CLINICAL INVESTIGATION

DOSE MODELING OF NONINVASIVE IMAGE-GUIDED BREAST BRACHYTHERAPY IN COMPARISON TO ELECTRON BEAM BOOST AND THREE-DIMENSIONAL CONFORMAL ACCELERATED PARTIAL BREAST IRRADIATION

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Purpose: To perform dose modeling of a noninvasive image-guided breast brachytherapy (NIIGBB) for comparison to electrons and 3DCRT.

Methods and Materials: The novel technology used in this study is a mammography-based, noninvasive breast brachytherapy system whereby the treatment applicators are centered on the planning target volume (PTV) to direct 192Ir emissions along orthogonal axes. To date, three-dimensional dose modeling of NIIGBB has not been possible because of the limitations of conventional treatment planning systems (TPS) to model variable tissue deformation associated with breast compression. In this study, the TPS was adapted such that the NIIGBB dose distributions were modeled as a virtual point source. This dose calculation technique was applied to CT data from 8 patients imaged with the breast compressed between parallel plates in the cranial–caudal and medial–lateral axes. A dose–volume comparison was performed to simulated electron boost and 3DCRT APBI.

Results: The NIIGBB PTV was significantly reduced as compared with both electrons and 3DCRT. Electron boost plans had a lower Dmin than the NIIGBB technique but higher V100, D90, and D95. With regard to PTV coverage for APBI, the only significant differences were minimally higher D90, D100, V80, and V90, with 3DCRT and Dmax with NIIGBB. The NIIGBB technique, as compared with electrons and 3D-CRT, achieved a lower maximum dose to skin (60% and 10%, respectively) and chest wall/lung (70–90%).

Conclusions: NIIGBB achieves a PTV that is smaller than electron beam and 3DCRT techniques. This results in significant normal tissue sparing while maintaining dosimetric benchmarks to the target tissue. © 2010 Elsevier Inc.

APBI, boost, breast, brachytherapy.

INTRODUCTION

Current noninvasive approaches for partial breast irradiation (PBI) use external-beam modalities such as en face electrons and three-dimensional conformal radiation (3DCRT). The application of these techniques typically requires extensive target volume expansion to account for uncertainty in tumor bed localization, intrinsic daily setup error, respiratory motion, and allowances for radiation beam physical penumbra. Bartelink et al. used a minimum margin expansion of 1.5 cm in the European Organization for Research and Treatment of Cancer (EORTC) boost vs. no boost trial (1), and the currently active Radiation Therapy Oncology Group (RTOG) 0413 protocol investigating accelerated partial breast irradiation (APBI) uses a 2.5-cm margin expansion for patients treated with 3DCRT APBI (2). The advent of computed tomography (CT)–based PBI planning has not definitively resulted in improved targeting accuracy. For example, Landis et al. found as much as a threefold range in the volume of tissue that was delineated as target by experienced physicians using CT for definition of the breast excision cavity (3). Mammography-guided breast irradiation is unique to the novel technology that is being evaluated in this study. Consequently, mammography has not been extensively studied for lumpectomy cavity localization for radiation planning purposes. However, mammographically detected postoperative changes in the breast are well characterized (4,5).
Furthermore, the accuracy of mammographic target localization has been well established in other clinical contexts including mammography-based biopsy and preoperative needle-localization.

The novel technology used in this study is a noninvasive, image-guided breast brachytherapy (NIIGBB) system designed to deliver PBI without the uncertainties associated with CT target delineation, respiratory motion, and daily setup error. Currently, the NIIGBB system (Advanced Radiation Therapy, Inc., Billerica, MA) is most commonly being used as an alternative to electron beam for tumor bed boost in conjunction with whole-breast irradiation. Application to APBI as an alternative to photon external beam 3DCRT is being explored. The objective of this study was to perform 3D dose modeling and dose–volume analysis of the NIIGBB system for comparison to electron beam boost and 3DCRT APBI techniques.

