THE HENRYK NIEWODNICZAŃSKI
INSTITUTE OF NUCLEAR PHYSICS
POLISH ACADEMY OF SCIENCES

Normal tissue injury induced by photon and proton therapies

Mechanisms, Gaps and Opportunities

Kraków, 13.05.2021

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Outline

- ✓ **Proton *vs.* photon therapy data for normal tissue injury (clinical trials)**
- ✓ **Impact of normal tissue response on radiotherapy process optimization – mechanisms**
- ✓ **Normal tissue response – pre-clinical studies**
- ✓ **Gaps and opportunities**
- ✓ **Future directions**

Due to physical properties, protons and heavy ions deposit energy more selectively than X-rays, allowing a higher local control of the tumor.

Thus, the damage induced in normal tissues surrounding the tumor is limited.

The general aim for radiotherapy is to **assist optimisation of cancer cells killing** while **minimising harmful effects** to **normal tissue of individual patients.**

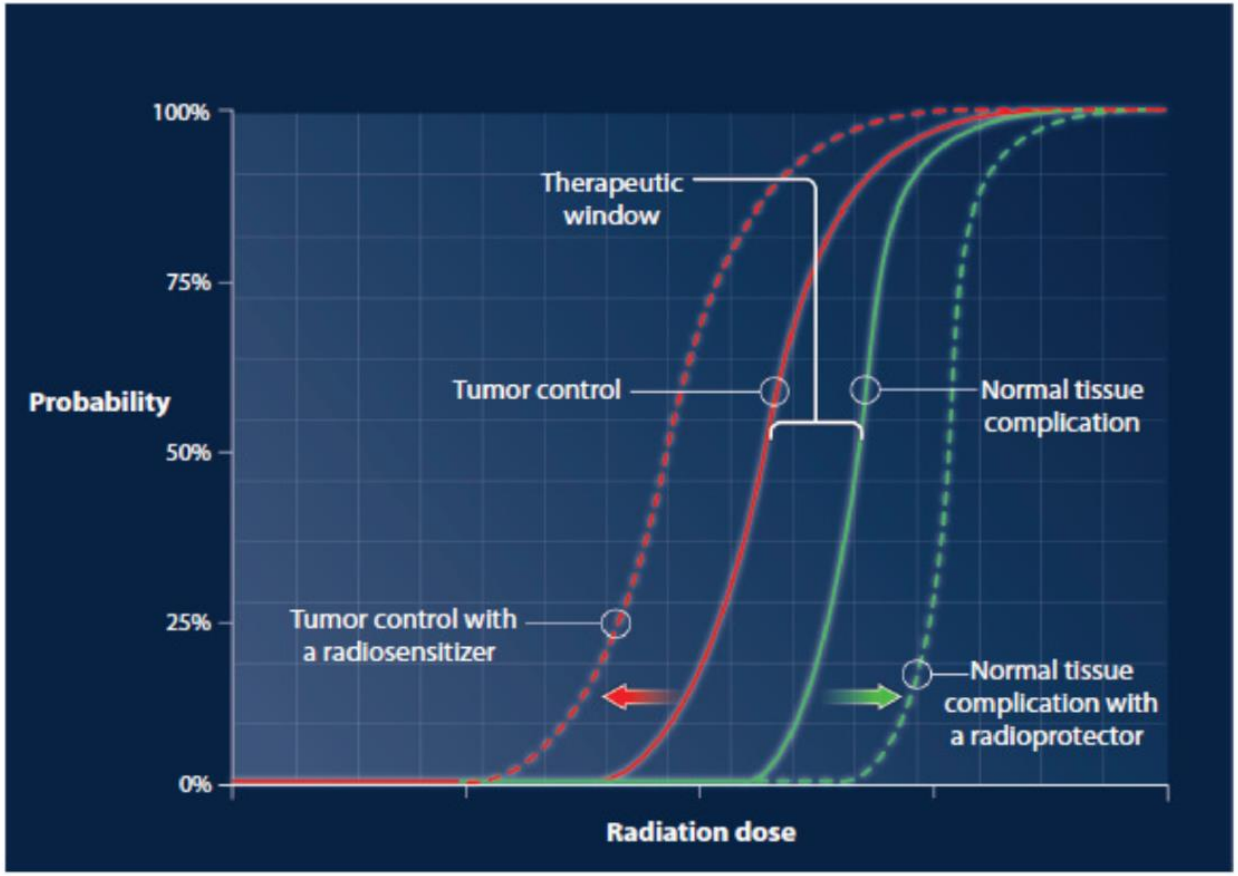

Fig. 1. An idealized graphical representation of tissue effects *vs.* radiation dose.

Irradiation of normal tissue is almost unevitable

The **tumor** and the surrounding **microenvironment** are closely related and interact constantly.

