Breast treatment planning

A treatment planning study comparing whole breast radiation therapy against conformal, IMRT and tomotherapy for accelerated partial breast irradiation

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Abstract

\textit{Purpose and background:} Conventional early breast cancer treatment consists of a lumpectomy followed by whole breast radiation therapy. Accelerated partial breast irradiation (APBI) is an investigational approach to post-lumpectomy radiation for early breast cancer. The purpose of this study is to compare four external beam APBI techniques, including tomotherapy, with conventional whole breast irradiation for their radiation conformity index, dose homogeneity index, and dose to organs at risk.

\textit{Methods and materials:} Small-field tangents, three-dimensional conformal radiation therapy, intensity-modulated radiation therapy and helical tomotherapy were compared for each of 15 patients (7 right, 8 left). One radiation conformity and two dose homogeneity indices were used to evaluate the dose to the target. The mean dose to organs at risk was also evaluated.

\textit{Results:} All proposed APBI techniques improved the conformity index significantly over whole breast tangents while maintaining dose homogeneity and without a significant increase in dose to organs at risk.

\textit{Conclusion:} The four-field IMRT plan produced the best dosimetric results; however this technique would require appropriate respiratory motion management. An alternative would be to use a four-field conformal technique that is less sensitive to the effects of respiratory motion.

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Keywords: Partial breast irradiation; Early breast cancer; Hypofractionation; IMRT; Tomotherapy

Accelerated partial breast irradiation (APBI) given over one week has been proposed as an alternative to whole breast radiation therapy, normally given over three and a half to five weeks for early stage breast cancer (T1, T2, N0) [25]. Proponents of APBI state that longer courses of breast radiation are associated with fewer patients choosing to receive postoperative breast radiation [21]. In addition, with the lumpectomy site as the most common site of local recurrence, APBI can reduce the amount of absorbed dose to normal breast and organs at risk, increasing the therapeutic ratio of the treatment.

The risk of increased late complications from hypofractionated, accelerated courses of radiation therapy may be mitigated by the reduction of the irradiated volumes and dose to the normal tissues. Presently, a randomized Phase III clinical trial is underway to compare whole breast radiotherapy against three-dimensional conformal radiotherapy (3DCRT), multi-catheter brachytherapy, and a commercially available balloon brachytherapy technique for APBI.

Multiple techniques of APBI have been in clinical use with an optimal technique still to be defined. Methods include low and high dose rate brachytherapy [16,17,22,26], balloon catheter brachytherapy (MammoSite\textsuperscript{\textcopyright} device) [1,2,18], kilovoltage X-ray applicators (Intrabeam), intra-operative electron beam radiotherapy [15], and external beam radiotherapy [3,5–8,12,20,21,23,24]. In a dosimetric comparison of 3DCRT, interstitial brachytherapy, and MammoSite\textsuperscript{\textcopyright}, Weed et al. [27] found that 3DCRT gave the best coverage of the planning target volume (PTV) at the expense of increased dose to normal tissues. In a cost comparison analysis of various APBI and whole breast radiation techniques in the United States, the 3DCRT and intensity-modulated radiation therapy (IMRT) techniques [19] were the least costly among the APBI techniques. Other advantages of external beam techniques include wider availability and less operator dependence. Tomotherapy has the potential advantage over 3DCRT and IMRT, using image guidance for each fraction [13]. Other techniques for external beam APBI
have been described [3,5–8,12,20,21,23,24], however, a full inter-comparison of different external beam techniques for APBI has not been published. In this report we compare standard whole breast tangents, small field tangents, 3DCRT, IMRT, and tomotherapy treatment plans for APBI.

Methods and materials
CT imaging
Treatment planning was performed on CT data sets (3 mm slice thickness) of 15 (7 right, 8 left) patients with T1 or T2 axillary node negative invasive mammary carcinoma of the breast. CT data sets of patients who had more than one lumpectomy procedure to the breast to obtain negative margins were not included in the study. A radio-opaque wire was placed around the ipsilateral breast by a radiation oncologist to define the clinical whole breast volume. All CT scans were done three to four weeks after definitive breast surgery. Eleven of the fifteen patients had surgical clips (mean: 5.5, median: 5, range: 3–8) implanted by the surgeon to help demarcate the lumpectomy site.

