

## Dynamic Contrast-Enhanced MR imaging for Early Detection of Vascular-Permeability Changes following Combination Therapy with Anti-EGFR Antibody and Irinotecan in Orthotopic Pancreatic Tumor Xenografts: A Pilot Study

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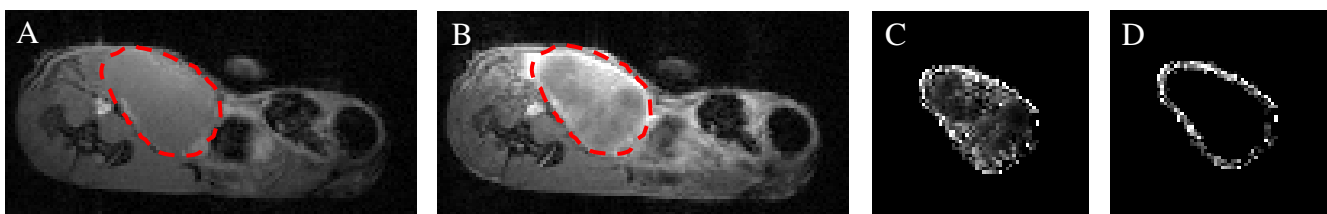
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**Purpose:** To measure the feasibility of dynamic contrast-enhanced MR imaging (DCE-MRI) for early therapy evaluation of anti-epidermal growth factor receptor (EGFR) antibody (IMC-C225) combined with Irinotecan in an orthotopic pancreatic tumor mouse model.

**Methods:** Two groups of SCID mice (n=4 and 3 for groups 1 and 2, respectively) bearing orthotopically implanted, luciferase-positive human pancreatic tumors (MIA PaCa-2) were used. Group 1 was injected i.p. with IMC-C225 (1 mg), an anti-EGFR antibody, and i.v. with irinotecan (25 mg/kg BW) on days 0 and 3 (post imaging), while group 2 was control. Four days prior to imaging, a vascular access port was implanted in each mouse to facilitate repeated i.v. Gd-DTPA injections. DCE-MRI was performed on days 0 and 3, while anatomical MRI and bioluminescence imaging were performed on days 0, 3, and 6. A total of five 1-mm thick slices (0.2-mm gap) were used to cover tumor regions of interest during MR imaging. The abdominal area was separated from chest region using an orthogonally bent plastic board to suppress motion artifact in MR images (1). For DCE-MRI, a T<sub>1</sub> map was acquired with a gradient-echo multiflip-angle approach (10°, 20°, 30°, 40°, 50°, 60°, and 70°), and then the DCE-MRI was performed with the fixed flip angle of 30°. Five baseline images were acquired before Gd-DTPA injection, and then 20 images were collected after Gd-DTPA injection (0.2 mmol/kg BW, 150 μl (10 μl/sec)) with a time resolution of 58 seconds. Reference Region (RR) model (2) was employed to calculate vascular permeability (K<sup>trans</sup>). The averaged K<sup>trans</sup> values in both the entire tumor region (fig. 1C) and the 0.5-mm thick peripheral tumor region (fig. 1D) were calculated, and compared with tumor volume and living tumor mass by bioluminescence.

**Results:** Figure 1 shows representative DCE MR images at (A) 1 minute before and (B) 5 minutes after Gd-DTPA injection, with K<sup>trans</sup> maps in (C) the entire tumor region and (D) the 0.5-mm thick peripheral region. In the treated group (group 1), the changes of K<sup>trans</sup> values at 3 days after therapy initiation (compared to day 0) were -16±12% (mean±SE) for the entire tumor region and -19±8% in the peripheral tumor region, while changes in the control group (group 2) increased 105±110% and 141±60% in the same regions, respectively. The difference in K<sup>trans</sup> values between groups 1 and 2 was significant in the peripheral tumor region (p=0.0260), but not in the entire tumor region (p=0.2533). The mean tumor-volume changes for group 1 at 3 and 6 days after therapy initiation were 12±4% and 5±7% respectively, while those of group 2 were 26±7% and 45±3%, respectively, for the same days. The tumor-volume difference between groups 1 and 2 was statistically significant on day 6 (p=0.0045), but not on day 3 (p=0.1284). The mean bioluminescence signal of group 1 gradually decreased during 6 days of therapy with a -40% change in signal, while that of group 2 increased 46% during the same time period. However, due to animal variability, these differences were not significant (p>0.05).

**Conclusion:** DCE-MRI detected a significant therapeutic response at 3 days after anti-EGFR antibody and irinotecan administration using peripheral-region analyses in the orthotopic pancreatic tumor xenografts, which correlates well with tumor-growth suppression and bioluminescence-signal decrease over the 6 days of treatment.



**Figure 1:** Representative dynamic contrast MR images of a mouse bearing an orthotopic pancreatic tumor at (A) 1 minute before contrast agent (Gd-DTPA) injection and (B) 5 minutes after contrast agent injection (tumoral regions were indicated with red dotted circles). K<sup>trans</sup> maps of tumor in (C) entire tumor region and (D) 0.5-mm thick peripheral tumor region.

### References:

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2. Yankeelov TE, Luci JJ, Lepage M, et al. Quantitative pharmacokinetic analysis of DCE-MRI data without an arterial input function: a reference region model. *Magn Reson Imaging* 2005; 23:519-529.