



PAPER

Radiochromic film *in vivo* dosimetry predicts early the risk of acute skin toxicity for brachytherapy partial breast irradiationGerson M Struik^{1,2} , Jeremy Godart², Taco M Klem¹, Thalut T Monajemi³, James Robar³ and Jean-Philippe Pignol^{2,3}¹ Department of Surgery, Franciscus Gasthuis and Vlietland, PO Box 10900, Rotterdam 3004 BA, The Netherlands² Department of Radiation Oncology, Erasmus MC Cancer Institute, PO Box 5201, Rotterdam 3008 AE, The Netherlands³ Department of Radiation Oncology, Dalhousie University, 5820 University Avenue, Halifax, Nova Scotia B3H1V7, CanadaE-mail: g.struik@franciscus.nl and g.struik@erasmusmc.nl**Keywords:** breast radiotherapy, *in vivo* dosimetry, skin toxicity, radiochromic filmsSupplementary material for this article is available [online](#)**Trial registration:** Netherlands Trial Register (www.trialregister.nl), NTR6549, the trial was registered prospectively on 27 June 2017. ABR number: NL56210.078.16**Abstract**

Brachytherapy accelerated partial breast irradiation (APBI) is well tolerated, but reported acute toxicities including moist desquamation rates range from 7% to 39%. Moist desquamation is correlated to long-term skin toxicity and high skin dose is the main risk factor. This study uses radiochromic films for *in vivo* skin dosimetry of low dose rate (LDR) APBI brachytherapy and prediction of skin toxicity. Patients participating in a clinical trial assessing skin toxicity of LDR seed brachytherapy were included in this study. Following the seed implantation procedure, patients were asked to wear a customized oval shaped radiochromic film on the skin projection of the planned target volume (PTV) for 24 h. Exposed films were collected, and maximum point doses were measured. In addition, maximum doses to a small skin volume ($D_{0.2cc}$) were calculated on the pre- and post-implant CT-scan. Acute skin toxicities (redness, pigmentation, induration and dermatitis) were scored by the treating physician for 2 months during follow-up visits. Skin dose measurements and acute toxicity were available for 18 consecutive patients. The post-implant calculated maximum skin doses ($D_{0.2cc}$), 60.8 Gy (SD \pm 41.0), were on average 30% higher than those measured *in vivo* ($D_{max-film}$), 46.6 Gy (SD \pm 19.3), but those values were highly significantly correlated (Spearman's rho 0.827, $p < 0.001$). Also, dermatitis and induration were significantly correlated with higher *in vivo* measured and post-implant calculated skin dose. Pre-implant dosimetry was not correlated with measured or post-implant skin dose or side effects. Radiochromic films can reliably diagnose excess dose to the skin during the first 24 h and predict skin toxicity, which enables preventative measures.

1. Introduction

Breast cancer is mostly diagnosed at an early stage (Peto *et al* 2000, SEER Database 2017). The treatment outcomes of patients undergoing breast conserving therapy (BCT), which includes a wide local excision followed by adjuvant radiotherapy, are excellent. In this group, BCT is equivalent to mastectomy in overall survival (Fisher *et al* 2002, Veronesi *et al* 2002). For selected low-risk patients, radiation therapy can be limited to the area around the surgical cavity. Since smaller volumes are treated, a larger amount of radiation dose can be delivered faster and the treatment accelerated using various techniques labelled accelerated partial breast irradiation (APBI) (Polgar *et al* 2010, Shah *et al* 2013, Vicini *et al* 2016, Correa *et al* 2017).

By essentially allowing breast preservation, adjuvant radiotherapy has primarily a cosmetic benefit (Kim *et al* 2015). One important organ at risk for the adjuvant radiotherapy of early stage breast cancers is the skin. Whole breast radiotherapy using external beam with a prescription dose of 50 Gy in 25 treatments leads to

skin toxicity rates of 31%–49%, though the rates are lower using hypofractionation (Lilla *et al* 2007, Pignol *et al* 2008). Brachytherapy APBI is well tolerated, with acute toxicity rates, including moist desquamation, ranging from 7% to 39% (Pignol *et al* 2015, Gitt *et al* 2016, Ott *et al* 2016). Moist desquamation is correlated to long term skin toxicity including telangiectasia, which impacts on cosmesis (Lilla *et al* 2007, Pignol *et al* 2016) and eventually impacts on the health related quality of life (Pignol *et al* 2016). The radiation dose to the skin is the main predictor of skin toxicity (Bentzen and Overgaard 1991, Keller *et al* 2012, Mashouf *et al* 2016) and detecting early an excess dose to the skin could allow preventative measures.

