RADIATION-INDUCED SKIN PIGMENTATION AFTER ACCELERATED PARTIAL BREAST IRRADIATION: DOSE-VOLUME HISTOGRAM ANALYSIS

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Abstract. This research demonstrates the treatment of breast cancer with high dose rate (HDR) brachytherapy in the 34 Gy mode performed in 10 twice-a-day treatments, six hours apart over a period of five days. According to the protocol the maximum allowable radiation exposure for the skin did not exceed 34 Gy. By May 2019, 28 patients were treated with a mean follow-up of 10.5 months, with the median of the study being 11 months. Among these patients, 7 had shown toxic effects on the skin in the form of pigmentation. For these patients parameters such as $D_{\text{max}}$, $D_{0.01c}c$, $D_{0.1c}c$, $D_{1c}c$, and $D_{2c}c$ were analysed. Among the patients, some had the same values or higher but did not exhibit toxic effects. Therefore, the expected effects, as well as the results of treatment, are very individual and dependent on many factors. We can only try to minimise them. As a result, it is necessary to show care with values of $D_{\text{max}} \geq 33$ Gy, $D_{0.01c}c \geq 32$, $D_{0.1c}c \geq 30$, $D_{1c}c \geq 27$ and $D_{2c}c \geq 24$.

Keywords: Breast cancer, dosimetric parameters, high-dose-rate brachytherapy, radiation therapy, skin pigmentation, toxic effects

1. Introduction

Breast cancer (BC) is the most common malignant disease among women all over the world. The number of first time cases of cancer and the number of cancer deaths in 2018 are shown in Fig. 1 and 2 [1].

![Number of new cases in 2018, both sexes, all ages](image1)

Number of new cases in 2018, both sexes, all ages

- Lung: 3,682,679 (11.0%)
- Breast: 2,088,849 (11.0%)
- Colon rectum: 1,891,516 (10.2%)
- Prostate: 1,579,108 (9.1%)
- Stomach: 1,033,703 (6.7%)
- Others: 4,670,981 (4.2%)

Total: 10,878,957 cases

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![Number of deaths in 2018, both sexes, all ages](image2)

Number of deaths in 2018, both sexes, all ages

- Lung: 1,781,887 (18.4%)
- Other cancers: 3,532,617 (36.8%)
- Breast: 626,679 (6.6%)
- Colon rectum: 580,595 (6.3%)
- Prostate: 422,242 (4.5%)
- Pancreas: 149,737 (1.6%)
- Others: 189,791 (2.0%)

Total: 10,555,577 deaths

Figure 1. Number of new cases of breast cancer in 2018 according to the World Health Organisation

Figure 2. Number of deaths from breast cancer in 2018 according to the World Health Organisation

Surgery is not the only necessary part of the BC treatment because of the high risk of frequent relapses and distant metastases. That is why it is carried out in combination with, for example, postoperative radiotherapy.

The latest observations have shown a tendency that the age of patients with this diagnosis has been decreasing. Therefore, organ-preserving methods of treatment are becoming more and more relevant. Lumpectomy with subsequent multicatheter interstitial brachytherapy is the most promising treatment of this
disease in its early stages. Thanks to this treatment, the
time of postoperative therapy decreases several times.
[2]. One of the main goals during the development of
the method is to assess the biological radiation
tolerance of the organs-at-risk (OARs), which include
skin, ribs, lungs, heart and liver. The first two are
closest to the target volume, so they received the most
attention. Because of their proximity, the risk of toxic
effects after irradiation is high. With regard to the skin,
pigmentation is one of the most common toxic effects.
Since Accelerated Partial Breast Irradiation (APBI)
is also used to achieve good cosmetic results, it is
important to assess what doses lead to an increased
risk of toxic effects.

A number of articles that describe different types of
contouring of the skin were written. In addition, the
articles discuss the skin radiation doses received after
the APBI [3-11]. Almost all researchers reported a
manifestation of pigmentation. However, these
manifestations usually refer to the G1 or G2 and are
considered acceptable.

This study presents around 7 cases of radiation-
induced skin pigmentation after APBI based on the
analysis of the dose-volume histograms (DVHs) of 28
patients.

