

The rationale, technique, and feasibility of partial breast irradiation using noninvasive image-guided breast brachytherapy

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ABSTRACT

PURPOSE: Noninvasive image-guided breast brachytherapy (NIBB) is a novel approach to deliver accelerated partial breast irradiation (APBI). NIBB is noninvasive, yet maintains a high degree of precision by using breast immobilization and image guidance. This makes NIBB an attractive alternative to existing APBI techniques.

METHODS AND MATERIALS: Forty patients were enrolled to an institutional review board-approved prospective clinical trial evaluating APBI using NIBB. The NIBB technique is described in detail. Briefly, patients were treated with the breast compressed and immobilized sequentially in two orthogonal axes for each fraction. Radiation was delivered using collimated emissions from a high-dose-rate iridium-192 source via specialized applicators. The prescribed dose was 34.0 Gy in 10 fractions. Feasibility and tolerability of treatment were assessed.

RESULTS: All patients completed protocol treatment. The median age was 68 years. Sixty-three percent of patients had invasive carcinoma, and 37% had ductal carcinoma in situ. All were node negative. Ninety-three percent of patients were postmenopausal. Mean tumor size, tumor bed volume, and breast volume were 1.1 cm, 22.4 cc, and 1591 cc, respectively. NIBB treatment was well tolerated. Median patient-reported discomfort was 1 on a 10-point pain scale. Treatment delivery times were reasonable. The average treatment time per axis was 14 min (5–20 min), and the average time from start of first treatment axis to completion of orthogonal axis was 43 min (30–63 min). Acute skin toxicity was Grade 0, 1, and 2 in 20%, 53%, and 28% of patients, respectively. There were no Grade 3 or greater acute toxicities observed.

CONCLUSIONS: NIBB holds promise as an alternative method to deliver APBI. NIBB is feasible and well tolerated by patients. Further investigation of NIBB to deliver APBI is warranted. © 2014 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords:

Noninvasive image-guided breast brachytherapy; NIBB; AccuBoost; Partial breast irradiation; APBI; Breast cancer

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Introduction

For patients with breast cancer, radiation after surgery has been shown to be an integral part of breast-conserving therapy, reducing the risk of recurrence and improving survival (1). Accelerated partial breast irradiation (APBI) is a radiation approach that decreases the volume of breast tissue receiving radiation and reduces the overall treatment time. Although APBI represents a significant advance in the management of breast cancer, the conventional APBI

techniques are not optimal for all patients. Noninvasive image-guided breast brachytherapy (NIBB) is a novel APBI technique that uses no invasive catheters or applicators, yet maintains a high level of precision by using breast immobilization and image guidance. This makes NIBB an attractive approach for the delivery of APBI. Here, we describe the NIBB technique in detail, present initial feasibility of using this technique to deliver APBI, and discuss the rationale for using NIBB as a novel approach to APBI.

Methods

Patient eligibility and enrollment

From 2011 to 2013, patients were enrolled on a prospective clinical trial evaluating NIBB to deliver APBI. This trial was run through the Brown University Oncology Research Group (BrUOG Br-251) and underwent review and approval by the institutional review board of each participating center (NCT01463007).

Patient eligibility was in accordance to the American Brachytherapy Society consensus guidelines for APBI (2). Patients had to be 50 years or older and had to have undergone breast-conserving surgery for invasive breast cancer or ductal carcinoma in situ (DCIS). Tumors had to be unifocal and ≤ 2 cm for invasive disease and ≤ 3 cm for DCIS. Final resection margins had to be negative by at least 2 mm. Lesser margins were acceptable when extending to the pectoralis fascia or skin. Patients with invasive disease had to have tumors that were estrogen receptor positive, had to be lymph node negative, and had to have no lymphovascular invasion. Patients were excluded if they had poor performance status, had limited life expectancy, were pregnant, had breast implants, or were diagnosed with active lupus or scleroderma.

NIBB technique

AccuBoost system

NIBB is delivered using the AccuBoost Brachytherapy System (Fig. 1) (Advanced Radiation Therapy, Inc., Billerica, MA). This system is designed and Food and Drug Administration cleared to deliver partial breast irradiation. The system uses a pair of breast immobilization plates, kilovoltage (kV) X-ray tube and film cassette, targeting grid, and a series of specialized applicators. Radiation is delivered using a high-dose-rate iridium-192 (^{192}Ir) source via remote afterloader.

