. Brachytherapy treatment using the MammoSite device is different from that using a double-plane interstitial implant in many ways, and although the early results of a registry trial appear promising, there are no 5-year data available concerning the safety and efficacy of treatments using the MammoSite device. Despite this, the majority of MammoSite treatments are currently being given outside of a protocol setting.

Whether APBI should be considered an investigational treatment or be accepted as an alternative to whole-breast irradiation is a controversial issue. Table 1.1 lists some reasons for and against considering APBI to be an accepted standard of care. In 2003, the American Brachytherapy Society issued a report suggesting that APBI could be considered an appropriate treatment option for selected patients provided there was an ad-

Table 1.1 Should APBI be considered investigational or an accepted standard of care?

Reasons to consider APBI as an investigational treatment	Reasons to consider APBI an acceptable standard of care for selected patients
There have been no completed phase III trials comparing more recent APBI approaches to whole-breast treatment. The only APBI phase III study completed to date showed this approach to be inferior	Mature results from a comparative phase III trial will likely not be available for a decade
The long-term efficacy of APBI with modern techniques remains unknown	Whole-breast irradiation is not an option for some breast cancer patients because of its protracted treatment schedule
The appropriate patient selection criteria for APBI treatment are unknown	Initial institutional and phase II multicenter trials investigating APBI have shown excellent local control rates and low rates of serious normal-tissue injury
The late normal-tissue effects of APBI are unknown. The majority of long-term quality-of-life complications associated with hypofractionated radiation treatments develop years after completion of treatment and are not necessarily related to the absence of short-term side effects	

equate quality-assurance program in place (Arthur et al. 2003). However, we and others have contended that whole-breast irradiation should continue to be the standard of care until longer term safety and efficacy data are available from well-designed clinical trials of APBI (Buchholz 2003; McCormick 2003). This is particularly true for patients who are able to undergo whole-breast treatment with only minor inconvenience. For those who are truly unable to receive a 6- to 7-week course of therapy and who do not have the option of conventional treatment, APBI should be considered as an unproven alternative that would likely be better than complete omission of radiation therapy.

1.3 Controversies Regarding the Use of APBI

The major question concerning the use of APBI as an alternative to whole-breast irradiation is whether APBI will prove to be as safe and effective. Breast cancer therapy has achieved considerable success over the past two decades. Since 1990, there has been a consistent 7% annual decrease in the breast cancer death rate in the United States (Wingo et al. 2003). Advances in public education, screening programs, diagnostic imaging, surgery, systemic treatments, and radiation therapy have all contributed towards this improved outcome. Specific examples of such advances in the field of medical oncology are the use of anthracyclines, taxanes, specific dose schedules, and new classes of compounds such as aromatase inhibitors and molecular specific therapies such as trastuzumab. There have also been advances in radiation therapy. Because of advances in radiation delivery techniques, important potentially life-threatening injuries can be overcome and treatment efficacy has been improved.

The benefits derived from radiation therapy as a component of breast-conservation are very significant. A meta-analysis of trials investigating radiation therapy after breast-conservation surgery has shown that radiation not only reduces the recurrence rate but also improves overall survival (Vinh-Hung and Verschraegen 2004). These considerations are particularly important in that other studies have indicated that the majority of patients are willing to accept the toxicity and inconvenience of treatments if they perceive there to be even a 1% decrease in the risk of recurrence (Ravdin et al. 1998).

Whether whole-breast irradiation offers an advantage over APBI in decreasing the risk of ipsilateral breast tumor recurrence will only be determined by a comparative phase III trial. The degree of difference between the two approaches will likely be dependent on patient selection criteria. It should be appreciated that patients with favorable disease characteristics achieve an excellent rate of success with conventional approaches, providing a high benchmark against which APBI needs to be compared. For example, for patients with lymph node-negative disease who are treated with surgery that achieves a negative margin, whole-breast irradiation, tumor bed boost irradiation, and some form of systemic therapy, the estimated annual risk of local recurrence is approximately 0.5% (Buchholz et al. 2001; Fisher et al. 2002b). It is highly unlikely that APBI will improve upon this excellent result, but when the risk of recurrence is so low, it may be appropriate to consider accepting a slightly higher risk for the convenience benefits.

