



Prescription dose evaluation for APBI with noninvasive image-guided breast brachytherapy using equivalent uniform dose

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ABSTRACT

PURPOSE: Noninvasive image-guided breast brachytherapy (NIBB) is an attractive novel approach to deliver accelerated partial breast irradiation (APBI). Calculations of equivalent uniform dose (EUD) were performed to identify the appropriate APBI dose for this technique.

METHODS AND MATERIALS: APBI plans were developed for 15 patients: five with three-dimensional conformal APBI (3D-CRT), five with multi-lumen intracavitary balloons (m-IBB), and five simulating NIBB treatment. Prescription doses of 34.0 and 38.5 Gy were delivered in 10 fractions for m-IBB and 3D-CRT, respectively. Prescription doses ranging from 34.0 to 38.5 Gy were considered for NIBB. Dose-volume histogram data from all 3D-CRT, m-IBB, and NIBB plans were used to calculate the biologically effective EUD and corresponding EUD to the PTV_{eval} using the following equation: $EUD = EUBED / (n [1 + EUD/\alpha/\beta])$. An α/β value of 4.6 Gy was assumed for breast tumor. EUD for varying NIBB prescription doses were compared with EUD values for the other APBI techniques.

RESULTS: Mean PTV_{eval} volume was largest for 3D-CRT (372.9 cm³) and was similar for NIBB and m-IBB (88.7 and 87.2 cm³, respectively). The EUD value obtained by prescribing 38.5 Gy with 3D-CRT APBI was 38.6 Gy. The EUD value of 34.0 Gy prescribed with m-IBB was 34.4 Gy. EUD values for NIBB ranged from 33.9 to 38.2 Gy for prescription doses ranging from 34.0 to 38.5 Gy.

CONCLUSIONS: Using EUD calculations to compare APBI techniques and treatment doses, a prescription dose of 36.0 Gy in 10 fractions using NIBB has a comparable biologic equivalent dose to other established brachytherapy techniques. © 2015 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords:

Breast cancer; APBI; NIBB; EUD

Introduction

Accelerated partial breast irradiation (APBI) is a localized form of adjuvant breast radiotherapy, which delivers

hypofractionated radiation to the tumor bed with a treatment margin. APBI can be performed using a variety of techniques including multicatheter interstitial brachytherapy (MIB), single lumen intracavitary balloon brachytherapy (s-IBB), multi-lumen intracavitary balloon brachytherapy (m-IBB), three-dimensional conformal external-beam radiotherapy (3D-CRT), and noninvasive image-guided breast brachytherapy (NIBB) using the AccuBoost system (Advanced Radiation therapy, LLC, Tyngsboro, MA). The isoeffective APBI prescription doses are 34 Gy in 10 fractions for the relatively heterogenous brachytherapy techniques and 38.5 Gy in 10 fractions for the relatively homogenous external beam techniques.

NIBB is a surface brachytherapy technique designed to deliver APBI via mammography-based image-guidance,

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breast immobilization and deformation, and treatment of the tumor bed with high-dose rate ^{192}Ir brachytherapy. Dose is prescribed to the breast mid-plane using applicators positioned on the breast compression paddles in a parallel opposed fashion along sequential orthogonal axes. Dose modeling of NIBB for APBI suggests that the dose homogeneity with NIBB may be intermediate between that of brachytherapy techniques and that of EB techniques (1). A Phase I/II APBI trial using NIBB has been initiated at our institution (2).

The equivalent uniform dose (EUD) concept was developed by Niemierko as a method to report biologic equivalence among inhomogeneous treatment plans (3, 4). EUD provides a basis for comparison of biologic effectiveness between more homogeneous EBRT plans and more heterogeneous brachytherapy plans. In the present study, EUD calculations were performed to identify the appropriate dose for APBI using the NIBB technique.