This study describes the use of radiochromic films for early *in vivo* skin dosimetry in patients prospectively treated with low dose rate (LDR) APBI brachytherapy. Skin dose measurements were compared to pre- and post-implant treatment planning system (TPS) calculations using CT images and to the clinical occurrence of acute skin toxicity.

2. Materials and methods

2.1. Patients

Patients included in this study were participating in a clinical trial evaluating the benefit of a skin spacer to reduce skin toxicity for low dose rate (LDR) seed brachytherapy APBI (Struik *et al* 2018). An ancillary study was performed to measure the skin dose, and to correlate those measurements to dose calculations and acute toxicity in 18 consecutive patients. The trial eligibility for LDR seed APBI followed international guidelines defining suitable patients. This includes, women 50 years of age or older, with a histologically proven invasive or *in situ* ductal carcinoma, excluding lobular features, a tumor size of 3 cm or less, and a negative axillary sampling. Also, the LDR seed brachytherapy must be technically feasible based on the absence of large fluid cavity and a limited treatment volume size. Patients were excluded from the study if they had neo-adjuvant chemotherapy, lymphovascular invasion, or an allergy for hyaluronic acid. The trial details have been described elsewhere (Struik *et al* 2018). The trial was approved by the Erasmus MC research ethic board (MEC-2016-400) and registered at the Netherlands Trial Register (NTR6549). The study was conducted according to the principles of the Declaration of Helsinki (version 10, October 2013). Written informed consents were obtained for all patients.

2.2. Brachytherapy

CT-simulation was performed with the patient in supine position, both arms elevated above the head on a breast board, in a similar set-up as for external beam radiotherapy. CT images were acquired with a spacing and thickness of 1.5 mm to enable image re-slicing in all directions. After contouring the post-surgical seroma, the clinical target volume (CTV) was created using an expansion of 1 cm limited 5 mm below the skin surface and above the *fascia pectoralis* (Pignol *et al* 2015). The planned target volume (PTV) consists of a further expansion of the CTV with 0.25 cm margin, also limited 5 mm below the skin surface and above the *fascia pectoralis*. The images were resliced in a direction perpendicular to the implantation direction using the MIM Symphony treatment planning system® (MIM Software Inc. Cleveland OH). Seed placement was optimized in order to cover at least 90% of the PTV with the 90 Gy prescribed dose ($V_{100} \geq 90\%$) and ensuring that less than 20% of the PTV receives 200% or more of the prescribed dose ($V_{200} \leq 20\%$). Finally, the skin dose over an area larger than 1 cm² was kept below 90% (or 81 Gy).

A 2 mm skin layer was contoured to calculate the maximum dose to a skin volume of 0.2 cc as a surrogate measure of maximum dose to a 1 cm² area (Hilts *et al* 2015). Additionally, a 2 mm skin contour limited to the PTV skin projection as used during the implantation was created. As we presumed this to be the high skin dose area, it was the target for the spacer injection and the skin area that was evaluated in this *in vivo* dosimetry study. Figure 1 shows a typical pre-implant dosimetry of a LDR seed brachytherapy patient.

The implantation procedure, including a 5–10 mm skin spacer injection (Barrigel, Palette Life Sciences) for the patients randomized to the experimental arm, has been described elsewhere (Struik *et al* 2018, 2019), and involved the placement of the seeds under light sedation using the Breast Microseed device (Concure Oncology, Seattle, WA).

2.3. Radiochromic film quality assurance

For radiation protection and skin dosimetry quality assurance purposes, we started in January 2018 using a 10 × 10 cm² EBT3 Gafchromic film (lot # 03311402, Ashland Specialty Ingredients, Wayne, NJ) placed directly above the implanted area. The films were cut in oval shape and placed above the PTV drawing on the skin. The radiochromic films were protected using a transparent Tegaderm™ (3 M, St. Paul, MN) film taped on the skin, to prevent any blood or sweat contamination of the film. The projected PTV centroid and the cranial, caudal, lateral and medial direction were marked on the film (figure 2). Patients were asked to keep