1.3.1 Does APBI Treat an Adequate Volume of Breast Tissue?

An important rationale for considering less than whole-breast treatment concerns the patterns of breast tumor recurrence in patients treated with breast conservation without adjuvant radiation therapy. Data from clinical trials suggest that of the 30% of patients who experience breast tumor recurrence when radiation therapy is not delivered, the vast majority (approximately 80%) will have the recurrence develop at the site of the original disease (Clark et al. 1992; Liljegren et al. 1999; Veronesi et al. 2001). In addition, the absolute percentage of recurrences that develop in a location far away from the tumor bed is low, ranging from 3% to 5% (Clark et al. 1992; Liljegren et al. 1999; Veronesi et al. 2001). From these data, many researchers have hypothesized that treatment directed solely to the site of the primary tumor may be adequate.

It is important to recognize that there is an inherent limitation in using data from studies that have investigated patterns of recurrence in patients treated with surgery alone to support the concept of treating only a small volume of breast tissue around the tumor bed. Most breast cancer recurrences develop from residual disease that was a component of the original primary tumor and therefore is in part adjacent to the surgical cavity. In fact, for patients with residual disease, it is likely that the greatest disease burden will be located next to the tumor bed cavity and that the density will diminish as a function of distance from the cavity. However, this does not mean that the area around the cavity will be the only site of residual disease. In fact, clinical evidence suggests that residual disease may also extend into volumes not included within APBI-targeted regions. A representation of this important concept is shown in Fig. 1.1. If a patient with such extent of disease did not receive any additional treatment, the regions closest to the tumor bed would be identified as the first sites of tumor recurrence. As effective treatment was given to an extended volume around the tumor bed, recurrences within that treatment volume may be avoided, but there would continue to be a risk that some volume of disease would be left untreated. In such a scenario, the first site of recurrence would again be at the margin of the treatment. If the margin were extended, the most common site of first recurrence would then be at the new margin of treatment.

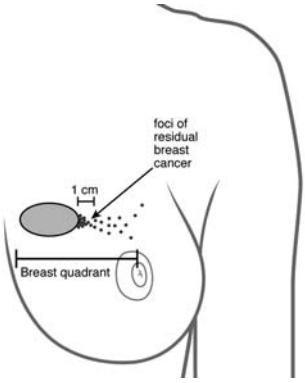

Fig. 1.1 Illustration of a medial tumor bed with residual disease extending from the tumor bed into the upper lateral quadrant. If no radiation was given in this situation, it is likely that the tumor would recur first at the tumor bed site. However, it is clear that giving radiation only to a volume of radius 1 cm around the tumor site would also be an ineffective strategy (reprinted with permission from Buchholz et al. 2005)

The concept described above is supported by studies of the distribution of disease in mastectomy specimens, which suggest that residual disease may extend beyond a margin of 1–2.5 cm around the tumor excision cavity. One of the first pieces of evidence for this came from the work of Holland et al. in 1985, in which mastectomy specimens from 282 women with localized T1 and T2 tumors were carefully examined (Holland et al. 1985). In this study, 28% of the cases of index tumors measuring 2 cm or smaller where found to have a focus of residual in situ or invasive carcinoma more than 2 cm from the primary tumor. Later, Faverly et al. (2001) mapped the disease extent in 135 patients with tumors smaller than 4 cm and again found that a large percentage of patients had disease that extended beyond the margins around the primary tumor that are typically included in APBI treatment. Finally, Vaidya et al. also performed a careful three-dimensional pathological analysis of whole-mount mastectomy specimens and reconstructed the residual tumor volume present after an initial lumpectomy (Vaidya et al. 1996). Residual disease was detected in 63% of the patients, and in 79% of these patients, the disease extended beyond 25% of the breast volume surrounding the lumpectomy cavity. It is important to recognize that if such patients were treated with breast-conserving surgery without radiation, the most common site of recurrence would be the primary tumor site. However, these data indicate that this pattern of failure does not provide a scientific rationale for directing therapies to a tissue margin of 1–2 cm around the tumor bed.

