The FLASH effect—An evaluation of preclinical studies of ultra-high dose rate radiotherapy: Supplementary Materials

1 Supplementary Materials for Results

Figure 1: Pearson's correlation coefficients in heat map form to show the correlations between each dosimetric parameter and the corresponding endpoint. The values range between -1 and 1, where the extremities (closest to -1 and 1) have the deepest colour and the weakest correlations (closer to 0) have a weak colour. Statistically significant correlations are identifiable by an asterisk at the top left of the corresponding correlation coefficient. Key: TIS- Therapeutic Index Score, TCS- Tumour Control Score, NTSS- Normal-tissue Sparing Score, ILS- Increased Lifespan, S_1- Survival % at 1 month, S_2- Survival % at 2 month, S_3- Survival % at 3 month.

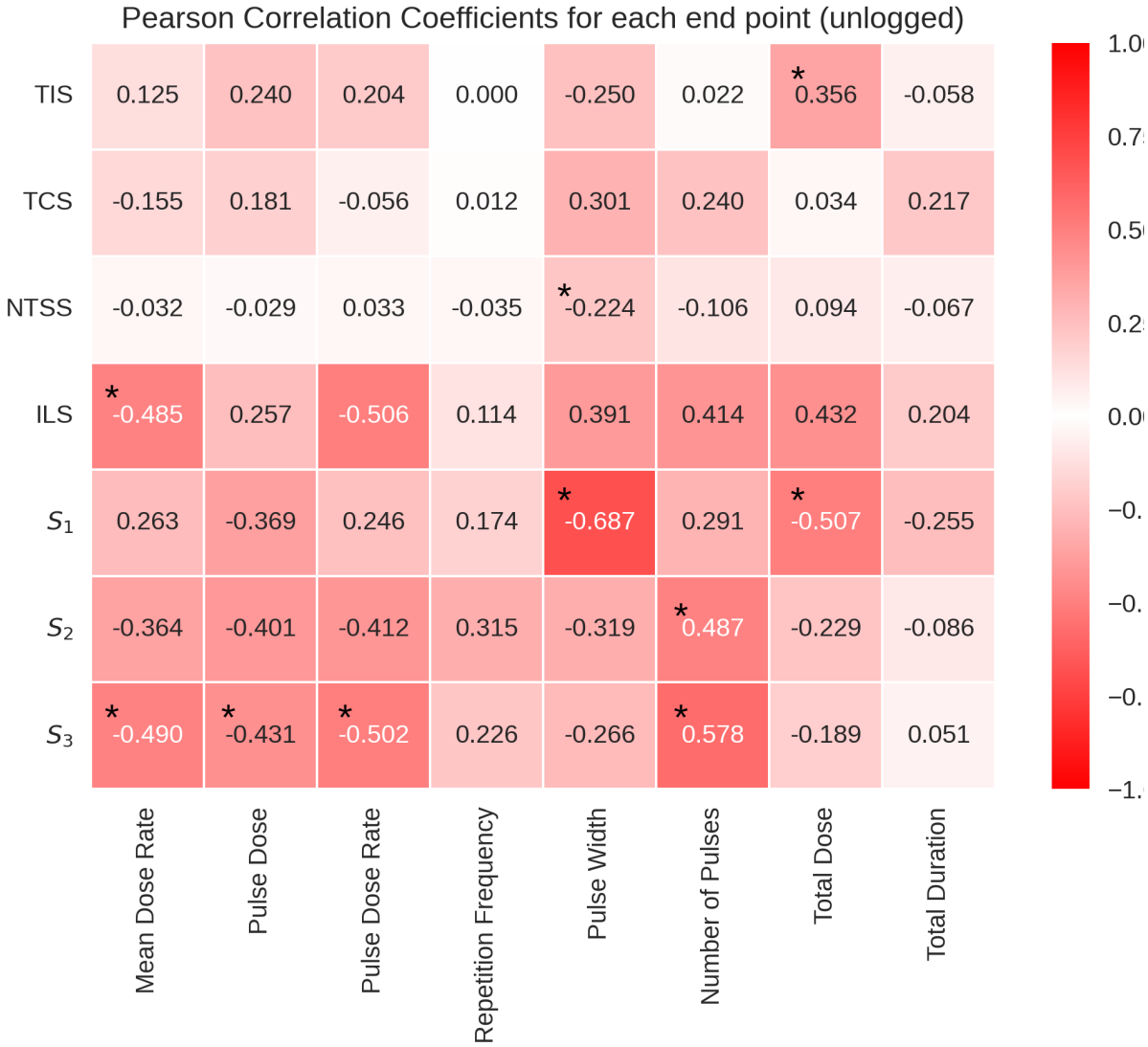
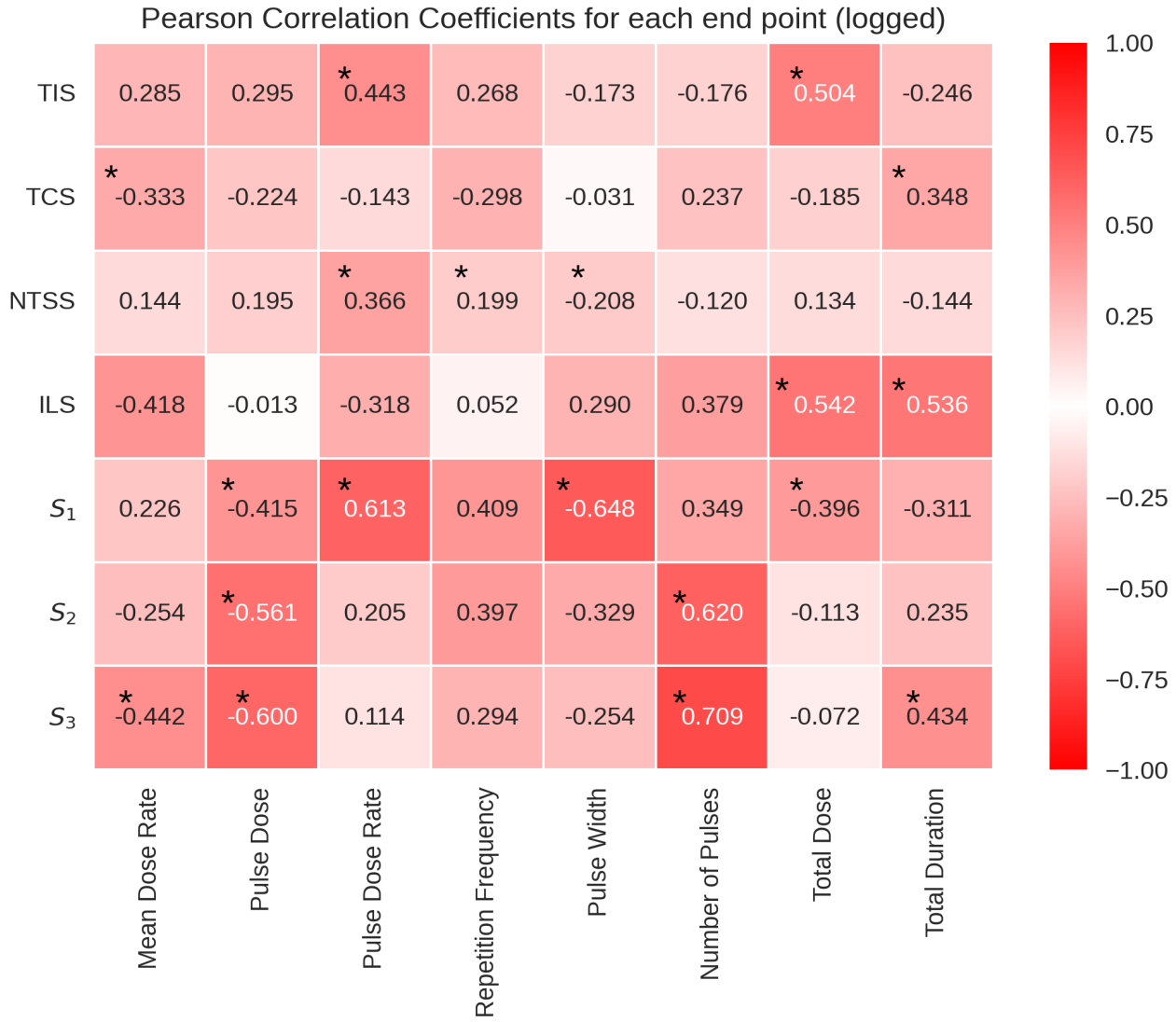


