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論　文　内　容　要　旨

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学位論文題目	Effect of dose rate on antitumor activity in hypoxic cells by using Flattening Filter Free beams （Flattening Filter Free における線量率と抗腫瘍効果の相関関係に関する評価と解析）		

内容要旨

Radiation therapy is one of the treatment method selected in cancer treatment along with surgery and chemotherapy. One in two of all cancer patients receive radiation therapy during the treatment course. The concept of radiation therapy is to radiate the tumor with appropriate prescribed dose and to spare risk organ from unnecessary radiation at the same time. It is well known that the radiation therapy usually does not carry prescribed dose at single fraction. Dose prescribed by physician is usually given by the patient in multiple fractions to treat cancer. The reason for fractionated irradiation is applying the difference of cell sensitivities between tumor and risk organ around the tumor.

Recently, there is a technique to treat the cancers affecting the thoracic region in few fractions, usually less than five fractions, with large dose per fraction. This is known as Stereotactic Body Radiation Therapy (SBRT). SBRT uses large doses of radiation per fractionation of treatment, and as a result, the treatment procedure is completed in only a few fractions. However, the usage of large doses also results in an increase in treatment time, thus, limiting the determination of patient status. Furthermore, the intrafractional motion may also limit the dose reaching the target during the procedure. Technologies have been developed to account for the respiratory movement in order to minimize normal tissue complications from internal organ displacement. During the respiratory gated treatment procedure, beams terminate automatically when the patient’s respiratory motion deviates from a predefined gated area. Therefore, this procedure requires longer treatment times, shortening of which is highly desirable.

There is also advanced technology named flattening filter free (FFF) beams, which allows for the dose rate to be increased by up to four times compared to the normal dose rate, has been incorporated into many radiation therapy machines. The most beneficial aspect of using FFF beams is the resulting shortening of treatment time, thereby improving patient comfort and total throughput. However, there exist questions concerning the effects of irradiating significantly larger doses in short time periods in radiation biology. In general, tumor cells are under hypoxic conditions and are much more resistant to irradiation because the availability of oxygen results in DNA damage due to its interaction with hydroxyl radicals. Studies investigating the effect of dose rates employing FFF beams are in limited number. Furthermore, these reports do not consider the cell oxygenation status. We suggest that the cell oxygenation condition needs to be considered in experiments aimed at studying the effect of dose rate when using FFF beams because of hypoxic environments is essence of cancer. The aim of the present study is to evaluate antitumor activity in hypoxic cells irradiated with different dose rates using flattening filter free (FFF) beams and to identify the mode of action through which cell damage occurs during irradiation.

EMT6 cells were treated with 95% N_2 and 5% CO_2 to maintain a hypoxic condition. Three dose rates, namely, 6.27 Gy/min, 12.00 Gy/min, and 18.82 Gy/min, were used to deliver the prescribed dose of 2 to 4 Gy using the TrueBeam linear accelerator. After irradiation, the number of colonies was counted to evaluate the cell survival fraction. To investigate the mode of action through which the cells were damaged by irradiation, additional experiments to detect reactive oxygen species (ROS) by aminophenyl fluorescein (APF) assay and DNA double-strand breaks (DSBs) by γH2AX assays were performed.

Irradiation of hypoxic cells using FFF beams increases antitumor activity as a function of dose rate. The fluorescence of APF assay, an indicator for ROS formation, was significantly increased when high dose rates were used. In addition to APF assay, results from our γH2AX assays show that the number of DNA DSBs increased as a function of dose rate. We demonstrate that there is a significant difference in antitumor activity only in hypoxic cells in a dose rate dependent manner when FFF beams are used. Our results suggest that using high dose rates using FFF beams may help achieve better tumor control.