Simulation

A planning CT scan was performed in the supine position for all patients. Although a CT scan is not required for the NIBB technique, it is very useful to evaluate the position and configuration of the tumor bed, delineate the number of surgical clips, and assess the relationship of

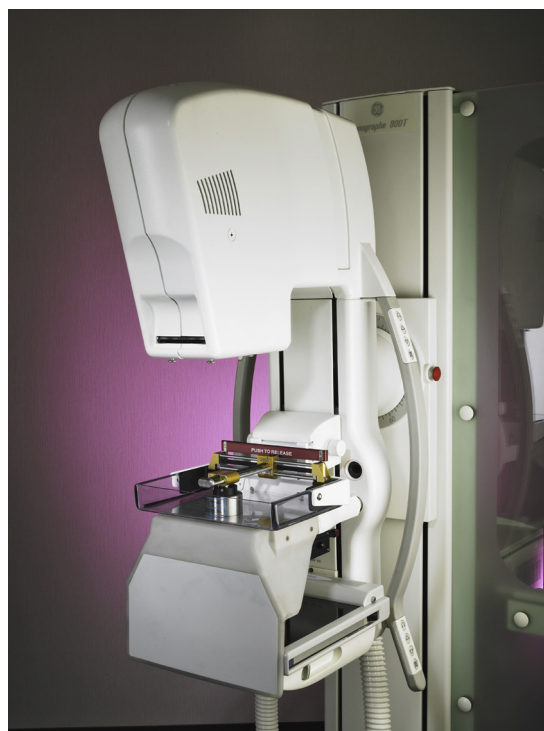


Fig. 1. AccuBoost system.

surgical clips to the tumor bed, skin, and chest wall. Despite the difference in patient and breast position between the CT simulation and NIBB, this information is helpful to determine optimal patient/breast position and ensure that the entire tumor bed is visualized on AccuBoost imaging. Surgical clips are also not required but are very helpful in ensuring that the tumor bed is well visualized and accurately defined. After CT simulation, patients undergo simulation on the AccuBoost System where kV imaging is performed in the treatment position. Patients are upright, either seated or standing, with breast compressed in two sequential orthogonal axes. To be candidates for NIBB APBI on this trial, the entire tumor bed had to be identifiable on AccuBoost imaging, the planning target volume (PTV) could be encompassed by one of the available applicators, and breast immobilization could be achieved with a separation of ≤ 8 cm.

Treatment immobilization and imaging

NIBB treatment is delivered via two orthogonal axes, typically oriented cranial–caudal and medial–lateral axes. For each treatment axis, the breast is positioned between the compression plates and immobilized with gentle compression (Figs. 2a and 2b). Maximum compression is based on patient comfort and should be less than the compression typically used with screening mammography. Once immobilized, imaging is obtained using 30 kV x-rays. This image is used to localize the tumor bed and select appropriate treatment applicators. The selected applicators

