# Modelling the radiobiological effect of intraoperative X-ray brachytherapy for breast cancer using an air-filled spherical applicator

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## Abstract

**Purpose:** We present a framework, in which we compare a conventional standard dose of 50 Gy in 25 fractions with accelerated partial breast irradiation (APBI) using electronic brachytherapy (eBT). We discuss how radiobiological modelling enables us to establish a framework, within which we can compare external beam radiotherapy (EBRT). This leads to a determination of the shell of isoeffect in breast tissue, at which very low kV eBT can be considered to be clinically equivalent to standard EBRT.

**Material and methods:** To estimate relative biological effectiveness (RBE) values as a function of dose and irradiation time, we used a modified linear quadratic (LQ) approach, taking into account the ability of this new device, to deliver 20 Gy at the surface of a 40 mm diameter rigid, hollow spherical applicator in less than 2 minutes. In this study, we considered the radiobiological effectiveness of the Papillon+™ X-ray brachytherapy device operating at 30 kV, 0.3 mA producing dose rates in excess of 14 Gy/min.

**Results:** Calculated clinical RBEs ranged from 1.154 at the surface of a 40 mm diameter applicator to 1.100 at 35 mm from the applicator surface for the Papillon+ device. The absolute physical dose D (abs) 30 kV ranged from 20.00 Gy at the applicator surface to 1.20 at 35 mm distant. The product of the isoeffective single dose of $^{60}$Co reference radiation – (RBE)$^{60}$Co, and the RBE corrected standard 2 Gy equivalent dose fractions (EQD$_2$) doses, EQD$_2$(30 kV) * (RBE)$^{60}$Co ranged from 98.62 Gy at the applicator surface to 1.13 at 35 mm. The 'shell of isoeffect', the value on the X-axis where the EQD$_2$(30 kV) * (RBE)$^{60}$Co line crosses the 50 Gy mark on the Y-axis, was found to be approximately 3.5 mm beyond the applicator surface.

**Conclusions:** The 'shell of isoeffect' can serve as a useful metric with which to compare the radiobiological effectiveness of low kV eBT with various regimes of conventional EBRT.

## Purpose

Accelerated partial breast irradiation in various forms is now often routinely used, and authoritative guidelines for its use have been published [1]. The acceleration of treatment time is at its most extreme in techniques of intraoperative radiotherapy (IORT), where a single fraction of radiation is delivered to the tumor bed immediately after resection of the cancer, before surgical closure. A large randomized trial, with permissive entry criteria, comparing one particular type of IORT (TARGIT-A) to external beam radiotherapy (EBRT) has reported comparable early results for local tumor control [2]. In a similar procedure using the Papillon+™ X-ray brachytherapy device, a hollow spherical applicator is placed temporarily in the surgical resection cavity; a kilovoltage X-ray tube, the tip

of which lies at the center of the applicator, generates the radiation. This type of treatment will be called here 'electronic brachytherapy' (eBT).

To understand radiobiologically why eBT and EBRT should give comparable clinical results, requires complex three-dimensional analysis, as the distribution of the radiation dose in tissue around the radiotherapy applicator is markedly different for eBT compared with EBRT. In our calculations, we are considering a tumor, for which the American Society for Radiation Oncology (ASTRO) consensus guidelines would regard partial breast radiotherapy as an acceptable option, and many clinicians using EBRT would treat such a patient with a homogeneous whole breast dose of 50 Gy in 25 fractions with no tumor bed boost. This dose regime is taken as the stan-

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dard treatment [3]. The radiation dose in tissue following eBT is inhomogeneous, with a very high dose adjacent to the applicator surface, falling off rapidly with increasing distance. At some point, at a distance from the radiation source, there will be a transition from the higher biological effect of eBT compared to EBRT at short distances to the lower effect seen further away. At this point, the two treatments will be equally effective, so this can be referred to as a point of isoeffect, as previously described by Herskind *et al.* [4]. Having defined this point at a (one-dimensional) distance from the central point of radiation emission, its implications for overall tumor control probability (TCP) are here analyzed in a way that takes into account the three-dimensional reality of the tissues. We have based our calculations on a different $\alpha/\beta$ ratio for breast tumor control of 3.5 Gy [3].

