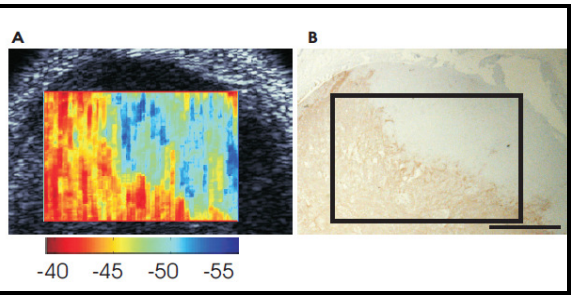
Registration of magnetic resonance, reconstructed 3D ultrasound imaging and whole–mount breast pathology for therapy assessment of breast cancer

Rationale: Currently, the early assessment of tumor response to cancer therapy with the available routine imaging modalities is limited. Quantitative ultrasound methods (QUS) using frequency dependent information of raw radio-frequency data are capable of characterizing cell death following cancer therapies in mouse models (1), ***Fig 1***. These methods are developed in clinical settings to assess therapy response on patients with locally advanced breast cancer following neoadjuvant chemotherapy (2). The aim of this project is to provide a base platform for developing QUS methods for therapy assessment in breast, by establishing procedures of registration between contrast enhanced MRI (DCE-MRI) used to identify the residual tumor, histology as the ground truth representation of the tumor, ultrasound (US) imaging and spatial maps created from QUS estimates.

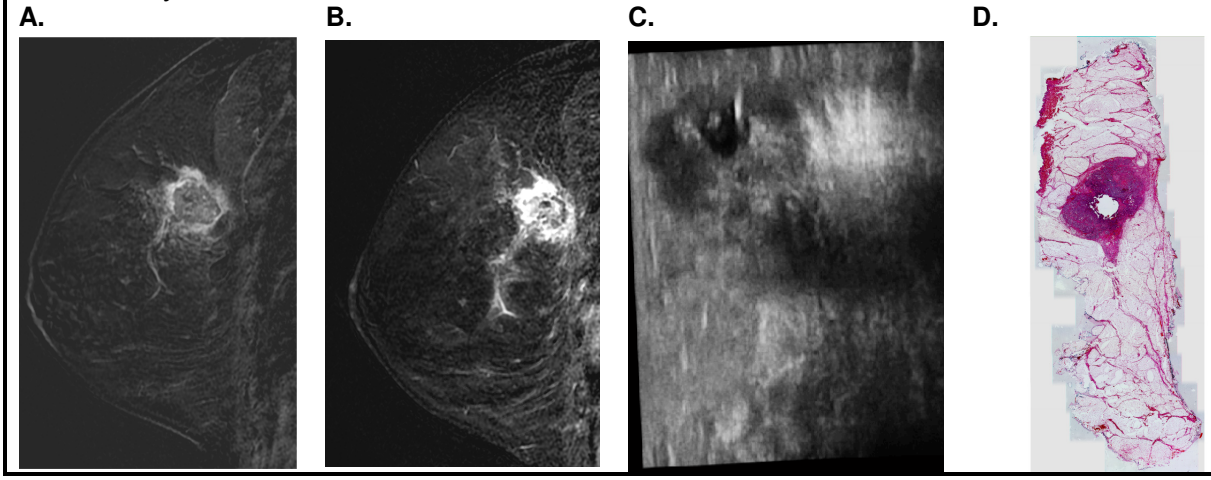
Fig 1. Imaging of cell death in a mouse model treated to 4 Gy and scanned 24 h after treatment administration. (A) Spatial maps created from QUS estimates superimposed on the ultrasound image; (B) TUNEL stained histological image indicating an area of cell death, the brown coloured area that corresponds to the higher QUS estimates.



In the example from ***Fig 2, A-B***, DCE-MR images were collected before and three months after neo-adjuvant chemotherapy treatment with no significant change in the size and appearance of the tumor following the treatment. For this type of patient, a reliable measure of tumor response early during the course of therapy would allow the treatment to be adapted to tumor aggressiveness earlier during the course of therapy with the benefit of sparing these patients from unnecessary side effects.

Ultrasound data (5-14 MHz) were collected using a freehand 2D US probe with a tracking tool affixed to the probe. The coordinates of the tracking tool were used to reconstruct 3D US volumes, ***Fig 2, C***. Following surgery, the mastectomy samples were whole-mounted and the pathology slices stained with hematoxylin and eosin were digitized and rigidly reconstructed in a 3D volume, ***Fig 2, D***.

