Phase One Randomized Two-Arm Dose Escalation of Flash RT In Veterinary Canine Osteosarcoma: Status Update In Year 2

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INTRODUCTION

- As of 2014 Studies of ultra-high dose rate (UHDR) radiotherapy (RT) have shown a normal tissue sparing effect, terms the FLASH effect. These studies have resulted in intense interest in a new pathway to expand RT in the clinic
- Although many studies investigating FLASH have been published in recent years showing sparing in skin, lung fibrosis, brain function, and crypt cell regeneration, a clear FLASH effect has not been robustly observed in large animal models.

HOW DOES FLASH OCCUR?

- The FLASH effect was first fully clearly demonstrated in 2014 by V Favaudon et al [1].
- The magnitude of the FLASH effect is roughly equivalent to delivering ~10-50% more dose to normal tissue to experience similar toxicity as seen in figure 1.
- The FLASH effect has been observed in electrons[1], protons[2], Carbon ions [3], and photons [4].
- Necessary parameters:
  - Dose rate >40 Gy/s
  - Dose threshold >8 Gy

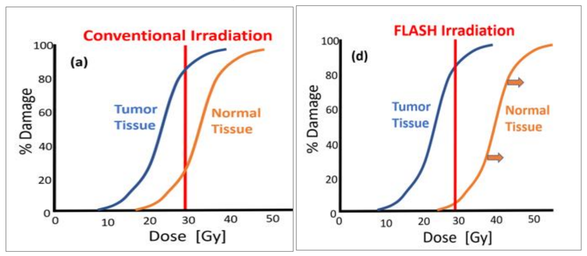

Figure 1: Example of the therapeutic ratio expanding as a result of UHDR induced FLASH effect

In this study we investigate the potential impact of FLASH RT in canine skin damage.

WHY CANINE OSTEOSARCOMA?

Canine osteosarcoma is a common cancer in middle to large breed dogs that is fatal if it metastases to the lung, 64% of Canine Osteosarcoma occurs in limbs. Treatments are primarily palliative and are coupled with amputation of the afflicted limb roughly 1 month post radiation.

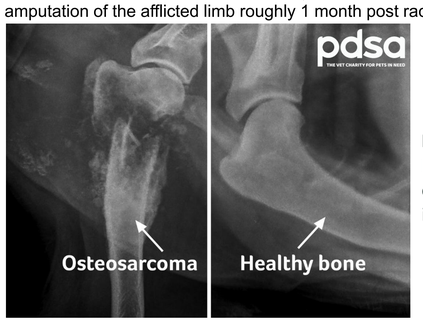

Figure 2: Example of osteosarcoma in a canine limb

This type of treatment is ideal for investigating acute skin toxicity with a follow-up time of ~ 1 month and a good candidate for electron UHDR therapy due to the superficial nature of appendicular osteosarcomas allowing for monitoring of acute skin damage over the study timeline.

METHODS

An IntraOp Mobetron was used for both UHDR and CDR irradiations.

This Linac delivers a 9 MeV electron beam at variable dose rates. In this study dose rates were 0.16 Gy/s for CDR and ~90 Gy/s for UHDR. Dosimetry was achieved via placing a EBT-XD Gafchromic film and a TLD-400 onto the skin surface. Additional online monitoring of UHDR beams occurred via monitoring current of individual pulses via a Beam Current Transformer (BCT).

1 fraction	UHDR (# patients)	CDR (#patients)
20 Gy	3/3	3/3
22 Gy	3/3	3/3
24 Gy	1/3	1/3
26 Gy	0/3	0/3
28 Gy	0/3	0/3

Table 1: Initial planned prescription dose to skin in canine treatments. T

Client owned Canines are recruited to the study and randomly assigned a study arm (CDR or UHDR). Follow-up of the treatment occurs over the next month with weekly photos of the irradiated location. After a month amputation of the limb occurs, and histology is preformed. The skin effects of each patient are examined blindly and graded according to VRTOG v2.0 for pain and skin damage (Table 2).

