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14. ABSTRACT
The IDEA grant proposal tested the feasibility of a regimen of conformal hypofractionated radiotherapy (5 fractions in 2 weeks)directed to the original tumor bed with margins in a selected subset of post-menopausal women with breast cancer with a very low risk for local risk for local recurrence elsewhere in the breast. The relevance of this approach consists of the fact that if proven equivalent in efficacy it would be more patient-friendly (30 fractions over 6 weeks) convenient and economical. This final report demonstrated feasibility in all treated patients, with minimal acute side effects. Among the 69 patients with at least 6 months follow-up late effects were limited to the rare occurrence of modest fibrosis and teleangectasia. With a median follow-up of 22.5 months, in none of the patients breast cancer has recurred. Prone partial breast radiotherapy, delivered by an external beam simple technique over 5 fractions was feasible and very well tolerated. These results need to be confirmed in a larger cohort of patients, ideally in a multiinstitutional setting

15. SUBJECT TERMS
Partial Breast Irradiation, Prone Setup

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NTRODUCTION:

n selected subset of post-menopausal women with breast cancer with a very low risk for local ecurrence elsewhere in the breast, a regimen of conformal hypo-fractionated radiotherapy (5 ractions in 2 weeks) directed to the original tumor bed with margins, could generate local ontrol rates and cosmetic results equivalent to those achieved by conventional post-operative adiotherapy (30 fractions over 6 weeks), while being much more convenient to the patient and nore economical.

he specific aims of this IDEA grant are:

. To determine the feasibility of a regimen of hypo-fractionated conformal radiotherapy to he tumor bed as part of breast preservation in selected post-menopausal women with T1 breast cancers.
. To explore the efficacy of this approach when compared to historical local control rates chieved by standard post-operative radiation.
. To prospectively assess the role of circulating TGF-β pre-treatment as a marker for post-reatment fibrosis.

ODY:

he study expected to accrue a total of 99 patients in 4 years.

ecause of the study design, that requires for patient to first refuse to undergo standard adiotherapy to be offered the protocol, Accrual of the target population required a longer time nterval. Currently, 95/99 patients have accrued to the study at the time of this final report. n NYU-IRB approved protocol testing the research hypothesis of this study has been actively ecruiting patients since October 2000, with independent funding from those allocated by the urrent award.

he first 29 patients in the protocol signed a consent form, as part of an IRB-approved protocol t NYU and originally submitted to the DOD. The modifications to the protocol and the consent equired by the DOD – IRB were minor and did not affect the research questions and xperimental design. The remaining patients have been accrued according to the amended rotocol and consent that reflects the minor changes required by the DOD-IRB.

Ve are hereby reporting the results obtained in 95 patients accrued. The study continues accrual o a total of 99 patients, as planned. Support for data managing and nursing for this last phase of he study is provided by the Research Fund of the NYU Faculty Group Practice.

Table 1 describes the pattern of accrual over the years:

Patient Accrual Figures per Year	
2000	12
2001	11
2002	11
2003	14
2004	11
2005	9
2006	16
2007	11
Average accrual/year	11.875
TOTAL	95

With regard to Task 1 and 2 of the approved statement of work: (year 1-4)

"To determine the feasibility of a regimen of hypo-fractionated conformal radiotherapy to the tumor bed as part of breast preservation in selected post-menopausal women with T1 breast cancers, and to explore the efficacy of this approach when compared to historical local control rates achieved by standard post-operative radiation."

At the time of the current report 95 patients have accrued (median age 68.7 years, range: 53 to 88). The median tumor diameter is 0.9 cm (range 0.1 to 1.9). 93/95 patients received treatment and are available for follow-up. One patient received 2/5 fractions and refused further treatment thereafter, for personal reasons, as previously reported. This patient remains in communication with her primary doctor and she is reported to be NED four years later. Two patients have signed informed consents, undergone simulation and planning, and are scheduled to start treatment in the next week.

All 93 patients treated appear to tolerate treatment very well with only mild discomfort reported when lying prone for planning and treatment. The most common acute toxicity was grade 1-2 erythema (50.54%) occurring in the treatment portal and fatigue usually manifesting in the second week of treatment. Two patients reported Grade 1-2 nausea. Two patients developed Grade 1 dry desquamation and one patient grade 1 breast edema. Six patients had induration at the surgical scar, pre-dating radiation therapy.

'here are 30 patients who have ≥ 36 months follow-up. Preliminary assessment of late toxicity, ncludes 14 patients who developed 17 events: grade 1-2 induration (5 patients), fibrosis (1 patient), breast edema (2 patients), teleangectasia (5 patients), hyperpigmentation (4 patients). Among the 93 patients who have received treatment no recurrence has occurred: median follow-up is 22.5 months.

During the first phase of the trial we have focused on two tasks:

1) designing a more comfortable and reliable treatment table that can enable geriatric breast cancer patients to comfortably withstand the treatment in prone position.

As a result of a partnership with one of our breast cancer survivor/advocates who is an architect, a new, much more comfortable table for prone imaging and treating was designed (designing and engineering was generously donated by our partner-advocate) and built, as per the attached digital photo (see appendix). The table underwent testing (2). A second development concerned the design of a mattress (picture attached).

2) developing preliminary **physics data about dose volume histogram (DVH) analysis** in the studied population.

Much of our initial research effort has been spent in studying geometric and anatomic issues of the tested technique and their dosimetric implications.

As described in the original proposal the breast tissue and tumor bed, identified at CT as the post-surgical cavity, are contoured on a 3D planning system (Varian Somavision/CadPlan) and a ' cm margin added to determine the PTV. A plan was generated in the attempt to treat the entire PTV to 90% of the prescription dose. Six Gy per fraction are delivered to the 95% isodose surface in 5 fractions over ten days to a total dose of 30 GY.

Planning in the prone position was feasible in 89 patients. Four patients were treated in the supine position (as accepted protocol deviations), 2 patients were unable to tolerate lying in the prone position secondary to paraplegia and 2 patients, the position of the tumor bed was located very lateral and better treated supine. The predominant technique for treatment was a pair of parallel-opposed mini-tangents. This arrangement assured good coverage given the constraints imposed by the PTV and its relationship to the table.

For the entire group the volume of breast receiving 30 Gy ranged from 10% to 45 %. We found heterogeneity of DVH based on the position of the original tumor bed and the size of the breast. In 26 of the 93 patients, in order to successfully treat the PTV, greater than 50% of the ipsilateral breast volume received >50% of the prescription dose. This was largely dependent on the size of the tumor bed and its location in comparison to the index breast. Doses to the heart and lungs were clinically insignificant.

In conclusion, these preliminary data confirm that in most cases it is possible to successfully plan and treat the PTV with parallel opposed tangent fields without exceeding 50% of the dose to .0% of the breast volume.

Task 3: (year 1-4)
To prospectively assess the role of circulating TGF-β pre-treatment as a marker for past-treatment fibrosis.

As planned, patients were seen once/week during treatment and once two weeks after. Thereafter they will be seen in follow-up every 3 months for the first year and every six months for the following five years. At each visit, physical exam to detect clinical recurrence was performed and mammography films (once/year) were reviewed. The data has been regularly collected in the Oracle forms specifically developed for data collection and submitted with the previous annual report.

Since post-radiotherapy breast fibrosis evolves over time and generally achieves a "plateau" at 24 to 30 months, we are planning to assess the incidence of fibrosis when 50% of the patients have reached the 24 months minimum follow-up, i.e. when at least 50 patients are available for evaluation after 24 months from treatment (based on our original design, with a planned accrual of 99 patients). We expect to reach this point in the next 3months.

KEY RESEARCH ACCOMPLISHMENTS:

1. feasibility is demonstrated in the first 93/99 patients

2. dosimetric findings obtained in the first 93 patients appear to confirm our predictions.

3. optimal patient accrual, with an acceptance rate of 96% among patients who refused the initial recommendation for conventional six weeks of post-segmental mastectomy fractionated radiotherapy.

4. divulgation of the NYU experience through publications and for formation of a School for Prone Partial Breast Irradiation (see appendix 1)

REPORTABLE OUTCOMES;

Since the award was received the study has been presented by the P.I. at following international and national conferences (all CME approved):

IV Madrid Breast Cancer Conference: changes in the treatment of breast cancer.
Madrid, June 7-9, 2001

Mayo Clinic Amelia Island Oncology Review Course
August 15-18, 2001

Manhattan Breast Cancer Society, Invited Speaker
January 17, 2002

V Madrid Breast Cancer Conference: changes in the treatment of breast cancer.
Madrid June 11-13, 2003

American Society for Therapeutic Radiology and Oncology (ASTRO) 45th Annual Meeting, Salt Lake City, Utah, October 19-23, 2003

Emerging Trends in Adjuvant Therapy of Breast Cancer: 2003 Symposium in New York, October 24-26, 2003

Future of Breast Cancer Meeting, Bermuda Islands: July 22-25, 2004

San Raffaele University, Milan, Italy. Grand Rounds Invited Speaker, December 20, 2004

4th International Conference of ISIORT (International Society of Intraoperative Radiation Therapy) InterContinental Hotel Miami, Florida, March 17-19, 2005

Columbia University Grand Rounds Invited Speaker, March 3, 2005

UCLA University Grand Rounds Invited Speaker, May 23, 2005

THE NYU SCHOOL FOR PRONE PARTIAL BREAST IRRADIATION

Through the support of this IDEA grant the NYU team has influenced the current "paradigm shift" of breast radiotherapy. The technique developed at NYU was reported in the recent issue of Seminars in Radiation Oncology. Investigators from other academic institutions have visited us to learn the technique and because of the growing demand we have established.

CONCLUSIONS:

The current trial has shown to be feasible and well tolerated. The encountered acceptance rate is ?6% in the studied population and the accrual is close to the expected target (95/90). Preliminary dosimetric findings encourage us to continue especially in view of the excellent tolerability of this approach. No one patient recurred so far. The study will continue in Stage 2 until at most ?9 patients are entered.

Longer follow-up is required for efficacy, cosmesis and to assess the role of circulating TGF-β pre-treatment as a marker for post-treatment fibrosis.

The study continues as planned and approved.

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PPENDIX 1

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. Volunteer Registry Data Sheet (USAMRDC 60-R) with list of patients.

lide Show of Prone Partial Breast Irradiation School (attached to June 2005 Final Addendum eport submitted 6/29/05)

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CLINICAL INVESTIGATION — Breast

PRONE ACCELERATED PARTIAL BREAST IRRADIATION AFTER BREAST-CONSERVING SURGERY: PRELIMINARY CLINICAL RESULTS AND DOSE–VOLUME HISTOGRAM ANALYSIS

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Purpose: To report the clinical and dose–volume histogram results of the first 47 patients accrued to a protocol of accelerated partial breast irradiation. Patients were treated in the prone position with three-dimensional conformal radiotherapy after breast-conserving surgery.
Methods and Materials: Postmenopausal women with Stage T1N0 breast cancer were eligible only after they had first refused to undergo 6 weeks of standard radiotherapy. Planning CT in the prone position was performed on a dedicated table. The postoperative cavity was defined as the clinical target volume, with a 1.5-cm margin added to determine the planning target volume. A total dose of 30 Gy at 6 Gy/fraction was delivered in five fractions within 10 days.
Results: The median age of the patients was 67.5 years (range, 51–88 years). The median tumor diameter was 9 mm (range, 1.3–19 mm). In all patients, the prescribed dose encompassed the planning target volume. The mean volume of the ipsilateral breast receiving 100% of the prescription dose was 26% (range, 10–45%), and the mean volume contained within the 50% isodose surface was 47% (range, 23–75%). The lung and heart were spared by treating in the prone position. Acute toxicity was modest, limited mainly to Grade 1-2 erythema. With a median follow-up of 18 months, only Grade 1 late toxicity occurred, and no patient developed local recurrence.
Conclusion: These data suggest that this approach is well tolerated, with only mild acute side effects and sparing of the heart and lung.

Hypofractionation, Prone, Partial breast irradiation, Early-stage breast cancer.

INTRODUCTION

The widespread use of screening mammography during the past three decades has generated a new patient population, consisting of postmenopausal women with mammographically detected, nonpalpable, early-stage, invasive breast cancer. These tumors are often T1N0M0, Stage I, estrogen receptor-positive tumors, ideal for breast-conserving therapy (BCT) (1). A more user-friendly regimen than the standard 5–7 weeks of postoperative radiotherapy (RT) has recently become an area of intense research, because in certain patient populations, including the elderly and patients living remote from radiation facilities, BCT and/or postoperative RT appear to be underutilized (2–6). Because no patient subgroup has had a sufficiently low risk of in-breast recurrence to avoid whole breast RT routinely after segmental mastectomy (7), a shorter RT regimen could minimize inconvenience and improve the use of BCT.

The results of five prospective randomized trials testing breast-preserving surgery with or without adjuvant RT have suggested that most failures occur at the tumor bed, thus questioning the necessity for routinely irradiating the whole breast (7–11). The ipsilateral breast tissue outside the tumor bed appears to carry a risk of recurrence or new breast cancer development that is equivalent to that of the contralateral breast (0.5–1% annually), which is routinely not irradiated. Limiting RT to a smaller target than the whole breast has the potential to reduce radiation-induced morbidity. The main advantage of partial breast RT is the opportunity to increase the dose per fraction to accelerate treatment by limiting the volume of treated normal tissue.

Although several groups have focused on brachytherapy

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able 1. Study schema for Stage I breast cancer ostmenopausal, nonpalpable tumors, after segmental nastectomy

	nformed consent	Blood collection for GF-β
	T planning in prone osition, determination of umor bed and ipsilateral reast tissue	
avs 1–10	Conformal tumor bed adiotherapy 6 Gy × 5 ractions in 2 wk Days 1, 3, , 8, 10 (total dose, 30 Gy)	
av 10	Last day of treatment	Blood collection for GF-β

s the technique to deliver accelerated partial breast irradi- ion (APBI) (12–16), in the early 1990s we started inves- igating an external beam RT approach for partial breast reatment (17). Prone positioning of the patient rapidly merged as the best technique, because it minimizes move- nent of the target breast tissue during breathing and chieves maximal sparing of normal heart and lung tissue. A ilot trial was conducted at the University of Southern alifornia (USC)/Kenneth Norris Jr. Cancer Center to test he feasibility of a short course of hypofractionated confor- nal RT to the tumor bed in the prone position as part of a reast conservation protocol in postmenopausal patients vith nonpalpable Stage pT1N0 breast cancer. A radiosur- gery-like technique of multiple noncoplanar fields was ested, and 10 patients were randomly assigned to five ractions of 5, 5.5, or 6 Gy, on the basis of radiobiologic inear-quadratic modeling. These doses were chosen in view f their radiobiologic equivalence to 50 Gy in 25 fractions vhen an α/β value of 4 is used for the prediction of tumor ontrol (18–20). Local control and cosmetic results were xcellent at a minimal follow-up of 36 months (21).

n 2000, funded by an IDEA grant from the Department f Defense, a Phase I-II trial was initiated in the Department f Radiation Oncology at New York University to deter- nine the feasibility and efficacy of prone, partial breast onformal RT to the tumor bed in postmenopausal women vith T1N0M0 breast cancer who had undergone segmental mastectomy and had refused standard postoperative whole breast RT.

METHODS AND MATERIALS

On the basis of the data originated from the initial pilot study (21), a regimen of 30 Gy delivered in five fractions within 10 days was chosen for this study. In addition, because the biologically effective dose (BED) (18) calculations predicted fibrosis as the dose-limiting toxicity, the study included blood collection for measurement of transforming growth factor-β1 levels in pretreatment plasma, as a marker for the development of post-RT fibrosis (Table 1) 22).

Justification of radiobiologic dose and fractionation

The linear-quadratic model and the BED equation, $BED = (nd)(1+d/\alpha/\beta)$, derived from this model (18, 23), were used to calculate the appropriate total dose and fraction size for the hypofractionated protocol. In this formula, n is the number of fractions and d is the dose/fraction. This equation was used to calculate the BEDs for early and late responses and tumor control for the hypofractionated schedule (five fractions of 6 Gy delivered within 10 days) and two standard schedules (25 fractions of 2 Gy within 5 weeks, considered the standard treatment without a boost [24] and 30 fractions of 2 Gy within 6 weeks—46 Gy to the entire index breast plus a boost of 14 Gy to the tumor cavity, considered the standard treatment with a boost). These calculations assumed that full repair takes place during the ≥24-h interval between fractions. Table 2 lists the BEDs for tumor control, in addition to the early responses, erythema and desquamation, and late responses, telangiectasia and fibrosis. The BEDs for the normal tissue acute responses were generally lower for the hypofractionated schedule than for the standard treatment regimens, indicating the risk of radiation-induced complications should be lower in the hypofractionated schedule (Table 2).

For tumor control, if we used an α/β value of 10 Gy, the typical value for many tumors (25, 26), in this calculation, the BED computed for the hypofractionated schedule would be substantially lower than that for the standard treatments.

able 2. Biologically effective doses

	α/β (Gy)	Standard (60 Gy/30 Fx)	Standard (50 Gy/25 Fx)	Hypofractionated (30 Gy/5 Fx)
rythema	8	75 Gy_8	63 Gy_8	53 Gy_8
esquamation	11	71 Gy_{11}	59 Gy_{11}	46 Gy_{11}
elangiectasia	4	90 Gy_4	75 Gy_4	75 Gy_4
ibrosis	2	120 Gy_2	100 Gy_2	120 Gy_2
umor	4	90 Gy_4	75 Gy_4	75 Gy_4
umor*	4	86 Gy_4	72 Gy_4	75 Gy_4
umor	10	72 Gy_{10}	60 Gy_{10}	48 Gy_{10}
umor*	10	68 Gy_{10}	57 Gy_{10}	48 Gy_{10}

* Taking into account cell proliferation during course of treatment.

However, if the α/β value is set at 4 Gy, as suggested by experiments involving irradiation of human breast cancer cell lines (18–20), the BED calculated and, therefore, the likelihood of tumor control associated with the hypofractionated schedule, would be identical to that of the standard treatment without a boost. In addition, because the hypofractionated regimen also represents an accelerated protocol in which the total dose is delivered in only 10 days, less tumor proliferation is expected to take place compared with that occurring during the standard treatment. By taking these factors into account, the difference between the BEDs for the two schedules is reduced (Table 2).

Study population

Study eligibility was limited to postmenopausal women with newly diagnosed, nonpalpable, mammographically detected, invasive breast cancer. Menopause was defined as at least 2 years without menstrual periods. In patients who had undergone prior hysterectomy, follicle-stimulating hormone levels were measured for confirmation of postmenopausal status. Only those with pT1, pN0 or sentinel node negative, or N0 clinically if the tumor was <1 cm in size, were eligible. In addition, patients were required to have undergone segmental mastectomy or reexcision with negative surgical margins (at least 5 mm) and to have estrogen and/or progesterone receptor-positive tumors. Antihormonal therapy (tamoxifen or anastrozole) was prescribed in all cases.

The exclusion criteria were previous RT to the ipsilateral breast, extensive intraductal component in the pathologic specimen, a diagnosis of multifocal breast cancer, or the inability to provide informed consent as assessed by the Principal Investigator. All eligible women who were referred to the Radiation Oncology Department at the New York University School of Medicine for RT after breast-conserving surgery for breast cancer were first offered standard conventional 6-week RT. Only women who declined standard RT were given the opportunity to participate in the current protocol by providing informed consent. The New York University institutional review board and the institutional review board of the Department of Defense reviewed and approved all aspects of the study.

