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Skin barrier function in patients under radiation therapy due to the head and neck cancers - Preliminary study

Jakub Pazdrowski[a], *Adriana Polańska*[b], *Joanna Kaźmierska*[c,d], *Wojciech Barczak*[a,e], *Mateusz Szewczyk*[a,□], *Zygmunt Adamski*[f], *Ryszard Żaba*[b], *Paweł Golusiński*[a,g,h], *Wojciech Golusiński*[a], *Aleksandra Dańczak-Pazdrowska*[f]

[a] *Department of Head and Neck Surgery, Poznan University of Medical Sciences, Poznan, Garbary 15, 61-866 Poland*
[b] *Department of Dermatology and Venereology, Poznan University of Medical Sciences, Przybyszewskiego 49, Poznan, 60-355, Poland*
[c] *Radiotherapy Department II Greater Poland Cancer Center, Garbary 15, Poznan, 61-866 Poland*
[d] *Electroradiology Department, University of Medical Sciences, Poznan, Poland*
[e] *Radiobiology Lab, The Greater Poland Cancer Centre, Garbary 15, Poznan, 61-866 Poland*
[f] *Department of Dermatology, Poznan University of Medical Sciences, Przybyszewskiego 49, Poznan, 60- 355 Poland*
[g] *Department of Biology and Environmental Studies, Poznan University of Medical Sciences, Poland*
[h] *Department of Otolaryngology and Maxillofacial Surgery, University of ZielonaGóra, Poland*

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ABSTRACT

Aim: To present the possibility of non-invasive monitoring of the skin after radiotherapy in regards of epidermal barrier function.

Background: Radiodermatitis constitutes 95% of all side effects in patients after radiotherapy. The proper assessment of the severity of radiodermatitis can be determined using semi-quantitative clinical scores [Common Terminology Criteria for Adverse Events v 4.0 (CTCAE)].The most accepted way to analyze the epidermal barrier function is to determine Transepidermal Water Loss (TEWL).

Material and methods: In prospective study, we included 16 patients diagnosed with head and neck cancer treated with radiotherapy or concomitant chemoradiation in whom we performed non-invasive assessments of the skin barrier function, including TEWL measurement. The final analysis included 6 patients (4 treated with adjuvant radiotherapy, 2 with radical chemoradiation). Clinical assessment of irradiated skin was based on target lesion score (TLS) and CTCAE v 4.0

Results: The mean TLS score in the middle of irradiation was 1.6 points, after last irradiation it was 2.3 points; 3 months later the mean TLS score was: 0. CTCAE v 4.0 criteria: 2 patients had grade 0, 3 patients - grade 1; 1 patient - grade 2. There were statistically significant differences in TEWL related to irradiated skin in the following time intervals: before vs. in the middle; before vs. day after; in the middle vs. day after; in the middle vs. 3 months after; day after vs. 3 months after.

□ *Corresponding author.*
E-mail addresses: jakub.pazdrowski@op.pl (J. Pazdrowski), adriana-polanska@wp.pl (A. Polańska), joanna.kazmierska@wco.pl (J. Kaźmierska), barczak.woj@gmail.com (W. Barczak), mateusz.szewczyk@wco.pl (M. Szewczyk), adamskiz@poczta.onet.pl (Z. Adamski), ryszardzaba@gmail.com (R. Żaba), pawel.golusinski@wco.pl (Paweł Golusiński), wgolus@ump.edu.pl (W. Golusiński).
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Conclusions: The study showed that radiotherapy causes skin barrier dysfunction in all patients independently of clinical radiodermatitis. The biophysical features of this dysfunction can precede clinical symptoms and they can be assessed by non-invasive and objective methods.

1. Background

The skin, being the largest organ of the human body, has many important functions, of which the crucial one is acting as a barrier. The protection of the skin from a wide range of harmful environmental factors including ionizing radiation nnrelies mostly on the outermost layer of epidermis, stratum corneum (SC).[1,2] The proper structure and function of SC controls permeability and provides mechanical protection. The X-rays induce the defect of the epidermal barrier function leading to radiodermatitis.