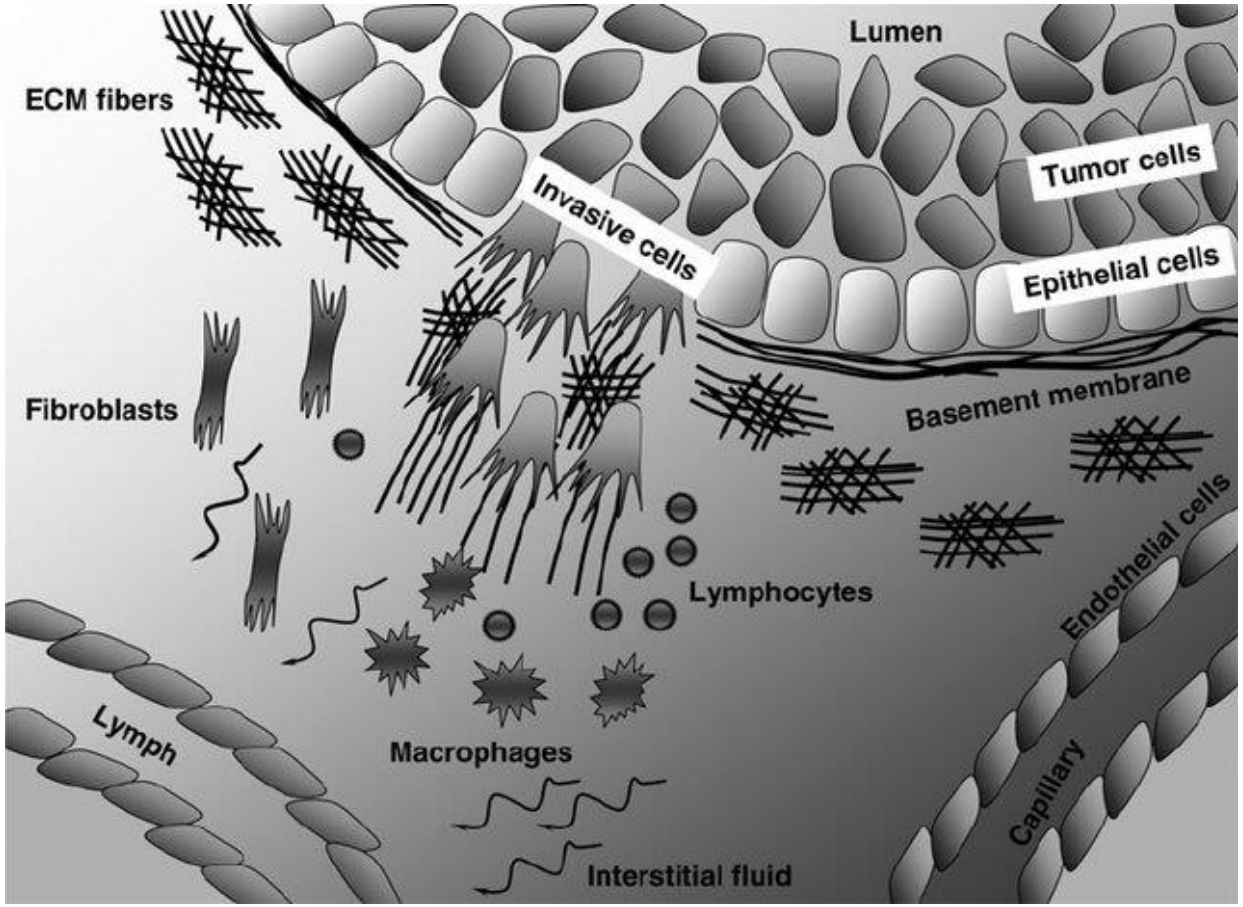

Fig. 2. A scheme of tumor microenvironment components.

A steady increase in PT literature is observed

International Journal of
Radiation Oncology • Biology • Physics ASTRO

CRITICAL REVIEW | ARTICLES IN PRESS

Normal Tissue Injury Induced by Photon and Proton Therapies: Gaps and Opportunities

Pataje G. Prasanna, Ph.D. • Kamila Rawojc, Ph.D. • Chandan Guha, M.B.B.S., Ph.D. • Jeffrey C. Buchsbaum, M.D., Ph.D., FASTRO • Justyna U. Miszczyk, Ph.D. • C. Norman Coleman, M.D., FASTRO

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Office of Portfolio Analysis, NIH,
a web application to access bibliometric information for publications.