2. Materials and Methods

In 2017 the protocol for breast cancer treatment
with a high dose rate (HDR) brachytherapy was
adopted in A. Tsyb Medical Radiological Research
Centre – branch of the National Medical Research
Radiological Centre of the Ministry of Health of the
Russian Federation. This protocol is the
mentioned mode of 34 Gy performed in 10 twice-
a-day treatments, six hours apart and over a period of
days.

The criteria (Table 1) for the selection of patients
was chosen based on recommendations of GEC-ESTRO
and the American Brachytherapy Society (ABS) and
other studies conducted by foreign colleagues [2, 12,
13].

Every patient previously had an ultrasound (US)
and computed tomography (CT) examination before
lumpectomy. During the surgery, the tumor along with
healthy tissue (at least one centimetre) and the sentinel
lymph node was removed and the metal mark was
installed into the tumour bed. It is important to note
that catheters were installed during the open cavity
surgery. In each case, a postoperative CT examination
was carried out after which radiation therapy began.

BrachyVision treatment planning system (Varian,
Palo Alto, CA, USA) and a device for contact radiation
therapy (GammaMedplus iX HDR/PDR Aflerloader)
(Varian, USA) with a 192Ir source were used for
treatment planning.

The gross target volume (GTV) for evaluation
consists of a nominal volume and the position of the
tumor before surgery. These measures are highly
similar to Imagine Related Target Volume (ImTV) and
Estimated Tumour Bed (ETB) in GEC ESTRO
recommendations [14]. The Clinical Target Volume
(CTV) is defined as GTV plus 1 cm radial expansion and
the Planning Target Volume (PTV) is CTV plus 0.5 cm
for the purposes of avoiding target positioning. CTV
and PTV are limited by the chest wall 5 mm away from
the skin surface [15]. Fig. 3 shows the example of the
irradiation target contour.

As OAR, the skin was drawn 3 mm inside from the
body surface. During treatment planning, all attempts
were made to limit the maximum dose (Dmax) applied
to the skin to less than 100% dose. The main criterion
for plan approving was the coverage parameter V90 ≥
90% of the total PTV.

Doses were normalised following international
standards. They were converted into an equivalent dose
of 2 Gy per fraction (EQD2) using Formula 1.

\[
EQD_2 = n \times d \times \frac{\alpha}{\beta} + \frac{\alpha}{\beta}
\]

where n is the number of fractions, d is the dose per
fraction (in Gy), and α/β is 3 for OARs and 4 for the
tumour.

After the treatment of 28 patients, 7 of them had
the G1 skin pigmentation. To establish the relationship
between these toxic effects and the doses received by
this OAR, an analysis of the DVH results of all patients
was carried out. It did not consist only of the protocol
parameter Dmax but also of other volumetric
parameters. These included D0.1cc, D0.1cc, D0.1cc and D0.1cc.

3. Results

By May 2019, 28 patients were treated with a mean
follow-up of 10.5 months and the study median of 11
months. Among these patients, 7 had shown toxic
effects on the skin in the form of pigmentation. The
results of the dose-volume histogram (DVH) were
analysed.

Dmax values to the skin for all patients are
presented in Fig.4.
As can be seen from Fig.3, doses of three patients (2, 10 and 21) exceeded values of the maximum dose limit. The fact that only 1 of them had pigmentation is of interest. At the same time, another 6 patients 5, 7, 9, 12 and 26 (highlighted in pink), whose $D_{\text{max}}$ was lower or equal to the permissible maximum of radiation exposure showed toxic effects. The patient 10 received the maximal skin dose of 1.2 Gy. The values of patients with toxic effects ranged from 34.6 to 33.3 Gy (33.8 ± 0.42 Gy averaged). Maximal EQD$_2$ for these patients was 44.7 Gy and minimal was 42.2 Gy (43.1 ± 0.8 Gy averaged).

In order to have a complete picture and find more accurate parameters for the prediction of toxic effects, it was necessary to perform an estimation of the volume dose ($D_{0.01\text{cc}}, D_{0.1\text{cc}}, D_{0.01\text{cc}}$ and $D_{0.1\text{cc}}$), which are presented in Table 1.

