Pre-surgical magnetic resonance imaging and photoacoustic-guided surgery with indocyanine green and superparamagnetic iron oxide nanoparticle clusters

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Introduction

Incomplete tumor resection is a common cause of local tumor recurrence following surgery of intrinsic brain tumors. Even with adjunctive technologies such as intraoperative MRI, MR-based navigation techniques, and ultrasound—there remains a high rate of local failure. Contrast-enhanced photoacoustic (PA) imaging offers a possible alternative to enable image-guided surgery. Using ICG as a PA imaging contrast agent allows for deep tissue imaging in real-time. We combined ICG with superparamagnetic iron oxide (SPIO) to create stable nanoparticle clusters (ISCs) composed solely of low-cost FDA-approved agents that are detectable by MR and PA imaging modalities, respectively. Therefore, the ISCs enable both pre-operative and intra-operative imaging.

Material & Methods

SPIO nanoparticles were prepared by thermal decomposition. ISCs were prepared using a proprietary method. The ISCs were characterized by UV-absorption spectroscopy, plasma optical emission spectroscopy (ICP-OES), DLS, TEM, and relaxometry (Figure 1). The biostability of ISCs was assessed in serum at 37C by monitoring leakage of ICG, hydrodynamic diameter (via DLS), and magnetic properties. Cytotoxicity of ISCs was examined in an MTT assay with U251 glioblastoma cells. The contrast enhancing capabilities of ISCs were tested in a murine flank tumor model, using U251 cells. T2*-weighted MR imaging was performed before and after administration of ISC. Photoacoustic imaging was used to guide tumor resection and recurrence was followed following surgery and compared with animals that received traditional microscopic surgical resection.

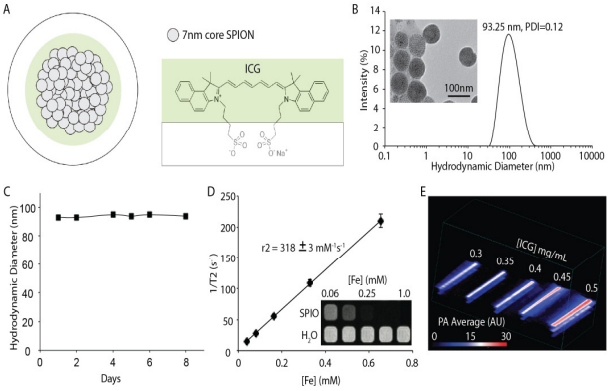

Figure 1. (A) Schematic representation of ICG SPIO clusters (ISCs). (B) Dynamic light scattering (DLS) profile of ISCs. Transmission electron microscopy (TEM; inset). (C) Particle size based on mean intensity in water. (D) Magnetic resonance (MR) relaxometry measurements of ISCs. MR phantom image (inset) of ISCs at various concentrations in a microplate. (E) Photoacoustic phantom of ISCs are shown, demonstrating increased PA intensity with concentration.

Results and Discussion

MR imaging before and 24 hours after injection of 1 mg/kg ISCs (based on ICG weight) revealed a notable loss in signal (i.e. hypointensity) in the flank tumors following injection. In a randomized, single-blinded surgical resection model following injection of ISCs, animals undergoing PA-guided surgery demonstrated increased progression-free survival compared to animals undergoing microscopic surgery (Figure 2).

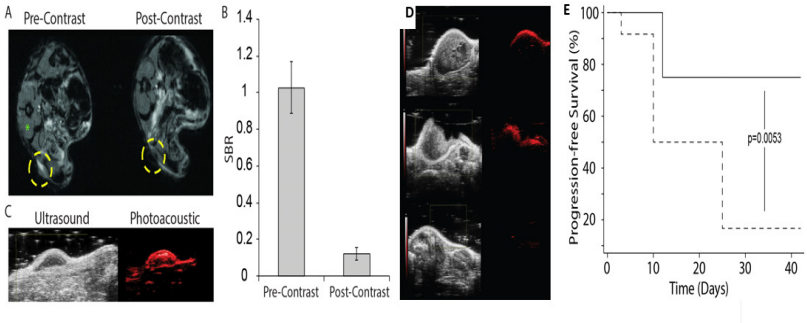

Figure 2. (A) T2*-weighted MR imaging before (left) and 24 hours after (right) injection (B) Signal-to-background ratio (SBR) (C) Ultrasound (left) and Photoacoustic imaging (right). (D) Animals were injected with ISCs and imaged 24 hours following injection. Ultrasound (left) and Photoacoustic (right) (E) Kaplan Meier analysis of surgical resection trial.

Conclusion

We developed a novel contrast agent comprised entirely of FDA-approved components that is detectable by MR and PA imaging in real-time. ICG SPIO clusters are stable in *in vitro* and in physiologic conditions, can be taken up within tumors by EPR, and are detectable in a preclinical animal model 24 hours following injection.