

For the Workshop Participants

Breast conserving surgery followed by radiation therapy has been accepted as an alternative to mastectomy in the management of patients with early-stage breast cancer. Over the past decade there has been increasing interest in a variety of radiation techniques designed to treat only the portion of the breast deemed to be at high risk for local recurrence (partial-breast irradiation [PBI]) and to shorten the duration of treatment (accelerated partial-breast irradiation [APBI]). To consider issues regarding the equivalency of the various radiation therapy approaches and to address future needs for research, quality assurance, and training, the National Cancer Institute, Division of Cancer Treatment and Diagnosis, Radiation Research Program, hosted a Workshop on PBI in December 2002. Although 5- to 7-year outcome data on patients treated with PBI and APBI are now becoming available, many issues remain unresolved, including clinical and pathologic selection criteria, radiation dose and fractionation and how they relate to the standard fractionation for whole breast irradiation, appropriate target volume, local control within the untreated ipsilateral breast tissue, and overall survival. This Workshop report defines the issues in relation to PBI and APBI, recommends parameters for consideration in clinical trials and for reporting of results, serves to enhance dialogue among the advocates of the various radiation techniques, and emphasizes the importance of education and training in regard to results of PBI and APBI as they become emerging clinical treatments. [J Natl Cancer Inst 2004;96:175–84]

Over the past few years, a number of studies (1–13) have detailed the rationale for and the various technical considerations of partial-breast irradiation (PBI), which is defined as radiation of the site of excision and adjacent breast tissue only. PBI can consist of brachytherapy or external modalities. Accelerated partial-breast irradiation (APBI) is defined as radiation that employs fractions higher than 1.8–2.0 Gy per day over a period of less than 5–6 weeks and uses any of four techniques: 1) brachytherapy implant, 2) external beam with 3D-conformal radiation therapy (3D-CRT)/intensity-modulated radiation therapy (IMRT), 3) the MammoSite device (a registered trademark of Proxima Therapeutics, Alpharetta, GA), or 4) intra-operative radiation therapy (IORT). Several clinical reports (1–13) of nonrandomized treatment groups with 7–8 year follow-up intervals have produced substantial interest and discussion of PBI/APBI in lay and medical circles. The efficacy of breast conserving therapy (BCT) compared with mastectomy has been supported and validated by recent publications (14,15) containing 20-year follow-up data from large, well-controlled, randomized phase III clinical trials. Such studies have demonstrated the importance of long-term data in determining the ultimate efficacy of a treatment.

It is recognized that BCT was introduced into clinical practice by single institution studies and that early data from BCT trials indicated that such an approach might be comparable to mastectomy. General acceptance of BCT did not occur, however, until the National Surgical Adjuvant Breast and Bowel Project (NSABP) published the results of its B-06 trial (14). Deciding on when exciting early results are sufficiently mature to allow practitioners and patients to consider utilizing a new treatment

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approach in routine practice is a complex issue beyond the scope of this summary. However, broad interest in PBI makes this an opportune time to build on the experience now available in the use of BCT and PBI.

To address issues regarding the equivalency of the various radiation therapy approaches, the National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis, Radiation Research Program, hosted a Workshop in Bethesda, MD, from December 8 through December 10, 2002. The intent of the Workshop was to review the current “State of the Art and the Science” related to PBI and APBI and to consider the need for additional research, training, quality assurance, and procedure standardization. It must be emphasized that it was not the purpose of the Workshop nor is it the role of the NCI to determine treatment policy or consider reimbursement issues. It is further emphasized that consensus on emerging treatment regimens is not always achievable but that an open exchange of information and expert opinion are critical to the evolution of patient care.

Workshop participants included individuals representing all clinical specialties involved in the care of patients with early-stage breast cancer, including experts in various radiation oncology approaches and representatives of cooperative clinical trial groups and agencies (see Appendix 1 for the full list of participants). Formal presentations by participants reviewed issues in regard to BCT, including pathology and radiation biology. Given that much of the PBI and APBI data are not yet published, experts from Europe, Canada, and the United States presented preliminary unpublished information from their geographic region to facilitate access to such information. These presentations were followed by open-ended discussions and a breaking-up of participants into three working groups that were assigned the task of further examining specific aspects of the issues relating to PBI and APBI and of making specific sets of recommendations. This Workshop report represents the opinions of the participants and illustrates that the field of PBI and APBI is in rapid development. Because it is not possible to provide a complete and balanced reference list and because it was the goal of the Workshop to expeditiously produce a report, only a limited number of references are included.

**WORKSHOP PRESENTATIONS**

Clinical Care and Research Considerations (A. Lichter)

Interest in the use of PBI and APBI has come from within the radiation oncology community as well as from surgeons, medical oncologists, and patients. The potential benefits of shorter treatment schedules include patient convenience and the potential for increasing the possibility of BCT in patients for whom the logistics of a longer course of radiation therapy precludes that option. Potential benefit to the patient must be balanced with the potential risk of recurrence within the untreated breast tissue in the breast receiving PBI or APBI and the unknown long-term cosmetic results and complications with accelerated radiation techniques. An important practical consideration for the use of PBI and/or APBI is the precise choice of technique, for example, interstitial brachytherapy (i.e., high-dose rate and low-dose rate), balloon-based brachytherapy (i.e., the MammoSite device), or external-beam radiation therapy (i.e., 3D-CRT and IMRT or IORT). Patient selection criteria remain to be fully defined, including questions regarding age exclusions and applicability of PBI and APBI with various primary tumor sizes, histopathology (invasive lobular, extensive intraductal carcinoma, and ductal carcinoma in situ [DCIS]), and positive axillary lymph-node status.