Figure 2: Pearson's correlation coefficients in heat map form to show the correlations between the log of each dosimetric parameter and the corresponding endpoint. The values range between -1 and 1, where the extremities (closest to -1 and 1) have the deepest colour and the weakest correlations (closer to 0) have a weak colour. Statistically significant correlations are identifiable by an asterisk at the top left of the corresponding correlation coefficient. Key: TIS- Therapeutic Index Score, TCS- Tumour Control Score, NTSS- Normal-tissue Sparing Score, ILS- Increased Lifespan, S_1- Survival % at 1 month, S_2- Survival % at 2 month, S_3- Survival % at 3 month.



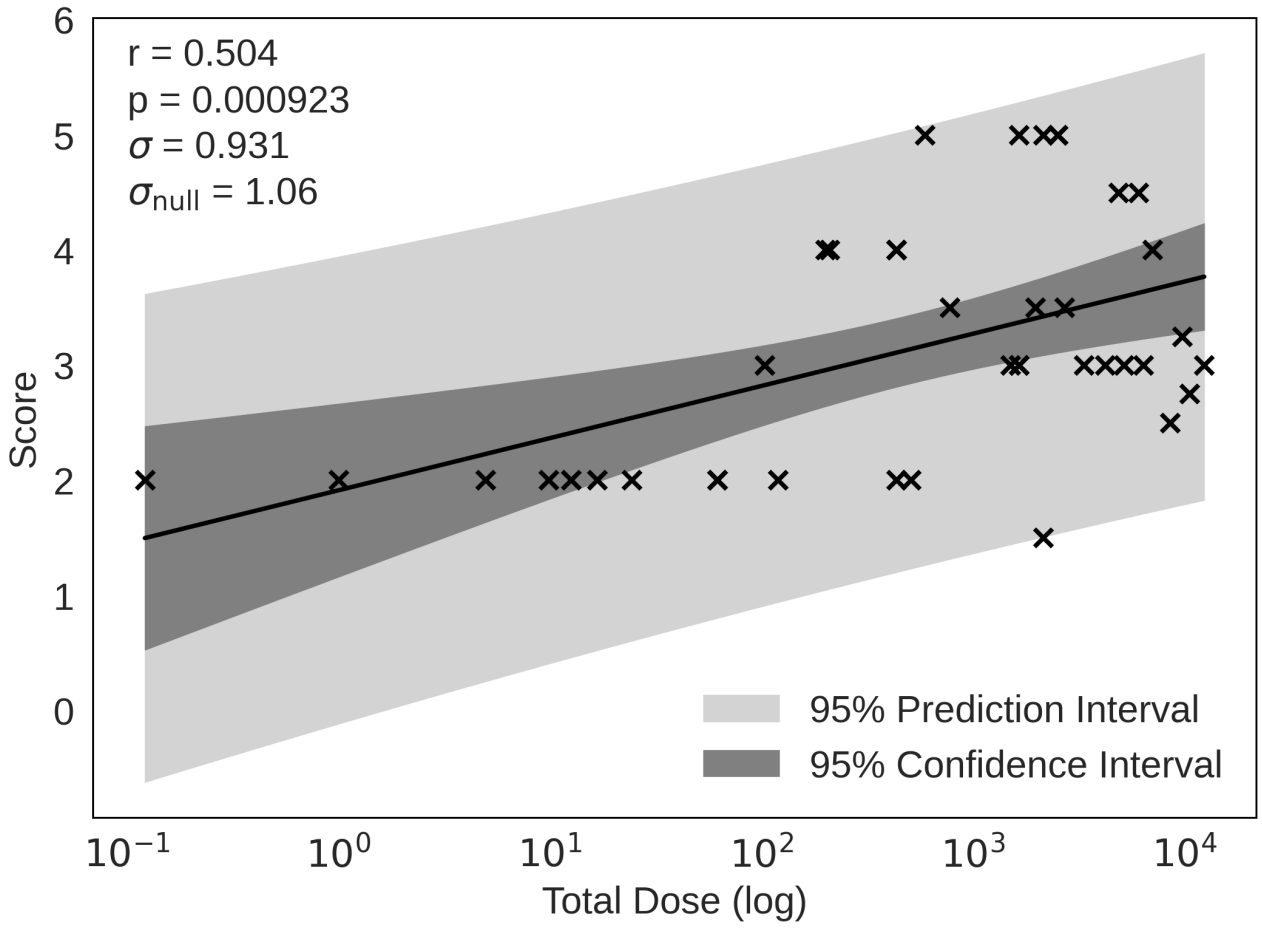


Figure 3: TIS plotted against the strongest dosimetric parameter, Total Dose. There is a strong positive correlation between the parameters, showing that an increase in dose will increase the chance of observing a higher therapeutic index.

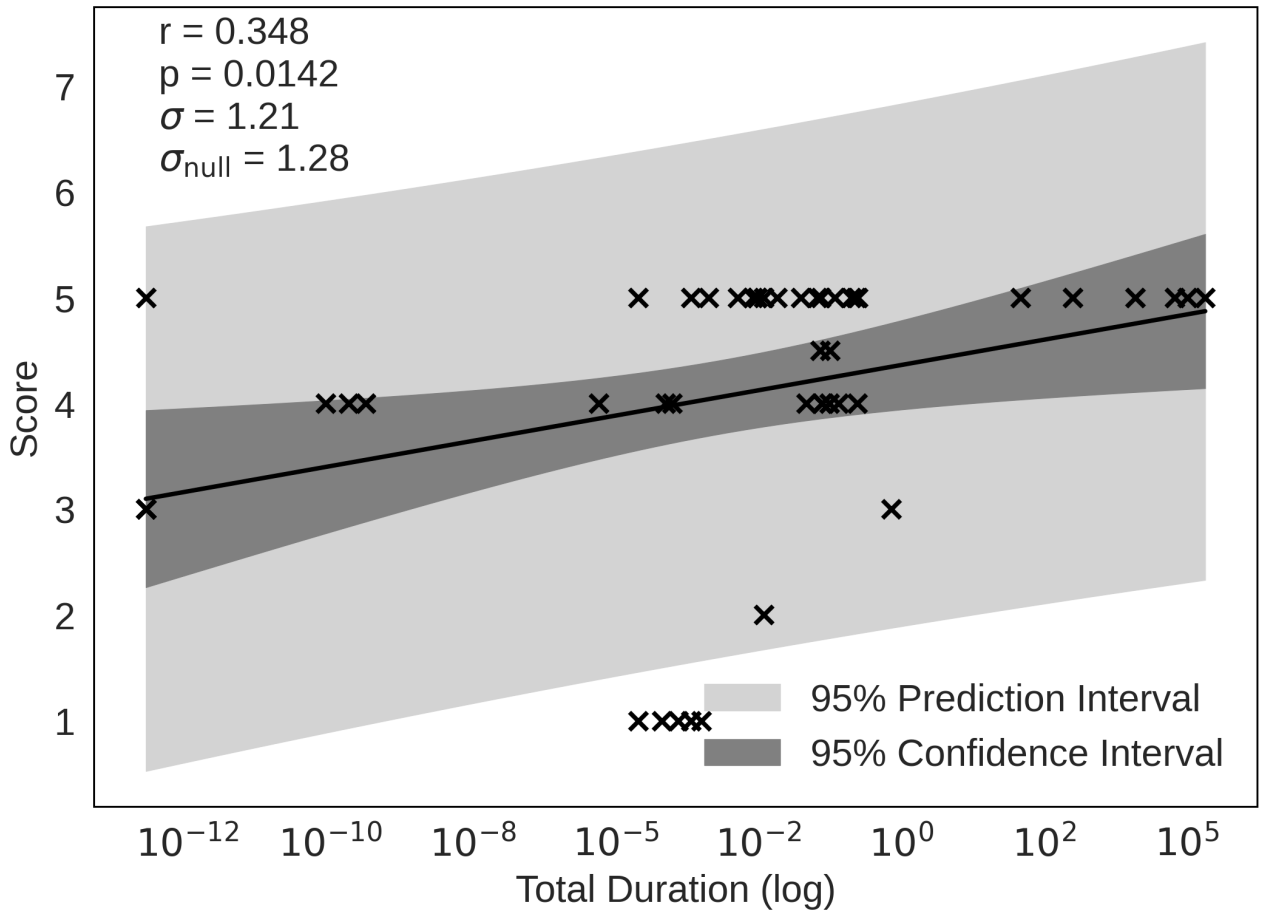


Figure 4: TCS plotted against the strongest dosimetric parameter, Total Time. There is a moderate positive correlation between the parameters, suggesting that an increase in irradiation duration may increase tumour control.

