Cytogenetic Dose Response on 6 MV Linear Accelerator: Reduced RBE of Megavoltage X-ray Photons Is Not Obvious

Volodymyr Vinnikov, PhD[1,2]

[1]Cancer Research Institute, Biomedical Research Centre of Slovak Academy of Science, Bratislava, Slovak Republic;
[2]S.P. Grigoriev Institute for Medical Radiology and Oncology of the National Academy of Medical Science of Ukraine, Kharkiv, Ukraine

INTRODUCTION

Modern methodology of cytogenetic biodosimetry necessitates the construction of a dose response curve (DRC) *in vitro* for each type of radiation that can potentially cause a radiation emergency. Also, due to a unified methodology of quantification of cytogenetic biomarkers, such experiments are beneficial in terms of fairly accurate assessment of the relative biological effectiveness (RBE) of different types of radiation. Currently there are controversial opinions about the RBE of X-ray photons, produced by megavoltage linear accelerators (LINACs), and published experimental data are fairly insufficient compared to orthovoltage X-rays or γ-rays. The aim of the present study was to generate a DRC for classical dicentric assay in human lymphocytes with exposure to 6 MV X-ray photons from a medical linear accelerator, and to compare the cytogenetic damage outcome per unit dose with that previously reported in the literature for radiation beams of similar radiation quality and orthovoltage X-rays.

MATERIALS AND METHODS

Peripheral blood samples from 4 healthy volunteers were irradiated with acute 6MV LINAC photons over a dose range of 0.46 – 5.46 Gy, at 3 Gy/min, in a water-filled mini-phantom at 37 °C, with a sham-exposed control. Blood lymphocytes were cultured in presence of 5-Bromo-2'-deoxy-Uridine for 48-50 h; metaphase preparations were stained with Fluorescence-plus-Giemsa. Photo-images of metaphases were collected on Metafer_v.4 (MetaSystems) and analyzed for the presence of unstable chromosome aberrations in the 1st division metaphases. Technical conditions of irradiation and dicentric assay was in strict compliance with international requirements [1, 2].

Also, published data on dicentric dose response yields induced *in vitro* by megavoltage X-ray photons or electrons or orthovoltage X-rays (≥ 85 keV) were extracted from the literature. Coefficients of the linear-quadratic (LQ) DRCs were fitted from the obtained experimental data or published datasets using the software package Dose Estimate_v.5.1.

Figure 1. Blood samples in secondary containers, placed into the mini-phantom, all filled with water

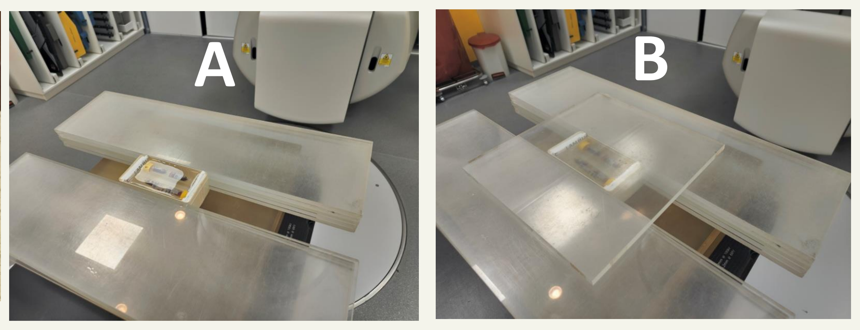


Figure 2. Irradiation setup under LINAC: mini-phantom surrounded by PMMA plates (A) and covered with a PMMA plate (B)

CONTACT

Volodymyr Vinnikov

Department of Radiobiology,
Cancer Research Institute,
Biomedical Research Centre of Slovak Academy of Science,
Bratislava, Slovak Republic

Email:
vlad.vinnikov@ukr.net

Website:
http://www.biomedcentrum.sav.sk/research-departments/department-of-radiobiology/

