Monitoring of photodynamic therapy tumor response using ultrasound-guided photoacoustic imaging

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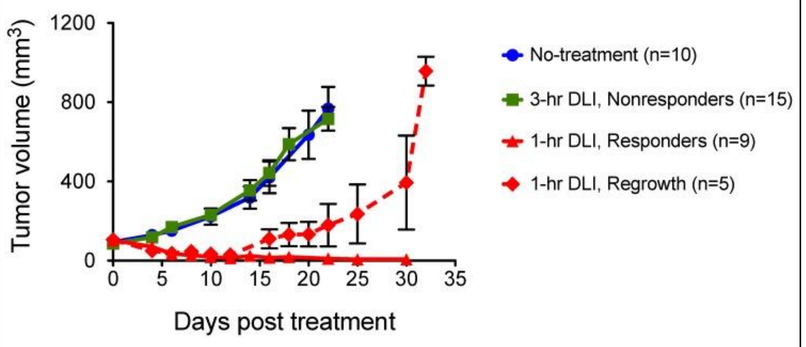
ABSTRACT

Photodynamic therapy (PDT) is a well-studied, photochemistry-based treatment modality approved for use in several malignancies. PDT effectiveness is dependent on the presence of tissue oxygenation and activation of a photosensitizer (PS). However, heterogeneity of tumor oxygenation can result in PDT response variability. We hypothesize that non-invasive, 3D measurement of blood oxygen saturation using photoacoustic imaging (PAI) can be used to monitor tumor response and predict the likelihood of tumor regrowth in a murine model of glioblastoma.

We demonstrate that the propensity for tumor regrowth after PDT can be predicted using PAI within 24-hours of treatment, potentially allowing for earlier intervention. Tumors with a response to PDT had a statistically significant 85% change in oxygenation by 24-hours post-therapy while no significant change in oxygen saturation was observed in the non-responding group. Immunofluorescence staining for hypoxia validated the oxygenation measurements obtained with PAI. An algorithm for predicting tumor regrowth based on PAI measurements of blood oxygen saturation was derived and validated with gross tumor measurement. The results of this study suggest that PAI is an effective method for monitoring PDT and can play an important role in the clinical setting for predicting PDT response.

Fig. 1 – Tumor volume monitoring
A drug-light interval (DLI) of one-hour between PS injection and PDT was used to simulate the responding group (red). A DLI of three-hours was used to simulate the non-responding group (green).



INTRODUCTION

- PDT is a approved for multiple clinical applications[1,2]
- PDT requires a photosensitizer, oxygenation, and light[3]
- Heterogeneity in tumor oxygenation can result in variable PDT outcomes[4]
- Photoacoustic imaging (PAI) can provide a volumetric atlas of tumor oxygenation (StO_2) at a resolution comparable to ultrasound imaging[5,6]
- PAI does not photobleach the PDT-required photosensitizer and does not induce PDT
- We hypothesize that PAI-based measurements of StO_2 during and post-PDT treatment can be used to predict responders and areas of tumor regrowth

METHODS

Animal Model
Athymic nude mice were implanted subcutaneously with 3 x 10^6 U-87 human glioblastoma cells obtained from the ATCC.

Photosensitizer
Benzoporphyrin derivative monoacid ring-A (BPD-MA) were prepared as a liposomal formulation.

PDT
Mice were injected IV with 0.5 mg/kg of BPD-MA and PDT was performed at either 1 hour or 3 hours post photosensitizer administration using a 690 nm laser diode at a fluence rate of 100 mW/cm^2 for a dose of 100 J/cm^2.

PAI
Image acquisition and quantitation were performed using Vevo LAZR.

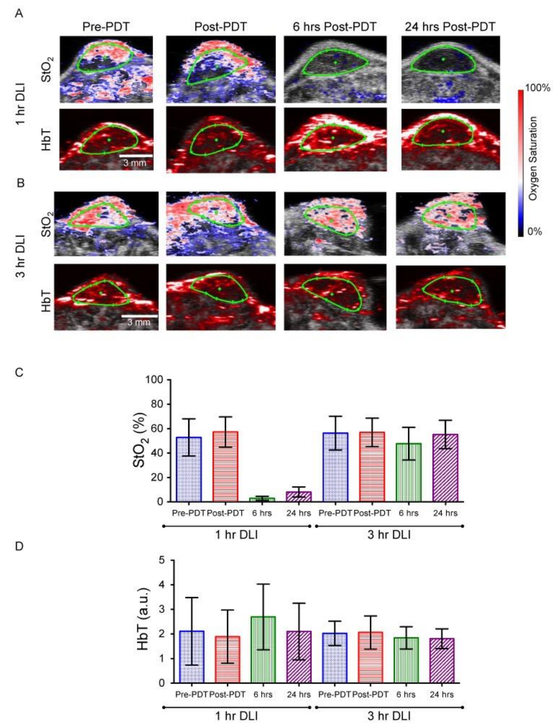
RESULTS

Fig. 2 – PAI of PDT responders and nonresponders

StO_2 and HbT images were obtained using PAI for the responders (1 hour DLI, panel A) and nonresponders group (3 hour DLI, panel B). A green ROI was used to identify the tumor region and measure mean StO_2 and HbT.