Toxicity was assessed every week during treatment. Patients were followed monthly with physical examination for the first 90 days, every 3 months for the first year, every 6 months for the next 4 years, and yearly thereafter to evaluate their status with respect to recurrence, long-term toxicity, and cosmesis. Toxicity was evaluated at each visit according to the Radiation Therapy Oncology Group toxicity scoring criteria. Cosmesis was recorded by the patient at baseline (before RT started) and then every 6 months.

Simulation and treatment planning

Patients were placed in the prone position on a dedicated treatment table for CT planning and treatment (Figs. 1–3). The table has an aperture to allow the breast to fall by gravity away from the chest wall (17). Patient positioning on the table was established by two lateral lasers and one overhead laser. Noncontrast CT images were acquired at 3.75-mm-thick intervals from the level of the mandible to below the diaphragm using a GE Light speed helical CT scanner. CT images were transferred to a Varian Eclipse treatment planning system (Varian Cadplan, Varian Medical Systems, Palo Alto, CA). The surgical cavity, identified at CT as the area of architectural distortion in the breast tissue, defined the clinical target volume (CTV) (Fig. 4). When necessary, information obtained from the surgical report, mammography findings, and other available imaging test results were also incorporated. Although not intentionally included by the CTV, the surgical incision was outlined by a wire placed over the incision before CT scanning.

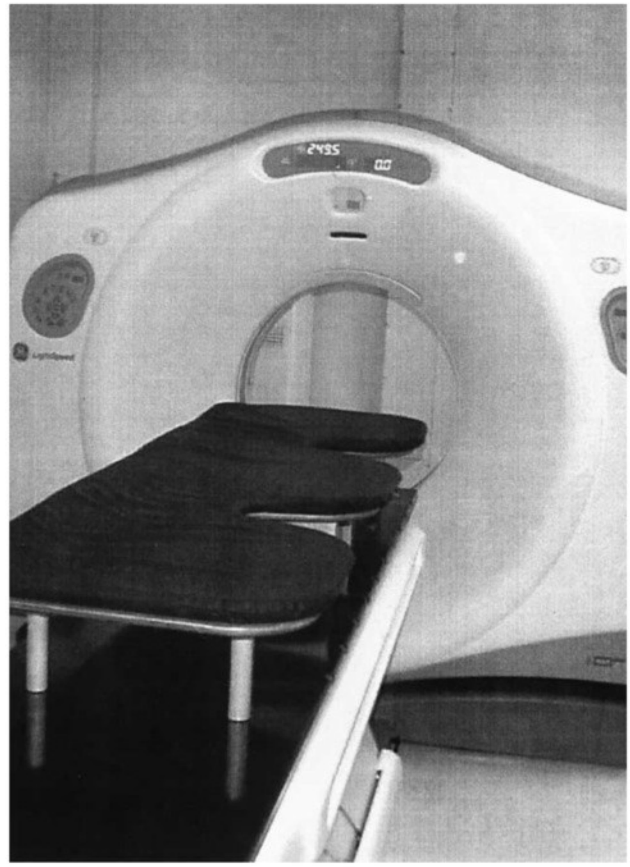
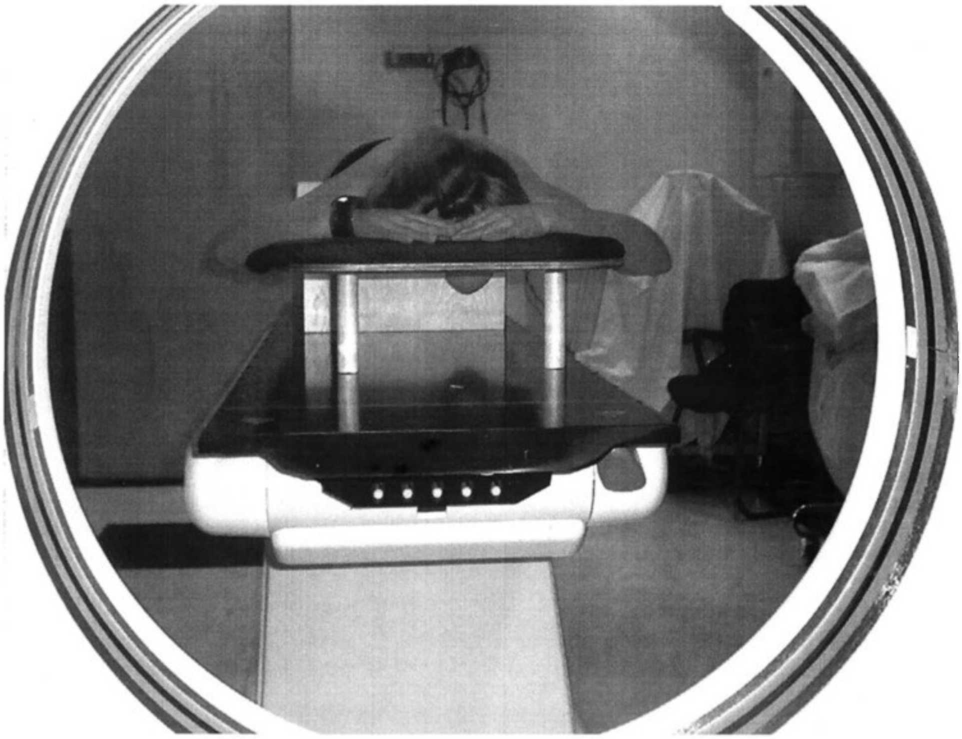


Fig. 1. Computed tomography simulator and prone breast table.

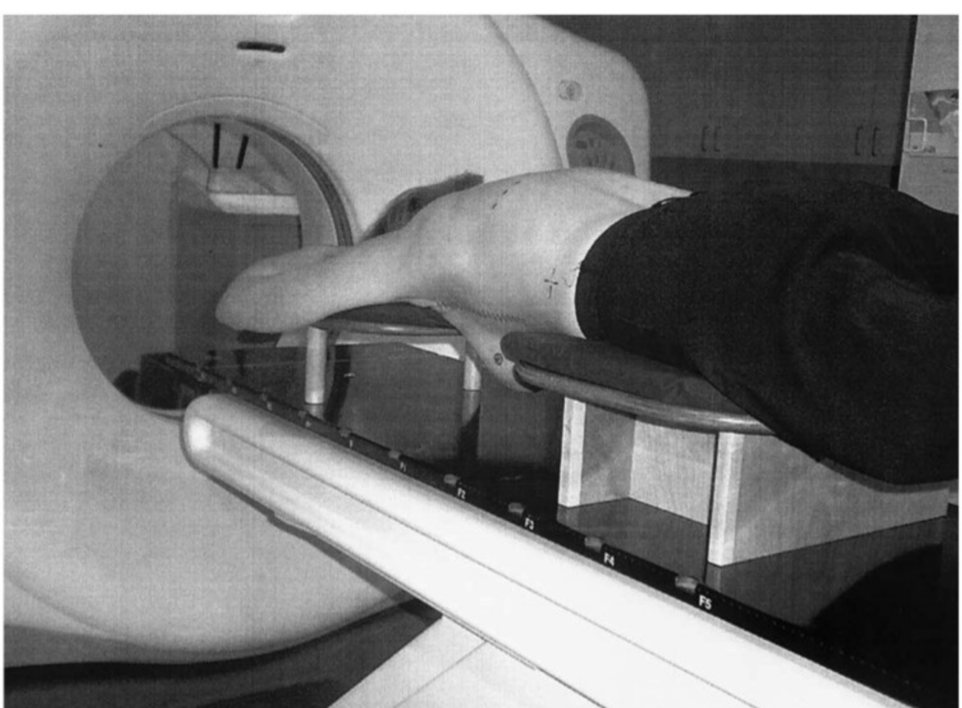
Adding a 1.5–2-cm margin to the CTV created the planning target volume (PTV). After uniform expansion, the PTV was limited anteriorly by the skin and posteriorly by the chest wall. An additional 7-mm margin was added to the PTV to the field edge to account for beam penumbra, for a total margin of 2.2–2.7 cm. The ipsilateral lung and heart were outlined. The normal ipsilateral breast tissue volume was defined by applying radiopaque wires in the supine position at the site of the medial, lateral, inferior, and superior borders of the classic opposite tangent breast fields to define the volume that would have been treated by classic whole breast tangents in the supine position.



'ig. 2. Positioning and setup. Patient is positioned prone on a dedicated table that allows the target breast tissue to fall 'reelv through the opening.

)ose–volume constraint guidelines

'reatment planning was performed using the CT-defined 'olumes, most often through an opposed pair of mini-angents. When required to increase dose distribution homogeneity, wedges were used. The isocenter was located approximately 5–7 cm from the midline along an axis passing through the center of the PTV. The dose was normalized to 100% at the isocenter before choosing an



'ig. 3. Patient undergoing computed tomography acquisition of images.

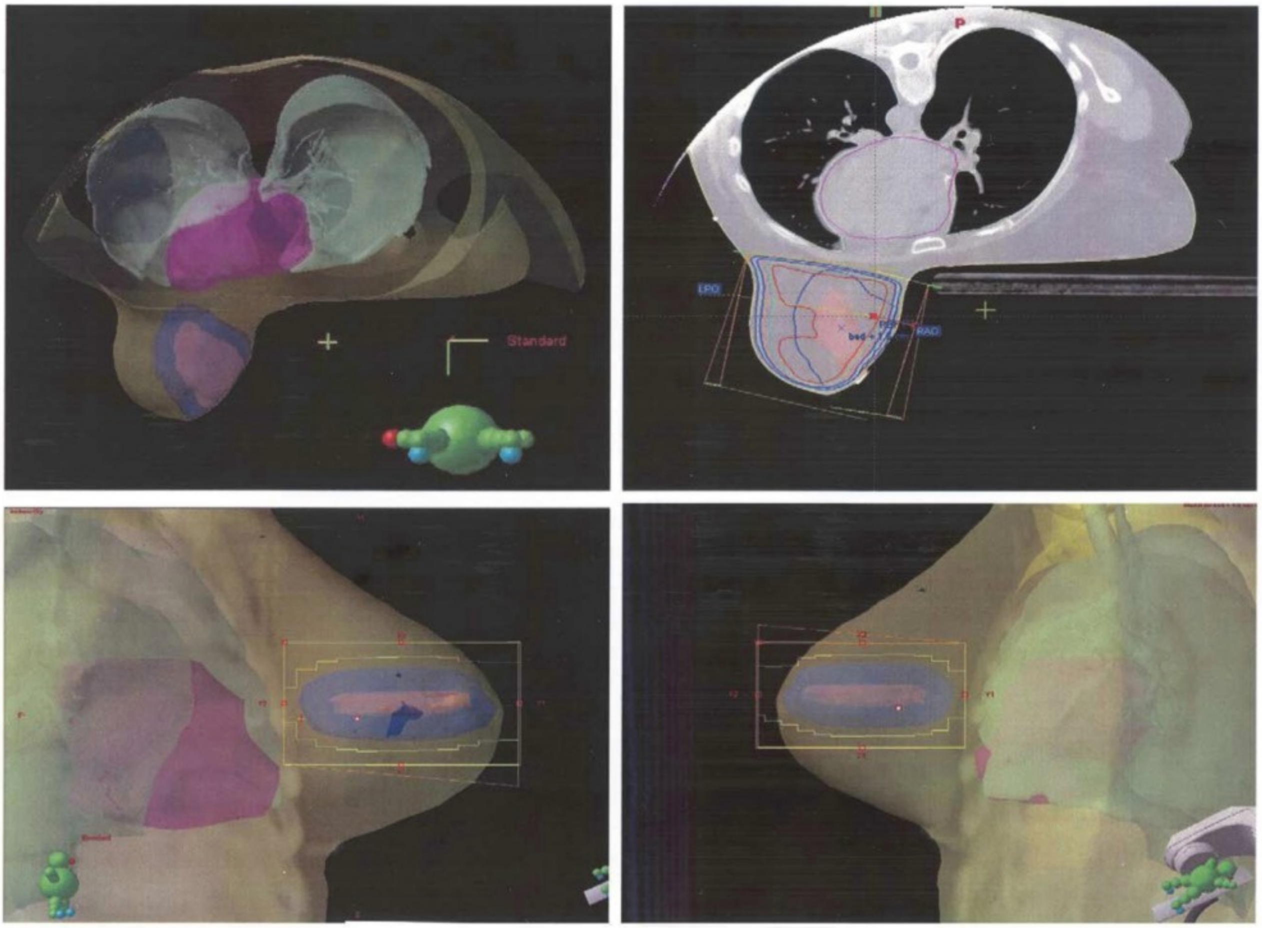


Fig. 4. (Upper) Example of relationship of tumor bed to planning target volume (PTV) demonstrated; tumor bed in red wash. PTV in blue, heart in pink, and lung in light green. PTV represents a 1.5-cm margin on tumor bed. (Lower) Digital reconstructed radiographs, right anterior oblique and left posterior oblique portals for left-sided breast cancer.

isodose surface that encompassed the PTV, typically 95%. Dose inhomogeneity was maintained at <110%.

Additional normal tissue dose guidelines included limiting 50% of the ipsilateral breast volume to <50% of the prescribed dose. In addition, the volume of heart and lung included in the treatment fields was expected to be <10%. Field arrangements were designed to avoid the contralateral breast and ipsilateral lung and heart tissue completely (Fig. 4). The dose fractionation schedule was 30 Gy delivered in five fractions of 6 Gy to the 95% isodose surface, given within 10 days (Monday, Wednesday, Friday, Monday, Wednesday).

Target positioning verification

Treatment room lasers were used to verify consistent positioning of the patient on the table. Daily setup reproducibility was ensured by leveling marks on the torso and triangulation marks placed on the back, ipsilateral side, and breast tissue (Fig. 5). The setup was designed to identify a plane orthogonal to the table that also crossed the tumor cavity. Before each fraction, portal films of each field verified treatment positioning. Accepted variance was limited to 5 mm from the isocenter position indicated on the digitally reconstructed radiographs (Fig. 6).

Statistical analysis

An optimal two-stage Simon design was used for this Phase II trial (27). It is based on testing the null hypothesis that the 3-year local recurrence rate is ≥9% vs. the alternative that the 3-year local recurrence rate is ≤3% (α 0.05; power of 0.80). The study was designed to enroll 31 patients in the first stage and up to 99 patients during the entire trial. If two or fewer local recurrences developed in the first 31 patients who completed at least 1 year of follow-up, accrual would continue up to completion of the second stage. If five or more local recurrences were observed at any point, the trial would be stopped. The trial will be terminated when at most 99 patients have been entered and followed for at least 1 year. Any ipsilateral breast local recurrence, whether a true local recurrence (within the radiation field) or breast local recurrence outside the field, was the main study endpoint (including both isolated recurrence and concomitant with distant disease).

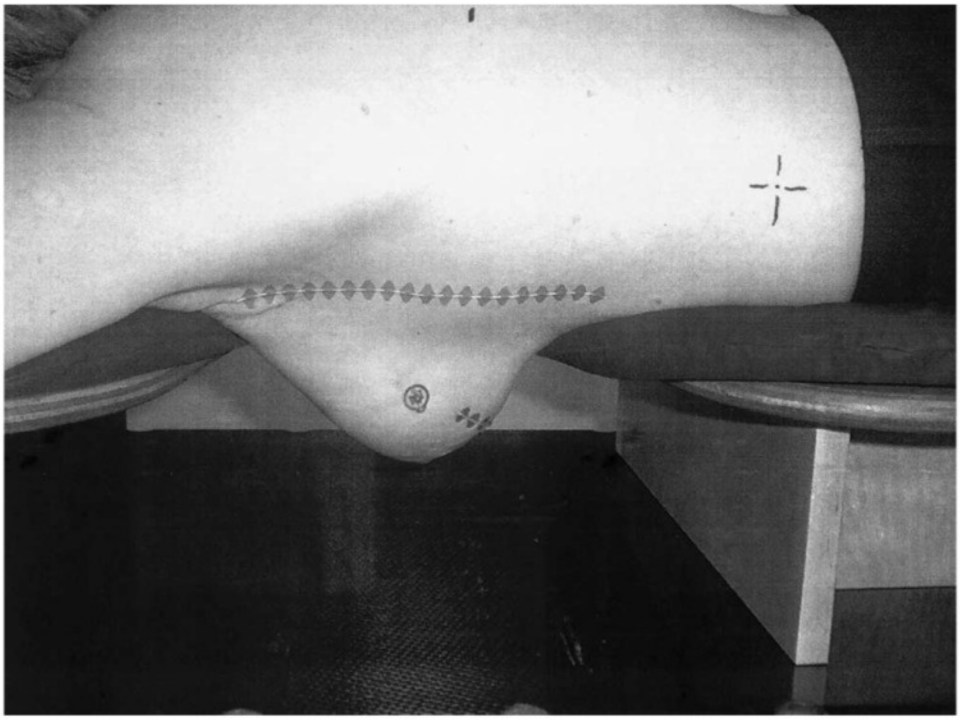


Fig. 5. Target position verification by triangulation marks placed carefully on back, ipsilateral side, and breast.

RESULTS

Clinical results

Between June 2000 and December 2003, 50 patients were enrolled in the study. A summary of the baseline patient and tumor characteristics is provided in Tables 3 and 4, respectively, and includes the mean, median, quartiles, and range for continuous variables and frequency distributions for categorical variables. Of the 50 screened patients, 47 entered the treatment phase and 46 completed treatment. Three patients were lost to follow-up before initiating any treatment, and 1 patient discontinued treatment after two fractions for personal reasons. She reported no acute toxicities.

The median length of follow-up was 18 months (range, 0.3–40.3 months). Of the 46 patients, 30 were followed for 1 year since the start of treatment without any local recurrences, and the study continues to accrue patients. The follow-up distribution is shown in Table 5.