RESULTS

A dose dependent increase of dicentric yields induced *in vitro* by LINAC 6 MV X-ray photons was observed; some tendency to underdispersion in aberration-per-cell distributions compared to Poisson statistics occurred at doses > 3 Gy (Table 1). The dose response for dicentrics fit well to the LQ model with linear coefficient $\alpha = 0.0318 \times cell^{-1} \times Gy^{-1}$, and quadratic coefficient $\beta = 0.0741 \times cell^{-1} \times Gy^{-2}$ (Chart 1). Coefficients of individual DRCs for 4 donors ranged within fairly narrow intervals: $\alpha = 0.0212 - 0.0419 \times cell^{-1} \times Gy^{-1}$, and $\beta = 0.0665 - 0.0875 \times cell^{-1} \times Gy^{-2}$, with a clear negative correlation between α and β (Chart 2). The values of α and β, obtained in our experiment, were comparable to the modal cluster of DRC coefficients for orthovoltage X-rays, to which several published LINAC DRCs also fell in.

Table 1. Dicentrics scoring data in the dose response experiment (4 donors combined)

Dose, Gy	Cells	Dicen-trics	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	Yield (Y)	±SE	σ²/Y	Papworth *u*-test
0.000	8000	4	7996	4	0	0	0	0	0	0	0	0	0.001	0.000	1.000	-0.027
0.455	4000	142	3860	138	2	0	0	0	0	0	0	0	0.035	0.003	0.993	-0.318
0.910	2000	168	1840	152	8	0	0	0	0	0	0	0	0.084	0.006	1.010	0.372
1.820	1600	505	1180	344	67	9	0	0	0	0	0	0	0.316	0.014	1.060	1.620
2.730	1400	788	796	453	122	25	4	0	0	0	0	0	0.563	0.020	0.999	-0.033
3.640	800	882	244	322	162	56	12	4	0	0	0	0	1.100	0.037	0.901	-1.980
4.550	400	647	74	130	108	59	23	5	0	1	0	0	1.620	0.064	0.912	-1.250
5.460	300	808	15	54	69	86	41	23	7	4	0	1	2.690	0.095	0.854	-1.790

Chart 1. Dicentric DRC for 6 MV LINAC X-ray photons, compared to dicentric yields, reported for megavoltage beams in 14 publications