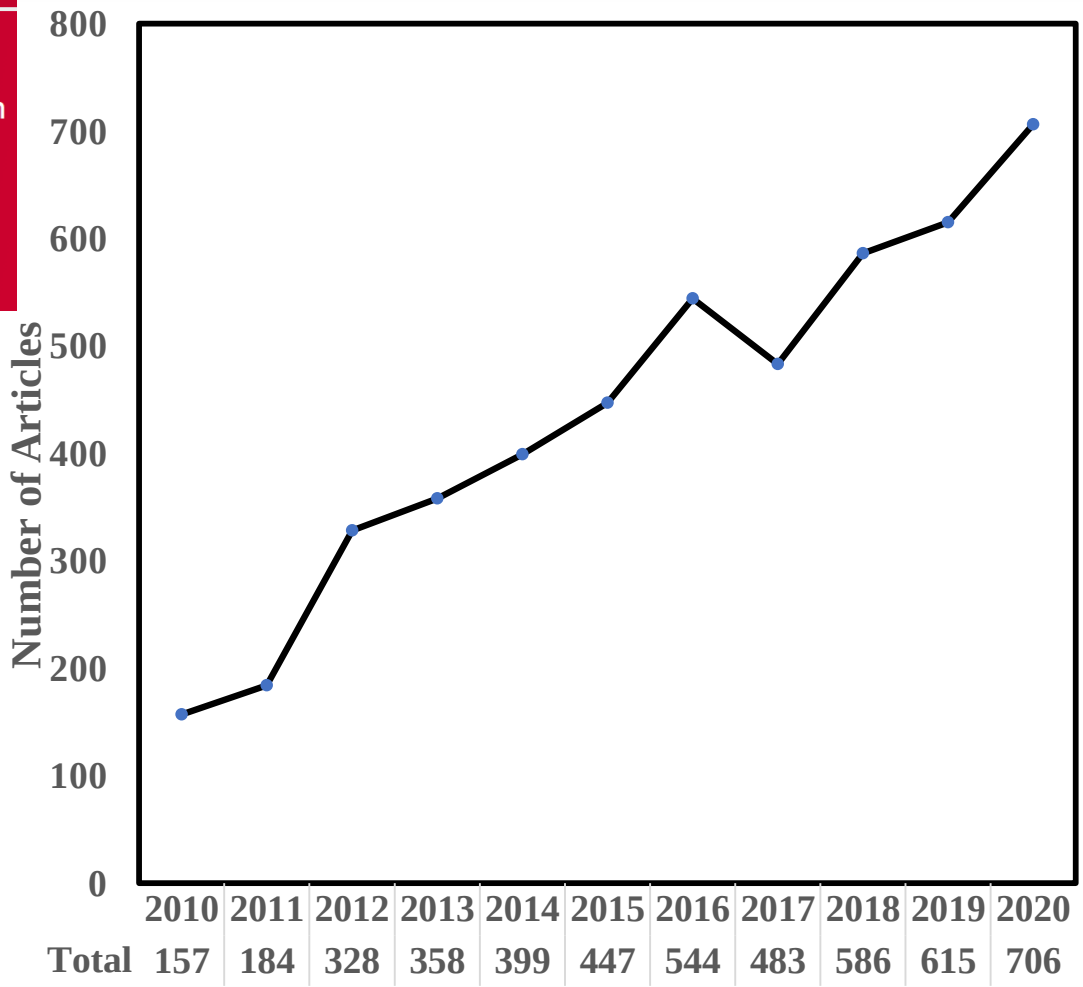


Fig. 3. Number of articles published in PT during the last decade.

Proton therapy is attracting attention worldwide

Article Type	Total Publications	Publications/Year	Citations/Year		
			Max	Mean	SEM
All Articles	4807	437	51.88	2.32	0.05

According to the latest updates (2020) of the Particle Therapy Co-Operative Group (PTCOG),

110 particle therapy facilities – in operation
37 under construction
28 in various stages of planning

More than **220,000 patients** have already undergone PT treatments.

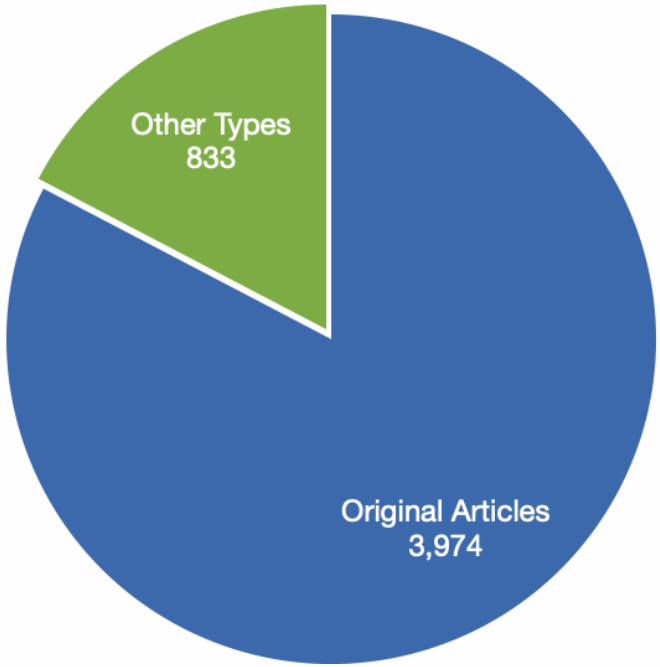


Fig. 4. Summary statistics of PT published articles.

https://www.ptcog.ch/index.php/other-news

As of Dec. 2020
180 clinical trials

U.S. National Library of Medicine's *ClinicalTrials.gov* (https://clinicaltrials.gov)

Fig. 5. Details of clinical trials conducted with PT.