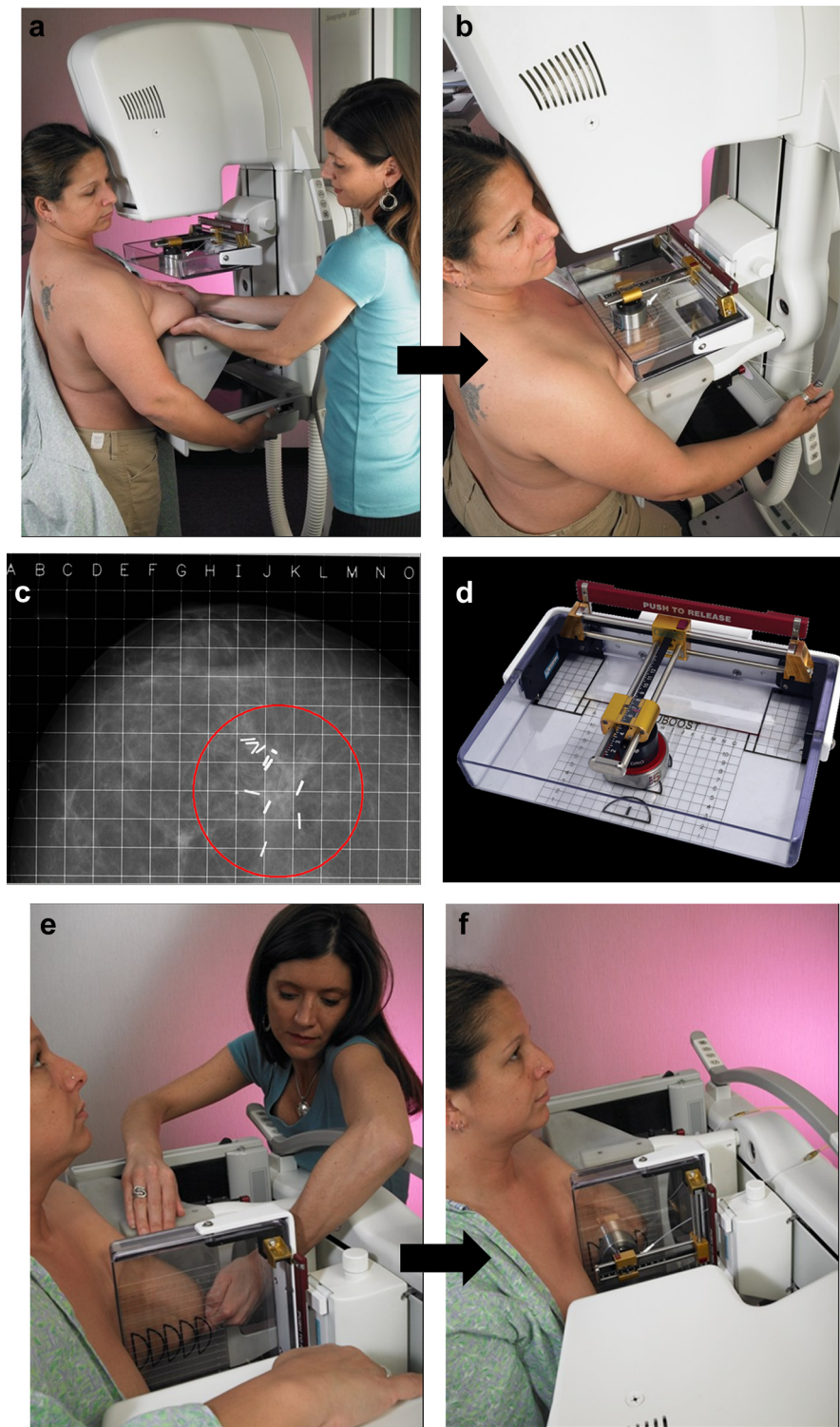


Fig. 2. Noninvasive image-guided breast brachytherapy treatment. (a, b) The breast is positioned between the compression plates and immobilized with gentle compression. A kV image is obtained where the tumor bed is identified. (c) An appropriately sized and shaped applicator is selected to target the tumor bed, and its position is determined by the localization grid. (d) The selected applicators are attached on each side of the compression plates in the selected grid position. The applicators are attached to an iridium-192 high-dose-rate remote afterloader for treatment delivery. (e, f) The process is then repeated in an orthogonal axis.

need to encompass the entire clinical target volume (CTV)/PTV (Fig. 2c). For this trial, the gross tumor volume was defined as the tumor bed as delineated by postoperative

changes, seroma, and/or surgical clips. Information from the planning CT and diagnostic imaging can be helpful to accurately define the tumor bed. Diagnostic mammography

is useful as it is performed in the same position as NIBB imaging (upright with breast compressed) and in the same orientation (cranial–caudal and medial–lateral). The CTV consisted of the gross tumor volume with a 1 cm margin expansion limited by the chest wall and skin to account for subclinical disease extension. With appropriate breast immobilization, a stable position of the tumor bed can be achieved, and thus no additional PTV expansion was used in this study.

Applicator selection and treatment delivery

Once immobilized, an appropriately sized and shaped applicator is selected to encompass the PTV. Three generations of applicators have been developed (Fig. 3). First-generation applicators consist of natural–round and D-shaped applicators. Second-generation conical–round applicators were developed to decrease both the skin dose and treatment time. These are optimized to maximally reduce skin dose (skin-dose optimized [SDO]) or to maximally decrease treatment time (dose-rate optimized). Third-generation conical–round applicators with posterior beveled wedge shielding allow for closer positioning of the applicator to the chest wall. These are also available in both dose-rate optimized and SDO. Generally, when second- and third-generation applicators were used in this trial, SDO applicators were preferentially selected to minimize skin dose. All three generation of round applicators are available in 5, 6, 7, and 8 cm sizes, and D-shaped applicators are available in 4.5, 5.3, and 6.0 cm sizes.

