Magnetization Transfer Rate and Amide Proton Transfer of dissected axillary lymph nodes of breast cancer patients at 7T MRI

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Introduction: Axillary lymph node status is one of the most important factors determining prognosis in breast cancer patients. Assessment of nodal status currently requires surgical resection. The development of a non-invasive procedure that can spare patients unnecessary surgery would be an important improvement. Morphological MRI criteria alone are not sufficient to discriminate benign from metastatic nodes. Recent studies have shown the potential of saturation prepared methods for discriminating benign from malignant tissues(1,2). This study explores the possibility of utilizing high resolution magnetization transfer (MT) and chemical exchange saturation transfer (CEST) measurements on a clinical 7T MR system as a tool to discriminate healthy from metastatic dissected lymph nodes of breast cancer patients. Each MR image was meticulously correlated to microscopic pathology images on a node to node basis. This allowed for selection of regions of interest within a node and avoiding inclusion non-nodal tissue.

Materials & Methods: 27 consecutive female patients about to undergo surgical nodal staging for the work-up of a histologically proven breast cancer were included. Following the operation, the nodes were fixated in formaldehyde for 24 hours. During scanning the nodes were submersed in fomblin to provide susceptibility matching. All scans were performed on a 7T MRI scanner (Philips Health Care, Cleveland, USA), using a T/R head coil with a 16 channel receive coil (Nova Medical Systems). The scan protocol included a 3D T1 weighted (T1w) fat suppressed fast field echo (gradient echo, fsFFE) with a 0.18mm isotropic resolution for anatomic correlation and a MT-weighted FFE [TR/TE 8.4/4.0ms, flip angle 15 º, FOV 24x110x110mm, resolution 1mm isotropic, MT saturation pulse flip angle/ maximum BW 750 º/400Hz]. The frequency of the saturation pulse was varied from -2800 to 2800 Hz with respect to the water frequency, in steps of 200 Hz, 30 dynamic scans. Pathological processing and examination were performed by an experienced pathologist. To maintain an accurate correlation of MRI to pathology, marks using black dye and digital pictures were used to track the MRI slice to the microscopic pathology slides. The high resolution 3D T1w scan (voxel volume 5.8 nanoliter) allowed reconstruction along arbitrary planes. This enabled accurate matching of the MR images to the sectioning plane of the microscopic pathology slides and subsequently to the MT data set. The MT data set was corrected for field inhomogeneities using the WASSR method(3). Maps of the Magnetization Transfer Rate (MTR, the signal change determined at 2800Hz), and the Amide Proton Transfer (APT, the signal change asymmetry determined at +/- 1042 Hz) were calculated for healthy and metastatic nodes. Using the microscopy slides for reference, ROI were drawn to select voxels that encompassed only lymph node tissue. Results were analyzed for statistical significant differences by means of a Mann Whitney test.

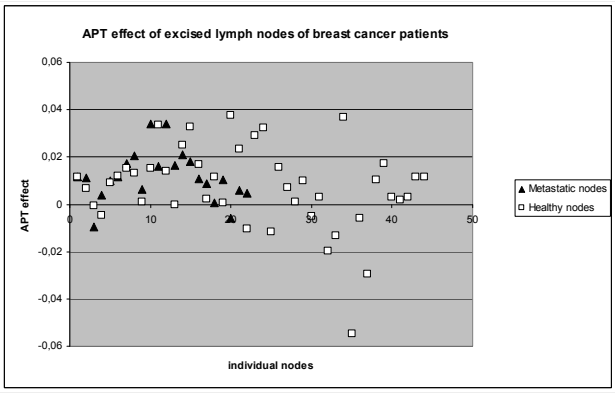

Figure 1. Amide proton Transfer (APT) of all metastatic and healthy nodes. There is a large overlap of the measured APT values between both groups, resulting in non significant differences.