Target and organ at risk delineation
The contours that were generated were the Gross Tumour Volume (GTV), Clinical Tumour Volume (CTV), Planning Target Volume (PTV), Planning Target Volume for dose evaluation (PTV_EVAL) ipsilateral lung, contralateral lung, ipsilateral breast, contralateral breast, heart, skin, and external. These were generated on AcQSim v4.9.1 (Philips Medical Systems, USA) and Oncentra Treatment Planning (OTP) v1.0 (Nucletron, Veenendaal, Netherlands) to exploit the advantages of each piece of software. The GTV was defined as the lumpectomy site by the union of the volumes defined by the surgical clips and the seroma, although the name Gross Tumour Volume is a misnomer in this situation. The CTV was defined by a 3-D uniform 1.5 cm margin expanded in all directions around the GTV; however, this volume was constrained to lie 5 mm within the external contour and up against the pectoralis major muscle. The ipsilateral whole breast volume was defined to lie within the radio-opaque breast wire and as deep as the anterior chest wall muscles. The lungs and the external surface were contoured using semi-automatic contouring techniques. The CTV, PTV, PTV_EVAL, and heart were generated in accordance with the RTOG 0319 protocol [24]. An example axial CT slice of some of the patient anatomy and contours is shown of a sample case as shown in Fig. 1. All contouring was done by one individual (M.O.) with the contours approved by a radiation oncologist (F.P.).

Treatment planning
All treatment plans were generated with 6 MV photon beams in order to evaluate the impact of treatment technique with a fixed photon energy. Treatment plans for linear accelerators were done on TheraPlan Plus v3.8 (Nucletron, Veenendaal, Netherlands). The types of beam arrangements included whole breast (WB) radiation therapy, small tangential rectangular fields (ST), two-field conformal radiation therapy technique (CRT2), and a four-field conformal radiation therapy technique (CRT4). Furthermore, two-field IMRT (IMRT2) and four-field IMRT (IMRT4) plans were generated with an inverse planning technique (Theraplan Plus v3.8) using the same gantry, and couch positions as in the conformal treatment plans. For the four-field plans (CRT4 and IMRT4), the gantry angles were the same as the two-field plans but the couch was placed at ±30° for each field, and one of the cases required a different beam arrangement to achieve an acceptable plan. These plans were simulated only on the treatment planning system and not delivered and there may have been instances where the chosen beam angles could not be implemented clinically. Tomotherapy treatment plans were generated using the HiArt2 Tomotherapy software (Tomotherapy Inc., Madison, USA).

Dose calculation and normalization
All dose distributions were calculated using our clinical treatment planning system Theraplan Plus by using a (0.5 cm)³ dose grid and all tomotherapy treatment plans were generated with a dose grid size (0.4 cm)³. Furthermore, after dose calculation was completed, all treatment plans were normalized such that 95% of the prescribed dose (95% × 37.2 Gy = 35.34 Gy) covered the entire PTV_EVAL. In order to ensure a more accurate dose calculation in the lung, inhomogeneity corrections were used by both treatment planning systems.

Plan evaluation
The radiation conformity index (RCI) was first described by Knoos et al. and a revised definition appears in ICRU 62 [10]. The Knoos et al. formulation used here is defined by

\[
\text{RCI} = \frac{V_{\text{PTV_EVAL}}}{V_{95\%}(\text{within external})}.
\]

where \(V_{\text{PTV_EVAL}}\) is the volume encompassed by the PTV_EVAL structure and \(V_{95\%}\) (within external) is the volume that receives a dose of 95% of the prescribed dose or higher.
It is important to note that the RCI can only be meaningful after normalization, because the PTV_EVAL must be encompassed by the isovolume with 95% of the prescribed dose.

