Mechanical properties of the metastatic liver in a breast cancer mouse model using Harmonic Motion Imaging

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Cancer is the second leading cause of death worldwide, and metastasis is the primary cause of cancer mortality. There is thus a need for new methods to identify the presence of metastasis. In this study, Harmonic Motion Imaging (HMI), an ultrasound-based elastography imaging technique, was used to characterize the stiffness of liver in metastatic and non-metastatic mouse models.

4T1 mammary carcinoma cells were injected into female BalbC mice ($1x10^5$ cells/mouse, n=5). The 4T1 cell line spontaneously metastasizes from the primary mammary tumor to multiple distant sites, with the liver being one of the initial sites. HMI scans of the breast tumor and liver were performed in four mice at 4, 9, 10, 13, and 14 days post-injection. Because these mice were imaged only up to two weeks post-injection, this group of four mice served as the non-metastatic group. One of the five mice was injected with 4T1 cells three weeks before the other animals to serve as the metastatic case. Two mice in the non-metastatic group and the metastatic mouse were imaged twice each at different tumor diameters and time-points.

The HMI setup consisted of an 18.5 MHz linear array confocally aligned with a 4-MHz FUS transducer. A 3D positioning system was used to move the HMI setup to acquire point-by-point raster scans. FUS exposure (11.96 MPa PNP) lasted 0.2 seconds at each point. Induced axial displacements were estimated using a 1-D cross correlation technique. Peak-to-peak displacements were used to construct 2D HMI displacement maps. HMI displacement maps were manually segmented using corresponding B-mode images. HMI displacements of the liver were averaged across two transverse planes.

Our findings indicate that there was a substantial difference in liver stiffness between non-metastatic and metastatic livers. Metastatic nodules in the liver of 4T1 mice were found when its primary tumor reached 8mm in diameter (Fig. 1.III). The metastatic mouse model was imaged when its primary tumor diameter was 7.8 and 9.8 mm, indicating that liver metastasis may have led to liver stiffening (Fig. 1.I and 1.II). HMI may thus be capable of identifying the onset of metastasis in the liver as a result of a breast primary tumor.

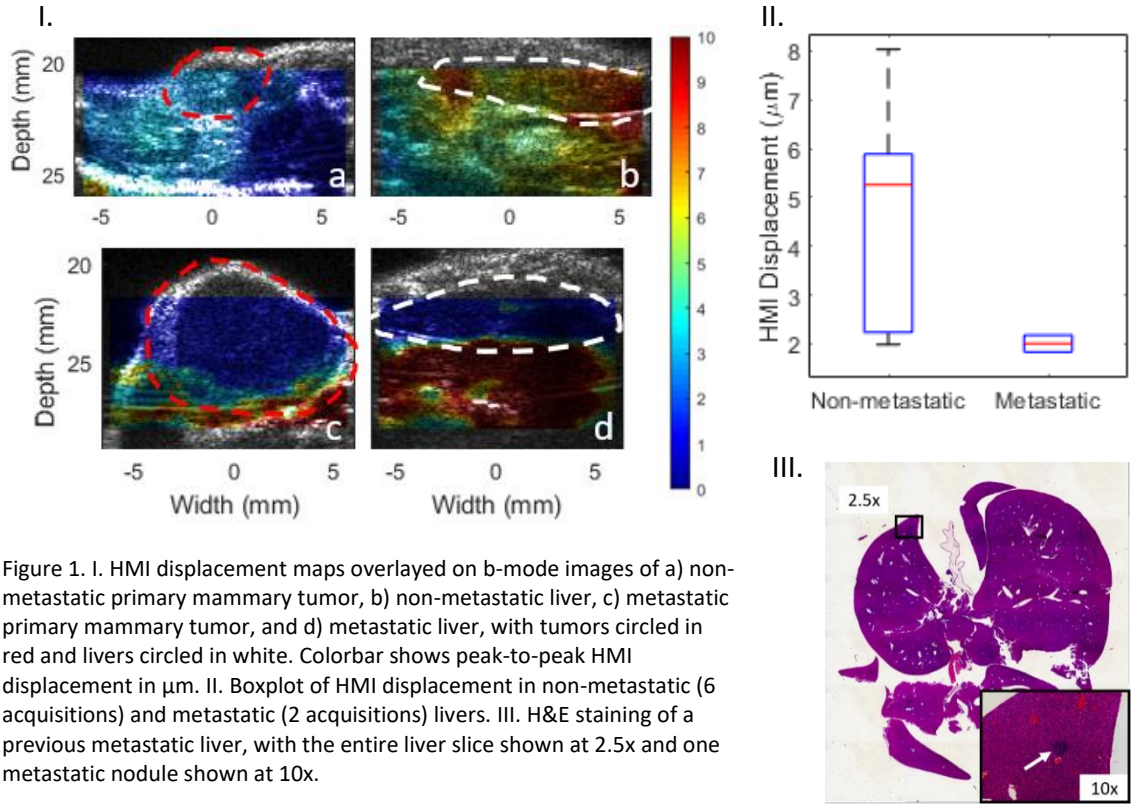

Figure 1. I. HMI displacement maps overlayed on b-mode images of a) non-metastatic primary mammary tumor, b) non-metastatic liver, c) metastatic primary mammary tumor, and d) metastatic liver, with tumors circled in red and livers circled in white. Colorbar shows peak-to-peak HMI displacement in μm. II. Boxplot of HMI displacement in non-metastatic (6 acquisitions) and metastatic (2 acquisitions) livers. III. H&E staining of a previous metastatic liver, with the entire liver slice shown at 2.5x and one metastatic nodule shown at 10x.