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Your submission:

Multimodal imaging in an experimental rat model for brain metastasis

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Introduction

Metastatic brain tumors are a severe problem in the treatment of patients with breast carcinoma. Preclinical models can play an important role in unravelling the underlying mechanisms behind the metastatic process and evaluation of new therapies.
We developed a rat model for brain metastasis that allows follow-up by MRI. Injection of cancer cells labeled with iron oxide particles, allows tracking from the single-cell stage until the appearance of full-blown metastases (1). Potential metastasis development outside the brain is evaluated with PET and CT.

Methods
MDA-MB-231br/EGFP human breast cancer cells were labeled with micron-sized particles of iron oxide (MPIO; 1µm). 13 female nude rats (Crl:NIH-Foxn1rnu, Charles River) were intracardially injected with 100.000 of these labeled cells at the age of 5 weeks (2).
MRI was performed on a 7T system (PharmaScan) at day 1, and then weekly until 10 weeks post-injection, taking human endpoints into account. T2*W images were acquired one day post-injection to show the initial distribution of MPIO-labeled cells in the brain. T2W and contrast-enhanced T1W sequences were acquired to visualize the brain metastases.
A static whole-body 18F-FDG PET-CT (Triumph-II, Trifoil, 37MBq, 30 minutes uptake, 60 minutes acquisition) was performed to determine metastasis development outside the brain. For detection of bone metastases full body spiral high-resolution CT acquisitions were performed (X-CUBE, MOLECUBES NV) with 460 µA tube current and 50 kVp tube voltage, resulting in a 7 minute acquisition time. Acquisitions were reconstructed into a 1400x1400x4000 matrix with 50 µm voxel size using an FDK-based algorithm (3).

Results
At week 3 to 4 the first signs of brain metastasis development were visible as hyperintensities on T2W images in all animals. The metastases visible on T2W images could be correlated to their corresponding hypointensities on T2*W images.
Whole-body PET imaging suggested hot spots in the lungs of 2 animals. Cellular alterations in the lung were confirmed with hematoxylin and eosin staining. Bone metastases were detected in 11 out of 13 animals with CT evaluation.

Conclusions
Our aim was to develop a rat model for brain metastasis. However, early formation of metastases outside the brain was observed in the lungs and bone, as evidenced by PET and CT, respectively. This indicates that this model is currently not suited for investigating brain metastasis and associated treatment strategies. Therefore, the brain metastatic propensity of the cell line will be optimized by in vivo passaging.

(1) De Meulenaere et al. Abstracts WMIC Seoul 2014
(2) Yoneda et al. J Bone Miner Res 2001. 16: 1486-1495
(3) Feldkamp et al. J Opt Soc Am 1984. 612–619

Acknowledgement
The MDA-MB-231br/EGFP cell line was a kind gift from Dr. P. Steeg from the National Cancer Institute, Bethesda.

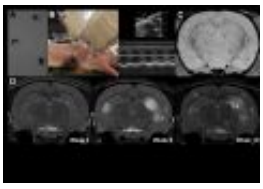

Figure 1:
A-B: Intracardial US-guided injection of MPIO-labeled MDA- MB-231Br/EGFP cells. C-D: Longitudinal MR tracking of the growth of a MPIO-labeled MDA-MB-231Br/EGFP cell into a brain metastasis.

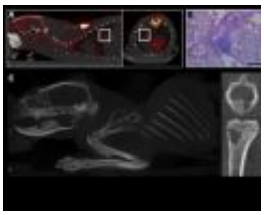

Figure 2:
A: PET-CT images. B: Hematoxylin and eosin staining of lung tissue. C: High resolution CT images.

Best regards

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