Data from studies investigating the value of magnetic resonance imaging (MRI) in patients with early-stage breast cancer also raise questions as to whether APBI treatment covers the appropriate volume of tissue at risk of residual disease. For example, in a study of 267 patients who were undergoing breast-conservation surgery, MRI scans showed that 18% of patients had foci of disease outside the index tumor bed (Bedrosian et al. 2003). Furthermore, in an international collaborative study of 417 patients with early-stage breast cancer, MRI scans showed incidental lesions away from the index site of disease in 24% of patients (Bluemke et al. 2004). Of these lesions, 71% were histologically confirmed to be cancer, and only 8% of these incidental lesions were detected by mammography. As MRI scans are not routinely performed prior to APBI, these studies suggest that a percentage of patients treated with APBI will have disease that extends beyond the treatment volume.

In addition to the pathological and radiological rationale for the use of whole-breast treatment, the clinical data available to date suggest that APBI approaches may not include all areas at risk of residual disease. Attempts have been made to avoid whole-breast irradiation by treating the tumor bed plus a wider margin with surgery, but these approaches have been unsuccessful. Specifically, the Milan III trial compared results using very wide excision (quadrantectomy) with and without whole-breast radiation (Veronesi et al. 2001). The 10-year rate of breast tumor recurrence in the quadrantectomy-only group was 24% versus 6% in the surgery plus whole-breast irradiation arm. The trial was not powered to analyze effects in particular subgroups, but a particularly high recurrence rate was noted in younger patients and those with tumors had an extensive intraductal component in the surgery-only arm. Another important finding was that patients with positive lymph nodes who were randomized to not receive radiation therapy had a poorer survival (P=0.038), again suggesting that the prevention of local recurrences by radiation is of paramount importance.

These data suggest that the volume of breast irradiated and the patient selection criteria will in part determine the success of APBI. It should be recognized that the volume

of breast treatment is determined both by the extent of surgical resection and by the type of APBI approach used. Ideally, the surgical resection should provide widely negative margins, and the APBI approach should treat as large a volume of tissue around the surgical cavity as possible. Indeed, some of the early data concerning outcomes after APBI treatment suggest that larger volumes are associated with lower rates of recurrence. For example, Vicini et al. at William Beaumont Hospital reported their single-institution experience. They achieved excellent 5-year tumor control rates in highly selected patients treated with a large-volume implant that included the tumor bed with 2-cm margins (Vicini et al. 2003a). However, Perera et al. at the London (Ontario) Regional Cancer Center used implants that treated only the tumor bed as delineated by surgical clips, and reported a 5-year breast tumor recurrence rate of 16%. Two-thirds of these recurrences developed outside of the implanted volume (Perera et al. 2003).

As these data indicate, one of the limitations to current APBI approaches is the uncertainty of what constitutes the most appropriate target volume. APBI is often considered to be a single therapeutic strategy, but it is important to recognize that different APBI approaches target different volumes of peritumoral tissue. In addition, the necessary volume of tissue to be included in APBI treatments is also dependent on the completeness of the surgical procedure. Currently, there is no consensus on the optimal volume of breast tissue that should be treated with APBI and the language used to describe treatment volumes is inconsistent. These factors make comparisons between institutional experiences difficult. There continues to be a need to standardize APBI treatments in order to provide a better understanding of benefits and shortcomings. A major advance in this area has been the development of standards for a national phase III APBI trial that recently began enrolling patients in the United States.

1.3.2 Which Patients May Be The Most Appropriate for APBI?

Patient selection is a critical determinant of whether APBI treatments will likely include the region at risk of residual disease. Randomized trials that have investigated radiation omission have helped define the factors that are associated with a lower risk of residual disease after surgery. These factors include older age (particularly over 70 years), wide negative surgical margins, T1 primary disease, lack of an extensive intraductal component, lack of lobular histology, estrogen receptor-positive disease, treatment with sys-

Table 1.2 Patient selection criteria for APBI

	ASBC[a]	ABS[b]	NSABP/RTOG
Age (years)	>50	≥45	>45
Histology	IDC, DCIS	Unifocal IDC	DCIS or any histology
Size (cm)	≤2	≤3	≤3
Margins	≥2 mm	No tumor on ink	No tumor on ink
Lymph nodes	Negative	Negative	<4 positive LN

