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A skin dose prediction model based on *in vivo* dosimetry and ultrasound skin bridge measurements during intraoperative breast radiation therapy

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ABSTRACT

PURPOSE: Using *in vivo* measurements from optically stimulated luminescence dosimeters (OSLDs) to develop and validate a prediction model for estimating the skin dose received by patients undergoing breast intraoperative radiation therapy (IORT).

METHODS AND MATERIALS: IORT was performed using INTRABEAM-600 with spherical applicators placed in the lumpectomy cavity. Ultrasound skin bridge measurements were used to determine the applicator-to-skin distance, with OSLDs placed to measure the skin surface dose at the corresponding points. The OSLD response was calibrated for the 50 kVp INTRABEAM-600 output. Models were fit to describe the dose fall-off with increasing applicator-to-skin distance and the best fitting model was chosen for estimating skin dose.

RESULTS: Twenty four patients with 25 lumpectomy cavities were included, and the average skin dose recorded was 1.18 Gy ± 0.88 Gy, ranging from 0.17 Gy to 4.77 Gy, with an average applicator-to-skin distance of 19.9 mm ± 5.1 mm. An exponential-plateau model was found to best describe the dose fall-off with a root-mean-square error of 0.73. This model was then validated prospectively using skin dose measurements from five consecutive patients. Validation measurements were well within the 95% prediction limits of the model, with a root-mean-square error of 0.52, showing that the prediction model accurately estimates skin dose using ultrasound skin bridge measurements.

CONCLUSIONS: This prediction model constitutes a useful tool for estimating the skin dose received during breast lumpectomy IORT. The model and accompanying 95% confidence intervals can be used to establish a minimum allowable skin bridge distance, effectively limiting the maximum allowable skin dose.

Keywords: Intraoperative radiation; Breast cancer; Skin dose; Prediction models

Introduction

While breast-conserving lumpectomy surgery followed by adjuvant whole-breast radiation therapy (RT) is standard of care for most patients with early-stage breast cancer, targeted partial breast irradiation using intraoperative RT (IORT) has emerged as a promising alternative, especially for select patients (1−5). The benefit of IORT as compared with external beam whole-breast RT is clear in terms of resource sparing, as the treatment can be delivered during the lumpectomy procedure, but it has also been shown to have considerably less toxicity and improved cosmetic outcome (4,6−8). During the IORT procedure, when performed according to the TARGIT trial protocol, a single fraction dose of 20 Gy is delivered to the lumpectomy cavity using a spherical applicator matched to the size of the cavity (5).

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Conflicts of interest: None to declare.

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Because of the high dose per fraction and the lack of individualized treatment planning, doses to organs at risk and especially the skin may vary from patient to patient and may be difficult to estimate. Therefore, *in vivo* dosimetry provides an opportunity for quality control and dose estimation that can identify errors in delivery and provide an estimate of organ at risk doses (9–11). Another important part of TARGIT IORT performed using the Zeiss INTRABEAM spherical applicators (Carl Zeiss Meditec AG, Oberkochen, Germany) is measuring the minimum distance between the applicator surface and the skin in the superior, inferior, lateral, and medial direction via ultrasound. This is to ensure that a minimum distance to the skin is maintained to limit the maximum skin dose received. As such, *in vivo* measurements of the skin dose at the ultrasound distance measurement points provides direct estimates of the dose fall-off from the applicator surface through a certain depth of tissue.

Previous studies have investigated and characterized the dosimetry and dose fall-off with various applicator sizes for the INTRABEAM x-ray source and applicators, either via film measurements (9, 12), Monte Carlo simulation (11), or even using *in vitro* cell line experiments (13, 14). For the purpose of our study, optically stimulated luminescence dosimeters (OSLDs) are small and can be used to measure surface doses to a point, which makes them ideal for measuring the dose at the skin surface at the point of the ultrasound distance measurement, provided proper calibration is performed. The dose measured at the skin surface is used as a surrogate for skin dose throughout this study, with the understanding that it is an approximation of the true skin dose received by the patient. In this study, we performed *in vivo* skin dose measurements in patients undergoing IORT for early-stage breast cancer at our institution and modeled the dose fall-off as a function of distance from the applicator surface. This provides a model for predicting the maximum skin dose based on the applicator-to-skin distance, which can also be used to define the minimum allowable skin bridge distance.