Mostly non-randomized early phase clinical trials

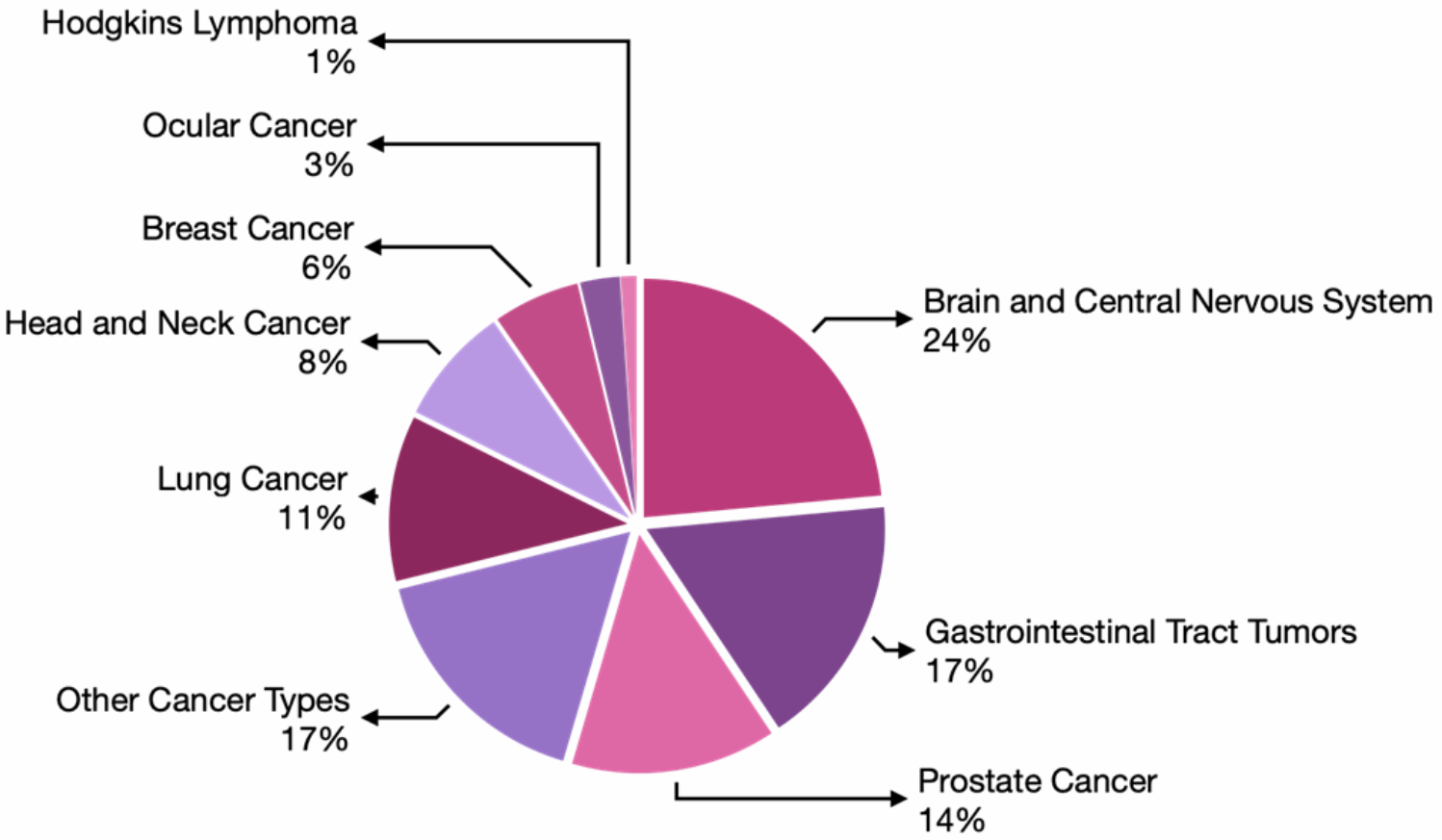


Fig. 6. Percent of clinical trials for different cancer types.

A head-to head comparison of AEs is desired but difficult

Refence| ClinicalTrials.gov ID	Title | Status of the trial	Objective| Number of participants	Intervention| Radiation type	Serious AE | Other AE (%)	Authors' Comments
Nantavithya et al. (2018) *(NCT01511081)*	SBRT *vs.* SBPT for high-risk early-stage NSCLC Terminated (low accrual)	Phase 2 Randomized to compare SBRT vs. SBPT for side effects, quality of life, cancer control 21	SBRT SBPT	No serious AE with SBRT, metastatic squamous carcinoma of the lung with SBPT Other AE none	No meaningful comparison could be made
Laio et al. (2019) *(NCT00915005)*	Randomized trial of image-guided adaptive conformal photon vs. PSPT with chemotherapy for NSCLC Completed	Phase 2 Randomized trial to study PSPT vs. IMRT reduces the risk of treatment related pneumonities or tumor recurrence 275	PSPT Photon therapy Paclitaxel Carboplatin	Serious AEs were sig. higher in the PSPT group (38.6%) vs. IMRT (30.4%) p<0.01	PSPT did not provide any benefit in normal tissue toxicity over photon therapy
Lin et al. 2020 *(NCT01512589)*	Randomized trial of proton beam therapy vs. IMRT for esophageal cancer	Phase 2 Randomized trial to compare PT to IMRT in combination with chemotherapy 180	PT IMRT Fluorouracil Capecitabine Taxane Carboplatin Oxaliplatin	Numerically fewer cardiopulmonary toxicities and post-operative complications in the PT arm	Results are promising, a larger multi-institutional trial is needed

AE – adverse events**, NSCLC** – non-small cell lung cancer, **IMRT** – intensity modulate radiotherapy, **PT** – proton therapy, **PSPT** – pencil scanning proton therapy, **SBPT** – stereotactic body proton therapy, **SBRT** – stereotactic body radiotherapy

Summary of randomized clinical trials that compared proton therapy *vs.* photon therapy.

A head-to head comparison of AEs is desired but difficult

- ✓ **Differences in treatment plans,**
- ✓ **Fractionantion schemes,**
- ✓ **Total dose,**
- ✓ **Patient characteristics,**
- ✓ **Tumor location,**
- ✓ **Medications and other agents,**

surgical history etc.

Box 1. Key issues that contribute to normal tissue injury with proton therapy

Key Issues	Contributing Factors
Uncertainties in the depth of penetration of beams	• Differences in tissue compositions • Target movement due to breathing motion, changes in bowel and bladder filling as well as other normal tissue changes
RBE: LET, dose, fraction, and tissue type	• Contentious use of a fixed RBE value assigned to protons may overdose normal tissue and underdose tumors • Strong impact of LET on normal tissue injury is not being included in the RBE definition • Not using variable RBE values limits personalization of RT
Delineation of the target volume	• Difficulty in achieving adequate tumor delineation due to want of high-quality diagnostic imaging i.e., CT-MRI or PET-MRI

Target Motion	• Changes in tumor location during treatment fractions caused by:
	  ○ discrepancies between day-to-day patient set up procedures
	  ○ breathing
	  ○ peristaltic movement
	  ○ bowel movement
	  ○ heart beats
	  ○ organ filling

Abbreviations: CT-MRI, computed tomography-magnetic resonance imaging; LET, linear energy transfer; PET-MRI, positron emission tomography-magnetic resonance imaging; RBE, relative biological effectiveness; RT, radiotherapy

Normal tissue injury induced by photon and proton therapies…, **Miszczyk J. et al., Int. J. Radiat Oncol. Biol. Phys. 2021**

Facts, gaps and opportunities articles and clinical trials – part 1

- ✓ **Despite technological advances in RT patients still experience adverse effects. Irradiation of normal tissue is almost unevitable. Normal tissue is an important determinant of the outcome.**
- ✓ **While a steady increase in PT literature is observed, mostly non-randomized early phase clinical trials with a relatively small number of patients are enrolled. Retrospective analysis and single arm studies will likely favor PT.**

<u>Proton therapy with favourable dose delivery can improve treatment outcomes vs. benefit in normal tissue toxicity</u>

Dosimetric benefit does not ensure PT has more favorable clinical outcomes but does form a basis for comparative prospective trials.