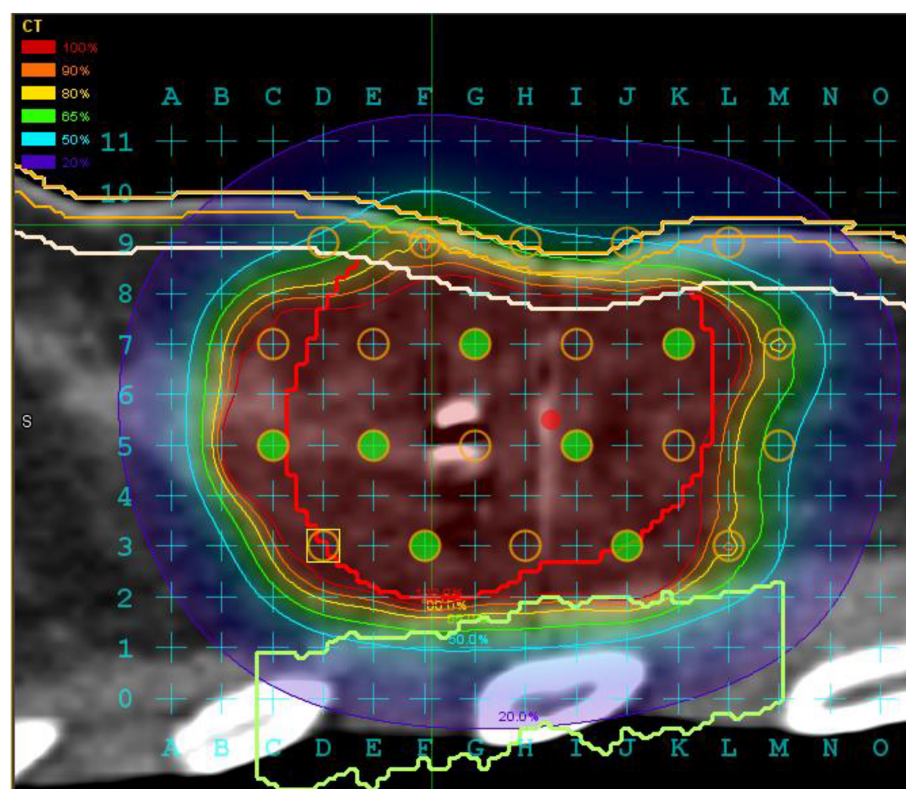


Figure 1. Typical pre-implant dosimetry of a seed brachytherapy patient, with PTV (red), thorax wall (green), skin (2 mm thick layer from the external contour; in sand color) and the 5 mm line below the external contour (white; excluded from the PTV) are shown, as well as the 20%–100% isodose lines. It illustrates that the skin can be exposed to high dose gradients (preplan $D_{0.2cc} = 77$ Gy).

the film applied to the skin for at least 24 h, which corresponds to the time of post-implant dry dressing. The time of film skin contact was carefully recorded.

The optical density of the exposed films was scanned with 72 dpi spatial resolution and 48-bit RGB color, using a flatbed Epson Expression 1680 scanner (Epson, Suwa, Nagano, Japan). The films were analyzed using the red channel.

Film calibration with low-energy brachytherapy seeds (e.g. ^{103}Pd ; 21 keV) involves high uncertainties and therefore, according to Morrison *et al* (2014) film calibrations should be done with an appropriate low-energy source with a comparable effective energy. We therefore performed a calibration of the batch of films used in our study using a 40 kVp beam Xstrahl 300 orthovoltage system (XStrahl Inc., Suwanee, GA) with a half value layer (HVL) of 0.92 mm Al, which corresponds to an effective energy of 23 keV. This energy is very close to the energy of ^{103}Pd -seeds (21 keV average energy). The calibration procedure used nine pieces of EBT3 films, each $5 \times 5 \text{ cm}^2$ in dimension. Films were irradiated on the surface of a solid water phantom at a 30 cm source-to-surface distance and with a 10 cm diameter cone. Nine different dose values were used: 0, 100, 150, 200, 250, 300, 350, 400, and 450 cGy to fully cover the dose range of exposure for the patients in this study. The film doses were calibrated against ion chamber measurement (Exradin A12, Standard Imaging, Middleton, WI). The output was calibrated following the TG61 in air calibration method with a quoted uncertainty of 4.7% (Ma *et al* 2001). An additional source of uncertainty is introduced with the approximation of a Pd-103 source by a 40 kVp beam. We conservatively suggest an uncertainty on the order of 5% for this component as well. The estimated maximum point skin dose was calculated using the maximum optical density of a single pixel (0.35 mm) with the patient plan verification software Verisoft, version 6.2.0.25 (PTW, Freiburg, Germany). Distribution of the maximum dose in the $1 \times 1 \text{ mm}^2$ region of interest (ROI) with the highest measured optical density was calculated per patient as suggested by Bouchard *et al* (2009) (supplementary file 1). These dose estimates were converted to the total treatment doses accounting for the ^{103}Pd half-life of 17 d and the film exposure time (figure 3). Overall, our conservatively estimated uncertainty of the measured film dose was 11% (table 1).