Methods and Materials

IORT procedure

The IORT procedure was performed using the Zeiss INTRABEAM-600 system, which consists of a miniature x-ray source delivering radiation to 20 Gy nominal prescription dose at the applicator surface in an isotropic geometry with 50 kVp energy and 40 μA tube current. At our institution, spherical applicators ranging from 3.0 to 5.0 cm in diameter are used for treatment. Once the lumpectomy has been performed, the cavity is sized using dedicated stainless steel sizing applicators (15) and the corresponding size spherical treatment applicator is attached to the x-ray source, which is then inserted into the lumpectomy cavity. The surgeon ensures that the entire applicator head is surrounded by tissue to avoid air pockets, and ultrasound readings are performed to measure the minimal applicator-to-skin distance in the superior, inferior, lateral, and medial direction. Four labeled and sterilized In-Light NanoDot OSLDs (Landauer Inc., Glenwood, IL) are then placed, one at each of the ultrasound reading positions on the skin. Before being brought to the operating room the NanoDots are labeled with the expected ultrasound reading position (superior, inferior, lateral, or medial) and sterilized using hydrogen peroxide vapor and low-temperature gas plasma sterilization. NanoDots are sterilized and placed on the patient's skin while kept in their individual plastic packaging to preserve sterile conditions throughout. Before the start of this study, we ensured that the NanoDots dosimetric readout was unaffected by the sterilization procedure. After the OSLDs are placed, sterile lead-equivalent shields are placed over the treatment area and the IORT is delivered during 16–45 min depending on the applicator size.

OSLD calibration and readout

The NanoDot OLSDs utilized in this study are 5 mm in diameter and 0.2 mm thick, encased in plastic and manufactured to provide accurate readings at external beam RT energies of about 6 MV, which is considerably higher than the 50 kVp used during IORT. It has been shown that these OSLDs have strong energy dependence, even in the range of orthovoltage and diagnostic x-ray energies (16, 17). In fact, the response of the NanoDot OSLDs is about 3.5–4 times higher in the 50 kVp range, as compared with x-ray energies above 300 kVp (17), so without proper calibration, the readings would grossly overestimate the dose measured by the OSLD. The calibration procedure was carried out by attaching four OSLDs to a 3.5 cm spherical applicator, each OSLD separated by 90° to average out any anisotropy in the output that would affect the readings. The applicator was then placed in the calibration phantom that comes with the INTRABEAM-600 system, and measurements of 2.5, 5.0, and 10 Gy prescribed at the applicator surface according to the TARGIT protocol were performed as illustrated in Fig. 1. As the TARGIT protocol has been shown to underestimate the absorbed dose to water (12), our calibration curve was scaled by a factor of 1.211 so that the OSLD readings would correspond to absorbed dose as per the V4.0 INTRABEAM calibration.

The linear response was derived based on four OSLD readings per dose level resulting in a calibration factor of 6.62×10^{-6} Gy/count, using the corrected counts considering the individual sensitivity of each OSLD chip. Of note, this calibration factor is ~4 times higher than what we previously measured for a ^{137}Cs source, which emits 662 keV gamma rays, illustrating the importance of accounting for the energy dependence of the OSLDs. The OSLDs from the calibration procedure and patient studies were all read

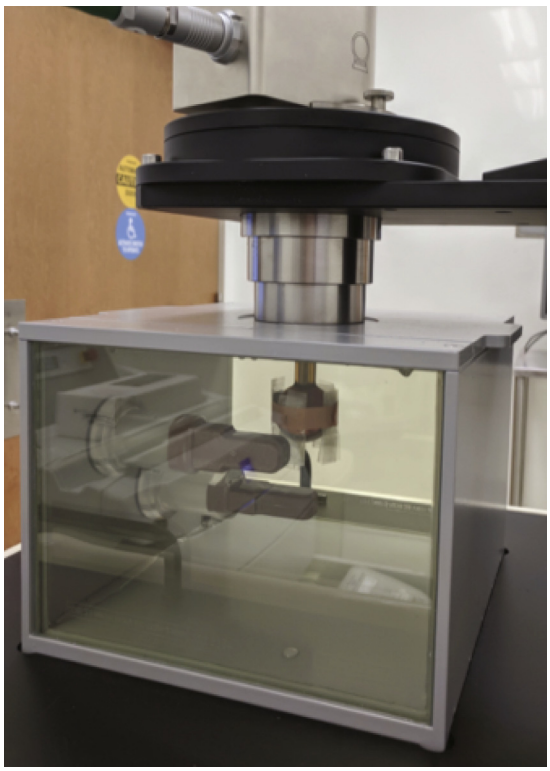

Fig. 1. The in air OSLD calibration measurement setup is depicted with four OSLD chips placed 90° apart on the surface of an INTRABEAM spherical treatment applicator. OSLD = optically stimulated luminescence dosimeter.

