Rare Earth Nanoparticle Imaging and Optical Phantom Fabrication for Surgical Guidance

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INTRODUCTION

When surgeons attempt resection, it is often difficult to adequately locate their subject. In the case of tumor resection, for example, a surgeon might have access to a camera-captured hypodermic image of the tumor's emissions without possessing a reference point to the patient's skin. Live feed imaging systems, displayed on an external monitor, aide in the process, but require surgeons to constantly shift their gaze between monitor and patient. To overcome this, our next step was to rig a projector system, displaying a processed image of the tumor's emissions upon the patient's tissue.

Rare Earth (RE) Nanoparticles are used as contrast agents, making their way to the object of interest after injection into the patient. An overhead camera with the appropriate highpass filter picks up the nanoparticle's emissions. Imaging processing programs designed in LabView are used to adjust brightness and contrast, and threshold the image to outline areas of high RE concentration.

It is also needed to establish standardized subjects to compare multiple surgical guidance systems, setups, and image processing styles. These phantoms, objects used to measure image techniques, often have absorbance and reflective properties similar to that of human tissue. These phantoms can be made with nanoparticles of different concentrations placed at different depths or within different substances such as silicon or gelatin.

CONTRAST AGENTS

Indocyanine Green (ICG), an FDA-approved dye absorbing at short wave infrared (SWIR) wavelengths, has been used for tissue and organ perfusion diagnostics. Rare Earths, contrastingly, operate with absorption spectrums at higher IR wavelengths. The longer wavelengths cause less light scattering, resulting in deeper penetration into the subject tissue.

The phantoms detailed in this paper make use of both pure RE Nanoparticles and RE Albumin Nanocomposites (ReANC). Albumin, a water-soluble family of globular proteins, is used to coat RE nanoparticles, thus increasing biocompatibility and allowing for in vivo testing. ReANCs have been administered as IV injections into the tail vein of mice. These particles migrate to tumors by the Enhanced Permeability and Retention Effect (EPR) as well as to organs, notably the spleen and liver. Additional biomarkers, only activated upon tumors, can be added to differentiate tumors from these organs.

PHANTOMS

METHODS

Two phantom types were created using two different 3D-printed molds designed in Solidworks (See Figure 1).

Phantom A tests for varying concentration and depth. The mold contains step-like platforms within a thin-walled box. The box contains 12 cylindrical holes (depth 2mm, radius 5mm, volume 0.157ml) arranged in a 4x3 grid, with 4 holes at each depth below the surface of the box (1mm, 3mm, 5mm). At each depth, 3 holes contain Erbium ReANCs of different concentrations (5x, 2.5x, 1.25x). The fourth hole acts as a control. Two molds were printed: one to be filled with silicone and TiO_2, the other with gelatin.

While gelatin's properties are more reactive of human tissue's water content than silicone, it is much less long-lasting. Gelatin's properties change over time as its hardens, leaving silicone as the default substance used for phantoms.

Phantom B compares multiple nanoparticle types. The 3D-printed mold contains 4 cylindrical holes (depth 5mm, radius 7.5mm, volume 0.884ml) containing Erbium, Holmium, and Thulium nanoparticles, along with a TiO_2 control. Desired concentrations of inclusions: 625 µg/ml.

TiO_2 , commonly used as a white pigment due to its high refractive index, is added to a phantom to simulate the light-scattering properties of human tissue. Nigrosin, a mixture of synthetic black dyes, can be similarly used for its absorbing properties. However, nigrosin absorbs at visible wavelengths and is therefore not needed for infrared analysis.

PROCEDURE

The procedure for both phantoms differ only in their first step. The creation of Phantom A begins with sonication of 20X Erbium ReANC stock solution until the pellet is completely dispersed. Phantom B begins with the mixing of coarse RE nanoparticles and ethanol to create a Rare Earth (RE) Solution. A 1:5500 ratio of RE Solution to Silicone Volume was used. An inclusion concentration of 625 µg/ml was used. For exact amounts used in both phantoms, see figure 2 & 3.

In a beaker, the solution is mixed with a silicone curing agent and base in a 9:1 ratio. The resulting solution is mixed with a stirring bar until homogenous. The mix is placed in a vacuum chamber (desiccator) until the solution is free of bubbles. The solution is poured into the mold. The mold is placed back in vacuum chamber until free of bubbles. Compressed air is used to pop surface bubbles if needed. The phantom is left to dry for 24 - 48 hrs.

For the control of both phantoms, TiO_2 was added to the silicone curing agent and vortexed for 15 seconds. They were then sonicated for 1.5 hours and subsequently mixed with the silicone base. The stirring and vacuuming procedure is the same as above.

Phantom A at maximum concentration (5X) resulted in a few silicone bubbles not adequately mixed into solution. Further mixing might improve the procedure, though the high concentration might serve as an inherent limitation in quality.