Methods and materials

APBI plans were developed for 15 patients: five with 3D-CRT, five with m-IBB, and five with NIBB. Prescription doses of 34.0 and 38.5 Gy were delivered in 10 fractions with m-IBB and 3D-CRT, respectively. Prescription doses ranging from 34.0 to 38.5 Gy were considered for NIBB.

Target volumes and treatment plans for 3D-CRT and m-IBB techniques were generated in accordance with the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39 and Radiation Therapy Oncology Group (RTOG) 0413 protocol. 3D-CRT APBI plans were generated in the Pinnacle (Philips Healthcare, Inc., Andover, MA) treatment planning system (TPS) using 4 to 5 non-coplanar beams. The planning target volume (PTV_{eval}) was used for plan evaluation and EUD calculations. The PTV_{eval} consisted of the tumor bed with sequential 1.5 cm (CTV) and 1.0 cm margin expansions both limited by the chest wall and 0.5 cm from the skin. Plans were

normalized such that at least 95% of the PTV_{eval} was covered by greater than 95% of the prescriptions dose. Dose-volume constraints were followed in accordance with the NSABP B-39/RTOG 0413 protocol. For m-IBB, plans were originally created in the PLATO (Nucletron, an Elekta Company, Veenendaal, the Netherlands) TPS, then transferred to and recreated within the Pinnacle TPS using its brachytherapy planning tool. The PTV_{eval} consisted of the 1 cm margin of tissue around the inflated balloon applicator limited by the chest wall and 0.5 cm from the skin. Plans were optimized to have at least 95% of the PTV_{eval} covered by greater than 95% of the prescriptions dose and to meet dose-volume constraints in accordance with the NSABP B-39/RTOG 0413 protocol.

With the NIBB technique, patients are currently treated using 2D planning as patient-specific 3D planning is not yet available. For this study, to obtain 3D planning data, patients underwent simulated NIBB treatment using methods previously described by Sioshansi *et al.* (1). Briefly, 3D CT data sets were acquired with the patients placed in the prone position with breast immobilized and compressed to a minimum tolerated separation using compression paddles in the craniocaudal and mediolateral orientations (Fig. 1a and b). Radio-opaque wires were placed along the breast surface to assist in orientation and composite dosimetry. The PTV_{eval} was contoured on each data set and consisted of the tumor bed with a 1 cm margin expansion limited by the chest wall and 0.5 cm from the skin. Treatment plans for NIBB were generated within Pinnacle using its brachytherapy treatment planning tool in combination with a dose calculation technique developed by Rivard *et al.* to model cylindrical dose distributions as virtual point sources delivered with NIBB applicators (5). NIBB treatment was modeled in accordance to the previously described NIBB APBI technique (6). A pair of first-generation round applicators was selected to encompass the PTV_{eval} in each of the two orthogonal treatment axes. Plans were prescribed to the mid-plane for each treatment axis and the cumulative prescription dose was delivered

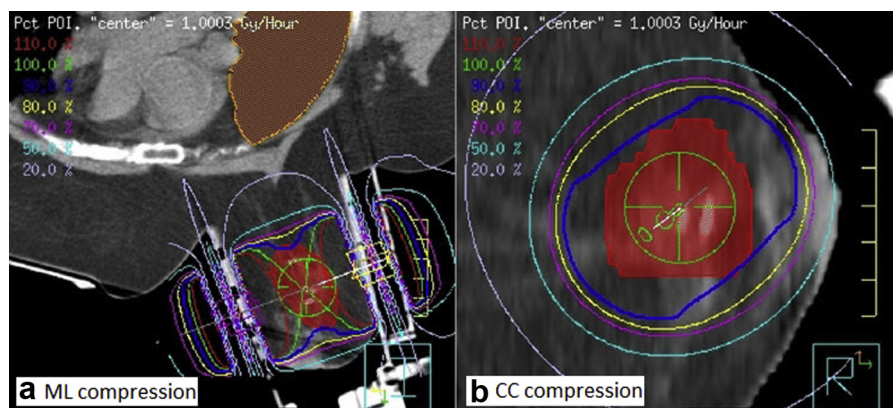


Fig. 1. Simulation of a breast (a) with ML compression and (b) with CC compression and modeled dose distribution of noninvasive image-guided breast brachytherapy applicators. ML = mediolateral; CC = craniocaudal.