The dose homogeneity index (DHI) is an index that typically describes the uniformity of dose within a brachytherapy treatment plan [14,26]. In this case, it is used to describe the uniformity of dose within the PTV for external therapy plans and this will allow us to better compare dose homogeneity between brachytherapy and external beam plans. Two distinct indices for dose homogeneity were used. The first, a radical dose homogeneity index (rDHI), is the ratio of the minimum dose \( D_{\text{min}} \) to the PTV_EVAL and the maximum dose \( D_{\text{max}} \) to the PTV_EVAL as defined by

\[
rDHI = \frac{D_{\text{min}}(\text{within PTV_EVAL})}{D_{\text{max}}(\text{within PTV_EVAL})} = \frac{35.34 \text{ Gy}}{35.34 \text{ Gy}}.
\]

In Eq. (2) the minimum dose to the PTV is 95% of the prescribed dose (35.34 Gy) after normalization.

Another homogeneity index that is less affected by steep dose gradients near field borders or to very small hotspots is the moderate dose homogeneity index (mDHI). The mDHI is defined as the ratio of the dose to 95% of the volume of the PTV \( D_{95\%} \) to the dose to 5% \( D_{5\%} \) of the PTV. Thus,

\[
mDHI = \frac{D_{95\%}(\text{within PTV_EVAL})}{D_{5\%}(\text{within PTV_EVAL})}.
\]

A dose volume histogram (DVH) is shown in Fig. 2 with points indicating the values used in the calculation of the rDHI and mDHI.

**Statistical analysis**

All statistical analyses were done using paired Student’s t-tests on all data using SPSS v12 (SPSS Inc., Chicago, USA). All error bars on accompanying graphs represent the standard error of the mean.

**Results**

**GTV volume and CTV/WB ratio**

The mean and median lumpectomy volumes (GTV) were 69.2 and 63.5 cm\(^3\) (range: 10.8–134.5 cm\(^3\)). The mean and median WB volumes were 795.1 and 653.0 cm\(^3\), respectively (range: 256–1767 cm\(^3\)). The mean and median ratios of GTV to WB volume (GTV/WB) were 9.9% and 7.7% respectively, with a range of values from 2.6% to 25.7%. Furthermore, the mean and median ratios of CTV to WB volume (CTV/WB) were 32.7% and 26.0%, respectively, with a range of values from 12.9% to 62.5%. The mean and median ratios of PTV_EVAL/WB ratio were 56.5% and 50.1% with a range from 27.6% to 99.4%. A histogram of the CTV/WB and PTV_EVAL/WB ratios is shown in Fig. 3 for the 15 cases analyzed in this study. Table 1 shows the side of the original lesion, number of clips used, GTV volume, CTV volume, PTV_EVAL volume WB volume, GTV/WB ratio and CTV/WB ratio, and PTV_EVAL/WB ratios for each of the cases.

**Radiation conformity index**

The average RCI over the 15 patients for all of the 6 different treatment techniques evaluated are shown in Fig. 4. The RCI values for all APBI techniques were significantly superior to the RCI values for traditional WB tangents. The results show that the conformity index is higher for ST \((t(14) = -7.634, p < 0.001)\), CRT2 \((t(14) = -12.272, p < 0.001)\), CRT4 \((t(14) = -14.872, p < 0.001)\), IMRT2 \((t(14) = -11.740, p < 0.001)\), IMRT4 \((t(14) = -18.511, p < 0.001)\), and TOMO \((t(14) = -16.869, p < 0.001)\) when compared to traditional WB radiation therapy.

**Dose homogeneity index**

A comparison of rDHI indices for WB tangents with each of the other techniques found three techniques, IMRT2 \((t(14) = -2.670, p < 0.05)\), IMRT4 \((t(14) = -5.115, p < 0.001)\), and TOMO \((t(14) = -2.14, p < 0.05)\), to be significantly superior as seen in Fig. 5. Similarly, paired Student’s t-tests of the mDHI values comparing WB tangents with the other techniques found all the other techniques to be better than ST \((t(14) = -2.694, p < 0.05)\), CRT2 \((t(14) = -2.723, p < 0.05)\), IMRT2 \((t(14) = -3.315, p < 0.01)\), IMRT4 \((t(14) = -7.389, p < 0.001)\), and TOMO \((t(14) = -4.034, p < 0.005)\) treatment techniques also seen in Fig. 5.