METHODS AND MATERIALS

NIIGBB system and applicators

The NIIGBB system consists of breast immobilization via moderate compression between mammography paddles followed by image guidance using ~30 kVp x-rays. Tungsten alloy applicators mounted on the mammography paddles are centered on the target and direct high-dose-rate (HDR) $^{192}$Ir photons along two intersecting orthogonal axes in a sequential manner (Fig. 1). Although dosimetric characterization of individual applicators has been performed (6, 7), 3D dose modeling has not been examined because of limitations in conventional brachytherapy treatment planning systems (TPS) to model variable tissue deformation as a consequence of sequential breast compression along orthogonal axes.

Reusable applicators for the NIIGBB system come in an assortment of sizes and shapes to accommodate a variety of excision cavity contours (Fig. 2). The round applicators used in this study ranged from 5 to 8 cm in diameter and were mounted on the external surface of the mammography paddles in a parallel-opposed manner. A catheter lines the inside of the applicator, positioned 2.767 cm above the skin surface directing the HDR $^{192}$Ir source to each circumferential dwell position spaced 10 mm apart. The number of dwell positions is proportional to the applicator circumference where applicator diameter (cm) × 3 = number of dwell positions.

Patient selection and simulation

Patients selected for the study had to meet the following criteria:
1. a clearly defined excision cavity on CT,
2. $0.5$ cm between the posterior aspect of excision cavity and chest wall, and
3. a breast that could be comfortably compressed to $\leq 8$ cm. Eight patients who met
these criteria were scanned in the prone position on a specially con-
structed board such that the breast fell freely away from the chest
wall and then was compressed with the Kuske breast applicator (Nu-
cletron Corp., Veenendaal, the Netherlands). The Kuske breast ap-
plicator is a CT-compatible, parallel-plate breast compression
device that readily simulated the mammographic compression pad-
dles for the purposes of this study. Two CT datasets were obtained
with sequential cranial–caudal (CC) and medial–lateral (ML) com-
pression. A third CT dataset of the patient in the conventional supine
breast-board position was also obtained for electron boost and
3DCRT APBI planning. The CT simulation was acquired with 3-
mm slice thickness using the AccuSim CT simulator (Philips Med-
ical Systems, Cleveland, OH). All datasets were entered into version
8.0dp1 of the Pinnacle TPS (Philips Medical Systems, Cleveland,
OH). The study was performed under approved institutional review
board protocol.

**Study design**

Boost (NIIGBB technique or electrons) and APBI (NIIGBB tech-
nique or 3DCRT) plans were performed for each patient. All lump-
ectomy cavity contouring was performed by one author and
confirmed by the senior author. The following target volume dosi-
metric parameters were assessed: $D_{\text{min}}$, $D_{\text{mean}}$, $D_{\text{max}}$, $V_{50}$, $V_{80}$,
$V_{90}$–$V_{100}$, $V_{110}$–$D_{50}$, $D_{90}$, $D_{100}$, as well as $D_{\text{max}}$ for the skin,
chest wall, and lung. $D_{\text{min}}$, $D_{\text{mean}}$, $D_{\text{max}}$ are defined as the minimum,
mean, and maximum dose delivered to a given volume. $V_x$ is defined
as the percentage of the volume receiving "x" percent of the pre-
scription dose. $D_x$ is defined as the percent of the prescription
dose that is delivered to "x" percent of a given volume. Separate
comparisons of these parameters were performed for the boost tech-
niques (NIIGBB vs. electrons) and APBI techniques (NIIGBB vs.
3DCRT). For comparison compatibility, the same simulated fraction-
ation regimens were used for the boost techniques (2 Gy per
fraction) and for the APBI techniques (38.5 Gy in 10 fractions).

**NIIGBB planning**

The excision cavity was delineated on CT (CC and ML) as a gross
target volume (GTV). The GTV was expanded by 0.5 cm and 1.0
cm, respectively, for the NIIGBB boost and APBI clinical target vol-
umes (CTV). The decision to use a 1-cm GTV to CTV expansion for
NIIGBB was made so as to be consistent with other brachytherapy
APBI techniques. The expanded volume was limited to the skin sur-
face. Additional margin between the CTV and the planning target
volume (PTV) was not necessary because the NIIGBB system
uses breast immobilization and image guidance before each dose frac-
tion minimized inter- and intrafractional motion. The NIIGBB
applicator size was selected to achieve $\geq95\%$ target volume cover-
age with the 90% isodose line. For purposes of this study, dose was
calculated at the 100% isodose line. The average of CC and ML plans
was used to calculate $D_{\text{mean}}$, $V_{50}$, $V_{80}$–$V_{90}$–$V_{100}$, $V_{110}$–$D_{50}$–
$D_{90}$–$D_{100}$, and $D_{100}$. Cumulative doses from the CC and ML plans were
reported for PTV $D_{\text{max}}$ and PTV $D_{\text{min}}$ and $D_{\text{max}}$ for the skin, chest
wall, and lung.

