APBI is a promising technique in selected patients with early-stage breast cancer, but further study is needed on outcome and toxicity associated with this approach.

Accelerted Partial Breast Irradiation: Potential Roles Following Breast-Conserving Surgery

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Background: Multiple randomized trials comparing mastectomy to lumpectomy and whole breast irradiation (WBI) have shown equivalent survival outcomes in early-stage breast cancer. WBI requires a treatment course of several weeks, which has resulted in limited access to breast-conserving therapy in certain populations. A shorter accelerated course of partial breast irradiation (APBI) has been investigated recently.

Methods: This article reviews the current medical literature, including randomized trials and prospective institutional studies of APBI and the current recommendations regarding the use of this emerging technique.

Results: Several APBI techniques have been developed, including brachytherapy and external beam methods. The longest follow-up data are available for multicatheter interstitial brachytherapy, a technique that is not commonly used. Other methods, including balloon brachytherapy and external beam three-dimensional conformal techniques, have limited follow-up that shows similar local control rates to whole breast irradiation in highly selected patients. Guidelines for the appropriate use of APBI have been published.

Conclusions: While APBI may increase access to breast conservation therapy for some women with early-stage breast cancer, follow-up data demonstrating the efficacy of this relatively new treatment approach are limited. Therefore, strict evidence-based selection criteria should be applied when evaluating patients who may be appropriate for APBI.

Introduction

After breast-conserving therapy for early-stage breast cancer with either lumpectomy or tylcectomy, the addition of adjuvant postoperative whole breast irradiation (WBI) has been demonstrated to significantly reduce the likelihood of local failure at or around the initial site of surgery. Furthermore, meta-analyses of a large number of randomized trials for breast-conserving surgery (BCS) have shown that this reduction in local failure potentially equates into a survival advantage favoring adjuvant WBI. For these reasons, postoperative WBI after BCS has become and still remains the standard of care for early-stage breast cancer.

Standard adjuvant WBI is delivered typically over the course of 3 to 6 weeks in a once-daily manner 5 days a week. Because of the length of radiation treatment duration and inaccessibility to radiation centers in some parts of the United States, many women have elected to undergo mastectomy rather than BCS or, more alarmingly, have decided to forgo WBI after BCS. These concerns, along with the prospect of improving compliance with recommended radiation, have led to further investigation of accelerated courses of WBI. These accelerated courses of WBI consist of shorter

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treatment durations whereby larger doses of radiation are delivered per daily treatment, called hypofractionation. About a decade ago, several institutions began investigating the use of accelerated partial breast irradiation (APBI) as an alternative to WBI after BCS. The scientific rationale for APBI is based on pathologic data regarding the spread of cancer within the breast and the study of patterns of in-breast recurrence following breast-conserving therapy performed with or without WBI.

The use of APBI has increased significantly in recent years. It is used by many as an alternative to WBI despite the limited long-term outcome data or results from randomized clinical trials. This review evaluates the data investigating the rationale for the use of APBI. In addition, the different modalities used for the delivery of APBI, their nuances, and the available clinical results are presented, and the current randomized trials investigating APBI vs WBI are discussed.

External Beam Whole Breast Irradiation

In recent decades, the use of BCS in combination with WBI has become a standard of care along with mastectomy alone in the treatment of early-stage invasive breast cancer. This acceptance is supported by multiple large randomized trials demonstrating equivalent survival outcomes when compared to mastectomy. Additionally, BCS used in combination with WBI has proven to have lower local recurrence rates compared with BCS alone. The NSABP B06, a seminal study initiated in 1976, evaluated 1,851 women with stage I or II invasive breast cancer < 4 cm randomized to mastectomy alone, lumpectomy alone, or lumpectomy followed by postoperative WBI. After 20 years of follow-up, the cumulative incidence of recurrent tumor in the ipsilateral breast was 14.3% in the women who underwent lumpectomy and breast irradiation compared with 39.2% in those who underwent lumpectomy without irradiation. However, no significant differences were observed among the three treatment groups with respect to disease-free survival, distant disease-free survival, and overall survival. More recently, a meta-analysis of randomized trials evaluating BCS with or without postoperative radiation therapy (RT) showed that the addition of WBI improves survival in most patient populations.

Hypofractionated Whole Breast Irradiation

Currently in the United States, the most commonly used schedule for WBI after BCS is 45 to 50 Gy delivered over 5 weeks with 1.8 to 2.0 Gy daily treatments, called fractions, given 5 days a week. At many centers, an additional boost to the lumpectomy site is given to deliver an additional 10 Gy to 16 Gy in 5 to 8 daily fractions. These schedules are generally just within the tolerance of normal breast tissue. Similar doses were utilized in the 1960s but were given with much higher daily doses or fractions. These hypofractionation regimens resulted in increased toxicity and an anecdotally poorer cosmetic outcome. A renewed interest in investigating whole breast hypofractionated regimens occurred in the 1980s. However, given past experience, it was realized that lower total doses had to be employed in order to maintain acceptable normal tissue toxicity. Subsequently, several case series and cohort studies emerged in the mid-1990s. Ash et al were among the first, reporting on 339 node-negative patients treated to a total dose of 40 Gy in 15 fractions over a 3-week course. With 7 years of follow-up, they demonstrated a local recurrence rate of 13.8% and a 5-year cosmetic outcome rated excellent or good at 66%. Four other investigations employing similar fractionation schemes have demonstrated similar results.

In these studies performed almost exclusively in node-negative patients and with 5 to 7.6 years of follow-up, local recurrence rates ranged from 3.5% to 15%. Two of these studies reported cosmetic outcomes with excellent or good cosmesis at 5 years of 77% and 89%.

Because of initial promising results with local control rates similar to traditional whole breast regimens, several randomized trials were undertaken investigating traditional WBI with a standard regimen of 50 Gy in 25 fractions vs a hypofractionated WBI regimen. One of the first of these studies was performed by the Ontario Clinical Oncology Group. This trial evaluated 1,234 node-negative patients treated with 50 Gy in 5 weeks vs 42.5 Gy in 3 weeks. The risk of local recurrence at 10 years was 6.7% among the 612 women assigned to standard irradiation as compared with 6.2% among the 622 women assigned to the hypofractionated regimen (absolute difference, 0.5 percentage points; 95% confidence interval [CI], −2.5 to 3.5). At 10 years, 71.3% of women in the control group as compared with 69.8% of the women in the hypofractionated-radiation group had a good or excellent cosmetic outcome (absolute difference, 1.5 percentage points; 95% CI, −6.9 to 9.8). Since this initial report, at least three larger randomized trials investigating standard WBI vs one or more hypofractionated WBI regimens have been performed in the United Kingdom in N0 and N1 women. These studies have shown similar local control rates and cosmetic outcomes with 5-year follow-up between standard and hypofractionated schedules. The earliest of these studies has now published 10-year results. An evaluation of three fractionated regimens — 50 Gy in 25 fractions, 42.9 Gy in 13 fractions, and 39 Gy in 13 fractions — showed 10-year local recurrence rates of 12.1%, 9.6%, and 14.8%, respectively (the difference between 39 Gy and 42.9 Gy groups: P = .027). However, the estimated 10-year percentages of patients with no evidence of marked or moderate breast induration were statistically different at 63.7% for 50 Gy, 48.9% for 42.9 Gy, and 72.3% for 39 Gy. Of note, all of these three regimens were delivered over 5 weeks even though the two hypofractionated regimens utilized fewer actual treatments. Despite the support of these large randomized trials showing equivalence in local control between standard WBI and hypofractionated WBI, it is unclear what role hypofractionated WBI will play in the United States.
Accelerated Partial Breast Irradiation