**Dose to organs at risk**

Mean doses to any organs at risk were calculated to help determine the optimal treatment. The average dose to each critical structure grouped by modality is shown in Fig. 6. For

![Fig. 2](image-url) An example of a cumulative dose volume histogram with relevant points that are used to define the two types of dose homogeneity indices used in this study.

![Fig. 3](image-url) A histogram depicting the CTV/WB and PTV_EVAL/WB ratios for the 15 different cases used in this study.
each of the structures, the mean dose to that structure was compared against the mean dose for WB radiation therapy and the significant differences are outlined in Table 2. The values that have an asterisk represent a significant difference at the \( p < 0.05 \) level. All doses to organs at risk using APBI techniques were significantly lower than the WB values except for the mean dose to the contra-lateral lung and contra-lateral breast with tomotherapy which were not significantly different (Fig. 6).

Discussion
With increasing sophistication in radiation treatment plans, there is a consistent improvement in conformity index from 0.208 for WB tangents to 0.749 for tomotherapy (Fig. 4).

### Table 1
The characteristics of the structures and location of all fifteen cases used in this study

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th># of clips</th>
<th>WB (cm³)</th>
<th>GTV (cm³)</th>
<th>CTV (cm³)</th>
<th>PTV_EVAL (cm³)</th>
<th>GTV/WB</th>
<th>CTV/WB</th>
<th>PTV_EVAL/WB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right</td>
<td>5</td>
<td>509.0</td>
<td>24.7</td>
<td>132.2</td>
<td>258.8</td>
<td>0.05</td>
<td>0.26</td>
<td>0.51</td>
</tr>
<tr>
<td>2</td>
<td>Right</td>
<td>4</td>
<td>299.0</td>
<td>29.6</td>
<td>142.0</td>
<td>253.0</td>
<td>0.10</td>
<td>0.47</td>
<td>0.85</td>
</tr>
<tr>
<td>3</td>
<td>Left</td>
<td>0</td>
<td>524.0</td>
<td>134.5</td>
<td>327.6</td>
<td>454.0</td>
<td>0.26</td>
<td>0.63</td>
<td>0.87</td>
</tr>
<tr>
<td>4</td>
<td>Right</td>
<td>5</td>
<td>616.0</td>
<td>134.0</td>
<td>370.0</td>
<td>612.0</td>
<td>0.22</td>
<td>0.60</td>
<td>0.99</td>
</tr>
<tr>
<td>5</td>
<td>Left</td>
<td>5</td>
<td>649.0</td>
<td>54.8</td>
<td>178.0</td>
<td>280.0</td>
<td>0.08</td>
<td>0.27</td>
<td>0.43</td>
</tr>
<tr>
<td>6</td>
<td>Right</td>
<td>6</td>
<td>653.0</td>
<td>97.4</td>
<td>270.0</td>
<td>455.0</td>
<td>0.15</td>
<td>0.41</td>
<td>0.70</td>
</tr>
<tr>
<td>7</td>
<td>Left</td>
<td>3</td>
<td>1245.0</td>
<td>32.9</td>
<td>161.0</td>
<td>344.0</td>
<td>0.03</td>
<td>0.13</td>
<td>0.28</td>
</tr>
<tr>
<td>8</td>
<td>Left</td>
<td>6</td>
<td>932.0</td>
<td>56.9</td>
<td>226.0</td>
<td>420.0</td>
<td>0.06</td>
<td>0.24</td>
<td>0.45</td>
</tr>
<tr>
<td>9</td>
<td>Left</td>
<td>7</td>
<td>823.0</td>
<td>38.6</td>
<td>176.0</td>
<td>331.0</td>
<td>0.05</td>
<td>0.21</td>
<td>0.40</td>
</tr>
<tr>
<td>10</td>
<td>Right</td>
<td>0</td>
<td>931.0</td>
<td>105.6</td>
<td>368.0</td>
<td>612.0</td>
<td>0.11</td>
<td>0.40</td>
<td>0.66</td>
</tr>
<tr>
<td>11</td>
<td>Left</td>
<td>8</td>
<td>1767.0</td>
<td>73.2</td>
<td>325.0</td>
<td>596.0</td>
<td>0.04</td>
<td>0.18</td>
<td>0.34</td>
</tr>
<tr>
<td>12</td>
<td>Right</td>
<td>0</td>
<td>647.0</td>
<td>113.1</td>
<td>283.0</td>
<td>463.0</td>
<td>0.17</td>
<td>0.44</td>
<td>0.72</td>
</tr>
<tr>
<td>13</td>
<td>Right</td>
<td>0</td>
<td>256.0</td>
<td>10.8</td>
<td>44.0</td>
<td>94.0</td>
<td>0.04</td>
<td>0.17</td>
<td>0.37</td>
</tr>
<tr>
<td>14</td>
<td>Right</td>
<td>6</td>
<td>1187.0</td>
<td>63.5</td>
<td>292.0</td>
<td>595.0</td>
<td>0.05</td>
<td>0.25</td>
<td>0.50</td>
</tr>
<tr>
<td>15</td>
<td>Left</td>
<td>5</td>
<td>888.0</td>
<td>68.0</td>
<td>215.0</td>
<td>378.0</td>
<td>0.08</td>
<td>0.24</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Mean 4 795.07 69.17 233.99 409.72 0.099 0.327 0.565
Median 5 653.00 63.50 226.00 420.00 0.077 0.260 0.501
Min 0 256.00 10.80 44.00 94.00 0.026 0.129 0.276
Max 8 1767.00 134.50 370.00 612.00 0.257 0.625 0.994

