Gadofosveset as a negative contrast agent for detecting metastatic axillary lymph nodes in breast cancer patients on diffusion and T2* weighted images - a proof of principle

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Introduction: Axillary lymph node status is the most important factor determining prognosis in breast cancer patients. Assessment of nodal status currently requires surgical resection. First a sentinel lymph node biopsy (SLNB) is performed, which, if positive for metastasis, is followed by a complete axillary lymph node dissection. These procedures are associated with morbidity and, in retrospect, are often performed unnecessarily. The development of a noninvasive procedure that can spare patients unnecessary surgery would be an important improvement. We have initiated a trial comparing non-invasive gadofosveset enhanced 3T imaging-based staging , to surgical axillary staging. The hypothesis is that gadofosveset, a blood–pool agent with a high albumin binding, will be transported with albumin-rich lymph and - like USPIOs - accumulate in a higher concentration in healthy than in metastatic lymph nodes. As a result the transverse relaxation rate in healthy nodes would increase which would cause a negative contrast effect on diffusion-weighted (DWI) scans, selectively preserving the signal of metastatic lymph nodes. The performance of the in vivo 3T MRI is controlled by 7T ex vivo MRI of all surgical specimens, which is followed by a node-to-node matching of all imaged nodes with pathology [1]. This abstract describes the results of the retrospective 3T MRI characterization of axillary lymph nodes of breast cancer patients, with pathology as the gold standard.

Material and Methods: We included 16 consecutive patients about to undergo SLNB during the work-up of a histologically proven breast cancer with a diameter of at least 2cm, as determined on mammography and ultrasound. Four days prior to the operation the patients were scanned on a 3T MR (Philips Health Care, Cleveland, USA), in prone position with the arms above the head in order to achieve the most comparable position to the position during operation. Four phased array, receive only, coils were used (Philips Healthcare, Best, the Netherlands), positioned around both breasts and both armpits. The scan protocol consisted of a 3D T1 weighted turbo field echo (TFE) [TR/TE 5.1/2.3ms, flip angle 10º, FOV 201.6x400x300mm, resolution 0.9mm isotropic] before and after contrast; a 3D T2*-map, obtained from a multi-echo gradient echo sequence [TR/first TE/ΔTE 21/4.6/4.6ms, 4 echoes, flip angle 15º, FOV 99.9x400x300mm, slice thickness 0.9mm, in plane resolution 1mm] post contrast and a multi-slice STIR based DWI [TR/TI/TE 18223/240/47ms, FOV 201.6x400x300mm, slice thickness 3.6mm, in plane resolution 3.0mm, b-values 0, 100 and 500s/mm^2] before and after contrast. Gadofosveset (0,03 mmol/kg i.v.) was manually injected followed by a 10cc saline flush. On the ipsilateral side of the breast cancer an MRI marker grid was taped to the axilla. The grid was also drawn on the patient. This drawing was still visible during surgery. For all excised nodes, the anatomical level and the position of the node with respect to the drawn grid was noted. For each patient the location of all nodes was detailed on a hand-drawn map of the axilla. To aid in the node-to-node matching of in-vivo imaging and subsequent pathologic examination, the excised nodes were scanned at 7T prior to further processing[1]. Retrospectively the mean absolute T2* relaxation times and the post contrast signal intensity of the lesion to spinal cord ratio (LSR) were determined for all excised lymph nodes. The LSR was determined on high-pass thresholded axial b=500s/mm^2 scans using loose hand-drawn regions of interest. The threshold was set at 1.5 times the noise-level. Statistical evaluation was performed by means of logistic regression analyses according to the generalized estimating equations method, correcting for the fact that several lymph nodes were derived from the same patient.

Results: 3 patients were excluded from analysis because of severe motion-induced degradation of the DWI scans. 13 patients were analyzed from whom in total 35 lymph nodes were excised. 9 nodes, from 7 patients, contained metastases. 2 patients (8 nodes, of which one had a metastasis) did not receive a T2* weighted scan due to fatigue of the patient. Table 1 shows the mean post contrast signal intensity ratio (LSR) and the mean T2* relaxation times for all nodes. Metastatic nodes had a significantly longer T2* time and significantly higher LSR compared to non-metastatic nodes.