[a] American Society of Breast Surgeons (2005)
[b] Arthur et al. (2003)

temic therapy, and pathological N0 disease (Veronesi et al. 2001). These factors are all associated with a lower risk of recurrence when patients are treated with surgery alone, so it is likely that those with residual disease after surgery will have a lower disease burden that is more often localized near the tumor bed. There is no uniform consensus on the patient and disease characteristics that are appropriate for consideration of APBI. Table 1.2 provides details about statements concerning patient selection that have been issued by the American Society of Breast Surgeons and the American Brachytherapy Society (American Society of Breast Surgeons 2005; Arthur et al. 2003). Also included is the eligibility criteria for an ongoing National Surgical Adjuvant Breast and Bowel Project (NSABP)/RTOG phase III trial that is comparing APBI to whole-breast treatment

1.3.3 Does APBI Deliver an Adequate Radiation Dose?

A final issue of importance when considering whether APBI will prove to be as effective as whole-breast treatment concerns the dose of radiation. In general, whole-breast irradiation plus a tumor-bed boost provides a significantly higher biologically effective dose to the peritumoral area. Although a variety of dose schedules have been used in APBI treatments, the most common prescription dose (and the dose selected for the planned American phase III clinical trial) is 34 Gy delivered in ten fractions, with fractions given twice daily over a period of 5 days. Rosenstein et al. recently estimated the biological equivalent dose (BED) of this schedule for tumors and late-responding normal tissues compared to standard whole-breast treatment plus a tumor-bed boost (Rosenstein et al. 2004). The BED for the tumor was 1.7 times higher for the whole-breast plus boost schedule compared to the 34-Gy in ten fraction schedule (assuming an alpha/beta ratio for tumor of 10 Gy) and 1.4 times higher for late effects in normal tissue (alpha/beta ratio of 2 Gy). These data indicate that the dose to the area at greatest risk of disease is less with APBI. This is an important consideration given that trials investigating use versus omission of a tumor-bed boost after whole-breast treatment suggest that dose escalation minimizes the risk of recurrence (Bartelink et al. 2002; Romestaing et al. 1997).

Estimating the success of APBI through calculations of BED significantly oversimplifies a very complex process. Most APBI techniques, particularly MammoSite, have significant dose inhomogeneity within the treated volume. For example, the treatment dose with a MammoSite device is almost twice as high at the surface of the balloon as it is at the prescription dose point located 1 cm from the balloon. Therefore, regions within the target volume may receive significantly higher BEDs if they are close to the applicator surface. In addition, the effectiveness of radiation is also dependent on treatment time and the shortened treatment course associated with APBI may reduce the risk of tumor cell repopulation during treatment. Finally, the biological properties of breast cancers vary; correspondingly, the alpha/beta ratios and proliferation rates are also likely to vary from case to case. Therefore, dose comparisons between the two treatment schedules are difficult.

1.3.4 Can APBI Increase Rates of Normal Tissue Injury?

Data from phase II trials and institutional reports suggest that APBI approaches are associated with low rates of acute injury to normal tissue (Keisch et al. 2003; Vicini et al. 2003a). However, the more important question that has yet to be fully answered is whether late normal-tissue complications may be increased. As highlighted above, dosages of 34 Gy in ten fractions provide a lower BED to late-responding normal tissues compared to 66 Gy in 33 fractions and, therefore, would be predicted to carry less risk of injury (Rosenstein et al. 2004). Furthermore, the decreased volume of irradiated tissue will also be an important factor in decreasing the risk of injury with APBI, and this component is not considered in BED calculations. One possible concern, however, is that, as previously noted, many APBI techniques have significant dose inhomogeneity within the treatment volume. For example, a MammoSite catheter placed against the chest wall may give a significantly higher BED to this important normal tissue than conventional therapy. Therefore, it is important that these promising APBI techniques be investigated in protocols that carefully track and record late radiation injuries. Late injuries to normal tissue resulting from radiation are difficult to study in that they may occur many years after treatment. For example, in a study of breast cancer patients who were treated with a hypofractionated radiation regimen, Bentzen et al. found that it took 15 years of follow-up after treatment to detect 90% of the ultimate incidence of late grade 3 complications (Bentzen et al. 1990).