To fully benefit from PT and justification of costs, comparative and prospective large-scale well-designed clinical trials are necessary incorporating suitable biological determinants (panels before, during or after) to optimizing treatment process.

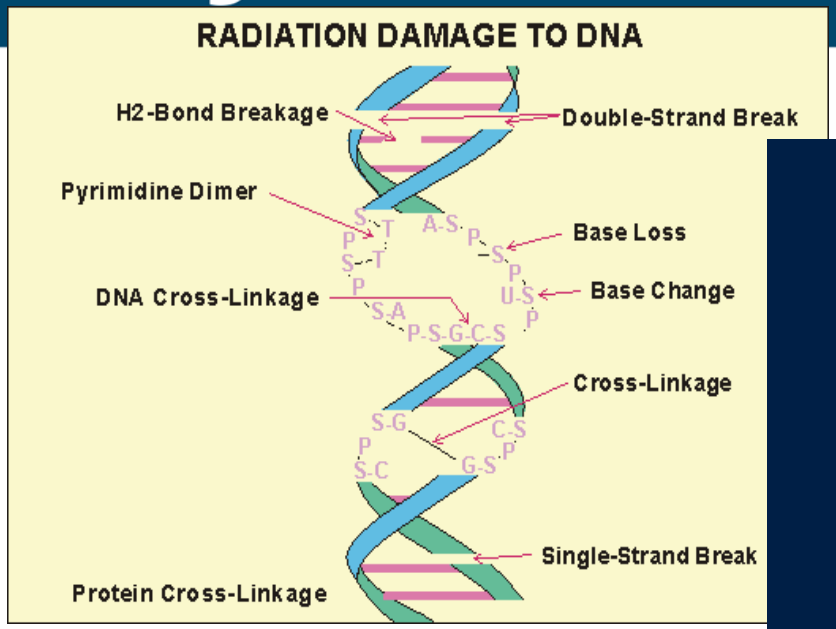
Proton Therapy: the Problem? Does it make any sense to spend over $100 million on a proton facility, with the aim to reduce doses to normal tissues and then to bathe the patient with a total body dose of neutrons", Hall, Technol in Ca Res Treat 2007;6:31-34.

Biological issues – the missing factor

Experimental studies on the biological effects of proton irradiation are relatively sparse and focus mostly on different cancer cells response and RBE.

There is an unmet need to recognize the possible differences in the mechanisms of radiation injury and the normal tissue toxicities with different radiation types.

Radiation interactions with biological, complex systems



The DNA is the critical target to induce lethal effects as a result of radiation exposure.

Radiation can induce damage either by direct action or indirect action (free radicals).

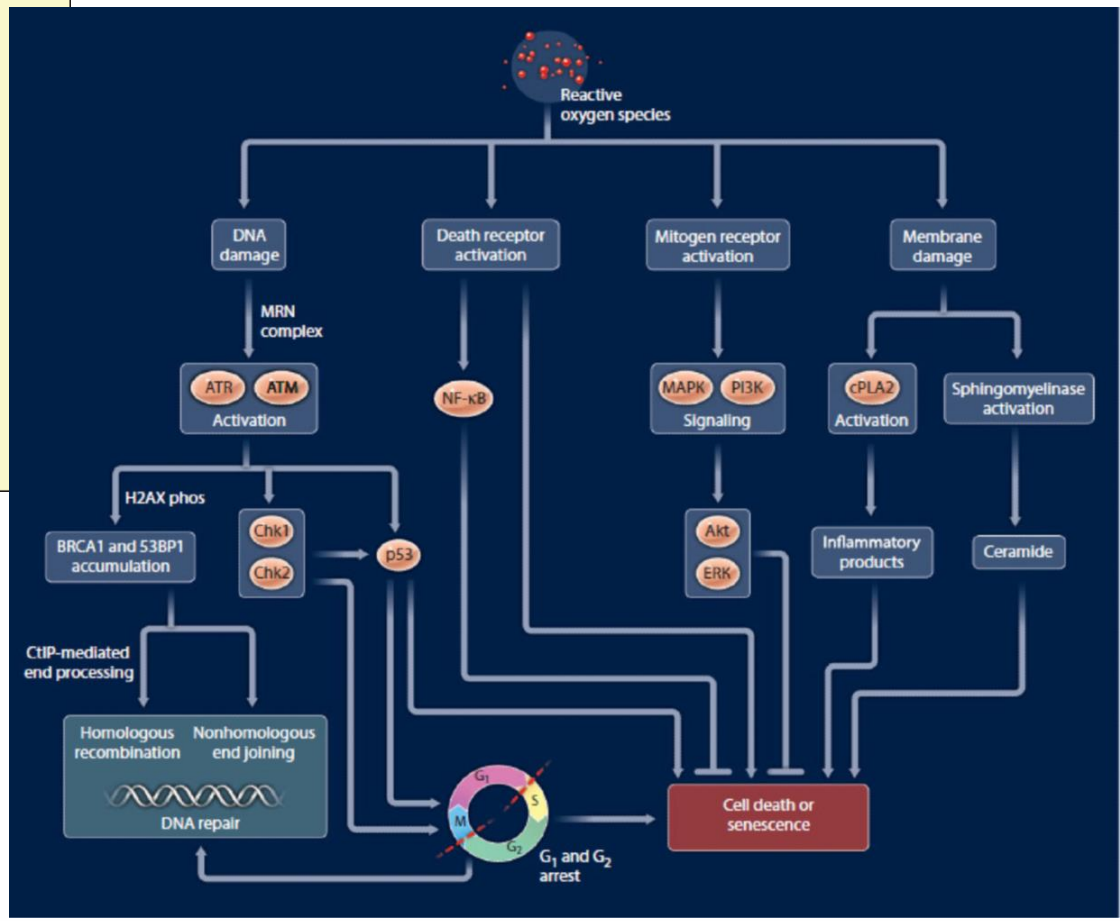


Fig. 7. Various cellular targets and responses that occur after radiation exposure.