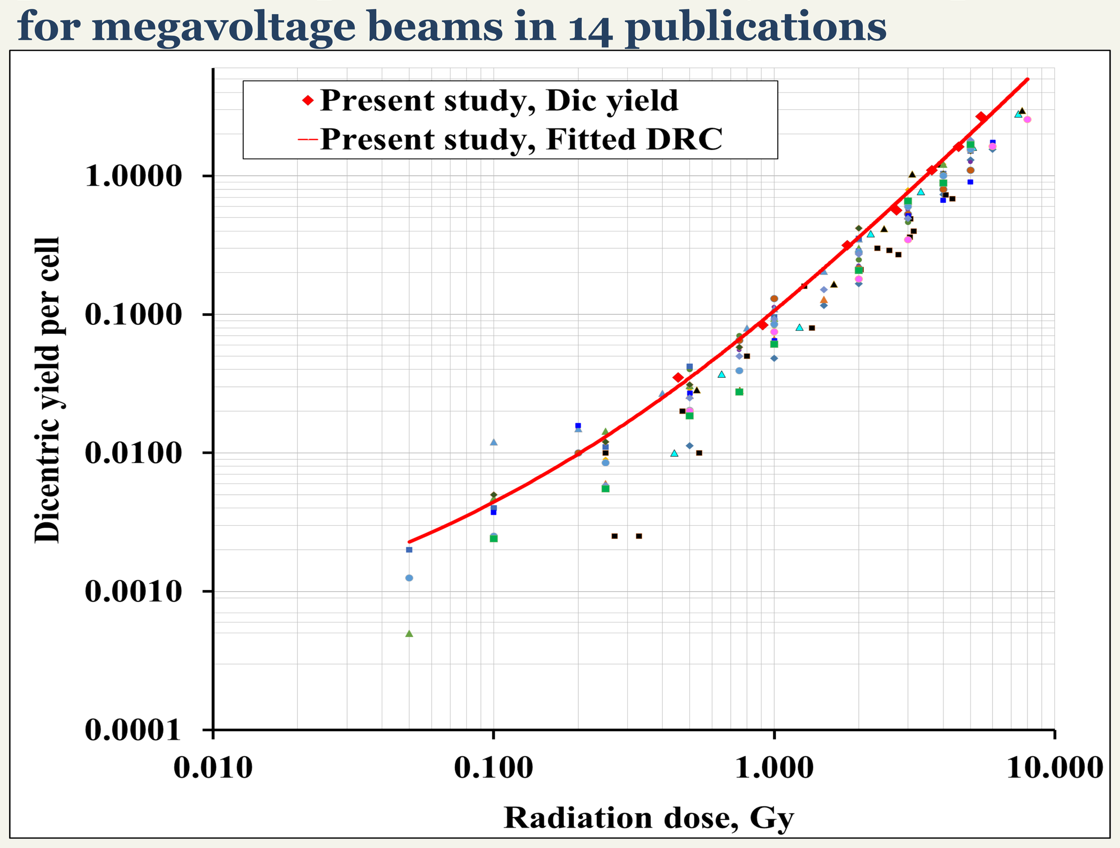
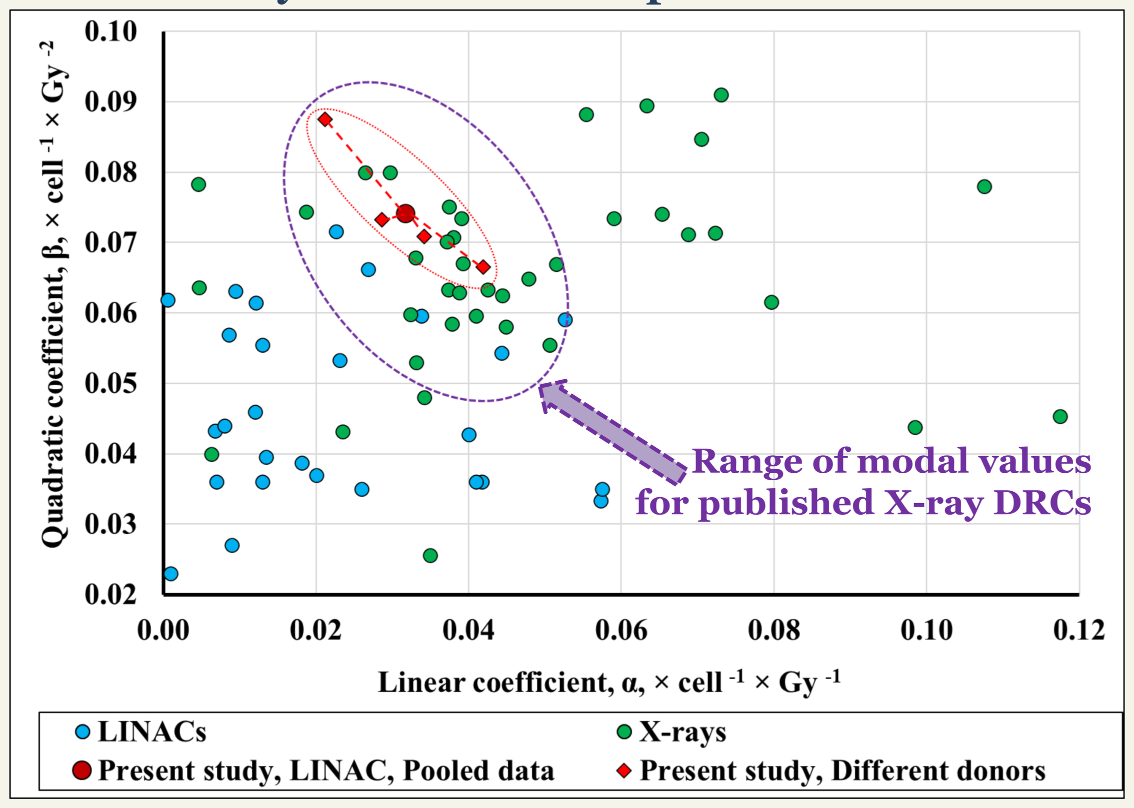


