Visualization, quantification, and therapuetic evaluation of angiogenic vessels in cancer by synchrotron microangiography

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Introduction

The purpose of the present study was to elucidate the usefulness of the microangiography system we developed for depicting small angiogenic vessels, quantitating the sequential changes in vessels during 1-4 weeks after transplantation, and evaluating the effects of antiangiogenic therapy with anti-VEGF antibody on the sequential changes in angiogenic vessels.

Methods

The monochromatic synchrotron radiation having an energy level of 33.3 keV was obtained from beamlines NE-5 and BL-14 in KEK. The monochromatic X-ray beam formed a contrast image of the object on a fluorescent screen (HR-mammo, Fuji Film, or FOS J6144, Hamamatsu Photonics). An area with sides 20.0-30.0mm and 20.0mm long was scanned at 15 or 30 frames/sec for 6 sec by a HD-TV camera equipped with an avalanche-type pick up tube with 1125 TV lines, and each frame consisted of a single field. The image was digitized to a resolution of 1024x1024 pixels, and 10 or 12 bit/pixel, and stored on a digital video tape (HDD1000, SONY) and/or in a frame memory (DFM-P, Keisoku-Giken, or custom-made 192 mega-words of 12 bits, Zenisu Keisoku). A modulation-transfer-function chart study revealed that the system enables to identification of adjacent 20 line-pair/mm leadlines. Assessment of contrast resolution using a vascular phantom (Type 76-700, Nuclear Associates, New York) showed that the minimum vascular phantom (0.5 mm in diameter) was visualized with a minimum concentration (2.5 mg/ml of iodine) through an acrylic block 75 mm thick.

Sequential changes in tumor size and in the angiographic features of angiogenic vessels of the cancer were evaluated in 20 mice, into which colon cancer (Colon 26) had been transplanted,. The cancer cells were subcutaneously injected in the axillary region. Five mice were treated with VEGF antibody. Microangiography was performed once or twice at 1, 2, 3, or 4 weeks after transplantation. In 10 mice, microangiography was performed a second time two weeks after the first angiography.

Results

The contrast material injected into the ascending aorta visualized the networks of tumor-feeding arteries originating from the mammary artery even at 1 week after transplantation. In the angiograms, 4th order branches could be identified. The tumor-feeding vessel exhibits the characteristic appearance of the vessels supplying malignant tumors. Conventional angiography by X-ray tube (DH-1513TM, Hitachi) with a tube voltage of 6.5 kV and Image Intensifier-TV system failed to show any proximal arteries or their branches.

In mice treated with VEGF antibody, growth of the networks of tumor feeding arteries has obviously been suppressed. The number of feeding arteries, the maximum order of branching, and the angiographic scores in the VEGF-antibody-treated mice 4 weeks after transplantation were significantly smaller than in the control group.

Discussion

Synchrotron microangiography was useful for the depiction, quantification, and therapeutic evaluation of angiogenic vessels in a murine model of cancer.

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References

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