Early Skin Reaction Following Superficial Proton Irradiation

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Balb/c mice were irradiated on the leg in the area of the spread out Bragg peak (SOBP) of a 30 MeV proton beam. The proton beam was modulated to different ranges in order to determine the early skin reaction versus beam quality at different portions of the SOBP. The respective 50% moist desquamation doses for 1, 3, and 8.5 mm penetration were 25.9, 30.0, and 30.4 Gy. Irradiation of the superficial layer with the distal portion of the SOBP produced a significantly more severe reaction than did whole layer irradiation.

INTRODUCTION

A proton beam has a well-defined range of penetration. The absorbed dose decreases sharply after the Bragg peak; therefore, tissues located deeper than the peak are spared radiation effects. This physical characteristic is used in clinical situations to minimize unnecessary irradiation of distal tissue, especially in critical organs.

Generally, the smaller the tissue volume irradiated, the less the effect of irradiation. This phenomenon is called the “volume effect.” We discuss “the depth-dependent volume effect”; the volume effect along the beam direction. The experiment on this volume effect on superficial tissue was possible because the proton beam allows us to limit the irradiated volume with depth.
MATERIALS AND METHODS

Animals

Female Balb/c mice that were approximately 13 weeks old and that weighed 20 to 25 g at the time of irradiation were used. Seven days prior to irradiation, their hind legs were shaved as follows: The mice were anesthetized with an intraperitoneal injection of 60 mg/kg body weight sodium pentobarbital, after which, the lateral sides of both hind legs were shaved with a razor blade, then the thicknesses of the hind legs of the mice were measured. Several mice were sacrificed 7 days after shaving in order to obtain histological specimens for the measurement of dermal thickness.

Irradiation

The mice were irradiated with a 30 MeV proton beam (original energy) form the SF cyclotron at the Institute for Nuclear Study, the University of Tokyo. A rotating range modulator was used to alter the depth-dose characteristic of the beam in order to achieve a flat distribution (spread out Bragg peak, SOBP) extending over a depth of 8.5 mm in water (Fig. 1). Acryl absorbers were placed downstream of the range modulator to regulate the penetration depth in water to 8.5, 3, and 1 mm. Therefore, the legs were irradiated whole layer, to a penetration depth of 3 mm, or superficially (1 mm penetration). A 25 µm tungsten
scatterer was installed 4 m upstream of the objective. Uniformity across the beam was checked by the film method and was within ±2%. It also was monitored by a profile-monitoring chamber at the time of irradiation\(^3\). The proton flux was collimated to a circular beam 2 cm in diameter with a copper collimating aperture before reaching the objective. The absorbed dose was measured by a tissue-equivalent chamber. The dose rate was 12 to 15 Gy/min.

The mice were anesthetized and fixed on an acryl plate with adhesive plaster, the lateral surface of the left hind leg being positioned facing the beam port. They were irradiated in 3 depth groups and at 8 dose points (18, 22, 26, 30, 34, 38, 42, and 60 Gy). A total of 135 mice that had been irradiated and had completed the observation were used for the analysis.

**Early skin reactions**

Observations were made every other day from the 7th to the 31st day after irradiation. The number of mice that showed moist desquamation during that period were recorded, a small area of moist desquamation being read as a positive reaction. Thus, early skin reaction was recorded as binary data whether or not there was moist desquamation.

**RESULTS**

The thicknesses of the irradiated parts of the hind legs of the mice used were measured, the average being about 8 mm. Dermal thickness was measured in histological specimens taken 7 days after shaving. The dermal thickness (epidermis + corium + subcutaneous tissue) was about 0.2 mm.

The percentage of mice that showed moist desquamation was plotted against the radiation dose (Fig. 2). The data, analyzed by probit analysis\(^3\), gave a 50% moist desquamation dose (MD50).

The respective MD50 values were 25.9, 30.0, and 30.4 Gy at a penetration depth of 1, 3, and 8.5 mm (Table 1). Therefore, the relative MD50 values in comparison to the value for the 8.5 mm range was 0.987 for the 3 mm range and 0.852 for the 1 mm range.

After the 30 Gy irradiation (dose near the MD50 points), 13 of 14 mice developed moist desquamation in the 1 mm depth group and 7 of 14 in the 8.5 mm depth group. These ratios were significantly different (p=0.015) using Fisher’s exact probability test.

**DISCUSSION**

The average thickness of the hind legs of the mice used was about 8 mm. Thus, an 8.5 mm beam penetrated the entire thickness of the leg, and a 3 mm beam penetrated part of the muscle layer. Dermal thickness was measured in histological specimens obtained 7 days after shaving. We found that the dermal thickness (epidermis + corium + subcutaneous tissue) was about 0.2 mm. Hansen et al.\(^3\) reported that on the 7th day after chemical depilation, the epidermal thickness was about 19 µm, the total dermal thickness, about 540 µm, and
the hair follicle depth, nearly 420 μm. Therefore, a 1 mm beam penetrated the entire depth of dermal tissue, including the subcutaneous tissue. Consequently, the basal cell layer absorbed the same radiation dose (physical absorbed dose) in all 3 depth groups.