With a hypothetical point source of radiation inside, a rigid, hollow spherical applicator embedded in homogeneous tissue, the point of isoeffect will occur at exactly the same distance from the radiation source in every direction, thus creating a three-dimensional contour that takes a spherical shape, and which we shall refer to as the shell of isoeffect. Within this shell, the eBT treatment will be more effective than EBRT, whereas outside it, the reverse is true. To compare the two treatments in terms of TCP, further factors must also be considered – the distribution and density of the biological targets of radiotherapy and their



**Fig. 1.** Set-up used for depth dose measurements. Experimental set-up used to obtain depth-dose curves showing the X-ray source, custom-built water equivalent phantom (with a simulated nylon applicator wall) of dimensions 100 mm × 100 mm × 100 mm. Gafchromic® EBT-2 dosimetry film (International Specialty Products, Wayne, NJ) was used to measure the dose at distances of 20 to 70 mm away from the tip of the probe, in increments of 1 mm

variations within these volumes. If all the targets lie within the shell of isoeffect, the higher effectiveness of eBT here would make it, the more effective treatment (higher TCP). Whereas if the targets were scattered evenly throughout the whole breast, the small volume within the shell where eBT is more powerful, would be overwhelmed in comparison to the volume of breast tissue outside, and so EBRT would have the greater TCP. We propose that there could be a region, possibly a spherical volume, where the therapeutic effect of eBT and EBRT are equivalent.

## Material and methods

### Measurement of depth dose data

Depth doses were measured in a tissue equivalent phantom using Gafchromic® EBT-2 dosimetry film (International Specialty Products, Wayne, NJ, USA). The film was cut to 100 mm × 100 mm and mounted within the phantom at right angles, along the central axis of the X-ray tube. Films were scanned 24 hours post-exposure using an Epson Expression 10000XL flatbed scanner. Scanning was performed in transmission mode with 150 dpi with red channel data extracted and saved in uncompressed tagged image format (TIFF). As shown in Figure 1, the top of the Papillon+™ X-ray tube was mounted in a custom-built jig to leave a 20 mm gap between the anode and the proximal edge of the EBT-2 film. This gap equates to the space inside a hollow 40 mm diameter applicator, and consists of a 17 mm air gap and a 3 mm nylon layer to simulate the applicator wall. With an inherent filtration equivalent to 0.4 mm Al, the percentage depth dose falls to approximately 50% after traversing the 3 mm nylon layer. The phantom does not exactly reproduce the scatter geometry of the intended clinical setup and somewhat underestimates the absorbed dose at depth. Exposures were made for 5 seconds, and the films were scanned and analyzed using public domain image analysis software (ImageJ, National Institutes of Health, Bethesda, MD, USA).

### Relative biological effectiveness at low dose

For any given geometry, the dose deposited by very low energy X-rays decreases with depth and the relative biological effectiveness (RBE) increases with decreasing dose. However, the increase in RBE is mitigated due to a 1-2% increase in beam hardening up to 10 mm deep in tissue [5]. Tissue attenuates low-energy X-rays more strongly than high energy ones, primarily because of photoelectric absorption. A heterogeneous beam traversing tissue becomes proportionately richer in high-energy photons, and hence more penetrating, or 'harder', with a lower RBE. Previous studies have found values of $\alpha_H/\alpha_L$ (low dose RBEs) in the range 0.97 to 1.17 for various cell lines irradiated with X-rays below 50 kV [6,7,8,9,10,11,12,13,14,15].

### Relative biological effectiveness calculations for high dose rate X-ray brachytherapy

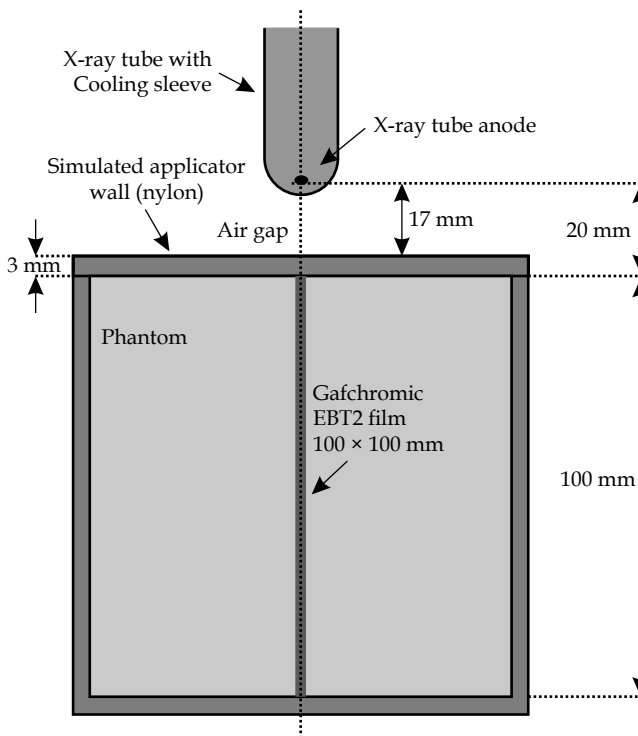To estimate RBE values as a function of dose and irradiation time, we modified the Linear Quadratic (LQ)