on the same InLight microStar reader (Landauer Inc., Glenwood, IL) in triplicate and the average reading was used to record the raw photomultiplier tube counts.

Investigating beam hardening effects on OSLD readout

It is reasonable to assume that the 50 kVp energy spectrum of the INTRABEAM-600 source will experience beam hardening even when only traversing a few cm of breast tissue. Because of the strong energy dependence of the OSLDs, we investigated whether the dosimeter response differed with increasing tissue depth, and whether correction factors would need to be applied to the measured skin doses. For this experiment, we used the Small Animal Radiation Research Platform (SARRP; XStrahl, Surrey, UK), which has a source capable of delivering 50 kVp x-rays. We used an Exradin P11 parallel-plate ion chamber (Standard Imaging Inc., Middleton, WI) cross-calibrated against a farmer type chamber based on the AAPM TG-61 protocol for orthovoltage x-ray dosimetry, more details are provided in the study by Brodin *et al.* (18). The parallel-plate chamber readings were used to obtain energy-independent reference readings at varying tissue depth, generated by adding solid water blocks in 1 cm increments. The relative readings were then compared against the relative OSLD readings using the same amount of tissue-equivalent build-up material, keeping the source-axis-distance constant, and any difference in the relative response between the ion chamber and OSLD readings would indicate energy-dependent effects due to beam hardening. Each measurement consisted of a 100s exposure at 50 kVp, 20 mA tube current with 1 mm Al filtration. The measurement setup is illustrated in Fig. 2 with two OSLDs used for each tissue depth, placed on the lateral sides of the ion chamber to avoid influence from the heel effect.

Statistical analysis

The *in vivo* skin doses measured using OSLDs were compared with the corresponding applicator-to-skin distances measured via ultrasound, and semiempirical functions of the dose-fall-off were fitted using the curve fitting toolbox in MATLAB v.2018a (The MathWorks, Inc., Natick, MA). The functions were anchored at the prescription point of 24.2 Gy at the applicator surface, corresponding to the absorbed dose to water as per the V4.0 calibration protocol, and the optimal fit was determined

Fig. 2. The energy dependence measurements related to beam hardening are shown with the parallel-plate ion chamber and OSLD chips placed as illustrated, with solid water blocks added to simulate varying tissue depth. OSLD = optically stimulated luminescence dosimeter.

Table 1
Relative measurements with varying tissue-equivalent build-up examining potential differences in parallel-plate ion chamber and OSLD response due to beam hardening

Experimental setup	Ion chamber reading	OSLD average reading	OSLD/Ion chamber reading
No build-up	100% (ref)	100% (ref)	1.00
1 cm build-up	59.0%	58.3%	0.987
2 cm build-up	37.0%	36.8%	0.993
3 cm build-up	22.1%	21.8%	0.986

OSLD = optically stimulated luminescence dosimeter.

based on examining the residuals and comparing the resulting root-mean-square error (RMSE), Akaike information criterion, and Bayesian information criterion.

Results

OSLD dependence on beam hardening

The relative parallel-plate ion chamber and OSLD measurements are shown in Table 1 for varying tissue-equivalent build-up depth. It is clear from these readings that the OSLDs have a comparable response to the ion chamber with increasing build-up depth and as such we find it safe to assume that any change in OSLD response due to beam hardening in tissue can be neglected in our measurements.

These results agree with the trend seen by Poirier *et al.*, where the energy dependence of the NanoDot OSLDs starts to flatten out and become much less pronounced at energies of 50 kVp and below (17).

