Non-Targeted Effects and the Dose Response for Heavy Ion Tumorigenesis
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Abstract

BACKGROUND

The usage of human cell culture models in 2D or 3D is needed to support the design of new experiments to detect NTE at low dose for validation. Power was determined by the ability to detect if NT Effects (x) are significant at low dose. Doses were chosen at 0.05 and 0.3 Gy and 3 or 6 irradiations chosen as seen in the figure with sample sizes such that all doses have equal binomial variances. Dosing Schemes for irradiated mice:

1. Three radiation doses (D1, D2, and D3 from figure) were considered and d = 2%
2. Three radiation doses were considered and d = 1%
3. Four radiation doses (D1, D2, D3, and D4 from figure) were considered and d = 2%

Table: Sensitivity of sample size to detect NTE with 80% power to the scheme choice and background ELPP prevalence (P0). P0 = 2.44

Scheme 1 Scheme 2 Scheme 3 Scheme 4
P0 = 2.44 P0 = 2.44 P0 = 2.44 P0 = 5
Fe1 Let1 Let2 Let3
LET = 70 100 120 140
D = 1 1 1 1 1

Power Analysis Specifications

The study focuses on low doses where the cell sterilization term can be ignored. Power analysis for the NTE model was used to investigate the dependency for each individual ion. Simulations were analyzed using conventional linear models with binomial errors following the low dose model. Power was determined by the ability to detect if NT Effects (x) are significant at low dose. Doses were chosen at 0.05 and 0.3 Gy and 3 or 6 irradiations chosen as seen in the figure with sample sizes such that all doses have equal binomial variances. Dosing Schemes for irradiated mice:

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Power Analysis Conclusions

Dosing Scheme 3 was optimal. More mice are needed as the value of P0 increases. The sample size estimates to test for NTE for single ions with the estimate sample size requirements when results from several ions are combined into a model that describes the LET dependence of the tumour response.

Red Bullets Gaps in Progress and Knowledge

The relative contribution to cancer risks from targeted effects and non-targeted effects remains elusive with too few experiments designed to test the shape of the dose response at low doses (0.3 Gy) applicable to space missions. 

Only a few murine model tumors have been studied with only a few ion types. The paucity of data limits the building and testing of models of cancer risk from space radiation.

The usage of human cell culture models in 2D or 3D is needed to support the applicability of murine models to human risk prediction, however much work remains in making the necessary connections. Of importance is the need for more expansive data sets on radiation quality at a variety of low doses to understand the shape of the dose response for cancer processes induced by heavy ions.