approach used by Brenner *et al.* [16]. In this study, we consider the radiobiological effectiveness of the Papillon+™ X-ray brachytherapy (eBT) device (Ariane Medical Systems Ltd, Derby, UK) operated at 30 kV, 0.3 mA with no added filtration delivering a single 20 Gy fraction to the surface of a 40 mm applicator in < 2 minutes, compared with over 20 minutes needed by the Intrabeam™ for an applicator of the same diameter [17,18].

From Brenner *et al.*,

$$RBE(D_H) = \frac{\gamma L}{2GD_H}\left[\sqrt{1 + \frac{4G}{\gamma L}\left(\frac{\alpha_H}{\alpha_L}D_H + \frac{G}{\gamma L}D_H^2\right)} - 1\right]$$

Equation 1,

where *G* is the generalized Lea-Catcheside time factor accounting for dose protraction during continuous irradiation at a constant dose rate for a delivery time (*T*). The quantity $\gamma_L$ is the conventional low-LET $\alpha/\beta$ ratio for the tumor relapse in the breast, $\alpha_H/\alpha_L$ equates to $RBE_{max}$ and $D_H$ is the prescribed dose. The quantity $T_{1/2}$ is the half-time for sublethal cellular damage repair. In this study, we consider only mono-exponential repair kinetics based on the assumption of a single, dose-independent rate of repair of sublethal injury in the target cells. A range of values for the repair half times of acute or late responding tissues is demarcated with a reasonable fit to the clinical data. For the acute effects (or tumor control), the best fits are obtained for repair half times of about 30 minutes [14].

We have used $T_{1/2}$ = 30 minutes as the halftime for cellular recovery from sublethal damage and with the Papillon+™ able to deliver 20 Gy in a time T < 2 minutes, then we can state that T«$T_{1/2}$ and G tends to 1. For tumor relapse in the breast $\alpha_H/\alpha_L$ equates to $RBE_{max}$, the maximum RBE as the dose approaches zero. Estimated low dose RBEs were adopted from Brenner *et al.* [16].

Equation 1 can be rewritten as:

$$RBE(D_H) = \frac{\gamma L}{2D_H}\left[\sqrt{1 + \frac{4D_H}{\gamma L}\left(RBE_{max} + \frac{D_H}{\gamma L}\right)} - 1\right]$$

Equation 2

Showing that the RBE at any dose is a function of $RBE_{max}$, $\alpha/\beta$ ratio and dose.

$D_H$ is the prescribed dose (PD) of 20 Gy to the surface of a 40 mm diameter rigid, hollow spherical applicator. A meta-analysis of START-A and the START pilot trial showed an adjusted estimate of $\alpha/\beta$ ratio for breast tumor control of 3.5 Gy (95% CI: 1.2-5.7) and this is used in subsequent calculations (Figure 1).

### Point of isoeffect for breast cancer

By correcting for the higher RBE of the eBT (Equation 1), and using the LQ model to adjust for fractionation differences, we have attempted to translate the depth dose curve of eBT into an equivalent dose (biologically equivalent dose) of conventional megavoltage radiotherapy given in 2 Gy fractions. For this calculation, an $\alpha/\beta$ ratio for breast cancer of 3.5 Gy is used, as suggested by the results of the START trial [3]. The point on the X-axis, at which the corrected curve crossed the 50 Gy point on the Y-axis, thus becomes a 'Point of Isoeffect' where we should expect the two schedules to have an equivalent

radiobiological effect on breast cancer. Nearer the applicator, the eBT treatment will be more effective, and less so beyond this point. If the biological "targets" at which the radiation is aimed were mainly to be found within the few millimeters between the applicator surface and the 'Point of isoeffect', then the higher RBE of electronic brachytherapy in this area might at least balance the lower RBE achieved in the tissue beyond this point, where the target population density is likely to be less.

