Development of a Pre-Clinical MR-Guided Radiotherapy Model to Assess Gadolinium-Induced Renal Toxicity

M Petronek[1]*, E Steinbach[1], A Kalen[1], C Callaghan[1], D Hyer[1], R Flynn[1], D Spitz[1], J Buatti[1], V Magnotta[1], D Zepedo-Orozco[2], J St-Aubin[1], B Allen[1]

[1]University of Iowa, Iowa City, IA, [2]Ohio State University, Columbus, OH

JULY 12–16 2020 VIRTUAL JOINT AAPM | COMP MEETING
EASTERN TIME [GMT-4]

INTRODUCTION

There are currently four operational high-field MR-Linac systems in the United States with many more institutions following suit. The advent of MR-Linac technology allows for the further enhancement of real-time image guidance due to the increased soft tissue contrast associated with MR imaging. For lesions that are difficult to localize using MRI, contrast enhancement is often necessary. A major concern associated with Gadolinium-Based Contrast Agents (GBCA) administration is increased risk for contrast-induced acute kidney injury (CI-AKI) leading to nephrogenic systemic fibrosis (NSF)[1]. This is primarily the result of free Gd^{3+} lodging in the glomeruli. Thus, we hypothesized that if ionizing radiation were able to liberate Gd^{3+} from its chelator shell, it would result in CI-AKI[2].

AIM

To assess the safety and nephrotoxicity associated with GBCA administration at the time of radiation, we have developed a reliable, pre-clinical MRIgRT system where an MRI is acquired using a 7T GE small animal scanner and RT is delivered on the Xstrahl SARRP in quick succession.

METHOD

- Female nude mice (Jackson Laboratories, Bar Harbor, ME) were subcutaneously injected with 2 x 10^6 glioblastoma cells (U251) in the left flank.
- Gadolinium contrast agent (Gadavist®) was intraperitoneally injected (4 mmol kg^{-1}) immediately prior to MR imaging.
- To generate T1-weighted images, a fat saturated, spin-echo sequence was obtained (TE = 9.3ms, TR = 900ms, FOV = 3x2.25cm, slice thickness / gap = 0.4 / 0.1mm, matrix= 256 x 192 resolution) (**Figure 1A**)
- T2* - weighted images were collected using a 2D gradient – echo pulse sequence and T2* maps were generated using an in-house python code (**Figure 1B**)
- Images were analyzed using the 3DSlicer software.
- Animals were irradiated using a Small Animal Radiation Research Platform (SARRP) at the University of Iowa in a 220 kVp radiation beam (HVL = 0.625 mm Cu), 35 cm source-to-axis distance (SAD) verified with the on-board laser system.
- Alignments were validated using a whole field, electronic portal imaging device (EPID) with a 5 mm aluminum metal marker placed externally at the site of the tumor (removed prior to RT) (**Figure 1C**).
- Radiation treatment doses of 2, 8 or 18 Gy at a depth of 1.5 mm were delivered using a 10 x 10 mm^2 collimator. (validated by TLD within ±8% based on a standard curve)
- Blood samples were collected by tail snip in serum separator tubes at 3 days and 7 days post-treatment
- Blood urea nitrogen (BUN) and creatinine analysis were performed by Antech Diagnostics (Des Moines, IA) as elevation of serum BUN/creatinine 72 hours post-treatment are considered useful markers of AKI[3]

RESULTS

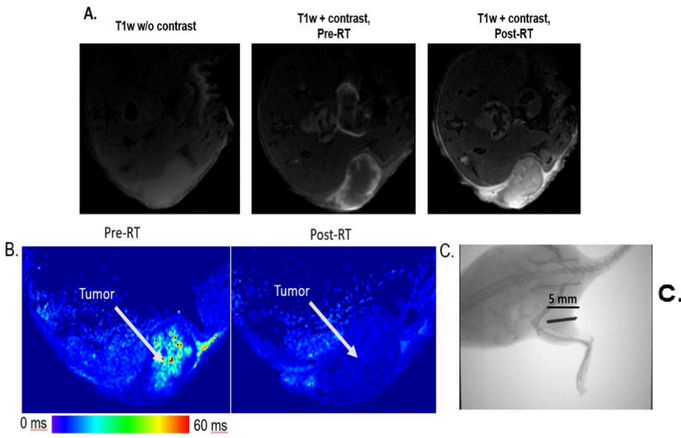

Figure 1. Pre-clinical contrast enhancing MR-guided radiotherapy model. A. Representative T1-weighted images showing Gadavist® uptake being present pre- and post-radiotherapy in a U251 flank tumor **B.** Representative T2* maps pre- and post-radiotherapy to quantitatively assess Gadavist® presence during RT. **C.** Representative whole-field portal CT image for tumor localization following animal set up. A 5 mm piece of aluminum wire is overlaying the flank tumor to confirm that the tumor is aligned at isocenter.