Based on the tumor bed location as visualized on imaging, a pair of the selected applicators is positioned on both sides of the compression plates using a localization grid (Figs. 2d and 2e). Applicators are then attached to a high-dose-rate ^{192}Ir remote afterloader for treatment delivery. The ^{192}Ir source travels through a circular channel at the base of each applicator. The tungsten shielding of each applicator collimates and directs the ^{192}Ir source photon

emission at the tumor bed (Fig. 4). Treatment is delivered in a parallel–opposed fashion. Source dwell positions within the applicators are symmetrically oriented at 1.0 cm intervals. The dwell positions for each applicator are predetermined and based on the applicator size and type. Source dwell times at each dwell position are equivalent and determined using a planning nomogram taking into account intended dose, source strength, breast separation, and selected applicator type and size.

After completion of treatment, breast compression is released, and the process is repeated along the orthogonal axis (Figs. 2e and 2f). The use of two orthogonal axes for each fraction results in conformal dose distribution to the target volume with decreased dose to skin and nontarget breast tissue compared with single axis treatment (Fig. 5).

Dose prescription

A prescription dose of 34.0 Gy in 10 fractions is delivered either twice daily over 1 week or once daily over 2 weeks. Twice-daily treatments are delivered at least 6 h apart. The choice of daily vs. twice-daily treatment in this trial was based on patient preference.

The treatment dose is prescribed to the midplane between paired applicators (100% isodose line). Patient-specific three-dimensional (3D) dosimetry is currently not available because of the significant amount of tissue deformity between the orthogonal treatment axes. Coverage of the PTV is based on two-dimensional treatment planning for each individual axis. 3D dosimetry models demonstrate good coverage of the PTV with this approach as discussed later.

Feasibility and outcomes assessment

Feasibility and patient tolerability of treatment were evaluated. Patient who reported discomfort during treatment was scored based on a standard 10-point pain scale. Toxicity was graded based on Common Terminology Criteria for Adverse Events, version 3.0. Acute toxicity



Fig. 3. Noninvasive image-guided breast brachytherapy applicators. Third-generation conical–round applicators with posterior wedge shielding.

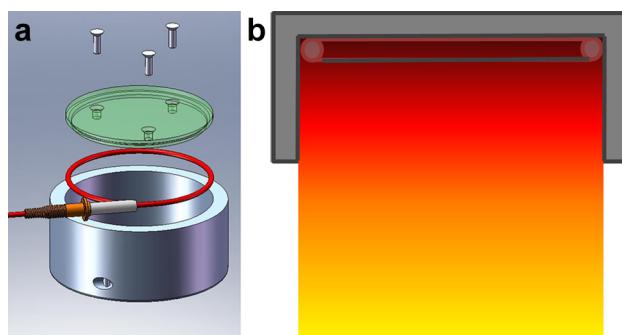


Fig. 4. (a) Applicator schematic. Circular channel at base of each applicator allows for high-dose-rate iridium-192 (^{192}Ir) source transit and dwell positions. (b) Tungsten alloy shielding collimates the photon emissions from the Ir source into a beam-like distribution.

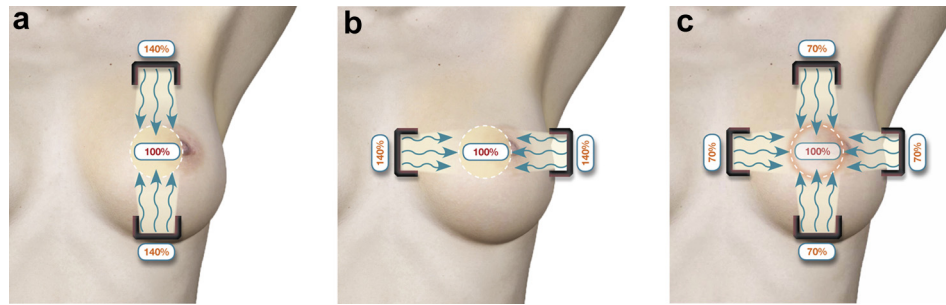


Fig. 5. (a, b) Use of two sequential orthogonal axes (c) results in conformal dose to the tumor bed with decreased dose to skin and nontarget breast tissue. Maximal skin dose varies based on prescription dose, applicator size and type, and the breast separation with compression. Approximate skin dose depicted is for a 6 cm round skin-dose optimized applicator at a breast separation of 6 cm.

was assessed during treatment and at 2- and 6-week follow-up. Late toxicity, cosmetic outcome, and tumor recurrence are prospectively assessed at regular followup intervals and will be reported separately as these outcomes mature.