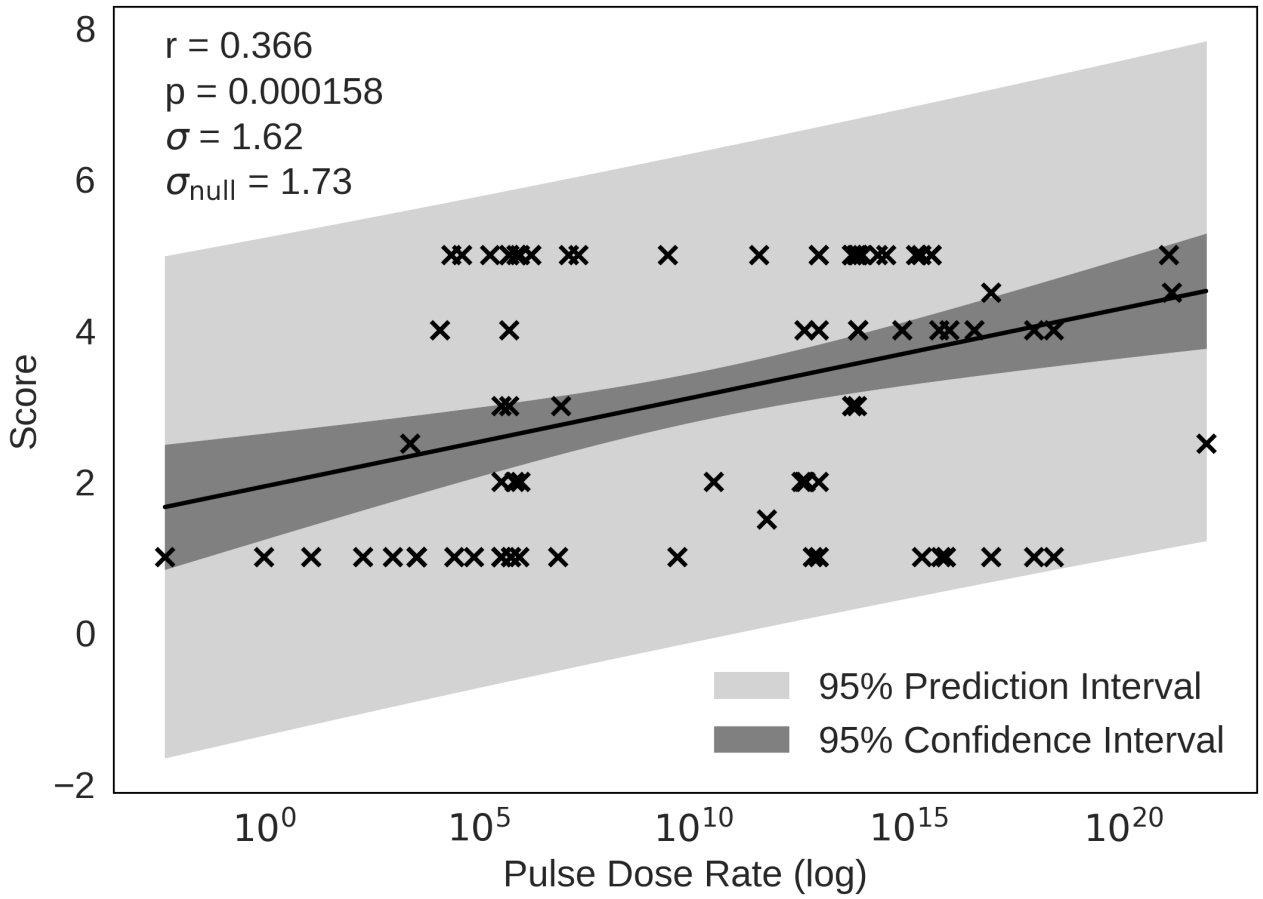


Figure 5: NTSS plotted against the strongest dosimetric parameter, Pulse Dose Rate. There is a moderate positive correlation between the parameters, suggesting that an increase in the dose rate of each pulse may increase the chance of observing a sparing effect in normal tissue.