**Dose calculation algorithm**

Conventional treatment planning systems cannot account for
high-Z shielding and collimation. To address this limitation, Rivard
et al. developed a dose calculation algorithm to use commercially
available TPS such that cylindrical dose distributions are modeled
as virtual point sources with appropriate radial dose and two-

<table>
<thead>
<tr>
<th>PTV vol (cm$^3$)</th>
<th>PTV $D_{\text{min}}$ (Gy)</th>
<th>PTV $D_{\text{mean}}$ (Gy)</th>
<th>PTV $D_{\text{max}}$ (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median NIIGBB</td>
<td>44.2</td>
<td>1.77</td>
<td>2.07</td>
</tr>
<tr>
<td>p25%–p75%</td>
<td>30.8–73.7</td>
<td>1.67–1.86</td>
<td>1.96–2.09</td>
</tr>
<tr>
<td>Median electron</td>
<td>68.8</td>
<td>1.11</td>
<td>2.14</td>
</tr>
<tr>
<td>p25%–p75%</td>
<td>43.5–110</td>
<td>1.00–1.58</td>
<td>2.10–2.16</td>
</tr>
<tr>
<td>$p$ Value</td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Abbreviations: NIIGBB = noninvasive image-guided breast brachytherapy; PTV = planning target volume.*
Cumulative dose evaluation for NIIGBB

The cumulative target volume D_{max} was obtained by identifying the tissue within the target volume that received the maximum dose in the CC plan and then identifying the same tissue in the ML plan. The calculated dose to this tissue in the ML plan was obtained and added to the D_{max} value from the CC plan. The same process was used to obtain the cumulative target volume D_{min}.

Surface wires were used to identify the composite skin D_{max}. Before being scanned, the patients had adhesive barium wires placed on the breast from the nipple toward the chest wall (Fig. 3). A double wire was placed at the 12:00 position to serve as the reference wire with single wires placed 45° apart at the 1:30, 3:00, 4:30, 6:00, 7:30, 9:00, and 10:30 positions. On CT, the skin directly beneath each wire was contoured individually and the wire receiving the highest dose on the CC plan was identified. The distance from the nipple to the point of highest dose along the wire was measured. This same position along the same wire was readily identified on the ML plan and the point doses from CC and ML plans were added to generate a value for the skin D_{max}. The same process in the reverse order (ML → CC) was also performed such that the wire receiving the highest dose on the ML plan was identified and then the same position along that wire on the CC plan was identified such that the doses were added. The two cumulative skin D_{max} values (CC → ML vs. ML → CC) were within 10% concordance and the largest D_{max} values were recorded.

Doses to chest wall and lung were minimal with the NIIGBB technique, <10% of the prescription dose delivered with one axis.

Table 3. NIIGBB boost vs. electron beam boost treatment planning results for PTV coverage on average. For simplification, the composite chest wall D_{max} was obtained by adding the maximum chest wall doses from the CC and ML plans. The same approach was used for lung D_{max}.

**Electron boost planning**

As with the NIIGBB planning, electron fields were planned with the excision cavity delineated as the GTV then uniformly expanded 0.5 cm to create the CTV. The expanded volume was limited to the skin surface. The electron energy was selected so the 90% isodose line completely encompassed the CTV. Additional margin for beam penumbra was allowed, but additional CTV to PTV expansion was not performed so as to maintain a balanced comparison between the boost techniques. The simulated prescription dose was to the 90% isodose line. Electron energies range from 6 MeV to 20 MeV (Varian Medical Systems, Palo Alto, CA).