Results

Forty patients were enrolled and completed protocol treatment. The median patient age was 68 years. Ninety-three percent of patients were postmenopausal. Sixty-three percent of patients had invasive carcinoma, and the remainder had DCIS. Mean tumor size was 1.1 cm. Most tumors were estrogen receptor positive (98%), and all patients were lymph node negative. Mean postsurgical tumor bed volume was 22.4 cc, mean PTV volume was 121.5 cc, and mean ipsilateral breast volume was 1591 cc (Table 1). Most patients (72.5%) were treated on a once-daily

schedule. Treatments were delivered using a first-, second-, and third-generation applicator 43.6%, 49.8%, and 6.6% of the time, respectively. The most commonly used applicator sizes were 4.5 D shape and 5.0 round.

All evaluable patients completed treatment. One additional patient was enrolled who had a significant treatment delay during her radiation course because of intracurrent illness unrelated to her breast cancer diagnosis or her radiation therapy. She ultimately completed her course of treatment but because of treatment under a nonprotocol time line was removed from the trial. Overall, treatment was well tolerated. Median patient-reported discomfort during treatment was 1 (range, 0–7) on a standard 10-point pain scale. Treatment delivery times were reasonable. During the first fraction, patients often required repositioning to adequately target the tumor bed. Thereafter, most patients were able to be effectively positioned and treated on the first attempt. The resulting average duration of radiation treatment time per axis was 14 min (range, 5–20 min), and the average time from start of first treatment axis to completion of orthogonal treatment axis was 43 min (range, 30–63 min).

Skin reaction was the most common radiation-related acute toxicity (Table 2). No acute skin reaction was noted in 20% of patients, whereas faint skin erythema (Grade 1) and moderate skin erythema (Grade 2) developed at the applicator site in 53% and 28% of the patients, respectively. No patient developed moist desquamation or Grade 3 or greater acute skin toxicity. There were no Grade 3 or greater acute toxicities of any kind observed. The most common acute toxicity other than skin reaction was fatigue, which was a maximum of Grade 2 in 5% of patients.

Discussion

Although whole breast radiation after breast-conserving surgery marks a significant advance in the management of early stage breast cancer, it requires a protracted course of daily treatments, up to 6–7 weeks, which can be disruptive to the patient's life. In addition, as many as one-third of patients will develop a significant skin reaction with moist desquamation (3). These acute reactions are associated with

Table 1
Treatment characteristics

Characteristics	Mean	Range
Tumor size, cm	1.1	0.3–3.0
Whole breast volume, cc	1591	365–3659
Tumor bed volume, cc	22.4	1.1–69.6
PTV, cc	121.5	33.0–461.5
Breast compression, cm	6.5	3.4–9.4
Treatment schedule	n (%)	
Daily	29 (72.5)	
BID	11 (27.5)	
Applicators	n (%) ^a	
Type		
First generation	359 (43.6)	
Second generation	398 (49.8)	
Third generation	53 (6.6)	
Size		
4.5 D-shape	254 (31.8)	
5.3 D-shape	95 (11.9)	
5.0 Round	212 (26.5)	
6.0 Round	142 (17.8)	
7.0 Round	81 (10.1)	
8.0 Round	16 (2.0)	

PTV = planning target volume; BID = twice daily.

^a Number of treatment axes using designated applicator, two treatment axes were used for each fraction of radiation.

Table 2
Acute toxicity

Toxicity	Grade/frequency
Pain (0–10)	
Median	1
Mean	1.7
Range	0–7
Fatigue, n (%)	
Grade 0	22 (55)
Grade 1	16 (40)
Grade 2	2 (5)
Grade 3+	0 (0)
Acute skin reaction, n (%)	
Grade 0	8 (20)
Grade 1	21 (52.5)
Grade 2	11 (27.5)
Grade 3+	0 (0)

pain and a reduction in health-related quality of life (3, 4). Furthermore, underlying normal tissue structures, including the lung and heart, often receive some incidental radiation with whole breast radiation techniques. These organs are potentially at risk for long-term complications and can result in treatment-related morbidity and mortality (1, 5).

To address these drawbacks, the concept of APBI has emerged. It arose out of the realization that most tumor recurrences occur at or near the region of the lumpectomy site, suggesting that for well-selected patients, radiation therapy may be safely limited to the tissue within and directly surrounding the tumor bed (6, 7). In reducing the treatment volume, a higher dose of radiation can be delivered in each treatment session, thereby reducing the overall treatment time. Furthermore, the more conformal radiation treatment results in reduced volume of treated breast tissue and reduced exposure to the heart and lung. APBI thus potentially reduces risk for acute and late toxicity with the added patient convenience of a shorter treatment schedule (8). In North America, the most commonly used APBI techniques are interstitial multicatheter brachytherapy (IMB), intracavitary brachytherapy (ICB), and external beam three-dimensional conformal radiation therapy (3D-CRT). These techniques have resulted in excellent tumor control rates and good outcomes with regard to toxicity and cosmesis in many patients (9–22). However, these techniques have not been optimal for all patients.