2.4. Post-implant dosimetry

A 2 months post-implant CT scan was performed for post-implant quality assurance ensuring the same patient set-up as the pre-implant CT-scan. The seroma was identified using deformable image registration of the pre-implant CT (Hilts *et al* 2015). An evaluation CTV was created using a 1 cm expansion

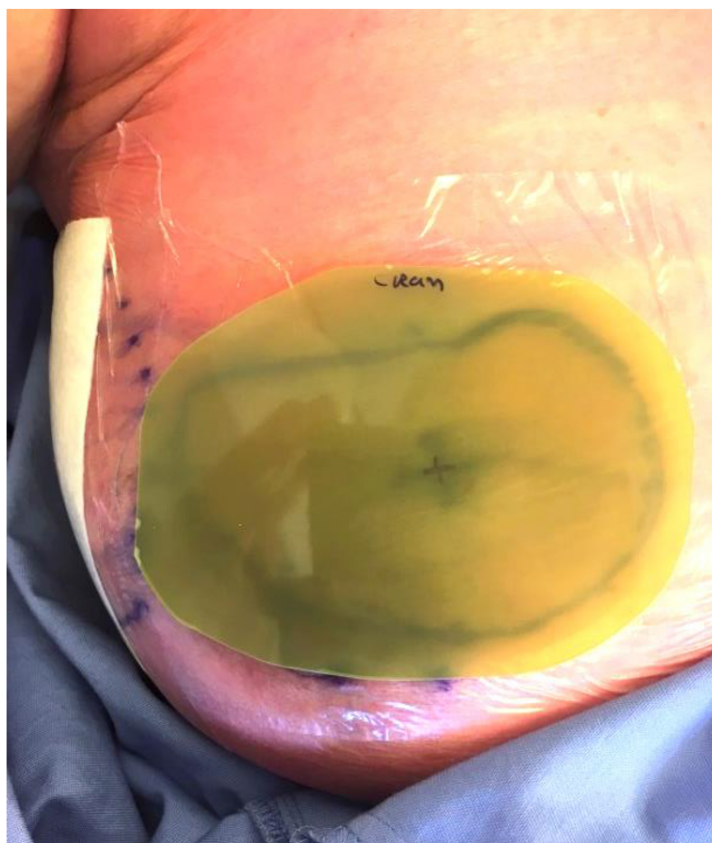


Figure 2. Placement of the radiochromic EBT3 film on a Tegaderm™ at the skin drawing (black line shining through) of the Planned Target Volume after the breast seed implant procedure. The film is carried for 24 h before collection and reading.

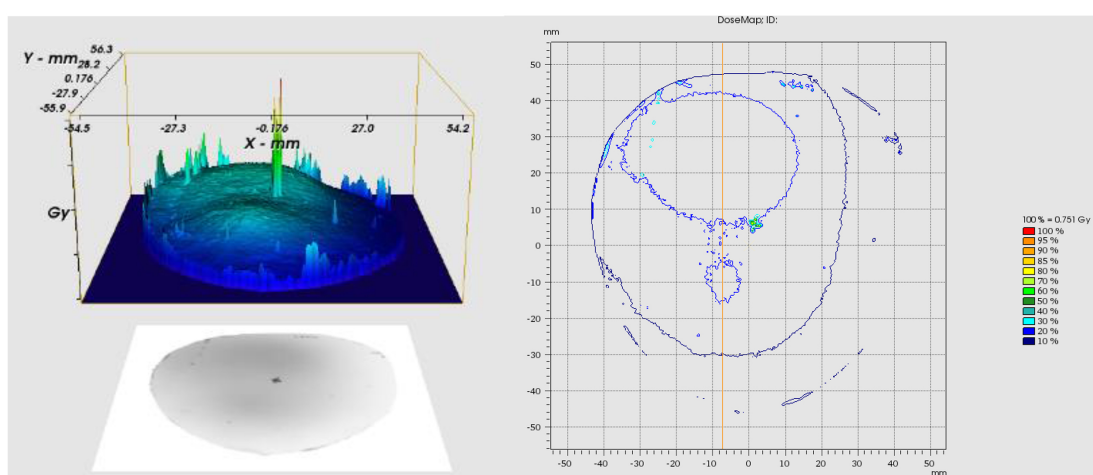


Figure 3. Analysis of a radiochromic film for a patient with a maximum skin dose of 26 Gy, including a 3D and an isodose chart.

(Pignol *et al* 2006) of the seroma. For the purpose of this study a PTV was also reconstructed using an additional 0.25 cm expansion, both limited to the *fascia pectoralis* and 5 mm below the skin surface and/or to the spacer volume, if administered. Finally, the 2 mm skin volume was contoured, limited to the PTV skin projection.