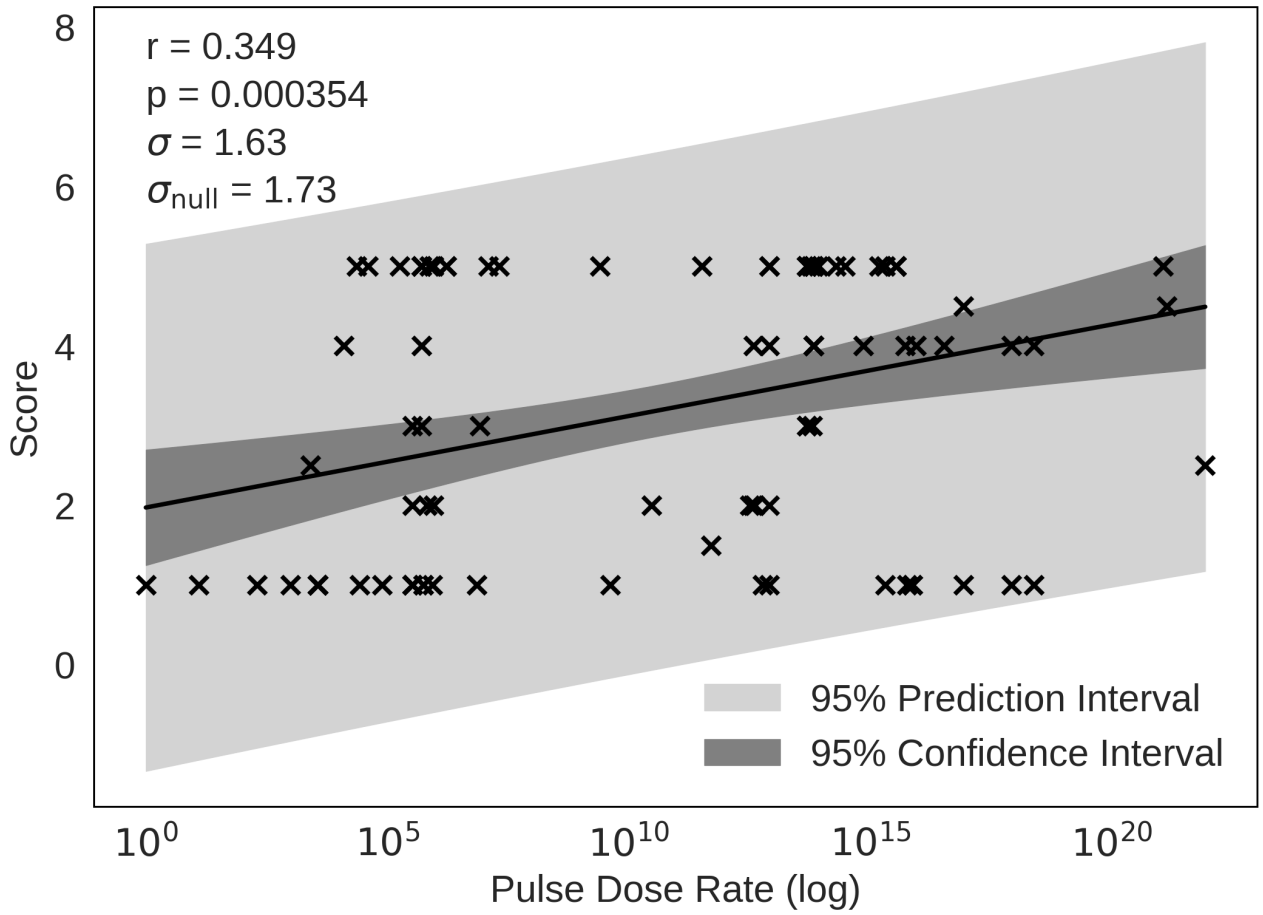


Figure 6: NTSS plotted against the strongest dosimetric parameter, Pulse Dose Rate **with the 0.1Gy/s extremity removed.** There is a moderate positive correlation between the parameters, suggesting that an increase in the dose rate of each pulse may increase the chance of observing a sparing effect in normal tissue.