The IMB and ICB techniques have the advantage of delivering radiation directly to the tumor bed. A typical CTV expansion of 1–1.5 cm beyond the lumpectomy cavity is used to account for subclinical disease. There is no need for additional PTV margin expansion. The disadvantage of IMB and ICB is that these techniques are invasive requiring the percutaneous placement of catheters, which need to remain in place for the entire treatment duration. This is not acceptable to many patients. In addition, instrumentation-related infection is a known complication that can have a deleterious effect on cosmetic outcome (23). Another disadvantage of IMB and ICB is the steep dose gradients seen with these techniques. Portions of

breast tissue receive doses of 150% and even 200% of the prescription dose. The volume of these high-dose regions has been associated with late tissue toxicity (24).

APBI using external beam 3D-CRT was designed as a noninvasive alternative to APBI using IMB and ICB and gained rapid popularity among both patients and clinicians. The disadvantage of 3D-CRT APBI is the need for an additional PTV margin expansion. Typically, a combined CTV and PTV expansion of 2.5 cm beyond the lumpectomy cavity is used. The addition of a PTV margin is necessary to account for interfraction and intrafraction inaccuracies because of daily setup variation, breast and patient motion, and respiratory motion. This PTV expansion, however, results in substantially larger volume of nontarget normal breast tissue within the irradiated volume. Data presented from Tufts/Brown Universities showed a higher than expected rate of late toxicity and suboptimal cosmetic outcome with this technique (25, 26). Dosimetric analysis showed that both toxicity and fair-to-poor cosmetic outcome correlated with the volume of breast tissue

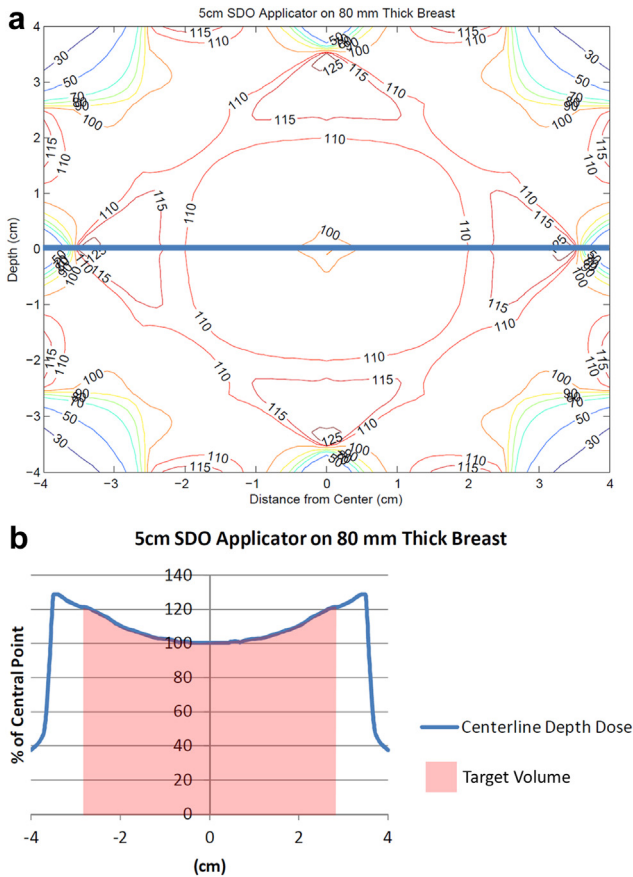


Fig. 6. Composite dosimetry using a fixed model. The example images depict full coverage of tumor bed by the prescription dose with relative sparing of skin and nontarget breast tissue. (a) The isodose distribution is depicted for an 8 cm block of tissue treated without compression/deformation using 5 cm SDO applicators in parallel–opposed fashion along two orthogonal axes. (b) Depth dose curve along the central axis. SDO = skin-dose optimized.