**3DCRT APBI planning**

Target volume margin expansion and planning were performed in strict adherence to the RTOG 0413 protocol with the exception of using a smaller GTV to CTV margin expansion in order to maintain consistency with the NIIGBB APBI technique to allow for a valid comparison of the dosimetry. In brief, the excision cavity was expanded by 1 cm (instead of 1.5 cm) and then limited to the posterior breast tissue extent (pectoralis muscle and chest wall were not included) and 0.5 cm from the skin surface. This volume was designated as CTV, expanded 1.0 cm as PT, and used to generate the beam aperture with the additional margin accounting for beam penumbra. The PTV was then limited to the posterior breast tissue extent and 0.5 cm from the skin surface as PTV_EVAL, and used for DVH analysis and comparison to the NIIGBB plans. From 3 to 5 noncoplanar 6-MV photon beams were used, and the critical organ dose constraints set by the RTOG 0413 protocol were respected.

**Statistical analysis**

Because of the sample size (n = 8), median values of the dose–volume parameters of the entire study cohort were analyzed. The respective median values of each dosimetric parameter for the boost and APBI techniques were compared (e.g., skin D_{max} for the NIIGBB boost was compared to electron boost, and skin D_{max} for the NIIGBB APBI was compared with 3DCRT APBI). A nonparametric signed-rank test was used to compare the techniques for each parameter, based on the difference score. Statistical comparisons were performed using version 9.1.3 of the SAS software (SAS Institute, Cary, NC). A p ≤ 0.05 threshold was used to determine statistical significance. Results were reported with 25% and 75% interquartile range values.

**RESULTS**

The comparison of boost techniques is summarized in Tables 1 to 3. Despite using the same 0.5-cm expansion,
Table 4. NIIGBB APBI vs. 3DCRT APBI treatment planning results for the PTV with dose normalized to 38.5 Gy

<table>
<thead>
<tr>
<th>PTV Vol (cm³)</th>
<th>PTV Dmin (Gy)</th>
<th>PTV Dmean (Gy)</th>
<th>PTV Dmax (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median NIIGBB</td>
<td>77.9</td>
<td>33.9</td>
<td>39.5</td>
</tr>
<tr>
<td>p25%–p75%</td>
<td>58.2–119</td>
<td>29.3–35.5</td>
<td>37.1–40.0</td>
</tr>
<tr>
<td>Median 3DCRT</td>
<td>149.1</td>
<td>31.7</td>
<td>38.5</td>
</tr>
<tr>
<td>p25%–p75%</td>
<td>138.6–274</td>
<td>30.1–33.5</td>
<td>38.0–38.7</td>
</tr>
<tr>
<td>p Value</td>
<td>0.01</td>
<td>0.38</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Abbreviations: APBI = accelerated partial breast irradiation; 3DCRT = three-dimensional conformal radiation therapy; NIIGBB = noninvasive image-guided breast brachytherapy; PTV = planning target volume.

The NIIGBB boost target volumes were 64% of the electron boost volumes (p = 0.02). The lumpectomy cavity contoured volumes were consistently smaller in the compressed breasts than in the uncompressed breasts for any given patient. This discrepancy is likely related to how the lumpectomy cavity deforms in response to compression. As a measure of internal quality control related to target delineation, it is important to note that there was remarkable consistency (within 10%) between the lumpectomy cavity volumes between the ML and CC compression scans for any given patient. PTV coverage for the boost techniques revealed no statistically significant differences between the two techniques for the PTV V110, V90, V80, V50, V20, Dmax, or D100. There was a statistically significant difference between the boost techniques PTV Dmean, but only by 0.07 Gy (2.07 Gy for the NIIGBB boost vs. 2.14 Gy for electron boost, p = 0.01). Electron boost plans had a lower Dmin than the NIIGBB brachytherapy boost (1.11 Gy vs. 1.77 Gy, p = 0.02) but higher V100 (98.1% vs. 54.6%, p = 0.01), D90, and D50. Boost delivered with the NIIGBB technique resulted in median skin Dmax 20% lower than with electron boost. Compared with an electron boost, the NIIGBB technique delivered significantly less dose to the chest wall and lung by factors of 7 and 11, respectively. Of note, the highest electron energy used for electron boost planning was 16 MeV, and the majority of patients were treated with 12 MeV or lower energy.

