MRI of Human Lung Cancer in Animal Models

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Introduction:

Lung cancer is the leading cause of cancer death worldwide. Survival rates are considerably more favorable when an early diagnosis is made, especially in cases of non-small cell lung carcinoma (NSCLC), which encompasses 80% of all lung cancers (1). The application of MRI for lung cancer diagnosis and monitoring is currently limited, mainly due to motion problems and limited time and spatial resolution, and most patients are diagnosed by computed tomography (CT) scans that involve ionized radiation, and invasive procedures. The purpose of this study is to develop advanced MRI methods for detection and characterization of lung cancer.

Methods:

Animal Models: We studied two types of animal models of human lung cancer:

1. Orthotopic NCI-H460 non small cell lung carcinoma (NSCLC) tumors implanted in the lungs of female nude rats of strain CR:NIH-RNU. Cells were injected intrabronchially into the right main bronchus, as previously described (2).
2. Metastases of MDA-MB-231 human breast cancer in the lungs of female SCID mice of strain C.B-17/ Ztm-*scid*. Cells were injected into the mammary fat pad, as previously described (3).

MRI: MR images were recorded with a 4.7T Biospec spectrometer (Bruker, Germany). The MRI protocol included coronal multislice spin echo T2-weighted imaging with TE=15/30/45 msec (3 echoes) and TR=2362 ms, and a 256x128 matrix. FOV was 6x6 cm^2 or 4.5x4.5 cm^2, and slice thickness 2.3mm or 1.5mm for rats and mice respectively. When it was feasible, the T2-weighted images were acquired with respiratory gating and cardiac triggering. Following that, a dynamic 3D gradient echo T1-weighted imaging sequence was applied, before and for 20 minutes after a bolus injection of GdDTPA into the tail vein. This sequence included TE/TR=2.1/25 msec, a flip angle of 60º, and a 256x128x16 matrix, resulting in 51sec acquisition time. Rats were recorded with a FOV of 6x6x4 cm^3 and mice with a 4.5x4.5x3.2 cm^3 FOV. Two algorithms were applied to analyze the time evolution of contrast enhancement at pixel resolution: (a) an algorithm that applies a nonlinear curve-fitting to analyze time-dependent, contrast enhanced intensities to yield separate k_{in} , k_{ep}, and EVF images, based on the physiological model of Tofts and Kermode (4). (b) An algorithm that assigns each pixel a color intensity and a color hue based on the wash-in and wash-out patterns in 3 pre-selected time points (5).

Histology: At the end of the experiment the lungs were removed and coronal slices were studied after staining with hematoxylin-eosin.

Results:

Orthotopic NSCLC tumors in nude rats: Tumors developed in the right lungs of the rats, either in the caudal lobe or in the accessory lobe. The tumors were followed for up to 25 days after implantation, reaching a maximal volume of 2.18 cm^3. In the T2-weighted images the distinction between the tumor mass and the healthy air-filled lung parenchyma was immediate due to the obvious signal intensity differences, and the tumors looked heterogeneous (Fig. 1). Analysis of the contrast-enhanced images showed that in most tumor regions, signal enhancement pattern did not fit the physiological model of Tofts (4). The wash-in and wash-out patterns differed between tumors and between areas in the same tumor. Most tumor areas showed very fast wash-in and fast wash-out within 1.5 minutes from contrast material administration, similar to the arterial input function measured in the heart and large vessels. However, in some inner tumor regions there was no contrast enhancement, not even 20 minutes after contrast administration, suggesting the presence of high interstitial pressure (Fig. 2).

Lung metastases of breast cancer in SCID mice: Metastases of breast carcinoma developed in the lungs within 5 weeks. Both the MR images and the histological sections showed a milliary spread of the cancer cells throuout both lungs, leaving scattered small "islets" of healthy air-filled lung parenchyma between them (Fig.3). In this model, analysis of the contrast material dynamics did not show any typical behaviour due to vast differences on a pixel scale.

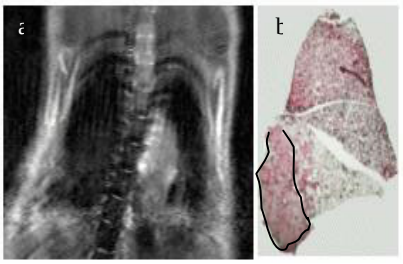

Fig. 1 a) T2-weighted image of the rat lungs showing a NSCLC tumor mass in the right lung, 21 days after tumor implantation. b) The equivalent histological slice of the right lung; the tumor is

Conclusions:

This study presents two different animal models of human lung cancer and the feasibility of detecting their distribution in the lungs by T2-weighted imaging and contrast-enhanced MRI. For the NSCLC tumors, the fast wash-in and wash-out of the contrast material may suggest both very high blood flow due to rich vascularization and high vascular permeability. Faster sequences should be applied in order to investigate the exact pattern of contrast-enhancement in these tumors. For the breast cancer metastases in the lungs, the unique spreading pattern of the cancerous tissue is well demonstrated in the T2-weighted MR images, but requires the development of new analysis tools for studying the contrast-enhancement patterns.

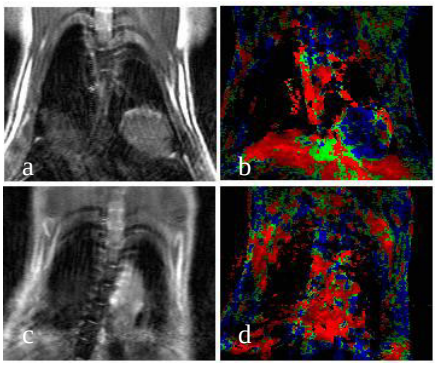

Fig. 2. wash-in and wash-out maps of two different NSCLC tumors in rats (b,d) shown next to the equivalent T2-images (a,c). The red pixels represent fast wash-in and wash-out within 1.55min from contrast administration, which is the prominent behavior in the tumor in d. Note the black inner region in the tumor in b, representing a non-enhanced region.

References:

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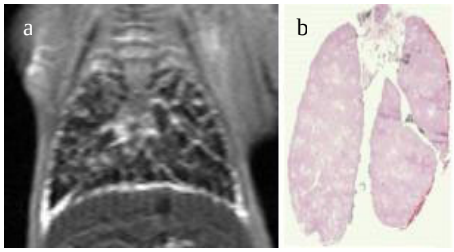

Fig. 3 a) T2-weighted image of the SCID lungs showing a high signal throughout the lungs due to metastatic spread, 36 days after cancer implantation. b) The equivalent histological slice, showing mostly cancer cells, with brighter 'islets' were lung parenchyma remained normal.