**Rationale**

The rationale for providing adjuvant WBI after lumpectomy in patients treated with breast-conserving therapy (BCT) is that, even if negative margins are achieved, many patients may harbor significant areas of occult, residual microscopic disease in the breast after tumor excision. Thus, RT must be delivered to the whole breast and the lumpectomy bed in an effort to “sterilize” these residual foci of cancer. However, patterns of failure after standard BCT and after excision alone without RT show that the majority of recurrences are in the immediate vicinity of the tumor bed. This suggests that the major value of postlumpectomy RT is to eradicate residual disease in the region of the tumor bed and that areas of occult disease in the remainder of the breast may be less significant in most patients. If this interpretation is correct, then achieving excellent local control may require delivery of only a tumoricidal dose of RT to the region of the lumpectomy bed without irradiating the rest of the breast. The therapeutic window of breast RT is a function of the total dose delivered over the total length of treatment and the volume of breast treated for the toxicity of treatment to be acceptable. By limiting RT to the treatment of a limited volume of tissue around the lumpectomy cavity, it may also be possible to reduce the overall treatment time by increasing the RT fraction size and still maintain the therapeutic window. These concepts form the scientific and practical rationale for the application of APBI in the adjuvant treatment of early-stage breast cancer. If this is accurate, then the first question that arises concerns the volume of normal breast tissue surrounding the lumpectomy cavity that needs to be treated to maintain comparable local control as WBI.

**Appropriate Target Volumes**

Pathologic margin status is an important predictor of local recurrence among patients undergoing BCS treated with WBI. Though definitions of margins are inconsistent, it is generally agreed that a positive margin is defined as the presence of invasive or ductal carcinoma in situ (DCIS) at the inked surface. However, the width of a clear margin and its effect on local failure is less clear. Several studies have investigated margin width and local failure after external beam RT. Three of these studies reported that local failure rates of 0% to 13% in patients with tumor-free margins > 5 mm. Additionally, those studies that evaluated patients with no tumor on re-excision demonstrated local recurrence rates between 2% and 8%. These data demonstrate that there is no clear trend showing that tumor margins > 5 mm further improve local control. However, in patients with margin widths < 5 mm, determining the appropriate margin size is less clear. In patients with margin widths of 0.1 to 1.0 mm, 1.1 to 2.0 mm, and > 2.0 mm, local recurrence rates have varied between 7% to 14%, 6% to 18%, and 6% to 10%, respectively.

In addition to margin width, tumor burden in the vicinity of the margin must also be considered. Two studies have quantified the amount of tumor at or near the margin and its impact on local failure. Park et al evaluated postoperative WBI in 122 patients with DCIS or invasive cancer at the inked margin across all inked slides encompassed by three low-power microscopic fields. The 8-year local failure rate was 14%; however, for those patients with defined “extensive” margins, the local failure rate was 27%. Investigators at William Beaumont Hospital performed a similar study evaluating the amount of disease within one-half low-powered microscopic field of the inked margin on all slides quantifying the linear extent of disease and number of ducts involved by DCIS. They categorized specimens as “least,” “intermediate,” and “greatest.” At 5 years, actuarial local failure increased only marginally, with increasing tumor burden among the three groups with rates of 1%, 3%, and 6%, respectively. However, the effect at 12 years was more pronounced, with rates of 6%, 8%, and 24%.

The above studies are relevant when considering the substitution of WBI with APBI and whether APBI treats the appropriate volume breast tissue at risk for harboring residual microscopic disease. Additionally, different modalities of APBI treat different volumes of residual breast tissue, which further complicates the issue. Trials that have evaluated patients treated with breast-conserving therapy and either treated or not treated with WBI have found that approximately 80% of local recurrence occurs at the site of original disease in patients when WBI was omitted. Although 20% of patients had failures outside of the lumpectomy region, the absolute percentage of these is only approximately 4%, and some may represent new primary breast cancers. These findings suggest that the majority of recurrence occurs in the immediate vicinity of the lumpectomy; irradiating only this region may result in similar local control as WBI in appropriately selected patients. An alternative interpretation of these data, however, has been suggested by Buchholz et al. After lumpectomy, in patients who harbor occult microscopic disease, the largest burden is adjacent to the lumpectomy cavity, and the burden decreases as distance away from the cavity increases. Therefore, in patients who undergo lumpectomy without adjuvant RT and fail locally, the failure will appear where the largest burden of microscopic disease occurs.

Theoretically, if only the tissue adjacent to the lumpectomy cavity is irradiated, then patients may fail just past the area of treated tissue where a smaller amount of microscopic disease persists; partial breast treatment may only alter the geographic pattern of failure within the breast. Initial outcome data using APBI have not demonstrated this alternative hypothesis. However, longer follow-up with specific techniques is required before it can be appropriately evaluated.

**Techniques**

Kuske et al at the Ochsner Clinic were the first group in North America to scientifically explore the use of APBI. Their initial technique involved the intraoperative
placement of interstitial catheters placed through the breast around the lumpectomy cavity in two or more separate planes, which was subsequently treated over 4 to 5 days and then removed. Since the introduction of this initial approach, several alternative methods have been developed. The MammoSite catheter (Hologic Inc, Bedford, Massachusetts) was approved by the US Food and Drug Administration (FDA) in 2002 and provided a single interstitial balloon catheter alternative that involved the same period of time. As an option to these two invasive techniques, an external beam approach was developed known as 3-dimensional conformal radiation therapy (3D CRT) APBI. Each of these modalities is discussed below in terms of technique and clinical results. In the context of the above discussion regarding the appropriate volume of tissue to treat, it is important to be aware that each of these modalities treats a different volume of breast tissue around the lumpectomy cavity. Furthermore, the biological effective radiation dose that is used is arguably different as well. It is only with long-term follow-up from current randomized trials that the clinical consequences of these factors in terms of local control, survival, toxicity, and cosmesis will be established.

