

Hyperpolarized ^3He MRI to Detect Lung Metastases Targeted by Magnetic Nanoparticles

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Introduction: In patients with cancer, the appearance of metastases in the lung greatly diminishes the prospect for survival. Therefore, it is critical to develop markers that can detect lung metastases early when treatment options still exist. To this end, Leuschner et al. recently reported a novel super paramagnetic iron oxide nanoparticle (SPION) that was conjugated with the lutenizing hormone releasing hormone (LHRH), the receptors of which are over-expressed in breast cancer cells (1). Leuschner showed that these SPIONs accumulate in primary and metastatic tumors in linear proportion to the number of cancer cells present. A logical next step is to use these cancer-targeted SPIONs for detection of lung metastases in a live animal. However, since SPIONs create their contrast by shortening T_2^* , their detection in lung tissue by ^1H MRI is problematic because T_2^* is already exceedingly short. However, hyperpolarized (HP) ^3He has a considerably longer T_2^* (~8 ms) in the airspaces of the lung because the ^3He atoms are motionally narrowed (2). Therefore, we tested whether ^3He MR imaging with long echo times ($1 \geq \text{TE} \geq 8$ ms) could be used to report the accumulation of SPIONs in metastatic cancer cells in the lung.

Methods: A female BALB/c nude mouse at 9 weeks of age was inoculated with MDA-MB-435S human breast cancer cells. After about 60 days, and 24 hours before the imaging session, the mouse received an IP injection of 100 mg/kg LHRH-SPIONs. The mouse was imaged using a 3D radial acquisition at a resolution of $156 \times 156 \times 2000 \mu\text{m}^3$. Images were acquired at $\text{TE}=0.3\text{ms}$ to show regional ventilation and $\text{TE}=4$ ms for T_2^* sensitivity. K-space was filled with 5280 radial views acquired either 20 per breath with $\text{TR}/\text{TE}=5/0.3$ ms or 10 views per breath with $\text{TR}/\text{TE}=10/4$ ms. All images used $\text{BW}=31.25$ kHz and a fixed flip angle of 13° or 18° . After imaging, the mouse was sacrificed and the lungs fixed for histology. Histology slides were stained with Prussian Blue to highlight iron.

Results and Discussion: ^3He images acquired at $\text{TE}=4$ ms showed numerous signal voids. These voids were not apparent on the ^3He images acquired at $\text{TE}=0.3$ ms, suggesting that the signal void is a T_2^* effect rather than a ventilation deficit. Several regions containing signal voids (numbered) were examined by histology, as shown below the lung images in Figure 1. Each section revealed significant accumulation of iron (brown dots, brown arrows), thereby indicating that the signal voids seen on imaging resulted from SPION accumulation in the metastatic cells. Iron was found diffusely throughout the lung, but only reached sufficient concentration in a few areas to cause susceptibility defects in the ^3He image. We speculate that these areas of accumulation correspond to regions where metastases would eventually form. In this mouse, the metastatic cells had not yet aggregated to a significant extent and would have been very unlikely to be detectable by conventional structural imaging methods.

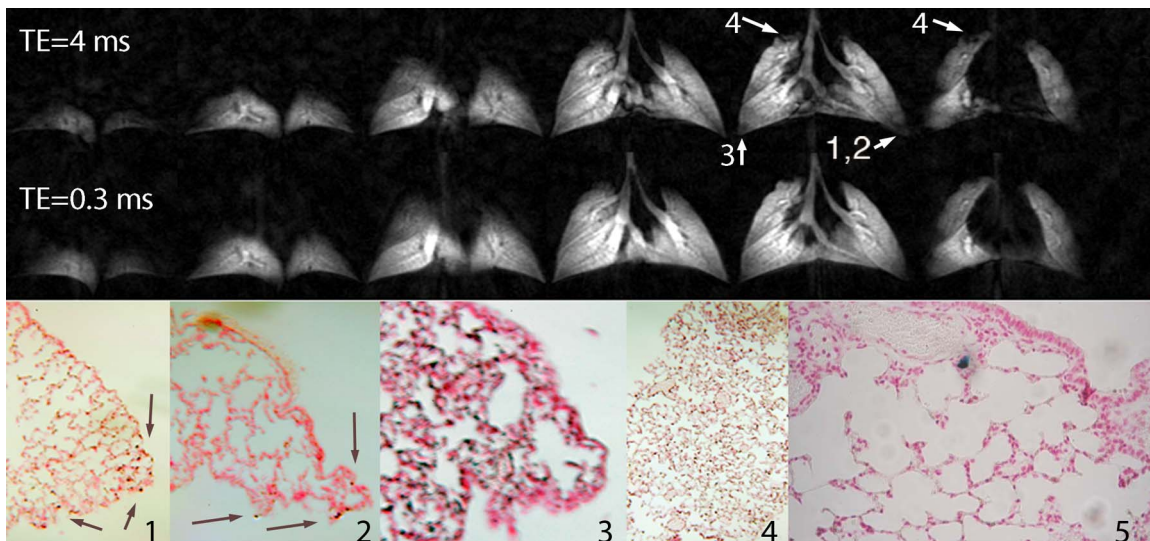


Figure 1: ^3He MRI in a mouse with lung cancer metastases after injection of LHRH-conjugated SPIONs. In the $\text{TE}=4$ ms image, numerous signal voids are visible and were subsequently examined by histology to reveal significant accumulation of iron (brown dots, brown arrows). Regions 3 and 4 were particularly full of iron deposits. Histology section #5 is from a control mouse without tumors, and shows no accumulation of SPION.

Conclusions: This pilot study offers encouragement that T_2^* -weighted ^3He MRI can be used to detect targeted SPION accumulation in lung metastases. A significant challenge remains to distinguish the signal dropout caused by SPIONs vs. susceptibility defects from nearby blood vessels. However, with continued optimization of image acquisition parameters, more sophisticated image analysis, and examination of more animals, the prospects are bright for this novel method to detect and monitor early metastatic lung disease.

References: 1) C. Leuschner, Breast Cancer Res. Treat. 99, 163 (2006). 2) X. J. Chen, Magn. Reson. Med. 42, 729 (1999).

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