## Results

### Depth doses for the Papillon+

The percentage depth dose obtained from the Papillon+™ operating at 30 kV 0.3 mA (inherent filtration 0.4 mm Al) for a typical 40 mm diameter applicator is shown in Figure 2. As there is no tissue within the applicator, the X-axis begins at the surface of the applicator and represents increasing depths in a tissue equivalent phantom. There will be the usual uncertainties associated with measuring depth doses using radiochromic film. Such as intra- and inter-film variations, scan reproducibility, and the uncertainty in experimental set-up. However, these are fully described elsewhere in the literature and are expected to contribute an overall error of the order of ± 5% [19].

### Shell of isoeffect for breast cancer

Physical doses were calculated from the 30 kV percentage depth dose in Figure 2, assuming a prescribed dose of 20 Gy in one fraction to the surface of a 40 mm diameter spherical applicator, and these were plotted on a semi-logarithmic graph as D(abs) 30 kV. This was then converted to the corresponding isoeffective acute dose of $^{60}$Co reference radiation by multiplying with the modelled RBEs at different depths. $^{60}$Co gamma rays were used as the reference radiation since over the depths of clinical interest, up to 20 mm, the change in the $^{60}$Co gamma ray



40 mm dia. applicator
30 kV, 0.3 mA
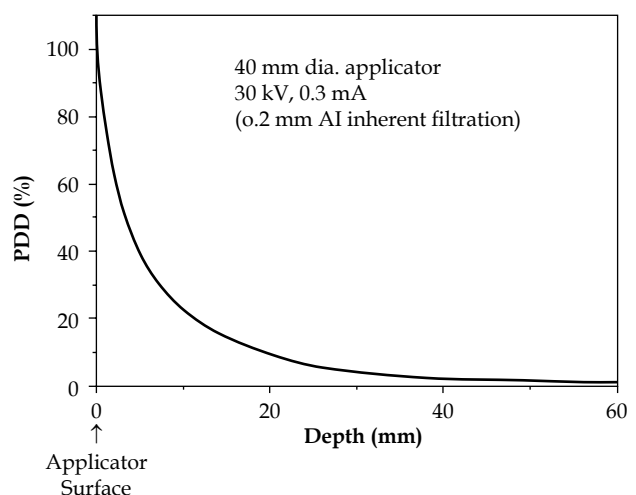(o.2 mm AI inherent filtration)

**Fig. 2.** Beam performance at 30 kV with only inherent filtration closely mimics the Intrabeam™ device as used during the TARGIT-A trial, the rapid dose falls off being due to low mean beam energy in addition to inverse square law effects

spectrum is negligible. Predicted low dose RBEs ($\alpha_H/\alpha_L$) were adopted from Brenner *et al.* and used in Equation 1 to calculate the (RBE) ^{60}Co for the Papillon+™ device operating at 30 kV. These calculated clinical RBEs ranged from 1.154 at the surface of a 40 mm diameter applicator to 1.100 at 35 mm from the applicator surface. These are somewhat lower than those found by Reniers *et al.* who calculated the RBE for breast tissue to be in the range 0.89 to 1.43. However, direct comparisons are difficult to make with a high degree of certainty due to large experimental uncertainties and how well microdosimetric mathematical modelling reflects real biological systems [20] (Table 1).

The product of the physical doses and the corresponding (RBE) ^{60}Co gives the isoeffective acute doses D(iso)

**Table 1.** Predicted low dose relative biological effectiveness (RBEs) ($\alpha_H/\alpha_L$) were adopted from Brenner [16] and used in Equation 1 to calculate the relative RBE ^{60}Co for the Papillon+™ device operating at 30 kV. These calculated clinical RBEs ranged from 1.154 at the surface of a 40 mm diameter applicator to 1.100 at 35 mm from the applicator surface

| Depth (mm) | Versus [60]Co [$\alpha/\beta$ = 3.5 Gy] | |
| --- | --- | --- |
| | $\alpha_H/\alpha_L$ | (RBE) [60]Co |
| 0 | 3.05 | 1.154 |
| 5 | 2.67 | 1.127 |
| 10 | 2.54 | 1.118 |
| 15 | 2.48 | 1.113 |
| 20 | 2.44 | 1.110 |
| 25 | 2.40 | 1.107 |
| 30 | 2.35 | 1.104 |
| 35 | 2.30 | 1.100 |