**Multiplane Interstitial Brachytherapy**

Multiplane interstitial brachytherapy (MPIB) is the initial technique developed for the application of APBI. Because studies using this technique have considerably longer follow-up than other modalities, their results have correctly or incorrectly been used as an argument for the acceptance of other approaches despite differences between techniques. In the Ochsner Clinic study,\(^3\) from January 1992 through October 1993, 50 patients with 51 breast cancers were assigned to receive either a low-dose rate (LDR) implant (45 Gy given over 3.5 to 6 days) or high-dose rate (HDR) implant (32 Gy in 8 fractions given over 4 days, using twice-daily treatments). LDR and HDR implants differ in that LDR delivers the radiation continuously over the treatment period and requires hospitalization due to radiation safety issues, whereas HDR delivers the radiation over 5 to 10 minutes with each fraction and can be done on an outpatient basis. A third method, used less frequently and known as pulse-dose-rate, utilizes an HDR-type treatment that is delivered in pulses to more closely replicate LDR treatment; this method was not used in this study. All patients had tumors < 4 cm with negative margins. Patients with negative or 1 to 3 positive axillary nodes were eligible, as well as patients with pure DCIS. The brachytherapy target volume included 2 cm of breast tissue surrounding the excision cavity. About half of the implants were placed at the time of excision of breast tissue. At a median follow-up of 75 months, 1 breast recurrence (2%) and 3 regional nodal failures (6%) were noted. The single local recurrence developed near the surgical scar 78 months after treatment. Two nodal recurrences occurred in patients with negative axillary nodes and in 1 patient among the 9 with positive nodes. This experience has been updated in abstract form to include 150 patients who had been treated since 1991.\(^3\) With a mean follow-up time of 46 months, there were 2 breast failures (1%) and 4 regional nodal failures (3%). Cosmetic outcome was good or excellent in 75% of patients. Grade 3 toxicities (requiring surgical correction) of abscess and hematoma (1 patient) and fat necrosis (2 patients) occurred in 3% of the study group. The Ochsner Clinic group retrospectively reported a matched paired analysis comparing 51 patients from their initial study treated with MPIB to 94 patients treated with WBI during that same time period.\(^3\) The local failure rate in the two groups was 2% for APBI and 5% for WBI after 75 months of follow-up. Grade 3 acute and late toxicities were similar in the APBI and WBI groups. Two patients treated with APBI required surgical intervention for symptomatic fat necrosis. However, cosmesis was similar in the two groups.

Vicini et al\(^3\) at William Beaumont Hospital reported the largest series of patients treated with MPBI, which included 199 patients with early breast cancer treated on one of three prospective protocols. Sixty percent of patients received 50 Gy LDR over 4 days, and 40% received 32 to 34 Gy HDR in 8 to 10 twice-daily fractions over 4 to 5 days. All implants included the lumpectomy cavity plus 1 to 2 cm margins. Seventy percent of patients received adjuvant treatment following RT consisting of tamoxifen (57%) or chemotherapy (13%). With a median follow-up of 65 months, the 5-year ipsilateral breast recurrence rate was 1%; the authors believed that 3 of the 5 recurrences represented second primaries in nonirradiated tissue. At 5 years, cosmetic result was good or excellent in 99% and fair in 1%, with asymptomatic fat necrosis and grade 2 fibrosis rates of 4% each. No grade 3 complications occurred. These patients have been recently compared in a matched-pair analysis to 199 patients treated with WBI.\(^3\) With a median follow-up time of 9.6 years, the 10-year ipsilateral breast recurrence rate was not statistically different between APBI (5%) and WBI (4%) (\(P = .48\)). No difference was reported between metastasis-free or cause-specific survival among the two groups, but overall survival favored WBI over APBI (82% vs 72%; \(P = .02\)).

Several other studies have been reported from the United States, including single-institution studies from Virginia Commonwealth Hospital,\(^3\) Massachusetts General Hospital,\(^3\) Brown Hospital/Tufts-New England Medical Center,\(^3\) University of Wisconsin,\(^3\) and Kansas University.\(^3\) In Europe at least four trials were performed at single institutions, including the London Regional Cancer Center,\(^3\) Guy’s Hospital,\(^3\) Orebro University,\(^3\) and Uzsoki Hospital in Budapest.\(^3\) The results of these studies are summarized in Table 1.\(^3\) The 5-year local failure rate for these studies ranged from 0% to 6%, with the exception of the London Regional Cancer Center, Guy’s Hospital, and the Budapest series; these institutions reported a local failure rate of 16.2%, 18%, and 24%, respectively.\(^3\)
high local failure rate in the London Regional Hospital series of 39 patients treated to a dose of 37.2 Gy in a twice-daily manner over 1 week has been attributed to distinct differences when compared to other series. In this study, the volume of breast treated consisted of the tissue encompassed by the surgical clips only. The median treatment volume was only 30 cm³ compared with 215 cm³ in the William Beaumont Hospital studies. Additionally, 30% of the 39 patients treated had tumor-free margins < 2 mm. These differences highlight the need to establish appropriate treatment volumes, which have not yet been standardized. Furthermore, the higher failure rate reported in the Guy's Hospital series of 49 patients may be related to their higher rate of involved margins used in 21 of 49 patients. It is difficult to ascertain the reason for the higher local recurrence rate in the Budapest series, although axillary lymph node dissections were not routinely performed and data regarding margin status and extensive intraductal component were not available for analysis.

In terms of outcome, the report from the University of Wisconsin is of particular interest as they evaluated 2 cohorts of patients, high-risk and low-risk, based on the current ongoing NSABP B39/RTOG 0413 trial. Of the 273 patients analyzed, 247 were treated using HDR MPIB, and all others were treated using a balloon catheter system. High-risk patients who satisfied one or more of the “high-risk” criteria (age < 50 years, estrogen receptor-negative, and/or positive lymph nodes; n = 90), with low-risk patients comprising the remainder of the cohort (n = 183). With a median follow-up of 48.5 months, no significant difference was found in outcomes at 5 years between the low- and high-risk groups. The local control rates were 97.8% vs 93.6% with a crude local recurrence rate of 2.2% (n = 4) vs 4.4% (n = 4) and overall survival rate of 92.1% vs 89.5% between low- and high-risk patients. These data support further investigation of APBI in younger, ER-negative, and positive lymph node patients who have been primarily excluded in previous studies.

Regarding side effects, the Tufts group noted that patients with grade 3 or 4 toxicity had larger treatment volumes (234 cm³) compared with patients who had grade 2 or less (148 cm³). The Massachusetts General Hospital study also noted a relationship between treatment dose and toxicity. This study, which employed LDR MPIB, escalated total dose from 50 Gy to 60 Gy and found an increased mammographic fat necrosis rate with higher dose resulting in an increased posttreatment biopsy rate. These findings illustrate the therapeutic window for tumor control vs normal tissue toxicity.