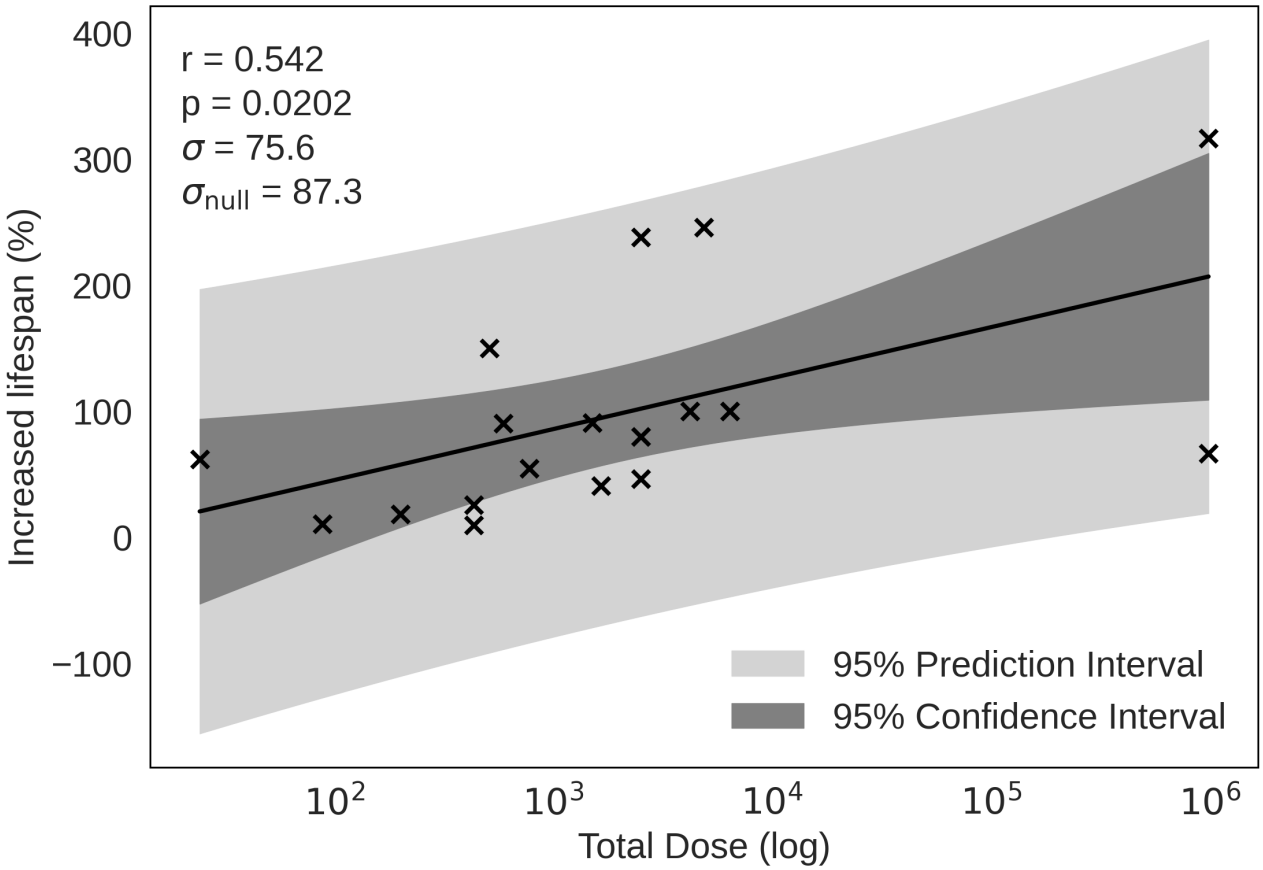


Figure 7: ILS plotted against the strongest dosimetric parameter, Total Dose. There is a strong positive correlation between the parameters, illustrating that an increase in dose can increase the lifespan of small animals.

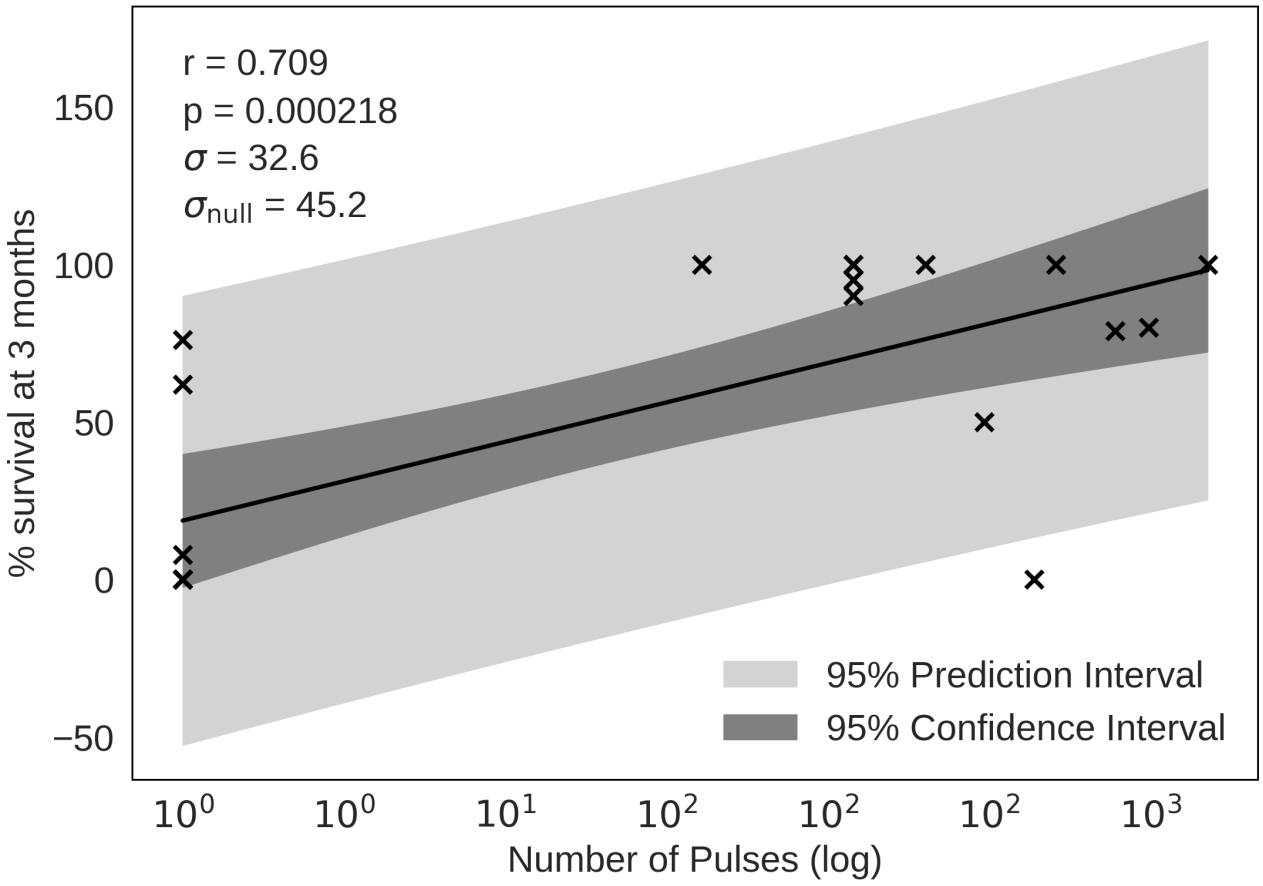


Figure 8: SS percentage plotted against the strongest dosimetric parameter, Number of Pulses. There is a strong positive correlation between the parameters, illustrating that an increase in the Number of Pulses can increase the survival time of small animals.