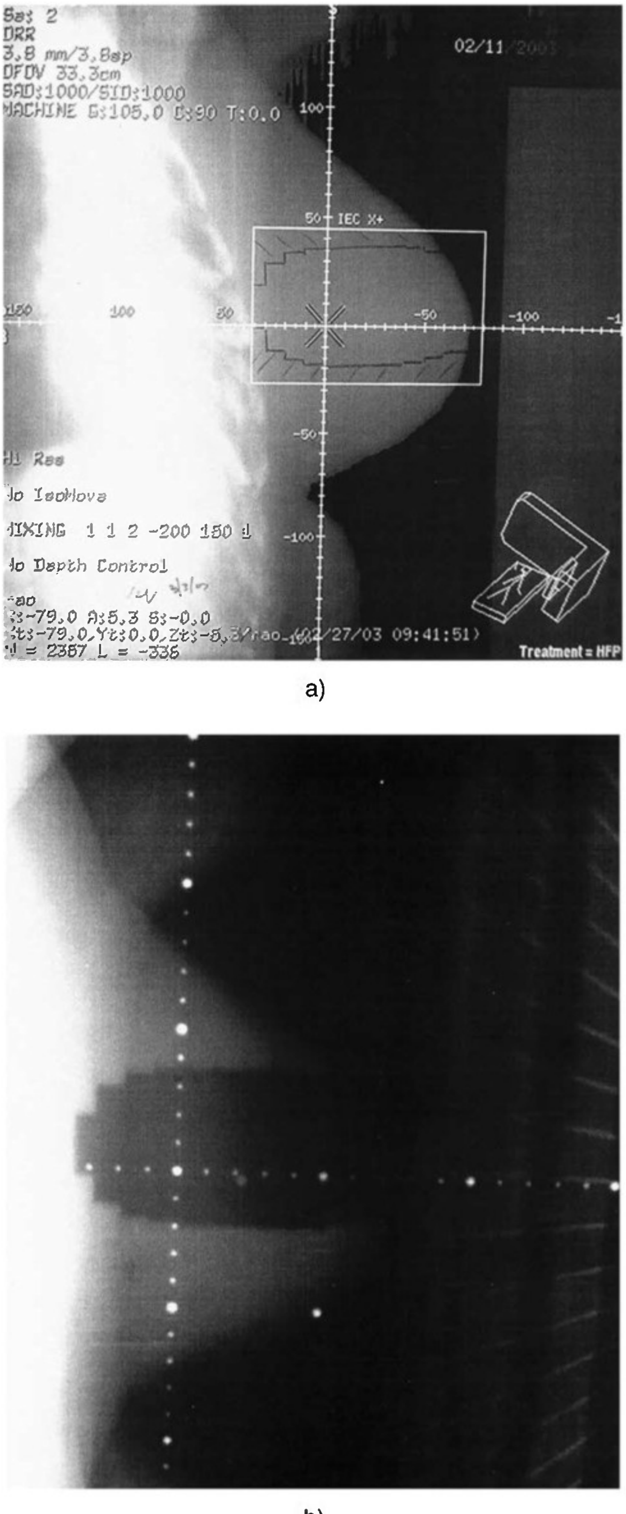
The most common acute toxicity noted was Grade 1-2 erythema, observed in 28 patients (60% of patients treated; Table 6). A preliminary assessment of late toxicity has indicated that these were primarily Grade 1 (Table 6). A total of 21 late toxicities have occurred in 14 patients. Eight patients had Grade 1 induration before RT, related to the surgery. Cosmetic results were rated as "good/excellent" in 7 patients with 6–12 months of follow-up, 3 patients with 12.1–18 months of follow-up, 5 patients with 18.1–24 months of follow-up, 12 patients with >2 years of follow-up, and 5 patients with >3 years of follow-up. In 2 patients, the cosmetic results were rated as "fair" at 12 and 18 months of follow-up. The remaining patients have had <6 months of follow-up. In none of the patients was the post-RT score worse than at the baseline postoperative assessment.

At last follow-up, no patient had developed local recurrence. One patient developed metastatic squamous cell carcinoma of the lung with mediastinal, paraspinal, and osseous metastases 2 months after RT completion. No evidence of malignancy could be found at review of the chest X-ray obtained before undergoing segmental mastectomy. Her condition rapidly deteriorated because of metastatic lung cancer and she died 3 months after completion of the protocol treatment.

Physics results

Of the 47 patients, 43 were treated in the prone position. Four patients were treated in the supine position (as accepted protocol deviations by the principal investigator). Of the 4 patients, 2 could not tolerate prone positioning because of a preexisting physical disability (hemiparesis due to a previous stroke in 1 and multiple sclerosis in another 1). The third patient could not be treated in the prone position without treating the arm and contralateral breast because of severe kyphosis, secondary to osteoporosis. In the fourth patient, the tumor bed was located lateral and superior in tail of Spence, and it was better treated in the supine position.

The predominant technique for treatment was a pair of parallel-opposed mini-tangents. This arrangement provided a simplified treatment setup and ensured good coverage, given the constraints imposed by the PTV and its relationship to the table (Fig. 4).



a)

b)

Fig. 6. (a) Right anterior oblique digital reconstructed radiograph. (b) Right anterior oblique port film.

Dosimetric findings

The dosimetric results are summarized in Tables 7 and 8. The mean and median size of the surgical cavity (CTV) at CT acquisition was 52 cm^3 and 34 cm^3 (range, 7–379 cm^3), respectively. The mean and median volume of the PTV was 228 cm^3 and 192 cm^3 (range, 57–1118 cm^3), respectively. The mean and median volume of the ipsilateral breast were 1102 cm^3 and 1006 cm^3, respectively (range, 258–3468 cm^3). The mean and median coverage of the PTV by the 30 Gy isodose surface were both 100%.

Dose–volume histograms of the ipsilateral breast volume (Fig. 7), lung and heart were generated. The mean and

Table 3. Baseline patient characteristics (n = 47)

	Patients (n)
Race	
Black	1 (2.1)
Hispanic	2 (4.3)
White	44 (93.6)
Performance status at screening	
)	19 (40.4)
	24 (51.1)
	1 (2.1)
Unknown	3 (6.4)
Breast side	
Left	27 (57.5)
Right	20 (42.6)
Hormonal replacement therapy	
Current	4 (8.5)
Past	15 (31.9)
None	27 (57.5)
Unknown	1 (2.1)
Tumor estrogen receptor status	
Negative	1 (2.1)
Positive	46 (97.9)
Tumor progesterone receptor status	
Negative	13 (27.7)
Positive	34 (72.3)
Tumor Her2-neu status by IHC	
)	31 (65.9)
	7 (14.9)
+	4 (8.5)
++	3 (6.4)
Unknown	2 (4.3)

Data in parentheses are percentages.

Table 5. Follow-up distribution from start of treatment to last observation

Follow-up (mo)	Patients (n)
0–6	11 (23.4)
6–12	6 (12.8)
12–18	7 (14.8)
18–24	4 (8.5)
24–30	5 (10.6)
30–36	6 (12.8)
36–42	8 (17.1)
Total	47 (100.0)

Data in parentheses are percentages.

Table 6. Acute and late toxicity

Toxicity	Worst grade	Toxicities (n)
Acute (n = 28/47)		
Breast swelling	1	1 (2.7)
Desquamation	1	2 (5.4)
Erythema	1	21 (56.7)
	2	5 (13.5)
Late (n = 14/47)		
Erythema	1	2 (9.5)
Fibrosis	1	2 (9.5)
Hyperpigmentation	1	3 (14.4)
Induration	1	8 (38.1)
Telangiectasia	1	5 (23.8)
Other	1	1 (4.8)

Data in parentheses are percentages.

median volume of the ipsilateral breast receiving 100% of the prescription dose was 26% and 27% (range, 10–45%), respectively. The mean and median volume receiving 50% of the prescription dose was 47% and 46% (range, 23–75%), respectively. We found heterogeneity in the dose–volume histogram based on the position of the original tumor bed and the size of the breast. In 25% of patients (12 of 47), to successfully treat the PTV, >50% of the ipsilateral breast volume received >50% of the prescription dose.

Dose to heart and lung

The mean percentage of lung volume receiving 20, 10, and 5 Gy was 0% (range, 0–4%, 0–6%, and 0–10% respectively) for all. The mean percentage of heart volume receiving 20, 10, and 5 Gy was also 0% (Table 8). These doses were less than what has been reported using partial breast irradiation in the supine position (28). Prone positioning allowed sparing of these critical structures by allowing the breast tissue to fall away from the chest wall and minimizing breast movement secondary to the respiratory excursion that commonly occurs in the supine position. In the 4 patients treated supine in this study, the median dose to the lung receiving 20, 10, and 5 Gy was 2%, 4%, and 6%, respectively.

DISCUSSION

The current study represents the largest reported experience of three-dimensional conformal external beam RT for APBI as part of BCT. With the limitation of a short median follow-up of only 18 months, these results support the safety and feasibility of the regimen.

Several differences characterize this approach compared

Table 4. Baseline tumor characteristics (n = 47)

Variable	Mean	O3	Median	Q1	Range
Age (y)	68	77	68	61	52–88
Tumor size (mm)	9.6	13.0	9.0	7.0	1.3–19
Follow-up (mo)	19.0	32.5	16.7	6.2	0.3–40.3

Abbreviations: O3 = third quartile; Q1 = first quartile.

Table 7. Dosimetric findings: CTV, PTV, and IBV

Dosimetric characteristics	Mean value	Median value	Range
IBV (cm^3)	1102	1006	258–3468
CTV (cm^3)	52	34	7–379
PTV (cm^3)	228	192	57–1118
Maximal dose (% of PD)	110	108	105–117
PTV coverage by 95% isodose surface (%)	100	100	—
Ipsilateral breast coverage (% IBV encompassed by % of PD)			
100% of PD	26	27	10–45
75% of PD	41	40	20–68
50% of PD	47	46	23–75
25% of PD	53	53	27–82
CTV/IBV (%)	5	4	1–22
PTV/IBV (%)	22	20	10–55
CTV/PTV (%)	20	20	6–46

Abbreviations: CTV = clinical target volume (tumor bed); PTV = planning target volume; IBV = ipsilateral breast volume; PD = prescribed dose.

Table 8. Dosimetric findings of normal tissue: heart and lung

Dosimetric characteristics	Mean (%)	Median (%)	Range (%)
Ipsilateral lung			
V 20 Gy	0	0	0–4
V 10 Gy	1	0	0–6
V 5 Gy	2	0	0–10
Heart			
V 5 Gy	0	0	0

Abbreviation: V = percentage of volume receiving specified dose.

Values rounded to nearest whole number.

with those reported by other groups studying partial breast RT with an external beam technique. First, the patients in this study received treatment in the prone position (21). The advantages of a prone technique are manifold. Prone positioning considerably reduces the breast tissue motion secondary to both cardiac systole and respiration (29), limiting the excursion of the chest wall to <5 mm (17). With the triangulation technique we developed for positioning, the breast tissue remains a predictably fixed target. In addition, prone positioning allows for exclusion of lung and heart tissue from the treatment fields (30). This is particularly relevant in view of the growing evidence of the late morbidities these organs derive from breast irradiation in the supine position (31–35). Moreover, in women with pendulous and/or large breasts, treatment in the prone position allows the breast tissue to fall away from the chest wall preventing skin desquamation along the inframammary fold, a common occurrence when treated supine. Finally, based on BED modeling, instead of the approach (twice daily during 5 days) used by the investigators at Beaumont Hospital (28, 36), the treatment described consisted of five fractions within 10 days, a schedule that was easy to adhere to, even for elderly patients.

Compared with partial breast RT using brachytherapy, the advantages of prone external beam APBI consist of its noninvasive nature, the simplicity of the field arrangements and ease of patient setup. Potentially, any RT facility equipped with CT planning and a linear accelerator could adopt this approach.

However, many challenges remain associated with this area of breast cancer radiation research. For example, the exact identification of the target remains to be defined. Placement of clips has been suggested to facilitate the radiographic identification of the cavity; however, signifi-

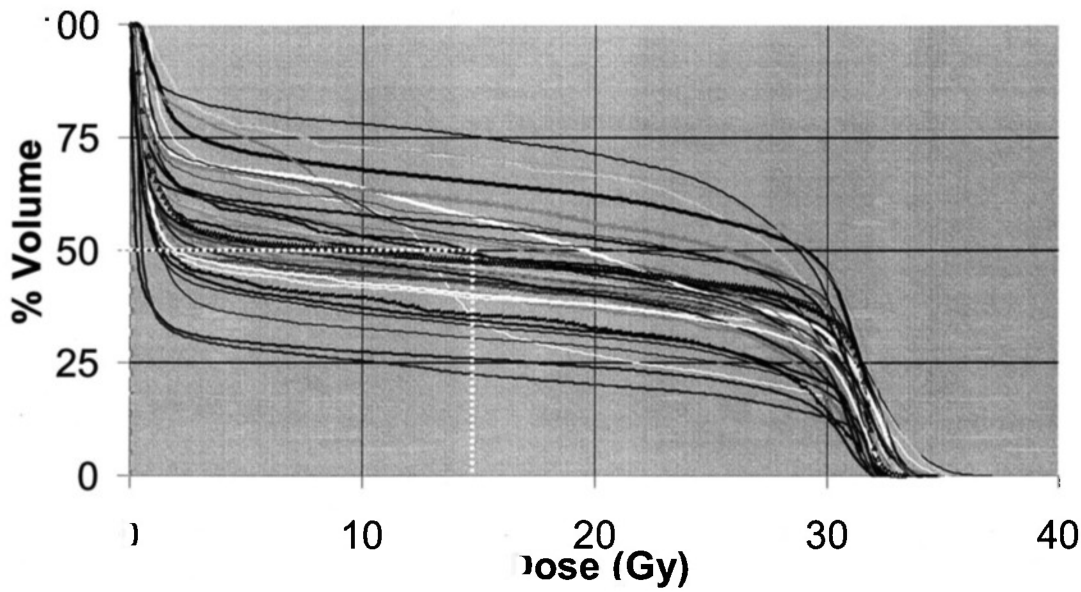


Fig. 7. Dose–volume histogram of ipsilateral breast of 47 patients.

ant clip migration has been reported, particularly after reast biopsy procedures, making reliance on the technique uestionable (37). In the current series of patients, the cavity vas identified by CT planning. Owing to our selection riteria, none of the patients had undergone chemotherapy, naking it possible to plan and start RT close to the time of urgery, when the postexcision cavity could more easily be dentified (Fig. 4). Although we found no correlation with he interval between surgery and the date of CT acquisition of the CTV, it could be possible that with increasing time ifter surgery, the accuracy of CTV definition by CT might liminish. In the future, if APBI is revealed to be equivalent o standard RT, the argument of delivering it before sysemic treatment could be made, in view of its brief course and the optimal visualization of the tumor bed soon after urgery.

he best dose/fractionation regimen for APBI also renains to be determined, in terms of both ensuring optimal umor control and cosmetic outcome. With regard to the atter, even if it is not predicted by the BED modeling, ypofractionated regimens may carry some risk of late effects, such as breast fibrosis and telangiectasia. Currently, no predictive markers are routinely available to determine vhich patients will develop radiation-induced late toxicity. n a study by Li *et al.* (22), a statistically significant correation between the pretreatment plasma levels of transforming growth factor-β1 (a multifunctional cytokine implicated n tissue fibrosis) was found in patients treated with BCT vho developed severe post-RT fibrosis. The regimen used onsisted of 40 Gy in 15 fractions to the whole breast. Other tudies have revealed that specific polymorphisms of the ransforming growth factor-β1 promoter gene might be issociated with the development of severe fibrosis. Quarmby *et al.* (38) reported that patients with the −509TT or +869CC genotypes were 7–15 times more likely to levelop severe fibrosis. Future genetic studies might enable he identification of a panel of polymorphic sites associated vith fibrosis that could make it possible to prospectively letect "fibrosis-prone" individuals. In the current study, pretreatment blood samples are prospectively collected to est this hypothesis.

 more serious concern is the risk of underdosing the umor bed. In an associated paper, we have discussed in lepth the results obtained by radiobiologic modeling of nost currently used partial breast irradiation protocols. All egimens currently used result in inferior BED values for umor effects compared with those achieved by 60 Gy in 30 ractions during 6 weeks. For the current regimen, the dose hosen was derived by matching the same BED values (75 Gy_2) for tumor control of a standard regimen of 50 Gy in 25 ractions. When the protocol was originally designed, controversy existed regarding the value of adding a boost after 0 Gy to the whole breast, the regimen used in the RT arm of National Surgical Adjuvant Breast and Bowel Project linical trial B-06. For instance, in a contemporary publicaion, Hayman *et al.* (39) had addressed the cost-effectiveness of an electron boost and, based on the evidence available at that time, concluded that its ratio in quality-adjusted life years was "well above the commonly cited threshold for cost-effective care." However, in view of the evidence subsequently generated by the European Organization for Research and Treatment of Cancer trial of a dose–response relation at the tumor bed, the currently used experimental regimen could be inadequate to ensure optimal local control in a nonselected cohort of women treated by BCT (40). Whether the hypofractionated regimen (30 Gy in 5 fractions within 10 days) will be revealed as adequate in ensuring tumor control in the carefully selected population studied in this trial warrants long-term follow-up.

The issue of optimal patients selection also remains unanswered: does a specific subset of women exist for whom partial breast RT is equivalent to whole breast RT? Controversy exists with regard to eligibility for partial breast RT studies. Contrary to the results of Vicini *et al.* (41), who reported a promising 1% local recurrence rate at a median follow-up of 65 months after partial breast brachytherapy, a recent report from another group had a 60-month actuarial rate of ipsilateral recurrence of 16.2% (42). Also, four of the six in-breast recurrences occurred outside the lumpectomy site, even though each of the women with recurrence had originally had a mammographically detected T1 primary (42). We deliberately focused our study on the rapidly growing subset of breast cancer patients, postmenopausal women with mammographically detected tumors, a population in which 96% of the detected breast cancers are T1 lesions (43, 44). Long-term results from the current study will provide important preliminary results on whether a more user-friendly, cost-effective regimen can be safely offered to this population of patients with generally indolent breast cancers.

Finally, characteristic of the current study is that eligible patients also need to have refused to undergo the standard 6-week RT regimen to be offered the current protocol. This approach reflects our bias regarding the ethics of studying a potentially "lesser" treatment in a setting in which the standard therapy has resulted in exceptionally high success rates. Thus, two other important measures of caution were taken. First, eligibility is limited to postmenopausal women with a very low risk of ipsilateral in-breast recurrence, including the requirement for estrogen receptor positivity and antiestrogen treatment and, second, a Stage 2 Simon statistical design with early stopping rules, based on a 5% actuarial recurrence rate at 5 years, was chosen to minimize the risk to the patients who have elected to participate in the protocol.

In view of these results and of the many potential advantages, including increasing compliance to RT, thereby increasing the rate of breast preservation treatment, reducing adjacent normal tissue morbidity, and reducing the cost of postoperative RT (5 vs. 30 treatments), we are continuing the planned accrual of 99 patients to this trial.

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CLINICAL INVESTIGATION **Breast**

BIOLOGIC COMPARISON OF PARTIAL BREAST IRRADIATION PROTOCOLS

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Purpose: To analyze the dose/fractionation schedules currently used in ongoing clinical trials of partial breast irradiation (PBI) by comparing their biologically effective dose (BED) values to those of three standard whole breast protocols commonly used after segmental mastectomy in the treatment of breast cancer.
Methods and Materials: The BED equation derived from the linear-quadratic model for radiation-induced cell killing was used to calculate the BEDs for three commonly used whole breast radiotherapy regimens, in addition to a variety of external beam radiotherapy, as well as high-dose-rate and low-dose-rate brachytherapy, PBI protocols.
Results: The BED values of most PBI protocols resulted in tumor control BEDs roughly equivalent to a 50-Gy standard treatment, but consistently lower than the BEDs for regimens in which the tumor bed receives a total dose of either 60 Gy or 66 Gy. The BED values calculated for the acute radiation responses of erythema and desquamation were nearly all lower for the PBI schedules, and the late-response BEDs for most PBI regimens were in a similar range to the BEDs for the standard treatments.
Conclusion: Biologically effective dose modeling raises the concern that inadequate doses might be delivered by PBI to ensure optimal in-field tumor control.

Biologically effective dose, Breast cancer, Partial breast irradiation.

