Fiducial Markers For MRI Pathological Correlation In Ex Vivo Or Short-Term In Vivo Animal Experiments: A Screening Study

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Introduction: The fiducial markers used to improve MR histological correlation are usually, in *ex vivo* or animal experiences, either external markers or needles implanted in the region of interest at different angles (1, 2). There is a need, however, for internal markers that could be easily cut during the pathological processing and that could define points (instead of lines). The objective of the study was to find such markers.

Material and methods: First, 35 potential markers have been tested in *ex vivo* porcine muscle specimens. The main end-points were: 1) visibility, size and shape of the markers on MR (Fast Spin Echo (FSE) and Gradient Echo (GRE)) images and at macroscopic examination, 2) their stability (size and shape) over a 24-h time period and 3) their microscopic appearance. Second, selected markers were tested in vivo, in two different animal models: rabbit's muscle and human breast carcinoma implanted in nude mice. The main end points were: 1) in vivo visibility and stability of the markers on MR images, over a 3-hour period, 2) their potential systemic and local toxicity over the same period of time, 3) their visibility in tumor tissue on microscopy. Finally, different dilutions of the two best markers were assessed again through the same screening tests to determine whether the marker size could be customized by dilution.

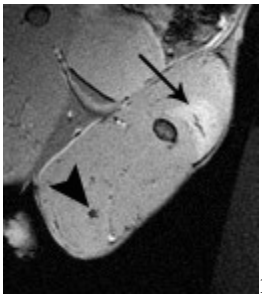
Results: Two fluid acrylic paints containing inorganic pigments were found to be potentially interesting markers. On MR images, they were visible owing to the susceptibility artifact they created. Thus, their size was larger on GRE than on FSE images.

For a 0.01 ml injection, the *Iridescent Bronze* paint (Iron oxide coated Mica particles) created markers the mean largest diameter of which was 7.7 mm on GRE images and 5.2 mm in tissue. With a 1/5 dilution, the markers' mean largest diameter was 4.5 mm on GRE images and 4 mm in tissue. However, diluting too much the paint seemed to reduce its viscosity, which may result in oval-shaped markers in anisotropic tissue, such as muscle. The *Iridescent Bronze* paint was easily visible on standard H&E sections on all tested tissues.

The *Iridescent Stainless Steele* paint (Iron, Chromium, Nickel) created *ex vivo* the smallest markers in tissue (mean largest diameter of 3.8 mm for a mean largest diameter of 6.6 mm on GRE images) but needed Colloidal Iron staining to be visible on microscopy and, even with this staining technique could not be visible in human breast cancer tissue. Furthermore, it could not be easily diluted.

With both paints, the markers showed stable size and shape ex vivo (24-hour period) and in vivo (3-hour period). None of these paints created hyper acute systemic or inflammatory local reactions in vivo.

Conclusion: Fluid acrylic paints are potentially interesting fiducial markers for MRI pathological correlations in *ex vivo* or short term *in vivo* animal experiments. Further studies are needed to assess their long-term properties.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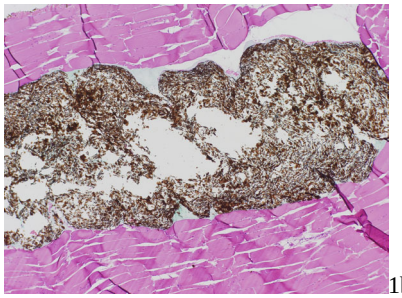
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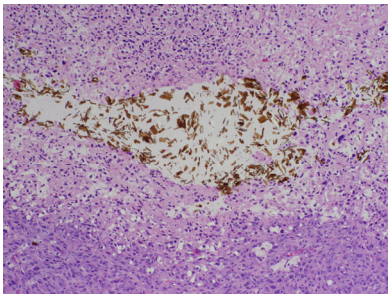
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Figure 1a-b: Diluted (1/5) Iridescent Bronze paint injected (0.01 ml) in rabbit muscle is visible on GRE image as a 4-mm signal void (Fig 1a, arrowhead). It is also easily visible on standard H&E section (Fig 1b). The edematous area visible on GRE image (Fig 1a, arrow) corresponds to the area where the anesthetic cocktail has been injected.

Figure 1c: Diluted (1/5) Iridescent Bronze paint is easily visible in human breast cancer, on microscopy (standard H&E stain)

References: 1) Breen MS et al, J Magn Reson Imaging 2003; 18:90-102. 2) Humm JL et al, Med Phys 2003; 30:2303-2314.