The first multi-institutional trial using MPIB was undertaken by the Radiation Therapy Oncology Group (RTOG). The RTOG 9517 design was to test toxicity, cosmesis, local control, and disease-free survival associated with this technique. From 1997 to 2000, 100 patients were enrolled in this phase II study. The eligibility criteria consisted of stage I/II breast carcinoma confirmed to be < 3 cm, unifocal, invasive nonlobular histology with 0 to 3 positive axillary nodes without extracapsular extension. APBI treatment was delivered with either LDR (45 Gy in 3.5 to 5 days) or HDR brachytherapy (34 Gy in 10 twice-daily fractions over 5 days). The study was designed to assess the HDR and LDR groups separately and without comparison. The results of this trial were updated in 2008. Of the 99

<table>
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<th>Trials in the United States</th>
<th>No. of Patients</th>
<th>Dose Rate</th>
<th>Dose (Gy)</th>
<th>Median Follow-up (mos)</th>
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LDR = low-dose rate, HDR = high-dose rate, PDR = pulsed dose rate.
patients who completed treatment, 87 had T1 lesions and 12 had T2. Additionally, 79 were pathologically N0 and 20 were N1. Median follow-up in the HDR and LDR groups was 6.14 and 6.22 years, respectively. The HDR 5-year estimates of in-breast, regional, and contralateral failure rates were 3%, 5%, and 2%, respectively. The LDR group experienced similar results, with 5-year estimates of in-breast, regional, and contralateral failure rates of 6%, 0%, and 6%, respectively. Grade 3 or 4 late toxicity was found to be higher in those patients treated with LDR when compared with HDR (9% vs 3%). These results were comparable to previously reported series and demonstrated that the technique could be applied across multiple institutions.

The German-Austrian multicenter trial was a phase II multi-institutional European study conducted between 2000 and 2005. This phase II trial included 274 patients with ≤ 3 cm tumors that were either pN0 or pN1mic and either ER or PR positive. Surgical margins were ≥ 2 mm in 93% of cases. With a median follow-up of 32 months, there were only two breast recurrences. The local control rate was 99.3% and the overall survival rate was 98.5%. Data for cosmetic results were available on all patients, and good or excellent cosmetic outcomes were 94% when rated by physicians and 92% when evaluated by patients.

Although large-scale randomized trials are currently active by both the NSABP and the Groupe Européan de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) to evaluate WBI vs APBI, only one completed randomized trial using MPIB has been published. The National Institute of Oncology in Budapest initiated a trial in 1996 whereby 45 women were treated with HDR MPIB and evaluated. Eligibility criteria included patients with unifocal tumor 20 mm or smaller (pT1), microscopically clear surgical margins, pathologically negative axillary nodes or only axillary micrometastases (< 2 mm), histological grade 1/2, and excluding lobular carcinoma, DCIS, and extensive intraductal component. A total dose of 30.3 Gy (n = 8) or 36.4 Gy (n = 37) in 7 fractions was delivered over 4 days. Seven-year follow-up has been published on this series in which they compared these study patients to 80 consecutive patients treated with WBI who would have met study eligibility. The 7-year actuarial rate of ipsilateral breast recurrence was 9% and 12% in APBI and WBI, respectively (nonsignificant). There was no significant difference in disease-free survival. These initial results led to the initiation of a phase III trial at the same institution. Between 1998 and 2004, a total of 258 selected patients were randomized after BCS to receive either WBI 50 Gy in 25 fractions (n = 130) or APBI (n = 128). The latter consisted of either 7 × 5.2 Gy HDR MPIB (n = 88) or electron beam irradiation 50 Gy in 25 fractions (n = 40). With a median follow-up of 66 months, the 5-year actuarial local recurrence rate was 4.7% and 3.4% in the APBI and WBI arms, respectively (P = .50). There were no significant differences in the 5-year probability rates of overall survival (94.6% vs 91.8%), cancer-specific survival (98.3% vs 96.0%), and disease-free survival (88.3% vs 90.3%). The rate of excellent to good cosmetic result was higher with MPIB treatment; however, 22% of patients receiving WBI were treated with an antiquated technique using cobalt teletherapy.

**Balloon Catheter Brachytherapy**

The initial balloon catheter system designed for the use in an APBI program was the MammoSite balloon catheter, which was approved by the FDA in May 2002. Several other balloon catheter systems have emerged recently, including Savi (Cianna Medical Inc, Aliso Viejo, California), Contura (SenoRx Inc, Irvine, California), and Axxent (Xoft Inc, Sunnyvale, California). However, given the absence of any clinical outcome data with these other systems, discussion in this section is limited to the MammoSite applicator.

The MammoSite catheter was developed in response to several practitioner-related issues associated with MPIB. Despite promising early clinical results, performing MPIB and planning its associated treatment are time-consuming and complex. Additionally, significant practitioner experience is required to achieve desired results. Training opportunities in performing the procedure are limited, and the procedure has been performed in only a few institutions. Alternatively, the MammoSite catheter is a relatively simple approach for delivering radiation to the lumpectomy cavity and requires less skill to perform. The device consists of a double-lumen catheter with a balloon at the tip of one end. The catheter is introduced into the lumpectomy cavity at the time of surgery or up to 10 weeks later (if the seroma persists), though placement at the time of surgery is discouraged because of higher infection and persistent seroma rates. The catheter’s balloon is inflated (30 to 70 cm³ inflated volume) with a mixture of contrast and saline solution to conform to the lumpectomy cavity. Treatment is delivered via an HDR source that is introduced via the inner lumen of the catheter to the center of the balloon to deliver the prescribed dose of radiation to a depth of 1 to 1.5 cm from the balloon surface. Typically, a total dose of 34 Gy is delivered over 5 to 7 days in a twice-daily manner. Treatments are almost exclusively performed on an outpatient basis, and the balloon is deflated with catheter removal on the last day of treatment.

As previously discussed, the widespread use of the MammoSite catheter as a delivery device for APBI has been based on the prior results from MPIB. However, there are differences between the two delivery systems. In terms of treatment volumes, the MammoSite device generally treats a 1-cm margin around the lumpectomy to the prescribed dose, whereas the MPIB technique typically treats a 2-cm margin. However, it has been argued that the balloon compresses surrounding tissue, functionally treating 1.5 cm. The MammoSite device inherently delivers the radiation dose in a more inhomogeneous manner compared to...
MPIB. With balloon brachytherapy, the inner surface of the lumpectomy cavity receives a much higher dose of radiation than that of the breast tissue 1 cm from the cavity surface. This is a result of radiation dose falling off in an exponential manner away from the center of the balloon where the radioactive source is positioned. A homogeneity index has been previously described as a means to measure this difference in dose distribution.58 As expected, the dose homogeneity index has been found to be lower with MammoSite than with MPIB (0.77 vs 0.93).57 Due to this inhomogeneity of radiation dose, the MammoSite treated a significantly larger volume of breast tissue to doses between 110% to 170% of the prescribed dose than did MPIB.57

Given the lack of long-term follow-up with MammoSite, it is unclear if treating a smaller volume or having significant dose inhomogeneity will be clinically relevant. However, data are emerging. Keisch et al54 published a multicenter prospective trial that was the first clinical study to test the safety and performance of the MammoSite application. This trial was the basis for FDA approval of MammoSite as a medical device. At nine institutions, 54 patients were implanted, 43 of whom received treatment from 2000 to 2001.54,59 Eleven patients were explanted and not treated due to poor balloon conformity, inadequate balloon-to-skin distance, or inadequate margins. Criteria for inclusion included tumors ≤ 2 cm, node-negative, patient age ≥ 45 years, and final margins negative. A dose of 34 Gy was delivered in 10 fractions using a twice-daily schedule. With a median follow-up of 5.5 years, the investigators reported no local, regional, or contralateral cancers failures.59 Seven of the 43 treated patients have been discontinued from follow-up due to death from metastatic disease (n = 3), lost to follow-up (n = 2), and placement in hospice for other medical conditions (n = 2). Following the FDA study, a multi-institutional phase II trial was conducted at 12 institutions and included 133 patients.60 Of these, 100 patients (17 explanted) received treatment of 34 Gy in 10 fractions twice daily. They had similar eligibility criteria as the initial study, but tumors up to 5 cm were allowed. With a median of only 9.5 months of follow-up, this study has reported 2 ipsilateral breast failures occurring at 8 and 11 months after treatment (Table 2).