Additional concerns about the use of PBI and APBI relate to the uncertainty in expected results because of a lack of long-term data from large-scale multi-institutional randomized trials, limited efficacy data, and the lack of establishment of equivalency of APBI and whole-breast irradiation (WBI) in the specifications of the Food and Drug Administration (FDA) approval of the MammoSite device. Notwithstanding these concerns, many radiation oncology practice sites and healthcare providers have received training from the manufacturer of the MammoSite device.

After being introduced by single-institution reports, randomized trials with large patient populations and adequate follow-up have established the standard-of-care for early-stage breast cancer as a choice between modified radical mastectomy and breast conservation surgery plus radiation therapy to the whole breast. Given that PBI was only introduced in the last decade, the analogous nature of the PBI and APBI results (i.e., in terms of local control, survival, and cosmesis) has not yet been confirmed. The radiation oncology community may be asked to deal with concerns regarding institutional review board approvals, the development of specialty-based organizational guidelines for appropriateness, and unresolved reimbursement issues.

**Radiation Biology Implications (S. Powell)**

The use of PBI has important implications in terms of the biologic equivalent doses of the altered fractionation and protraction schedules. The effectiveness of breast conservation surgery plus radiation therapy is based on the delivery of 60 or more Gy to the tumor bed in a 6-week period, where current results have shown more than 95% local control at 10 years (16–30). Therefore, adoption of a novel dose regimen for PBI has to be performed with great caution in order to provide a biologically equivalent radiation dose. The methods available for calculating the dose equivalence of PBI and WBI are derived from clinical data; however, the main limitations of this type of data are that the ranges of radiation dose per fraction and the overall protraction time of treatment are similar and do not include regimens used to date in PBI, thus, dose equivalence between WBI and PBI has to be derived by extrapolation.

The linear quadratic model is most commonly used to predict dose equivalence, and it is represented mathematically as follows: $E = e^{\alpha D + \beta D^2}$, where $D$ is the dose and $\alpha$ and $\beta$ are the linear and quadratic coefficients of dose dependence, respectively. This equation can be adapted to calculate dose equivalence as follows:

$$\frac{D_1}{D_2} = \frac{d_2 + \alpha/\beta}{d_1 + \alpha/\beta}$$

where $D_1$ is the total dose equivalent to the new total dose $D_2$ and $d_1$ and $d_2$ are the radiation doses per fraction for the reference and new radiation regimens, respectively. The $\alpha/\beta$ ratio was derived empirically for tumor tissues to be approximately 10 and for late normal tissue reactions to be in the range of 2 to 4; for the following examples, a value of 3 will be used. Two commonly used schedules for PBI are 34 Gy in 10 fractions twice a day and 32 Gy in eight fractions twice a day. Using the
above equation, the total dose equivalent comparing 2 Gy per fraction (i.e., the standard radiation dose in WBI) to 34 Gy in 10 fractions is a total of 38 Gy for an α/β ratio of 10 and 43.5 Gy for an α/β ratio of 3. This schedule was chosen for safety on normal tissues, but might be regarded as biologically lower than 60 Gy in 2 Gy fractions. Similarly, the total dose equivalent for 32 Gy in 8 fractions is 37.3 Gy for an α/β ratio of 10 and 44.8 Gy for an α/β ratio of 3.

The linear quadratic model does not take into account the effect of overall treatment time in its calculations. However, when the nominal standard-dose formula is applied to the same treatment schedules, the calculation for acute responding tissues is 45.5 Gy, which is a little higher than the linear quadratic model’s estimated total dose equivalent but still lower than the standard effective dose of 60 Gy. It may be that a patient selected for PBI requires a lower dose of radiation than is used for all patients treated with BCT. However, the European Organization for Research and Treatment of Cancer (EORTC) boost trial (31) demonstrated an advantage of 65/66 Gy to the partial breast over 50 Gy to the whole breast, and this advantage was seen in both T1 and T2 tumors. Hence, determining the required radiation dose for equivalent local control between PBI and WBI may ultimately be derived empirically, but further maturation of the existing PBI data is required so that there is a larger number of patients who have 5–10 years of follow-up.

When considering individual fraction size, there was consensus among the workshop participants that large single doses of radiation per fraction were more worrisome than small single doses of radiation per fraction for late normal-tissue complications. For example, regimens using single fractions of 21 Gy have a calculated dose equivalence of 54.3 Gy for tumors, but a dose equivalence of 100.8 Gy for late normal-tissue complications. Low-dose rate regimens such as 45 Gy administered at 0.5 Gy/hour are generally thought to be equivalent, dose-for-dose, to 2 Gy per fraction by external beam radiation. However, the accelerated nature of the treatment delivery may increase the effective dose by as much as 22% and would make 45 Gy low-dose rate the most equivalent to current external beam regimens. Phase I data on high-dose rate brachytherapy (32) from Massachusetts General Hospital suggest that low-dose rate up to 60 Gy can be well tolerated.