Chart 2. LQ coefficients of DRCs constructed using megavoltage LINAC beams or orthovoltage X-rays: Present study *versus* re-fitted published data



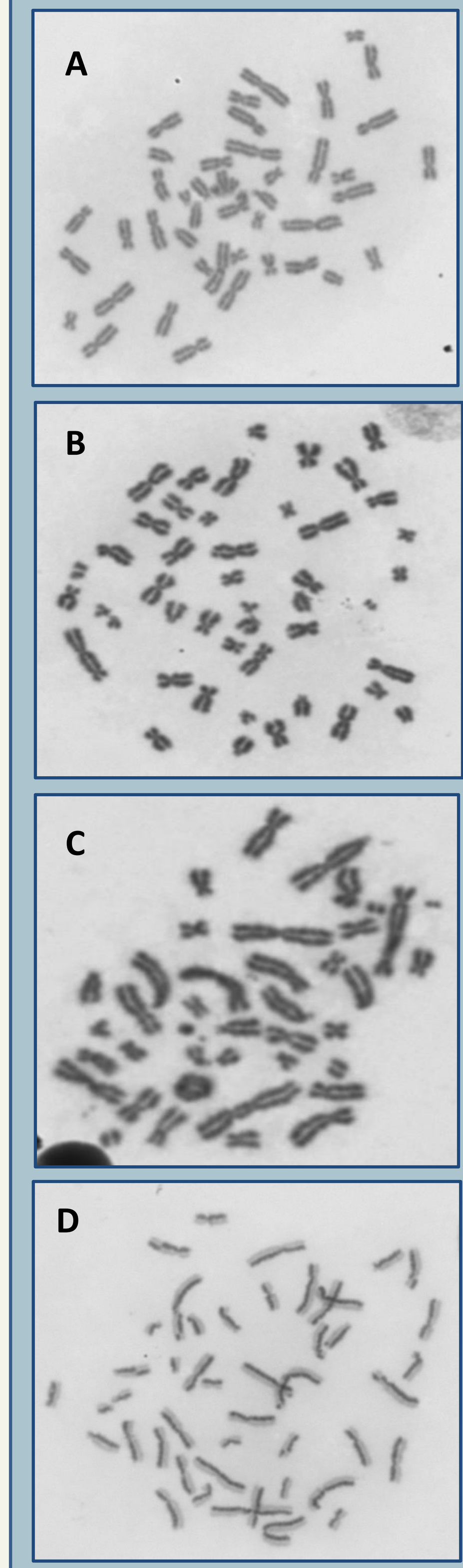


Figure 3. Metaphase spreads in cytogenetic study: Normal cell without aberrations (A), Cell with one dicentric and accompanying fragment (B); Cell with multiple radiation-induced chromosome aberrations (C), and 2nd division cell, excluded from analysis (D).

DISCUSSION & CONCLUSIONS

Theoretically, the yield of cytogenetic damage caused by megavoltage X-ray photons should be lower per unit dose than that induced by orthovoltage X-rays. However, in our study, at each experimental dose point, the frequency of dicentrics was at the upper limit of the range of values, reported in the literature for megavoltage beams, and only a limited number of datasets, obtained with orthovoltage X-rays, showed higher RBE.

Apart from the effect of beam energy and donors' inter-individual differences in chromosomal radiosensitivity, there are experimental factors that may have an impact on cytogenetic DRCs, e.g. the number of scored cells and dicentrics included into statistical analysis on different dose points, the depths of sample placement in the water phantom for irradiation, the method of control of post-radiation mitoses in culture, and, most obviously, significant inter-laboratory variations in aberration scoring criteria.

Further cytogenetic assessment of the RBE of megavoltage beams in the interests of radiological protection or radiation oncology requires more stringent standardization of experimental conditions.

REFERENCES

1. International Atomic Energy Agency (IAEA). Cytogenetic dosimetry: Applications in preparedness and for response to radiation emergencies. Vienna: IAEA.
2. ISO 19238:2014. Radiological protection — Performance criteria for service laboratories performing biological dosimetry by cytogenetics.

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