Currently the largest ongoing trial specifically studying MammoSite APBI outcomes is the American Society of Breast Surgeons (ASBS) MammoSite brachytherapy registry trial.61 A 4-year update on the efficacy, cosmetic results, and complications of MammoSite has been recently published.62 A total of 1,440 patients with early-stage breast cancer undergoing BCS were treated with APBI (34 Gy in 3.4 Gy fractions) delivered with the MammoSite device. Registered cases represented a highly favorable subset of patients with early-stage disease. The median age was 65 years, median tumor size was 1.0 cm, and 92% of invasive tumors were lymph node negative with negative margins. Patients with DCIS comprised 13% of the registered cases, with a median tumor size of 8 mm. With a median follow-up of 36.1 months, the 3-year actuarial rate of ipsilateral breast tumor recurrence in the first 400 patients registered was 1.8%, with a 2-year actuarial rate of 1.0% in the whole group. The 3-year actuarial rate of axillary recurrence in the first 400 patients was 0.27%, with a 2-year rate of 0.46% in the whole group.

Cuttino et al63 have reported a second large multi-institutional analysis including nine participating institutions. All of the 483 evaluated patients had tumors < 3 cm with negative margins and no multicentricity. With a median follow-up of 24 months, the authors reported an in-breast failure rate of 1.2%, with 4 of these failures being remote from the lumpectomy cavity. Cosmetic outcome was rated as good to excellent in 91% of patients. While these early clinical outcomes are favorable, longer follow-up is required to ensure that in-breast recurrences and axillary nodal failures are comparable to either WBI or MPIB.

Complications after MammoSite therapy have been reported. Published rates at 3 years for the ASBS registry trial are as follows: infection, 9.5%, seroma, 26.8% (symptomatic seroma, 12.7%), and fat necrosis, 2.0%.62 The percentages of breasts with good or excellent cosmetic results were 95% at 12 months, 94% at 24 months, 94% at 36 months, and 91% at 48 months. In a series that included 92 patients treated with MammoSite, Haley et al64 reported that the seroma rate was as high as 79% in the 77 patients who had intraoperative placement of the catheter, but the authors did not note how many of these patients were symptomatic.64 In a phase II trial published by Belkačemi et al65 from France, investigators found a persistent seroma rate of 52% among the 25 women treated with MammoSite. A stepwise linear regression analysis to identify factors associated with any seroma and the subset of symptomatic has been reported by Watkins et al.66 The analysis of 109 patients treated with MammoSite found a persistent seroma rate of 41%, with one-third of seromas (13% of all patients) having symptomatic seromas. The only factor identified as statistically significant was placement of the catheter at the time of lumpectomy (59% vs 33%, P = .0066). Infection was highly statistically significant for the development of a symptomatic seroma (64% vs 7%), and prophylactic antibiotics reduced the infection rate from 37.5% to 6%. These seroma rates with MammoSite may reflect the earlier technique of implanting at the time of lumpectomy, thus with an associated high-

Table 2. — MammoSite APBI Brachytherapy Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Dose (Gy)</th>
<th>Median Follow-up (mos)</th>
<th>Ipsilateral Breast Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benitez et al59</td>
<td>36</td>
<td>34</td>
<td>66</td>
<td>0%</td>
</tr>
<tr>
<td>Benitez et al59</td>
<td>100</td>
<td>34</td>
<td>9.5</td>
<td>2%</td>
</tr>
<tr>
<td>Nelson et al62</td>
<td>400</td>
<td>34</td>
<td>36.1</td>
<td>2.15%</td>
</tr>
<tr>
<td>Cuttino et al63</td>
<td>483</td>
<td>34</td>
<td>24</td>
<td>1.2%</td>
</tr>
</tbody>
</table>
er rate of infections, which is now discouraged. This is supported by Cuttino et al, who noted that infection rates were 9% overall with an open technique but only 4.8% if the catheter was placed after lumpectomy.

Three-Dimensional Conformal APBI

While the original techniques for performing APBI primarily involved either interstitial or intracavitary balloon brachytherapy as described in the preceding sections, there was interest in developing a technique to administer APBI using linear accelerator-based treatment with an external beam irradiation technique (3D CRT APBI). Such a technique offers several advantages: it precludes the need for additional invasive procedures and the requirement for instrumentation and implantation of the breast for several days, it eliminates the risk of implant-related infection, bleeding, and discomfort, and it is potentially more versatile than brachytherapy techniques that have technical and anatomical limitations. External beam techniques also provide a more uniform, or homogeneous, dose to the target volume, which in theory may result in less long-term fibrosis and fat necrosis, and it also may reduce cosmetic problems due to reduction of “hot spots” (areas of dose inhomogeneity that are inherent to brachytherapy treatment). As previously discussed, the inherent inhomogeneity of brachytherapy leads to higher doses in closer proximity to the radiocative sources, which may provide a theoretical improvement in the biological dose to any tumor cells in that specific tissue, but this advantage is hypothetical. Disadvantages compared to brachytherapy include the necessity to account for motion of the breast with respiration and daily setup uncertainties, resulting in a somewhat larger target volume in 3D CRT APBI.

The most common dose fractionation for APBI brachytherapy is 34 Gy in 10 fractions of 3.4 Gy each, given twice daily with a minimum 6-hour interfraction interval. This same dose has been used in some 3D CRT APBI studies, but many have instead used the slightly higher dose of 3.85 Gy per fraction to a total dose of 38.5 Gy. Radiobiological models were used to estimate the accelerated dose that is a biologically equivalent dose (BED) to 45 Gy in 1.8 Gy per fraction as is commonly given to the whole breast, noting however that the often utilized boost dose after WBI delivering a total tumor bed dose of 60 Gy or more was not used as the reference dose for these BED calculations. The BED dose distinction may be important during long-term follow-up and relevant to local recurrence rates, as randomized data from the European Organisation for Research and Treatment of Cancer (EORTC) have shown a significant reduction in local recurrence with the addition of the tumor bed boost dose to a total of 66 Gy compared to WBI alone to a total of 50 Gy, especially in women under 50 years of age. A controversial topic in 3D CRT APBI, as in other partial breast techniques, is target volume definition. In WBI, since the entire breast parenchyma is included in the treatment field, a “marginal miss” (ie, tumor cells outside of the irradiated area) is not a concern. However, when radiation is applied only to the breast tissue surrounding the postoperative tumor bed, the method for defining the target volume for treatment is critical. The most appropriate volume for treatment of partial breast is currently not known and has not been determined empirically, but it has typically been defined as the visible postoperative tumor bed (as delineated by seroma, postoperative changes on computed tomography of the breast, and ideally by surgical clips marking the periphery of the lumpectomy cavity) plus a 1- to 1.5-cm margin of surrounding normal tissue, excluding certain normal structures like the skin, chest wall, or lung. This volume is termed the clinical target volume. This margin is theoretically based on the observation that residual tumor cells most commonly reside within 1 to 2 cm of the primary lesion in the majority of patients, as well as the observation that the majority of local recurrences are in this vicinity of the breast as well. An additional margin, typically 1 cm, is added for breast motion or breathing motion and daily setup variation, called the planning target volume. As a result, the volumes treated with 3D CRT APBI often include a larger volume of normal breast as compared to either interstitial or balloon brachytherapy techniques for APBI.