INTRODUCTION

The possibility of completing the course of postsegmental mastectomy radiotherapy (RT) in a smaller number of treatments within a shorter period is very appealing to breast cancer patients. If a shorter regimen proves equivalent to standard treatment, it could represent important progress in terms of cost-effectiveness for RT. Furthermore, the implementation of a breast cancer radiation protocol that is less cumbersome may help to address the logistical problems faced by many patients, particularly the elderly or those who live distant from a RT facility. These difficulties cause many patients who are candidates for breast conserving therapy either to select mastectomy or, worse, to simply forgo the RT portion of breast conserving therapy (1–3).

One method to accomplish this aim was attempted in the 1970s in several countries, where breast cancer patients received postmastectomy RT to the chest wall and draining nodes involving the use of larger-than-standard (1.8–2 Gy) fraction sizes or hypofractionation. For example, in one series, postmastectomy breast cancer patients were given 12 fractions to either a maximal absorbed dose of 51.4 Gy or a minimal target dose of 36.6 Gy specified at the level of the mid-axilla (4, 5). Many of the patients treated with these hypofractionated protocols subsequently developed chronic radiation injury, primarily fibrosis (4, 5). This discouraging experience rendered radiation oncologists hesitant to reexplore the use of large-dose fractions in the treatment of breast cancer.

It was only with the recent recognition of the common topographic pattern of local recurrence after segmental mastectomy that it became reasonable to question whether it is always necessary to irradiate the entire breast (6–10). The results from five prospective randomized trials are available to understand this issue better (6–9, 11). For instance, in the National Surgical Adjuvant Breast Project (NSABP)-06 study, all recurrences were reported to be within, or close to, the quadrant of the original tumor (10, 11). In the study by Liljegren*et al.* (9), a significantly greater rate of local recurrence was found in the arm receiving segmental mastectomy alone compared with the arm receiving segmental mastectomy and postoperative RT (18.4% vs. 2.3%). Again, 77% of the recurrences in the surgery-alone arm occurred within the initial tumor bed (9). A similar geographic pattern of local recurrence was recorded in the three other studies (6, 7). When the local recurrence data were classi-

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ied as "within" vs. "outside" the original tumor bed, the risk of recurrence outside the original tumor bed appeared to be equivalent (or inferior) to the risk of new primary cancers in the contralateral breast, which conventionally is not irradiated. The incidence of contralateral breast cancer for these studies was within the expected range of 0.5–1% annually. These data support the rationale for treating the original tumor bed as the area that could most benefit from the addition of adjuvant RT, omitting the remaining breast tissue in the ipsilateral and contralateral breast.

Limiting adjuvant RT to a volume inclusive of the tumor with sufficient margins among selected patients enabled the exploration of hypofractionated regimens (12–14). A number of protocols have since been developed with the intent of treating the original tumor bed with margins. This approach is based on the rationale that if much of the breast receives a dose below a clinically relevant threshold, it may be possible to treat a small volume with larger fraction sizes and maintain a low risk of late effects. Thus, through treatment of a smaller volume, it may be possible to avoid the classic dilemma encountered when a hypofractionated protocol is substituted for a standard treatment plan, which is the choice of either a reduced probability of tumor control or an increased risk of late complications (4, 5). Hypofractionated, partial breast irradiation (PBI) is actively being investigated by the use of several distinct techniques. Evidence is rapidly accumulating on the feasibility of performing PBI, as well as the need for careful patient selection and appropriate techniques to encompass the target volume adequately (15).

Although many PBI protocols are currently being used, relatively few data have been reported to justify the chosen schedules by predicting the biologic effects associated with the use of large-dose fractions delivered within a short period. Because it is possible to compare the anticipated biologic effects in terms of tumor control and normal tissue reactions by estimating a "biologic dose" through appropriate computations of biologically effective dose (BED) values, we report such calculations to compare the different PBI regimens with three commonly used protocols for whole breast RT.

METHODS AND MATERIALS

Breast RT protocols used in analysis

Standard fractionation studies. The fractionation regimen used for the RT component of breast conservation treatment has varied. The NSABP trials of breast preservation (16, 17), as well as the standard arm of the recent randomized Canadian trial studying whole breast hypofractionation (18), used 50 Gy in 25 fractions within 5 weeks (Standard$_{50}$). An alternative standard regimen is 46 Gy to the whole breast followed by an electron boost of 14 Gy to the tumor bed (Standard$_{60}$), a commonly used approach in the United States (19, 20).

In addition, the European Organization for Research and Treatment of Cancer has assessed the role of a boost to the tumor excision site (21–23). In this trial, the entire breast was irradiated with 50 Gy in 25 fractions followed by either no additional treatment or 16 Gy in 8 fractions (electron therapy or implantation) to a total dose of 66 Gy (Standard$_{66}$). At 5 years of follow-up, the use of the boost significantly reduced the local failure rate to 4.3% for patients randomized to receive the boost compared with 7.3% for those given whole breast treatment. These results suggest that irradiating the tumor bed with 66 Gy further reduces the local recurrence rate in breast conserving therapy. The main benefit was derived by patients <40 years, who demonstrated a 46% reduction in the rate of local recurrence at 5 years with the RT boost.

PBI studies. A variety of PBI protocols have been developed with the intent of treating the original tumor bed with margins; these are summarized in Tables 1, 2, and 3. PBI is based on the rationale that if much of the breast receives a very limited dose, it may be possible to treat with larger fraction sizes and maintain a low risk of late effects. A variety of treatment approaches have been used, including interstitial brachytherapy, MammoSite balloon brachytherapy, and external beam RT (EBRT) using three-dimensional conformal RT, intensity-modulated RT, or intraoperative electron beam RT (IORT). The design, treatment, and results of a series of brachytherapy PBI trials using both high-dose-rate and low-dose-rate brachytherapy included in the BED analysis are described in Table 1. With the exclusion of the Guy's Hospital study, which accepted patients with large tumors and positive margins, these series showed good local control rates of 0–16%, even if often reported with <5 years of follow-up. The European Institute of Oncology at the University of Milan, Italy has investigated IORT. They delivered electron beams of 3, 5, 7, or 9 MeV. Patients either received an IORT dose of 10–15 Gy after initial quadrantectomy with 1–2-cm clear margins, as an anticipated boost to EBRT, or an IORT dose of 17–21 Gy to the cavity as the only treatment (24).

An EBRT approach to PBI was first used at Christie Hospital. They compared EBRT PBI with whole breast RT for patients with tumors <4 cm in size. This study demonstrated a greater incidence of recurrence among infiltrating lobular histologic type tumors, 34% for PBI vs. 8% for whole breast RT (25), possibly reflecting the different natural biologic course between the two histologic types. Two different approaches of EBRT PBI have been reported from William Beaumont Hospital and New York University. The EBRT series are summarized in Table 2. Formenti *et al.* (26) pilot tested a Phase I feasibility study of hypofractionated conformal EBRT to the tumor bed (30 Gy in five fractions within 10 days) in a small series of selected postmenopausal women with T1 breast cancer, using immobilization in the prone position on a dedicated breast board (27). A Phase I-II study is currently ongoing at New York University. All patients completed treatment with only mild acute toxicity (28). Baglan *et al.* (29) also piloted an accelerated PBI protocol in patients with early-stage breast cancer. Three-dimensional conformal RT was used to treat 'able 1. Accelerated partial breast irradiation brachytherapy (HDR and LDR) and IORT studies

;eries	'atients (*n*)	Age (y)	Tumor size (cm)	N stage	EIC	Margin status	Dose fractionation	Median follow-up (mo)	CTV margin (cm)	-y Ipsilateral recurrence rate (%)
iuy's Hospital Trial 14, 71)	27	<70	<4	N0	Positive	Positive	HDR 55 Gy/5 d	72	2	37
)chsner Clinic (72)	50	All	Tis and 4	N1	Positive	Negative	LDR 45 Gy/4 d IDR 4 Gy × 8	75	2–3	2
Villiam Beaumont Iospital (13, 15, 73)	199	>40	<3	N0	Negative	Negative	LDR 50 Gy/4 d IDR 4 Gy × 3. 3.4 Gy × 0	65	1–2	1
,ondon Regional :ancer Centre, Canada (74, 75)	39	All	<5	N0	Positive	Positive	HDR 3.72 Gy in 10 Fx b.i.d.	91	0	16.2
RTOG 95-17 (12)	100	All	<3	N1	Excluded	Negative	HDR 3.4 Gy × 0 b.i.d. ,DR 45 Gy/4 d	32	2	—
/irginia Commonwealth Jniversity (76)	44	All	<4	N1	Excluded	Negative	LDR 45 Gy/4 d IDR 3.4 Gy × 0 b.i.d.	42	1–2	0
Mammosite Multicenter 'rial (77, 78)	43	>45	<2	N0	Excluded	Negative	HDR 3.4 Gy × 10 b.i.d.	21	>1	—
National Institute of)ncology, Hungary 79)	Phase I-II, 45 'hase II. 63	All	<2	N0	Excluded	Negative	Ph I-II, HDR 4.33 Gy × 7, 5.2 Gy × 7; Phase III. HDR 5.2 Gy × 7	Phase I-II, 57 Phase III, 30	1–2	Phase I-II, 4.4 Phase III, 0
:uropean Institute of)ncology (24)	101	All	<2.5	—	Excluded	Negative	IORT electron beam therapy 0–21 Gy	8	0	—

ıbbreviations: HDR = high dose rate; LDR = low dose rate; IORT = intraoperative radiotherapy; EIC = extensive intraductal component; CTV = clinical target volume; b.i.d. = twice ıaily.

Table 2. [illegible] studies

Series	Patients (n)	Age (y)	Tumor size (cm)	N stage	EIC	Dose fractionation	Median follow-up (mo)	Technique	Field arrangement	Tumor bed definition (CTV)	Margin (cm)	Ipsilateral breast recurrence rate (%)
Christie Hospital (25, 80)	353	<70	<4	N0	—	5 Gy × 8 in 10 d	96	Supine, 10-MeV electrons	Single electron beam	Tumor bed at surgery	0	6 (21/355)
NYU (26, 28)	47	Postmenopausal	<2	N0	Negative	6 Gy × 5 in 10 d	17	Prone, 6-MV photons	2 coplanar minitangents	Architectural distortion on CT	1.5–2	0
WBH (30, 31)	31	50	<3	N0	Negative	3.4 Gy × 10 in 5 d or 3.85 Gy × 10 in 5 d	10	Supine, 6-, 18-MV photons	3–5 noncoplanar beams	Architectural distortion and surgical clips on CT	1–1.5	—

Abbreviations: EBRT = external beam radiotherapy; NYU = New York University; WBH = William Beaumont Hospital; other abbreviations as in Table 1.

the lumpectomy cavity, plus a 1.5-cm margin. Their technique used an active breathing control method to account for breast movement related to respiratory excursion. More recently, Chen *et al.* (30) and Vicini *et al.* (31) published an update of their PBI experience using three-dimensional conformal RT. A dosimetric comparison of the William Beaumont and New York University EBRT PBI techniques is shown in Table 3.

Calculation of BEDs

The linear-quadratic model (32) was used to determine whether a partial breast RT protocol should result in a roughly equal probability of tumor control compared with a standard schedule, but without increasing the potential for normal tissue damage. The BED equation used for these calculations was

$$\mathrm{BED} = \mathrm{nd}\left(1 + \frac{\mathrm{d}}{\alpha/\beta}\right)$$

where n is the number of fractions, d is the dose per fraction, and α/β is a tissue- and effect-specific parameter associated with the linear-quadratic model (33–35).

A modification to this BED equation was also used to take into account the cellular proliferation that may take place during treatment:

$$\mathrm{BED} = \mathrm{nd}\left[1 + \frac{\mathrm{d}}{\alpha/\beta}\right] - \left[\frac{(\ln 2)\mathrm{T}}{\alpha(\mathrm{Tpot})}\right]$$

where T_{pot} is the potential doubling time and T is the treatment time during which cellular proliferation occurs after any initial lag period (33, 36–38).

Because an interfraction interval of at least 6 h was used for all the twice-daily high-dose-rate and EBRT treatments, it was likely that full repair of sublethal damage between fractions was permitted. It was, therefore, not necessary to include an incomplete repair factor in the equation used to calculate BEDs for these protocols.

The equation used to calculate the BEDs for the low-dose-rate treatments was

$$\mathrm{BED} = \mathrm{RT}\left\{1 + \left[\frac{2\mathrm{R}}{\mu(\alpha/\beta)}\right]\left[1 - \frac{1 - e^{-\mu T}}{\mu \mathrm{T}}\right]\right\}$$

where R is the dose rate, T is the length of the irradiation, and μ is the repair rate constant, which was equal to $ln2/t_{1/2}$, with $t_{1/2}$ the tissue repair half-time (39, 40).

RESULTS

BED values

Biologically effective dose calculations were performed for the three chosen standard whole breast EBRT protocols and 12 different hypofractionated PBI regimens delivered by EBRT,

Table 3. Dosimetric comparison of EBRT partial breast techniques

Series	PTV (cm^3)	PTV/TBV* (%)	Ipsilateral breast coverage 100%	75%	50%	25%	Lung dose† (%)	Cardiac dose‡ (%)
NYU (26)								
Median	192	22	27	40	46	53	0	0
Range	57–118	10–55	10–45	20–68	23–75	27–82	0	0
WBH (30, 31)								
Median	240	17	21	35	46	60	16	0‡
Range	82–482	11–22	14–39	26–53	34–60	39–92	0–37	0–7

Abbreviations as in Tables 1 and 2.
* Planning target volume/total breast volume.
† Percentage of lung volume that received 5 Gy.
‡ Percentage of cardiac volume that received 5 Gy (NYU) or 10 Gy (WBH).

high-dose-rate, and low-dose-rate techniques. The BEDs computed are listed in Tables 4 and 5 and shown in Fig. 1.

The selection of the α/β value used for these calculations was based on those reported in previous studies for the late effects of fibrosis and telangiectasia, in addition to the acute radiation reactions of erythema and desquamation: these values were 2, 4, 8, and 11 Gy, respectively (37, 41, 42). The tumor control BED values were determined using an α/β value of either 4 Gy, which has been suggested for breast carcinoma (43–46), or 10 Gy, which is the approximate value used for most tumors (46, 47). In addition, the BEDs were calculated for the low-dose-rate treatments assuming repair half times of 0.5, 1, 2, or 3 h. The repair kinetics for the tissues associated with acute and late responses, as well as breast carcinoma cells, are likely to fall within this range (48). As for the specific repair half-time appropriate for each effect, evidence has been obtained that sublethal damage repair

Table 4. EBRT and HDR brachytherapy BED values*

Institution (reference)	Protocol schedule	Fibrosis (α/β = 2 Gy)	Tumor control/ Telangiectasia (α/β = 4 Gy)	Erythema (α/β = 8 Gy)	Tumor control (α/β = 10 Gy)	Desquamation (α/β = 11 Gy)
$Standard_{50}$ (16–18)	2 Gy × 25	100	75	63	60	59
$Standard_{60}$ (19, 20)	2 Gy × 30	120	90	75	72	71
$Standard_{66}$ (21–23)	2 Gy × 33	132	99	83	79	78
London Regional Cancer Center (74, 75)	3.72 Gy × 10	106	72	54	51	50
Ochsner Clinic (72), William Beaumont Hospital (13, [illegible]5)	4 Gy × 8	96	64	48	45	44
National Institute of Oncology, Budapest, Hungary (79)	5.2 Gy × 7 4.33 Gy × 7	131 96	84 63	60 47	55 43	54 42
William Beaumont Hospital (31)	3.85 Gy × 10	113	76	57	53	52
Christie Hospital (25, 80)	5 Gy × 8	140	90	65	60	58
New York University (26, [illegible]8)	6 Gy × 5	120	75	53	48	46
RTOG 95-17 (12), Mammosite Multicenter Trial (77), Virginia Commonwealth University (76), William Beaumont Hospital (15)	3.4 Gy × 10	92	63	48	46	45
European Institute of Oncology (24, 81)	21 Gy × 1†	241	131	76	65	61

Abbreviations: BED = biologically effective dose; $Standard_{50}$ = whole breast to 50 Gy in 25 fractions; $Standard_{60}$ = whole breast to 46 Gy in 23 fractions plus 14 Gy in 7 fractions to tumor bed (total 60 Gy); $Standard_{66}$ = whole breast to 50 Gy in 25 fractions plus 16 Gy in 8 fractions to tumor bed (total, 66 Gy); RTOG = Radiation Therapy Oncology Group; other abbreviations as in Tables 1 and 2.
* BED values given in Gray.
† The formula used to calculate BED may not yield an accurate value for a single fraction treatment.

Table 5. LDR brachytherapy BED values

Series	Repair half-time (h)	Fibrosis (α/β = 2 Gy)	Tumor control/ telangiectasia (α/β = 4 Gy)	Erythema (α/β = 8 Gy)	Tumor control (α/β = 10 Gy)	Desquamation (α/β = 11 Gy)
Ochsner Clinic (72) 45 Gy in 4 d						
	0.5	60	53	49	48	48
	[illegible]	76	60	53	51	51
	[illegible]	104	75	60	57	56
	[illegible]	133	89	67	63	61
Guy's Hospital (14, [illegible]1) 55 Gy in 5 d						
	0.5	73	64	60	59	58
	[illegible]	91	73	64	62	62
	[illegible]	127	91	73	69	68
	[illegible]	161	108	81	76	74
WBH (13) 50 Gy in 4 d						
	0.5	69	59	55	54	53
	[illegible]	87	68	59	57	57
	[illegible]	123	86	68	65	63
	[illegible]	157	103	77	71	69

Abbreviations: BED = biologically effective dose; other abbreviations as in Table 2.

rates are often slower for late-responding normal tissues compared with either early-responding normal tissues or tumors (48, 49), although in some instances, this generalization may not be correct (50–52).

BED calculations taking into account tumor repopulation

It should be noted that all the PBI treatments were accelerated schedules, because the total dose was delivered in less time than with the standard whole breast protocols. Therefore, relatively little cellular proliferation is likely to occur during the course of these treatments compared with the standard protocols, in which it is probable that more extensive repopulation will take place, thereby both decreasing the chances for tumor control and reducing the severity of acute radiation responses. The lack of tumor repopulation represents a potential advantage to the use of an accelerated partial breast protocol compared with a standard treatment, and the BEDs were also calculated assuming cell repopulation during treatment. To accomplish this, it was necessary to select values for α, the initial slope of the cell survival curve, as well as for T_{pot} and T. For the purpose of these calculations, values of 0.3 for α (43, 44), 13 days for T_{pot} (53, 54), and a time lag of 14 days were used. However, it must be stressed that the actual values for any given patient may differ significantly. This correction for cell proliferation causes the tumor and acute response standard treatment BED values to decrease by approximately 3–5 Gy. No change would be expected in the fibrosis or telangiectasia BEDs, because compensatory proliferation would not be expected to begin until after treatment was complete. In addition, no correction was made to any of the PBI schedules, because all these treatments are accomplished within a period that is shorter than the lag period even in the tumor and acutely responding normal tissues. Taking possible tumor growth during treatment into consideration results in a closer alignment of BED values between the PBI and standard schedules. If cell proliferation is considered, this also diminishes the BEDs of the early responses for the standard schedules compared with the accelerated PBI schedules. However, it would still be anticipated, based on the computed BEDs and only a portion of the breast being irradiated, that the severity of the early responses would remain lower for the PBI treatments compared with the standard protocols.