The potential clinical significance of inhomogeneity of brachytherapy dose was also discussed among the workshop participants. From a biologic point of view, increases in the dose of radiation per fraction can have a multiplicative effect on biologic equivalent dose in that regions of the implant volume can receive more than 150% of the prescribed dose. For these regions, the biologic equivalent dose can increase to as much as 86.4 Gy for a schedule prescribed as 32 Gy in eight fractions. The positive aspect of dose inhomogeneity is that it contributes to the effective tumor dose in a volumetric analysis. Using a tumor-control probability model (32), the inherent inhomogeneity of implants can increase the effective tumor-control probability; however, the magnitude of the effect of inhomogeneity on the probability depends on the level of local control that would be observed with a perfectly homogeneous application of the prescribed dose. The use of external beam to deliver PBI, which will have conventional variations of less than 10% in dose within the target volume, may result in a reduction in local control with the standard regimens of 34 Gy in 10 fractions or 32 Gy in 8 fractions. Overall, the results with the currently used high-dose rate regimens appear to be satisfactory, despite concerns about biologic equivalence. However, further analysis of the data is warranted to maximize the information that can be learned with the clinical data currently available.

Pathologic Implications (J. Connolly and N. Goldstein)

A detailed pathologic study utilizing correlative mammographic–histologic evaluation of breast lesions in patients with clinically detected cancers in the early 1980s has shown that the majority of women have residual tumor at a distance from the primary site (33–36). For this reason, careful selection criteria must be applied when PBI is considered. Examining consecutive clinically unifocal cancers up to 5 cm in size showed that histologically identifiable cancer was present in 63% of patients with invasive cancer and that 43% of these breasts revealed tumors greater than 2 cm from the reference tumor. These findings were independent of reference tumor size, which was 2–5 cm in diameter. In fact, reference tumors that were 2 cm or smaller were just as likely to have residual carcinoma distant from the edge of the reference tumor as larger tumors.

It is clear that certain factors associated with a tumor predict a higher probability of finding foci of tumor at distances from the margin of the reference tumor (36,37). These factors include a positive margin of excision, the presence of an extensive intraductal component, and areas of lymphatic small-vessel invasion. Such patients are typically excluded from PBI. In contrast, it is very difficult to identify subgroups of patients with a very low risk for having carcinoma greater than 1 cm from the edge of the reference tumor. A mammographic–pathologic correlative study (34) of 135 carefully selected mastectomy specimens from women with infiltrating carcinoma 4 cm or smaller was recently reported. These mastectomy specimens excluded cases of infiltrating lobular carcinoma, invasive carcinoma, DCIS, or lymphatic invasion pathologically described beyond 1 cm from the edge of the reference tumor. In this study, there was no statistically significant association between finding tumor in the breast and the patient’s age, tumor size, histologic type (infiltrating lobular carcinoma excluded), histologic grade, or lymph node status. Thirty-five to 40% of the patients had microscopic foci of carcinoma greater than 1 cm beyond the edge of the reference tumor. Patients with a macroscopic 2 cm negative margin and a microscopic 1 cm tumor-free margin still had an 11% likelihood of finding tumor in the remainder of the breast. Even in meticulously performed studies such as this one (34), pathologists are only sampling a small fraction of the mastectomy specimens; therefore, the 11% risk of finding tumor in the remainder of the breast may be a low estimate.

Radiotherapy improves local control of invasive and non-invasive breast carcinoma by eradicating or sterilizing residual carcinoma following breast conserving surgery. The maximum distance of extension of tumor cells beyond the known tumor excision margin is an important factor in the current discussion because the region of dose homogeneity of PBI is generally limited to a 1- to 2-cm perimeter field beyond the known tumor margin. A recent re-evaluation of this issue (38), using initial and re-excision breast conserving surgery specimens of 333 invasive carcinomas (mean dimension 1.4 cm), obtained similar results to tumors with extension greater than 1–2 cm; 269 (81%) of the re-excision specimens had less than a 10-mm maximum tumor extension from the known tumor exci-
sion margin and 64 (19%) of the re-excision specimens had a 10 mm or more maximum tumor extension. Of these 64 re-excision specimens, 34 had a 10- to less than 15-mm maximum tumor extension and 30 had more than 15 mm of maximal tumor extension. Thus, 91% (303/333) of specimens in this study had a tumor extension of 15 mm or less beyond the tumor excision margin. Two factors were found to be predictive of less than 1 cm maximum tumor extension beyond the edge of the tumor excision margin: 1) the distance of the resected margin in relation to the extent of tumor near the margin, and 2) the ratio of total invasive carcinoma to the maximum dimension of the tumor. In this analysis, a radiation field of 1–2 cm beyond the final excision margin appeared to be adequate to cover residual carcinoma in most of the patients reviewed, although 9% (30/333) of patients had tumor cells extending more than 15 mm from the tumor excision margin. Using NSABP criteria, residual disease was limited to less than 10 mm from the lumpectomy margin (if present) in 90% of all patients with an initial negative margin prior to re-excision.