Homogeneity indices (rDHI and mDHI) showed much smaller but consistent gains with increasing treatment complexity, peaking with four-field IMRT and tomotherapy (Fig. 5).

The dose to organs at risk was significantly lower for all APBI techniques as compared with WBRT except the dose to the contra-lateral lung and contra-lateral breast with tomotherapy which was not significantly lower than WBRT. With inverse treatment plans, the choice of the importance parameters has a direct impact on the dose to organs at risk. The trade-off between a very conformal and uniform dose to the target and lower doses to organs at risk is often required, and these decisions are guided by the risks associated with different doses to certain volumes of organs at risk and the possibility of different treatment outcomes [4].

The present RTOG 0413/NSABP B-39 clinical trial of 3DCRT APBI constrains the ipsilateral whole breast volume...
receiving 50% or more of the prescribed dose to less than sixty percent and the volume of breast receiving the prescribed dose should be less than 35%. For the present treatment planning study, all CT scans were done within 3–4 weeks of definitive breast surgery. In addition, the ipsilateral breast volume was defined as the clinical breast volume delineated by a breast wire around its periphery and limited to the anterior pectoralis muscle. Thus the ratio of PTV_EVAL to whole breast volumes would be larger than the RTOG/NSABP ratio for these two reasons. Nevertheless, this study suggests that dose conformity deteriorates only slightly with larger PTV to whole breast ratios. Thus, other than extending the PTV well beyond a quadrant of the breast, the APBI approach may still be feasible. The groups were sub-divided so those breast volumes less than or equal to the median were put into a group and breast volumes greater than the median were put into the second group. Breast volumes less than or equal to the median had an average PTV_EVAL/WB ratio of 0.678 and the larger breast volumes had a PTV_EVAL/WB ratio of 0.440.

An important difference in this study compared to other studies is the mean and median volume of the lumpectomy site (GTV) and the time after surgery that the volume measurements were taken. The volume results in this study were obtained 3–4 weeks after surgery. Vicini et al. have reported smaller GTV volumes 22 cm³ (mean) and 14 cm³ (median) with a range (3–70 cm³); however their study only included T1N0 cases [23]. Formenti et al. have also reported slightly smaller lumpectomy site volumes of 52 cm³ (mean) and 34 cm³ (median) with a range (7–379 cm³) [7]. The results obtained for our lumpectomy site volume [mean: 69.2 cm³, median: 63.5 cm³, range: (12–134 cm³)] seem to agree very well with Formenti’s results but their study included only T1N0 patients.