**Table 2.** The product of the isoeffective single dose of ^{60}Co reference radiation, relative biological effectiveness (RBE) ^{60}Co and the RBE corrected standard 2 Gy equivalent dose fractions (EQD$_2$) doses, EQD$_2$ (30 kV) * RBE ^{60}Co ranged from 98.62 Gy at the applicator surface to 1.13 at 35 mm

| Depth (mm) | D$_{(abs)}$ 30 kV | (RBE) [60]Co | EQD$_2$ (30 kV) * RBE [60]Co |
| --- | --- | --- | --- |
| 0 | 20.00 | 1.154 | 98.62 |
| 5 | 12.00 | 1.127 | 38.11 |
| 10 | 7.50 | 1.118 | 16.76 |
| 15 | 4.60 | 1.113 | 7.54 |
| 20 | 3.40 | 1.110 | 4.74 |
| 30 | 1.60 | 1.104 | 1.64 |
| 35 | 1.20 | 1.100 | 1.13 |

[60]Co. The LQ model was then used to convert the single isoeffective acute D(iso) ^{60}Co doses to the biologically equivalent total dose of conventional EBRT administered in 2 Gy fractions (EQD$_2$) as given by Equation 3.

$$EQD_{2Gy} = [D_x Gy\, (x + \alpha/\beta)]/(2 + \alpha/\beta) \qquad \text{Equation 3,}$$

where $D_x$ is the total dose at a particular depth and $x$ is the dose per fraction. The EQD$_2$ was then corrected for the decreasing RBE at depth to give EQD$_2$ (30kV) * (RBE) [60]Co (Table 2).

As described above, the point of isoeffect can be read off as the value on the X-axis where the EQD$_2$ (30 kV) * (RBE) ^{60}Co line crosses the 50 Gy mark on the Y-axis, a distance (isoeffective depth) of approximately 3.5 mm beyond the applicator surface (Figure 3).

## Discussion

We have established a framework within which to compare the biological effect of eBT (prescribed as 20 Gy at applicator surface) with EBRT (prescribed as 50 Gy in 25 fractions). Using this, we have calculated that for a 40 mm diameter rigid, hollow, spherical applicator radiobiological equivalence will occur at an approximate distance of 3.5 mm from the surface of the applicator. If we consider individual radiation beamlets, as each beamlet progresses into breast tissue, it will encounter an unknown concentration of targets along its path. The radial probability of destruction of targets is constant for all beamlets at a given distance in breast tissue that is, at the surface of a sphere. Combining such spheres, we have a range of probabilities forming concentric, minutely thin, radial probability shells of quasi-spherical outline. Each combination of applicator size and EBRT
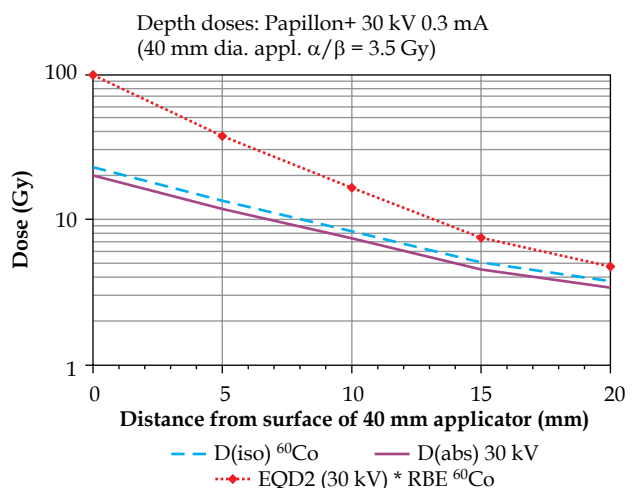


**Fig. 3.** Dose distribution for 30 kV X-rays generated by the Papillon+™ with a 40 mm diameter spherical applicator. The absolute physical dose D(abs) 30 kV, the isoeffective single dose of the ^{60}Co reference radiation, D(iso) ^{60}Co, and the RBE corrected EQD$_{2Gy}$ doses, EQD$_2$ (30 kV) * RBE ^{60}Co are shown as a function of distance from the surface of the applicator. EQD$_2$ (30 kV) * RBE ^{60}Co accounts for the effect of RBE with distance from the applicator surface

prescription regime could be expected to have a unique 'shell of isoeffect'. Against biological targets of radiotherapy that lie closer to the applicator surface than this shell, eBT will be more effective than EBRT, and less effective for those lying further out.