2.5. Skin toxicity assessment

At 2 months follow-up, acute skin toxicities were recorded by the treating physician, using the NCI Common Toxicity Criteria for Adverse Events (CTCAE 4.03) including redness, hyperpigmentation, induration and radiation dermatitis.

Table 1. Uncertainty estimate of the measured film dose according to The AAPM/ESTRO TG138 report.

Row	Source of uncertainty	Estimated uncertainty
1	TG61 in air calibration method	4.7%
2	Approximation of a Pd-103 source (effective energy = 21 keV) by a 40 kVp beam (effective energy = 23 keV)	~5%
3	Translation of optical density values to dose	1.5%
	Overall estimated uncertainty	~11%

Table 2. Clinical and pre-implant dosimetry characteristics of the 18 patients included in the study.

Characteristic	Value and range or proportion
Age in years, median [range]	65 [53–76]
Microscopic tumor diameter in mm, median [range]	11.5 [5–20]
Histology (proportion)	
Ductal carcinoma	7/18 (39%)
DCIS	2/18 (11%)
Ductal carcinoma + DCIS	9/18 (50%)
CTV, mean in cc (SD)	8.9 (± 4.7)
PTV, mean in cc (SD)	77.5 (± 24.0)
Number of seeds implanted, mean (SD)	91 (± 22)
Total source strength/activity implanted, mean in U (SD)	217 (± 53)
% of PTV volume receiving $\geq 100\%$ of prescription dose ($V_{100\%}$), mean (SD)	95.6 (± 0.7)
% of PTV volume receiving $\geq 200\%$ of prescription dose ($V_{200\%}$), mean (SD)	19.4 (± 1.1)
Maximum skin dose ($D_{0.2cc-pre}$) in Gy, mean (SD)	71.6 (± 19.9)

Table 3. Acute toxicity at 2 months using the CTCAE v4.03 for the 18 patients included in the study.

Symptom	CTCAE grade	Frequency (%)
Redness	None	4/18 (22)
	Yes, but no effect on ADL	11/18 (61)
	Yes, and effect on ADL	3/18 (17)
Pigmentation	None	6/18 (33)
	Grade 1	11/18 (61)
	Grade 2	1/18 (6)
Skin induration ^a	None	4/17 (23)
	Grade 1	10/17 (59)
	Grade 2	2/17 (12)
	Grade 3	1/17 (6)
Radiation dermatitis	None	6/18 (33)
	Grade 1	5/18 (28)
	Grade 2	5/18 (28)
	Grade 3	2/18 (11)

^aSkin induration was not scored in one patient.

