Angiogenesis and cell tracking with iron oxide-labeled tumor cells: Correlation between cell growth and the formation of the tumor vascular bed using high resolution magnetic resonance (MR) angiography, T1, T2 and T2* mapping and histology

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Purpose

To correlate super paramagnetic iron oxide (SPIO) labeled tumor cell growth and distribution with high resolution magnetic resonance (MR) angiography, T1, T2 and T2* parametric mapping and histology.

Material and Methods

Animals and pre-treatment: BN175 soft tissue sarcoma tumor cells were labeled with SPIO particles with pre-defined protocols for the cell line and injected subcutaneously in the hind limbs of healthy brown Norway rats.

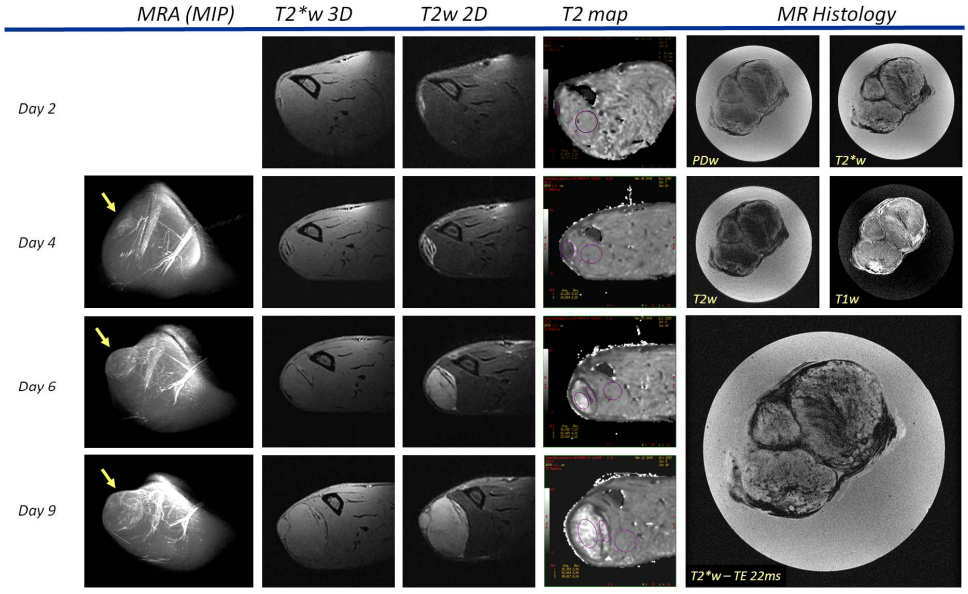
MR imaging: A 3.0T clinical MRI scanner with 1-2 cm ID loop coils for signal reception was used for imaging. An intravascular contrast agent prepared in house using Gd-DTPA loaded liposomes was employed to delineate the vascular bed. At (50-72) x (50-72) x 100 μm^3 voxels T1-, T2- T2*- and proton-density-weighted (PDw) contrast protocols were used.

Image processing: T1, T2 and T2* maps were reconstructed on all scanning days for quantitative data analysis. Histology was used to correlate the end-stage MR data to recognize viable and non-viable tumor regions.

Data were reformatted using the multi-planar reconstruction (MPR) platform of the MRI scanner. Likewise, maximum intensity projections (MIP) were generated to illustrate spatial-temporal relationships of vascular growth/angiogenesis, tumor size and signal distribution of labeled cells.

Results

Tumor growth was visualized with increased recruitment of vascular components around the tumor mass for a period of three weeks. Dark SPIO-labeled cells distributed non-uniformly during tumor growth. The vascular bed was denser in places where the contrast of labeled cells faded more rapidly. Volume rendered reconstructions provided a cue to interpretation, showing vascular redistribution and enhancement patterns within the tumor volume. Parametric maps showed shorter T2 and T2* in certain tumor regions in comparison to controls using non-labeled tumor cell injections.



5 x 10^5 BN175 sarcoma cancer cells were injected with a ratio of 50/50 SPIO-labeled cells. MR angiograms collected using a fat-suppressed T1-weighted 3D sequence and Gd-DPTA containing liposomes (1st column) show the development of neo-vasculature in the surrounding of the injected tumor cells. The T2-weighted 3D scan (TE=7 ms, 2nd column) depicts streaks of darker regions during the early development of the tumor, better appreciated on the T2-weighted fast spin echo (FSE) 2D scan (TE=45 ms, 3rd column). On T2 maps (4th column) the T2 value of muscle nearby stays constant at around 25 ms while tumor exhibits different T2 values; regions with rapid cell division demonstrate longer T2 values. High resolution MR histology was compared with standard histology. The heavily T2*-weighted 3D scan (TE=22 ms) illustrates best the viable regions in the tumor (brighter signals) with remnant SPIO-labeled cells and vascular components (darker signals).*

Conclusion

Multi-contrast datasets using SPIO-labeled tumor cells provide an insight to the process of tumor growth and a novel tool to facilitate the interpretation of vascular bed formation, vascular recruitment and cell proliferation.