Determining the semiempirical dose fall-off based on ultrasound and OSLD readings

Skin dose readings were obtained for 24 consecutive patients receiving IORT to 25 lumpectomy cavities (one patient was treated for bilateral disease) of 14 left-sided and 11 right-sided lesions. An example of the OSLD placements after the ultrasound skin distance measurements is shown in Fig. 3.

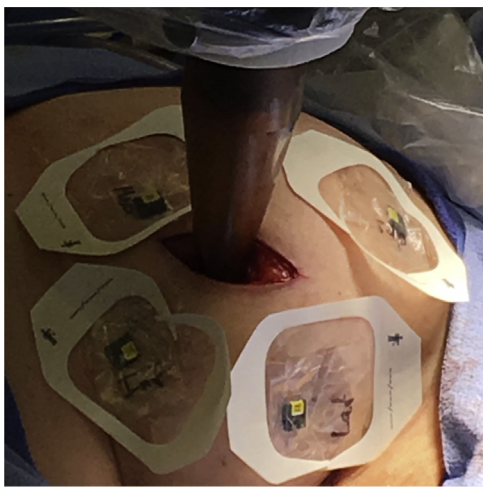

Fig. 3. Sterile NanoDot OSLDs placed at the inferior, medial, superior, and lateral portion of the skin surrounding the lumpectomy cavity and spherical treatment applicator. OSLD = optically stimulated luminescence dosimeter.

Four distance measurements and skin dose readings were obtained for each treatment case, except for one instance where a reliable ultrasound reading could not be obtained, resulting in 99 individual measurement points. The average skin dose measured during the treatment of these 25 cavities was 1.18 Gy ± 0.88 Gy, ranging from 0.17 Gy to 4.77 Gy. The average skin bridge distance was 19.9 mm ± 5.1 mm, ranging from 9.9 mm to 32.3 mm.

Two semiempirical functions were used to fit the skin dose measurements as a function of skin-to-applicator distance, an exponential (Eq. 1) and an exponential-plateau (Eq. 2) function:

$$D_{skin}(Gy) = 24.2\exp\left(\beta_{\exp}X_{dist}(mm)\right) \quad (1)$$

$$D_{skin}(Gy) = 23.535\exp\left(\beta_{\exp-plat}X_{dist}(mm)\right) + 0.685 \quad (2)$$

where anchoring the fit at 24.2 Gy at the applicator surface results in an optimal fit corresponding to a plateau of 0.685 Gy for the exponential-plateau model given the data. The resulting fits are shown in Fig. 4 along with the residuals and 95% prediction intervals.

As can be seen, both functions fit the data quite well, although the exponential model tends to consistently underestimate the skin dose at distances beyond 20 mm. The model comparison and parameters are shown in Table 2 with the exponential-plateau model showing a better fit to the data with a lower RMSE, Akaike information criterion, and Bayesian information criterion.

Prospective validation of the skin dose prediction model

The exponential-plateau model showed the best fit to the measured skin dose data and was considered the model of choice. To test the performance in predicting the skin dose based solely on the measured skin-to-applicator distance, we prospectively evaluated the performance of the model in five consecutive patients receiving breast IORT.

The validation measurements showed good agreement with the exponential-plateau model as shown in Fig. 5, where all of the data points are well within the 95%