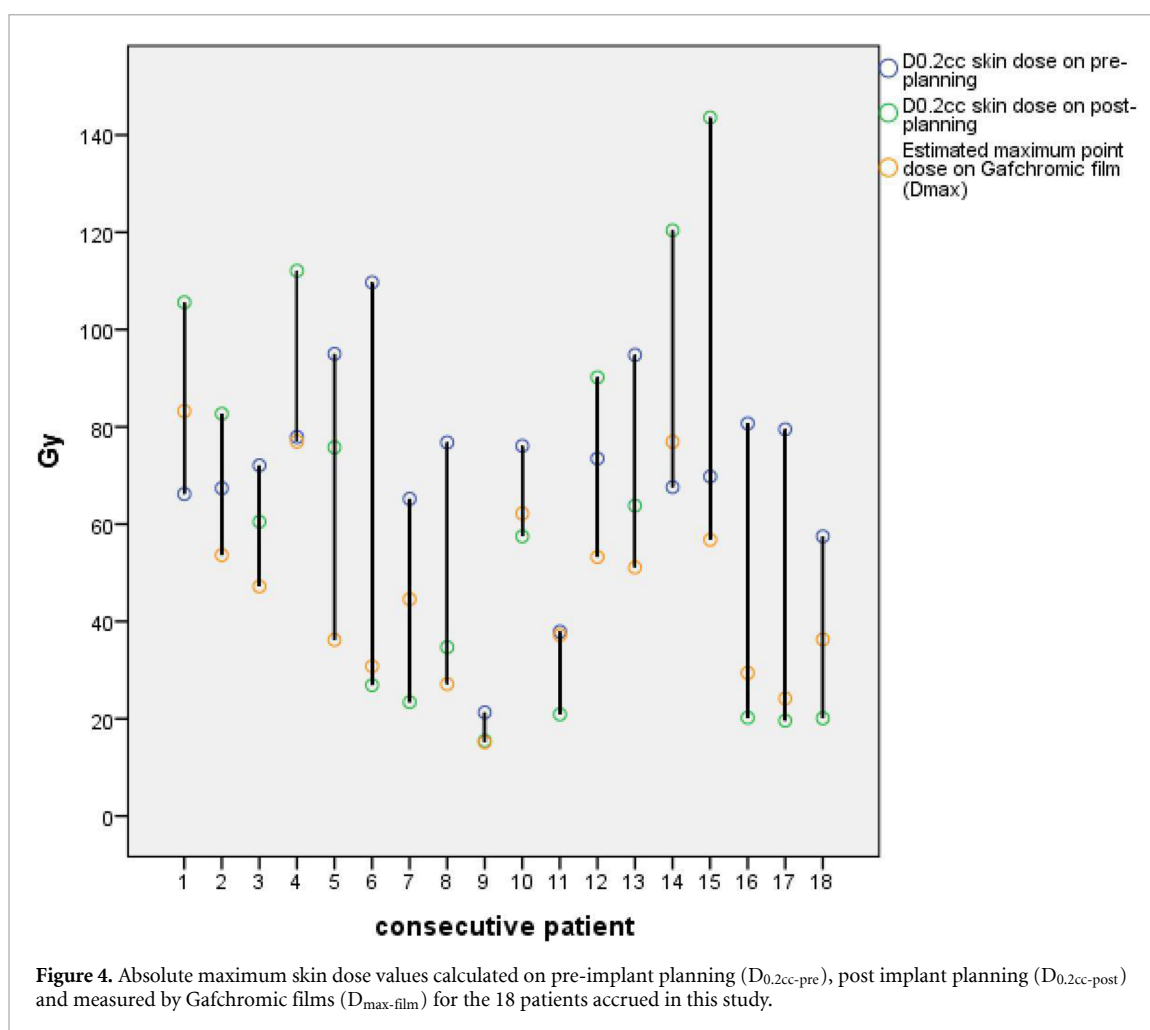
3. Results

3.1. Patients

A total of 18 patients were included in the *in vivo* radiochromic film dosimetry study. Table 2 summarizes the patients and pre-implant dosimetry characteristics. As per protocol all patients were above 50 years old, had an infiltrating ductal carcinoma or DCIS of less than 3 cm and were node negative. Table 3 summarizes the maximum acute toxicity seen at 2 months after implant. Film dosimetry and pre- and post-treatment planning data were available for all patients. Subcutaneous spacer was injected in 10 of those 18 patients.

3.2. Film dosimetry

The average calculated maximum skin dose to small volumes ($D_{0.2cc}$) was lower on post-implant planning, 60.8 Gy (SD ± 40.1), than on pre-implant planning, 71.6 Gy (SD ± 19.9). However, there was no correlation between the pre-implant and the post-implant calculated doses (Spearman's $\rho = 0.129$, $p = 0.61$), nor with the ones measured with the radiochromic films (Spearman's $\rho = -0.156$, $p = 0.537$). There was also no correlation between the pre-implant calculated skin dose and skin toxicities, including redness ($p = 0.40$),



hyperpigmentation ($p = 0.30$), skin induration ($p = 0.86$) or dermatitis ($p = 0.54$). Those results suggest that pre-implant dosimetry is a poor predictor of skin dose and toxicity.

The post-implant maximum calculated skin doses ($D_{0.2cc}$) of 60.8 Gy ($SD \pm 41.0$), were on average 30% higher than those measured *in vivo* ($D_{max-film}$), 46.6 Gy ($SD \pm 19.3$). Figure 4 shows the maximum pre-implant calculated, post-implant calculated and *in vivo* measured doses for all 18 patients in this study. Importantly, the 2 months post-implant calculated dose and the 24 h measured skin doses were highly significantly correlated (Spearman's rho = 0.827, $p < 0.001$). Also, the occurrence of skin redness, skin induration and dermatitis were statistically significantly correlated with both a higher *in vivo* measured skin dose and post-implant calculated skin dose (table 4 and figure 5). Correlations with skin induration and dermatitis were still statistically significant after Bonferroni correction for multiple testing. This suggests that the 24 h film dosimetry could be used as an early marker of skin over-irradiation and risk of skin toxicity.