The European Experience (H. Bartelink and R. Orecchi)

A number of European groups have been interested in investigating of PBI and APBI for some time. The Christie Hospital trial (39) randomly assigned 708 patients to either WBI or PBI. The WBI arm demonstrated fewer local relapses (15% versus 25%) and better cosmetic results than the limited-field radiation therapy arm. Severe fibrosis was noted within the irradiated field in a substantial number of the limited-field radiation therapy patients. With a median follow-up of 65 months, the incidence of tumor recurrence in the breast (as a first site of failure) at 7 years was 7% (26/355) in the WBI arm and 14% (49/355) in the PBI arm. The 5-year actuarial local recurrence rates were 8% and 17%, respectively, and the 7-year actuarial recurrence rates were 11% and 20%, respectively (39).

In an attempt to accelerate PBI, some European groups have studied IORT, and for this purpose, a mini-electron generator capable of delivering orthovoltage x-rays to small regions during surgery has been developed (40). IORT permits rapid attenuation and easy shielding of radiation; however, penetration of x-rays is limited and two of 25 patients initially studied (40) with IORT developed skin necrosis. IORT has limitations because using 50 keV x-rays necessitates a small volume of irradiated tissue.

A Hungarian prospective trial (41) reported 5-year results of a phase I–II study comparing brachytherapy alone (i.e., APBI) versus WBI after breast conserving surgery. Patients eligible for APBI had only unifocal tumors. In a subsequent prospective randomized trial (42), 221 patients were enrolled in which 111 patients underwent APBI (high-dose rate brachytherapy or electron beam radiation therapy) and 110 underwent WBI. With a median follow-up of 2 years, there were few complications. Data such as these supports the addition of this option for a subsequent phase III study as discussed by the workshop participants.

Using another approach to treatment acceleration, the European Institute of Oncology (EIO) has evaluated Electron Intra-Operative Treatment (ELIOT) for the treatment of patients with early-stage breast cancer. A phase II prospective dose-seeking trial (40) was conducted from June 1999 through October 2000 in which a total of 101 patients were enrolled, 70 of whom received IORT at the highest dose level of 21 Gy and 31 received IORT at low doses. Preliminary results indicated that one of the 21 Gy IORT patients had acute side-effects and five had late side-effects. Based on these results, a randomized trial was begun in November, 2000 (43), in which patients were first treated with breast conserving surgery and then randomly assigned to receive ELIOT up to 21 Gy or external-fractionated conventional WBI consisting of 50 Gy WBI plus 10 Gy boost to the tumor bed. Through December 24, 2002, a total of 337 patients had been entered on the trial, with 168 receiving ELIOT and 169 receiving conventional WBI. One case of distant metastasis has been observed in the conventional WBI arm (43).

The Canadian Experience (T. Whelan)

Canadian investigators have limited experience with PBI in the clinical trial setting but have utilized a program of accelerated WBI (AWBI) in the treatment of early-stage breast cancer, which can provide important information regarding radiation dose and fractionation (44). Similar to the long-term results from the NSABP and Milan (without a quadrantectomy alone arm) trials (14,15), results from a Canadian trial (45) in which patients underwent PBI or AWBI recently demonstrated a dramatic reduction in local recurrence with WBI as compared with PBI, with a reduction on distant and secondary failure as well. No differences in overall survival between AWBI and conventional WBI were noted. Radiation therapy was associated with a substantial decrease in deaths due to breast cancer. This decrease was partially offset by an increase in deaths from other causes. A more recent randomized trial (44) evaluated hypofractionated AWBI following breast conserving surgery, and showed that 42.5 Gy in 16 fractions administered over a period of 3 weeks was equivalent to 50 Gy in 25 fractions over a period of 5 weeks. Both treatment arms had a 3% failure rate at a median follow-up of approximately 6 years. Half of all patients had systemic therapy (i.e., hormone therapy or chemotherapy), which reduced failure rates in those patients despite the presence of greater risk factors, such as lower age and positive lymph node status. Cosmetic outcomes and complications/toxicity were the same for both treatment arms. These results support the notion that modest increases in fraction size with reductions in total radiation dose are not associated with a loss of tumor control or increased toxicity.

Early data from another Canadian trial (44), which evaluated the role of WBI in older women treated with tamoxifen, suggested that with appropriate selection criteria and adequate systemic therapy, we may be able to identify a group of patients with a low risk of local recurrence following breast conserving surgery, where the advantages of WBI or even APBI may be marginal.