DISCUSSION

The current work compared BED values at the tumor bed/boost area for the PBI regimens vs. those from standard whole breast RT protocols. The tumor control BED values computed for the PBI protocols were uniformly lower than the BEDs for any of the standard schedules when these calculations were performed using an α/β of 10 Gy, considered typical of most tumors (46, 47). In contrast to this generalization, evidence exists from *in vitro* studies that breast carcinoma cell lines display an α/β value of about 4 Gy (43–46). Use of this α/β, with correction for cellular proliferation, yielded BED values for the PBI treatments that were generally comparable to the BED obtained for $Standard_{50}$. However, when compared with either $Standard_{60}$, a fractionation regimen commonly used in the United States, or $Standard_{66}$, the BED values were nearly all lower for the PBI treatments. This is of significance because of available evidence

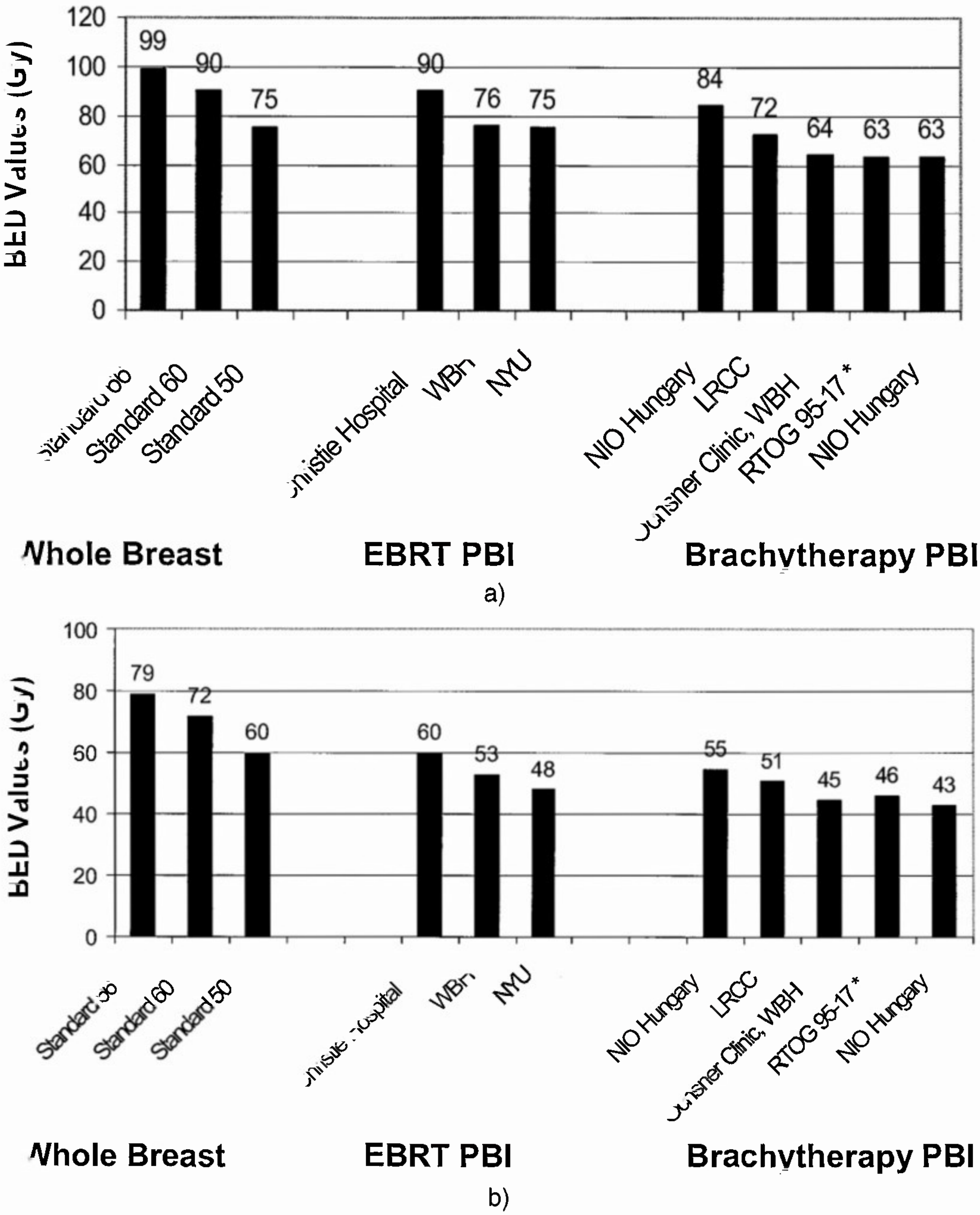
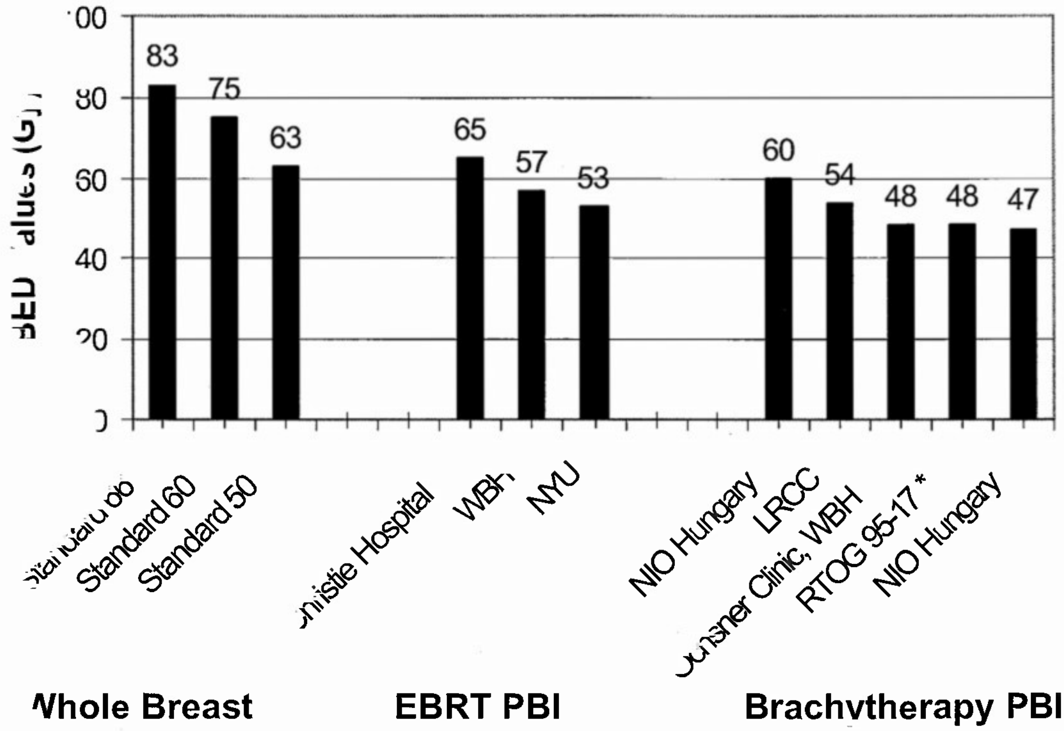


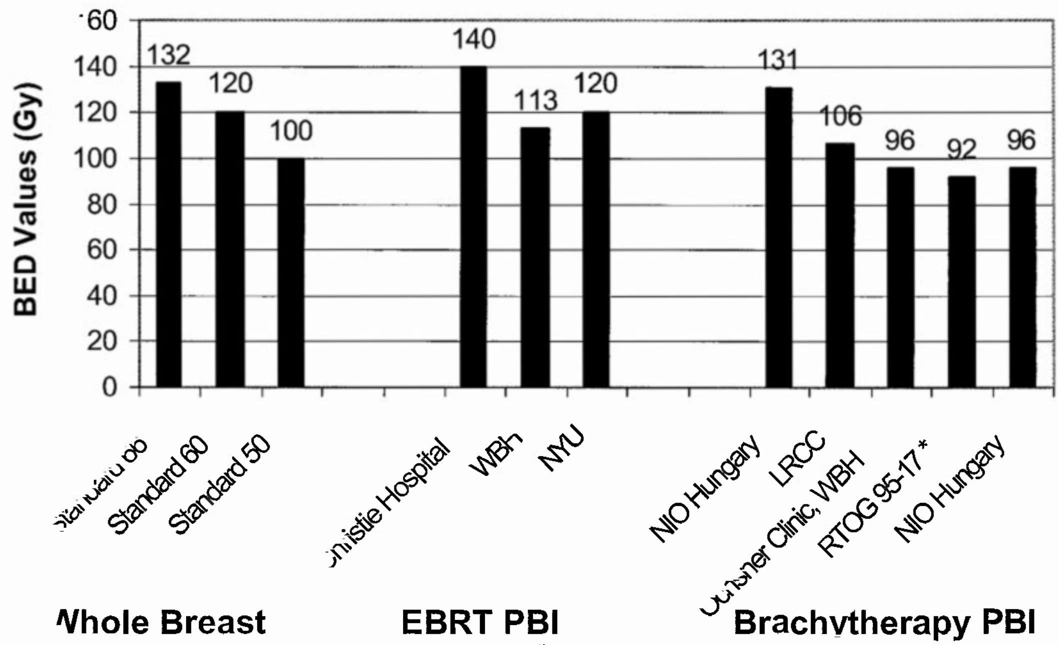
Fig. 1. Histograms demonstrating biologically effective dose (BED) values for partial breast irradiation (PBI), external beam radiotherapy (EBRT), and brachytherapy protocols compared with standard whole breast protocols for tumor control, acute effects, and late effects. BED values for PBI protocols for tumor control with (a) α/β of 4 Gy and (b) α/β of 10. BEDs for PBI protocols for (c) acute effects (erythema, α/β of 8 Gy) and (d) late effects (fibrosis, $\alpha/\beta = 2$ Gy). *Same fractionation used in Mammosite Multicenter Trial, Virginia Commonwealth University and William Beaumont Hospital.

showing a dose–response effect at the boost site, as demonstrated by the finding that the Standard$_{66}$ treatment resulted in a decreased incidence of tumor recurrence compared with the Standard$_{50}$ (22).

It is important to note, however, that a basic assumption often made in the use of BED values to predict a particular level of tumor control or normal tissue damage is that the probability of tumor control or the development of a normal tissue radiation effect is linearly proportional to the BED. This may be correct for certain doses, but it is not true across an entire dose range (55). That is, the tumor control probability may already be sufficiently high, so that it is in a "plateau" region where relatively little benefit would be expected with increasing dose. Similarly, the normal tissue effect curve may be at a level below a threshold for a particular radiation response so that increasing the BED would still have no impact, as long as the threshold were not exceeded.



c)



d)

'ig. 1 (*Continued*).

Iowever, the evidence from the European Organization 'or Research and Treatment of Cancer boost trial (22) suggests that the doses tested by the PBI trials were less than this theoretical plateau.

Also, the use of relatively large doses per fraction in PBI protocols presents specific radiobiologic concerns because of a possible reduction in reoxygenation and reassortment (56). This is particularly relevant to the case of IORT in which only one fraction is delivered at a high dose rate. It is well known that because solid tumors often outgrow their neovasculature, viable cells may be present that exist in a relatively low oxygen concentration (57, 58). This radioresistance of hypoxic tumor cells is usually overcome through the delivery of a treatment dose in a series of fractions during a period of weeks, enabling hypoxic cells to reoxygenate and regain a normal level of radiosensitivity (59, 60).

Another concern regarding the use of a single fraction is the inability of cells to reassort through the cell cycle. Cells in more radioresistant phases of the cell cycle, such as the S phase, tend to exhibit a greater level of survival compared with cells in more radiosensitive phases, such as G_2 or mitosis (61).

In a standard fractionation protocol, the surviving cells continue progression in the cell cycle so that at the next RT session, the cells may be located in a more radiosensitive phase and, therefore, be killed. Normally, this sensitization associated with fractionation is beneficial, because tumor cells are generally more actively progressing through the cell cycle compared with cells that comprise late-responding tissues.

A more generalized problem affecting all PBI techniques is that a significant volume of normal breast tissue receives a relatively low, but potentially carcinogenic, radiation dose, thereby possibly increasing the probability of secondary malignancies (62). Although the available data suggest that the cancer risk remains elevated across a large dose range (63), it may also be possible that the relatively high doses associated with whole breast RT carry a low risk of inducing a new tumor, because a dose of 40–50 Gy may primarily cause cellular lethality rather than neoplastic transformation. In contrast, for all of the PBI techniques, a substantial portion of the breast receives a comparatively low noncytocidal dose. Potentially, PBI should be limited to an older population of women who would have a lower risk of developing secondary malignancies.

Because the therapeutic ratio for postsegmental mastectomy is a balance between local control and an acceptable risk of late effects, even after successful modeling of tumor/normal tissue effects, the central issue of optimal patient selection remains unsolved. Ideally, only those patients who carry a risk of recurrence/new primary in the breast tissue outside the target of PBI that is expected to be roughly equal to that of the contralateral, conventionally nonirradiated breast, should be offered this alternative treatment approach. The available data suggest that these women are likely to be postmenopausal carriers of hormonally sensitive, mammographically detected breast cancers. Noticeably, these women are also likely to undergo systemic antihormonal treatment to reduce their bilateral breast cancer risk. Because of the high cure rate these women are likely to enjoy after standard treatment, it is very important to study PBI rigorously, especially in regard to its risk of long-term sequelae and second malignancies (17).

For most of the published brachytherapy protocols with long follow-up, the total breast dose–volume histogram data have not been reported. Therefore, in the absence of this information, it is not possible to compute BED values that take into account partial breast volumes (64, 65). It is hoped that future publications will contain this information so that it will be possible to compute integrated BEDs (66) for regions outside of the target volume representing normal breast tissue.

In addition, the follow-up for both the brachytherapy and EBRT techniques is too short for adequate assessment of long-term toxicity and fibrosis. As demonstrated in a series from the M. D. Anderson Cancer Center, the length of time to the expression of 90% of the ultimate frequency of fibrosis and telangiectasia was 4.7 years (95% confidence interval, 4.0–4.8) (4). For all the PBI regimens, careful follow-up and analysis of patients for late effects will help ascertain whether increased late effects will be seen in patients treated with hypofractionated protocols.

As a final note, increasing interest has focused on the role that genetic factors may play in radiosensitivity. Evidence is mounting that genetic alterations present in certain genes associated with radiation responses, such as *ATM* (67, 68), *TGF-β* (69), *SOD, XRCC1,* and *XRCC3* (70), may play an important role rendering some patients radiosensitive. If true, it is possible that the patients with these genetic alterations may represent essentially a radiosensitive subpopulation, possibly comprising 5–10% of women who develop breast cancer. These women may be the most likely candidates to develop radiation responses such as fibrosis, telangiectasia, or chronic skin changes after RT completion. If it were feasible to identify these patients prospectively before the start of RT, they could be spared the risk of late radiation effects that may be associated with PBI treatment. Although this is not currently practical, with the advances being made in DNA sequencing, the time may not be far off when many breast cancer patients will arrive at their initial consultation with a radiation oncologist, armed with the DNA sequence of their entire genome. With this information, and the knowledge as to the important genetic alterations associated with radiosensitivity, the radiation oncologist may then be able to tailor the RT so that it is appropriate for each patient and thus to increase the probability of tumor control and diminish the risk of normal tissue late effects.

CONCLUSION

The PBI protocols that have been developed, and are currently being tested in clinical trials, yield BED values that are generally comparable to the Standard$_{50}$ schedule, corrected for tumor repopulation during treatment. However, the PBI BEDs are consistently lower than the BEDs for either the Standard$_{60}$ or Standard$_{66}$. Therefore, it may be anticipated that the tumor control rates, at least in the field receiving the full treatment dose, may be lower for the PBI regimens compared with standard whole breast RT using an additional boost dose to the tumor bed. Finding the balance between adequate imaging and irradiation of the target and limiting the breast volume receiving the full treatment dose to avoid an increased probability of late radiation sequelae, together with correct selection of patients at low risk of recurrences outside the target volume, underlie the successful outcome of PBI trials. An additional concern associated with the use of PBI is the unknown risk of second malignancies in the remaining breast tissue, outside the PBI volume. For all these reasons, and because equivalence to standard protocols for both efficacy and morbidity has yet to be proved, PBI protocols remain investigational.

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xternal-Beam Partial-Breast Irradiation

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lthough most studies treating patients with partial-breast irradiation have used brachyherapy, giving such treatment with external-beam techniques has many potential advanages. However, there is only limited published experience using this approach. These nclude a randomized trial of partial-breast and whole-breast irradiation performed at the hristie Hospital in Manchester, England, and pilot studies (using much more rigorous election criteria and sophisticated treatment planning) from groups at the University of outhern California, New York University (using prone positioning of patients), and the Villiam Beaumont Hospital (using the supine position). A multi-institutional pilot trial based n the latter technique has been completed, which was designed to test the feasibility of sing this approach in the cooperative oncology group setting. The unprecedented rapidity vith which the study completed its target accrual indicates the degree of interest in this pproach. This review focuses on the rationale and the reported studies of external-beam artial-breast radiation and identifies some specific issues and remaining problems assoiated with this approach.

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Although most studies treating patients with partial-breast irradiation (PBI) have used brachytherapy, in theory an xternal-beam approach to PBI (EB-PBI) has many potential dvantages. First, it easily allows treatment to be given after umpectomy when complete pathological information about he original tumor and the status of the resection margins are vailable. without subjecting the patient to a second invasive urgical procedure or anesthesia. Second, it is likely that EB-BI will be easier for radiation oncologists and cooperative ncology groups to adopt than brachytherapy approaches ecause the technical demands and quality assurance issues re much simpler. Third, treatment results with EB-PBI may e more uniform between radiation oncologists because the utcome depends less on the experience and operative skills f the person performing the procedure than does brachyherapy (especially using interstitial implantation). Fourth, it eems less likely that technical issues arising during EB-PBI will require the procedure to be aborted, as is not infrequently the case when brachytherapy techniques are used. Fifth, EB-PBI is intrinsically likely to generate better dose homogeneity and thus possibly may result in a better cosmetic outcome when compared with brachytherapy. Finally, EB-PBI may be considerably cheaper than brachytherapy techniques, especially if an extra surgical procedure and (for low-dose rate brachytherapy) hospitalization are needed.[1,2]

Despite these theoretical advantages, there has been very little study of EB-PBI. This may be because of the difficulty of adequately locating the excision cavity and planning multifield photon treatment plans in the era before computed tomography (CT)-based simulation. At present, there are only a few published experiences using EB-PBI. These include a randomized trial comparing partial-breast and whole-breast irradiation performed in England[3,45] and pilot studies (using much more rigorous selection criteria and sophisticated treatment planning) from groups at the University of Southern California and New York University[6-8] (using prone positioning of patients) and the William Beaumont Hospital (using the supine position).[9,10] A multi-institutional pilot trial based on the latter technique was recently conducted by the Radiation Therapy Oncology Group (RTOG 0319) under the direction of Dr Frank Vicini to test the feasibility of using this approach in the cooperative oncology group setting, and the study rapidly completed its target accrual.

This review therefore focuses on the techniques and reported outcome of reported studies of EB-PBI. I will also

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dentifv some specific issues and problems associated with his approach.