with equal weighting between the craniocaudal and mediolateral axes. The resulting dose distribution revealed that at least 95% of the PTV_{eval} was covered by greater than 95% of the prescriptions dose. Dose-volume histogram (DVH) data from composite dose distribution of the two orthogonal treatment axes were generated using previously described methods (1).

DVH data from all 3D-CRT, m-IBB, and NIBB plans were used to calculate the biologically effective EUD (EUBED) using Eq. 1 and the corresponding EUD to the PTV_{eval} using Eq. 2.

$$\text{EUBED} = -\frac{1}{\alpha} \ln \left(\sum_{i=1}^N v_i e^{-\alpha \text{BED}_i} \right) \quad (1)$$

$$\text{EUD} = -\frac{\text{EUBED}}{n \left(1 + \frac{\text{EUD}}{\alpha/\beta} \right)} \quad (2)$$

A value for α of 0.03 Gy⁻¹ and for α/β of 4.6 was used for breast tumor as per the START trials (7). EUD values for varying prescription doses for NIBB were compared with the EUD values for the other APBI techniques following the methods outlined in the AAPM TG-166 report (8). Additional calculations were performed for α/β of 3.4 Gy (presumed α/β of normal breast tissue) and 10 Gy (assumed α/β for tumor in general) to examine the impact of α/β on EUD.

Results

General treatment characteristics for the 15 patients are displayed in Table 1. For m-IBB plans, the balloon diameters ranged from 3.9 to 5.4 cm with a mean diameter of 4.5 cm. The mean PTV_{eval} volume was 372.9 cm³ for

Table 1
Treatment characteristics

APBI modality	
3D-CRT	
<i>n</i> = 5	
PTV _{eval} volume (cc)	372.9
Median # of beams	4
Mean D _{max} (Gy)	40.9
NIBB	
<i>n</i> = 5	
PTV _{eval} volume (cc)	88.7
NIBB applicator size	5–7 cm round
Mean D _{max} (Gy)	45.5
m-IBB	
<i>n</i> = 5	
PTV _{eval} volume (cc)	87.2
Balloon diameter (cm)	4.5
Mean D _{max} (Gy)	127

APBI = accelerated partial breast irradiation; 3D-CRT = three-dimensional conformal APBI; PTV_{eval} = planning target volume; NIBB = noninvasive image-guided breast brachytherapy; m-IBB = multi-lumen intracavitary balloon brachytherapy.

3D-CRT, 87.2 cm³ for m-IBB, and 88.7 cm³ for NIBB. The mean PTV_{eval} volume was significantly larger for 3D-CRT compared with NIBB and m-IBB due to the additional PTV expansion with the 3D-CRT technique ($p = 0.002$). No such expansion is required for m-IBB or NIBB. As expected, mean D_{max} was significantly higher for m-IBB than for 3D-CRT (127 Gy vs. 40.9 Gy; $p = 0.004$). The D_{max} for NIBB was calculated using the methods from Sioshansi *et al.* (1). The D_{max} for NIBB APBI was 45.5 Gy, slightly higher than that for 3D-CRT APBI.