Four randomized trials have been reported that compared postlumpectomy WBI to some form of APBI. Two of these studies were conducted in the 1980s, when CT or other imaging techniques for tumor bed localization were not in use. The Christie Hospital trial was conducted from 1982 to 1987 and included 708 women with tumors ≤ 4 cm and a clinically negative axilla (without axillary dissection). They were randomized to limited-field radiation to only the tumor bed (LF group) or to the whole breast and lymph node regions (WB group). Women over age 70 years were excluded from this study, and no systemic therapy was given. The LF group was treated with electrons to a total dose of 40 to 42.5 Gy in 8 fractions with an average field size of 8 cm × 6 cm, while the WB group received a dose of 40 Gy in 15 fractions with tangential photon fields and a matched supraclavicular field. At a median follow-up of 5.4 years, the 7-year local recurrence rate was 20% in the LF group and 11% in the WB group (P = .0008). There was a particularly high rate of local recurrence in the LF group in patients with invasive lobular cancer (34%) and in those with an extensive intraductal component (21%). Among the local recurrences in the LF arm, 64% were in the same quadrant as the original tumor. Axillary recurrence was also more common in the LF arm (23%) compared with the WB arm (10%). Regarding toxicity, “marked” fibrosis was seen in 5% of patients in the WB group and in 14% of patients in the LF group. A number of issues exist in this trial due to the era in which it was conducted, including lack of pathologic tumor size for 42% of the patients and lack of a complete excision (thus possible positive margins) in up to 20%.

A second randomized trial of WB vs tumor bed radiation therapy (TBRT), or partial breast irradiation, was...
conducted by the Yorkshire Breast Cancer Group from 1986 to 1990. They patients with pathologic stage T1-2 N0-1 cancers after excision of the tumor with negative margins and axillary dissection were eligible. All of the 174 women who were entered on the study had also received adjuvant chemotherapy and tamoxifen for 5 years. WBI consisted of breast tangent fields (without any supravacuicular fields) treated to 40 Gy in 15 fractions and a tumor bed boost of 15 Gy in 5 fractions. TBRT was delivered at 55 Gy in 20 fractions using either photon or electron beam irradiation, targeting a clinically defined area including the scar position, patient recollection, and preoperative information as available regarding the tumor location. The trial was closed early due to poor accrual rates. At a median follow-up of 8 years, the locoregional recurrence rates in the WB arm were 9% compared with 24% in the TBRT arm ($P = .05$). Of the in-breast recurrences in the TBRT group, 70% were within or near the irradiated volume, suggesting issues with target definition. Overall survival was not significantly different between the two arms.

Both of these 1980s era trials were conducted at a time when the current standards of pathologic assessment, surgical clearance of the margin in the breast, assessment of the axilla, CT-based radiotherapy planning, standards for tumor bed target definition, precise daily radiation setup verification, and even mammographic follow-up for surveillance were not routinely practiced. Both trials showed a statistically significant higher rate of local recurrence in the partial breast group. This was true even in the Yorkshire trial, despite the routine use of systemic chemotherapy and hormonal therapy in all trial participants. Due to the inherent inaccuracy of tumor bed targeting without 3D imaging, these studies are not truly comparable to current techniques used for APBI. However, they highlight the importance of appropriate patient selection, thorough patient workup and pathologic tumor assessment, and the application of precision radiation techniques.

The National Institute of Oncology in Hungary conducted a randomized trial of 258 patients with stage I (or N1mic) breast cancer from 1998 to 2004. Patients in the partial breast treatment arm were primarily treated with multicatheter interstitial brachytherapy, which was discussed in the previous section on MPIB. However, 40 patients (31%) in the APBI arm were technically ineligible for the brachytherapy and were therefore treated with partial breast electron beam irradiation, although in conventional fractionation of 50 Gy in 25 fractions. This trial also did not uniformly utilize CT-based 3D target delineation but did require surgical clips to define the tumor bed, then applied a 2-cm margin around this tumor bed target. Only available electron cutouts (conical or square), rather than custom-shaped cutouts, were used to define the electron field. Such techniques are not comparable to the current standard of 3D CT-based target definition and custom-shaped fields. At a median follow-up of 66 months, this trial has found a similar local recurrence rate of 3.4% in the whole breast treatment arm and 4.7% in the partial breast treatment arm (relative risk, 1.24 for APBI). Local recurrence outcomes were not analyzed separately by APBI technique (interstitial vs electron beam), although cosmetic outcome for each technique was reported. Excellent or good cosmesis was recorded in 81% treated with brachytherapy and in 70% treated with electron beam irradiation ($P = .95$).

Based on the fact that many breast cancers recur locally in proximity to the original tumor location and also on the observation that radiation targeted only to the periphery of the surgical tumor bed may allow larger doses per fraction to be administered and thus lead to a shorter overall treatment time, investigators at William Beaumont Hospital first published a technique for the delivery of 3D CRT APBI. The goals of the study were to develop and test this new technique and to define the target volumes for partial breast treatment, normal tissue constraints, and standardized beam arrangements. The clinical target volume was defined as the postoperative lumpectomy cavity visualized on the planning CT scan plus a 1.5-mm margin, limited to within 5 mm under the skin surface and the lung-chest wall interface. Whole breast volume was determined clinically by palpation and marked with wires at the time of planning CT, using the skin and chest wall as the anterior and posterior borders. The planning target volume included an additional 10-mm margin around the clinical target volume to account for any breathing motion and daily setup variation. Standardized field arrangements were developed using a limited range of beam angles, with a 4-field plan for right breast and a 5-field plan for left breast. In their report on the first 9 patients treated using this new technique in 2003, the investigators noted that the 10-mm planning target volume was adequate to accommodate organ motion and setup variation during treatment delivery. Treatment was well tolerated as well, with no acute skin reactions and only mild pigmentation changes at 4 to 8 weeks following treatment. This technique has been widely adopted by other institutions administering 3D CRT APBI. The William Beaumont group have recently published 4-year cosmesis and toxicity outcomes from their experience of 94 patients with stage 0 to II breast cancer with 3D CRT APBI. This cohort of patients had a median age of 62 years, and the median follow-up was 4.2 years. The in-breast tumor recurrence rate was 1.1%, the regional recurrence rate was 0%, and the distant failure rate was 3.9%. Cosmesis was scored as good or excellent in 89%, and grade 3 toxicity (breast pain or fibrosis) was seen in 4%. These results are similar to those seen at a similar time in follow-up after conventional WBI, although the selection criteria for APBI are generally stricter.