Table 1. Values of the volumetric dosimetric parameters to the skin

<table>
<thead>
<tr>
<th>Patient</th>
<th>$D_{0.01\text{cc}}$, Gy</th>
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<td>32</td>
<td>30.4</td>
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<td>12</td>
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<td>30</td>
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<td>33.4</td>
<td>31.8</td>
<td>29</td>
<td>27.7</td>
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<td>33</td>
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</tbody>
</table>

Table 1. Values of the volumetric dosimetric parameters to the skin

Patients with skin pigmentation

<table>
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<tr>
<th>Patient</th>
<th>$D_{0.01\text{cc}}$, Gy</th>
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Patients with exceeded maximum dose and without skin pigmentation

<table>
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<tr>
<th>Patient</th>
<th>$D_{0.01\text{cc}}$, Gy</th>
<th>$D_{0.1\text{cc}}$, Gy</th>
<th>$D_{0.01\text{cc}}$, Gy</th>
<th>$D_{0.1\text{cc}}$, Gy</th>
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<td>15</td>
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<td>10</td>
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Mean $D_{0.01\text{cc}}$ to the skin was 32.34 ± 0.77 Gy and its EQD$_2$ was equal to 40.2 Gy. At the same time, $D_{0.1\text{cc}} = 30.6 ± 1.0$ Gy (EQD$_2 = 37.1$ Gy); $D_{0.1\text{cc}} = 26.7 ± 1.6$ Gy (EQD$_2 = 30.3$) and $D_{0.01\text{cc}} = 24.2 ± 2.2$ Gy (EQD$_2 = 23.5$).

Two patients with the doses that exceed (2, 10) the $D_{\text{max}}$ parameter were analysed separately (Table 1). So, patient 2 had $D_{0.01\text{cc}}$: 28 Gy (EQD$_2 = 32.5$ Gy), $D_{0.1\text{cc}}$: 22 Gy (EQD$_2 = 22.9$ Gy), $D_{0.01\text{cc}}$: 16 Gy (EQD$_2 = 14.7$ Gy) and $D_{0.1\text{cc}}$: 15 Gy (EQD$_2 = 13.5$ Gy). The values for patient 10 were $D_{0.01\text{cc}}$: 34 Gy (EQD$_2 = 43.5$ Gy), $D_{0.1\text{cc}}$: 32 Gy (EQD$_2 = 39.7$ Gy), $D_{0.01\text{cc}}$: 27 Gy (EQD$_2 = 30.8$ Gy) and $D_{0.1\text{cc}}$: 25 Gy (EQD$_2 = 27.5$ Gy).

Finally, to complete the picture understanding, there are mean dose values for all 28 patients below:

- $D_{\text{max}} = 30.4 ± 2.3$ Gy (EQD$_2 = 36.7$ Gy);
- $D_{0.01\text{cc}} = 28.6 ± 2.1$ Gy (EQD$_2 = 33.5$ Gy);
- $D_{0.1\text{cc}} = 26.4 ± 2.0$ Gy (EQD$_2 = 29.8$ Gy);
- $D_{0.01\text{cc}} = 21.9 ± 2.1$ Gy (EQD$_2 = 22.7$ Gy);
- $D_{0.1\text{cc}} = 19.7 ± 1.9$ Gy (EQD$_2 = 19.6$ Gy);

So, it can be noted that when the maximum dose limit was exceeded, patient 2 had lower values of volumetric doses compared with patients with skin pigmentation and mean dose values of all patients. At the same time, $D_{0.01\text{cc}}, D_{0.1\text{cc}}, D_{0.01\text{cc}}$ and $D_{0.1\text{cc}}$ parameters of the patient 10 are similar to patients with toxic effects. But compared with mean data, his values are higher.

5. CONCLUSION

The expected effects, as well as the results of treatment, are very individual and depend on many factors.

Based on our results, it appears that, when it comes to maximal permissible doses, we should assess the maximal setting as volumetric in order to predict toxic effects. So, it is necessary to be careful with values of $D_{\text{max}} ≥ 24$ Gy, $D_{0.01\text{cc}} ≥ 32$, $D_{0.1\text{cc}} ≥ 30$, $D_{0.01\text{cc}} ≥ 27$ and $D_{0.1\text{cc}} ≥ 24$.

Nevertheless, given the limited number of patients involved in the investigation and the short follow-up period, this study should be continued with the selection criteria and radiation exposure restrictions perhaps reviewed in the future.

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