T2 VALUES OF BREAST LYMPH NODES AT 1.5 T IN PATIENTS PRE AND POST SUBCUTANEOUS INJECTION OF SUPERPARAMAGNETIC IRON OXIDE - INITIAL RESULTS FROM A SENTINEL NODE NEGATIVE POPULATION

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Background. The introduction of the sentinel lymph node (SLN) biopsy has revolutionized axillary surgery and is now standard of care for early breast cancer although it still involves a surgical procedure with associated morbidity. Up to 70% of these patients do not have metastatic spread to the axilla after histological examination of the SLN (1). Pre-operative axillary ultrasound and biopsy can identify 37% patients with metastatic nodes, avoiding the need for an unnecessary SLN biopsy (2) but as a result, the remaining patients are less likely to have an involved SLN. Superparamagnetic iron oxide nanoparticles (SPIOs) have been investigated in a range of cancers as an imaging based method for the identification of involved nodes (3) In these studies the nanoparticles are usually administered by infusion and require pre and post imaging on different days, with normal nodes identified as those that show reduced signal intensity on T2(*)-weighted imaging due to the uptake of the iron oxide. However, preclinical work using a subcutaneous injection of SPIO has demonstrated significantly less reduction of T2 values in metastatic nodes compared to uninvolved nodes as soon as 2 hours post administration (4).

Sex: 10 Female, 1 Male
Mean age: 47.3 years (30-67)
Side: Right 36%, Left 64%
Histology: 44% Ductal
18% Lobular
18% Other
9% Microinvasion
Tumour size: 19 mm (0.5-39)
Needle localized: 36%
Neoadjuvant chemotherapy: 27%

Aim. The goal of this study was to measure changes in the T2 relaxation time of axillary lymph nodes associated with uptake of iron following subcutaneous SPIO injection in patients with early breast cancer.

Methods. Consecutive breast cancer patients attending for SLN biopsy were invited to undergo pre-operative MRI scanning of the axilla. All imaging was acquired on a 1.5 T Achieva MRI scanner (Philips, Best, Netherlands) using a pair of large loop coils (Flex-L) positioned on the affected side over the breast and under the axilla. After a T2 weighted morphological scan, T2 mapping (turbo spin echo, 8 equi-spaced TEs from 10 to 80 ms, TR = 2136 ms, 3 mm slices with an in-plane resolution of 1.4×1.4 mm) was performed. 2 mL of Endorem (Guerbet, Paris) was then injected subcutaneously into the circumareolar margin in the upper outer quadrant of the affected breast. T2 mapping was repeated around 10 minutes post injection and again at around 120 minutes if time allowed. Image data were imported into Osirix (v3.5, 64-Bit) for analysis. Regions of interest (ROIs) were defined on the T2-weighted images (acquired as part of the T2 mapping sequence) around the axillary lymph nodes (excluding hilar fat) as identified by a consultant MRI radiologist with the assistance of the pre-injection morphological images. The mean T2 value was noted for each node ROI and time point. Control ROIs were also defined on areas of muscle away from the injection and lymph node sites. Comparison of T2 values at different time points was performed using the Wilcoxon signed-rank test in SPSS Statistics 18 (SPSS Inc, Chicago). Following imaging, SLN biopsy was performed using the preferred combined technique of blue dye and Technetium^{99m}.

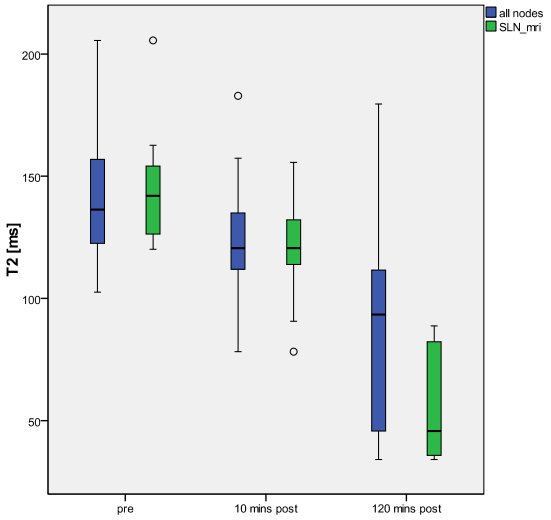

Figure 1. T2 values pre/post iron oxide administration in all identified lymph nodes (blue) and designated SLN_{MRI} (green)