A comparison of APBI techniques is summarized in Tables 4 to 6. The NIIGBB APBI target volumes were 50% smaller than the 3DCRT APBI volumes (p = 0.01). The PTV coverage for the APBI techniques revealed a slightly higher D90 (93.1% vs. 96.3%, p = 0.02), D100 (71.4% vs. 85.8%, p = 0.02), V80 (99.9% vs 100%, p = 0.03), and V90 (95.9% vs. 99.9%, p = 0.01) with 3DCRT. The NIIGBB APBI PTV Dmax was higher with only borderline statistical significance (45.5 Gy vs. 40.2 Gy, p = 0.055). There were no statistically significant differences between the two techniques for PTV Dmin, Dmean, V50, V100, and D50. The NIIGBB APBI skin Dmax was 10% lower than 3DCRT, and delivered significantly less dose to the chest wall and lung by factors of 3.0 and 4.8, respectively.

A critical issue for the NIIGBB system evaluation as compared with external beam PBI techniques is the question of relative skin dose. The dosimetric profile of a single NIIGBB applicator is such that maximum dose is delivered at the skin surface. To achieve skin sparing with the NIIGBB system, treatment is delivered with a combination of four applicators oriented in two orthogonal axes. A novel technique was developed for this study to measure this effect in a 3D planning system (Figs. 3 and 4). The use of wires on the skin of the breast allowed accurate and reproducible calculation of composite dose to the skin in any designated region. This method demonstrated that maximum skin dose with the NIIGBB technique was significantly lower than that of electron boost and 3DCRT APBI (Tables 3 and 6). Furthermore, this method provided evidence supporting two fundamental assumptions inherent in the NIIGBB technique: (1) distribution of the delivered radiation dose over four nonoverlapping areas of skin beneath the two CC and two ML applicators; and (2) sequential breast compression such that the skin receiving maximum dose in one compression axis was effectively displaced to the low-dose region in the orthogonal compression axis.

The NIIGBB system directs radiation parallel to the chest wall, in contrast to the en face beam orientation with electron boost or tangentially oblique to the chest wall as with most 3DCRT beams. As such, doses to the chest wall and lung were comparatively negligible with NIIGBB (Tables 3 and 6).

Table 5. NIIGBB APBI vs. 3DCRT APBI treatment planning results for PTV coverage

<table>
<thead>
<tr>
<th>PTV V50 (%)</th>
<th>PTV V80 (%)</th>
<th>PTV V90 (%)</th>
<th>PTV V110 (%)</th>
<th>PTV V100 (%)</th>
<th>PTV D50 (%)</th>
<th>PTV D90 (%)</th>
<th>PTV D100 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median NIIGBB</td>
<td>100</td>
<td>99.9</td>
<td>95.9</td>
<td>54.4</td>
<td>22.2</td>
<td>100.8</td>
<td>93.1</td>
</tr>
<tr>
<td>p25%–p75%</td>
<td>100–100</td>
<td>99.4–100</td>
<td>91.9–97.7</td>
<td>47.7–56.4</td>
<td>18.9–25.6</td>
<td>99.9–102.2</td>
<td>91.3–93.7</td>
</tr>
<tr>
<td>Median 3DCRT</td>
<td>100</td>
<td>100</td>
<td>99.9</td>
<td>57.4</td>
<td>&lt;0.1%</td>
<td>99.8</td>
<td>96.3</td>
</tr>
<tr>
<td>p25%–p75%</td>
<td>100–100</td>
<td>99.6–100</td>
<td>45.9–70</td>
<td>NA</td>
<td>98.9–100.6</td>
<td>95.2–98</td>
<td>83.7–88.6</td>
</tr>
<tr>
<td>p Value</td>
<td>NA</td>
<td>0.03</td>
<td>0.01</td>
<td>0.46</td>
<td>NA</td>
<td>0.31</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Abbreviations: APBI = accelerated partial breast irradiation; 3DCRT = three-dimensional conformal radiation therapy; NIIGBB = noninvasive image-guided breast brachytherapy; NA = not applicable; PTV = planning target volume.
DISCUSSION

Image guidance and methods to account for or reduce target motion have become an integral part of radiation therapy. The application of these principles to breast irradiation with a brachytherapy technique could result in improved accuracy of dose delivery to the tumor bed as part of conventional whole breast irradiation and provide an alternative to 3DCRT external beam APBI. The purpose of this study is to provide a dose modeling comparison analysis; the study is not designed to provide clinical recommendations.