Table 1.	Healthy	Metastatic	Sign. (p<0.05)
SI ratio (LSR) Mean (±SD)%	37.6 (±36.2)	75.3 (±11.9)	0.001
T2* Mean (±SD)ms	26.7 (±7.8)	36.8 (±15.5)	0.029

Table 1. Mean Signal Intensity (Lesion to spinal cord ratio, LSR) and T2* relaxation times for all nodes

Discussion & Conclusion

Inclusion was limited to 16 patients with 35 analyzed nodes, and a prospective, per-patient MRI diagnosis of nodal status was not attempted in this study. As a proof of principle however, the in vivo results suggest metastatic nodes are selectively highlighted on gadofosveset-enhanced diffusion-weighted images, presumably because of a difference in transverse relaxation rate. Metastatic depots are hypothesized to interfere with gadofosveset accumulation, which would explain the shorter T2* of healthy nodes compared to the metastatic nodes, in vivo at 3T.

However we have also studied various groups of lymph nodes ex vivo at 7T[1, 2]: In autopsy-retrieved nodes of healthy patients we found 7T T2* relaxation times of 17ms. In nodes from the current group of breast cancer patients, excised after gadofosveset administration 4 days earlier, we found a mean 7T T2* time of 15 ms in the non-metastatic nodes[1] and of 19 ms in metastatic nodes.

The combined results suggest that metastatic nodes have a longer T2* relaxation time than non-metastatic nodes derived from healthy patients and than non-metastatic nodes derived from breast cancer patients. The non-metastatic nodes from breast cancer patients however also showed a shorter T2* time than the autopsy-derived healthy nodes from non-breast-cancer patients. Theoretically, apart from experimental variation, this difference could be at least in part explained by a T2-shortening effect of residual gadofosveset in the non-metastatic nodes from the breast cancer patients. After 4 days however only a minimal quantity of gadofosveset is expected to remain. Also, long-term conservation in the autopsy-derived healthy nodes is not expected to explain the slightly longer T2* relaxation time [3]. Gambarota et al. found longer T2 relaxation times in metastatic liver tissue as compared to normal liver tissue as well [4]. The difference in T2* may thus, tentatively, be explained by a synergistic effect of intrinsically longer T2* in metastatic nodes combined with an increased gadofosveset-induced T2* shortening in healthy nodes.

The exquisite CNR of DWI-based lymph node-depiction, in combination with the selective suppression of healthy nodes by gadofosveset, would make gadofosveset-enhanced DWI a one-stop nodal staging tool. First and foremost however, prospective validation of the per-patient diagnostic accuracy is required.
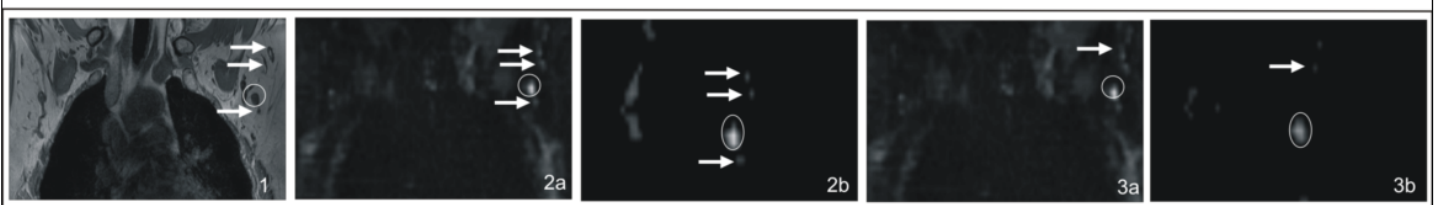

Figure 1: Coronal views of a patient showing a metastatic lymph node (circle) and 3 benign nodes (arrows). **Fig 1** 3D T1 FFE weighted scan **Fig 2** corresponding slice of the b=500 s/mm^2 scan as acquired (**2a**) and zoomed-in after high pass-thresholding (**2b**). **Fig 3.** corresponding slice of the post-contrast b=500 s/mm^2 scan as acquired (**3a**) and zoomed-in after high pass-thresholding (**3b**). The non-metastatic nodes have a lower signal intensity post-contrast than pre-contrast. The intensity of the metastatic node more or less remains unchanged.

References

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