1.4 Convenience Benefits of APBI

It is clear that APBI offers a convenience advantage over whole-breast irradiation. Five-day APBI treatment approaches are potentially 85% shorter than conventional whole-breast plus tumor-bed boost therapy. However, for patients treated with surgery and chemotherapy, the shortened course of radiation would lead to only a 10–15% decrease in the overall length of the breast cancer treatment. In addition, it should be recognized that there is an alternative to APBI for patients for whom treatment time is a major issue. A Canadian phase III trial found equivalent 5-year control and toxicity rates for a 3-week hypofractionated whole-breast irradiation schedule (42.5 Gy in 16 fractions) compared to a 5-week irradiation schedule for carefully selected patients (Whelan et al. 2002). When compared to this whole-breast treatment approach, most APBI schedules require only six fewer treatment visits, making the convenience benefits of APBI less relevant. Finally, some patients may find the twice-daily treatment required by most APBI schemes to cause a greater disruption to their lives than once-daily treatment.

1.4.1 Will APBI Increase Access to Medical Facilities and Reduce Costs?

One potential advantage of APBI would be to improve access to radiation therapy facilities. However, unlike in other countries, few patients in the United States endure long delays before starting radiation therapy because of limited access to treatment machines. In the Unites States, more common rate-limiting steps in getting patients onto treatment is limited physician time and treatment planning resources. Most APBI approaches re-

quire significantly greater treatment planning and quality assurance and, therefore, require significantly more physician and physicist time than conventional external beam whole-breast treatments. Therefore, the total impact of APBI in improving access to care may not be significant in the United States.

With respect to treatment cost, there is currently no evidence that treatment with either MammoSite or a double-plane interstitial implant costs less than conventional whole-breast irradiation followed by a boost. In fact, in a recent study, Suh et al. calculated direct medical costs and Medicare fee schedules and modeled treatment costs to the patients and society (Suh et al. 2003). These authors found that APBI using either of these brachytherapy techniques was significantly more expensive than conventional whole-breast plus tumor-bed boost therapy.

1.5 Conclusions

APBI has the potential to be an exciting improvement in radiation treatment for patients with early-stage breast cancer. However, new advances in breast cancer treatment should be carefully evaluated in clinical trials that are appropriately designed to assess safety and efficacy end-points. Premature adoption of initially promising therapies can lead to long-term setbacks. A perfect example of this in breast cancer was the premature adoption of high-dose chemotherapy with bone marrow transplant. Widespread adoption of this approach after favorable short-term phase II trials impaired the completion of phase III studies. As most of the phase III trials were eventually negative, it became apparent that thousands of patients received a treatment that was later proven to be less than optimal.

Studying APBI as an alternative to whole-breast treatment is difficult because it requires long-term follow-up. Furthermore, depending on the patient selection criteria used, differences between these two approaches may be subtle, and detecting such a difference in comparative trials would require thousands of patients. To date, such trials have not been completed. The only relatively mature studies available concerning efficacy and safety of APBI have been from institutional studies using double-plane interstitial brachytherapy as the APBI technique. No 5-year follow-up data are available from the external beam or MammoSite APBI approaches.

It is imperative to recognize that short-term success may not translate into a long-term satisfactory result, with respect to both efficacy and toxicity. As previously indicated, the complications of a hypofractionated APBI scheme may not appear for many years. An example of the necessity for long-term follow-up is found in the unsuccessful phase II trial at Guy's Hospital that investigated APBI with an interstitial brachytherapy technique. The original publication of the Guy's Hospital experience reported "encouraging" results in 1991 (Fentiman et al. 1991); however, in 1996, as the data matured, the authors concluded that this approach was inadequate (Magee et al. 1998).

Modern conventional whole-breast irradiation provides excellent outcomes for patients treated with breast conservation, providing a high benchmark against which new treatments must be compared. It is highly unlikely that APBI will improve upon these excellent results, because it is a less intensive approach, both with respect to volume of treatment and the dose delivered to the targeted treatment volume. Whereas some patients may accept a small increase in probability of recurrence for the added convenience