New paradigms and future challenges in radiation oncology…, **Liauw SL., Connell PP&Weichselbaum RR.**
http://www.radiologyandphysicalmedicine.es/radiation-induced-lesions-in-dna/

A modulation of normal tissue response can be expected in all dose ranges

Circulating lymphocytes represent normal tissue and traffic throughout the body including irradiated tumor volume.

Following a standard regime of thirty fractions of 2Gy, 98.8% of the blood pool has been exposed to more than 0.5 Gy.

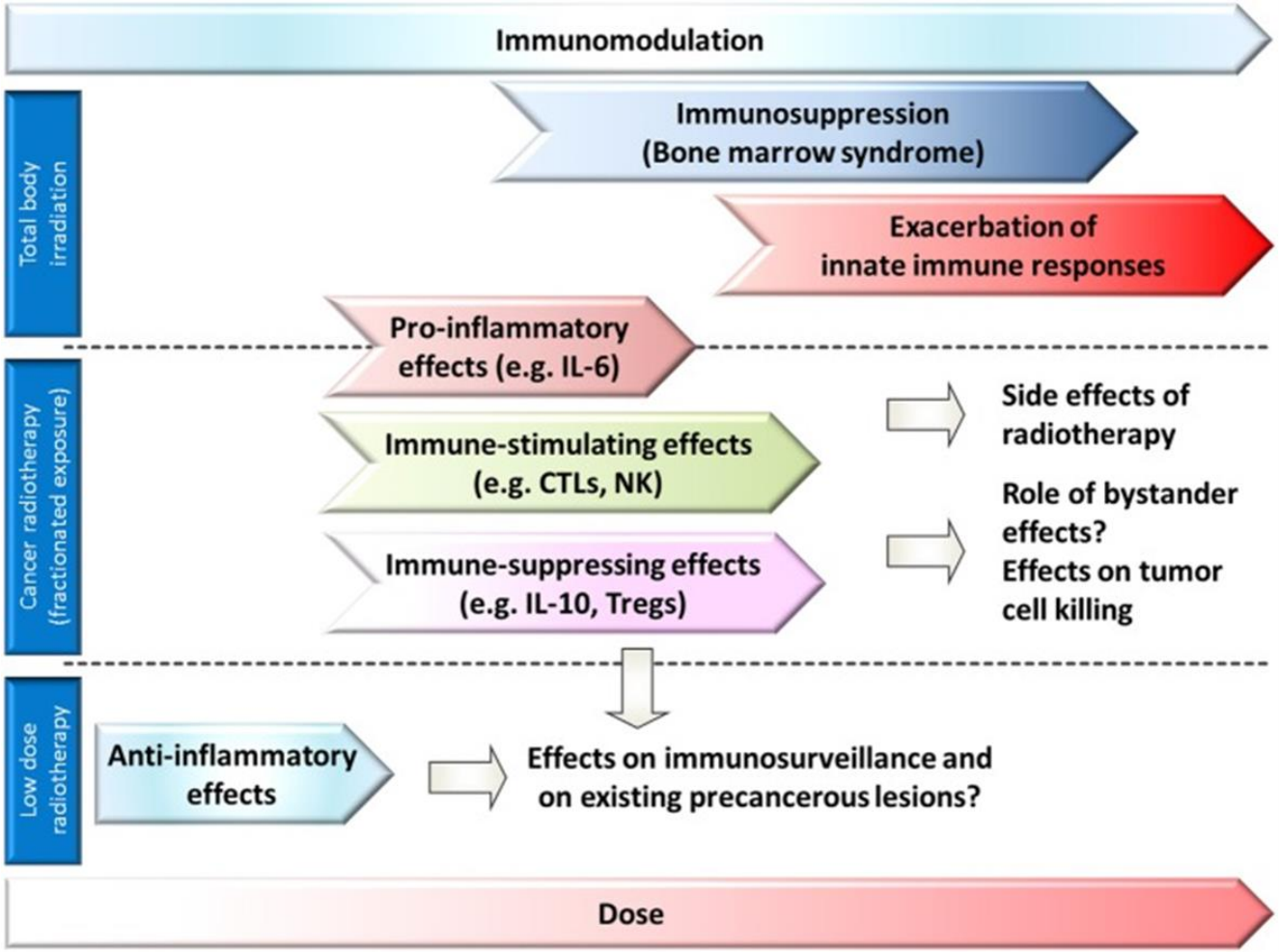
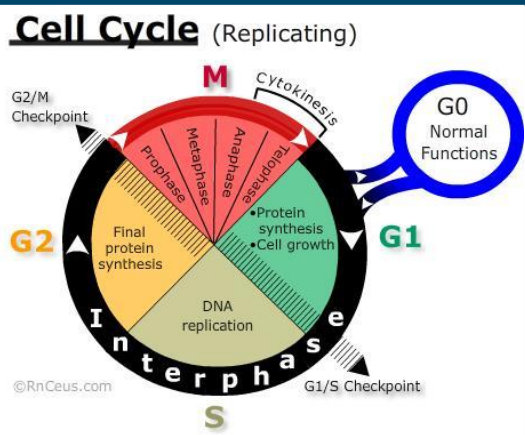


Fig. 8. Role of immune response in different dose ranges after WBE and PBE.