- Continual uptake of Gadavist® can be visualized by increased T1 signal intensity following RT (**Figure 1A**)
- Following RT there was a 4-fold decrease in T2* relaxation times to confirm continual uptake of Gadavist® during radiation delivery since Gadavist® is known to decrease T2* relaxation times (**Figure 1B**)
- The average time to RT following Gadavist® administration was 18 ± 3 min, whereas the time to imaging completion post RT delivery was 28 ± 1 min; very similar to current clinical MRI-linac treatment times.

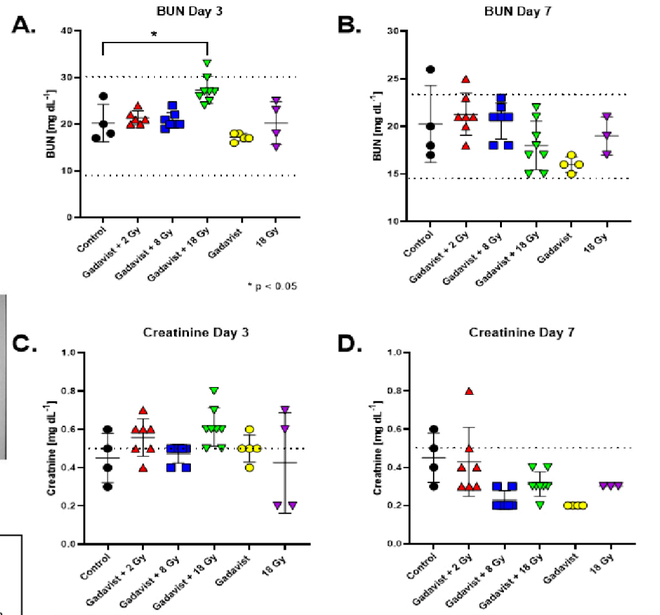

Figure 2. Assessment of nephrotoxicity following Gadavist® administration in combination with ionizing radiation shows little effects on kidney function. Serum BUN and creatinine levels were measured at 3 days (**A, C**) and 7 days (**B, C**) following treatment with intraperitoneally injected 4 mmol kg^{-1} Gadavist® and 2 Gy, 8 Gy, and 18 Gy; Gadavist® alone, and 18 Gy alone. All groups were compared to a cohort of normal, healthy control animals. Dashed lines indicate normal reference levels provided by the Antech Diagnostics.*indicates $p < 0.05$ using a one-way ANOVA test.

- Despite a statistically significant increase in serum BUN 3 days post-RT in the group receiving Gadavist® with 18 Gy (**Figure 2A**), serum BUN and creatinine stay largely within the normal ranges for each treatment group (**Figure 2B**)
- Serum BUN (**Figure 2C**) and creatinine (**Figure 2D**) return to normal levels with no significant difference from healthy controls by day 7 indicating no acute injury actually occurred

CONCLUSIONS

From these data, we conclude that in mice with normal kidney function, there is limited risk for CI-AKI following Gadavist® administration during RT. Therefore, GBCA administration during radiation therapy could be a useful tool in the context of MRIgRT. Further work regarding GBCA and RT dosing is required for validation.

ACKNOWLEDGEMENTS

This work was supported by NIH grants T32 CA078586, P01 CA217797, R01 CA169046, R01 CA182804, and the Gateway for Cancer Research grant G-17-1500. Core facilities were supported in part by the Carver College of Medicine and the Holden Comprehensive Cancer center, NIH P30 CA086862.

The Radiation and Free Radical Research Core provided invaluable support in the completion of this work. The content is solely the responsibility of the authors and does not represent views of the National Institutes of Health.

REFERENCES

1. Chien C-C, Wang H-Y, Wang J-J, Kan W-C, Chien T-W, Lin C-Y, et al. Risk of Acute Kidney Injury after Exposure to Gadolinium-Based Contrast in Patients with Renal Impairment. Renal Failure. 2011 Sep 1;33(8):758–64.
2. Rogosnitzky M, Branch S. Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms. Biometals. 2016 Jun;29(3):365–76.
3. Wasung ME, Chawla LS, Madero M. Biomarkers of renal function, which and when? Clinica Chimica Acta. 2015 Jan 1;438:350–7.

CONTACT INFORMATION

Michael Petronek, MS; michael-petronek@uiowa.edu; Tel: (319) 335-8019