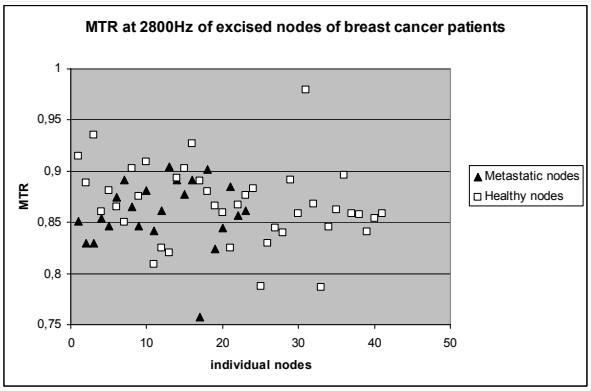

Figure 2. Magnetization Transfer Rate (MTR) at 2800Hz of all metastatic and healthy nodes. The measured values are similar for both groups.

Results: Of 27 patients 66 nodes were excised. 24 nodes (36%) of 14 patients contained metastases. Of the 24 nodes with metastases 4 (17%) contained micro metastases (tumor depositions <0.2mm). All nodes were succesfully correlated to pathology. The mean APT difference was 0.0073 (±0.02 SD) for healthy nodes and 0.012 (±0.01 SD) for metastatic nodes. This was not statistically significantly different (fig. 1). The mean MTR at 2800Hz was similar for both groups; 0.87 (±0.038 SD) for healthy nodes and 0.86 (±0.03 SD) for metastatic nodes. This was not statistically significantly different (fig. 2). An example of a node; histopathology slide correlated to high resolution MR image and MTR map, is shown in figure 3.

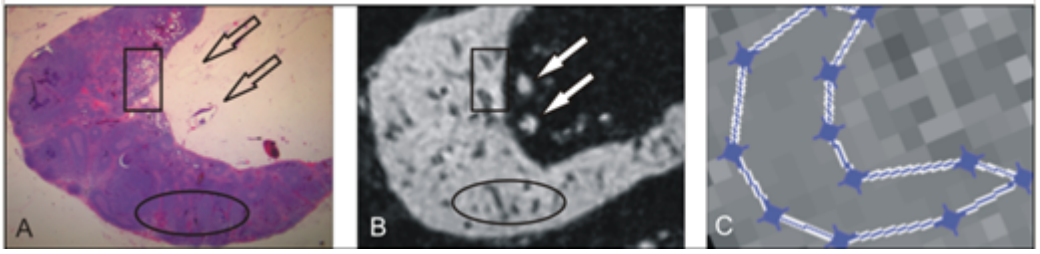

Figure 3. Healthy lymph node depicted on (A) H&E stained histopathology slide, (B) corresponding 3D T1w FFE scan and (C) MTR MAP. Efferent lymph vessels (arrows), fatty areas (square) which are dark on the fat suppressed MRI sequence and small intranodal capillaries (oval) which are dark on MRI due to the susceptibility effect of the hemoglobin content are depicted in figure A and B.

Discussion: This research method was designed to assess the feasibility of in vivo discrimination between malignant and normal lymph nodes using a MT sequence on a clinical 7T MR scanner. Prior in vivo studies have shown promising results for saturation prepared methods for discriminating benign from malignant tissues, but using lower resolution and therefore less precise comparison to pathology(2). In this study, MR images were meticulously correlated with pathology slides, facilitating an accurate distinction of fat, metastases and normal lymphatic tissue. Additionally, the MT voxel size was very small (1mm³). Therefore hypothetically small local effects could be detected. The results however show no significant changes in quantitative values for both APT and MTR in normal lymph node tissue as compared to metastatic lymph node tissue. For APT this effect could have been expected as the pH of excised tissue is lower than in in vivo tissues and APT is known to be sensitive to pH. Nevertheless in this ex vivo study also no significant changes or differences were shown regarding MTR. It remains unclear whether this is the result of crosslinking of the tissue during fixation or whether the differences in cellular density in these metastases are too small to detect.

1) J.Zhou et al., Practical data acquisition method for human brain tumor amide proton transfer (APT) imaging. Magn Reson Med. 2008 Oct;60(4):842-9.
2) S.Mastsushima et al., Equivalent cross-relaxation rate imaging of axillary lymph nodes in breast cancer. J Magn Reson Imaging. 2008 Jun;27(6):1278-83.
3) Zhibo Wen et al., MR imaging of high-grade brain tumors using endogenous protein and peptide-based contrast. NeuroImage. 2010 Jun;51(2): 616-622.