\ Phase III Trial of External-Beam Partial-Breast Irradiation (EB-PBI)

)nlv 1 prospective randomized trial has been performed to ompare the efficacy of EB-PBI to whole-breast radiotherapy. 'his trial was conducted at the Christie Hospital, Manches-er. United Kingdom.[3-5] Seven hundred eight patients with umors 4 cm or smaller of infiltrating ductal or lobular his-ology were randomized after segmental mastectomy to un-lergo radiation to a small breast field, including the tumor ed (the limited field [LF] arm) or to the whole breast and egional nodes (the wide field [WF] arm). The 2 arms differed n field size. treatment modality, and dose fractionation. For he LF arm. the dose given was 40 to 42.5 Gy in 8 fractions lelivered over 10 davs, using 8 to 14 MeV electrons (pre-cribed to the 100% isodose line) with an average field size of 3 × 6 cm. For the WF arm. the dose was 40 Gy in 15 ractions. over 21 days, delivered by opposed tangential ields to the breast and a separate anterior supraclavicular/ xillarv nodal field using 4-MV photons.

Vith a median follow-up of 65 months, the 8-year actuar-al overall survival rates were comparable between the arms 73% and 71% for the LF and WF groups, respectively). The ctuarial breast recurrence rates (scoring only first failure ites) were 20% for patients in the LF arm and 11% for patients in the WF arm ($P = 0.0008$). However, when the lata were analvzed according to histological type, the risks of ocal failure in patients with infiltrating ductal carcinoma vere 15% in the LF and 11% in the WF arm, whereas, for patients with infiltrating lobular carcinoma, the respective ecurrence rates was 34% and 8%. A high recurrence rate was ound in both arms for patients with extensive ductal carci-noma in situ (21% and 14%, respectively). Importantly, the ailure rate outside the quadrant of the original tumor for patients with infiltrating ductal carcinoma (IDC) in the LF rm was onlv 5.5%. Salvage surgery was possible in 86% and 0% of patients in each arm, respectively. Cosmetic results vere worse in the LF arm than the WF arm. with much more ibrosis and telangiectasias in the former group. The authors oncluded that. although the recurrence rate in the breast fter lumpectomy and wide field irradiation was comparable vith others reported in the literature of the time, in selected ubsets of patients limited field irradiation resulted in a ligher breast recurrence rate.[4]

'here were manv differences in the way patients in this rial were managed and how patients are treated today. Axil-arv dissection was not performed, and systemic therapy was lot used. Most patients did not have pre- or postoperative nammographic evaluation, and specimen margins were not valuated microscopically. Therefore, although the local fail-ire rate was considerablv higher in the LF arm than the WF rm for the population as a whole, the much smaller differ-nce between the arms for patients with infiltrating ductal arcinomas actuallv is quite encouraging that the approach of B-PBI is worth pursuing. The high rate of telangiectasias in the LF arm is not surprising, considering the high skin dose delivered by pure electron beams, but the increased risk of ibrosis mav also be a problem facing EB-PBI approaches using photons. This issue will be discussed at some length later.

Prone External-Beam Partial-Breast Irradiation

Rationale for Prone Patient Positioning

One common challenge that must be addressed by any tech-nique of breast radiotherapy is the anatomic/geometric con-straints required to treat the breast tissue volume, a target that is generally shaped as a concave, irregular dome. Although several techniques have been studied, treatment of the entire breast using opposed tangent fields in the supine position tends to include some part of the lung and, for left-sided tumors, the heart. Moreover, respiratory and systolic motion often increase the amount of normal tissue unnecessarily treated.

Positioning patients prone considerably reduces the breast tissue motion associated with both cardiac systole and respi-ration,[11] limiting the excursion of the chest wall to less than 5 mm.[12] In addition, prone positioning allows for exclusion of lung and heart tissue from the treatment fields.[13] This is particularly important in view of the growing evidence that treatment of these organs may cause late morbidity.[14-17] Most importantly, if patients are placed on a special tabletop that has a hole in it (Fig. 1) that allows the breast tissue to fall away from the chest wall, the excision cavity can be treated by fields that do not include any portions of the heart or lungs. Figure 2 shows how both the shape and the position of the excision cavity vary when the same patient is imaged either in the supine (Fig. 2A) or prone position (Fig. 2B). When prone, the cavity tends to be dislocated away from the chest wall by gravity.

Initial Studies Using the Prone Position

Based on these considerations, we initiated a research pro-gram at the University of Southern California, Los Angeles, to study EB-PBI given in the prone position. We started by exploring the physical and dosimetric aspects of multiple noncoplanar fields directed toward the tumor bed in the prone patient.[12] The first dedicated table for prone partial-breast treatment was designed. Dosimetry was analyzed for 2 "radiosurgical" approaches, one using 7 fixed horizontal beams and the second using six 45° arcs and a 90° sagittal arc; both used a 4-MV x-ray beam with a 32-mm diameter colli-mator. Both field arrangements resulted in adequate tumor coverage; the minimum target dose was 83% of the dose maximum in the fixed-beam arrangement and 86% in the multiarc setup.

Originally, we had envisaged using this approach in a ra-diosurgery-like fashion, with the long-term aim of substitut-ing breast radiosurgery for surgical excision for patients with breast cancers measuring 5 mm or smaller. However, al-though giving such treatment was technically feasible,

igure 1 Example of a patient under-;oing CT simulation in prone posi-ion, on a dedicated treatment table lesigned for partial-breast radiation. Color version of figure is available mline).

planned excisions performed 8 to 10 weeks later in the first 3 patients so treated with 15, 18, and 20 Gy showed that re-idual viable tumor was consistently within the treated target volume. This was despite the careful selection of the study patients, who each had a tiny mammographically detected umor, marked by a tantalum clip placed at the time of core biopsy. This small but significant experience redirected the esearch goal to the exploration of a hypofractionated ap-proach, directed to treat the postoperative tumor cavity with added margins.

:election of a Dose-Fractionation Scheme or Postoperative Prone EB-PBI

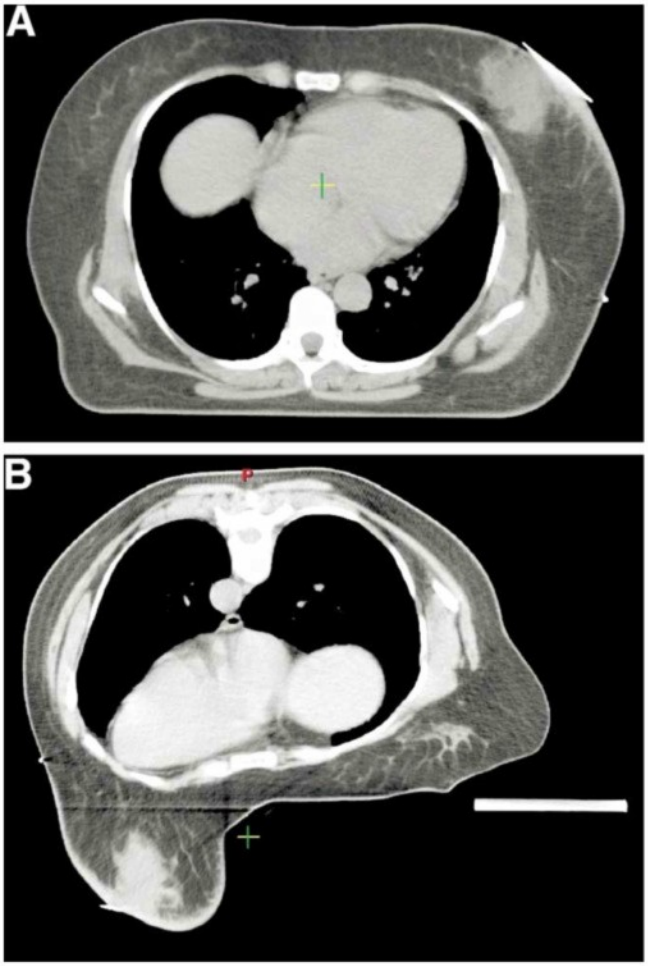
'he accessibility of the target in patients treated in the prone position, unencumbered by constraints of treating surround-ng normal lung or heart tissue, together with the relatively mall volume associated with PBI created the ideal conditions o safely explore an accelerated, hypofractionated regimen.

\t the time, the only prospective randomized study on this ssue was that of Baillet and colleagues[18] at the Necker Hos-pital in Paris. They reported equivalent local control but in-erior cosmetic results at 4 years in elderly patients receiving a hypofractionated regimen of 23 Gy delivered in 4 fractions over 3 weeks to the entire breast, compared with a regimen of '5 Gy in 25 fractions given in 5 weeks. Therefore, it became necessary to derive a rational dose-fractionation regimen of accelerated radiation therapy from published preclinical and linical data.

3y applying the linear-quadratic cell survival model with in alpha-beta value for breast carcinoma of 4,[19-21] a dose of 0 Gy given in 5 fractions of 6 Gy per fraction over 10 days was found radiobiologically equivalent in tumor control to a lose of 50 Gy given in 25 fractions of 2 Gy over 5 weeks, which is the dose commonly used in studies of the National Surgical Adjuvant Breast And Bowel Project.[22] At the same time, this hypofractionated scheme resulted in the same bio-logic equivalent dose (BED) for late breast tissue complica-tions[23] (including desquamation, fibrosis, erythema, and tel-angiectasia) as that of 60 Gy in 30 fractions, a regimen used at many institutions to treat the tumor bed (46-50 Gy to the whole breast plus a boost of 10-14 Gy), which has been reported to have excellent cosmetic results.[24] Table 1 com-pares the BED values for these 3 different fractionation regi-mens and for the fractionation regimen used in supine EB-PBI for different endpoints.

Rationale for Patient Selection Criteria for Prone EB-PBI Postoperative

The impetus for investigating prone EB-PBI was the epidemi-ological evidence of a rapidly emerging new breast cancer population in the United States because of the widespread use of mammographic screening: postmenopausal women with small, estrogen receptor–positive tumors, who com-monly have negative nodes and 5- and 10-year survival rates of 95% and 85%, respectively.[25,26] Because of the limited risk of breast cancer death in this subset of patients, the likelihood that potentially suboptimal radiation therapy would affect survival seemed very small, making it acceptable to conduct trials exploring PBI in this group. Moreover, there is evidence that postoperative radiation therapy has often been omitted for elderly women, especially those with significant comor-bid conditions because of concern that they will not be able to complete (for medical or logistical reasons) 6 weeks of daily treatment.[27-29] It appeared that a more cost-effective, user-



igure 2 One month after breast surgery, the same patient as in igure 1 was scanned both in the supine (Fig. 2A) and prone (Fig. B) positions. Radio-opaque markers were placed while supine to efine the lateral extent of the breast and to identify the lumpectomy car. A supine and a prone scan at the level of the lateral marker are nown to exemplify how the shape and site of the postsegmental xcision seroma varies based on patient's position. When prone, the avity elongates and is more distant from the chest wall.

riendly regimen could best satisfy the needs of this specific opulation, ideally without compromising local recurrence ontrol and breast cancer survival. Finally, a radiotherapy echnique that completely avoids including any of the lung or eart is particularly appealing in a patient population in which late cardiovascular effects might be added to preexisting illness.

esults of Pilot Phase I Trial University of Southern California)

rom January 1997 to June 1998, we conducted a pilot ose-escalation study of hypofractionated conformal EB-BI external-beam radiotherapy to the tumor bed in seected postmenopausal women with T1 breast cancers onsecutively seen at the University of Southern California.[5] All patients were required to be postmenopausal, with nonpalpable, mammographically detected tumors measuring less than 1 cm in diameter, which were excised with negative margins, with pathologically negative axilary lymph nodes. The study randomly assigned cohorts of patients each to 3 dose levels (5 fractions of 5, 5.5, or 6 y each, respectively, delivered over 10 days). Treatment was found to be feasible in 9 of 10 consecutive patients; he only excluded patient had a tumor cavity that was xtremely lateral (in the tail of Spence), and it was determined that she was best treated supine. With a minimum ollow-up of 3 years, there were no recurrences and all atients had "good or excellent" cosmetic results.

reliminary Results of the Subsequent hase I/II Study (New York University)

ecause of these encouraging results, we designed a phase /II study that opened at New York University in 2000 and s ongoing. Results on the first 47 patients entered (of the total accrual goal of 99 patients) have been recently reported.[7,8] Five fractions of 6 Gy each are delivered over 10 days, for a total dose of 30 Gy. After taking a planning CT in the prone position, the postsurgical cavity is defined as the clinical target volume (CTV), and a 1.5-cm margin is added to generate the planning target volume (PTV). An example is given in Figure 3. In this case, opposed tangential fields with 15° wedges were used. The corresponding ose-volume histogram results show that less than 45% of he ipsilateral breast volume received more than 50% of the prescribed dose.

For the 47 patients currently on study, the mean volume of the ipsilateral breast receiving 100% of the prescribed dose was 26% (range, 10%-45%), whereas the mean volume of the breast contained within the 50% isodose surface was 47%

able 1 Biologically Equivalent Doses of Different Fractionation Schemes

ndpoint	α/β	50 Gy/25 fx	30 Gy/5 fx	60 Gy/30 fx	34 Gy/10 fx
rythema	8†	63 Gy_8	53 Gy_8	75 Gy_8	48 Gy_8
esquamation	11†	59 Gy_{11}	6 Gy_{11}	71 Gy_{11}	45 Gy_{11}
elangiectasia	4†	75 Gy_4	75 Gy_4	90 Gy_4	63 Gy_4
ibrosis	2†	100 Gy_2	120 Gy_2	120 Gy_2	92 Gy_2
umor control	4	75 Gy_4	75 Gy_4	90 Gy_4	63 Gy_4
umor control*	4	72 Gy_4	75 Gy_4	86 Gy_4	63 Gy_4

*Taking into account cell proliferation during the course of treatment.[19,38,21]
Data from Archambeau et al.[23]

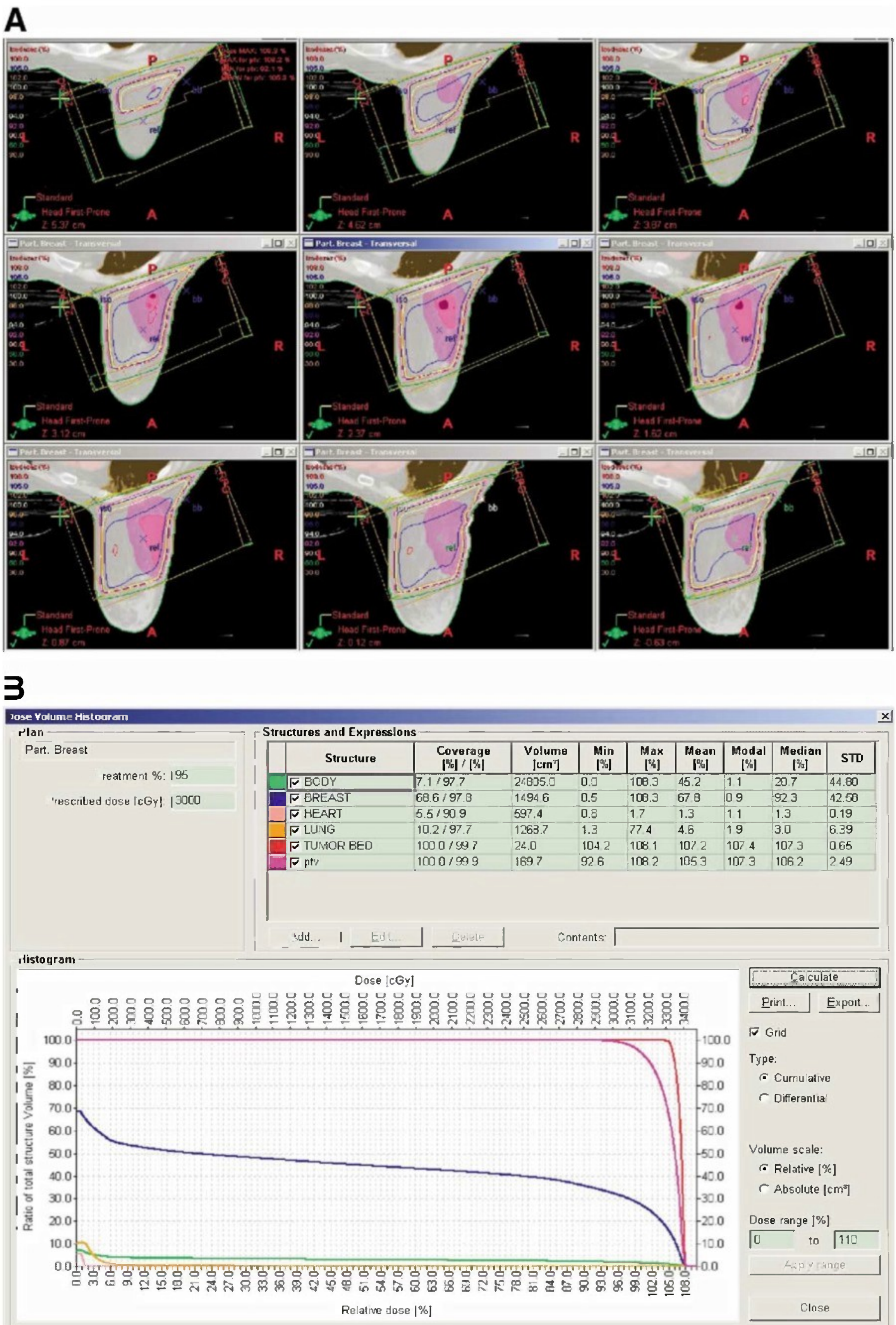


Figure 3 (A) A set of transverse CT slices (acquired every 0.37 cm, but here displayed every 0.75 cm) for a prone EB-PBI treatment are shown, with isodose distribution around the tumor bed (CTV, shown in red) and around the PTV (shown in magenta). Opposed tangential fields with 15° wedges were used to improve dose homogeneity. (B) Dose volume histograms of the treatment plan are shown. (Color version of figure is available online).

range, 23%-75%). The lung and heart were consistently spared. Acute toxicity was modest, limited mainly to grade 1 to 2 erythema. With a median follow-up of 18 months, only grade 1 late toxicity has occurred, and no patient has developed a local recurrence.

Supine External-Beam Partial-Breast Irradiation

William Beaumont Hospital Experience

The group at William Beaumont Hospital, near Detroit, pilot-tested giving supine accelerated PBI in 9 patients, using active breathing control to compensate for breast movement related to respiratory excursion.[9] The dose-fractionation scheme initially chosen was nominally the same as in their brachytherapy PBI experience. The first five patients received 34 Gy in 10 fractions, given twice daily over 5 days, while the following four patients received 38.5 Gy in 10 fractions. The technique appeared to be feasible and well tolerated.

Based on this preliminary data, Vicini and colleagues[10] conducted a phase I-II study in 31 patients, using eligibility criteria similar to those applied in RTOG trial 95 to 17. Most patients (29/31) had surgical clips placed at the time of surgery to define the lumpectomy cavity. The CTV consisted of the lumpectomy cavity plus a 10- to 15-mm margin. The PTV consisted of the clinical target volume plus a -cm margin to account for breathing motion and daily variability of treatment setup. Active breathing control was not used in this study. In the first 6 patients, the prescribed dose was 34 Gy in 10 fractions given twice daily (with a minimum 6-hour interfraction interval) over 5 consecutive days, whereas for the subsequent 25 patients, the prescribed dose was increased to 38.5 Gy in 10 fractions. The study was designed to treat the clinical target volume with less than 10% inhomogeneity and to give a comparable or lower dose to the heart, lung, and contralateral breast than standard whole-breast tangents.

