Effect of x-ray irradiation on the ultrasound imaging signal of a novel photoacoustic contrast agent

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INTRODUCTION

Phase Change Contrast Agents (PCCAs) have received extensive interest from the ultrasound and photoacoustic imaging community for diagnostic and molecular imaging applications, and for potential use as therapeutic agents [1]. PCCAs, also known as "droplets", are stabilized nanometer sized liquid droplets that act as contrast agents by undergoing a phase-transition to the gaseous state when they are subjected to an external energy pulse. PCCAs are not echogenic, but can be vaporized (activated) into highly echogenic microbubbles during ultrasound imaging. The activation source of PCCAs can be an optical or acoustic pulse. When PCCAs change from liquid to gas, a volumetric expansion occurs and they expand up to 100 times their initial size, leading to up to 50dB enhancement of the pulse which activates them.

AIM

To investigate a novel mechanism for measuring radiation dose in-vivo. This mechanism is based on a dose specific ultrasound imaging signal arising from a change in the material properties of PCCAs as photoacoustic contrast agents following x-ray irradiation.

METHOD

- The effect of x-rays on the physical characteristics of a novel endoskeletal droplet designed for x-ray photoacoustic dosimetry was investigated at the microscopic scale.
- Droplets were irradiated with 10 MV x-rays from a medical linear accelerator. Ultrasound imaging, coherent anti-Stokes Raman scattering (CARS) and bright field (BF) microscopy were performed on samples of irradiated and non-irradiated droplets.
- CARS and BF images were co-registered and droplet sizes measured in each image.
- CARS signal density was calculated as the ratio of CARS signal intensity to the droplet sizes in BF.

RESULTS & DISCUSSION

- Fig. 1 Illustrates the Bright Field and CARS images of pre- and post-irradiated droplets. The co-registered images of CARS overlaid over the BF are also shown. It can be observed that not all the droplets display CARS signal.
- Fig. 2A shows the enhanced number of droplets with CARS signal in irradiated droplets as compared to non-irradiated droplets. Fig. 2B shows the box-whisker plot of the CARS signal density.
- An increased number of the irradiated droplets exhibited detectable CARS signal (52% for non-irradiated versus 86% for irradiated droplets).
- Irradiated droplets displayed a statistically significant (p=0.029) increase in CARS signal density (mean value = 0.30±0.21) compared to non-irradiated droplets (mean = 0.21±0.25).
- Additionally, qualitative ultrasound imaging of the irradiated droplets, which were acoustically vaporized into microbubbles, showed that the acoustic response lasts for a shorter period of time, potentially due to their mechanical (stiffness) change.
- The decrease in ultrasound imaging stability and corresponding increase in the intensity of the CARS signal density post-irradiation both indicate an alteration of the material properties in the hydrocarbon endoskeleton of the droplets, possibly due to radiation-induced cross-linking.

Our hypothesis for the increase in CARS signal is as follows:

- The droplets contain a long chain flourocarbon as the liquid phase and long chain polymer as the solid endoskeleton. The surfactant of the droplet contains a fluorocarbon ether polymer.
- Irradiation will induce crosslinking/crystallinity in polymers [2].
- Radiation induced-crosslinking increases the crystallinity order of the system.
- This change in the polymer can affect the mechanical properties (stiffness) of the droplets, and as a result their echogenic response to an acoustic pulse post irradiation is altered.

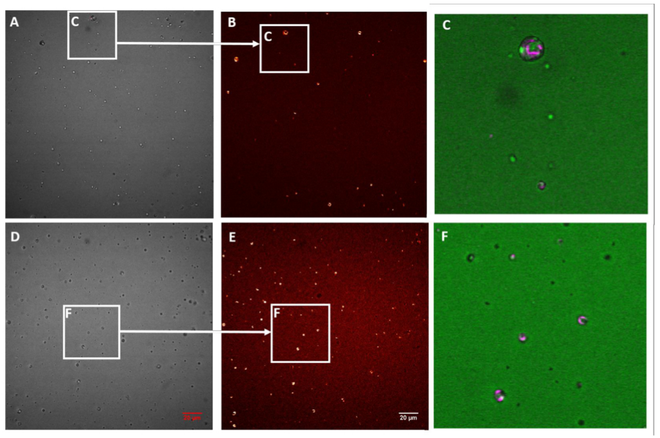

Figure 1: Microscopic images of non-irradiated (top row) and irradiated droplets (bottom row). A & B and D & E show BF and CARS images. As the droplets are in liquid, due to their movement the images are co-registered using control point registration to account for droplet motion. C & F show co-registered BF-CARS images of the enlarged area shown by white square, for non-irradiated and irradiated droplets, respectively. CARS signal in C and F is in magenta and overlaid over green BF images. Note, not every droplet in BF displays CARS signal.

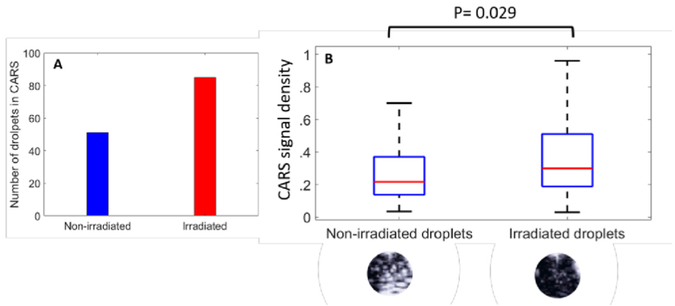

Figure 2: A) Bar plot of the number of droplets with CARS signal. B) Whisker plot of the CARS signal density (ratio of CARS signal intensity to the droplet sizes in BF). Initial ultrasound imaging examples, shown below the whisker plot, suggest irradiated droplets produce microbubbles with shorter time when activated due to stiffer structure.

CONCLUSIONS

- These initial results suggest that photoacoustic contrast agents such as PCCAs/droplets may offer a mechanism for measuring radiation dose in-vivo during the radiation therapy.
- This mechanism arises from the change in the material properties of PCCAs following x-ray irradiation -- similar to polymerization that occurs in radiochromic film.
- In their application to radiation therapy, droplets could be injected prior to radiation and may yield a dose-specific acoustic signal that in combination with ultrasound imaging, would enable a true real-time 3D in-vivo dosimetry technique.

ACKNOWLEDGEMENTS

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REFERENCES

1. **Brambila C.J.** et al, Bubble Inflation using Phase Change Perfluorocarbon Nanodroplets as a Strategy for Enhanced Ultrasound Imaging and Therapy, Langmuir, 2020.
2. **Bednarik M.** et al, Surface and Adhesive Properties of Low-Density Polyethylene after Radiation Cross-Linking, Key Engineering Materials, 2014.

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