**Introduction:** Radiation neuropathy is one of the severe complications of radiotherapy. The exact pathophysiology underlying the development of radiation neuropathy remains unclear, however direct effects of radiation on schwann cells and radiation-induced fibrosis in the environment of the nerves have appeared to play an important role in the onset of this neuropathy [1,2]. In the clinical setting, neurolysis of the affected nerve from fibrotic tissue is indicated as the preferred surgical treatment. However, although many clinical reports have shown that pain relief is achieved with neurolysis, there is no evidence of recovery of either sensory or motor function impairment [1,3,4]. In other words, just releasing the radiated nerve from fibrosis is not sufficient to treat the radiation-induced neuropathy [2,6]. The aim of this study is to investigate the direct effects of radiation on rat sciatic nerves that are isolated from surrounding soft tissue.

**Methods:** Twenty rats were utilized in this study. The left sciatic nerve was exposed through a 3 cm long longitudinal straight incision on the lateral aspect of the left thigh. After the entire length of sciatic nerve was made visible, a 1-cm-length lead plate was placed under the exposed nerve. Then the epineurium of the exposed sciatic nerve was marked with 8-0 nylon at both ends of the lead plate. Next, other tissue was covered with another lead plate, in order to radiate only the marked 1-cm-length sciatic nerve (Figure 1). In the radiation group (R group n=10), the exposed sciatic nerve was irradiated with 90Gy using an X-radiation device. The lead plate was then immediately removed, the radiated nerve was returned to its original bed, and the skin was closed with 4-0 nylon. In the sham group (S group n=10), the surgical procedure was completed without radiation. However, in order to parallel the radiation time of the radiation group, we waited 15 minutes before removing the lead plate. We performed the procedure with the aid of an operation microscope to prevent injury to the nerve. Postoperatively, the rats were allowed to move freely within the cage. We assessed sciatic functional index (SFI) as functional assessment [5], electrophysiological assessment and histological assessment. The functional assessments were made before surgery and postoperatively at 4, 8, 12, 16, 20 and 24 weeks. At 24 weeks after surgery, we assessed each group electrophysiologically and subsequently all rats were killed in order to perform histologic assessments. The left sciatic nerves were resected and divided into three portions: proximal, central, and distal (Figure 2).
Figure 1

The method of sciatic nerve exposure before radiation. (a) The markings were sutured on the epineurium at both edges of the lead plate. (b) All soft tissue except the nerve between 1 cm width markings was covered by lead plates.
Results: The sciatic functional index (SFI) result demonstrated no statistical differences between the R group and S group (Figure 3). However, even though the surrounding soft tissue was not irradiated, the macroscopic findings of the R group at 24 weeks after radiation showed scar formation around the radiated nerve (Figure 4). The results of the CMAP examination are shown in Figure 5. The values of CMAP in the radiation group were significantly lower than those observed in the sham group. The histologic observations confirmed that vacuolated axons and myelin ovoids were present in the radiation group, while the axonal fibers in the sham group were circular and relatively uniform in size (Figure 6). We examined the axon packing density of the myelinated fibers in each portion [7-9]. The density was significantly lower in the radiation group than in the sham group of each area (Table 1.)
Figure 3. Time course of changes in the SFI.
Figure 4. Macroscopic findings at 24 weeks. The arrow heads indicate the epineurium markings of 1cm width. (a) Sham group. (b) Radiation group (yellow arrow indicates scar formation).
Figure 5. Electromyography
Discussion: Contrary to our expectation, there were no significant differences between the R group and S group in terms of the results of the SFI as a functional evaluation. However, Evans GRD reported that, despite reductions in the myelinated regenerating fibers, no reductions in the motor function of the rats were observed, as measured by the walking track analysis [9]. We think that a walking track analysis of incomplete paralysis may demonstrate good motor function despite partial nerve injury, because uninjured axons and regenerated axons can cover the motor function which was lost by partial nerve injury.  

![Image of histology](image)

**Figure 6.** Histology at the central portion of each group. Histological findings of the cross-sections of the common sciatic nerve in the sham and radiation groups. The radiation group exhibited vacuolated axons (arrow heads) and myelin ovoids (black arrows).

<table>
<thead>
<tr>
<th></th>
<th>Sham (%)</th>
<th>Radiation (%)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Proximal</td>
<td>80.1±3.57</td>
<td>73.0±5.0</td>
<td>0.0007</td>
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<tr>
<td>Central</td>
<td>70.2±5.8</td>
<td>57.6±7.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Distal</td>
<td>64.4±5.4</td>
<td>54.4±11.7</td>
<td>0.025</td>
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induced by radiation in rats. The electromyographic examination showed decreased amplitude, indicating axonal degeneration. In addition, we could find various stages of axonal degeneration during the histological evaluation and axon packing density as a quantitative histological assessment of nerve regeneration have been clearly demonstrated how much nerve regeneration is impaired by radiation. The macroscopic findings in the R group at 24 weeks after radiation showed scar formation around the radiated nerve, even though the surrounding soft tissue was not directly irradiated. This finding may indicate that neurohumoral factors derived from the radiated nerve itself caused this scar formation, but the role of these factors contributing to nerve fibrosis has not been explored [4]. In addition, the proximal portion of the radiated site degenerated retrograde, which were similar to the pathology of ‘dying back’ neuropathy. We believe that our study is a first step toward identifying an accurate pathophysiology for intractable radiation-induced peripheral neuropathy.

**Significance:** The knowledge about the pathophysiological elucidation of the radiation neuropathy due to our research contributes to future new curative development.

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**References:**