2 Supplementary Materials for Discussion

Figure 9: Pearson's correlation coefficients in heat map form to show the correlations between the log of each dosimetric parameter and the corresponding endpoint **for all data with mean and pulse dose rates above 30Gy/s.** The values range between -1 and 1, where the extremities (closest to -1 and 1) have the deepest colour and the weakest correlations (closer to 0) have a weak colour. Statistically significant correlations are identifiable by an asterisk at the top left of the corresponding correlation coefficient. Key: TIS- Therapeutic Index Score, TCS- Tumour Control Score, NTSS- Normal-tissue Sparing Score, ILS- Increased Lifespan, S_1- Survival % at 1 month, S_2- Survival % at 2 month, S_3- Survival % at 3 month.

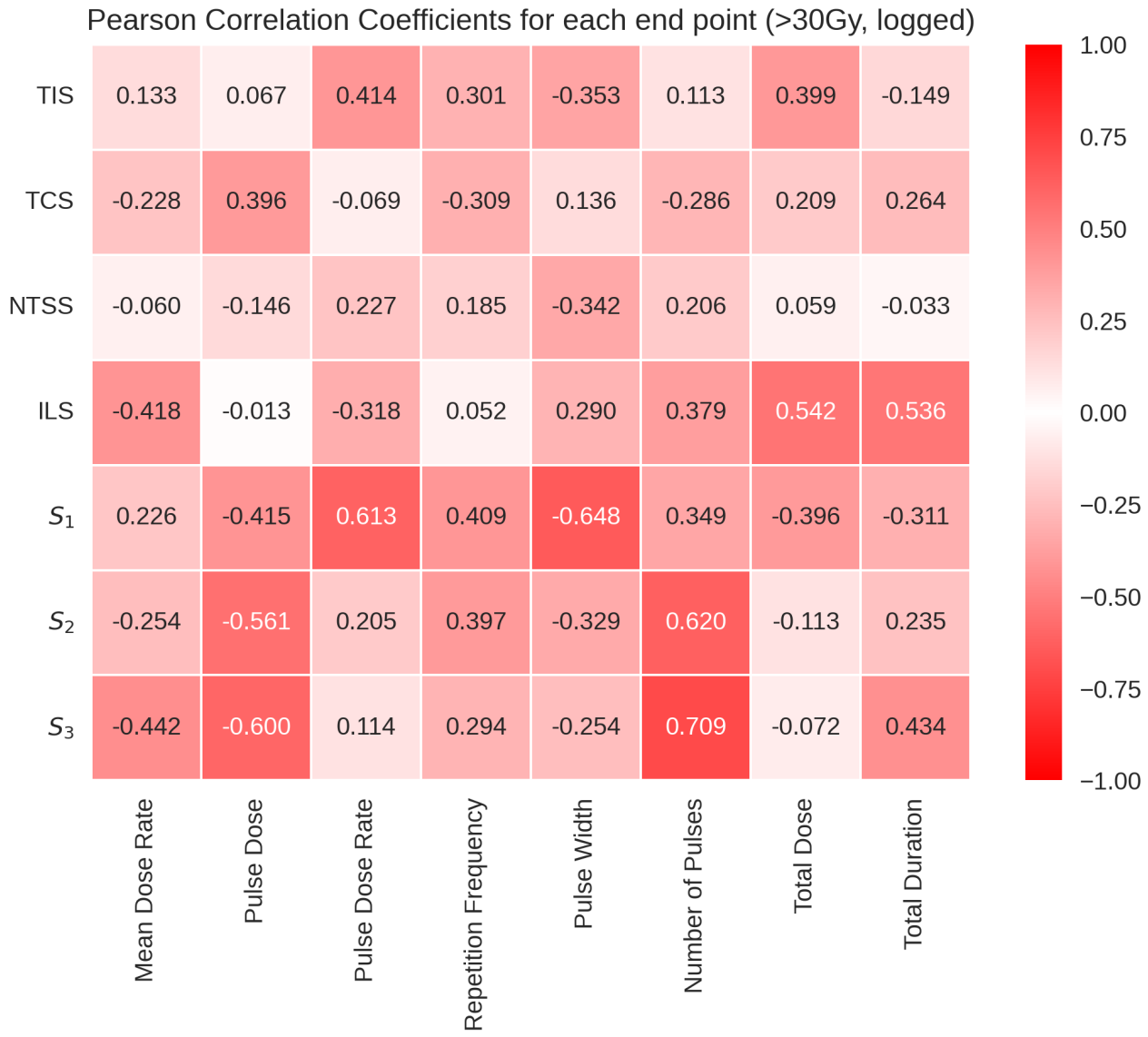
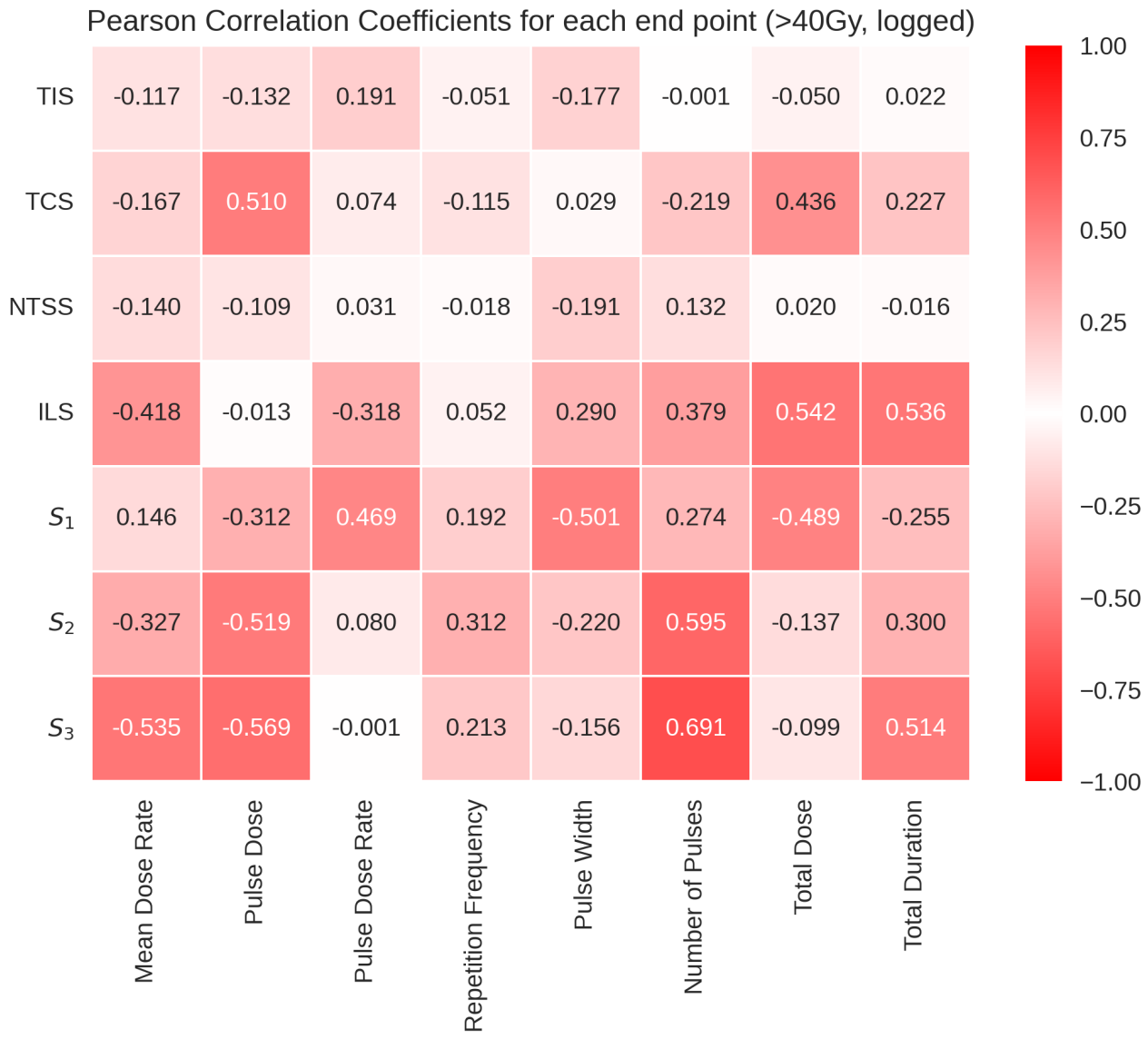


