

High-Resolution [18F]FDG-PET Measurement of a Murine Fibrosarcoma Treated With Proton Therapy Combined With the Vascular Disrupting Agent AVE8062

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IV. 1. High-Resolution [¹⁸F]FDG-PET Measurement of a Murine Fibrosarcoma Treated With Proton Therapy Combined With the Vascular Disrupting Agent AVE8062

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Recently, therapeutic strategies targeting tumor vasculature have received a great attention in cancer treatment. Although vascular disrupting agents (VDAs) cause a rapid vascular shutdown in solid tumors leading to extensive tumor necrosis as a result of oxygen and nutrient deprivation. However, tumor cells in the tumor periphery survive VDA treatment alone. It is suggested that the tumor cells in the tumor edge are expected to be nutritionally supported in part by normal vessels in the surrounding healthy tissue¹⁾. In order to kill these surviving cells, VDA treatments are needed to be combined with conventional treatment such as radiotherapy or chemotherapy.

In the previous CYRIC annual report²⁾, we demonstrated that tumor growth delay was significantly enhanced in NFSa fibrosarcoma tumors by the combined treatment of proton irradiation and the vascular disrupting agent AVE8062 in comparison to proton therapy alone or AVE8062 treatment alone, as shown in Fig. 1. It is expected that the proton irradiation may induce therapeutic effects on tumor cells at the tumor periphery which survive AVE8062 treatment alone. In this work, we performed a high-resolution PET study using a semiconductor animal PET scanner (Fine-PET)³⁾ and ¹⁸F-labeled fluorodeoxyglucose (FDG) to evaluate therapeutic effects caused by the combined treatment.

NFSa fibrosarcoma cells ($5 \times 10^6/50\mu\text{L}$) were transplanted into both hind legs of

C3H/HeSlc male mice aged around 12 weeks old. When each tumor diameter reached about 8 mm, the tumors of the right hind leg were locally irradiated (15 or 30 Gy) using a clinical proton beam provided from a horizontal proton irradiation system⁴⁾ so that the tumor volume was covered by the maximum depth dose distribution, the so-called spread-out Bragg peak (SOBP). The size of SOBP was 20 mm in this work. The tumor of the left hind leg was not irradiated. AVE8062 was administered intraperitoneally to a part of the mice receiving 15 Gy at a dose of 40 mg/kg 2 hours after irradiation. As a result, we classified the tumors of the right and left hind legs into proton therapy (15 or 30 Gy), AVE8062 treatment (40 mg/kg), combined treatment (15 Gy + 40 mg/kg) and control groups. Therapeutic effects caused by each treatment in this work were evaluated 1 day and 4 days after each single treatment on the basis of glucose uptake inside the tumor. FDG (37 MBq) was administered to the mice from the tail vein. The FDG-PET scan was performed using the Fine-PET scanner from 60 to 120 min after the FDG administration.

Figure 2 shows results of the FDG-PET measurements. A significant difference was observed in the distribution of FDG uptake between the tumors treated with and without AVE8062. For control and 15-Gy proton therapy groups, FDG uptake was significantly high in the whole tumor region on both day 1 and day 4. On the other hand, FDG concentrated only in the tumor periphery on day 1 in the AVE8062 treatment alone and the combined treatment due to the shutdown of tumor vasculature. In addition, FDG accumulation in the tumor edge of the combined treatment decreased on day 4 in comparison to that of AVE8062 treatment alone. On the basis of these findings, it is expected that AVE8062 may give rise to necrosis in the central region of the tumor and that proton irradiation may cause therapeutic effects leading to reduction in FDG uptake on cells in the tumor periphery.

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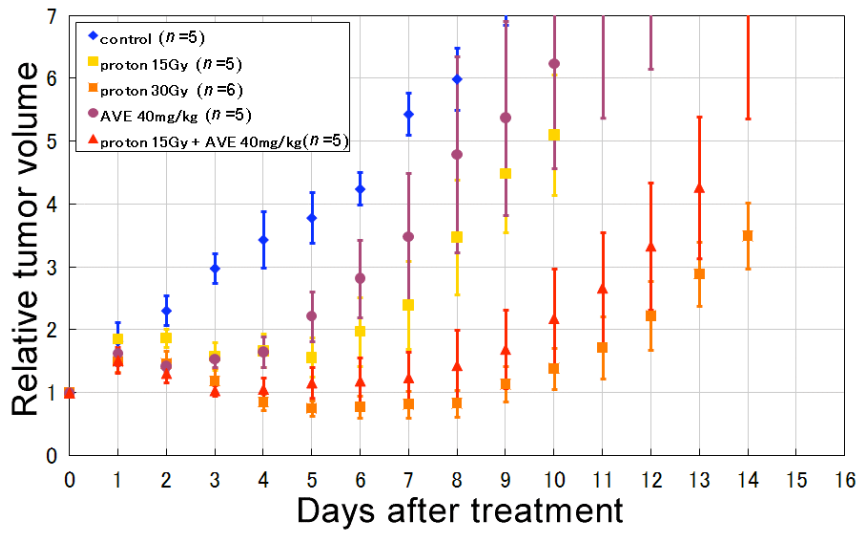


Figure 1. Time course of changes in relative tumor volume caused by each single treatment on day 0. Data are shown with the mean \pm standard error. The number of the tumors in each group is indicated with *n*.

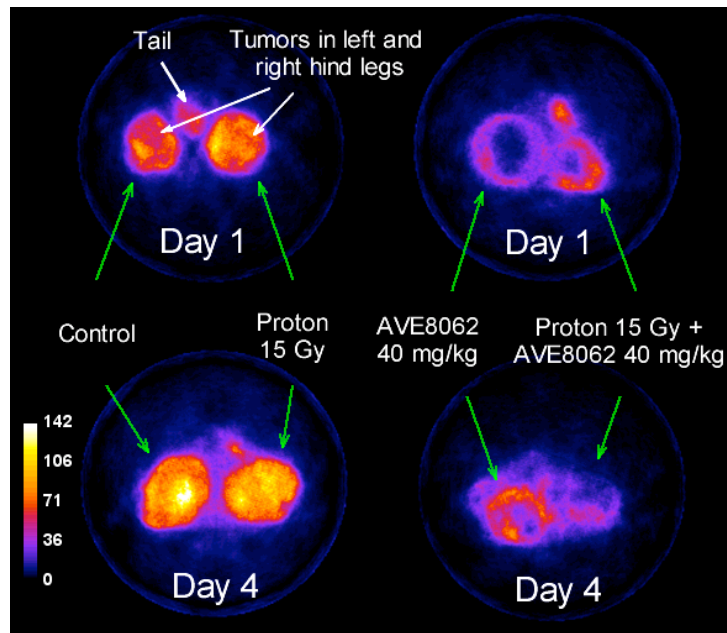


Figure 2. High-resolution $[^{18}\text{F}]$ FDG-PET images of NFSa tumors 1 or 4 days after each single treatment.