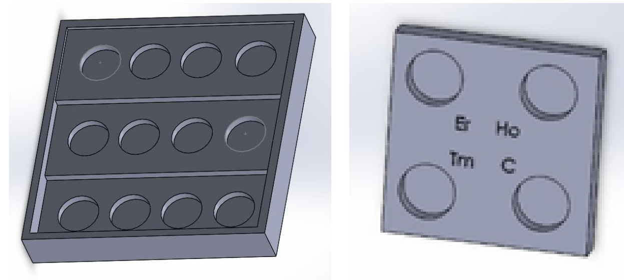


Figure 1: Phantom A; Phantom B (*left to right*)

	5x	2.5x	1.25x	
ReANC Calculations				
Total Volume Inclusions (mL) (6 holes)	0.942	0.942	0.942	
Desired ReANC Concentration (X)	5	2.5	1.25	
Stock ReANC Concentration (X)	20	20	20	
Stock Volume Required (mL)	0.236	0.118	0.059	Sum (mL)
Stock Volume Required with 50% Extra (mL)	0.353	0.177	0.088	0.619
Inclusions				**Control**
Total Volume (mL) (6 holes, 50% more)	1.413	1.413	1.413	1.413
Silicone Activator (mL)	0.1059570826	0.1236285413	0.1324642707	0.1413
Silicone Base (mL)	0.9536137438	1.112656872	1.192178436	1.2717
ReANCs (mL)	0.353	0.177	0.088	0
TiO(g)	0	0	0	0.00105975

Figure 2: Phantom A Components.
Volumes stated are for 6 inclusions, 3 for each mold. Extra 50% volume for increased yield.

Inclusions		TRIPLE	Control	TRIPLE CONTROL
Total Volume (mL) (1 hole, 50% more)	1.325		1.325	3.976078202
Silicone Activator (mL)	0.1301266338	0.3903799013	0.1325359401	0.3976078202
Silicone Base (mL)	1.171139704	3.513419112	1.192823461	3.578470382
RE initial solution (ml)	0.024	0.07227918928	0	0
TiO(g)	0		0.0009940195505	0.002982058652

		Triple
Mass RE (ug)	828.3496255	
Mass RE(mg)	0.8283496255	2.485048876
Ethanol(ml)	0.024	0.07227918928

Figure 3: Phantom B Components.
Tripled volume for increased yield of small quantity.

SURGICAL GUIDANCE

METHODS

Lab setup includes a Sensors Unlimited (SUI) model PSA21R-050 camera and Optoma projector facing downwards attached to a vertical optical breadboard. A PSU-H-LED 980nm Opto Engine LLC laser is also attached to breadboard at various heights and angles from imaging subject. Lower heights generally correspond with greater angles from the vertical in efforts to keep laser head out of camera frame. Laser is collimated with diffusers of either 50° or 20° diversion angles. Varying highpass filters are screwed onto camera based on the nanoparticle imaged. SWIR intensity for Er_2 (Yb_{20}) peaks at 1400-1650nm. Tm (Yb_{20}) peaks at 1400-1500nm. Ho (Yb_{20}) peaks at 1100-1200nm. Setup has been tested both with and without surrounding opaque box used to block out ambient light.

Camera feed output is run through a LabView program used to threshold the image, highlighting all areas with significant RE concentration. Threshold sliders can be altered at will during operation. A display mapping slider can also adjust the maximum pixel value. Other written LabView programs can be used to differentiate particles or prioritize particles based on size.

Prior to use of a projector, and only use of an external monitor, image overlays were used to locate objects of interest and resection instruments. Previously, low-powered lasers have only been capable of covering small areas with significant power. Accordingly, the laser would have to be run over the subject by hand, with a LabView program recording and overlaying maximum pixel intensities until the entire camera field of view had been covered. Higher-powered lasers distributed over larger areas offer an alternative technique.

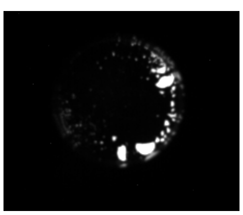


Figure 4: RE Particles.
Er imaged at 0.5mA.
In petri dish.

DISCUSSION

The collimated laser, when attached with a diffuser of smaller diversion angle (20°), covered a smaller subject area. With a smaller area, lower wattages of around 1.5 Watts could produce visible emissions, compared to the necessary 3 Watts and up for a 50° diversion angle. With laser about 21cm above subject plane, a 50° diversion angle covers 301 cm^2 area, with 0.0133 W/cm^2 at 4W. A 20° diversion angle covers 43.1 cm^2 area, with 0.0929 W/cm^2 at 4W. Both wattages per area fall below a biologically healthy limit of 0.726 W/cm^2.