Patients included in this analysis had a clearly defined excision cavity visible on CT to accommodate the CT-based planning that was used for this study. In clinical practice, however, the NIIGBB system requires less stringent visualization criteria such that the tumor bed need be readily defined only on mammography. Postoperative parenchymal scarring, surgical clips, and residual seroma are clearly imaged for target localization. These postoperative changes are well defined and well described in the context of diagnostic imaging (4, 5). Among the potential advantages of mammography-guided radiation therapy are the ability to readily compare pre- and postoperative images to precisely identify the location and extent of the surgical bed.

A particular challenge in the execution of this study was evaluation of the cumulative PTV dose with simulated 3D planning of NIIGBB (and associated D\(_{\text{min}}\) and D\(_{\text{max}}\)) because of the orthogonal breast compression and the resultant tissue deformation. We addressed this issue through an iterative approach whereby we meticulously identified anatomic landmarks in the tissue contained within the target volume that received the maximum dose in the CC plan, then subsequently identified the same landmarks in the ML plan and summed the values. Although this method has inherent error, dose measurements were nonetheless reproduced within \(\pm 10\%\) with each attempt. To minimize potential bias in the analysis, only the highest composite values for each patient were retained for data collection. To provide a conservative estimate of the NIIGBB technique composite dose distribution in 3D, some PTV parameters were reported as CC and ML plan averages resulting in an underestimation of the NIIGBB dose distribution homogeneity.

An additional challenge was estimation of radiation dose to surrounding normal breast tissue with the NIIGBB system. Modeling radiation dose peripheral to the PTV requires precise modeling of tissue displacement during compression and deformation along the two treatment axes (CC and ML). This requirement is simply beyond the capabilities of currently available planning software. However, NIIGBB will likely result in a lower integral dose to normal breast as compared with 3DCRT. This is because of the intrinsic properties associated with NIIGBB whereby the breast is immobilized with mammography paddles to control respiratory motion and other factors associated with intrafractional target displacement. Coupled with mammographic image guidance before each treatment fraction, these factors would appear to allow significantly smaller target volume margin expansion (and associated normal breast tissue exposure) when compared with the commonly used 3DCRT APBI technique. Additional research to develop 3D modeling to more thoroughly evaluate normal breast dose distributions because of tissue deformation from sequential orthogonal compression is being pursued.

CONCLUSION

By virtue of breast immobilization and mammographic image guidance with NIIGBB, the necessity for extensive margin expansions is decreased, resulting in boost and APBI target volumes that are smaller when compared with associated with electron beam and 3DCRT techniques. This target volume reduction results in significant normal tissue sparing while maintaining PTV dosimetric benchmarks.

<table>
<thead>
<tr>
<th></th>
<th>Skin D(_{\text{max}}) (cGy)</th>
<th>CW D(_{\text{max}}) (cGy)</th>
<th>Lung D(_{\text{max}}) (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median NIIGBB</td>
<td>94.8</td>
<td>32.4</td>
<td>18.7</td>
</tr>
<tr>
<td>p25%–p75%</td>
<td>76.5–101.0</td>
<td>27.4–88.4</td>
<td>17.6–25.4</td>
</tr>
<tr>
<td>Median 3DCRT</td>
<td>104.4</td>
<td>97.2</td>
<td>89.5</td>
</tr>
<tr>
<td>p25%–p75%</td>
<td>103.3–105.4</td>
<td>95.5–99.2</td>
<td>84.1–92.3</td>
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<tr>
<td>p Value</td>
<td>0.04</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Abbreviations: CW = chest wall; NIIGBB = noninvasive image-guided breast brachytherapy.
REFERENCES


