Original paper

Dose estimation for different skin models in interstitial breast brachytherapy

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Abstract

Purpose: Skin is a major organ at risk in breast-conserving therapy (BCT). The American Brachytherapy Society (ABS) recommendations require monitoring of maximum dose received, however, there is no unambiguous way of skin contouring provided. The purpose of this study was to compare the doses received by the skin in different models.

Material and methods: Standard treatment plans of 20 patients who underwent interstitial breast brachytherapy were analyzed. Every patient had a new treatment plan prepared according to Paris system and had skin contoured in three different ways. The first model, Skin 2 mm, corresponds to the dermatological breast skin thickness and is reaching 2 mm into an external patient contour. It was rejected in a further analysis, because of distinct discontinuities in contouring. The second model, Skin 4 mm, replaced Skin 2 mm, and is reaching 2 mm inside and 2 mm outside of the External contour. The third model, Skin EXT, is created on the External contour and it expands 4 mm outside. Doses received by the most exposed 0.1 cc, 1 cc, 2 cc, and the maximum doses for Skin 4 mm and Skin EXT were compared.

Results: Mean, median, maximum, and standard deviation of percentage dose difference between Skin EXT and Skin 4 mm for the most exposed 0.1 cc ($D_{0.1cc}$) of skin were 18.01%, 17.20%, 27.84%, and 4.01%, respectively. All differences were statistically significant ($p < 0.05$).

Conclusions: Monitoring of doses received by skin is necessary to avoid complications and obtain a satisfactory cosmetic effect. It is difficult to assess the compatibility of treatment plans with recommendations, while there is no unambiguous way of skin contouring. Especially, if a mean difference of doses between two models of skin contouring is 18% for the most exposed 0.1 cc and can reach almost 28% in some cases. Differences of this magnitude can result in skin complications during BCT.

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Key words: breast cancer, boost, breast-conserving therapy, interstitial brachytherapy, skin.

Purpose

Breast-conserving therapy (BCT), including breast-conserving surgery (BCS) and postoperative radiotherapy (RT), has become a standard treatment in early stages (T1, T2) breast cancer for the last 30 years [1,2]. Breast-conserving therapy was determined as primary treatment at the National Institutes for Health Consensus Development Conference in 1990, for tumours up to 4 cm [3]. Many long-term studies confirm that breast-conserving surgery followed by radiotherapy results in outcomes comparable to mastectomy, allowing women to preserve their breast [1,4-8]. The standard postoperative RT after BCS consists of external beam radiotherapy of the whole breast (whole breast irradiation – WBI) using two tangential fields up to a total dose of 45-50 Gy [3]. A significant role in reducing a risk of local recurrence rate is performed by an additional boost treatment to the tumour bed up to a dose of 10-25 Gy [9-13], although choice of an optimal technique of boost treatment between brachytherapy, photons beams or electrons remains controversial. This issue is a case of many studies, but none of them has definitely shown the superiority of any of these techniques [9,10,14-19]. An advantage of brachytherapy is the delivery of a high dose in limited volume, due to a large dose gradient, minimizing the treated volume to the tumour bed and it's immediate surroundings, resulting in limitation of post radiation injuries [20]. Moreover, in case of brachytherapy, a dose intensity measured in minutes is higher than that of external radiotherapy measured in days, what increased a biological effectiveness against resistant tumour cells [21]. A role of brachytherapy as a boost increases especially in case of lesions deeply seated in breast [22-24] and is also used in the treatment of local relapse [25].

A skin is a significant organ at risk in breast-conserving therapy. Modern, image-based brachytherapy planning systems allow for an assessment not only of a dose

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at a certain point, but doses received by respective volumes of structures. It is a huge advantage enabling to avoid a single point dose estimate uncertainty caused by a large dose gradient of brachytherapy sources. According to American Brachytherapy Society (ABS) recommendations it is required to monitor maximum dose received by a skin, however, there is no unambiguous way of skin contouring provided [26,27]. There are two most often ways used to define maximum skin dose. The first way represents it as a dose at a point on the body surface (determined by external patient contour, "External") [28-35]. The second one defines maximum skin dose as the maximum dose to a relatively small volume (0.1-1 cc) in the structure created by expanding an external patient contour by 5-10 mm [36-38]. The structure defined this way is in fact placed outside the body and doses calculated should be treated as a dose at surface rather than a dose in volume [39]. Only the part directly on the External contour is relative and representative [38]. More corresponding to the anatomical model of skin is a structure made by reduction of external patient contour by some value representing breast skin thickness [39,40].