Fig. 2 displays the mean EUD (and standard deviation) for the five 3D-CRT plans treated to 38.5 Gy total dose, for the five m-IBB plans treated to 34.0 Gy, and for the five NIBB plans treated to varying doses of 34.0–38.5 Gy. The mean EUDs for m-IBB and 3D-CRT are 34.4 Gy (95% CI, 28.4–40.4) and 38.6 Gy (95% CI, 37.4–39.8), respectively. The mean EUDs for NIBB are 33.9 Gy, 34.9 Gy, 35.8 Gy, 36.7 Gy, and 38.2 Gy for prescription doses of 34 Gy, 35 Gy, 36 Gy, 37 Gy, and 38.5 Gy, respectively. The EUD range is greater for the m-IBB technique due to variations in balloon size and number of dwell positions utilized. Conversely, both 3D-CRT and NIBB have a relatively narrow range of EUD values.

Table 2 presents EUD for α/β values 3.4, 4.6, and 10. Small variations in α/β have only a minor influence on the calculation of EUD. EUD increases with increasing α/β similar to the results presented for a range of α and β values by Cuttino *et al.* (9).

Discussion

EUD is an established method for evaluating and comparing the biologic equivalence of treatment plans with differing degrees of dose heterogeneity across the target volume. Using EUD, this work sought to identify the NIBB treatment dose most biologically equivalent to established methods for delivery of APBI. The analysis in the present study compared EUD values using the NIBB technique to the 3D-CRT and m-IBB techniques. In addition, a literature review was performed to compare these results to those of previously published analyses. This review also included other commonly used APBI techniques: s-IBB and MIB.

Three studies were identified that evaluated EUD for APBI techniques (9–11). The calculated EUD values for 3D-CRT and m-IBB in the present study compared favorably with the results from these studies. Bovi *et al.* calculated EUD from PTV DVH data using Eq. 3:

$$\text{EUD} = \frac{-\log(S)}{\alpha + \beta d - 0.5\gamma/d} \quad (3)$$

They reported a mean EUD value of 37.6 Gy for 3D-CRT, 37.2 Gy for s-IBB, and 35.0 Gy for MIB (10). In the present study, the calculated EUD is similarly higher for 3D-CRT than for m-IBB; the mean EUD for 3D-CRT is 4.3 Gy higher than that of m-IBB. Cuttino *et al.* used