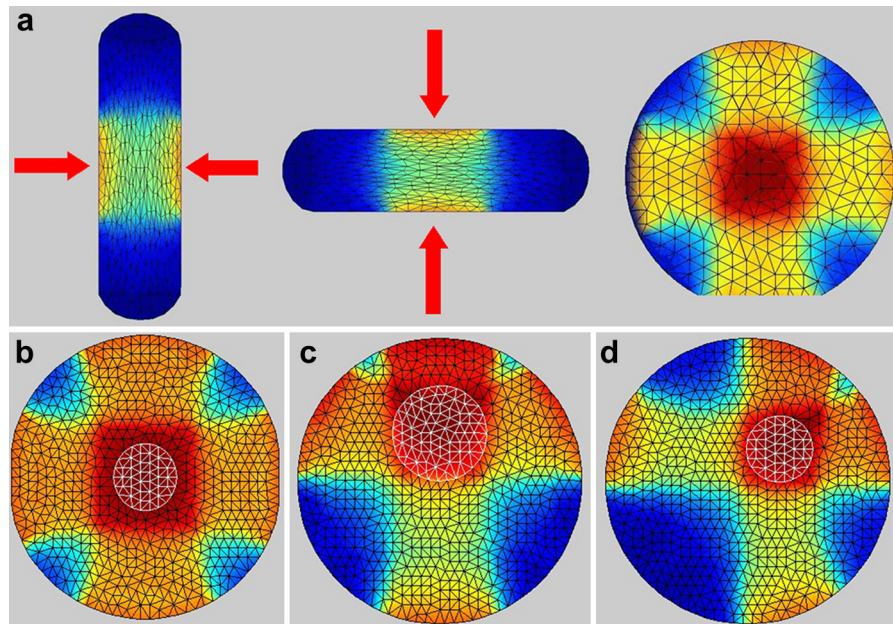


Fig. 7. Composite dosimetry using a deformable finite element analysis (FEA) model. This model was created using a two-dimensional Galerkin finite element method approach that provided the ability to track the displacement of tissue as a function of serial compression along orthogonal axes. (a) Individual FEA cells were tracked through serial compression with dose recorded and summated from treatment in each orthogonal exposure. (b–d) The example images depict full coverage of tumor bed by the prescription dose with relative sparing of skin and nontarget breast tissue for varying target size, target location, and extent of breast compression. (b) A 3.5 cm tumor bed positioned centrally treated with compression from 14 to 6 cm along each treatment axis. (c) A 5.0 cm tumor bed positioned off center treated with compression from 14 to 6 cm. (d) A 3.5 cm tumor bed positioned eccentrically with treated compression from 14 to 5 cm.

irradiated. A prospective trial of 3D-CRT APBI performed at the University of Michigan showed similar suboptimal cosmetic results (27). These early results have now been validated by the Canadian RAPID (Randomized Trial of Accelerated Partial Breast Irradiation) trial. This Phase III trial randomized patients to 3D-CRT APBI or whole breast irradiation. Olivotto *et al.* (28) presented interim cosmetic

and toxicity result and showed that the rate of good-to-excellent cosmetic outcome decrease from 83–82% with whole breast irradiation to 74–65% with 3D-CRT APBI, based on assessment by the patient, nurse, and blinded physician panel ($p < 0.001$).

APBI using NIBB holds potential advantages over APBI using other techniques. Similar to IMB and ICB, NIBB has