There are many studies focused on measuring breast skin thickness, both healthy and changed by disease or after radiotherapy [41-47]. It has been shown that in case of tumour or when radiotherapy was applied, the skin is thickening [41-43,46,47]. According to different studies, mean skin thickness in normal breast varies in range of 1.44-2.05 mm, while in breasts after radiotherapy – 1.44-2.68 mm [41-43,46,47].

This study compares doses received by different models of skin of 20 patients, who underwent interstitial brachytherapy as a boost in breast-conserving therapy.

Material and methods

Twenty patients with recognized breast cancer and treated with radiotherapy after breast-conserving surgery were examined. All patients underwent external beam radiotherapy (WBI) up to a dose of 45-54 Gy and interstitial brachytherapy HDR as a boost. Brachytherapy was performed 2-3 weeks after completing WBI. Patients were treated with remote afterloading microSelectron v2 HDR (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) using an ^{192}Ir stepping source with nominal activity of 10 Ci. Each patient received 10 Gy in a single BT fraction.

Interstitial brachytherapy procedure were performed under local anaesthesia. From 4 to 9 metal needles in 1 or 2 planes (3 patients – 1 plane, 17 patients – 2 planes) were inserted with template guidance (Nucletron®) into tumour bed. All patients with interstitial implant were scanned using CT scanner Somatom Sensation Open (Siemens Medical Solutions Inc., Erlangen, Germany) with a slice thickness of 2 mm. The CT images were sent to the brachytherapy planning system Oncentra Masterplan (version 4.3, Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden), where structures were outlined and treatment plan was made. Planning target volume (PTV) and organ at risk: skin, most exposed rib, and ipsilateral lung were contoured.

For this examination, PTV was defined by interstitial implant reaching 5 mm from needles in orthogonal plane and separated by 5 mm from the body surface, because the purpose of this study is not the evaluation of optimal treatment plan, but the examination of differences between doses received by skin based on the way of contouring of this structure. Application of the standard 2D planning Paris dosimetry system was perform to all patients, enabled invariable conditions for the entire analysed group.

The skin was outlined in three different ways. The first model of skin, made by expansion of external patient contour by 4 mm, was named Skin EXT (EXT = external) for the purpose of this study. It was created by an addition of a 4 mm bolus to the External contour. The second model, Skin 2 mm, corresponds to the dermatological breast skin thickness. It was reaching 2 mm into an external patient contour and was created by contouring 2 mm inner margin of an External contour. A 2 mm wide bolus was placed on this inner contour. The third model of skin, Skin 4 mm, was made by inserting a 4 mm bolus onto the same contours as Skin 2 mm (External contour reduced by 2 mm margin). All models of skin were spatially limited to the treated breast in order to avoid a shift in dose-volume histograms (DVH), caused by a large volume of this structure receiving only a insignificant dose. All skin models are presented in Figure 1. An evaluation of doses received by Skin 2 mm was not performed in this study, because of an incorrect estimation of dose distribution for this structure, due to computing limitations of the planning system. During CT scanning, breasts of all patients were very tightly compressed by templates, causing a large contour gradient in proximity of templates. During the outlining of Skin 2 mm, a certain discontinuity occurred in this structure (despite using the biggest available accuracy – structure set grid – 1 mm) in some particular configurations of templates relative to CT scans (parallel or slightly sloped). The dose distribution was not calculated in these parts, so dose parameters for Skin 2 mm did not correspond with the actual dose. In this connection, the analysis was done only for Skin EXT and Skin 4 mm, both 4 mm wide. Figure 2 shows the problem with Skin 2 mm.