Surgical Implications (A. Giuliano)

Regardless of the method of radiation therapy under consideration, the overriding surgical principle continues to be an attempt to attain a complete resection with negative tumor margins. In-breast recurrence, which results from incomplete tumor excision, increases as margins become closer or involved. Appropriate use of re-excision and post-operative radiation therapy reduces recurrence rates after surgical excision. Recurrence rates for multicentric and multifocal tumors range from 9% to 75%, which could be an argument against consideration of PBI in patients with these types of tumors. Hence, there is concern
regarding which patients would ultimately benefit from PBI. However, more effective breast imaging techniques might be helpful in determining tumor margins, multicentricity, and second primary tumors. With selection of appropriate patients, improved imaging techniques, wide excision, accurate histopathology, post-operative radiation therapy, and tumor-free margins, the problems of local recurrence could be reduced.

Another concern raised by the participants of the workshop was in regard to bias in surgical selection of patients treated with PBI or APBI versus the more conventional BCT. A recommendation was made by the workshop participants that, as part of any clinical trial, surgeons should not be aware of the selected radiation therapy option prior to surgical excision. Standardization of the extent of tumor excision could be problematic, because the size of the post-excision cavity could impact the methods employed in subsequent trial-based PBI. A volume approach, based on the surgical resection, would be necessary to define the surgical cavity size. Use of different PBI or APBI techniques may determine the appropriate method of volume determination and verification of cavity size.

Technical and Physical Considerations (G. Edmundson, J. Hevezi, and J. Wong)

A variety of brachytherapy approaches have been utilized, and it is essential to evaluate each one of these approaches independently, using standardized criteria. Technical and physical elements for consideration include the following categories, with the understanding that the introduction of new techniques requires appropriate training, quality assurance and, potentially, additional personnel (2–6).

Dose-rate. Although there are certain physical, dosimetric, and reproducibility advantages to high-dose rate brachytherapy, there are certain potential radiobiologic advantages to low dose-rate brachytherapy. Usually, there are no new facility infrastructure requirements for low-dose rate brachytherapy; however, admission of the patient to the hospital is required and there is staff exposure to radiation from the implanted patient. High-dose rate brachytherapy procedures can be performed on an outpatient basis and dose homogeneity can be optimized prior to therapy.

Catheter/needle insertion technique for target volume coverage. Free-hand catheter/needle insertion techniques require a skilled operator and offer flexible options for spacing of radiation sources, but the irregularity of spacing may produce dose hot or cold spots and treatment planning can be tedious. Template techniques provide regular spacing and simplicity of planning, but the rigid geometry may yield a poor fit to tumor anatomy. Deviations in linearity of the radiation sources are common even with use of templates, and x-ray reconstruction is necessary to verify position of the radiation sources for dosimetry. There will always be hot spots immediately adjacent to the catheter carrying sources. New image-guided template insertion provides ideal and reproducible target volume coverage.

Points and methods of radiation dose prescription. Prescribing a radiation dose to simply encompass the target volume is not optimal because it could result in a high mean central dose, potentially resulting in fat necrosis. Therefore, good geometric coverage of the target volume is essential. The ratio of the prescription dose to the mean central dose should equal or exceed 0.85. At least 90% of the target volume should be covered by the prescription isodose line.

Treatment planning methods. Ideally, the treatment plan should ensure that the prescription isodose curve tightly conforms to the target volume, while at the same time, the high-dose regions in the center of the target volume are within normal tissue tolerance. Applicator-based planning is rapid, requires little data input, and is reproducible; however, it requires perfect implant geometry. Radiograph-based planning is universally acceptable and accommodates clip-derived information, but is time consuming. Computed tomography (CT)-based planning combines the full anatomic information of the breast and adjacent normal tissues in a comprehensive plan. Development of a dose-volume histogram is possible, but not yet widely available. Virtual simulation planning provides anatomic-based guidance that is accurate, but can be awkward and time consuming and has little current vendor support. Image-guided catheter insertion, for example, under fluoroscopic guidance, provides visualization in the operating room and is accurate.

Verification of cavity location and size. An open surgical cavity provides direct visualization of the implant site; however, operative time may be extended and there may be a level of over-confidence in the placement of the implant related to the extent of surgical resection. Surgical clips are widely used in the verification of the surgical cavity and provide a permanent record of the extent of excision; however, their use may be problematic with the balloon-based techniques because of the potential for perforation of the balloon. Post-operatively, the surgical cavity is well visualized for 4–6 weeks. CT scanning provides the best level of 3D accuracy in visualizing the surgical cavity; however, there is a potential for under-estimation of the cavity size with this technique. Ultrasound also may be useful in visualizing the surgical cavity and can provide a good depiction of deep tumor margins; however, total evaluation of the regional tissues is poor and 3D-reconstruction is not possible. Verification may also be provided by non-ionic contrast solution injected into the surgical cavity and can be used for 3D delineation of the seroma. Four or six surgical clips cannot visualize the full extent of the surgical cavity as well as contrast material. Subsequent catheter insertion at a predetermined distance from the surgical edge is mammographically facilitated by real-time visualization of the surgical cavity using non-ionic contrast.