Radiodermatitis (radiation dermatitis) constitutes almost 95% of all side effects in patients after radiotherapy. It may manifest clinically as an acute phase (usually after days to weeks) or a late phase which may occur more than 90 days after the completion of radiotherapy.[3] The symptoms of acute radiodermatitis include primary transient erythema, generalized erythema, skin dryness and desquamation, while in late stage dermal atrophy, telangiectasia together with fibrosis may be evident.[3] The proper assessment of the severity of radiodermatitis is crucial in decision on therapy continuation. It can be determined using semi-quantitative clinical scores [Common Terminology Criteria for Adverse Events v 4.0 (CTCAE)] which until now were not validated and may present the risk of inter- and intra-rater variability.[4–7]

The most accepted way to analyze the epidermal barrier function is to determine Transepidermal Water Loss (TEWL) which is the most sensitive indicator of skin damage. Additionally, the measurement of skin hydration (corneometry) as well as objective evaluation of skin inflammation by determination of skin color (erythema) may be useful in non-invasive assessment.[1,2,8]

2. Aim

In this paper we present the possibility of non-invasive monitoring of the skin after radiotherapy, especially in regards of the epidermal barrier function.

3. Materials and methods

In this prospective study, we included 16 patients diagnosed with head and neck cancer treated with radiotherapy or concomitant chemoradiation. From this group, 3 patients died during the study protocol (death was independent from the treatment) and 7 were excluded because they had withdrawn their consent (they completed the course of radiotherapy but failed to undergo dermatological assessment due to the time-consuming process). The final analysis included 6 patients (4 treated with adjuvant radiotherapy only, 2 with radical chemoradiation). The radiotherapy was delivered according to the protocol: the highest dose of radiotherapy to the tumor or tumor bed (70-64 Gy in 2 Gy daily fraction), lower dose to the areas of the neck with a high risk of microscopic spread of the tumor and microscopic infiltration of lymph nodes (60 Gy), the lowest dose to the area of elective irradiation where the risk of microscopic infiltration is relatively low (50 Gy).

4. Clinical assessment

Clinical assessment of the irradiated skin was based on target lesion score (TLS) and CTCAE v 4.0. TLS evaluates erythema, infiltration and scaling on a 4-point scale, as follows 0=none, 1=mild, 2=moderate, 3=severe; may range from 0 to 9.

5. Non-invasive assessment

TEWL was evaluated with the use of Tewameter TM 300 (Courage-Khazaka, Cologne, Germany) according to the guidelines of the standardization group of the European Society of Contact Dermatitis.[1] At least 10 measurements given as a mean value and expressed in SI units ($g/m^2/h$) were carried out (normal range: 0□25 $g/m^2/h$). Hydration of SC (corneometry) was determined by Corneometr CM 825 (Courage-Khazaka, Cologne, Germany) and six measurements given as a mean value in arbitrary units (range: 0□130) were determined in accordance with guidelines. Erythema and melanin were obtained using Color Meter II (Cortex Technology, Hadsund, Denmark) on the basis of reflectance spectroscopy. Three independent measurements were made at an interval of 30 s, on the basis of which the average value was determined. Bioengineering measurements and clinical assessment were determined 4 times: before radiotherapy within the skin area with planned radiation, during ionizing radiation, in the middle of radiotherapy within the affected skin, day after the last irradiation and 3 months after radiotherapy. The same analysis was performed within the non-irradiated, contralateral skin region. The measurements were obtained after 15□30 min acclimatization in the same room conditions (temperature 20□22 °C, humidity 40%) by the same trained physician, always in the same order: TEWL, corneometry, spectroscopy (erythema and melanin).

The study was approved by the Poznan University of Medical Sciences Ethical Committee (No. 1013/12) and all patients provided written informed consent.