All treatment plans were done according to Paris dosimetry system. Usage of a breast template enables an obtainment of a perfect implant, composed of parallel and

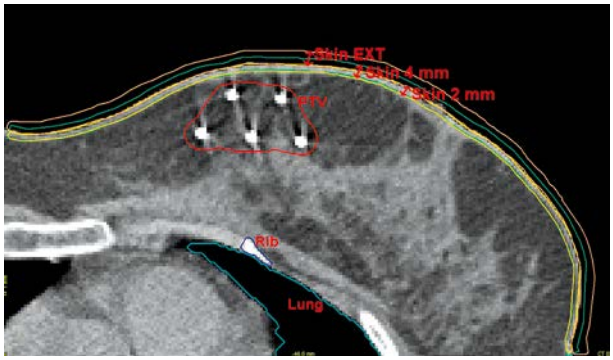

Fig. 1. A presentation of different skin models. Skin EXT (orange) = External + 4 mm, Skin 2 mm (yellow) = External – 2 mm, Skin 4 mm (green) = External ± 2 mm

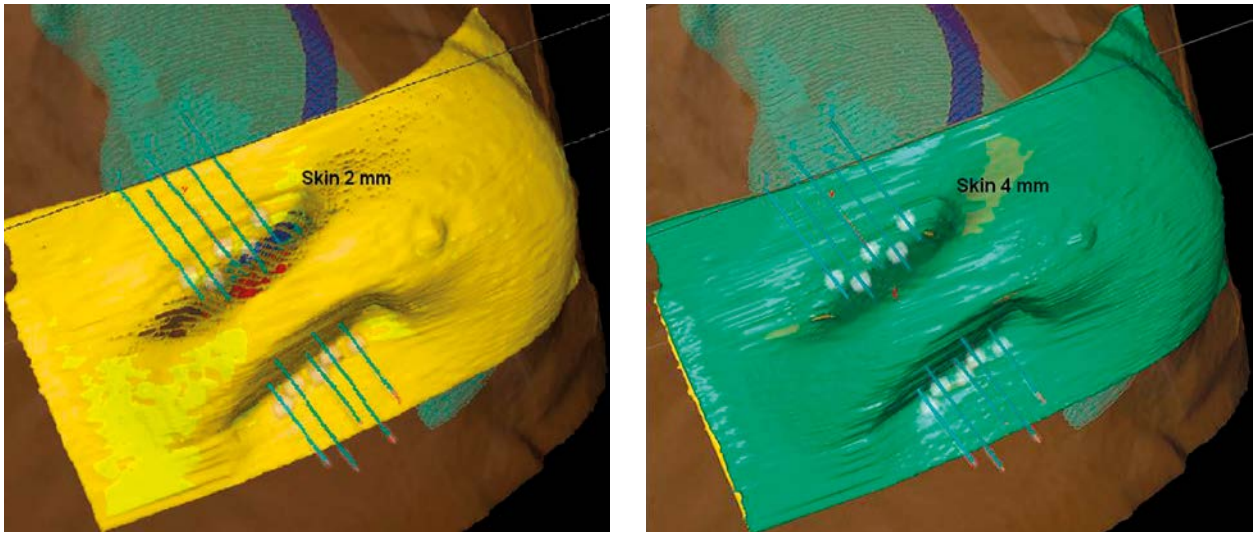

Fig. 2. A comparison of Skin 2 mm (yellow) and Skin 4 mm (green) in the same case. Skin 2 mm with a certain discontinuity in places where template compressing the breast caused high contour gradient. In case of Skin 4 mm, this problem does not occur

equidistant needles (distance between needles – 16 mm). Dose is specified at basal points, defined in the central plane of an implant, and placed between needles at points of lowest dose. In case of a single plane implant, basal points are placed midway between each pair of needles. In case of two or more planes, needles create set of equilateral triangles and basal points are in the center of gravity of each triangle. A reference dose is defined as 85% of basal dose in order to gain a reference isodose 5 mm from external needles. All treatment plans were optimized by geometrical distance or volume optimization, depending on type of interstitial implant (one or two planes).

Statistical calculation was performed in Statistica 8.0 (Stat-Soft, Inc., Tulsa, USA). A normality of the dose distribution was checked for all volumes of both skin models using the Shapiro-Wilk test. Only the distribution of D_{max} for both models of skin was not normal. These variables were compared using the Wilcoxon signed-rank test, while normally distributed variables (Skin $D_{0.1cc}$, D_{1cc}, D_{2cc}) were compared using the Student's *t*-test for dependent samples. A difference between two variables was considered statistically significant when the *p*-value was less or equal than 0.05. In all cases, a statistically significant difference was proven.

