Early Skin Reaction Following 250 MeV Proton Peak Irradiation

HIDEO TATSUZAKI, TETSUO INADA*, TAKESHI SHIMIZU*, TAKURO ARIMOTO*, SHINICHIRO SATOH**, and MASAYOSHI AKISADA

Department of Radiology, Institute of Clinical Medicine, University of Tsukuba, Sakura, Ibaraki 305 JAPAN,
*Particle Radiation Medical Science Center, University of Tsukuba, Sakura, Ibaraki 305 JAPAN, and
**National Institute of Radiological Sciences, Anagawa, Chiba 260 JAPAN
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Early skin reactions were observed on mouse legs irradiated in the spread out Bragg peak (SOBP) of a 250 MeV proton beam, and the unmodified Bragg peak of that beam, or 290kVp X-rays. The fifty percent moist desquamation doses for the proton SOBP, proton peak, and for X-rays were 29.7 Gy, 24.5 Gy, and 21.9 Gy, respectively. The Bragg peak caused more severe early skin reactions than did SOBP.

INTRODUCTION

A proton beam has a well-defined range of penetration; its depth dose curve declines sharply after the Bragg peak. Tissues located deeper than the peak are thus spared radiation effects. This physical characteristic is clinically useful for minimizing unnecessary irradiation of the distal tissues, especially of critical organs. For a thin target, the beam is used without modification; for a thick target, the peak region is expanded to make a spread out Bragg peak (SOBP).

In this study, we compared the biological characteristics of a proton beam in its peak and in the SOBP, both of which are currently used for cancer radiotherapy.

MATERIALS AND METHODS

ANIMALS Female 10 week old ICR mice weighing 25 to 32g at irradiation were used in this investigation. Seven days before irradiation, the mice were anesthetized with 65 mg/kg body weight sodium pentobarbital intraperitoneally. The lateral aspects of the hind legs were shaved.

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立崎英夫，秋田雅祥；筑波大学臨床医学系放射線医学，茨城県新治郡桜村天久保1-1-1 〒305
稲田哲雄，清水義志，有本卓郎；筑波大学粒子線医科学センター，同上
佐藤真一郎；放射線医学総合研究所臨床研究部，千葉市津川4-9-1 〒260
Two punctate tattoos were made intracutaneously in the shaved regions, to observe contractions later. This is not a subject of this study.

**IRRADIATION** Proton irradiation was performed using a 250MeV proton beam. The energy of the 500MeV proton beam of the booster synchrotron at the National Laboratory for High Energy Physics is degraded to 250MeV. The unmodified Bragg peak of this degraded beam was thus broadened as shown in Fig. 1. A ridge filter was used to alter the depth-dose characteristics of the beam to achieve a flat distribution (spread out Bragg peak, SOBP) extending over 6cm in water (Fig. 1). Mix-DP absorbers and a water-bath-degrader were positioned upstream of the objective with respect to the range modulator for modulating the depth of penetration in water. A brass collimating block was used to collimate the proton flux to a 2.5cm × 10cm slit beam before it reached the objective (Fig. 2). The absorbed dose was measured using an ionization chamber (Applied Engineering Inc., 0.6cc JARP chamber). A 6cm Mix-DP scatterer was installed 5m upstream of the objective. Degree of uniformity across the beam was assessed by the chamber scanning method, and was within ±2.8%. The dose rate was 0.8 to 1.8Gy/min for SOBP and 2.5 to 3.0Gy/min for peak.

X-ray irradiation was performed using X-rays produced by a 290kVp, 10mA X-ray generator, and filtered by 0.5mm Cu +0.5mm Al. The focus-target distance was 60cm. The beam was collimated to a 2.5cm × 10cm slit shape. The dose rate was 0.43Gy/min.

The mice were anesthetized and immobilized on an acrylic plate using adhesive plaster. The lateral surface of the left hind leg was positioned so as to face the beam port. The animal's

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`Fig. 1. Depth dose curve of proton beam. Bragg peak curve and spread out Bragg peak (SOBP) curve. Skin surface positions are indicated by arrows.`
feet were excluded from the irradiation field. The SOBP of proton irradiation was performed for 7 dose levels (19, 22, 25, 28, 31, 34, & 37Gy), and each group contained 5 to 6 mice. Peak proton irradiation was carried out for 6 dose groups (19, 22, 25, 28, 31, & 34Gy), each group of which contained 6 mice. The X-ray irradiation was carried out for 5 dose groups (17, 20, 23, 26, & 29Gy), each group of which contained 10 mice. Single irradiations were used in this study.