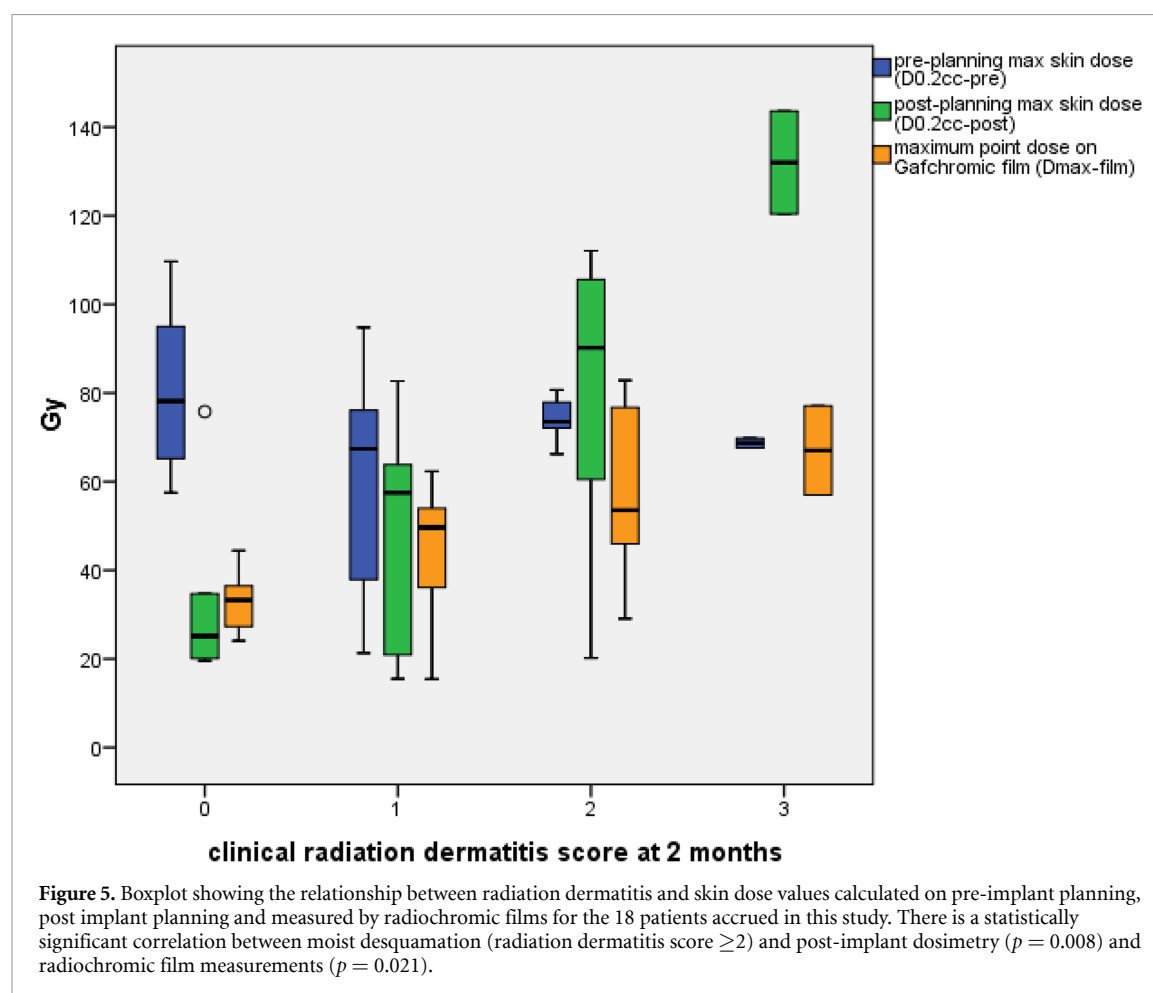
4. Discussion

This study aimed to evaluate early during the treatment and *in vivo* the skin dose using radiochromic films in LDR seed breast brachytherapy. Patients had the film placed for 24 h on the high dose skin area immediately after the palladium-103 radiation sources were implanted in the breast.

The first finding of this study is that *in vivo* dosimetry using radiochromic film to assess the skin dose of breast seed implant is feasible. The second finding of this study is the strong correlation of the early measured *in vivo* skin dose with the skin toxicities and with the post-planning maximum skin dose. This suggests that *in vivo* skin dosimetry using radiochromic films is a useful tool for early prediction of skin toxicity. An excess in the early skin dose measurement could justify an intervention to reduce the skin dose. For example, if it was not used, a spacer could be used to lift the skin above the implanted seed area. This strategy is currently tested in a randomized clinical trial (Struik *et al* 2018). For permanent breast seed implant (Pignol *et al* 2015), the spacer could be injected 24 h after the implant since only a fraction of the dose has been delivered, 4% for palladium-103. Following the same principle, for HDR brachytherapy using multicatheter,

Table 4. Correlations between pre-implant, post implant dosimetry and skin side effects. Values shown are Spearman's correlation coefficient (r) and p -values. Significant correlations after Bonferroni correction are shown in bold.