Results

Parameters of target and OAR dose distributions are presented in Table 1. Minimal coverage of 90% of the prescription dose V_{90} exceeded 95.98% in all cases (mean – 97.94%). Mean coverage of 100% of the prescription dose V_{100} was 91.83% (85.26-97.41%). Mean volume of PTV encompassed by 150% and 200% (V_{150}, V_{200}) of the reference isodose was 30.98% PTV (8.10 cc) and 15.47% PTV (3.99 cc), respectively. Mean minimum dose at PTV (D_{100}) was 76.46% (62.83-87.65%), while mean value of a parameter more relevant for BT – D_{90} – was 102.22% (95.00-110.58%). Mean dose at 0.1 cc of the most exposed

Table 1. Parameters of target and OAR dose distributions

	Mean [%]	Median [%]	Min. [%]	Max. [%]	SD [%]
PTV V_{90}	97.94	98.24	95.98	99.89	1.53
PTV V_{100}	91.83	91.35	85.26	97.41	3.24
PTV V_{150}*	30.98/8.10 cc	30.43/8.48 cc	25.22/3.87 cc	39.51/11.68 cc	3.27/2.01 cc
PTV V_{200}*	15.47/3.99 cc	14.65/4.16 cc	11.86/2.14 cc	22.13/5.49 cc	2.46/0.86 cc
PTV D_{90}	102.22	101.45	95.00	110.58	3.85
PTV D_{100}	76.46	77.16	62.83	87.65	6.18
Skin EXT $D_{0.1cc}$	63.01	62.59	51.79	79.42	6.76
Skin 4 mm $D_{0.1cc}$	81.02	78.79	65.40	98.62	9.49
Rib $D_{0.1cc}$	17.18	16.65	9.86	33.10	6.08
Lung D_{2cc}	13.45	13.09	9.28	22.88	3.91

**According to the ABS recommendations, the values of PTV volumes encompassed by high doses V_{150} and V_{200} are given both as percentage and in absolute values [23].*

Table 2. Doses received by different skin volumes for two skin models

	Mean [%]	Median [%]	Min. [%]	Max. [%]	SD [%]
Skin EXT $D_{0.1cc}$	63.01	62.59	51.79	79.42	6.76
Skin 4 mm $D_{0.1cc}$	81.02	78.79	65.40	98.62	9.49
Skin EXT D_{1cc}	53.01	51.75	44.80	65.22	5.23
Skin 4 mm D_{1cc}	64.23	63.64	54.36	77.29	5.80
Skin EXT D_{2cc}	48.79	48.00	41.41	60.62	4.70
Skin 4 mm D_{2cc}	58.57	58.14	49.94	71.48	5.37
Skin EXT D_{max}	74.81	74.36	58.25	92.29	8.95
Skin 4 mm D_{max}	125.16	120.71	79.97	208.07	32.70

Table 3. Percentage difference in doses received by Skin EXT and Skin 4 mm for particular skin volumes

Difference between:	Mean [%]	Median [%]	Min. [%]	Max. [%]	SD [%]
Skin $D_{0.1cc}$ 4 mm/EXT	18.01	17.20	13.27	27.84	4.01
Skin D_{1cc} 4 mm/EXT	11.22	11.55	6.69	14.35	1.78
Skin D_{2cc} 4 mm/EXT	9.78	10.15	5.33	11.75	1.63
Skin D_{max} 4 mm/EXT	50.35	41.32	20.09	127.47	27.23

rib was 17.18% of the reference dose (9.86-33.10%), and mean dose at 2 cc of ipsilateral lung was 13.45% (9.28-22.88%). Mean, median, minimum, maximum, and standard deviation of dose at 0.1 cc for Skin EXT and Skin 4 mm were, respectively: 63.01%, 62.59%, 51.79%, 79.42%, 6.76% for Skin EXT, and 81.02%, 78.79%, 65.40%, 98.62%, 9.49% for Skin 4 mm.

Table 2 contains doses received by most exposed 0.1 cc, 1 cc, 2 cc, and the maximum dose for both models of skin. Table 3 contains mean percentage differences between doses received by particular volumes of both models of skin, Skin EXT and Skin 4 mm. Values of these differences for particular patients are shown in Figures 3-6. A bold line on every figure points at the value of mean difference between doses received by both models of skin and equals, respectively: 50.35% (20.09-127.47%) for maximum dose, 18.01% (13.27-27.84%) for $D_{0.1cc}$, 11.22% (6.69-14.35%) for D_{1cc}, and 9.78% (5.33-11.75%) for D_{2cc}.

