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Physics Contribution

Noninvasive Monitoring of Microvascular Changes With Partial Irradiation Using Dynamic Contrast-Enhanced and Blood Oxygen Level-Dependent Magnetic Resonance Imaging

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Summary

A partial irradiation approach with a xenograft tumor was proposed to investigate the intratumoral response to radiation therapy using dynamic contrast-enhanced (DCE) and blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI). The irradiated region of the tumor had a significantly increased K^{trans}, a reduced BOLD response to carbogen and a reduced microvascular

Purpose: The microvasculature of a tumor plays an important role in its response to radiation therapy. Dynamic contrast-enhanced magnetic resonance imaging (DCE MRI) and blood oxygen level-dependent (BOLD) MRI are both sensitive to vascular characteristics. The present study proposed a partial irradiation approach to a xenograft tumor to investigate the intratumoral response to radiation therapy using DCE and BOLD MRI.

Methods and Materials: TRAMP-C1 tumors were grown in C57BL/6J mice. Partial irradiation was performed on the distal half of the tumor with a single dose of 15 Gy. DCE MRI was performed to derive the endothelium transfer constant, K^{trans}, using pharmacokinetic analysis. BOLD MRI was performed using quantitative R2* measurements with carbogen breathing. The histology of the tumor was analyzed using hematoxylin and eosin staining and CD31 staining to detect endothelial cells. The differences between the irradiated and nonirradiated regions of the tumor were assessed using K^{trans} values, $\Delta R2^*$ values in response to carbogen and microvascular density (MVD) measurements.

Results: A significantly increased K^{trans} and reduced BOLD response to carbogen were found in the irradiated region of the tumor compared with the nonirradiated region ($P<.05$). Histologic analysis showed a significant aggregation of giant cells and a reduced MVD in the irradiated region of the tumor. The radiation-induced difference in the BOLD response was associated with differences in MVD and K^{trans}.

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density compared with the non-irradiated region. These results suggested that both DCE and BOLD MRI could potentially serve as noninvasive biomarkers to detect the intratumoral response to radiation therapy.

Conclusions: We demonstrated that DCE MRI and carbogen-challenge BOLD MRI can detect differential responses within a tumor that may potentially serve as noninvasive imaging biomarkers to detect microvascular changes in response to radiation therapy.

Introduction

The tumor microvasculature plays an important role in the tumor response to radiation (1). After antiangiogenic and radiation therapies, the abnormal function of the tumor vasculature could be transiently normalized, and the efficacy of radiation therapy is increased during the normalization window (2). Noninvasive imaging techniques that are sensitive to the microvascular changes of the tumor are therefore of clinical interest.

Several functional magnetic resonance imaging (MRI) techniques have been developed that yield physiologic information about the tumor microenvironment (3). For example, dynamic contrast-enhanced (DCE) MRI investigates microvascular function by tracking the pharmacokinetics of injected contrast agents as they pass through the tumor vasculature (4). Blood oxygen level-dependent (BOLD) MRI uses deoxyhemoglobin as an endogenous contrast mechanism to reflect alterations in blood oxygenation, blood flow, and blood volume (5). The functional status of the tumor vascular bed can also be assessed by the change in the transverse relaxation rate, R2*, during challenge with a high-oxygen-content gas, such as carbogen (95% O_2 and 5% CO_2) (6, 7).

In preclinical studies, the evaluation of the treatment response typically relies on comparisons between different groups of animals, each of which has received a different type of treatment. However, the measurement of treatment efficacy can be hindered by intersubject variation. For example, the selection of an arterial input function from each individual could lead to substantial variations in the extracted pharmacokinetic parameters in DCE MRI (8), or the physiologic condition of the subject during the carbogen breathing in BOLD MRI could influence the sensitivity of the BOLD response.

In this study, the intratumoral response to radiation therapy was investigated by DCE and BOLD MRI through the irradiation of one-half of a tumor. Through the implementation of this partial irradiation approach, microvascular changes can be assessed within the same tumor without intersubject variation.

Methods and Materials

Animals and irradiation

All experiments were performed with 7- to 8-week-old male C57BL/6J mice following the guidelines of the Institutional Animal Care and Use Committee. The tumors were generated by intramuscular inoculation of 3×10^6 transgenic adenocarcinoma of the mouse prostate (TRAMP)-C1 cells into the thigh. Mice were anesthetized by a mixture of ketamine and rompun during irradiation. On the 10th day after tumor implantation (tumor diameter = 1.1-1.3 cm), single-fractionated irradiation for 15 Gy was performed with a dose rate 8 Gy/min and a 0.5-cm bolus on the surface. The irradiation was conducted using the 6 MV Novalis system (BrainLab, Feldkirchen, Germany) with a 2-cm stereotactic radiosurgery cone. This conical collimator provides a steep dose gradient with 20% and 80% doses within a 4-mm distance. For the partial irradiation tumor model, irradiation was targeted to the distal half of the tumor, and the dose distribution was illustrated by the treatment planning system (iPlan v.4.5) (Fig. 1a,b) and verified by Monte Carlo simulation and a Gafchromic EBT-2 film (data not shown).

MRI experiments

In a pilot study, we investigated the feasibility of DCE and BOLD MRI for monitoring the effect of a partial irradiation tumor model. Animals were divided into 3 groups: (*1*) control group, which received no irradiation; (*2*) whole irradiation (WR) group, which received irradiation of the whole tumor; and (*3*) partial irradiation (PR) group, which received irradiation of the distal half of the tumor. For each group (n = 4), longitudinal DCE MRIs were obtained at days 0, 2, 4 and 6 after radiation therapy. The BOLD MRI was performed on the 6th day after radiation therapy (n = 3 for each group). In the final study, a combined BOLD MRI and DCE MRI protocol was performed in the PR group (n = 8) on the 6th day after partial irradiation of the tumor.

The MRI was performed using a 7-Tesla animal MR scanner (ClinScan, Ettlingen, Germany). Mice were anesthetized during the MRI experiment with 1% to 2% isoflurane in air. The body temperature was maintained at 37°C with a water-bed heating system (Model 1025, SA instrument, New York). The respiration rate was kept in 30 to 40 cycles/min by manually adjusting the concentration of isoflurane.

BOLD MRI

A series of quantitative R2* measurements was obtained using a multiple gradient-echo sequence with 12 echo times ranging from 2.4 to 36 ms and the following parameters: repetition time, 444 ms; flip angle, 40°; field of view, 34×50 mm^2; slice thickness, 1 mm; in-plane resolution, 0.29×0.29 mm^2; and temporal resolution, 60 seconds. A dynamic time series of images was obtained for 20 minutes. The carbogen gas challenge was performed with a block design experiment, which consisted of 2 stimuli: 5 minutes of room air inhalation and 5 minutes of carbogen challenge, with 2 cycles of this regimen. The R2* maps during the dynamic time series were calculated by fitting the exponential multiple gradient-echo signal decay. The dynamic