Figure 10: Pearson's correlation coefficients in heat map form to show the correlations between the log of each dosimetric parameter and the corresponding endpoint **for all data with mean and pulse dose rates above 40Gy/s.** The values range between -1 and 1, where the extremities (closest to -1 and 1) have the deepest colour and the weakest correlations (closer to 0) have a weak colour. Statistically significant correlations are identifiable by an asterisk at the top left of the corresponding correlation coefficient. Key: TIS- Therapeutic Index Score, TCS- Tumour Control Score, NTSS- Normal-tissue Sparing Score, ILS- Increased Lifespan, S_1- Survival % at 1 month, S_2- Survival % at 2 month, S_3- Survival % at 3 month.



References

[1] P. Montay-Gruel, M. M. Acharya, P. Gonçalves Jorge, B. Petit, I. G. Petridis, P. Fuchs, R. Leavitt, K. Petersson, M. Gondré, J. Ollivier, R. Moeckli, F. Bochud, C. Bailat, J. Bourhis, J.-F. Germond, C. L. Limoli, and M.-C. Vozenin, "Hypofractionated FLASH-RT as an effective treatment against glioblastoma that reduces neurocognitive side effects in mice," *Clin. Cancer Res.* **27** (Feb., 2021) 775–784.

[2] E. Konradsson, E. Liljedahl, E. Gustafsson, G. Adrian, S. Beyer, S. E. Ilaahi, K. Petersson, C. Ceberg, and H. Nittby Redebrandt, "Comparable long-term tumor control for hypofractionated FLASH versus conventional radiation therapy in an immunocompetent rat glioma model," *Adv. Radiat. Oncol.* **7** (Nov., 2022) 101011.

[3] E. Liljedahl, E. Konradsson, E. Gustafsson, K. F. Jonsson, J. K. Olofsson, C. Ceberg, and H. N. Redebrandt, "Long-term anti-tumor effects following both conventional radiotherapy and FLASH in fully immunocompetent animals with glioblastoma," *Sci. Rep.* **12** (July, 2022) 12285.

Table 1: % survivors of Glioma-bearing rats at 3 months post FLASH (ultra-high dose rates, dose rate of FLASH-RT recorded in columns 2 and 3) vs CONV (conventional radiotherapy, conventional dose rates). Average and standard error recorded for both modalities.

Journal Citation	Mean Dose Rate (Gy/s)	Pulse Dose Rate (Gy/s)	% survivors post FLASH	% survivors post CONV
[1]	5600000.00	5555555.56	0.00	0.00
[2]	571428.57	285714.29	50.00	48.00
[2]	595238.10	297619.05	78.80	100.00
[2]	535714.29	267857.14	100.00	93.00
[3]	66.00	133.33	100.00	85.00
[3]	74.00	73.53	0.00	0.00
		Average	54.80	54.33
		Error	7.71	7.63