Lymphocytes (HPBL) as a unique dosimeter



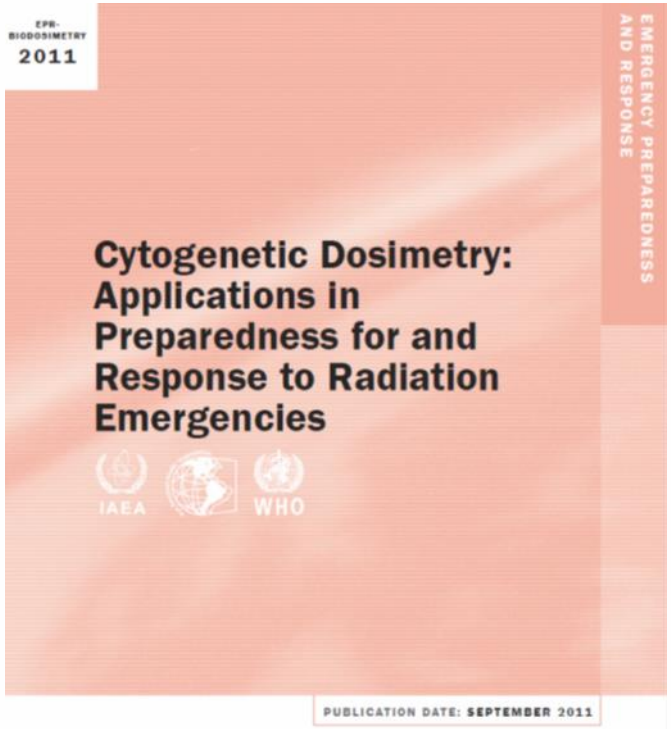
- **Predominantly in a resting G0 phase, consist of T and B cells.**
- **Synchronous and homogeneous cell population.**
- **Circulate throughout the body and can be stimulated to undergo mitosis,** recirculation time~ 12h, 80%. Even when a small part of the body was irradiated – dosimetry is possible.
- **Involved in many key mechanistic roles following exposure to radiation therapy,** persistence of DNA damage 3.5 years.
- **Used to interrogate radiation injury to normal tissue during tumors irradiation** (critical targets for radiotherapy and immunotherapy). Blood taking is not-invasive.

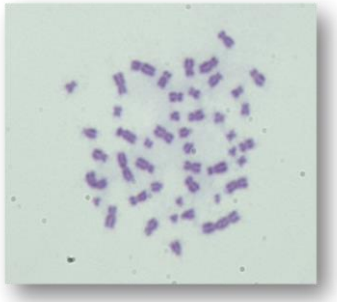
HPBL is a well-accepted model to study the effects of radiation on normal tissue.

Response of human lymphocytes to proton radiation of 60 MeV…, Miszczyk et al.
http://rnceus.com/chem/cycle.html

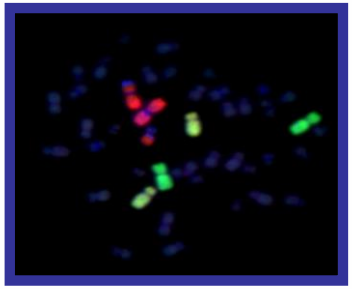
Methods used for dose and DNA damage assessment

DSBs are critical lesions and their misrepair or non-repair are involved in the formation of chromosome aberrations.

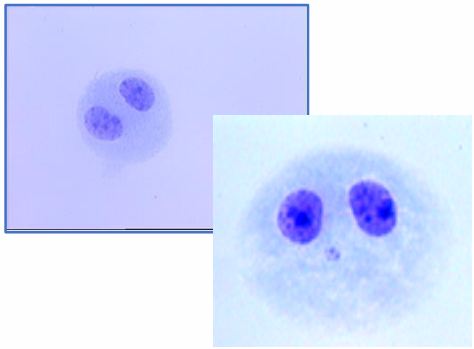




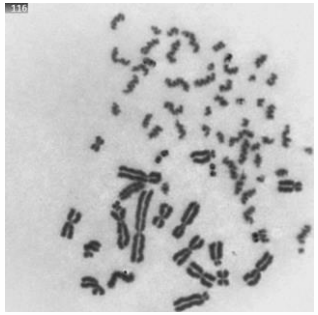
Dicentric analysis (DA)



Translocation analysis (FISH)



The cytokinesis-block micronucleus (CBMN)



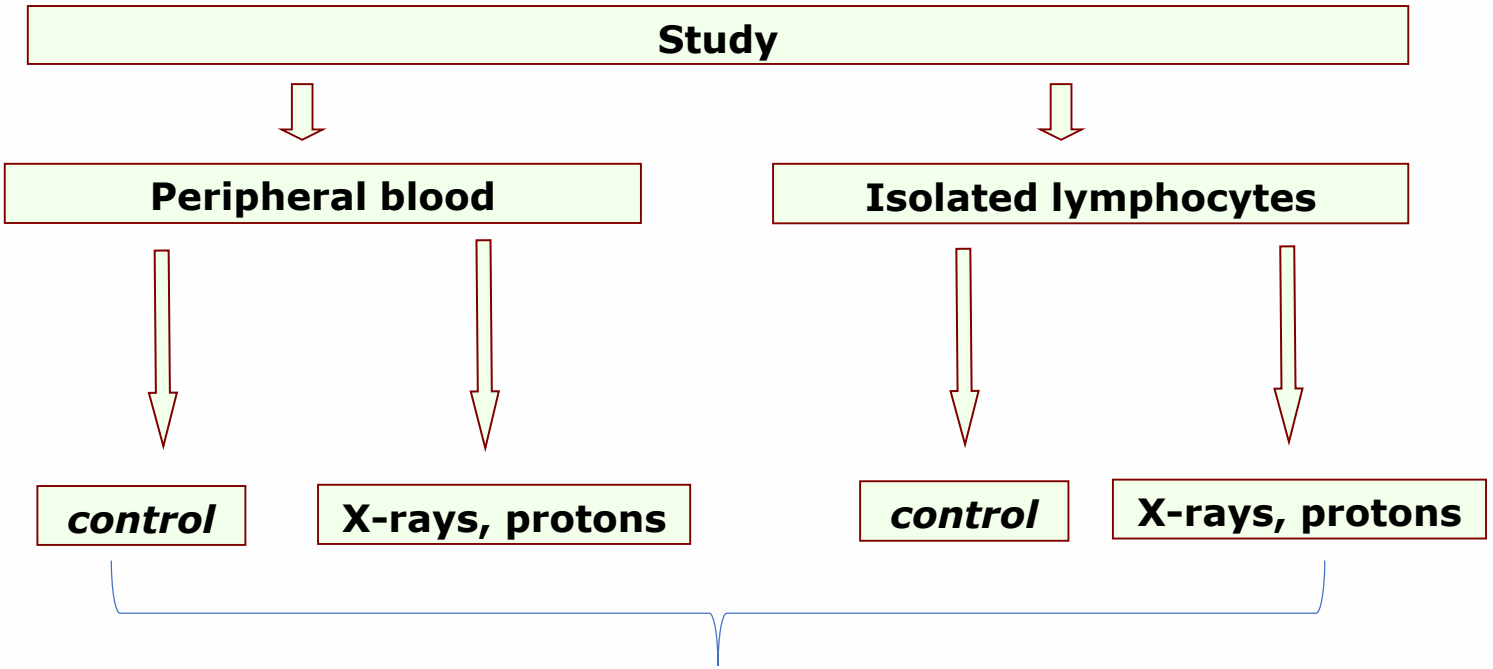
Premature chromosome condensation (PCC)