Discussion

The development of brachytherapy planning systems based on a three-dimensional imaging brings in many previously unavailable possibilities. Image-based planning allows for an outlining of the planning target volume, and creation of a treatment plan based on the PTV instead of implementing standard dose distributions related to the geometry of applicators or interstitial implant. 3D-planning enables also a precise dose evaluation in defined volumes of organs at risk instead of an evalua-

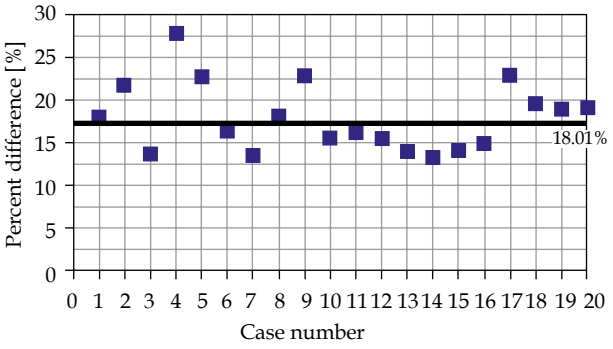

Fig. 3. Percentage difference in $D_{0.1cc}$ of skin between Skin EXT and Skin 4 mm. A bold, horizontal line at 18.01% indicates a mean percent difference

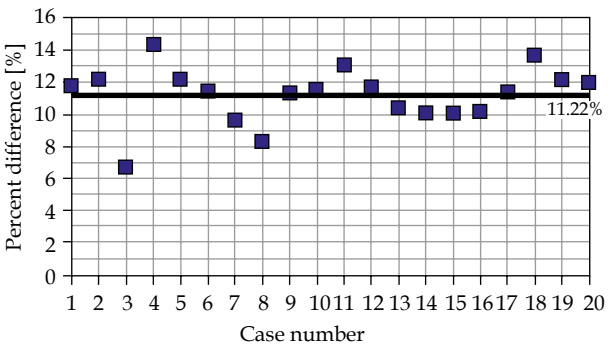

Fig. 4. Percentage difference in D_{1cc} of skin between Skin EXT and Skin 4 mm. A bold, horizontal line at 11.22% indicates a mean percent difference

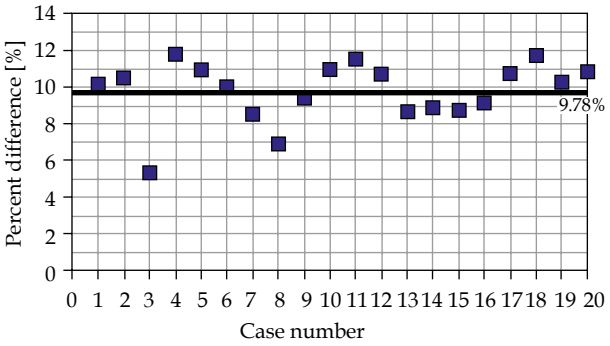

Fig. 5. Percentage difference in D_{2cc} of skin between Skin EXT and Skin 4 mm. A bold, horizontal line at 9.78% indicates a mean percent difference

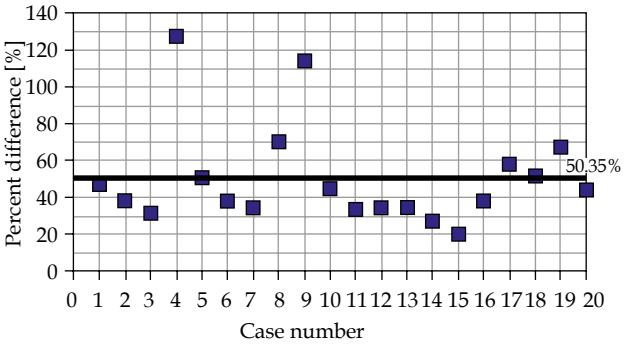

Fig. 6. Percentage difference in D_{max} of skin between Skin EXT and Skin 4 mm. A bold, horizontal line at 50.35% indicates a mean percent difference

tion of a point dose. Doses for the most important OARs in the breast brachytherapy (rib, lung, and skin) have to be monitored according to ABS recommendations [26]. For a skin, it is important to determine the maximum dose received by this structure. This parameter is mainly impacted by the way of defining the skin. A few millimetre shifts may result in dose difference of a dozen up to several dozen percent, due to a large dose gradient in brachytherapy.

