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EASTERN TIME [GMT-4]

Optimal Dose-Rate for PLDR

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INTRODUCTION

Pulsed Low Dose Rate (PLDR) is potentially a re-irradiation treatment technique that allows dose to be delivered to a prior treated volume, with a corresponding decrease in the biological effectiveness of radiation to healthy adjacent tissue. (1-4)

AIM

To investigate the optimal radiation dose rate for pulsed low-dose-rate (PLDR) radiation therapy using in vitro clonogenic analysis.

METHOD

Lung cell line A549 (Adenocarcinomic human alveolar basal epithelial cells) and human prostate cancer cells (PC3) were cultured using Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum, with penicillin (50 U/ml), and streptomycin (50 µg/ml) at 37°C under 95% humidity and 5% CO_2 atmosphere. All experiments used cells in the exponential growth phase by seeding ~200 cells into T-25 flasks, in triplicate, 8-10 hours before use. A clinically calibrated beam from a Varian-2100-iX machine was used to deliver a total dose of 0.25, 0.5, 1, 2 and 4 Gy to the cells. The dose rate for the CRT group was 200 cGy/min.

CRT 4Gy	Plate Cells ↓	Incubate ←12h→	CRT(x1) 4 Gy ↓	Incubate ←2w→	Count ↓

PLDR 3m 4 Gy	Plate Cells ↓	Incubate ←8h→	PLDR (x1) 0.25 Gy ↓ Wait ←3m→	PLDR (x2) 0.25 Gy ↓ Wait ←3m→	PLDR (x3) 0.25 Gy ↓ Wait ←3m→	PLDR (x4) 0.25 Gy ↓ Wait ←3m→	• • •	PLDR (x13) 0.25 Gy ↓ Wait ←3m→	PLDR (x14) 0.25 Gy ↓ Wait ←3m→	PLDR (x15) 0.25 Gy ↓ Wait ←3m→	PLDR (x16) 0.25 Gy ↓ Wait ←3m→	Incubate ←2w→	Fix Stain Count ↓

The effective dose rates (EDR) for PLDR (8.3, 25, 60, 150 cGy/min) were determined by varying time between a train of radiation pulses, each 0.25 Gy. After irradiation, cells were incubated for 8 to 9 days, colonies were counted, and the surviving fractions of clonogenic cells were determined. This method generally follows that of published studies by S. Terashima (5)

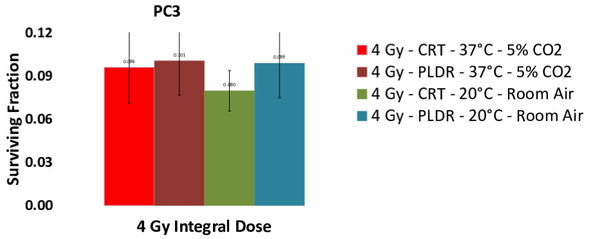
PLDR treatment times are much longer compared to CRT; this implies that cells are out of their 'comfortable' incubator-like conditions; it is possible normal intra-cellular mechanisms may be altered sufficiently to affect measurable outcomes.

	CO_2 pp	Temperature	Humidity
Incubator	5%	37°C	95%
LINAC	0.04%	20°C	Unsure

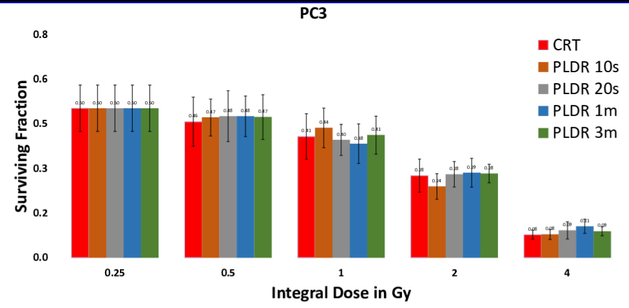
To determine if there is an effect between cells maintained at incubator-like conditions of 37°C and 5% CO_2 atmosphere and cells maintained at the temperature in the treatment vault of 20°C with room atmosphere; four groups of cells were created, in triplicate, for total of 6 experiments.

RESULTS

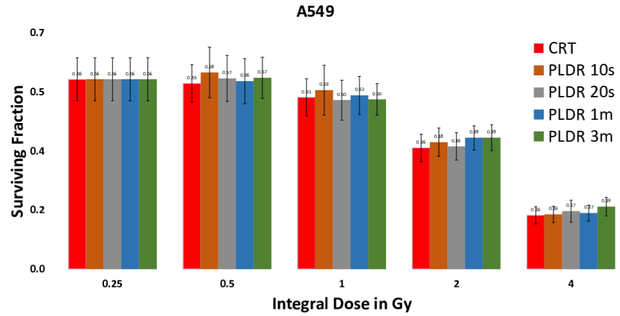
Both cell lines showed comparable responses between CRT and PLDR with different EDRs, where their survival fractions decreased with dose but were unremarkable. All PLDR groups were statistically indistinguishable among each other, and from CRT. Both cell lines were observed to be agnostic towards variation with the dose rate in radiation repair response or low-dose hyper-radiosensitivity in this study.



Incubator conditions were maintained by using tightened non-filtered caps immediately after leaving the incubator. Temperature was maintained by use of custom heated and insulated tank. This result show that the preservation of 5% CO_2 atmosphere and 37°C produced no statistically significant survival difference.



Survival of CRT cells were typical. PC3 cells showed comparable responses between CRT and PLDR. Cell response agnostic among different EDRs. Low dose hyper-radiosensitivity was not observed. Enhanced survival of PLDR due to ongoing radiation repair was not observed.



Survival of CRT cells were typical. A549 cells showed comparable responses between CRT and PLDR. Cell response agnostic among different EDRs. Low dose hyper-radiosensitivity was not observed. Enhanced survival of PLDR due to ongoing radiation repair was not observed.

CONCLUSIONS

PLDR effect at different EDRs is comparable to that of CRT against two human cell lines. This result adds to the body of research showing PLDR's clinical efficacy, due its equivalent tumor control and normal tissue sparing properties with decreased EDRs. PLDR may be developed into a clinically viable alternative for treating large tumor masses and/or recurrent cancers with decreased normal tissue tolerances. We were not able to replicate the results of S. Terashima et al. (5) Enhanced survival of PLDR due to ongoing radiation repair was not observed in this study, however, these results do not preclude that this mechanism is not intact, and measurable, for non-cancerous 'healthy' cells, such as those adjacent to a targeted volume.

REFERENCES

1 **K. Rogacki et al.** Review of Pulsed Reduced Dose Rate Re-irradiation for Recurrent Tumors; J Cancer clin Trials 2018, 3:2

2 **C. Ma et al**. Pulsed Low-Dose-Rate Radiation Therapy (PLDR) for Recurrent Cancers: Treatment Planning Strategies for IMRT and VMAT. Radiation Oncology; VOL 90, IS 1, SUP , S941, 2014.

3 **J. Li et al**. Intensity-modulated radiation therapy for pancreatic and prostate cancer using pulsed low–dose rate delivery techniques; Medical Dosimetry; 2014.

4 **S. Kang et al.** Optimization strategies for pulsed low-dose-rate IMRT of recurrent lung and head and neck cancers. Journal of Applied Clinical Medical Physics; VOL 15, NO 3, 2014.

5 **S. Terashima et al.** Impact of time interval and dose rate on cell survival following low-dose fractionated exposures; Journal of Radiation Research, Vol. 58, No. 6, 2017, pp. 782–790

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