In Vivo evaluation of 68Ga-labeled Iron Oxide Nanoparticles as a PET/MR Imaging Probe

Renata Madru[1], Thuy Tran[2], Adnan Bibic[3], Sarah Fredriksson[4], Freddy Stahlberg[5], Linda Knutsson[5], and Sven-Erik Strand[5]

[1]Medical Radiation Physics, Lunds University, Lund, Sweden, [2]Lund University BioImaging Centrum, Lund University, Lund, Skane, Sweden, [3]Lund University BioImaging Centrum, Lund University, Lund, Sweden, [4]Genovis AB, Lund, Sweden, [5]Medical Radiation Physics, Lund University, Lund, Sweden

Purpose: Breast cancer carcinomas and malignant melanoma spread through the lymphatic system. The sentinel lymph node (SLN) is defined as the first node receiving lymphatic drainage from the primary tumor site and the first node to which metastatic cancer cells are likely to anchor [1]. Therefore, identification of the SLN and differentiation between normal and metastatic nodes are of major importance for staging and choice of therapy. The current SLN identification-technique relies on intradermal injection of ^{99m}Tc-labeled colloids and blue dye to intra-operatively identify the SLN followed by histopathological examination. However, this technique is limited by the non-specificity of the tracers. Radiolabeled superparamagnetic iron oxide nanoparticles (SPIONs) can, however, be used as alternative tracer for SLN mapping [2] and may also differentiate between negative and positive nodes *in vivo* [3] **The aim** of this study was therefore to develop a specific probe based on ^{68}Ga-labeled SPIONs for future PET/MR imaging of the SLN. Such a probe may differentiate between normal and metastatic SLN nodes pre-operatively *in vivo* and also guide the surgeon to find the SLN intra-operatively.

Methods: ***Labeling***: SPIONs were radiolabeled with ^{68}Ga ($T_{1/2}$=67.7 min, β+=89%) as follows. A fraction of 0.4 mL of ^{68}Ga (~50 MBq) eluted from a ^{68}Ga/^{68}Ge-generator (IDB Holland) was added to a vial containing ammonium acetate (38 mg, final pH 5.5). SPIONs (40 µL, 0.13 mg Fe) in physiological saline was mixed with 40 µL ammonium acetate buffer (0.2 M, pH 5.5) and added to the vial containing the ^{68}Ga. Samples were taken after 5, 10, 15, and 25 min and analyzed for labeling efficiency by instant thin layer chromatography. Colloidal stability studies of the ^{68}Ga-SPIONs were performed in ammonium acetate buffer (pH 5.5 and 7) and human serum up to four ^{68}Ga half-lives. ***Animal studies***: An amount of 0.07-0.1 mL (~5-10 MBq) of ^{68}Ga –SPIONs was subcutaneously injected in the dorsal side of the right hind paw of 6 normal Wistar rats. The animals were imaged with positron emission tomography/computer tomography (PET/CT, Bioscan) 0-3 h post injection (p.i.), dynamic scan and a 9.4T MR system (Agilent) at 3 h p.i. and 24 h p.i. A biodistribution study was performed by dissecting and measuring the radioactivity in lymph nodes, kidneys, spleen, liver and the injection site.

Results: The labeling efficiency of SPIONs with ^{68}Ga was found to be over 95 % within 5 min and 98 % after 10-15 min.^{68}Ga-SPIONs were stable at pH 5 and pH 7 in ammonium acetate buffer and in human serum. The PET and MR images clearly showed the SLN (Figure 1). The highly sensitive, quantitative PET images can easily identify the SLN while high resolution anatomical MR images are required for the characterization of SLN. Normal nodes containing ^{68}Ga –SPIONs are dark in MR, PD weighted gradient echo (GRE) images, which was found optimal for SLN imaging. The mean uptake of ^{68}Ga-SPIONs after 3 h p.i. was 225 %ID/g in SLN (popliteal node), 53 %ID/g in the inguinal node, 0.07 % ID/g in kidneys, 0.1 % ID/g in the spleen and 0.3 % ID/g in the liver.

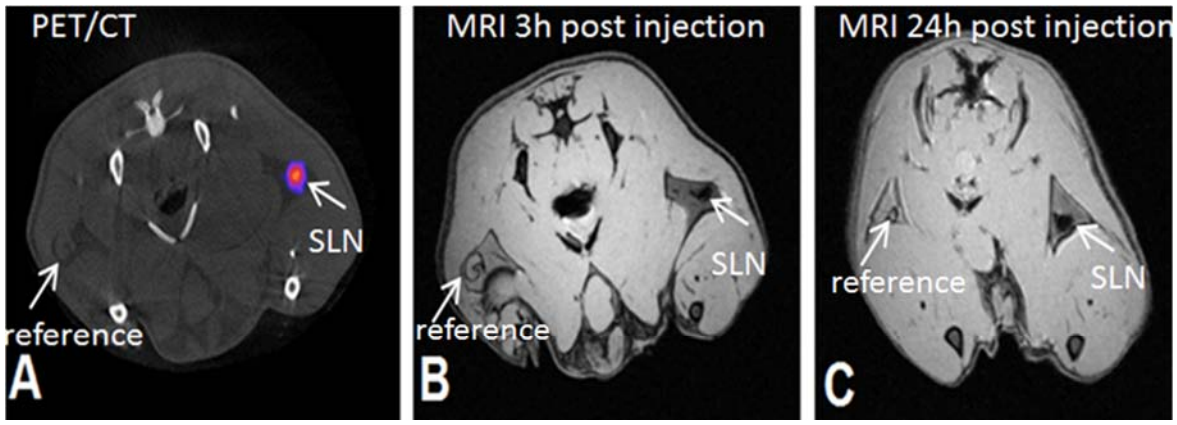

Figure 1 Visualization of SLN using ^{68}Ga-SPIONs A) PET/CT image 3 h post injection (rat1), B) MRI 3h post injection (rat1) and C) MRI 24h post injection (rat2). MR imaging parameters: PDw GRE, TR 95 ms, TE 2.53 ms, Average 4, slice thickness 1 mm, Matrix 512 x 512 x

Conclusion: In this study a fast, one step labeling method of SPIONs with generator-produced ^{68}Ga for combined PET/MR imaging of SLN was demonstrated. The accumulation of ^{68}Ga-SPIONs in the SLN after subcutaneous injection in animals, verified by PET and MRI, is encouraging for application in early breast cancer and malignant melanoma.

References:

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