‘Real time’ identification of the sentinel lymph node in breast cancer using dynamic MRI sequences following subcutaneous injection with superparamagnetic nanoparticles

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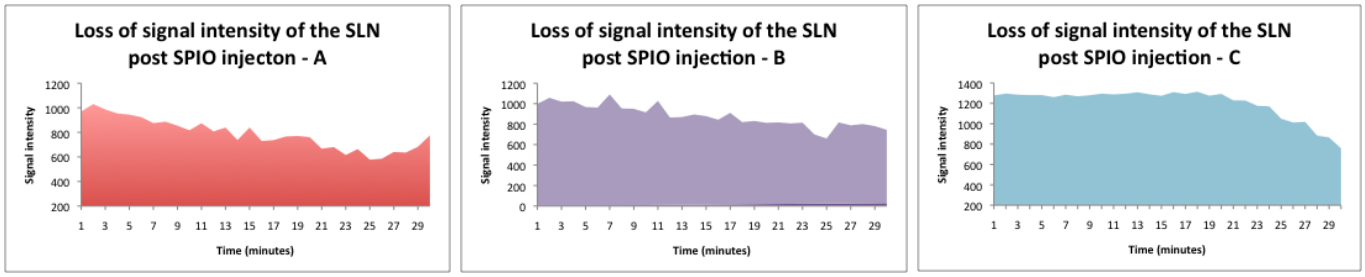
Background. We have developed, patented and CE marked a sensitive magnetometer (SentiMag, Endomagnetics, UK) for the intraoperative identification of the sentinel lymph node (SLN) in early breast cancer following subcutaneous administration of super-paramagnetic iron-oxide nanoparticles (SPIOs) (1). The current combined technique using blue dye and radioisotope (Technetium^{99m}) has several drawbacks to include, tattooing of the skin, anaphylaxis, obscuring the surgical field intra-operatively and legislation for the use and disposal of radioactive material. Importantly the combined technique carries at least a 5% false negative rate. To optimize the technique of intraoperative identification of the SLN using SPIOs and a hand-held magnetometer, a better understanding of the pharmacokinetics of SPIOs following subcutaneous injection is required.

Aim. To demonstrate, using dynamic magnetic resonance imaging (MRI) sequences, the transport of SPIOs to the SLN with subsequent loss of signal intensity of the SLN following subcutaneous injection in patients with early breast cancer.

Methods. Patients undergoing SLN biopsy as part of the surgical management of early breast cancer were invited to undergo pre-operative MRI scanning of the axilla. All images were acquired on a 1.5 T Achieva MRI scanner (Philips, Best, Netherlands) using a pair of large loop coils (Flex-L) placed anterior and posterior to the ipsilateral axilla. Following a T2 weighted morphological scan, the patient was injected with 2ml of SPIO subcutaneously into the circumareolar margin in the upper outer quadrant of the affected breast. Immediately a slightly T2*-weighted dynamic scan was performed (gradient echo, TE = 1.53 ms, TR = 2.9 ms, flip angle = 7 degrees, 3mm slice). In addition to the dynamic scan a T2 mapping sequence was performed at 10 minutes and 120 minutes post injection (turbo spin echo, 8 equi-spaced TEs from 10 to 80 ms, TR = 2136 ms, 3mm slices with an in plane resolution of 1.4x1.4mm). These images allow for a more detailed identification of the lymph nodes enabling transposition onto the dynamic sequences. Image analysis was undertaken using Osirix (v3.8, 64-bit). Two consultant radiologists experienced at reading breast and axillary MRI who were blinded to the results evaluated the images. Region of interest (ROIs) were drawn around the SLNs (excluding hilar fat) and ROI enhancement curves created.

Results. Eleven patients underwent SPIO injection and pre-operative axillary scanning. Of these, 10 were female and 1 was male, with a mean age of 47.3 years (range 30-67 years). A total of 27% patients had undergone neoadjuvant chemotherapy to downsize the primary tumour. Following excision and histological examination none of the SLNs were found to contain metastases. 5 patients (45%) were seen to have signal intensity loss on the dynamic images when viewed in real time.

In patients where signal intensity loss was demonstrated in the SLN, two distinct patterns were seen, gradual decline (graphs A&B) and sudden drop off (graph C). One patient demonstrates gradual signal intensity loss with subsequent recovery of signal intensity 26 minutes post injection.



Discussion. ‘Real time’ visualisation of the SLN is feasible following subcutaneous SPIO injection into the affected breast. The pattern of loss of signal intensity is variable, and in this series was only demonstrated in 45% of patients. Patient A may demonstrate the beginning of a washout phase associated with recovery of the SLN signal intensity. This may be associated with the loss of signal in higher nodes suggesting continued transit of SPIO to echelon nodes, however in the absence of prolonged dynamic scanning, this remains a theoretical explanation. Information from T2 scanning acquired 120 minutes post injection demonstrates continued loss of signal intensity at the first SLN as identified on the dynamic sequences indicating retention of SPIO in the SLN over a prolonged period. In addition, all 11 patients (100%) showed loss of signal intensity of the SLN on the delayed T2 mapping scans suggesting the dynamic scans had not run for a sufficient length of time to capture the transport in real time in all patients.

This has important implications for the intraoperative use of a hand held magnetometer, which relies on the reliable and predictable transit of SPIO from the site of injection to the SLN where it should remain. Difficulty arises to optimise the delay between injection and intra-operative identification since there is vast variability between cases with no definable factors to predict speed and pattern of SPIO transit. Further delayed images up to 24 hours may clarify whether the SPIO remains in the SLN in the medium term or whether it transits to echelon nodes.

1. Joshi T, *et al.* 2007(33):1135.