There are many studies focusing on measuring breast skin thickness. Huang *et al.* used breast CT acquisition techniques, combined with algorithms based on Monte Carlo method, designed for determining specific breast skin thickness metrics [46]. He has examined 51 patients, determining mean breast skin thickness as 1.45 (1.0-2.2 mm) among the cancer-free breasts, 1.53 mm (1.2-1.9 mm) among those with benign findings, and 1.46 (0.9-2.3 mm) among breasts with biopsy-confirmed breast cancer. However, there was no significant difference between these three groups [46]. Shi *et al.* using algorithms similar to that described by Huang *et al.*, analysed 137 tomograms of breasts, both healthy and changed by a disease, determined breast skin thickness as 1.44 mm (0.87-2.34 mm) and also no statistically significant difference between these groups [47].

Liu's ultrasound scanner research has shown a significant breast skin thickness difference between healthy and treated by radiotherapy breasts. He has noted mean skin thickness increased by 27.3%: from 2.05 mm (1.66-2.38 mm) in untreated breasts to 2.61 mm (1.53-3.65 mm) in treated breasts [41]. A comparison of skin thickness in healthy breasts and those after radiotherapy was also made Libshitz *et al.* According to his research, skin thickness in breasts after radiation treatment returned to normal (defined as equal to the thickness of the healthy breast) in 2 years for 60% of the patients, in 3 years for 80% of the patients, and in 4 years for all the patients [43]. Warszawski *et al.* also used ultrasonography for measurements comparing healthy breasts to breasts that undergone radiotherapy. Their measurements of corium (the deep vascular inner layer of the skin) thickness for non-irradiated breast was on average 1.68 ± 0.3 mm), increasing to the maximum value of 2.68 ± 0.7 mm) after 3 months (early reactions), and then decreased to 2.31 mm (± 0.9 mm) for late reactions (6-8 months later) [42].

Basing on these studies, it seems reasonable to define mean breast skin thickness for irradiated patients as 2 mm. This thickness was assumed by Gifford and his co-workers in their study comparing the doses received by skin in differently defined models in case of APBI brachytherapy provided by Contura and SAVI balloons [39]. Gifford analysed a group of 70 patients and compared the doses received by the most exposed 0.1 cc ($D_{0.1cc}$) of skin defined by two models. The first model, 2 mm thick, was created by 2 mm contraction of an external patient contour. The second one, named "ext + 5 mm" was also based on the external patient contour, but created by expanding this structure 5 mm outside. Mean, median, maximum, and standard deviation of percentage difference between these two models for the whole examined group were 12.5%, 12.5%, 23.8%, and 3.6%, respectively. Taking into consideration the treatment delivery method, smaller differences were recorded for Contura balloon (SenoRx, Inc., Aliso Viejo, CA, USA): 10.1%, 10.9%, 14.1% and 2.6%, respectively. The differences between doses for patients treated by SAVI applicator (Cianna Medical, Aliso Viejo, CA) were 14.4%, 14.4%, 23.8%, and 3.1%, respectively. All differences were statistically significant.

Our study compares the doses received by Skin 4 mm, defined as 2 mm inside and 2 mm outside of the External contour, and Skin EXT, defined as a structure based on the External contour and expanding 4 mm outside. Skin 4 mm replaced Skin 2 mm, created earlier and representing actual breast skin thickness, which was not representative, because of discontinuities in its structure. However, Skin 4 mm may successfully constitute an equivalent of two-millimetre skin used by Gifford, because both of them were based on the same contour. The analysis of doses for small volumes – $D_{0.1cc}$, D_{1cc}, D_{2cc}, and D_{max} compares exactly the same volume inside the External patient contour both for our model and Gifford's. Moreover, Skin EXT can be an equivalent for "ext + 5 mm" from Gifford's study, so the percentage difference between Skin 4 mm and Skin EXT can be compared. Mean, median, maximum, and standard deviation of percentage dose difference for the most exposed 0.1cc ($D_{0.1cc}$) of skin in our study were 18.01%, 17.20%, 27.84%, and 4.01%, respectively. These values were higher than these received by Gifford for Contura and SAVI balloons. It must be re-

membered that the group examined by us underwent interstitial brachytherapy with needles stabilized by a template compressing the breast. The planning target volume was not limited to the tumour bed, but was defined by the needle implant on the full length of the needles preserving the 5 mm margin from External patient contour. Probably extreme active source positions in needles were placed closer to patient's skin than in the case of balloons. It means that in our case both models of skin were in a region of higher dose gradient.