Other techniques have also been reported. In a comparison of 3D CRT to intensity-modulated radiotherapy (IMRT) techniques for APBI in 56 patients, Rusthoven et al. showed that significantly less normal breast tissue was treated at various percentages of the prescribed dose, while the target coverage was maintained with the
IMRT technique. Moon et al compared four different external beam techniques in 30 patients, including 3D CRT, IMRT, helical tomotherapy, and proton beam. They defined the planning target volume margins based on the width of the surgical margin, giving more treatment margin around regions where the surgical margin was closer to tumor. All techniques provided adequate planning target volume coverage. Proton beam and IMRT gave the lowest lung and heart volumes, although 3D CRT was acceptable for both, and tomotherapy had substantially higher normal tissue dose volumes. Investigators at New York University have reported on 47 patients treated on a prospective study of prone position APBI, using a dose of 6 Gy once daily to a total dose of 30 Gy in 5 fractions. Eligibility was limited to postmenopausal patients with T1 N0 breast cancer who refused standard WBI. At a median of 18 months of follow-up, the investigators noted that all target volumes were adequately covered by the treatment plans and that acute toxicity was limited to grade 1 to 2 erythema.

The RTOG conducted a phase I/II study (RTOG 0319) to assess the feasibility and reproducibility of the planning and delivery of 3D CRT APBI. A total of 42 cases from 17 institutions were analyzed. The primary endpoint of reproducibility was assessed as technical feasibility as defined by strict target volume and normal tissue dose volume adherence to specified constraints. The technique was deemed feasible in this multi-institutional trial, as major violations were found in fewer than expected cases (4 cases). However, 32 cases had minor violations in the treatment plan, and only 6 cases had no violations. This study formed the basis for the 3D CRT APBI arm of the ongoing NSABP-B39/RTOG 0413 trial, which opened in 2005 and randomizes patients with early-stage disease treated with breast conservation therapy to either WBI or one of the APBI techniques. This study is continuing to accrue patients, and results will not be available for several years.

While studies of clinical outcomes are generally lacking due to the short follow-up time for most institutional series assessing the 3D CRT APBI technique, reports on toxicity with limited follow-up have recently been published. Jaggi et al reported on 34 patients enrolled in an institutional study of IMRT APBI that included deep-inspiration breath hold and delivered the current accepted dose of 38.5 in 10 fractions of 3.85 Gy twice daily. At a median follow-up of 2.5 years, new unacceptable cosmesis was noted in 7 of 34 patients (21%) despite the fact that the treatment plans adhered to the required normal tissue dose constraints being utilized in the RTOG 0413 trial. The mean whole breast volume receiving 50% of the prescribed dose was lower in patients with consistently acceptable cosmesis (35%) than in those with unacceptable cosmesis (46%), suggesting that stricter whole breast dose limits may be appropriate. Hepel et al reported on 60 patients treated with 3D CRT APBI using the same dose constraints as required in the RTOG 0413 trial. They also assessed late toxicity at a median follow-up of 15 months. These investigators similarly found that the volume of whole breast receiving portions of the prescribed dose correlated with the development of late fibrosis. They noted grade 3 or 4 fibrosis in 8% of patients and grade 2 fibrosis in 17%, with perhaps a somewhat higher than expected rate of fair cosmesis compared to that seen with conventional WBI. Size of the excision specimen also correlated with fair or poor cosmetic results. The William Beaumont group reported 4-year outcomes in their cohort of 94 patients treated with 3D CRT APBI. They found good to excellent cosmesis in 89% of patients. They also reported 3 cases (3%) of grade 3 fibrosis and 5 cases (5%) of grade 2 fibrosis. Both Jaggi et al and Hepel et al reported strict adherence to the dose constraints required by the RTOG 0413 trial, while the William Beaumont group used a range of clinical and planning target volume margins. This may partly account for the difference in degree of toxicity observed in the different studies.

Several investigators have suggested that while a certain degree of hypofractionation may allow for acceptable long-term toxicity in the normal breast tissue, specific parameters including the volume of breast tissue that can receive certain proportions of the total dose still need to be defined in order to obtain acceptable long-term cosmesis and soft tissue toxicities. The data suggest that more precise targeting of the target volume is desirable and that variations in daily setup error must be minimized to reduce the volume expansions on the target volume used to account for the daily setup variation. Leonard et al published their experience with image-guided radiation therapy (IGRT) for APBI using an IMRT treatment technique involving gold fiducial marker placement. In 19 patients studied, the authors found an average vector displacement of the daily setup of 6 mm and a mean vector shift of 6 mm (± 6 mm), with no apparent fiducial migration during the 5 treatment days. A vector shift of ≥ 5 mm was required in 51% of treatments. Despite using daily IGRT, this group continued to incorporate a 1-cm planning target volume margin into the treatment plan. A pilot study of the feasibility of IGRT for APBI was reported at the 2009 meeting of the American Society for Radiation Oncology (ASTRO). This study found that breathing motion was minimal, at a mean of 1.5 mm intrafraction, and that fiducial markers implanted in the breast tissue at the time of lumpectomy were stable, with minimal migration from planning through the course of treatment. Based on this pilot study, a reduction in planning target volume margin appears feasible with IGRT for positioning, allowing the volume of normal tissue treated at high doses per fraction to be significantly reduced.

Current Recommendations and Future Directions
Although long-term data regarding the efficacy and toxicity profiles of APBI are generally lacking, particularly for the most commonly used techniques of bal-
loon brachytherapy and 3D CRT, the shortened overall treatment time has been appealing to both physicians and patients. As a result, APBI has become widely available. Several consensus statements to guide patients and physicians in the selection criteria and appropriate use of APBI have been developed from governmental and academic societies. The National Cancer Institute (NCI) published the recommendations of a 2002 workshop on APBI. The discussants agreed that APBI should not be considered standard of care and that further research was needed to provide evidence of efficacy or equivalence to WBI. The panel concluded that, ideally, patients treated with APBI would participate in clinical trials. When not feasible, patients would be fully informed of the status of ongoing research and provided with special informed consents that explain in detail the lack of long-term data for this treatment approach. A consensus statement from three German oncology societies (the German Society for Radiation Oncology, the German Society of Senology, and the Working Group for Gynecologic Oncology of the German Cancer Society) was published in 2007, with a similar conclusion that the current lack of data regarding long-term effectiveness and side effects of APBI does not support the routine use of this treatment technique as an alternative to WBI but is still an “experimental treatment.”