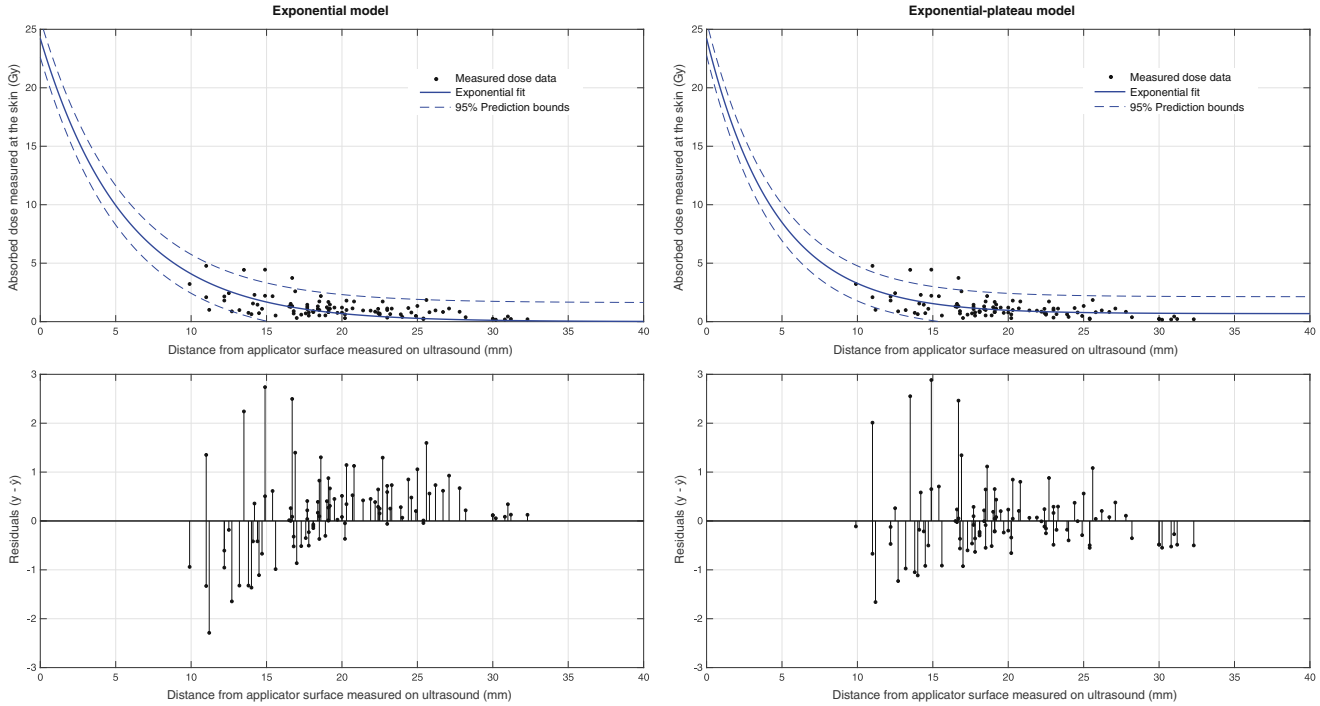

Fig. 4. The skin dose readings are shown as a function of measured skin-to-applicator distance along with the optimal fit and 95% prediction limits. The residuals show the difference between the measured and predicted skin dose for each data point.

prediction limits. The RMSE for the prediction model in the validation data set was 0.52, representing the average uncertainty in Gy when using the model for prospective skin dose prediction.

Because different sized spherical applicators result in a different inverse square law dependence, we further investigated whether there were differences in the dose fall-off depending on the applicator size that was used in each case. Figure 6 shows that there were no discernible differences between different applicator sizes, and that they all appeared to follow the exponential-plateau model well in the given range of measured skin bridge distances.

Discussion

We developed and prospectively validated a prediction model to estimate the skin dose received at the closest superior, inferior, medial, and lateral points from the treatment applicator during partial-breast IORT. The model only requires the ultrasound skin bridge measurements taken at these points as input, allowing the skin dose to be estimated as part of the routine IORT procedure. This should help investigators establish data-driven limits of the allowable minimum skin bridge distance.

Sethi *et al.* (19) performed phantom measurements using Gafchromic film to measure depth doses in water for INTRABEAM spherical applicators. Their measured dose fall-off in water is similar to what we found in our study with close to exponential fall-off. Although not directly comparable because we performed *in vivo* skin dose measurements, they found slightly higher doses at 5, 10, and 20 mm depth of 9.9 Gy, 5.7 Gy, and 2.4 Gy, as compared with 8.5 Gy, 3.3 Gy, and 1.0 Gy, respectively, based on our model. However, this difference is expected as our measured skin doses lack the backscatter component of films submerged in a water phantom. Similarly, Avanzo *et al.* (9) performed *in vivo* film measurements for spherical

Table 2
Parameters and comparison metrics for the fitted skin dose fall-off models

Model fit	Function	Parameters (95% CI)	RMSE	AIC	BIC
Exponential	$y = a\exp(bx)$	$a = 24.22$ (fixed) $b = -0.178$ (-0.187, -0.169)	0.817	245.9	253.7
Exponential-plateau	$y = a\exp(bx) + c$	$a = 23.535$ (fixed) $b = -0.221$ (-0.236, -0.206) $c = 0.685$ (fixed)	0.729	225.3	235.7

AIC = Akaike information criterion; BIC = Bayesian information criterion; RMSE = root-mean-square error.