Table 1. 50% Moist desquamation dose (MD50)

<table>
<thead>
<tr>
<th>Depth (mm)</th>
<th>MD50 (Gy)</th>
<th>95% fiducial limits (Gy)</th>
<th>Relative value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25.9</td>
<td>22.3–28.2</td>
<td>0.852</td>
</tr>
<tr>
<td>3</td>
<td>30.0</td>
<td>26.1–33.2</td>
<td>0.987</td>
</tr>
<tr>
<td>8.5</td>
<td>30.4</td>
<td>27.1–33.7</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig. 2. Percentage of mice showing moist desquamation as a function of the radiation dose from a 30 MeV proton beam. Penetration depths of the beam were 8.5 mm (closed circles), 3 mm (open circles), and 1 mm (open squares). Lines fitted by probit analysis: 8.5 mm (solid line); 3 mm (dashed-and-dotted line); and 1 mm (dashed line).

The concept of the volume effect, the belief that "the smaller the volume irradiated, the less the radiation effect," is widely accepted \(^4\); but, our results did not conform to this. There are several interpretations of this difference: One is that a chemical mediator from the underlying unirradiated tissue exacerbates the skin reaction. Irradiation of the tissue beneath the skin may reduce this reaction.

The simplest interpretation is that the RBE differs depending on the position in the depth-dose curve. The RBE has been reported to be higher in the distal portion of the Bragg peak. Kliauga et al. \(^5\) measured the distribution of lineal energy density, analogous to linear
energy transfer (LET), and found that the lineal energy density increased by a factor of two from the center to the distal area of SOBP. The RBE value depends on LET; the higher the LET the higher the RBE in the LET range of 100 keV/µm of tissue or less). Moreover, Robertson et al.\textsuperscript{7} reported an increase in RBE at the distal parts of the SOBP. Bettega et al. also reported a higher RBE value at the peak of a 31 MeV proton beam\textsuperscript{9}. They showed the RBE at the peak was 1.50 (to \textsuperscript{60}Co gamma ray) and 1.00 at the plateau. These tendencies are comparable to those given in this report. If the distal portion of the Bragg peak has a higher RBE, the SOBP would have an RBE gradient dependent on the depth. In the proximal part of the SOBP, the Bragg peak component would be diluted by the entrance plateau component. Consequently, the distal parts of the SOBP would have higher RBE values than the proximal parts.

In our experiment, the basal cell layer, the primary target of the early skin reaction, was irradiated with proton beams at different points of the depth-dose curve (Fig. 1). To obtain this flat peak distribution (spread out Bragg peak; SOBP), a steplike rotating range modulator was used. The proton beam was a mixture of many Bragg peak curves. Consequently, in each penetration group the basal cell layer was irradiated with a mixture of proton beams of different energies. The linear energy transfer (LET) of a proton beam at various depths in soft tissue can be estimated\textsuperscript{9}. The composition of proton beams with different energies depends on the shape of the range modulator or the angle of the fan-shaped absorbers. The LETs of this SOBP proton beam were calculated at three depths in soft tissue (arrows, Fig. 1) by averaging the LET of each proton beam composing SOBP. The track-averaged LET at the basal cell layer is 5.8 keV/µm for a 1-mm-penetration beam, 3.7 keV/µm for a 3-mm-penetration beam, and 2.5 keV/µm for a 8.5-mm-penetration beam. Moreover, these values are based on the mono-energy hypothesis, in which it is assumed that each original Bragg curve has mono-energy (line spectrum) at each depth. In practice, a proton beam, even at the Bragg peak, has a broader energy distribution around the calculated energies. The lower energy component has such a high LET value that the actual LET values are higher than the track-averaged LET described above\textsuperscript{10}.

The RBE values of the proton beam at the Institute for Nuclear Study (to \textsuperscript{60}Co gamma rays) has been examined by a colony formation assay\textsuperscript{11}. The report shows that the RBE values respectively were 1.2, 1.2, and 1.5 at the plateau (unmodified), the SOBP, and the peak (unmodified)\textsuperscript{9}. Based on these data, the RBE value of our proton beam which was spread out entirely flat was deduced to be almost 1.5 in most distal portion of the SOBP; which mainly contains the peak component. In contrast, the most proximal portion of the SOBP had a small peak component, but was mostly composed of the plateau component. The RBE value of the most proximal portion of the SOBP was deduced to be almost 1.2. The values of our relative MD50 multiplied by these RBE values were almost identical for the 8.5 mm and 1 mm penetrations; 1.2 for a penetration depth of 8.5 mm and 1.28 for 1 mm; the MD50 values corrected by the RBE were almost constant. Consequently, the early skin reaction appears to depend only on the dose to the basal cell layer multiplied by RBE, not on the depth of beam penetration beyond the corium. The MD 50 for the 3 mm penetration was almost the same as that for the 8.5 mm penetration. The interpretation,
based on the above argument, is that the point of the 3-mm-penetration beam which correspond to skin surface is mainly composed of the plateau component, and the high RBE peak component is diluted at this point.

Our present data obtained from an in vivo experimental system confirmed the in vitro results showing a high RBE at the peak of a proton beam. When tissue is irradiated superficially with a proton beam, the high RBE value in the distal portion of the SOBP produces a severe early skin reaction. If a critical organ is to be spared by the distal fall off of a proton beam in clinical use, special precautions are needed.

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REFERENCES