For ethical reasons, patients were asked not to use any topically applied products only in the morning at the day

of measurements. All patients used the same commercially available product.

6. Statistical analysis

Statistical analysis was performed using Two-way ANOVA test followed by Tukey's or Sidak's multiple comparisons test (GraphPad Software, CA, USA). *P* values lower than 0.05 were considered significant and are labeled by asterisks (*) for $p < 0.05$, (**) for $p < 0.01$, (***) for $p < 0.001$, and (****) for $p \leq 0.0001$.

7. Results

The mean TLS score in the middle of irradiation was 1.6 points, after the last irradiation was 2.3 points, while 3 months later the mean TLS score was: 0 (as before irradiation).

CTCAE v 4.0 criteria: 2 patients had grade 0, 3 patients had the highest grade 1 and 1 patients had grade 2. There were no patients with grade 3□5.

The results of clinical assessment according to TLS and CTCAE are presented in Table 1.

The results of bioengineering methods are summarized in Tables 2□5.

There were statistically significant differences in TEWL measurements related to the irradiated skin in the following time intervals: before vs. in the middle ($p = 0.0007$); before vs. day after ($p < 0.0001$); in the middle vs. day after ($p < 0.0001$); in the middle vs. 3 months after ($p = 0.0044$); day after vs. 3 months after ($p < 0.0001$). There was no difference between before vs. 3 months after in relation to TEWL measurements related to the irradiated skin ($p = 0.85$).

There were no differences in TEWL measurements between the irradiated and non-irradiated skin, except the measurement made day after the last irradiation ($p < 0.0001$).

We found no significant differences in corneometry values of the irradiated skin at the assessed time intervals ($p > 0.05$) nor any difference in corneometry values between the irradiated and non-irradiated skin ($p > 0.05$).

There were statistically significant differences in erythema measurements related to the irradiated skin in the following time intervals: before vs. in the middle ($p < 0.0001$); before vs. day after ($p < 0.0001$); in the middle vs. day after ($p = 0.0006$); day after vs. 3 months after ($p < 0.0001$). There was no difference between erythema measurements before vs. 3 months after ($p = 0.54$) and in the middle vs. day after ($p = 0.09$).

We observed the significant difference in erythema measurements between the irradiated and non-irradiated skin in the following intervals: in the middle ($p < 0.0001$) and day after ($p < 0.0001$).

Melanin measurements of the irradiated skin presented significant differences between the following time intervals: before vs. day after ($p < 0.0001$); in the middle vs. day after ($p = 0.002$); day after vs. 3 months after ($p = 0.0047$). The differences in measurements of melanin content within the irradiated skin were not significant in the following time intervals: before vs. in the middle; before vs. 3 months after; in the middle vs. 3 months after (in all $p > 0.05$).

We found the significant difference in melanin measurements between the irradiated and non-irradiated skin in the following intervals: day after ($p < 0.0001$) and 3 months after ($p = 0.32$).

The ionizing radiation affects the skin by the generation of free radicals, which causes DNA damage and disturbances in the production of proper skin components. The effect of this process leads to the impaired barrier function, which may be even evident weeks after therapy.[3,5] The epidermal barrier disruption inradiodermatitis may be observed clinically in the form of skin dryness, inflammation (erythema) and exudation. The evaluation of skin symptoms with the use of different scoring systems, like widely accepted CTCAE, seems to be subjective and carries the risk of inter-and intra-rater differences. For more accurate assessment in this study we used two clinical scores in skin evaluation: CTCAE and TLS, in which we could recognize 4 stages. TLS score gives the opportunity to differentiate between distinct skin symptoms like erythema, infiltration and scaliness, while CTCAE grades diagnoses certain conditions (urticaria, Steven-Johnson□s syndrome) together with symptoms (induration, teleangiectasia) and their involvement (percentage of body area affected)(1,6,7). One day after the last irradiation, we observed the most severe skin reaction and in two patients TLS reached 3 and 4 points, while CTCAE 2 points.

