Gadolinium Neutron Capture Therapy Using FDA-Approved MRI Contrast Agents

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INTRODUCTION

Several decades ago, Boron Neutron Capture Therapy (BNCT) was introduced as a prospective "best of both worlds" treatment modality combining the cancer-targeting mechanisms of chemotherapy and localization methods of radiotherapy. This is important for control and management of radioresistant cancers including pancreatic adenocarcinoma and glioblastoma. BNCT however suffers from the disadvantage of inducing systemic toxicity. This investigation explores the potential improvement of this modality using locally administered gadolinium (Gd). The significantly greater thermal neutron absorption cross-section of Gd can provide a similar interaction rate to that of boron at a lower dose. By these methods, Gadolinium Neutron Capture Therapy (GdNCT) has the potential to provide non-inferior outcomes with reduced systemic toxicity for radioresistant cancers.

AIM

Explore the use of Gadolinium (Gd) contrast agents as radiation-enhancing material via neutron capture.

METHOD

- Panc02 subcutaneous mouse tumors were harvested at clinical mouse endpoints (~2 cm diameter).
- Tumors were injected with 50 μL of Omniscan MRI contrast agent (~4 mg of Gd).
- Tumors received 4 cGy dose from thermal neutrons at the Umass Lowell Research Reactor thermal column.
- Tissue was fixed in 10% formalin and submitted to iHisto for phosphor-histone γ-H2AX stain fluorescence imaging.
- Statistical analysis was performed on resulting images to assess true nuclei damage. (Figure 1)
- Experimental results were compared to Geant4 Monte Carlo simulations of dose enhancement in tissue with versus without Gd contrast agent.
  - Simulations estimated ~4 cGy absorbed dose due to incident neutron beam.
  - Model was a 2 cm sphere with a homogeneous Gd mixture just under the surface of a block tissue phantom

RESULTS

- *Preliminary ex-vivo experiments showed a 73% increase in DNA damage when the tumor was treated with both Gd and thermal neutrons. (Figure 2)*
- *Monte Carlo Simulations estimated about 8 times greater absorbed dose within the Gd present tumor tissue with significantly steep dose gradient. (Figure 3)*

Figure 1: Phosphor-histone γ-H2AX assessment of radiation-induced DNA DSBs. Nuclei (black circles) were binned by mean fluorescent intensity. Unbound fluorophor background signal was modeled by a lognormal distribution (blue) and subtracted from the data, leaving the remaining DSB-positive nuclei (red).

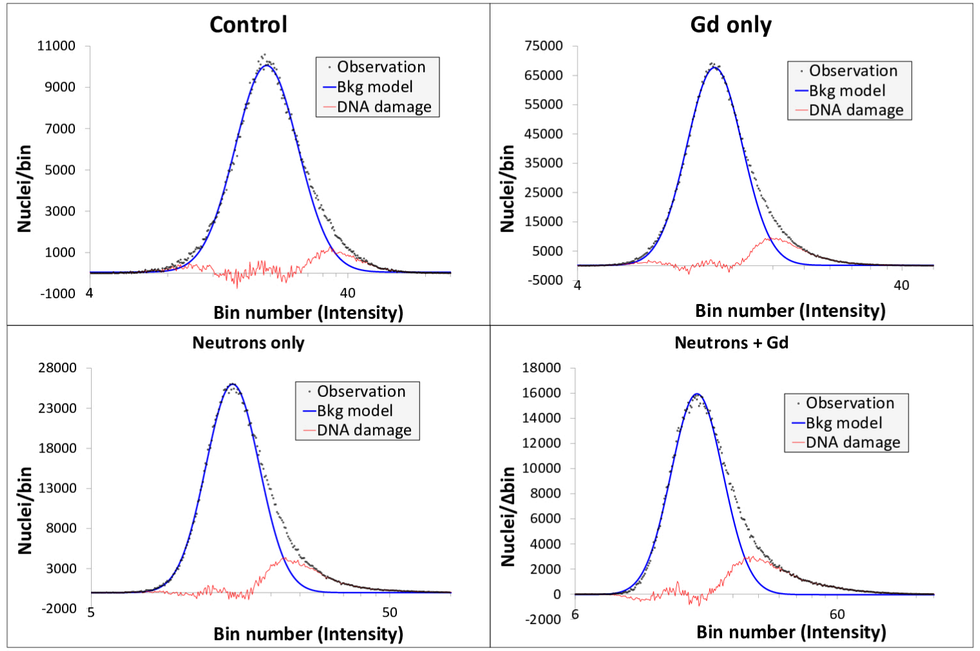


Figure 2: The fraction of total nuclei with DSB-positive expression by phosphor- histone γ-H2AX staining.

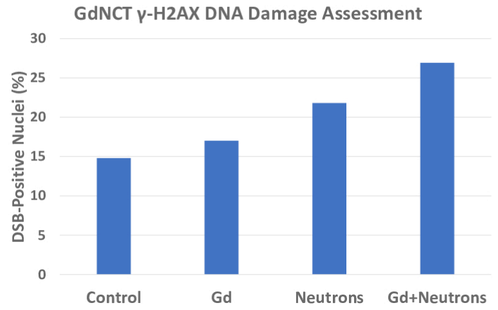
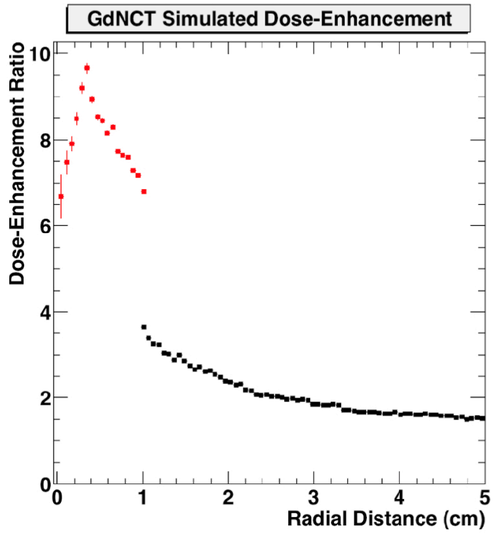


Figure 3: Geant4 simulated dose enhancement due to Gd(n,γ) emissions compared to absorbed dose from neutrons alone as a function of distance from the tumor centroid inside the tumor volume (red) and outside the tumor volume (black).



CONCLUSIONS

Experimental DNA damage assessment and Monte Carlo Simulated dose-enhancement suggest Gd as a strong radiosensitizing material at low concentrations with few incident neutrons, demonstrating potential for GdNCT as a strong modality for radioresistant cancers.

REFERENCES

Moeglin E, Desplancq D, Conic S, Oulad-Abdelghani M, Stoessel A, Chiper M, et al. Uniform widespread nuclear phosphorylation of histone H2AX is an indicator of lethal DNA replication stress. Cancers (Basel) 2019;11. https://doi.org/10.3390/cancers11030355

Nedunchezhian K. Boron Neutron Capture Therapy - A Literature Review. J Clin DIAGNOSTIC Res 2016;10:ZE01–4. https://doi.org/10.7860/JCDR/2016/19890.9024.

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