Multimodal Image Guided Oxygen Delivery for Improved Radiation Therapy Outcomes in Head and Neck Cancers

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Background, Motivation and Objective

The absence of oxygen in hypoxic regions of tumors reduces the production of reactive oxygen species that can further cause DNA damage during radiation therapy (RT) [1]. There is a need to identify oxygen levels within the tumor and provide a localized delivery of oxygen to re-oxygenate hypoxic regions for better RT efficacy. We have developed a photoacoustic/ultrasound (PA/US) imaging platform that can image oxygen saturation (sO_2) in the tumor. We have also developed novel biocompatible oxygen loaded nanodroplets (OLNDs) capable of transporting clinically relevant doses of molecular oxygen to the tumor. These nanoparticles can be optically or acoustically triggered non-invasively to deliver their payload and be imaged using ultrasound. By combining both our imaging platform and nanodroplets, we have developed a system that can deliver oxygen to hypoxic tumors while imaging the tumor sO_2 in real-time to help improve RT outcomes.

Statement of Contribution/Methods

We developed a multimodal imaging platform consisting of a nanosecond pulsed laser (Phocus Mobile, Opotek) and a 128 element, 18 MHz linear array ultrasound system (Vantage 256, Verasonics) capable of imaging sO_2. Additionally, we synthesized ONLDs by encapsulating perfluoropentane (PFP) and indocyanine green (ICG) dye inside a lipid monolayer shell via ultrasonic emulsification. Molecular oxygen was dissolved into the PFP core of the nanodroplets. We performed *in vivo* studies of our imaging system and nanodroplets using subcutaneous FaDu cell tumors in nu/nu mice. Photoacoustic sO_2 maps were acquired before an intravenous injection (1.7 mg/kg) of the OLNDs. Post injection, the OLNDs were activated non-invasively using a HIFU transducer (H-151, Sonic Concepts) or by a laser depending on the group. Immediately after the activation of the nanodroplets, the mice were subjected to RT, a single fraction of the same dose (10-20 Gy). Tumors were continued to be measured after RT for all the groups and mice were euthanized at any signs of distress or when tumor volumes exceeded 1.5 cm^3.

Results/Discussion

Electron paramagnetic resonance (EPR) oximetry was used to confirm the release of oxygen in vitro[2]. Preliminary *in vivo* studies have shown an increase in mean photoacoustic signal of hemoglobin by a factor of 2 after the activation of the OLNDs, suggesting oxygen delivery into the tumor. These results demonstrate the ability to increase tumor oxygenation on demand by locally delivering oxygen, while also using PA/US to monitor the re-oxygenation dynamics and directly image the nanodroplets. This technology has the potential to be a RT efficacy predictor providing oncologists with valuable information on treatment outcomes and planning.

References

[1] B. Muz, P. de la Puente, F. Azab, and A. K. Azab, "The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy," *Hypoxia*, vol. 3, pp. 83–92, Dec. 2015.

[2] S. Jandhyala and G. P. Luke, "Optically Activated Oxygen-Loaded Perfluorocarbon Nanoparticles for Ultrasound-guided Radiation Therapy," in *Optics in the Life Sciences Congress*, 2015, p. OmW3D.7.