In radiodermatitis grading besides the clinical scores no additional, more objective and instrumental methods are widely used according to the recommendations. In our previous observations, we found high-frequency ultrasonography to be useful in measurement of the degree of inflammation in patients treated with radiotherapy after head and neck cancers (article under preparation).

In this study, we present the possibility of skin monitoring in patients under radiotherapy with the use of objective methods in relation to clinical scores. We used complex available methods to determine different skin symptoms/signs in vivo. To evaluate the epidermal barrier function (TEWL), skin dryness (hydration, corneometry) as well as inflammation (erythema) together with melanin (hyperpigmentation), we used standardized bioengineering tools.

TEWL is a well-known parameter recommended in different fields of dermatology to indicate the damage of SC. The more disrupt the epidermal barrier function, the more elevated the TEWL value. TEWL negatively correlates with skin hydration and good hydrated skin presents a low TEWL value.[1,8] The proper function of SC usually presents with TEWL underneath 20 $g/h/m^2$. We found the highest values of TEWL day after last irradiation, which, clinically, was associated with the highest scores. Generally, non-irradiated skin presented lower TEWL values; however, also in this specific area we could observe a slight increase of TEWL and, as a consequence, a significant difference was observed between the irradiated and non-irradiated skin only in measurements taken one day after the last irradiation. Normalization of TEWL was observed 3 months after the last irradiation and similar results were obtained within the affected and non-affected skin region. To sum up we found that the skin barrier function assessed by TEWL was affected in all studied patients independently of skin symptoms. Contrary to our results, Schuth et al. observed increased TEWL only in patients with clinical features of

Table 1 – The results of clinical scores.

No of patient	TLS				CTCAE v 4.0			
	A	B	C	D	A	B	C	D
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	1	2	0	0	1	1	0
4	0	2	3	0	0	1	2	0
5	0	3	4	0	0	1	2	0
6	0	1	1	0	0	0	1	0

Abbreviations: TLSTotal Lesion Score; CTCAE v. 4.4Common Terminology Criteria for Adverse Events Version 4.0; AB, C, D-time of assessments: A, before irradiation; Bin the middle; C- day after; D; 3 months after.

Table 2 – The results of TEWL measurement (g/h/m^2).

No of patient	TEWL irradiated skin				TEWL non-irradiated skin			
	A	B	C	D	A	B	C	D
1	7.3	14.6	26.7	10.1	7.5	12.4	14.5	8.8
2	8.1	12.1	28.4	8.9	8.7	11.5	15.1	7.4
3	9.1	14.6	30.1	7.9	7.9	11.7	13.7	8.5
4	8.4	15.1	32.1	9.5	9.2	14.1	15.1	11.2
5	7.8	16.1	36.1	11	9.3	13.4	12.8	11.5
6	8.2	13.2	24.8	7.8	6.9	8.9	11.3	8.1

Abbreviations: TEWL- Transepidermal Water Loss; A, B, C, D-time of assessments: A, before irradiation; B, in the middle; C- day after; D; 3 months after.

Table 3 – The results of skin hydration (corneometry) measurement (u).

No of patient	Corneo irradiated skin				Corneo non-irradiated skin			
	A	B	C	D	A	B	C	D
1	36.3	37.5	38.2	43	37.4	38.2	37.2	40.8
2	44.6	38.4	36.1	41.8	45.1	37.8	38.1	44
3	40.1	37.9	32	39.4	39.6	32.0	35.1	38.4
4	37.8	36.3	28.1	36.5	39.3	37.9	36.8	40.4
5	36.1	32.1	31.6	35.9	39.3	40.2	37.8	45.7
6	43.3	38.9	37.2	45.1	41.9	40.7	38.9	42.8

Abbreviations: Corneo- Corneometry; A, B, C, D-time of assessments: A, before irradiation; B, in the middle; C- day after; D; 3 months after.

Table 4 – The results of erythema measurement within irradiated skin and non-irradiated skin (u).