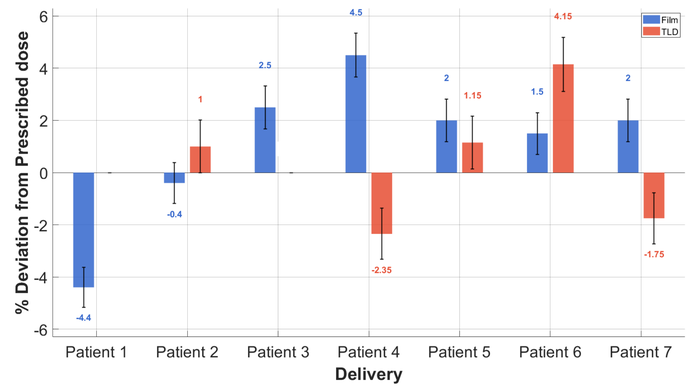

Figure 3. Figure 3: in vivo dosimetry results showing deviation from prescribed dose for both EBT-XD Gafchromic film (Blue, left bars), and TLD-400 (Orange, right bars) for each patient in the 20 Gy (A.) and the 22 Gy (B.) groups.

RESULTS

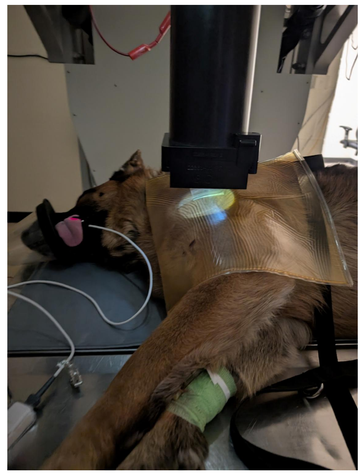

Figure 4. Examples of **A.** treatment set up on a shoulder Osteosarcoma on a patient

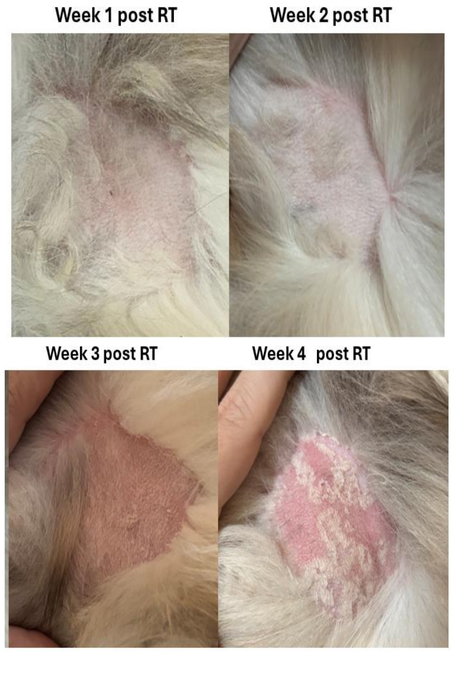

Figure 5 Example from this study of acute radiation skin toxicity developing over the 1-month evaluation period with initial alopecia forming a week post treatment manifesting into dry desquamation of the treated area.

Organ/Tissue	Grade 1	Grade 2	Grade 3
Skin	Erythema; alopecia; dry desquamation	Focal edema or moist desquamation affecting < 50% of treated area	Edema or moist desquamation affecting >50% of treated area
Pain	Mild pain not altering daily activities	Pain intermittently altering daily activities	Pain persistently altering daily activities

Table 2. VRTOG v2.0 Acute Morbidity scoring Scheme. Grade 3 is our limiting toxicity value in this study.

CONCLUSIONS

- Initial Dose of 1x20 and 1x22 Gy has showed no Dose limiting Toxicities (VRTOG grade 3)
- Higher grade toxicity (Grade 2) has only be observed in the CDR dose group.
- Delivered dose is appropriate between both groups as validated by two dosimeters.
- With successful deliveries and followups for the current dose levels, the trial will continue on to the next dose level of 1x24 Gy.

REFERENCES

[1] V. Favaudon et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice https://pubmed.ncbi.nlm.nih.gov/25031268/

[2] E Diffenderfer et al. The current status of preclinical proton FLASH radiation and future directions. https://pubmed.ncbi.nlm.nih.gov/34644403/

[3] W Tinganelli.et al. Flash with carbon ions: tumor control... https://www.thegreenjournal.com/article/S0167-8140(22)00238-9/fulltext

[4] Montay-Gruel et al. X-rays can trigger the FLASH effect... https://pubmed.ncbi.nlm.nih.gov/30177374/

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MRRC
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