Organ motion during treatment has not been accounted for in inverse planning. During breathing motion, the PTV_EVAL may move outside the external contour (as defined on the planning CT) and result in a geographic miss of the target. This motion is not particularly a problem in most radiation therapy treatment plans because the PTV is designed to take into account geometric uncertainties and intra-fraction organ motion. However, the breast is a peripheral organ and often the CTV, or even the GTV, will extend to the skin surface. In these cases, the restriction of the PTV_EVAL to 5 mm from the skin surface will not provide an adequate margin for intra-fraction breathing motion. The main concern would be the CTV (or even GTV) being under-irradiated; however, a recent study has shown that intra-fraction breathing motion was less than inter-fraction setup uncertainty indicating that patient setup should have a higher priority than breathing [11]. If breath hold or gating is used, the PTV margins can be reduced by the 5-mm margins that are used to account for breathing. There are two ways in which one may take into account breathing motion. The first is to implement an active breathing control that ensures that the patient’s breast and hence lumpectomy cavity motion is minimized while the beam is on by controlling the amount of air inhaled and exhaled [28]. An alternative way is to gate the dose delivery, by allowing the patient to breathe freely but deliver radiation when the PTV_EVAL is in a predetermined phase of the breathing cycle. In order to use gating, the PTV_EVAL motion must be in phase with the breathing cycle or must at least be able to be predicted from the breathing cycle using technology such as real-time position management (Varian, Palo Alto, USA). The correlation of rib motion with breast motion has been reported to be about one-half of the magnitude of displacement, displaying a dampening effect of the breast with free-breathing [23]. Adjusting treatments in tomotherapy in real time is even more difficult; however, there are investigations underway addressing this problem [9]. Ultimately, prudence must be exercised when attempting to use an inverse treatment plan with radiotherapy to the partial breast due to breathing motion.

### Table 2

<table>
<thead>
<tr>
<th>Technique</th>
<th>WB mean (Gy)</th>
<th>ST mean (Gy)</th>
<th>CRT2 mean (Gy)</th>
<th>CRT4 mean (Gy)</th>
<th>IMRT2 mean (Gy)</th>
<th>IMRT4 mean (Gy)</th>
<th>TOMO mean (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung-Ipsi</td>
<td>9.99</td>
<td>4.29a</td>
<td>3.10a</td>
<td>3.30a</td>
<td>2.84a</td>
<td>3.28a</td>
<td>4.12a</td>
</tr>
<tr>
<td>Lung-Contra</td>
<td>1.03</td>
<td>0.52a</td>
<td>0.49a</td>
<td>0.53a</td>
<td>0.19a</td>
<td>0.18a</td>
<td>1.43</td>
</tr>
<tr>
<td>Breast-Contra</td>
<td>1.57</td>
<td>1.01a</td>
<td>0.79a</td>
<td>0.93a</td>
<td>0.37a</td>
<td>0.38a</td>
<td>1.50</td>
</tr>
<tr>
<td>Heart</td>
<td>2.58</td>
<td>0.95a</td>
<td>0.81a</td>
<td>0.94a</td>
<td>0.51a</td>
<td>0.63a</td>
<td>0.99a</td>
</tr>
</tbody>
</table>

*a* Indicates significant difference than WB at the $p < 0.05$ level.
The dosimetric properties of the breast must be well understood before inverse planned IMRT treatment is performed.

Conclusions

All of the APBI techniques proposed in this paper deliver a significantly higher conformity index than WB irradiation without compromising the dose homogeneity in the target. Tomotherapy produced the best treatment plans. However, in practice these plans would only be superior if intra-fraction motioned is handled properly. If intra-fraction motion cannot be appropriately addressed then a four-field conformal plan is superior.

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