Optical and acoustic characterisation of multimodal contrast agents for colorectal cancer lymph node detection

Georgia Adam[1], Vladimir Denisov[2], Zahra Rattray[3], Adrian Thomson[4], Susan Moug[5], Susan Farrington[6], Carmel Moran[4], Helen Mulvana[1]

1. Department of Biomedical Engineering, University of Strathclyde, Glasgow UK
2. Biomedical Engineering, Department of Clinical Sciences Lund, Lund University, Lund, Sweden
3. SIPBS
4. Centre for Cardiovascular Science, University of Edinburgh, UK
5. Department of Surgery, Royal Alexandra Hospital, UK
6. Cancer Research UK Edinburgh Centre, Institute of Genetics and Cancer, University of Edinburgh, UK

Introduction [600]

Localisation and characterisation of lymph nodes in colorectal cancer (CRC) is integral to staging, resection surgery and patient outcomes [1]. However, appropriate imaging technologies capable of providing detailed information to the oncologist to inform these processes remain severely limited. We are investigating magnetic ultrasound contrast-agents, delivered either as gas microbubbles or phase-change nanodroplets each with streptavidin-biotinylated magnetic nanoparticles, for combined contrast-enhanced and magneto-motive ultrasound imaging CE-MMUS and more sensitive disease detection.

Methods [800]

Magnetic-microbubbles were prepared from Target-Ready Micromarker (Fujifilm, Visualsonics) and biotinylated magnetic nanoparticles [2] and condensed to produce phase-change magnetic-nanoparticles [3]. Contrast agents were sized, concentration and magnetic loading measured using dynamic light scattering and nanoparticle tracking analysis (Zetasizer & Nanosight NS300, Malvern Panalytical) to inform acoustic drive conditions required to activate phase-change, returning them to microbubbles and later confirmed using single-element excitation transducers (frequencies: 1, 3.5, 5 MHz) and a passive cavitation detection (Precision Acoustics). Phantoms mimicking acoustic and mechanical properties of lymph node tissue were fabricated using polyacrylamide [4] incorporating each contrast agent.

Results [1000]

Contrast enhanced ultrasound imaging was performed (18MHz, Vevo 3100, Fujifilm VisualSonics) in a wild type mouse to assess lymphatic drainage of magnetic microbubbles after bolus injection, with peak enhancement occurring at 3.7s. An externally applied magnetic field (solenoid, in-house fabrication; 4 & 20 Hz, 1.3T) was used to produce preliminary MMUS data demonstrating proof of concept of each formulation. Data were also used to inform a finite-element model to assess magneto-mechanical interactions of a magnetic microbubble with an elastic solid [5]. The estimated relationship between tissue displacement and microbubble / nanodroplet size was compared against formulation size distribution and predictions relating to tissue displacement were validated in tissue phantoms. Finally, tissue displacements generated and recovered via MMUS in our pre-clinical model for each formulations (magnetic microbubbles, magnetic nanodroplets) were investigated.

Conclusions [450]

Multimodal magnetic contrast agents are easily fabricated from commercial formulations to support CE-MMUS. Phase-change agents are readily returned to microbubble-state once in a region of interest. We previously demonstrated perfusion dynamics can indicate lymph node metastatic involvement [6]. Smaller diameter agents, optimised for lymph node microvessel drainage may improve our technique sensitivity and preserve full utility in CE-MMUS.

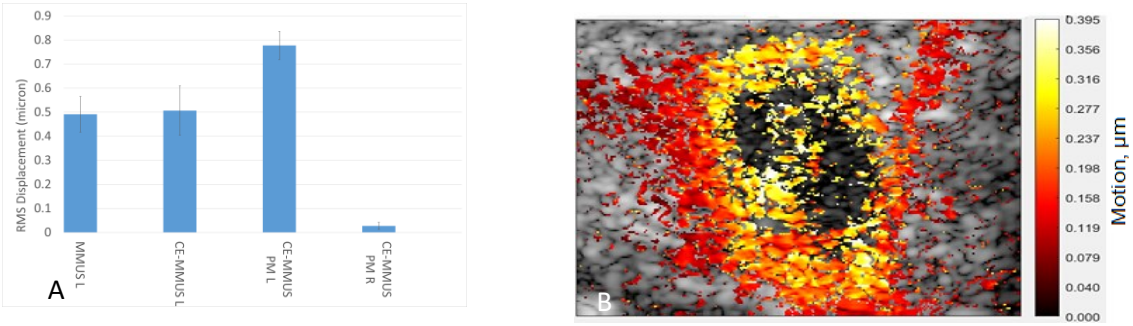

Figure 1. (a) The root mean square tissue displacement recorded in the left (magnetic nanoparticle injected) inguinal lymph node and right (control) inguinal lymph node of our colorectal cancer mouse model under varying magneto-motive conditions (20Hz): MMUS - magnetic nanoparticles alone, CE-MMUS – magnetic-microbubbles, CE-MMUS PM L – magnetic-microbubbles, tissue displacement recorded *post mortem*, CE-MMUS PM R – tissue displacement recorded in the (right) control hind limb *post mortem.* (b) Example magneto-motive ultrasound image showing tissue displacement with sub-micron amplitude range as overlay on a B-mode image when magnetic nanoparticles are used alone.

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