At the time of publication, the median follow-up time for this cohort was 10 months (range, 1-30 months). The only toxicity during treatment was grade 1 erythema. At the initial 4- to 8-week follow-up visit, 19 patients (61%) experienced grade 1 toxicity and 3 patients (10%) grade 2 skin toxicity. No grade 3 toxicities were observed. The remaining 9 patients (29%) had no observable radiation effects. Cosmetic results were rated as good or excellent in all evaluable patients at 6 months (n = 3), 12 months (n =), 18 months (n = 6), and in the 4 evaluable patients followed more than 2 years after treatment. The mean coverage of the clinical target volume by the 100% isodose line (IDL) was 98% (range, 54%-100%, median: 100%); its coverage by the 95% IDL was 100% (range, 9%-100%). The mean coverage of the planning target volume by the 95% IDL was 100% (range, 97%-100%). The mean percentage of the breast receiving 100% of the prescribed dose was 23% (range, 14%-39%), whereas the mean percentage of the breast receiving 50% of the prescribed dose was 47% (range, 34%-60%). The study supported feasibility of this approach and generated the background experience for RTOG 0319.

RTOG 0319: A Multicenter Phase I/II Trial to Evaluate Three-Dimensional Conformal Radiation Therapy Confined to the Region of the Lumpectomy Cavity for Stage I and II Breast Cancer

This study assesses the technical feasibility and acute toxicity of irradiating the region of the tumor bed (identified by surgical clips placed at the time of lumpectomy) with 3-dimensional conformal radiation therapy. Eligible to the trial were newly diagnosed breast cancer patients with stage I to II disease and negative margins of excision (at least 2 mm) after lumpectomy. Patients with up to 3 positive nodes were eligible. Patients were excluded if they had tumors larger than 3 cm, lobular histology, or if an extensive intraductal component was present. A dose per fraction of 3.85 Gy was delivered twice daily, with each treatment separated by a minimum of 6 hours, for a total dose of 38.5 Gy given in 10 consecutive fractions (delivered from Monday to Friday). The planned accrual of 46 patients was rapidly achieved. Results are not yet available.

Other Studies

A few other groups have begun studies of EB-PBI in the supine position. These include investigators at Evanston Northwestern Health care in Evanston, IL (giving a dose of 43.2 Gy in 16 once-daily fractions using intensity-modulated radiation therapy),[30] and at the institutions of the Dana-Farber/Harvard Cancer Center in Boston, MA (giving 32 Gy in 8 fractions, delivered twice daily, using conformal photon or mixed photon-electron plans).[31] So far, only very early results are available that show such treatment is feasible with minimal acute toxicity.

Potential Pitfalls of External-Beam Partial-Breast Irradiation

Preliminary experience with EB-PBI has identified common problems that investigators are likely to encounter with this approach. One is the correct identification of the excision cavity. The ability of the radiation oncologist to correctly target treatment depends on the type of surgical technique used as well as the time interval between excision and treatment planning. Placing surgical clips at the time of segmental mastectomy to define the cavity boundaries has the advantage of permanently marking the site of excision, but migration of clips after placement has been reported, making reliance on the technique questionable.[32] Usually, the postoperative cavity can easily be identified within a few weeks after lumpectomy because of the seroma that rapidly forms, which has fluid-like density and can be easily identified at CT planning. If there is too long of a delay between surgery and

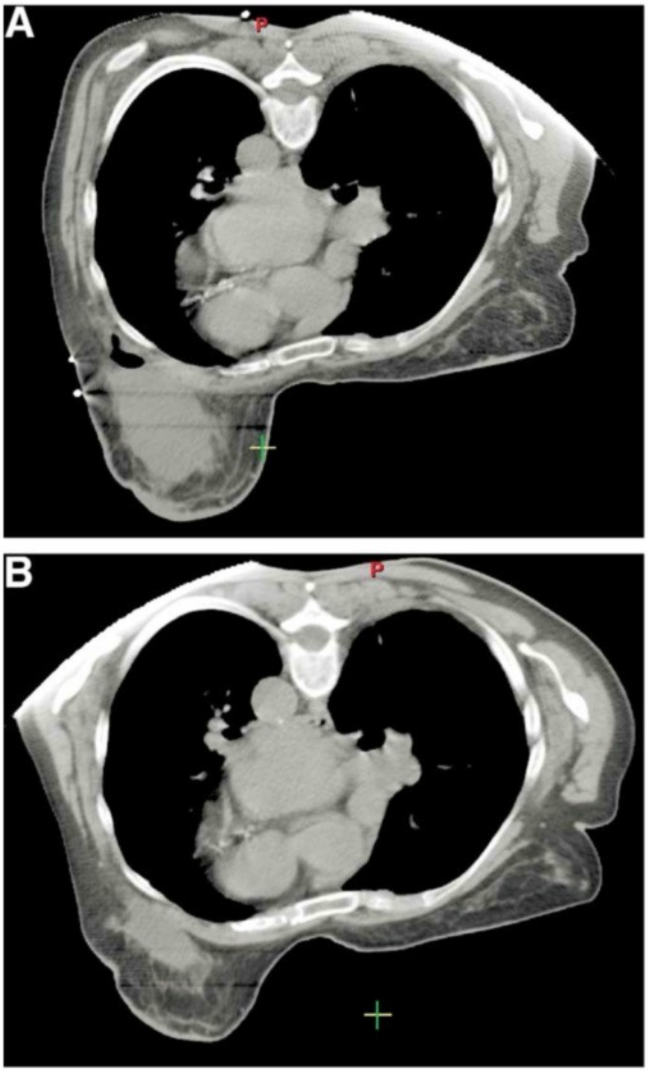


Figure 4 (A) This patient was originally imaged 18 days after segmental mastectomy. When the patient came to start treatment 10 days later (28 days after surgery), it was noted that the ipsilateral breast contour had changed. (B) When imaged again, the postoperative seroma had partially resolved, with absorption of the air present at the first CT, and the contour and size of the breast had also changed. A new treatment plan was developed.

simulation, the cavity may be very difficult to see. However, if treatment planning is done too soon, it is possible that the lumpectomy cavity and breast will change in size and shape between the time of treatment planning and initial treatment because of the resolution of postoperative changes. For example, Figure 4a shows a patient who, when first simulated, 18 days after surgery, had a large fluid collection with an air level visible on CT. The ipsilateral breast was also enlarged and deformed by postoperative edema. Ten days later, when she came to start treatment (28 days from initial surgery), the size of the breast had decreased, and it also became evident that the excision cavity had changed in size, as confirmed by a new treatment planning CT (Fig. 4B).

Another concern is whether the dose chosen for EB-PBI is adequate for tumor control. We have addressed this issue in a recent manuscript that compares the biological effective doses used in PBI studies to those delivered to the tumor bed by more standard whole-breast regimens of 50 Gy in 5 weeks or whole-breast plus boost regimens of 60 Gy in 6 weeks.[33] It appears that the BED values of most PBI protocols (with either external-beam or brachytherapy techniques) resulted in tumor control BEDs roughly equivalent to a 50 Gy standard treatment but consistently lower than the BEDs for regimens in which the tumor bed receives a total dose of either 60 Gy or 66 Gy. In view of the results of trials demonstrating significantly better local control when a boost is added to the tumor bed,[34,35] future studies of external beam PBI should consider whether a higher dose should be given.

Finally, when large fraction sizes are used, differences in normal-tissue radiosensitivity are likely to be magnified. There are currently no predictive markers to determine which patients will develop radiation-induced late toxicity. Li and colleagues[36] detected a significant correlation between pretreatment plasma levels of tumor growth factor-β-1 (a multifunctional cytokine implicated in tissue fibrosis) and the risk of severe fibrosis among patients treated with breast-conservation therapy. Other studies have revealed that specific polymorphisms of the tumor growth factor-β-1 promoter gene could be associated with the development of severe fibrosis. In 1 study, patients with the −509TT or +869CC genotypes were 7 to 15 times more likely to develop severe fibrosis.[37] Hopefully, studies of "radiation genomics" may result in a panel of markers that can be used to prospectively detect "fibrosis-prone" individuals.

Future Directions

The phase III NSABP/RTOG protocol is described elsewhere in this issue by Vicini and Arthur. Completing this study is critical to establish the role of PBI in the management of patients with early-stage breast cancer. Until then, any form of PBI remains experimental and must be conducted as part of a trial approved by an institutional review board.

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IN RESPONSE TO DR. ROQUES *ET AL.*

To the Editor: We would like to thank Roques and colleagues for their interest and comments regarding our study. We agree that accuracy is the main priority in immobilization over patient comfort, but this randomized trial failed to show any significant differences in accuracy between the two types of thermoplastic masks studied.

We also agree that a low shoulder position is important in radiation therapy for head-and-neck cancer patients, but we believe that this could be achieved without using a head-shoulder mask (HSM). For instance, a head mask (HM) could be used in combination with a shoulder retractor system (straps with handles fixed to the treatment couch) to achieve a low shoulder position without increasing the risk of severe skin toxicity or claustrophobia.

It may be true that the skin toxicity is high in our study, but regardless of where the World Health Organization (WHO) Grade 3 toxicity occurred, the study shows a statistical significant difference between the HM and the HSM. The highest grade of skin toxicity according to WHO was reported weekly, and even small areas of toxicity (for instance, in skin folds on the neck or behind the ears) were reported. We also would like to point out that the two compared groups of patients (using HM or using HSM) were similar in age, gender, tumor stage and site, type of treatment, beam energy, boost by electrons, and skin types.

We did not find any other studies that focused on the patients' experiences of using immobilization systems and were surprised that more than half (58%) of the patients experienced claustrophobia using the HSM and 25% of the patients using HM. However, all patients in our study were treated by the same specialist-trained cancer nurses with long experience, as suggested by Roques *et al.*, but we could not detect a statistical significant difference between patients using HM and patients using HSM.

The purpose of our study was not to prove which type of fixation is the best on the market. Instead our purpose was to compare the two types of thermoplastic masks that are being used at our department and to find differences that are detectable in a randomized trial.

New fixation devices are developed constantly and will hopefully improve the reproducibility. Some are commercially available and others remain in use locally. The two types of thermoplastic masks compared in our study were those in use clinically at the time of the study (and still with slight alterations). We have failed to find any published data regarding the reproducibility of the vacuum-formed PolyEthyleneTerephtalate glycol (PETG) mask in combination with the Norwich head rest, but would be interested to take part of such data if there are any available.

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BIOLOGIC COMPARISONS OF PARTIAL BREAST IRRADIATION SCHEDULES: IN REGARD TO ROSENSTEIN *ET AL.* (*INT J RADIAT ONCOL BIOL PHYS* 2004;60:1391–1404)

To the Editor: In the treatment of breast cancer, many plausible scientific theories have proved illusory when put to the test in clinical trials. The article by Rosenstein *et al.* (1) contains much elegant mathematical and biologic analysis of various radiotherapy schedules used for partial breast irradiation (PBI), as well as an excellent exposition of the rationale for using such techniques, but the conclusions they arrive at on the basis of their calculations are unduly pessimistic, an assertion that has already been shown to be correct in the clinic by the gold standard of a randomized controlled clinical trial. They conclude that, whereas certain PBI schedules are likely to be as effective as a schedule of 50 Gy in 25 fractions, they will be clinically inferior to schedules giving higher doses (60–66 Gy) in fractions of 2 Gy. Correctly interpreted, the available data show that there is minimal clinical benefit in using the higher dose in the sort of patients most likely to be offered PBI.

The European Organization for Research and Treatment of Cancer (EORTC) "boost" trial (2) is widely regarded as justifying the use of these higher doses, but this is a misinterpretation of that pivotal trial, except for certain readily identifiable patients: the younger ones. It is worth reviewing that EORTC trial in some detail. In its design, randomization between treatment arms was stratified for various factors; importantly, patient age at time of entry. The stratification was between those younger or older than 40. (Incidentally, in the original publication, results for those who were older than 40 were presented in three groups, 40–50, 50–60, and older than 60 years, but statistically this lacks validity, because the stratification was simply two-way, so only two groups should have been considered). For the younger patients, whose "baseline" rate of recurrence was much higher, the absolute reduction of risk produced by use of a higher dose was substantial, and clinically as well as statistically significant. For older patients, the absolute gain was minimal, even if statistically significant, because local control in the 50-Gy arm was already excellent. The data clearly show that for those older than 40 years, there is little additional benefit from higher doses, and it is suggestive that the impact of higher dose gets progressively less as patient age increases, but this latter conclusion has to be tempered with caution for the statistical reasons just mentioned.

The most rational interpretation of the EORTC study is that "low-risk" patients gain minimal or no benefit from doses higher than 50 Gy. Age is the most dominant predictor of risk in this trial, and this accords with numerous other studies, but other prognostic features have been widely recognized, such as vascular invasion, lymph node positivity, and extensive intraduct component. The authors refer to a "plateau" effect on the dose–response curve: the evidence from the EORTC trial points to 50 Gy as being very close to such a "plateau" for most older patients. They correctly identify that such patients are the ones most likely to be offered PBI.

It is precisely for these low-risk patients that PBI is seen as an attractive option—and for such patients, 50 Gy should be regarded as the standard comparator among schedules using 2 Gy per fraction. If the biologic calculations of Rosenstein *et al.* are correct, the better PBI schedules will, clinically, be perfectly adequate. Clinical confirmation of this hypothesis is, of course, still awaited.

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IN RESPONSE TO DR. MORGAN

To the Editor: We completely agree with Dr. Morgan's opening statement with regard to the necessity to test any hypothesis or theory in the setting of clinical trials: this is in fact the last sentence in the conclusion of our article (1).

Regarding the correct interpretation of the available data and, in particular, of European Organization for Research and Treatment of Cancer (EORTC) Trial 22881: at the 2004 European Society for Therapeutic Radiology and Oncology (ESTRO) meeting, Antonini *et al.* presented the results on local control and age from the EORTC Trial 22881, with the updated follow-up of 77.5 months (range, 0.53–147.5 months). Quoting from the published abstract: "On the relative hazard scale, there is no evidence that the effect of the boost treatment on local control depends on age ($p = 0.871$)" (2). Regarding the correct interpretation of our conclusions: we stress the importance of patient selection for partial breast irradiation (PBI), a point we have made before (3–5). Accrual to our current trial of prone PBI is limited to selected postmenopausal women who are treated by 30 Gy in five fractions. In fact, we have hypothesized that such a dose could be sufficient in this population. As stated in the recent manuscript about this trial, "whether the hypofractionated regimen (30 Gy in five fractions within 10 days) will be revealed as adequate in ensuring tumor control in the carefully selected population studied in this trial warrants long-term follow-up" (4).

Through radiobiologic modeling, we wanted to stress the difference between currently used PBI regimens and standard whole-breast radiotherapy, a relevant exercise in view of the fact that many current PBI trials are offered to women of any age, with the same potentially insufficient dose.

Standard adjuvant whole-breast radiotherapy is a highly effective component of breast conservation: "lesser" regimens require cautious exploraion, including initial patient selection criteria that reflect what we already know. Ignoring heterogeneity of breast cancer and its distinct natural history in different age groups, including patterns of local recurrence, is unlikely to foster progress in this field.

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MINIMIZING URINARY BLADDER RADIATION DOSE DURING BRACHYTHERAPY FOR CARCINOMA OF THE CERVIX USING BALLOON INFLATION TECHNIQUE: IN REGARD TO MALAKER *ET AL.* (*INT J RADIAT ONCOL BIOL PHYS* 2005;61:257–266)

To the Editor: It was with great personal interest that we read the article by Malaker *et al.* (1) on the reduction of bladder radiation dose during brachytherapy for cervical cancer using balloon inflation technique. With extensive experience using balloon catheters to minimize bladder *and* rectal dose during gynecologic brachytherapy at our institution, we have incorporated the balloon catheter technique as a standard of care and have written extensively on this subject (2, 3). It was thus with surprise that we found no references to the work we have already done in the very journal that Malaker's article is printed. Perhaps this oversight is also shared partially by the reviewers.

In addition, there are some technical issues we would like to point out. Figure 2 of the article shows lateral simulation films of the uterine applicators *in situ*, in which the tandem is clearly placed too anteriorly in relation to the ovoids. Although the purpose of the film is to show the displacement of the bladder that can be achieved by inflating the balloon catheter, we also advocate correct placement of the applicators, especially in a published article.

It is also apparent from these simulation films that no internal shields were used with the ovoid applicators. Using such shields is a practice standard at our institution and the lack of such shields may have very well skewed the bladder (and rectal) exposure.

Next, the use of the distal opening of the catheter as an anchor to the tandem, though resourceful, does not take into account variations seen in patient anatomy, particularly location of the bladder. Some bladders sit more cephalad, others more caudal. In our institution, adjustments often have to be made in the placement of the balloon catheter if the bladder does not sit directly above the balloon. This involves deflating the balloon, making the adjustment, then reinflating the balloon with another simulation film taken. Therefore, the authors' technique may not be practical for all patients.

In summary, the authors' findings only served to confirm what we have already demonstrated—that balloon catheters can reduce unnecessary dose to the bladder, although we have conclusively shown that rectal dose can also be reduced (2). Nevertheless, we are happy to learn of the authors' use of the balloon inflation technique and look forward to seeing the use of balloon catheters incorporated as a standard of care in more centers besides our own.

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IN RESPONSE TO DR. LUH *ET AL.*

To the Editor: For potential users of the balloon inflation technique for cancer of cervix, we would like to respond to the issues raised by Luh and Eng to inform practicing colleagues. We were happy to learn of the adoption elsewhere of a balloon inflation technique for treatment of cancer of the cervix, a technique that we previously described in our widely internationally circulated Annual Report of 2002 (1), a copy of which is available on request. After submission of our article to this journal in August 2003 (2), we subsequently learned of its application at the University of Texas Health Science Center at San Antonio after publication of an article by Eng *et al.* (3) in May 2004.

Regarding the anterior placement of the tandem, Fig. 2 in our original article was included as an example to demonstrate that, even when it is markedly anteriorly placed, the dose to the bladder is reduced by increasing the separation between the tandem and the bladder. Second, spherical ovoids tend to hold the tandem on their curved surfaces as they meet together; as a result, the tandem is pushed upward. However, if cylindrical ovoids are used, the tandem will lie in the middle of the ovoids; this is the system we usually use. Consequently, if the patient has posterior packing behind the tandem in the gap between the two ovoids, it holds the lower end of the applicator system and, if the packing is done satisfactorily, this would not be a practical problem in performing this procedure.

It should also be noted that by lifting the vaginal portion of the applicator, it acts as a retractor, and posterior packing becomes relatively easy. In this case, posterior packing can be done well under direct vision and posterior displacement of the rectum can be assured, thus helping to reduce the rectal dose.

Shielded ovoids can be employed, but the BrachyVision computer calculation system we use does not allow for a shielded applicator (4). Any shielding correction would have to be applied to the results determined by the BrachyVision system by a physicist, but the perturbation effect of the shielding cannot readily be calculated, nor is there a program available to our knowledge to incorporate a shielding correction into the calculation module. Consequently, although in principle it may be a good idea because we do not have an accurate method of calculation, we have chosen to employ the approach of increasing the distance to the rectum by packing and to use an accurate method of calculation rather than using less packing and a dose approximation.