Balloon techniques. The balloon-ended catheter technique (i.e., the MammoSite device) for localized treatment of post-lumpectomy breast cancer was approved by the FDA in May, 2002, on the basis of safety results for 43 patients (treated at eight institutions) who reported minimal toxicity. Efficacy data for this technique are anticipated. Additional facilities have applications to utilize the MammoSite device in patients with early-stage breast cancer in the institutional review board application process and are participating in a registry established by the manufacturer of the device. Most facilities offer the option of MammoSite therapy to patients prior to lumpectomy. The balloon is placed in the surgical cavity during or following surgery and is initially inflated with a mixture of saline to assess its fit and to ensure an absence of air pockets. The distance of the balloon from the skin and the chest wall should be greater than 7 mm and the average diameter of the balloon is 4–5 cm. Fat necrosis is anticipated to be limited with balloon treatment because the balloon is not in contact with tissues other than the margins of the lumpectomy, and the maximum dose of radiation
to any tissue does not exceed approximately 200% of the prescription dose. In filling the surgical cavity, the balloon also stretches surrounding tissue, presumably enhancing dose conformity, and increasing the effective tissue volume treated. Efforts to evaluate this process are ongoing. It is unknown if tissue-at-risk expands equally around the balloon or if it is pushed away. The balloon technique is designed to treat 1 cm of tissue surrounding the lumpectomy cavity; however, how balloon expansion and tissue compression affect the physiology of the tissue or the tissue-at-risk that is treated remains to be determined.

**3D-CRT/IMRT.** 3D-CRT and IMRT have been used to develop a conformational external beam technique to treat the lumpectomy cavity. Advantages of 3D-CRT/IMRT over other radiation techniques include the absence of additional surgery and improved dose homogeneity. However, there are certain persistent geometric uncertainties with 3D-CRT and IMRT, including breathing motion and surgical clip motion. There is evidence that surgical clips can be used as a surrogate source of information for evaluation of the lumpectomy cavity and to guide treatment. 3D-CRT/IMRT for accelerated radiation therapy confined to the lumpectomy cavity may be feasible with minimal acute toxicity. Similar to other PBI techniques, the target volume of tissue for irradiation using 3D-CRT/IMRT has not yet been established, and the potential for breast conserving treatment following failure within the irradiated breast is uncertain. Hence, the precise role of IMRT in PBI and APBI has not yet been determined.

**LITERATURE REVIEW AND DISCUSSION OF THE PROS AND CONS OF PBI AND APBI**

Recognizing that there is debate as to the optimal use of PBI and APBI, the workshop organizers included presentations designed to highlight the more controversial aspects of PBI and APBI to allow the workshop to focus on research issues. The following sections represent issues raised in the “pro” and “con” presentations and do not represent either consensus statements or conclusions of the workshop.

**Summary of the Literature and Clinical Discussion against the Routine Use of PBI (L. Pierce, L. Solin)**

Taking a different opinion, several workshop participants, in their evaluation of the available data, commented that they believe that PBI remains an experimental therapy under active investigation. The results of WBI in terms of local recurrence, survival, cosmesis, and toxicity, are mature and excellent. These results set a high standard in terms of outcome results for the introduction of new therapies. The early positive results of PBI may be related to patient selection, and unresolved issues in regard to the routine use of PBI include patient selection, optimum volume of treatment, dose fractionation, total dose, integration with chemotherapy and hormone therapy, advantages and disadvantages of the various PBI techniques, relationship to BCS, and impact on overall outcomes of local control, survival, and quality of life measures. The role of tamoxifen in the delay of local disease recurrence has been established, and the clinical significance of selective estrogen-receptor modulators and other hormonal manipulation agents with regard to local control and survival is being further investigated. The relationship of these agents with the currently reported end-results for PBI and APBI and their actual role when these therapies are employed has yet to be established (45,46). In the United States, approximately 80% of patients received radiation therapy after breast conservation surgery and it appears unlikely that this percentage will change substantially with availability of PBI, APBI, or newer techniques (46–49). However, it is recognized that a shorter course of therapy may make the option of breast conserving therapy available to women who would normally not consider such a therapy because of the prolonged treatment time.

Although the comparisons of the PBI results are not precise, lessons for the use of PBI may be learned from evaluation of BCS alone. Studies have been performed in this area and long-term follow-up data are available. In the Milan trial (15), younger patients who received WBI demonstrated an increase in local failures compared with older patients who received WBI. There was an increase in local failure among patients with grade 3 lesions and positive lymph nodes and distant failure was higher among patients who did not receive WBI than those who did.

There has been intense pressure and interest from within the radiation oncology community and from patients for the consideration of PBI and APBI to be part of routine treatment in breast conserving therapy. This interest may relate to convenience or a reduction in radiation exposure to surrounding tissues. Convenience, availability of therapies, and financial considerations should not jeopardize the substantiated and good results of

The MammoSite technique represents a simplification of breast brachytherapy techniques; however, it may not be ideal for every patient and long-term follow-up is necessary to fully understand the limits of its applicability. Patients who are not acceptable candidates for breast conserving surgery should not be considered candidates for PBI. Based on the data available from two institutions and a phase II trial (3,5), and in the absence of long-term data, PBI is considered by some radiation oncologists who have extensive experience in the treatment of breast cancer to be an appropriate radiation therapy option. However, phase III trials are desirable to fully understand the relationship and equivalence of PBI to WBI (7–13).
breast conserving surgery plus WBI. However, until safety, efficacy, and long-term outcomes for PBI are demonstrated, the participants of the workshop believe that PBI should be considered as investigational, and should require institutional review board approval before being routinely used in clinical practice. Patients should be informed that PBI is not the currently accepted standard-of-care for the treatment of early-stage breast cancer (16–30,50).