Fig2. (A) DCE-MR image of the left breast before the treatment and (B) three months after treatment indicating no significant change in the size and appearance of the tumor. (C) Corresponding section trough the 3D reconstructed US volume. (D) Corresponding breast mastectomy slide.



All image data sets were rigidly registered and the tumor was contoured on each imaging data set and on the histological images. Each set of contours was converted to a volumetric mesh, ***Fig 3.*** The differences related to the tumor representation in DCE-MRI, US imaging and pathology are presented in ***Table 1***.

Fig 3. Volumetric mesh of the breast and residual tumor, blue mesh, as delineated on DCE-MRI. The red mesh is the representation of the tumor delineated on the histological slides. The green mesh represents the tumor as delineated on US images.

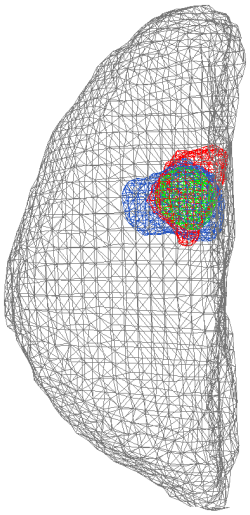


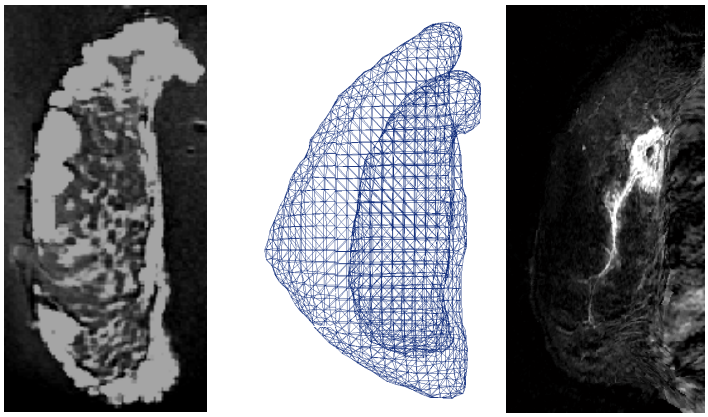
Table 1.

Imaging modality	Vol (cc)	COG (cm)	Dice coefficient
MRI	18.4	18.9	MRI-His: 0.53
US	7.0	19.5	MRI-US: 0.54
His	12.5	19.4	US-His: 0.60

There are considerable deformations between imaging modalities due to different breast positions at the time of scanning and between imaging and pathology. Part of these deformations were estimated using the MRI *exvivo* scans of the breast collected before histological processing and applying a biomechanical-based model deformation algorithm (3) to calculate the deformation map from DCE-MRI *invivo* to MRI-*exvivo*. The algorithm constructed the 3D finite element models (FEM) of breast, assigned corresponding elastic properties to the breast tissue and calculated the deformation map from DCE-MRI-*invivo* to MRI–*exvivo*, ***Fig 4.***

After applying the deformation map, the mesh volume representation of the residual tumor in the DCE-MRI deformed image decreased to 14.1 cc with modest Dice index improvements from 0.53 to 0.56 (MR-to-histology) and from 0.54 to 0.61 (MR-to-US).

Fig 4. (A) MRI-*exvivo* image of the breast, (B) FEM model of the breast used to calculate the deformation from DCE-MRI to MRI-*exvivo*, (C) the resulted DCE-MRI image after applying the deformation map.



Discussion. This is the first reported attempt to register 3D whole-mount histology of the breast with multimodality imaging MRI and US. The project provides metrics of comparison between the residual tumor volume assessed from ground truth histology and the residual tumor volume assessed from US and DCE-MRI in breast cancer patients.

Tumors are stiffer than surrounding breast tissue, therefore considering only the breast elastic properties in calculation of the deformation map overestimates the tumor deformation. Future work will consider including tumor elastic properties in calculating the deformation map MRI-*invivo* to MRI-*exvivo* and estimating the breast deformations from MRI to US.

1. Vlad RM, Brand S, Giles A, Kolios MC, Czarnota GJ (2009) Quantitative ultrasound characterization of responses to radiotherapy in cancer mouse models. *Clinical cancer research;* 15:2067-75.
2. Papanicolau N et al. (2010) Conventional frequency evaluation of tumor cell death response in locally advanced breast cancer patients to chemotherapy treatment administration. *Journal of the Acoustical Society of America* 128:2365.
3. Brock KK, Dawson L a, Sharpe MB, Moseley DJ, Jaffray D a (2006) Feasibility of a novel deformable image registration technique to facilitate classification, targeting, and monitoring of tumor and normal tissue. *Int journal of rad onc, biol, physics* 64:1245-54.