**EARLY SKIN REACTIONS** Early skin reactions were observed and documented by the same observer throughout this study, under identical conditions every other day from the 7th until the 35th day after exposure. The mice showing moist desquamation regardless of the areas involved were recorded and analyzed.

**RESULTS**

The percentages of mice showing moist desquamation were plotted against the radiation doses (Fig. 3). These data were analyzed by logistic analysis\(^1\) to calculate a 50% moist desquamation dose (MD50), at which half of the mice would be expected to exhibit moist desquamation\(^2\).

As shown in Table 1, MD50 values were 29.7Gy, 24.5Gy, and 21.9Gy for proton-SOBP,
Fig. 3. Percentage of mice showing moist desquamation as a function of radiation dose by a proton beam. Lines indicate the fit by logistic analysis.

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Beam</th>
<th>MD50 (Gy)</th>
<th>SD</th>
<th>RBE</th>
<th>95% fiducial limit of RBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-rays</td>
<td></td>
<td>21.9</td>
<td>1.09</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Proton</td>
<td>SOBP</td>
<td>29.7</td>
<td>1.26</td>
<td>0.74</td>
<td>0.55-0.99</td>
</tr>
<tr>
<td>Proton</td>
<td>peak</td>
<td>24.5</td>
<td>1.10</td>
<td>0.89</td>
<td>0.66-1.19</td>
</tr>
</tbody>
</table>

proton-peak, and X-rays, respectively. The relative biological effectiveness compared with X-rays was 0.74 for proton-SOBP and 0.89 for proton-peak.

**DISCUSSION**

The average thickness of the hind legs of the mice used in this study was 6mm. We measured the dose in acrylic 7mm distal to the Bragg peak and it was 88.2% of the peak. Thus, at peak irradiation, the peak was adjusted to the skin surface; the posterior aspect of the leg absorbed nearly 90% of the peak dose. Though the posterior aspect of the leg absorbed less radiation, the dose at the basal cell layer - - - a depth of 50 micron - - - was identical for both the proton-SOBP and the proton-peak. Since early skin reaction is induced mainly by basal cell damage, the differences in dose distributions for three radiations are negligible when estimating RBE.
The depth dose distribution of a proton beam is known as the Bragg curve. It is formed principally by the energy absorbed through a direct ionizing process. The distribution obtained by measurements within appropriate phantom material is therefore identical to the kerma distribution and is applicable to specific structures, such as the mouse leg. The distribution of 290 kVp X-rays is relatively uniform over the epidermis of the mouse since the build-up and attenuation effects are negligible.

The RBE of proton beams has been studied in other facilities and some investigators have compared the peak portions to SOBP or plateau. Kliauga et al. 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 of the SOBP to the peripheral area. Wainson et al. derived RBE values for the peak of a proton beam to its plateau, being 1.44 for colony formation assay of Chinese hamster cells and 1.90 for chromosomal aberration. Moreover, Robertson et al. reported an increase in RBE at the distal parts of the SOBP. Bettega et al. reported a relatively high RBE value of 1.5 at the proximal portion of the Bragg peak of a 31MeV proton beam, while that in a plateau was 1.0. Inada et al. reported that the RBE value of a 60MeV proton beam at the plateau was 1.0 and at the peak, it was 1.05. There have been few RBE studies of the peak portion of a proton beam in vivo. For example, Sweet et al. reported a high RBE value for the distal portion of the Bragg peak for brain lesions of Cebus monkeys. These values are compatible with our present report.

The estimated LET value of the proton beam was possibly as high as 2.0keV/micron in the distal portion of the Bragg peak; whereas, it is 0.9 keV/micron at best, in the center of SOBP. This difference of LET possibly contributed to the difference of RBE.

A proton beam having a higher energy passes through a longer track. While passing through that track, its energy spectrum gradually becomes broader. Therefore, the higher the original energy of a proton beam, the higher the average energy of the Bragg peak. The characteristic of an unmodified Bragg peak, or high RBE, was expected to be less distinct, when the original energy was higher. However, a 250MeV proton beam which is now clinically used is considered to have a higher RBE value at the unmodified Bragg peak than the SOBP.

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