The StO_2 was significantly reduced at 6 and 24 hours after PDT in those cases that subsequently responded to treatment (panel C).

A similar difference in HbT (panel D) was not observed and consequently it was not implemented in the algorithm used to predict treatment regions.



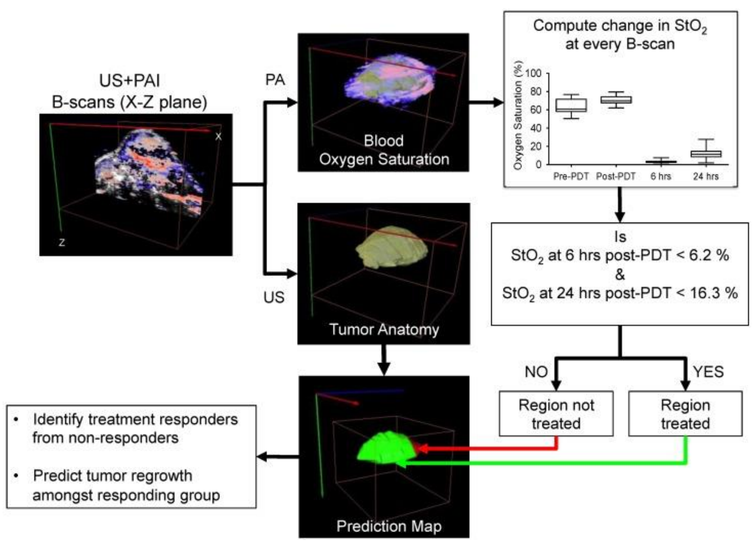


Fig. 3 – Algorithm for predicting PDT response using PAI
A volumetric prediction map can be generated using StO_2 measurements at 6 and 24 hours post PDT.

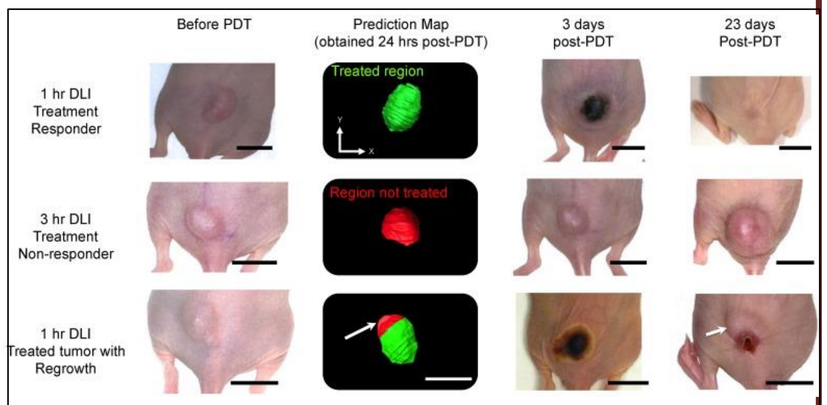
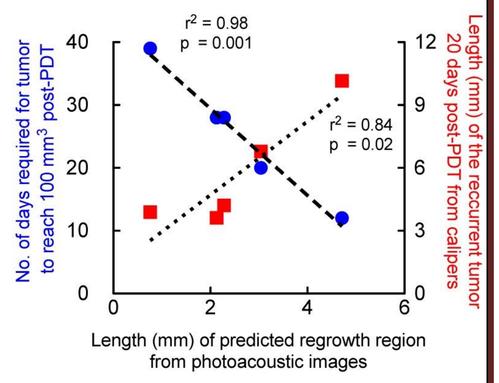


Fig. 4 – Prediction and response of PDT treatment
Representative cases from the responder, non-responder, and regrowth groups show the association between the PAI-derived treatment prediction maps and observed clinical response. The prediction maps were based on StO_2 threshold at 24-hours post-PDT with the green region indicating the region expected to respond.

Fig. 5 - Predicted and actual regrowth region size

Greater diameter of the PAI-predicted regrowth region was directly correlated with the tumor diameter at 20 days post-PDT (red) and indirectly correlated with the time required to reach 100 mm^3 post PDT (blue).



CONCLUSION & FUTURE WORK

- Heterogeneity in tumor oxygenation and in PDT response can be assessed using PAI
- **Propensity for tumor regrowth after PDT can be predicted using PAI**
- Using the algorithm suggested by our results, PAI can provide a high resolution, volumetric prediction atlas of PDT response
- PAI can play an important role in the clinical and laboratory setting for assessing PDT effectiveness

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