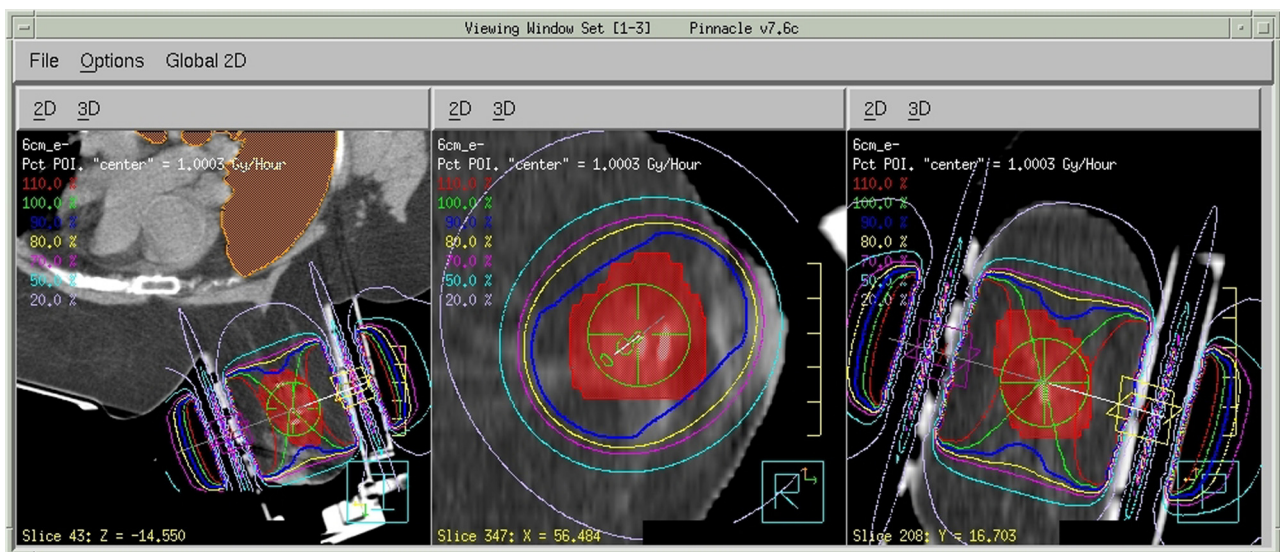


Fig. 8. Dosimetry model using CT data of patients simulated with breast compression and modeled dose distribution of noninvasive image-guided breast brachytherapy applicators (31).

the advantage of delivering radiation to the tumor bed with a high degree of precision. However, unlike IMB or ICB, NIBB is completely noninvasive. NIBB is thus more acceptable to patients not willing to undergo percutaneous catheter placement and carries no instrumentation-related risk of infection. However, unlike the 3D-CRT technique, NIBB does not require additional PTV margin expansion. By using breast immobilization and image guidance for each fraction of radiation, the inaccuracies related to set up errors and patient or breast motion are eliminated. Furthermore, breast compression displaces nontarget breast tissue out of the irradiation field. This results in much smaller target and irradiated volumes, thereby reducing the risk of toxicity associated with larger treatment volumes as seen with 3D-CRT APBI (25). Thus, NIBB APBI has the potential to reduce the higher rate of toxicity and sub-optimal cosmetic outcome reported with the 3D-CRT technique.

Dosimetric evaluation of the NIBB applicators and technique has been performed (29–31). One of the current limitations of the NIBB technique is that treatment planning is limited to simple two-dimensional planning of each individual treatment axis. Patient-specific composite 3D treatment planning is not currently available. Composite dosimetry has been a challenge because of significant tissue deformity from one compressed state to the compressed state in the orthogonal treatment axis. To verify the dose distribution using NIBB, composite 3D dosimetry has been evaluated using several models. Figures 6 and 7 depict examples of composite dosimetry using a fixed model with no tissue compression or deformity and a deformable model simulating sequential compression via two orthogonal axes. Both models show coverage of the target volume by the prescription dose with relative sparing of nontarget tissues.

Using a relatively low-energy brachytherapy source externally to treat a target at depth, the skin dose needs to be a consideration. Skin dose using NIBB in this study was limited by using two orthogonal axes for each treatment, ensuring that there was no significant skin overlap between treatment axes, and limiting breast separation with compression to ≤ 8 cm. Although the optimal skin dose constraint for this technique is not yet known, using these restrictions, the resulting maximum skin dose is expected to be $<100\%$ of prescription dose. Dose to the chest wall or structures deep to the chest wall, that is heart and lung, is not expected to be a concern using the NIBB technique as the treatment axes are tangential to the chest wall. The resulting dose to the chest wall is expected to be significantly less than prescription dose in all scenarios. This has been confirmed by direct measurements (32).

To further evaluate the 3D dosimetry of NIBB, Sioshansi et al. (31) performed a modeling study of composite dosimetry using CT data sets of patients undergoing simulated breast compression. They performed a dosimetric comparison between NIBB and 3D-CRT techniques for the delivery of APBI (Fig. 8). This comparison showed

good target coverage by the prescription dose for both NIBB and 3D-CRT, V_{90} of 96% and 100%, respectively. However, the doses delivered to normal tissues were significantly lower with NIBB. PTVs were 50% smaller with NIBB. The maximum skin dose (D_{max}) was 10% lower. The chest wall and lung D_{max} were lower by factors of 3.0 and 4.8, respectively. Dose distribution was more heterogeneous for NIBB compared with 3D-CRT but less heterogeneous than other brachytherapy techniques.

Based on the potential advantages of NIBB, the current trial was initiated. Early experience shows that NIBB to deliver APBI is feasible. The technique was well tolerated by all patients with minimal discomfort related to breast compression. Acute toxicities were mild and infrequent. Treatment times were acceptable with most patients completing each treatment within 1 h. Followup is needed to assess efficacy, late toxicity, and cosmetic outcome of this novel APBI approach.

Conclusion

NIBB holds promise as an alternative method to deliver APBI. NIBB is feasible and well tolerated by patients. Further investigation of NIBB to deliver APBI is warranted.

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