It now becomes important to consider what constitutes these "targets". In conventional radiobiology, these are considered to be viable tumor clonogens, and it is thought that these will have a physical distribution that coincides with the outlying tumor cells [21]. It was found that such cells regularly occurred at considerable distances from the edge of the main tumor mass, although in general, the shorter the distance, the more the cells. However, there are increasing reasons for thinking that there may be other targets of therapeutic radiation, which can broadly be considered as aspects of the tumor microenvironment.

It has been found that wound fluid stimulates the proliferation and invasion of breast cancer cell lines. However, this effect was almost completely absent when wound fluids from TARGIT-treated patients were used. Analysis showed that these fluids displayed an altered expression of some cytokines and failed to stimulate the activation of some intracellular signal transduction pathways.

It may be that IORT directly to the tumor bed alters the molecular composition and biological activity of surgical wound fluid from those patients. This could partially explain the very low recurrence rates found in a large pilot study using TARGIT [22].

The surgical act precipitates an avalanche of local biological responses, some of which may well enhance tumor growth, and these responses are likely to be at their maximum at the rim of the surgical cavity – the tissue that is in direct contact with the applicator used for eBT. This rim is indeed the locus of much of the "target" that is indirectly supported by recent guidelines published by ASTRO/SSO on the desirable width of tumor-free margin found on histological examination of the excision specimen [1]. On reviewing the available evidence, the authors of this guideline concluded that, as long as the cut edge (which equates to the "rim") was tumor-free, the depth of tumor-free margin beyond this did not influence outcomes after EBRT. This could be interpreted as indicating that the number of putative clonogens found lying in tissue within a few millimeters of the surgical rim has very little importance, and that the rim of the cavity itself is more important a target than the outlying cells. In turn, this implies that TCP is heavily dependent on the effectiveness of the radiation at very short distances from the applicator, as is the case with eBT. This could be an important factor in the non-inferiority of IORT to EBRT shown by the TARGIT-A Trial.

As breast cancers of different phenotypes express different biological behavior in various ways, this might influence how the biological targets were distributed in tissue. For tumors where the targets were mainly concentrated at the cavity rim, eBT would be expected to have a higher ultimate TCP than for those where they diffuse more extensively into adjacent tissue. Both TARGIT-A and the ELIOT trials give initial hints that some categories of breast cancer are more likely to be controlled by eBT than others [23]. The capability of the Papillon+™ to vary its X-ray energy (30 to 50 kVp, 0 to 3 mA) and filtration might prove a fruitful area of future investigation in this respect. For example, at 30 kVp and 0.20 mm Al (half value layer), the Papillon+™ mimics the Intrabeam and at 50 kVp and 0.8 mm Al added filtration it mimics treatment with $^{192}$Ir.

A further consideration in respect of biological targets that were humorally influenced, is that there would be a time, probably soon after surgery when they would be most potent, and this is when radiation therapy should occur. The better results seen in the TARGIT-A trial when IORT was used immediately after surgery rather than at a later date ("pre-" and "post-pathology" strata in the trial) supports this view.

## Conclusions

We have presented a theoretical framework, which enables determination of the radiobiological equivalence of two different treatment modalities for breast cancer namely, X-ray brachytherapy and EBRT. In this study, we considered the radiobiological effectiveness of the Papillon+™ X-ray brachytherapy device operating at 30 kV, 0.3 mA using a 40 mm diameter rigid, hollow, spherical applicator, and producing dose rates in excess of 14 Gy/min at the applicator surface. For this case, radiobiological equivalence between eBT (prescribed as 20 Gy at applicator surface) and EBRT (prescribed as 50 Gy in 25 fractions) was found at approximately 3.5 mm distance from the surface of the applicator.

While the ultimate test of any new modality is its proof of effectiveness in well-designed clinical studies, the methodology used here in identifying a 'shell of isoeffect' may be useful in the clinical interpretation of trial results, and may possibly help gain further biological insights into the pathophysiological mechanisms involved. The methodology can also be readily transferred to calculations of predicted effects on important normal tissues such as skin, and to the effects that beam modification (changes in kV or filtration) and applicator size will have.

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## Disclosure

Authors report no conflict of interest.

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