With regard to the distal opening of the catheter, it must be used as an anchor to the tandem to make it secure against slipping, because, if the packing is not done with care, when the balloon is inflated, it can slip backward and between the ovoids or sideways, defeating the whole purpose of the exercise.

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0360-3016/06/$–see front matter

ELSEVIER

LETTERS TO THE EDITOR

IN REGARDS TO GLATSTEIN: THE WHIRLIGIG OF TIME (*INT J RADIAT ONCOL BIOL PHYS* 2006;65:322–323)

To the Editor: In response to the editorial by Dr. Glatstein (1), I, as a radiation oncologist with many years of academic and private practice experience, have the following comments. First, medical school curricula need to have a separate course in which the medical student can get a well-balanced education in oncology. It is my observation that new graduates and primary care physician have limited knowledge of various malignancies. Second, in the residency program of radiation oncology, we need to put emphasis on caring for patients and being physicians first, rather than putting too much emphasis on the technical side. Being a physician who is able to address day-to-day problems is of paramount importance, and implementing daily hospital rounds and respond to ER calls provides invaluable experience. Third, it is true that we have made wonderful advances in the technical portion of radiation oncology, but we should not forget the day-to-day care of patients and their needs. Fourth, the follow-up process is a very important part of the practice of radiation oncology, and we should not delegate the process of follow-up to other physicians. It is truly a learning experience for the natural history of malignancies as well as for the early and late side effects of radiotherapy.

The time has come to join forces and work together to reinvent cancer teaching at the medical schools, as well as to place emphasis on radiation oncology residency programs so they are producing oncologists that are committed to the long-term care of patients.

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1. Glatstein E. The whirligig of time [Editorial]. *Int J Radiat Oncol Biol Phys* 2006;65:322–323.

EXTERNAL BEAM PARTIAL-BREAST RADIOTHERAPY: CRUCIAL DIFFERENCES BETWEEN NYU 00-23 AND RTOG 0319: IN REGARD TO VICINI *ET AL.* (*INT J RADIAT ONCOL BIOL PHYS* 2005:63:1531–1537)

To the Editor: We have read with interest the first report of Radiation Therapy Oncology Group (RTOG) 0319 by Vicini *et al.* (1). Although the design and the main intent of the RTOG study were similar to those of New York University (NYU) 00-23, it is important to carefully consider the crucial differences between these two trials of partial-breast external beam radiotherapy to interpret the data correctly (2).

With respect to eligibility criteria, only women who declined a standard regimen of 6 weeks of conventional breast radiotherapy were entered into NYU 00-23. Moreover, a specific cohort of women at a particularly low risk of recurrence was selected for this trial (nonpalpable primary tumor, stage pT1pN0M0, with negative surgical margins measuring at least 5 mm).

In NYU 00-23, both the dose and the fractionation schedules differed from those used in RTOG 0319. A dose of 600 cGy was delivered once a day in 5 fractions over 10 days to a total dose of 3,000 cGy. Although on radiobiologic grounds the two regimens were predicted to have comparable efficacy (3), the NYU protocol is arguably more convenient for patients because it does not require two treatments per day and therefore reduced the number of visits to the radiation facility by half in comparison with the RTOG study.

However, the most crucial differences concern the technique and the dosimetric data. Prone positioning did not require any additional margin to compensate for respiratory motion (4) and, in NYU 00-23, the surgical cavity was easily identified by computed tomography imaging without any need to rely on surgical clips (5).

In addition, although both studies tested the feasibility of three-dimensional conformal radiotherapy and although the field arrangements were selected at the discretion of the treating physicians, the treatment technique and the number of fields employed were different. RTOG 0319 used multiple fields that differed according to tumor laterality: four for right-sided lesions and five for left-sided ones. In contrast, NYU 00-23 overwhelmingly used a pair of parallel-opposed minitangents. The simplicity of the NYU approach assured a reliable daily setup, easily confirmed by portal imaging obtained before each of the five fractions. It was therefore also likely to be more easily reproducible in a multiple-center setting.

Another crucial difference involved permissible dose to nontarget critical tissues. In all 47 patients treated, the *only* dose received by thyroid, contralateral lung, and heart was dose from internal scatter and leakage from the head of the collimator. In fact, the NYU 00-23 study required that field arrangements be designed to completely avoid the contralateral breast, the contralateral lung, the heart, and the thyroid. The ipsilateral lung was permitted to receive up to 5 Gy (16.7% of the dose prescribed to the tumor bed), but only to a volume not exceeding 10% of the ipsilateral lung. In all 47 patients, these constraints were satisfied.

We believe the enumerated differences are both relevant and crucial and that the technique employed in NYU 00-23 presents several important strengths, including its potential for large-scale reproducibility and its improved toxicity profile with respect to reducing the risk of long-term complications (6, 7).

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IN RESPONSE TO DR. FORMENTI *ET AL.*

To the Editor: We thank Drs. Formenti, Wernicke, and DeWyngaert for their comments regarding Radiation Therapy Oncology Group (RTOG) 0319 (1) and their partial-breast irradiation (PBI) technique. It is critical that additional methods to deliver PBI with three-dimensional (3D) conformal external-beam radiotherapy (EBRT) are investigated to determine if this concept is practical, reproducible, and equivalent to conventional whole-breast irradiation. We would, however, like to make some additional comments related to several of the issues they discussed.

First, patient selection criteria for our study were based on recommendations from the American Brachytherapy Society and the American Society of Breast Surgeons and also match criteria used to generate the excellent long-term local control rates observed in the numerous published Phase I/II studies addressing this issue (2). The more restrictive selection criteria used by the authors (although very reasonable) potentially overlap with criteria used to identify patients who may not require any radiation at all. It has always been our belief that PBI may be most optimally suited for those subsets of "intermediate-risk" patients who clearly do not require 5 to 7 weeks of conventional whole-breast radiation but who would do significantly better than with no radiation at all. Only data from the numerous ongoing Phase III trials of PBI will help clarify the selection criteria for this technique to be optimally applied.

Second, the dose fractionation schedule we selected was based both on radiobiologic calculations and preliminary toxicity results generated from published data applying this identical technique and fractionation schedule (3). Larger fraction sizes (although more convenient) were avoided out of concerns that these larger doses per fraction could potentially result in significantly increased late toxicity (as experienced in the Phase III trial of PBI using EBRT from the Christie Hospital, where fractions of 531 cGy were given [4]). If similar rates of local control and toxicity can be obtained, the 3D conformal PBI technique with the least number of fractions will obviously be the most convenient for patients. Until this optimal fraction size is identified, it is important that several different schedules are tested, because most of these fraction sizes and total doses are based on radiobiologic estimates and not long-term toxicity data.

Third, we agree that the supine technique used in our study has certain practical limitations, as does any PBI technique (including the author's prone technique). Regarding the normal tissue dose constraints that were established in our protocol, these were mandated to prevent the use of unusual beam angles that could potentially increase normal tissue doses. As noted in the trial, this was not necessary because these criteria were easily met in the vast majority of patients. It should also be noted that our technique has been shown to result in lower doses to normal tissues than conventional whole-breast irradiation with tangential fields (5).

Finally, we strongly encourage the investigation of other techniques to deliver PBI (including brachytherapy), because it is our belief that no single technique is applicable to all patients. In recognition of this important point, we are allowing three different PBI techniques (including the technique investigated by the authors) to be used in the NSABP B39/RTOG 0413 Phase III trial comparing PBI to whole-breast radiation. These three techniques include the MammoSite breast brachytherapy catheter, catheter-based interstitial brachytherapy, and 3D conformal EBRT. As of March 31, 2006, >1,000 patients (33%) have been successfully enrolled in the trial with more than 70% of the PBI patients treated with the same 3D conformal EBRT technique used in RTOG 0319.

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LINEAR QUADRATIC MODELING OF INCREASED LATE NORMAL-TISSUE EFFECTS IN SPECIAL CLINICAL SITUATIONS: IN REGARD TO JONES *ET AL.* (*INT J RADIAT ONCOL BIOL PHYS* 2006;64:948–953)

To the Editor: This is in reference to the article by Jones *et al.* published in your esteemed journal (1). I wish to draw your kind attention that in my opinion there are some major flaws, which do not explain the proper mathematical formulation.

The authors have described a late tissue isoeffect by the following equation:

$$e^{-N_1(\alpha_1 d_1^2+\beta_1 d_1)} = e^{-N_2(\alpha_1 d_2+\beta_1 d_2^2)} \quad (1)$$

The subscripts 1 and 2 refer to the dose in the unsensitized state and in the sensitized state, respectively.

However, Equation 1 should be written as:

$$e^{-N_1(\alpha_1 d_1+\beta_1 d_1^2)} = e^{-N_2(\alpha_2 d_2+\beta_2 d_2^2)} \quad (1)$$

In the same mathematical derivation, the authors have multiplied Equation 4 throughout by α_1 and achieved Equation 9, which is:

$$\alpha_1 \cdot \mathrm{BED}_{\mathrm{unsensitized}} = \alpha_1 \cdot \mathrm{BED}_{\mathrm{sensitized}} \quad (9)$$

However, in my opinion, it needs correction in that only if we multiply Equation 7 throughout by α_1 can we achieve Equation 9. If it is not so, it needs explanation.

This is for your information and evaluation.

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doi:10.1016/j.ijrobp.2006.05.048

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IN RESPONSE TO DR. MANDAL

To the Editor: We are grateful that the typographical error in our Eq. 1 has been detected. This shows the difficulty of assessing on-screen subscripts in exponentials.

Our Eq. 1 should be presented as:

$$e^{-N_1\left(\alpha_1 d_1+\beta_1 d_1{}^2\right)} = e^{-N_2\left(\alpha_2 d_2+\beta_2 d_2{}^2\right)} \quad (1)$$

from which:

$$N_1\left(\alpha_1 d_1 + \beta_1 d_1^2\right) = N_2\left(\alpha_2 d_2 + \beta_2 d_2^2\right) \quad (2)$$

where all subscripts 1 refer to the unsensitized state and subscripts 2 the sensitized state for a given isoeffect.

If $\alpha_2 = x\alpha_1$ and $\beta_2 = x^2\beta_1$, then the BED equations for nonsensitized and sensitized states are:

$$N_1 d_1\left(1 + \frac{d_1}{\left(\frac{\alpha_1}{\beta_1}\right)}\right) = N_2 d_2\left(x + \frac{x^2 d_2}{\left(\frac{\alpha_1}{\beta_1}\right)}\right) \quad (3)$$

This equation can be expressed in words as:

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External-beam-based partial-breast irradiation

Silvia C Formenti

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Partial-breast irradiation (PBI) is becoming a new paradigm for breast cancer radiation, as discussed previously by Professor Sarin in this journal.[1] No type I or type II evidence is currently available to demonstrate equivalence of this technique to standard whole-breast radiotherapy, and a prospective randomized trial jointly sponsored by the NSABP and RTOG (NSABP B-39 and RTOG 0413) is currently accruing patients to compare whole breast radiotherapy with PBI, performed either by brachytherapy or external-beam techniques. Until the results of this or similar trials are available PBI remains a research domain and should be offered to patients only in the context of a clinical experimental protocol.

Despite the fact that less extensive experience is available for external-beam PBI than for brachytherapy, PBI delivery through an external-beam approach presents many advantages. Firstly, external-beam PBI is likely to be more acceptable to the patient since it is noninvasive and does not require a surgical procedure or anesthesia. Moreover, since external-beam PBI is delivered after surgery the pathological analysis of the segmental mastectomy specimen is available to identify the best candidates for this approach. Secondly, external-beam PBI is likely to become more widely reproducible than brachytherapy, since successful application of external-beam PBI does not rely on the experience and skills of the radiation oncologist, unlike brachytherapy. Thirdly, once the technique of external-beam PBI is established, it can be widely applied at any facility that has a linear accelerator. Some brachytherapy approaches cannot be completed because of the unfavorable interplay of the patient's anatomy with the technical limitations of the applicator.[2] External-beam PBI does not present this problem. Finally, in terms of health care economics, an external-beam approach spares the costs of an extra surgical procedure and those of several days of hospitalization (in the case of low-dose-rate brachytherapy).[3]

External-beam PBI was originally tested in a prospective randomized trial at the Christie Hospital in Manchester, UK. This trial compared external-beam PBI with radiation of the whole breast and associated nodes.[4] After a follow-up of 65 months, while survival in the two arms was comparable, the local recurrence rate in the external-beam PBI arm was double that of the whole-breast radiation arm (20% versus 11%). Noticeably, patients with tumors as large as 4 cm in diameter were eligible for the trial, and external-beam PBI was delivered by 8 or 12 MeV electrons with a generally small target field, without the imaging support currently available to target the tumor bed. Certain histological characteristics of the primary tumor—lobular type and presence of ductal carcinoma *in situ* in the specimen—were more likely than others to be associated with recurrence of the primary tumor. Conversely, in patients with infiltrating ductal carcinomas treated by PBI, the failure rate outside the original quadrant was only 5.5%.

This experience informed the careful patient selection in the contemporary external-beam PBI clinical trials, which limit eligibility to patients with small tumors and negative margins of resection, and without an extensive intraductal component.[5–8] The clinical target volume (CTV) usually consists of the tumor cavity, which is visualized at CT planning, plus 1–1.5 cm of margin. An extra 1–2 cm is added to the CTV to render the planning target volume (PTV), which takes into account some variability in the position of the patient from day to day.

A prone approach for external-beam PBI has been tested at New York University in a clinical trial sponsored by a grant from the US Department of Defense Breast Cancer Research Program. Results for the first 47 patients accrued have demonstrated feasibility.[7] Eligibility for enrollment into this study is limited to postmenopausal women with nonpalpable, mammographically detected tumors. In addition, the protocol requires patients to have first refused to undergo the standard 6 weeks of radiotherapy. Five fractions of 6 Gy are delivered to the PTV over 10 days (Monday–Wednesday–Friday,

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(Monday–Wednesday). This dose and fractionation schedule was calculated by radiobiological modeling and was predicted to be as effective in terms of tumor control as 50 Gy in 25 fractions, while maintaining a risk of fibrosis at the tumor bed comparable to that of a standard regimen of 60 Gy in 30 fractions.[7,9] An $\alpha/\beta = 4$ for tumor control was used, and its validity was confirmed in 2006 by the results of a prospective randomized trial that compared hypofractionated with standard fractionation of whole-breast radiotherapy.[10]

RTOG tested conformal external-beam PBI in the supine position in a phase I–II trial (RTOG 0319), which rapidly accrued its target population of 58 patients.[8] Through multi-institutional accrual, this important trial confirmed the feasibility of external-beam PBI in the supine position. Ten fractions of either 3.4 Gy or 3.85 Gy were delivered twice a day, separated by an interval of 6 h, to a total dose of 34 Gy or 38.5 Gy. The dose and fractionation schedules were chosen to mimic those widely used for PBI with brachytherapy, on the basis of the original assumption of $\alpha/\beta = 10$ for tumor control.

At a very early follow-up point of 2–3 years it was encouraging to notice that external-beam PBI had achieved excellent local tumor control and cosmetic results, with either prone or supine patient positioning. The results of prone external-beam PBI are slightly superior to those of supine external-beam PBI in terms of normal tissue sparing, owing to the fact that when the patient is in the prone position the treating beam can be directed to avoid exiting through the rest of the body.[11] Supplementary Figures 1A and B online exemplify a case in which the prone position enhances conformality and reduces the dose to normal tissue.

Several important challenges remain regarding the optimum role and implementation of external-beam PBI, which include establishing the PTV and CTV (in view of the natural evolution over time of the tumor cavity), selecting the most reproducible conformal technique, and determining the optimum accelerated fractionated regimen over 5 days.

In conclusion, accelerated regimens of external-beam radiotherapy are rapidly becoming a standard radiation approach after breast-conserving surgery. Until equivalence of PBI to whole-breast radiotherapy is proven, targeting the whole breast to provide additional protection from recurrences elsewhere in the index breast is likely to be safer.[10,12] It is conceivable, however, that in specific patient subsets PBI will adequately treat the initial tumor site, while a systemic approach (tamoxifen or other antihormonal therapy) can be added to reduce the risk of new tumors in the residual breast tissue in both breasts.

Supplementary information in the form of a figure is available on the *Nature Clinical Practice Oncology* website.

Competing interests
The author declared she has no competing interests.

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·9. USAMRDC Form 60-R

/OLUNTEER REGISTRY DATA SHEET (USAMRDC 60-R)

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·. AUTHORITY: 5 USC 301; 10 USC 1071-1090; 44 USC 3101; EO 9397

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'ART A - INVESTIGATOR INFORMATION
To Be Completed By Investigator)

'LEASE PRINT, USING INK OR BALLPOINT PEN

·. Study Number: NYU 00-23 IRB# H9096) **2. Protocol Title:** Hypo-Fractionated Conformal Radiation Therapy to the Tumor Bed after Segmental Mastectomy

:. Contractor (Laboratory / Institute Conducting Study): NYU School of Medicine

·. Study Period: From: 07 / 01 /01 To: 07 / 31 / 07
ɔD MM YY DD MM YY

:. Principal / Other Investigator(s) Names(s):
·. Silvia C. Formenti, MD
·.
:.

6. Location / Laboratory
NYU School of Medicine /
/

'ART B - VOLUNTEER INFORMATION
To Be Completed by Volunteer)

'LEASE PRINT USING INK OR BALLPOINT PEN

. SSN: / / **8. Name: See attached list**

:. Sex: M F √ 10. Date of Birth: / / 11. *MOS/Job Series: ___ 12. Rank/Grade: ___

·3. Permanent Home Address (Home of Record) or Study Location:

[redacted]
Street) (P.O. Box/Apartment Number)

[redacted] [redacted] [redacted] [redacted]
City) (Country) (State) (Zip Code)

'ermanent Home Phone Number: See attached list

·4. *Local Address (If Different From Permanent Address):

Street) (P.O. Box/Apartment Number)

City) (Country) (State) (Zip Code)

ocal Phone Number: See attached list

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-5. *Militarv Unit: ____________________ Zip Code: ____________

›rqanization: ____________ Post: ____________ Duty Phone Number: ____________

'ART C - ADDITIONAL INFORMATION
To Be Completed by Investigator)

'LEASE PRINT USING INK OR BALLPOINT PEN

-6. Location of Studv: 160 East 34^{th} Street, New York, NY 10016

-7. Is Studv Completed?: Y: √ N: ______

›id volunteer finish participation?: Y: √ N: ____ If YES, date finished: See attached list
›D MM YY

f NO. date withdrawn: ___/___/___ Reason Withdrawn: 2 patients - See attached list
›D MM YY

-8. Did anv Serious or Unexpected Adverse Incident or Reaction Occur?: Y: ______ N: √
f YES. explain:
\o serious or unexpected adverse reactions occurred, however, one patient #38 died of a different primary cancer, not related to treatment

-9. *Volunteer Follow-up: See attached list

'urpose: ____________________

›ate: /___/___ Was contact made?: Y: ______ N: _____

f no action taken. explain:

-0. *Hard Copy Records Retired: Place: ____________ File NR: ____________

-1. *Product Information:

'roduct: ____________________

Manufacturer: ____________________

ot #: Expiration Date: ____________

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