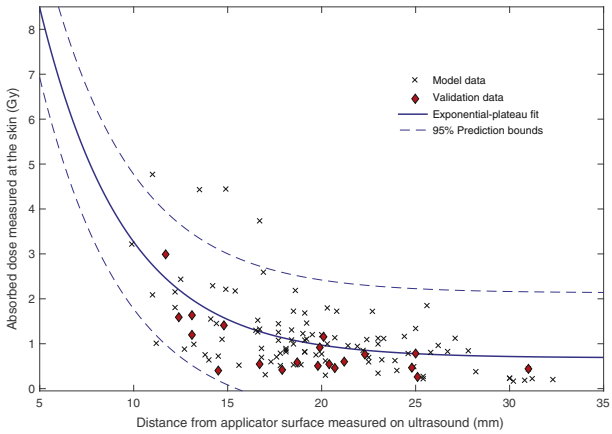

Fig. 5. The skin dose prediction model is shown with 95% prediction limits together with the individual measurement points from the data used to fit the model (crosses) as well as the prospectively collected validation data (diamonds).

applicator INTRABEAM treatments and found an average skin dose of 2.22 Gy at distances 1−2 cm from the applicator surface, with a range of 0.88−4.69 Gy. Their results agree well with our data where the average skin dose measured at distances of 1−2 cm was 1.43 Gy with a range of 0.31−4.77 Gy, and our model predicts an estimated dose of 3.3 Gy at 1 cm and 1.0 Gy at 2 cm.

A limitation of our study includes the uncertainty in accurately measuring the skin bridge distances on ultrasound as this depends on the pressure applied to the ultrasound probe by the surgeon, which in turn impacts tissue compression for the distance measurement. This is evidenced by a relatively large spread in the measured data and highlights the importance of validating the prediction model using prospectively collected data to ensure that skin doses are accurately estimated. It is important to note

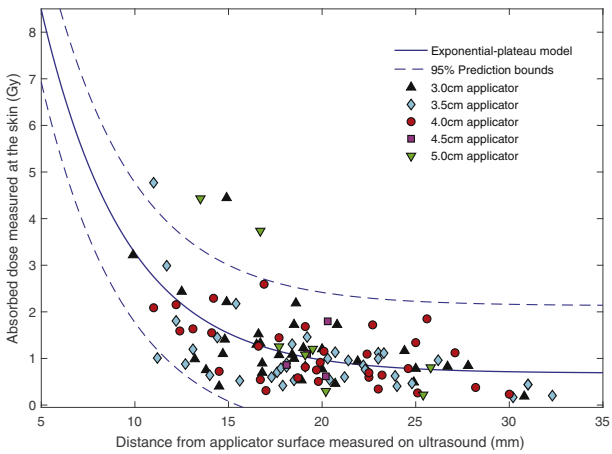

Fig. 6. The skin dose readings are shown as a function of measured skin-to-applicator distance for each spherical applicator diameter used in this study. This includes the measurements used to construct the model as well as the validation data. As can be seen most data points were collected based on 3.0 cm, 3.5 cm, and 4.0 cm applicators.

that one should be cautious to extrapolate the results presented here to applicator sizes outside of the 3.0−5.0 cm diameter range, as these might be subject to a different dose fall-off.

Using the developed model and 95% prediction limits we can derive guidelines for the minimum required skin bridge distance to ensure that a certain maximum skin dose is not reached. Based on our results the estimated skin dose and 95% confidence interval would be 8.5 Gy (7.0−10.1 Gy), 5.2 Gy (3.7−6.7 Gy), or 3.3 Gy (1.8−4.8 Gy) for skin bridge distances of 5, 7.5, or 10 mm, respectively. Conversely, to keep the estimated skin dose below 5 Gy or 7.5 Gy with 95% confidence one would require a minimum skin bridge distance of 9.7 mm or 6.8 mm, respectively.

In conclusion, the prediction model presented here provides practitioners with a simple and efficient tool for estimating the skin dose received during breast IORT. Another example use case would be if one wishes to limit the maximum skin dose received by patients undergoing INTRABEAM breast IORT to <5 Gy, then the model would suggest keeping a minimum skin bridge distance of at least 10 mm.

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