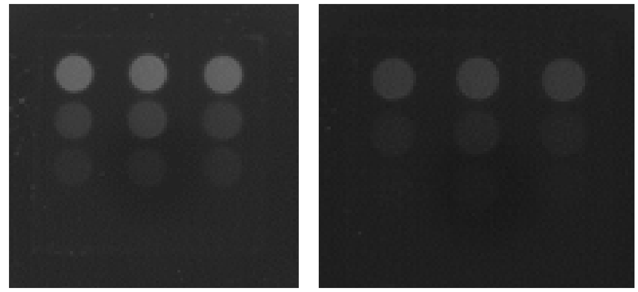
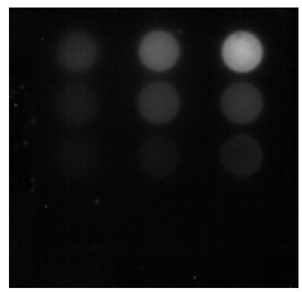


Figure 5: 20° (left) and 50° (right) Diversion Angles.
Imaged at 4mA, no silicone fill, contrast -40%. Top row Er 5X. Fourth row TiO_2 control. Phantom A, Phantom #1.
Both images: Collimated laser, 50° diversion angle, 301cm^2 area.



	5mm	3mm	1mm
5X			
2.5X			
1.25X			
C			

Figure 6: Silicone Fill
Imaged at 4mA, silicone fill, brightness +50%. 20° diversion angle, laser 15cm above subject.
Phantom A, Phantom #1.

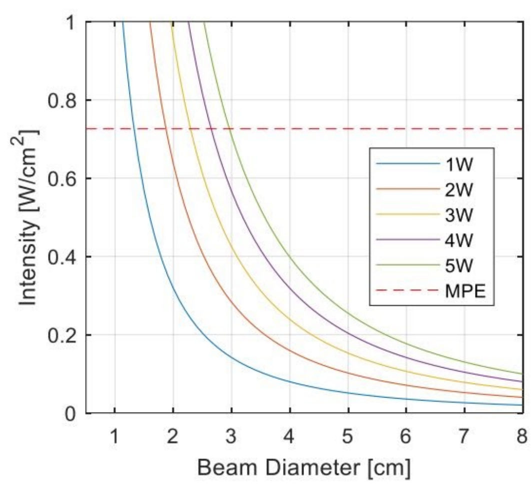
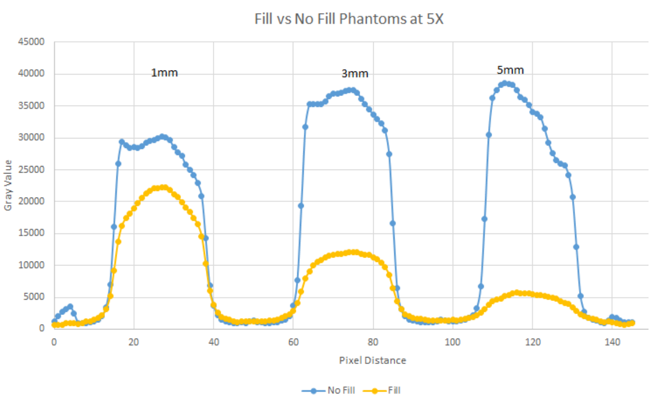


Figure 7: Intensity vs Beam Diameter.
Maximum Permissible Exposure (MPE) for exposure time > 10 sec is 0.726 W/cm^2

Current (mA)	0	980	1590	2110	2670	3150
Power (mW)	0	500	1000	1500	2000	2500
Current (mA)	3730	4170	4830	5140	5460	
Power (mW)	3000	3500	4000	4500	4800	

Figure 8: Laser Power Chart
Given laser current and power relation.



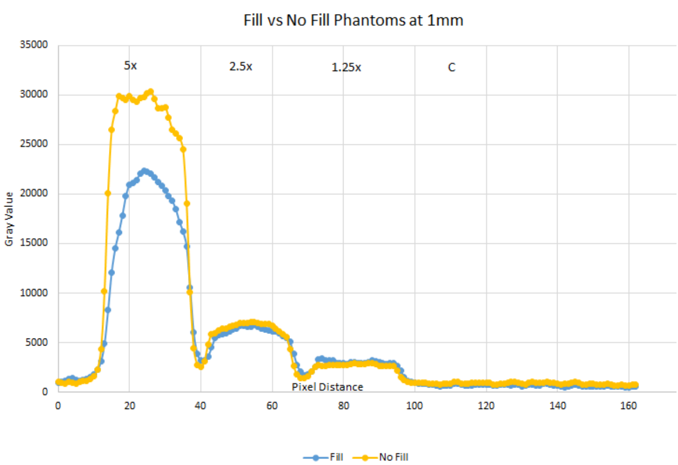


Figure 9: Pixel Value at 1mm (top) and 5X (bottom)
Gray Value vs Pixel Distance. SUI Software. Data extruded from Figure 6.

FURTHER STUDY

Further improvements on this surgical guidance system would be focused around the challenges of depth perception and engineering a mobile housing unit. Making use of a camera with multiple highpass and lowpass filters (or multiple cameras), we can receive data isolating emissions of different wavelengths. As shorter wavelengths penetrate less deeply into tissue, this data can be used to determine a tumor's depth below the surface of a tissue.

Additionally, the equipment used in this system would need an engineered robust, small, and mobile casing for it to become viable in a surgical setting.