

Differential response to radiotherapy in a mouse xenograft model with half-field irradiation detected by combined DCE and BOLD MRI

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Purpose:

To investigate the treatment response after radiotherapy on half-field of the tumor by using dynamic contrast enhanced (DCE) and blood oxygen level dependent (BOLD) MRI with gas challenge

Methods and Materials:

Transgenic adenocarcinoma of the mouse prostate (TRAMP)-C1 tumors were grown in C57BL/6J mice (n=6) by i.m. inoculation of 3×10^6 viable cells into the thigh. Irradiation was performed on the peripheral half of the tumor with a single dose of 15Gy on the 10th day after tumor implantation. 6 days after irradiation, MR images were acquired using a 7 Tesla MR scanner (ClinScan, Bruker). The imaging protocols included: (1) DCE MRI: a spoiled 3D gradient echo sequence with multiple flip angles (5, 10, 15 and 20 degrees) for baseline T1 calculation and a series of dynamic scans after a bolus injection of Gd-DTPA (Magnevist; Bayer Schering) in a temporal resolution of 2.1 seconds. The quantitative parameters were derived using the extended Kety model^[1] in a voxel-wise manner. (2) BOLD MRI: quantitative R2* measurements were obtained by a gradient-echo sequence with 12 echo times, evenly ranging from 2.4 to 36 ms, in a temporal resolution of one minute. Dynamic time series of images were obtained for 20 minutes. The block design experiment consisted of 2 stimuli: carbogen gas challenge and room air inhalation. The stimuli were interleaved and each lasted for 5 minutes. BOLD response ($\Delta R2^*$) was calculated from the difference of the R2* between both stimuli. Significance was determined when $\Delta R2^*$ exceeding the range of repeatability in the baseline, as determined by the Bland and Altman statistics^[2]. Animals were sacrificed immediately after MRI acquisition and the tumor tissue was obtained. Sections were stained by H&E and immunohistochemistry was performed using a CD31 stained on endothelial cells.

Results:

All six mice showed significant increased Ktrans on the irradiated portion of the tumor when compared with that on the non-irradiated part. Fig.1 shows a tumor section with H&E staining (a), where the non-irradiated (b) and irradiated (c) region of the tumor were enlarged. The Giant cells (dark blue nuclei) aggregated in the irradiated part of the tumor. The corresponding Ktrans map (d) showed a significant increase at the irradiated area of the tumor and is consistent with the reduced BOLD response (arrowhead). However, no difference was noticed in the conventional T1 weighted image (f). Fig.2 shows the $\Delta R2^*$ was reduced at the irradiated portion (5.64%, blue line) when compared with that in non-irradiated portion of the tumor (20.67%, red line). The microvascular density at corresponding irradiated regions (Fig. 2b) was decreased as compared with that of non-irradiated region (Fig.2c).

Discussion

First, the current study proposed a self-controlled tumor model that allows the intra-tumor comparison of the treatment response to radiotherapy. A significant radiation induced Giant cell on the irradiated portion confirms the feasibility of the method. The functional changes revealed by Ktrans and BOLD response can be validated by the histology using the same subject, which reduced the inter-subject variations. Second, the increased Ktrans suggests an acute hyperaemic response following radiotherapy^[3]. The reduced BOLD response to carbogen is related to the decreased microvascular density, such that the capillaries have a limited capacity to transport erythrocytes.

Reference: [1]Toft PS et al. J Magn Reson Ima 1999. [2] Alonzi R et al. Br J Cancer 2009. [3]Alonzi R et al. Eur J Radiol 2007, 63: 335–50.

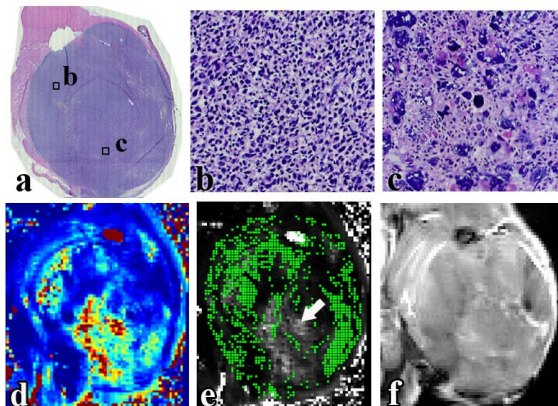


Fig. 1 (a-c) Histology with H&E staining. (d) Ktrans map (e) Significant BOLD response (green dots) overlaid on the Ktrans map (in gray scale). (f) Contrast enhanced T1 weighted image.

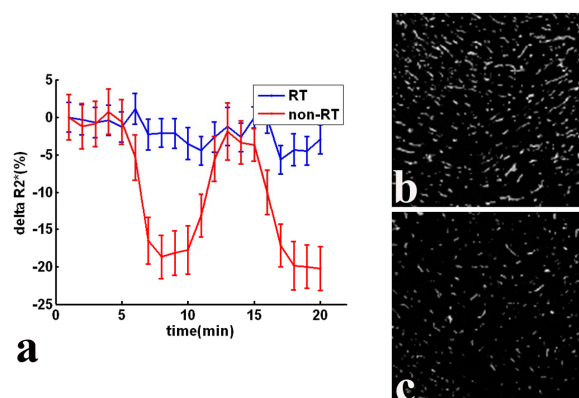


Fig.2 (a) Time course of R2* change in response to carbogen. Immunohistochemical images of CD31 at non-irradiated (b) and irradiated (c) region of the tumor.