Experimental studies of the microangiarchitcture of
tumors using synchrotron radiation
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Purpose: The present studies aimed to quantitative evaluate changes in tumor microvessels using synchrotron radiation in vivo after intraarterial and intravenous administration of anticancer drugs.

Material and Methods: VX2 carcinomas were transplanted into the auricles of 50 rabbits. Three days later, rabbits were divided into three groups. Group IA was administered anticancer drugs by intraarterial injection over 5 min. Group DIV was administered anticancer drugs by drip infusion over 15 min. The two groups were administrated cisplatin, carboplatin, docetaxel hydrate and adriamycin, respectively. Untreated VX2 rabbits that were administrated sodium saline served as the Control group. In all groups, tumor microvessels were microangiologically evaluated before and after administration. Microangiograms of VX2 carcinomas were obtained using a synchrotron radiation system.

Image analysis was done with Image-Pro Plus.

Among the field where the microvessels with diameters of less than 200 μm were observed within the tumor, the field of 2 by 2 mm was decided as the Area Of Interest (AOI). The area of the AOI was measured and evaluated in tumor microvessels after administration of anticancer drugs quantitatively.

Results: In the control group, the number of tumor microvessels remained stationary during the experimental time, and there was no significant difference in the AOI between before and 30 min. After administration. As for the degree of the changes in microvessels, there was a difference among each drug. The number of tumor microvessels had decreased after administration of cisplatin and docetaxel hydrate, significantly. Changes in microvessels of approximately 50 to 200 μm in diameter in the central zone of tumor were observed in both groups.

Conclusion: The synchrotron radiation system was a useful tool for quantitative evaluation of changes in tumor microvessels after administration of anticancer drugs.

(Objective) An experimental model in which tumor microvascular structure was observable using synchrotron radiation was prepared. Next, tumor cells were transplanted into athymic rats and the transplanted tumor was treated with electron beam irradiation. B-EGF (angiogenesis promoter: AP) or anti-VEGFR neutralizing antibody (angiogenesis inhibitor: A1). Changes in radiosensitivity of the tumor after the treatment were compared with those in the control group, and the time-course effects on the microvascular structure (changes in the vascular structure and vascular density investigated by static or dynamic imaging) were observed using synchrotron radiation at SPring-8.

(Methods) 1) A catheter was indwelled in the abdominal aorta in an athymic rat under anesthesia, and angiographic images of the normal lower epigastric vein and artery were obtained using a 9.0-keV monochromatic X-ray beam.
2) In the lower abdominal wall in athymic rats, 1×10^6 cells of N-nitrosomethyurea (NMU)-induced rat mammary adenocarcinoma were transplanted to prepare a lower abdominal wall tumor transplantation model. Changes in the tumor microvascular structure were observed using the monochromatic X-ray beam in the control group (n=6), 10Gy electron beam irradiation group (n=4), AP treatment group (n=4), and A1 treatment group (n=4), and the time-course morphological changes were compared among the tumors.

Results) 1) The microvascular structure of tumors measuring 20-30 microns were observable by synchrotron radiation in the tumor transplantation model using the lower epigastric artery and vein as the nutrient blood vessels.
2) The tumor microvascular structure was observed for 1-4 weeks after transplantation. In the control group consisting of athymic rats transplanted with NMU tumors followed by no treatment, abnormal tumor blood vessels grew as the tumor volume increased. Formation of minute tumor blood vessels was inhibited in the A1 treatment group, but promotion of tumor neovascularization was not clear in the AP treatment group. In the electron beam irradiation group, the minute tumor blood vessels were clearly inhibited and impaired one week after irradiation, but outgrowth of tumor blood vessels was observed two weeks after irradiation.

(Discussion) Tumor nutrition blood vessels in tumors transplanted into the lower abdominal wall in athymic rats are smaller than those in tumors transplanted below the back skin and in the cornea in vivo tumor neovascularization analysis, this model allows contrast medium at a higher concentration to reach peripheral blood vessels. In our model, the tumor microvascular structure could be observed in vivo using synchrotron radiation. The microvascular structure was also observable over time using synchrotron radiation in the tumors treated with electron beam, AP, or A1 alone, which may lead to elucidation of the relationship between the angiogenesis-related factors and radiation that affects radiosensitivity. Continuation of this study may obtain important information related to combination therapy using A1 and radiation. The effects of angiogenesis factors on radiotherapy may be clarified by accumulation of additional data.