ASTRO convened a task force of breast cancer experts in 2008 who reviewed all of the available prospective data on the use of APBI and published a consensus statement of guidelines on the use of APBI for patients and physicians in 2009. This statement proposed three patient groups as follows: a “suitable” group for treatment with APBI outside of a clinical trial, a “cautionary” group, for whom limited data were available to justify the use of APBI, and an “unsuitable” group, for whom APBI should not be offered as a treatment option (Table 3).

Ongoing randomized trials are testing the premise of APBI compared to conventional WBI, including the NSABP B39/RTOG 0413 trial. Opened in 2005, the NSABP B39 trial continues to accrue participants at this time. This study randomizes women between conventional WBI to 50 to 50.4 Gy, with an optional tumor bed boost of 10 to 16 Gy, vs APBI using any of three techniques as deemed appropriate by the treating physician. Interstitial brachytherapy and balloon brachytherapy APBI patients receive 34 Gy in 10 fractions of 3.4 Gy each twice daily, and 3D CRT APBI patients receive 38.5 Gy in 10 fractions of 3.85 Gy each twice daily. The study has broad eligibility criteria, including women with DCIS, invasive lobular or invasive ductal cancers less than 3 cm, up to 3 positive axillary lymph nodes, and any age over 18 years. Negative margins, estrogen receptor status, and axillary assessment are required, and systemic therapy with either chemotherapy or hormonal therapy is to be prescribed as indicated. Adherence to strict technical guidelines in both treatment arms is required, and there is a quality assurance and credentialing program for the APBI arm for participating centers. The main endpoints of the study are local control, survival outcomes, and toxicity. An analysis comparing the three APBI techniques will also be likely, although the study is not randomizing participants within the APBI arm. Results from this study are not expected to be available for several years.

APBI is an attractive option to patients and physicians alike due to the increased convenience of a 1-week course of RT compared with the longer whole breast regimens of either 5 to 6 weeks using conventional daily doses of 1.8 to 2 Gy or the 3- to 4-week hypofractionation.

Table 3. — ASTRO Accelerated Partial Breast Irradiation (ACBI) Task Force Consensus Statement Guidelines for Use of APBI

<table>
<thead>
<tr>
<th>“Suitable” for APBI if all criteria are met:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60 yrs</td>
</tr>
<tr>
<td>Tumor size ≤ 2 cm; T1; unicentric</td>
</tr>
<tr>
<td>Clinically unifocal with total size ≤ 2 cm</td>
</tr>
<tr>
<td>Margins negative by at least 2 mm</td>
</tr>
<tr>
<td>Any grade</td>
</tr>
<tr>
<td>ER positive</td>
</tr>
<tr>
<td>Invasive ductal or other favorable histologies</td>
</tr>
<tr>
<td>Pathologic stage N0, after sentinel node or axillary dissection</td>
</tr>
<tr>
<td>Not allowed:</td>
</tr>
<tr>
<td>Lymphovascular space invasion</td>
</tr>
<tr>
<td>BRCA1/2 mutation present</td>
</tr>
<tr>
<td>Pure DCIS or extensive intraductal component (associated LCIS allowed)</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“Cautionary” group: ANY of the criteria invoke caution for use of APBI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 50–59 yrs</td>
</tr>
<tr>
<td>Tumor size 2.1 to 3 cm; T0 or T2</td>
</tr>
<tr>
<td>Clinically unifocal with total size 2.1 cm to 3 cm</td>
</tr>
<tr>
<td>Close margin (&lt; 2 mm)</td>
</tr>
<tr>
<td>Limited or focal lymphovascular space invasion</td>
</tr>
<tr>
<td>ER negative</td>
</tr>
<tr>
<td>Invasive lobular histology</td>
</tr>
<tr>
<td>Pure DCIS ≤ 3 cm</td>
</tr>
<tr>
<td>Extensive intraductal component ≤ 3 cm</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>“Unsuitable” for APBI outside of a clinical trial if any criteria are present:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 50 yrs</td>
</tr>
<tr>
<td>Tumor size &gt; 3 cm; T3-4; multicentric</td>
</tr>
<tr>
<td>Microscopic multifocality &gt; 3 cm total size</td>
</tr>
<tr>
<td>Positive margins</td>
</tr>
<tr>
<td>Extensive lymphovascular space invasion present</td>
</tr>
<tr>
<td>Pure DCIS &gt; 3 cm</td>
</tr>
<tr>
<td>Extensive intraductal component &gt; 3 cm</td>
</tr>
<tr>
<td>Pathologic stage N1, N2 or N3, or no nodal surgery performed</td>
</tr>
<tr>
<td>BRCA1/2 mutation present</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy used</td>
</tr>
</tbody>
</table>

treatment regimens that deliver 2.5 to 2.65 Gy per day. Acceleration beyond this daily dose to the whole breast has not been considered advisable due to concerns about long-term fibrosis and negative impact on cosmesis. As suggested by some of the studies discussed above, there are likely limits to the volume of breast tissue that can be treated at the highly accelerated doses associated with APBI without incurring excessive toxicity and increasing the rates of unacceptable cosmesis. Convenience should never take precedence over optimal cancer treatment. Advantages with the use of APBI are possible in some patients (particularly those with left-sided cancers) to reduce normal tissue heart and lung dose-volumes, but it should be recognized that this potential advantage is not universally achievable and that normal tissue doses are highly dependent on tumor location and patient anatomy. Many questions regarding the appropriate patient selection criteria remain unanswered at this time, such as optimal tumor size, histology, differentiation, lymph-vascular invasion extent, nodal status, and patient age. Uncertainties remain regarding target definition and appropriate treatment volume, normal breast-target volume ratios, and dose fractionation, and such technical parameters have not been tested empirically. Finally, no randomized trials with long-term results are available yet that demonstrate equivalence between standard WBI (which has been subjected to numerous randomized trials with long-term follow-up data available) and any of the accelerated partial breast techniques. Other than the Hungarian trial,53 which applied fairly strict eligibility criteria, the randomized trials currently reported show a statistically significant increase in local recurrence rates when APBI was used, while trials utilizing current standards are ongoing.

Conclusions

As the ASTRO consensus guidelines illustrate, APBI remains for many women an uncertain or cautionary approach to the treatment of their early-stage breast cancer, generally a highly curable malignancy. Concerns remain that longer follow-up of APBI will demonstrate increased rates of local, regional, or even distant recurrence that are detrimental to overall survival outcomes. Excessive toxicity has been reported in some series, and the reasons for this need further study. Overall clinical appropriateness criteria for APBI need to be determined by ongoing studies. Thus, until further studies mature and additional randomized data are published, we recommend that evidence-based criteria like those developed by the ASTRO Task Force be applied by all practitioners offering any form of APBI to their patients. Patients should be informed of the lack of long-term outcome data for APBI, and appropriate informed consent documenting this information should be obtained.

APBI is an interesting paradigm shift in the approach to breast conservation therapy for early-stage breast cancer, and early results appear promising for selected patients. Because of the shortened overall treatment time, APBI has the potential to expand the availability of breast conservation therapy to women in rural areas and underserved areas throughout the world. However, this technique needs to be offered to appropriately selected patients whose outcomes will not be compromised by omitting whole breast or lower axillary radiation.

References


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