Results. 11 patients underwent pre-operative MRI scanning. Axillary lymph nodes were identified in all patients on the pre-contrast MRI, totaling 40 nodes. In all patients the node demonstrating the greatest reduction in T2 value after 2 hours was designated the SLN_{MRI}. The mean (±standard deviation) reduction in T2 value for the SLN_{MRI} at 120 mins post SPIO administration was 62.9±13.8%. Fig. 1 shows the distribution of measured T2 values at each time point for all nodes and the designated SLN_{MRI} for all patients, with changes in T2 shown at 10 and 120 mins post SPIO administration shown in fig. 2. At biopsy 29 SLNs were excised using the combined technique of blue dye and Technetium^{99m}, none of which contained metastases following histological assessment. Differences in T2 values between pre-injection and both 10 minute and 120 minute post-injection were significant in both cases ($p<0.001$). Three patients had lymph nodes identified on the morphological MRI scan that failed to demonstrate a reduction in their mean T2 value. Assessment of the nodes that were excised in these patients using an in house developed magnetometer to detect the presence of iron oxide nanoparticles (5) and subsequent histological assessment confirmed that they contained iron.

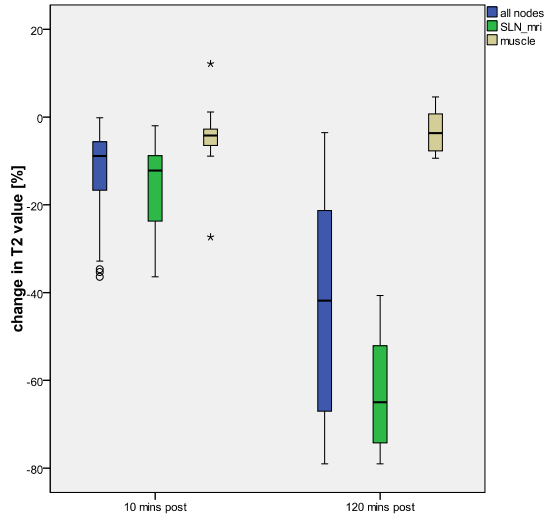

Figure 2. Changes in T2 values of all identified lymph nodes (blue) designated SLN_{MRI} (green) and muscle controls (c) 10 mins and 120 mins post iron oxide administration.

Discussion. To our knowledge these are the first clinical measurements of T2 values in axillary lymph nodes following subcutaneous injection of SPIOs. The difference between T2 changes in the SLN_{MRI} and all identified lymph nodes demonstrates the variation of uptake in the nodes at these time points. Further studies are required to better understand the pharmacokinetics of SPIOs following subcutaneous administration. Limitations of this work include the lack of a definitive mapping between node identified *in vivo* and subsequent histopathology. This may explain the apparent discrepancy between the unchanged T2 values in some nodes, for patients in whom the excised SLNs were shown to contain Endorem, since at least 11 nodes identified on MRI were not subsequently excised. Other reasons for this include the delay between imaging and surgery which was on average 42 minutes (range 29-67), allowing additional time for the transit of nanoparticles into these nodes, and the possibility that the nodes with unchanged T2 values contained metastases inhibiting uptake of the nanoparticle and subsequently the uptake of the conventional blue dye and radioactive tracers in SLN biopsy **(1)**. In summary this work demonstrates significantly reduced T2 values associated with uptake of SPIOs in apparently uninvolved lymph nodes within 2 hours of subcutaneous injection in patients. Further work will investigate corresponding dynamic measurements of T2 values in metastatic axillary nodes.

References. [1} Veronesi U, *et al*. J Natl Cancer Inst.1999.17;91(4):268-72. [2] Swinson C, *et al*. Eur J Surg Oncol.2009;35(11):1152-7. [3] Michel SC *et al*. Radiol.2002;225(2):527-36. [4] Weissleder R, *et al*. Radiol.1989;171(3):835-9. [5] Joshi T, *et al*. Eur J Surg Oncol.2007(33):1135.