No of patient	Erythema irradiated skin				Erythema non-irradiated skin			
	A	B	C	D	A	B	C	D
1	15.8	19.5	23.9	17.8	14.8	16.7	13.8	13.4
2	15.2	20.4	21.9	16.8	15.4	15.6	16.4	15.2
3	16.2	21.6	22.8	19.8	16.9	14.9	15.4	15.9
4	12.4	22.5	25.9	13.4	12.9	8.9	11.8	10.3
5	13.8	22.7	24.9	12.9	13.4	11.8	10.4	11.9
6	14.5	19.8	22.6	15.7	15.9	12.1	16.2	16.1

Abbreviations: A, B, C, D-time of assessments: A, before irradiation; B, in the middle; C- day after; D; 3 months after.

radiodermatitis during irradiation for breast cancer.[9] However, in our study we analyzed the special area of the skin which is the neck. This area is exposed to environmental factors such as UV irradiation, pollution or wind more than the covered area of the breast. Such circumstances may increase the susceptibility of the neck skin to the disruption of the skin barrier.

We found no significant differences in corneometry values of the irradiated skin in the assessed time intervals nor any difference in corneometry values between the irradiated and non-irradiated skin. Nonetheless, during the whole irradiation period we observed a gradual reduction of skin hydration and its normalization 3 month later. However, it should be stressed that because of ethical reasons, emollients were allowed according to the study protocol (except for mornings on the day of measurement). Such procedure could prevent dehydration of the skin, which was confirmed previously by other authors.[10]

Table 5 – The results of melanin measurement within irradiated skin and non-irradiated skin (u).

No of patient	Melanin irradiated skin				Melanin non-irradiated skin			
	A	B	C	D	A	B	C	D
1	32.8	36.2	48.9	44.8	31.7	36.1	35.3	34.5
2	31.8	40.1	50.9	39.8	33.6	34.2	36.9	34.2
3	33.9	38.4	97.5	49.7	32.5	31.8	43.2	35.2
4	30.5	39.2	80.6	48.6	29.5	30.3	38.4	34.2
5	35.1	37.9	98.5	58.5	34.7	32.8	35.1	35.1
6	30.1	38.6	66.8	47.4	33.4	33.1	32.7	35.8

Abbreviations: A, B, C, D-time of assessments: A, before irradiation; B, in the middle; C- day after; D; 3 months after.

The most difficult part in objective clinical assessment seems to be the evaluation of skin color, especially in regards of the intensity of the erythema, which is the prominent feature of skin inflammation. We observed significant differences in erythema between measurements before irradiation and assessment in the middle and one day after the last irradiation, anderythema was significantly more intense in the middle of irradiations and one day after the last irradiation than 3 months after discontinuation. There were also differences in erythema measurement between the affected and non-affected skin region at the later stages of the treatment procedure (in the middle and one day after the last radiotherapy), which indicates an inflammatory process and corresponds to the highest clinical scores. It is also worth to stress that more intensive erythema was observed in all patients within the irradiated skin independently from clinically obvious radiodermatitis.

Additionally, we observed an increase in skin melanin to the highest values one day after the last irradiation. Also, the difference was obtained between the affected and non-affected region 3 months after the last irradiation. This may reflect increased melanin production under inflammatory condition and correspond to postinflammatory hyperpigmentation of the skin.[11]

8. Conclusions

Although the limitation of the study is a small sample of included patients, we show that radiotherapy causes skin barrier dysfunction in all patients, independently of clinically obvious radiodermatitis. Moreover, the biophysical features of this dysfunction can precede clinical signs and symptoms and they can be easily assessed by non-invasive and objective methods. Proper understanding of skin changes during and post radiotherapy may affect managing patients□ skin to prevent temporary or permanent treatment discontinuation as well as distant complications. A well-known method to maintain a proper barrier function in patients during and post radiotherapy is a proper skin care, especially in the form of topically used emollients.

Conflict of interest

None

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