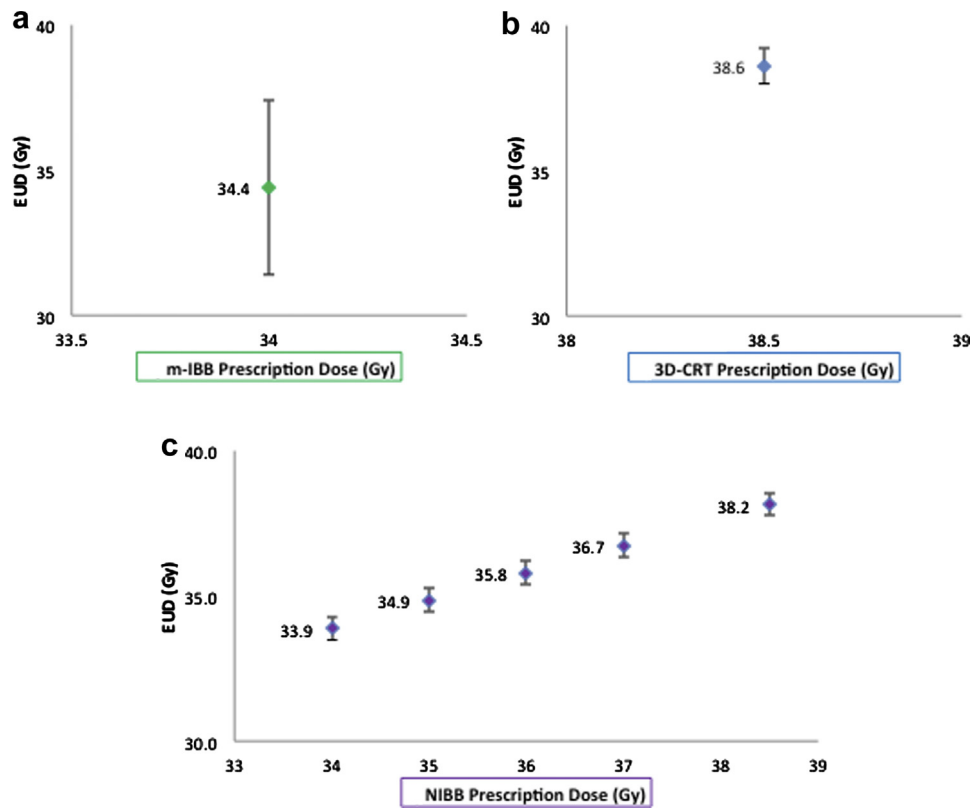


Fig. 2. Mean calculated EUD (with standard deviation) by APBI modality and dose using Eq. 1 and Eq. 2 for (a) m-IBB 34 Gy, (b) 3D-CRT 38.5 Gy, and (c) NIBB 34–38.5 Gy. EUD = equivalent uniform dose; APBI = accelerated partial breast irradiation; m-IBB = multi-lumen intracavitary balloon; 3D-CRT = three-dimensional conformal APBI; NIBB = noninvasive image-guided breast brachytherapy.

DVH data to solve for EUD using Eq. 2 and reported mean EUDs for MIB ranging from 36.7 to 36.9 Gy (depending on α/β used) (9). EUD calculations thereby suggest that the total dose of 38.5 Gy used for 3D-CRT APBI is more than sufficient to account for the relative homogeneity of this technique. Stewart *et al.* calculated the EUD for single dwell s-IBB to range from 37.4 to 37.6 Gy (depending on balloon diameter) and the EUD values for multi-dwell s-IBB to range from 36.6 to 36.9 Gy (11). Thus, using multiple dwell positions and/or multiple catheters leads to an increase in the homogeneity of the dose distribution. This results in a decrease in values for the EUD. In the present study, the m-IBB technique, as one would expect, is associated with dose distributions and resulting EUD values

intermediate between those of the s-IBB and MIB techniques. Using a technique similar to EUD, the equivalent biologically effective dose, Lymberis *et al.* concluded that the biologic equivalent dose for 3D-CRT and s-IBB were higher than that for MIB (12). Based on composite results from the present study and from values found in the literature, EUD calculations for each of the APBI modalities are summarized in Table 3.

Table 2
EUD values by modality for range of α/β 3.4, 4.6, 10

APBI modality	Prescription dose (Gy)	Mean EUD (Gy) for $\alpha/\beta = 3.4$	Mean EUD (Gy) for $\alpha/\beta = 4.6$	Mean EUD (Gy) for $\alpha/\beta = 10$
3D-CRT	38.5	38.3	38.5	38.7
NIBB	36.0	36.6	35.8	36.1
m-IBB	34.0	33.3	34.2	35.7

EUD = equivalent uniform dose; 3D-CRT = three-dimensional conformal external-beam radiotherapy; NIBB = noninvasive image-guided breast brachytherapy; m-IBB = multi-lumen intracavitary balloon brachytherapy.

Table 3
EUD values range by APBI modality as compiled from results of the present study and following a review of the literature

APBI modality	Prescription dose (Gy)	EUD range (Gy)	Study
3D-CRT	38.5	37.5–38.6	Bovi <i>et al.</i> (10)
3D-CRT	38.5	37.8–39.1	Present study
NIBB	36	35.8	Present study
Single dwell s-IBB	34	37.4–37.6	Stewart <i>et al.</i> (11)
Multi dwell s-IBB	34	36.6–36.9	Stewart <i>et al.</i> (11)
m-IBB	34	34.4	Present study
MIB	34	35.0–36.9	Bovi <i>et al.</i> (10), Cuttino <i>et al.</i> (9)

EUD = equivalent uniform dose; APBI = accelerated partial breast irradiation; 3D-CRT = three-dimensional conformal external-beam radiotherapy; NIBB = noninvasive image-guided breast brachytherapy; s-IBB = single lumen intracavitary balloon brachytherapy; m-IBB = multi-lumen intracavitary balloon brachytherapy; MIB = multicatheter interstitial brachytherapy.