	Pre-implant planning skin dose	Post-implant planning skin dose	Film <i>in vivo</i> skin dose
Redness	$r = -0.212$ $p = 0.398$	$r = 0.534$ $p = 0.022$	$r = 0.553$ $p = 0.017$
Pigmentation	$r = -0.261$ $p = 0.296$	$r = 0.313$ $p = 0.207$	$r = 0.190$ $p = 0.450$
Skin induration	$r = -0.046$ $p = 0.862$	$r = 0.785$ $p < 0.001$	$r = 0.789$ $p < 0.001$
Radiation dermatitis	$r = -0.155$ $p = 0.540$	$r = 0.641$ $p = 0.004$	$r = 0.637$ $p = 0.004$



balloon brachytherapy or breast stereotactic body radiotherapy, the spacer could be injected between successive fractions if an excess skin dose were detected (Obayomi-Davies *et al* 2016, Major *et al* 2017).

In contrast, the pre-planning skin dosimetry was found to be a poor predictor of post-implant calculated and *in vivo* measured skin doses. Also, the pre-implant planning skin dose was not correlated with clinical skin toxicity. This might be explained by the uncertainty of the seed positioning during the procedure and/or the changes in the breast anatomy after the seed implantation including the occurrence of edema (Keller *et al* 2012, Hilts *et al* 2015, Morton *et al* 2016, Watt *et al* 2018). There is a very high sensitivity of the skin dose to those factors because of the rapid dose fall-off around radioactive seeds. For example, Mashouf *et al* showed that a 5 mm reduction of the distance between center of the implant and the skin can result in a dose increase of 50% (2016).

There was a 30% difference between the *in vivo* radiochromic film measurements and the post-implant dosimetry. These findings are in line with literature on APBI brachytherapy, reporting an overestimation of skin dose by treatment planning systems as compared to *in vivo* measured skin dose between 9% and 16% (Mangold *et al* 2001, Kinkhikar *et al* 2006, Raffi *et al* 2010), which could be explained by several factors. The skin dose calculation in regions of electronic disequilibrium is challenging, such that the calculated dose would be overestimated. The MIM Symphony treatment planning system uses the TG43 formalism to calculate the dose, which assumes the breast and the volume beyond it to be water. It overestimates the skin dose neglecting the loss of return electrons beyond the skin surface (Panettieri *et al* 2009, Afsharpour *et al* 2012). In addition, the post implant planning is performed on a static image of the breast while the

radiochromic film captures the skin dose in a more dynamic way. In wearing it for 24 h, the radiochromic film measure may better capture the changes in skin dose over time caused when patients are changing position and could hence be a more realistic evaluation of the true skin dose.

We selected radiochromic films in this study since they are a well validated, accurate and user-friendly dosimetry tool for quality assurance in radiotherapy (Reinhardt *et al* 2012, Dreindl *et al* 2014). They have previously been used for *in vivo* breast skin dosimetry in several studies on external beam radiotherapy (Rudat *et al* 2014) and IORT (Avanzo *et al* 2012). In this study we found additional advantages of *in vivo* skin film dosimetry using radiochromic films. First, the skin dose is integrated over 24 h with no patient discomfort. Also, they account for the dose variations due to breast motion while patients live their normal lives (Rudat *et al* 2014). Finally, they provide a rapid and accurate estimation, within 24 h, of the potential skin overdosage, at a time when a remote amount of the total dose has been delivered.

A limitation of this study is that the skin dose was only evaluated in a predefined area corresponding to the PTV projection on the skin. We did not observe any toxicity outside this area, but it is possible that high skin doses may occur outside this area if a seed is misplaced or migrate closer to the skin. Using stranded seeds, such displacements are unlikely (Morton *et al* 2016). The limited size and oval shape of the presumed high skin dose area makes the film easy to apply without causing any discomfort to the patient.

Another limitation is the fact that we could not calibrate the films with the Pd-103 sources as used in our study itself. Calibration with low-energy brachytherapy seeds (e.g. ^{103}Pd) has high uncertainties and therefore, following Morrison *et al* (2014) we performed film calibration with an appropriate low-energy beam with a comparable effective energy. By doing so, the estimated uncertainty of our film doses was 11%, which is comparable to other studies using low-energy sources with doses above 1 Gy (Morrison *et al* 2014). Also, as this study aims to investigate the correlation between film dosimetry and skin toxicity rather than as a prove of absolute measured film doses, this uncertainty was deemed acceptable. The last limitation is that this study was performed in a small number of 18 patients. Therefore our findings on correlation between post planning calculated skin dose, *in vivo* measured skin dose and skin toxicity serve as an indication for further clinical validation in the larger clinical trial.

In conclusion, we recommend using radiochromic film for brachytherapy skin dose quality assurance as an early marker for skin toxicity. If excessive dose is detected preventative measures could be decided. In this study, radiochromic films have a strong correlation to post-implant skin dosimetry and are well tolerated.

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