This study compares also the maximum dose (D_{max}) and the doses for the most exposed 1 cc (D_{1cc}) and 2 cc (D_{2cc}) of skin. Mean percentage difference between Skin 4 mm and Skin EXT for D_{max}, $D_{0.1cc}$, D_{1cc}, and D_{2cc} decreases with the increase of measured volume and was 50.35%, 18.01%, 11.22%, and 9.78%, respectively. The high value of percentage difference for D_{max} comes from a high dose gradient. Calculations of D_{max} is based on single voxels, so this might not be authoritative. Hence, the dose for the most exposed 0.1 cc ($D_{0.1cc}$) is often treated as the maximum dose in brachytherapy.

A comparison of different breast skin contouring methods was made by Berger using a self-made phantom by inserting 7 needles in two planes [38]. In his study he created three skin models contoured from the External contour inwards to the depth of 1, 2, and 3 mm, respectively, and three skin models based on the same contour, but extended 5, 10, and 15 mm outside of the phantom surface. All these structures were outlined in Oncentra MasterPlan by means of an automatic contouring and transferred to the Plato system. The values from both planning systems were compared to the real volumes of all six structures calculated, based on the dimensions of the phantom. In case of the inside structures, only the 5 mm one was within the tolerable 5% accuracy, whereas the models defined outside the phantom showed high accuracy of contouring. A similar tendency of discontinuities in structures of small thickness was found in our study (Skin 2 mm). In order to avoid unstable and uncertain parameters of histogram for structures inside the phantom, Berger suggested to choose the structures outlined outside the phantom. Moreover, Berger [38] considered the analysis of dose-surface histograms (DSH), a better way to report skin dose than the dose-volume histogram (DVH). Only the position of the contour directed on the External patient contour is relevant in case of skin models outlined to outside, if an appropriate thickness is chosen and a histogram parameters for these skin models can be a good approximation of surface dose. Berger analysed D_{max}, $D_{0.1cc}$, D_{1cc}, and D_{10cc} for these skin models, but skipped the evaluation of doses received by the inside skin models.

According to Turesson and Notter, 30% of patients who received 50 Gy to the skin will develop teleangiectasia [24]. Van Limbergen noticed that 97% of the skin blood vessels, that are concerned by this complication, are located within the first 5 mm below the surface of the skin [48]. These vessels receive about 40-80% dose from external beam radiotherapy (20-40 Gy). The dose received by skin as the result of an additional brachytherapy, can be crucial in the development of teleangiectasia [48]. The results of this study suggest that it should be considered to introduce an additional skin model inside patient body and 5 mm thick.

We have to remember that dose calculation algorithms in commercially available treatment planning software are still performing the calculations of the dose based on the TG-43 report, assuming that the radiation source is in the middle of a homogeneous phantom with a radius of 15 cm and full backscatter [49]. In practice, the tissues are heterogeneous and there are limited volumes around the radiation source. The difference in density is especially observable near the body limits (tissue-air). Karaiskos *et al.* analyzed the difference in doses estimated theoretically and experimentally for points near the border of a water phantom containing a radiation source – ^{192}Ir. He noticed that these difference can reach even 25% [50]. Pantelis *et al.* compared breast doses computed by a treatment planning system with measurements based on the Monte Carlo method, and noticed that the doses for volumes encompassed by dose larger than 60% do not change, because of the proximity of a skin border or the presence of a lung. However, treatment planning systems overestimate the skin dose by 5-10% at points near body surface or lung and relatively far from implant compared to a Monte Carlo calculation [51].

Conclusions

A skin is one of the main organs at risk during BCT. Monitoring of doses received by this structure is necessary to avoid complications and to obtain a satisfactory cosmetic effect. It is difficult to assess the compatibility of skin doses of treatment plans with recommendations, while there is no unambiguous way of skin contouring provided. Especially, if a mean difference of doses between two models of skin contouring is 18% (1.8 Gy) for the most exposed 0.1 cc and can reach almost 28% (2.8 Gy) in some cases. In order to evaluate the clinical usefulness of both skin models it would be necessary to analyze the actually used treatment plans for a larger group of patients and a much longer observation time is essential to assess the cosmetic effect after the radiotherapy.

Disclosure

Authors report no conflict of interest.

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