Potential for a Phase III Clinical Trial (T. Julian)

The NSABP is considering a phase III trial in which WBI will be compared with PBI. This trial is currently under discussion with Cancer Therapy Evaluation Program (CTEP). The primary end-point of the study would be in-breast tumor recurrence (IBTR) as a first event. Secondary end-points would be non-IBTR loco-regional failures, distant failures, contralateral breast cancers, and overall survival. Planned accrual is 6,300 women, but the final number of participants will depend on the percentage of difference anticipated in the end-point in what is an equivalency study. The proposed study will be powered to determine a relative risk of 1.4 with primary analysis occurring after 303 IBTR events over a period of 10 years. A site approval process will be developed to ensure training of all participating physicians and for quality control purposes. A quality-of-life section will be incorporated into the study to evaluate such factors as cosmesis, pain, morbidity, time, and cost. A correlative science section will also be incorporated into the study to address prognostic factors. Planned inclusion criteria, which are currently in the concept proposal stage, include tumors treated by lumpectomy, negative margins (per NSABP criteria), lesions less than or equal to 3 cm, 0–3 positive lymph nodes (with no extracapsular extension), tumors with an extensive intraductal component (permitted if margins are clear), invasive or non-invasive tumors (DCIS but not LCIS), and all ages.

The issues of inclusion of young patients or patients with positive lymph nodes in the proposed inclusion criteria of the NSABP phase III study were discussed because of a potential for higher rates of recurrence in young patients and increased risk of loco-regional recurrence in patients with positive nodes. The Radiation Therapy Oncology Group (RTOG) has also developed potential PBI clinical trials that are currently under discussion with CTEP. In addition to accumulating treatment data, the potential values of organized research studies include an opportunity to provide important practitioner education and the standardization of techniques and quality assurance by those who provide these support services to cooperative group protocols.

WORKING GROUP REPORTS

Research Issues (L. Solin, T. Julian – Leaders)

The discussions of the research issues group focused primarily on four areas, including the need and potential for randomized phase III trials, issues related to possible phase I and II trials, standardization of patient selection, and outcome measurements. The discussion also included concepts for the types of prospective clinical trials, including a two-arm trial comparing AWBI and APBI; a three-arm trial comparing conventional WBI, AWBI, and APBI; and a three-arm trial comparing different PBI/APBI techniques. It is recognized that with the large patient population necessary and the long duration of follow-up required for such trials, it is simply not possible to address all of the questions and issues of interest. Hence, the need for such large trials provides an impetus for developing inter-group studies.

In the design of various phase II and phase III trials, accurate and consistent assessment of end-points is essential. Evaluation across various breast cancer trials has frequently been rendered problematic because of variation in measured parameters. Standardized end-points should be considered, including total local failures, in-field/marginal versus elsewhere (in the treated breast) failures, distant metastases, mastectomy-free survival, quality-of-life measures, adherence to trial parameters, survival, complications, toxicity, total time of treatment, cost of treatment, and cosmetic result.

Although the research issues group agreed that a phase III trial comparing PBI and APBI to WBI is appropriate at this time, consideration should also be given to several smaller and more focused phase I and II trials that might better address questions that they felt remained unclear. Such trials could include an improved definition of appropriate patient inclusion criteria, intra-operative versus post-operative insertion of the MammooSite device, an improved definition of tumor and target volume, the impact of balloon compression on adjacent tissues and uniformity of dose distribution, translational questions related to tumor biology, and questions regarding the integration of surgery and chemo/hormonal therapy.

The research issues group also had a lengthy discussion regarding the definition of research (i.e., discussion items such as reimbursement and informed consent) with respect to PBI and APBI and the acceptability of routine use of these techniques. A recommendation about the use of PBI, approved only within the context of the working group, stated that, in the absence of proof of equivalence of PBI with conventional methods of BCT (as would be demonstrated by a randomized clinical trial), patients should be treated on institutional review board–approved clinical trials with appropriate research-related informed consent. In addition, consideration could be given to routine use of trial pre-enrollment in an attempt to monitor the eventual penetration of clinical trials in the management of this patient population. Further discussion of the need for institutional review board-approval is included in the general discussion below.

Technology/Education/Quality Assurance (L. Pierce, J. Wong – Leaders)

The technology/education/quality assurance group discussed the current state of brachytherapy training and practice and recommended development of formal training programs for the various techniques used in PBI and APBI. This group also recommended that a minimum level of expertise be demonstrable before individual physicians could participate in phase III trials. Following completion of the training program, a site visit by the trial trainers to observe actual practice of the techniques may be necessary and appropriate.