For all APBI techniques the EUD varies based on technique-specific variables as seen in Fig. 2. For NIBB, heterogeneity across the PTV and thus EUD are dependent on several factors including size of applicator, breast separation, and position of the PTV relative to the applicators. For larger applicators, an increased number of dwell positions is used, which results in a relatively lower EUD. With increasing breast separation, the heterogeneity increases resulting in a relatively higher EUD. Lastly, as the position of the PTV moves from mid-plane to a more superficial position nearer one of the applicators, the heterogeneity across the PTV also increases resulting in a relatively higher EUD.

Mature long-term outcomes are available for MIB APBI (13–17) and have shown excellent ipsilateral breast tumor control rates. Early outcomes of intracavitary balloon brachytherapy (IBB) have shown good local control rates (18–21). These clinical data would suggest that either the 3D-CRT APBI dose of 38.5 in 10 fractions is higher than necessary or that the calculated EUD underestimates the BED for the MIB and m-IBB techniques.

Comparing the calculated results for NIBB APBI shows that the EUD is intermediate between those of MIB or m-IBB techniques and the 3D-CRT technique. The 34.0 Gy prescribed to the 100% isodose line delivered with NIBB using first-generation round applicators produces an EUD of 33.9 Gy, which is near the 34.4 Gy delivered using m-IBB. With NIBB, a prescribed 35.0 Gy is near the 35.0–36.9 Gy EUD of a 34.0 Gy prescription using MIB. With an NIBB prescription dose of 36.0–37.0 Gy, its EUD of 35.8–36.7 Gy is near the 37.5–36.8 Gy EUD using s-IBB. A prescription dose of 38.5 Gy with NIBB produces an EUD of 38.2 Gy, which is within the EUD range of 37.8–39.1 Gy for a 38.5 Gy prescription using 3D-CRT. Based on these calculations, a prescription dose of 36.0 Gy in 10 fractions seems to be an appropriate prescription dose for APBI using the NIBB technique.

Early clinical experience using NIBB to deliver breast boost and APBI has been reported (22, 23). This initial Phase II trial used a prescription dose of 34.0 Gy in 10 fractions and has shown good local control and favorable toxicity and cosmetic outcomes. However, long-term followup is not yet available. Based on the presented EUD calculation, this prescription dose may not be optimal. A strength of the present study is the method by which the EUD values were calculated. Using DVH data from treated brachytherapy cases to perform EUD calculations, similar to the methods used by Cuttino *et al.* (9), limits assumptions made when calculating EUD based on modeling. Furthermore, the α/β value used for EUD calculations was based on clinical outcomes from a large randomized trial (7). Using a clinically derived value for α/β , these calculations provide the best estimate of EUD.

The present study is limited in that EUD calculations for NIBB were based on DVHs calculated independently along two orthogonal axes. The resultant EUDs from each axis were subsequently added together to give the composite

EUD. Although we have used the technique published by Sioshansi *et al.* (1) of placing barium wires along the breast to account for composite surface dose, this method does not assure that the dose, or the resultant EUD, to each voxel is additive along orthogonal axes. Moreover, these methods do not model tissue deformation between treatment axes for the NIBB technique, which may influence dose summation and subsequent EUD calculations. Furthermore, the present work was performed using first generation round applicators. The dose heterogeneity of second-generation conical applicators, which substantially diminish skin dose (24), is different and may influence the resulting EUD values. Evaluation of EUD values for these new skin-sparing applicators is being considered.

Conclusions

Using EUD calculations to compare APBI techniques and treatment doses, a prescription dose of 36.0 Gy in 10 fractions using NIBB was determined to have a comparable BED to other established brachytherapy techniques.

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