A number of technical parameters for the use of PBI and APBI were discussed and certain guidelines were recommended for consideration (representing the opinion of the participants in this working group), including upper and lower volume limits beyond or deficient of covering the target volume should be set; 50% of the breast should be less than 50% of the prescribed dose during PBI (not all workshop participants con-
Multimodality Integration (R. Kuske, B. McCormick – Leaders)

The multimodality integration group addressed four principal topics that were almost exclusively related to design and implementation of phase II–III clinical trials, including patient accrual, surgical considerations, sequencing of therapy, and training/education.

One important concern regarding patient accrual to clinical trials is related to the potential for patient unwillingness to consider randomization to non-APBI arms and how this issue might compromise end-results. Potential for bias in assigning a particular patient to a particular treatment would require consideration in trial design recognizing that such bias or preference occurs in many realms of medical care when one treatment is recommended over another. Randomized clinical trials provide balance (i.e., in terms of patients and investigators) not necessarily achieved in a single arm phase II trial or in a single institution report. Sequencing of therapies that prolonged or delayed treatment completion could also adversely impact patient accrual.

Surgical considerations raised for discussion included concerns regarding the placement of surgical clips for lesion/cavity localization and the potential damage to the balloon of the MammoSite device from the surgical clips. Approximately 14%–20% of MammoSite balloons are removed from the patient prior to placement of radiation sources because of distance from the balloon surface to skin or additional histopathology findings, such as DCIS or positive margins (14% in the current registry and 20% in the current manufacturer’s registry). To avoid these potential concerns, use of non-balloon-bursting surgical clips should be encouraged and precise standards for reporting and recording histopathology prior to randomization should be developed; the size and sophistication of participating pathology departments should also be taken into account. Among possible solutions to histopathology quality control is that participating sites could submit 100 consecutive cases to the trial organizers for review, with subsequent development of a training program if more than 20% of cases reviewed were challenged. Although considered as ideal, budgetary considerations might preclude central pathology review and to improve consistency of reporting, the RTOG web-site could possibly be used to train pathologists for a DCIS study.

The variability in sequencing of the interventions is also a consideration. If clinical trial design required that patients undergo excisional biopsy prior to random assignment, sequencing of therapy for a WBI arm may include chemo- or hormonal therapy (if indicated), followed by radiation therapy, whereas patients treated in an APBI arm might have their radiation therapy first, then their chemotherapy. These variations in the sequencing of therapy—excision, systemic therapy, and radiation therapy—could raise concerns regarding appropriate comparison of results across trial sites. Therefore, the multi-modality integration group recommended consistency, if possible, in sequencing of therapeutic modalities.

Education and standardization of techniques will be a key to successful design, completion, and evaluation of any clinical trial, particularly phase III studies. Available training programs may be supplemented by manufacturer, organizational, and institutional-based programs. These programs, as well as necessary technical quality assurance, may require additional funding support. Education and quality assurance are also important for use of these techniques in a non-research setting.

Summary

Workshop participants actively discussed, but did not reach agreement, on the precise definition of research and appropriateness criteria for introduction of new therapies into the mainstream of clinical care. It is recognized that new treatments have entered clinical medicine in the past based on only single institution reports. There was also extensive discussion on the definition of research issues specifically related to PBI and APBI. This discussion recognized that including all PBI and APBI patients on institutional review board-approved protocols was not practical. Patients not treated on approved clinical trials should be informed of the status of on-going trials and the current absence of proof of equivalency of the various radiation techniques considered. The use of conventional department or facility radiation oncology consent forms should be strongly discouraged, and the treatment of cohorts of patients in a similar pre-determined manner, in anticipation of subsequent data collection and reporting, should be considered as an investigational research activity.

In the past, the NSABP had developed guidelines for participation in sentinel lymph node biopsy trials and the RTOG had similar requirements for participation in the phase II breast brachytherapy protocol 95–17, 3D/CRT, and IMRT trials. These trials “models” could be used for the design and implementation of training programs for participants in future PBI and APBI trials. As a routine practice, quality assurance of radiation therapy for NCI-sponsored clinical trials is overseen by the Radiation Research Program and CTEP. Education for participants in clinical trials has been partially supported by NCI and educational activities for practitioners of new radiation therapy techniques have been supported by the American Association of Physicists in Medicine, American Society for Therapeutic Radiology and Oncology, and/or various vendors.

The many variables in patient selection, radiation technique, dose and volume utilized, impact of systemic adjuvant therapy, and follow-up evaluation makes it clear that the implementation of PBI and APBI requires open dialogue, exchange of information and data, and well-designed clinical studies. It can be readily seen from the discussions documented in this commentary that firm conclusions about the use of PBI and APBI cannot be drawn at this time. Nevertheless, the Bethesda workshop served the oncology community as a point-in-time to scrutinize the state of the art and science of PBI and APBI and to coordinate future efforts to address the issues raised at the Workshop.
## Appendix 1. Workshop participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Role*</th>
<th>Institution/Organization</th>
<th>Location</th>
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*Org = Organizer; P = Presenter; G = Group leader; Obs = Observer.

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Notes
R. Kuske is a consultant for Nucletron Corporation (Columbia, MD), a maker of brachytherapy equipment.

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