IAEA
International Atomic Energy Agency

Time-consuming, expensive, up to 4.0 Gy, protocols…

Every laboratory must optimize protocols and obtain own calibration curves.

Study design and goals



- **To prepare phantom, laboratory and optimize methods for low and high radiation dose assessment**
- **To study the response of normal tissue after protons vs. photons**
  (DNA damage, cell death, cell cycle)
- **To propose mechanisms of molecular and cellular injury by protons in HPBLs.**

Approval from the human bioethical committee of the Regional Medical Board (No. 124/KBL/OIL/2013) and (184/KBL/OIL/2020).

Study design – phantom and irradiations

Radiotherapy and Oncology 115 (2015) 128–134

Contents lists available at ScienceDirect

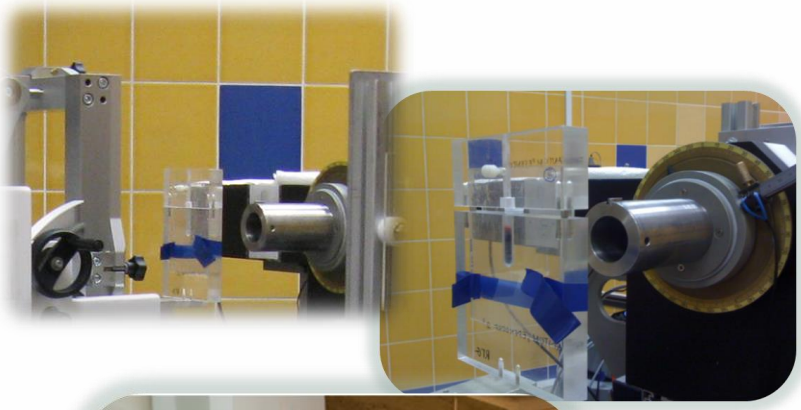
Radiotherapy and Oncology

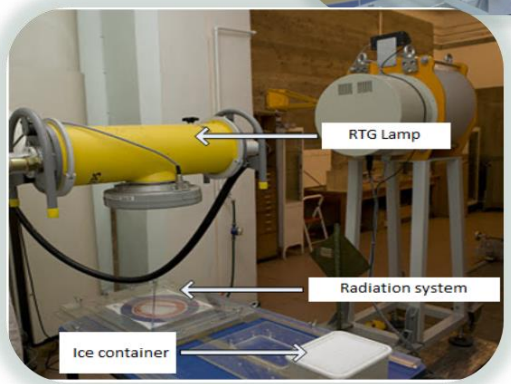
journal homepage: www.thegreenjournal.com

Proton radiobiology

Response of human lymphocytes to proton radiation of 60 MeV compared to 250 kV X-rays by the cytokinesis-block micronucleus assay

Justyna Miszczyk [a,*], Kamila Rawojć [a,b], Agnieszka Panek [a], Jan Swakoń [c], Pataje G. Prasanna [d], Marzena Rydygier [c]





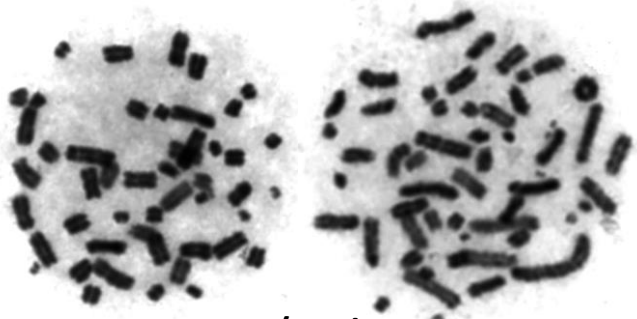
Whole blood or isolated lymphocytes
(10 donors, ♀ 42.0±4.5, ♂ 44.0±5.6
were irradiated in the dose range from 0.3 – 20.0 Gy
(0.3, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0)
(8.00, 13.64, 15.00, 20.00)

Cells were irradiated with a 60 MeV proton beam in 2-cm Eppendorf vials. A specially designed PMMA - Poly(methyl methacrylate) phantom was placed at the irradiation setup isocentre (in the middle of SOBP) and in the centre of the flat beam. Average dose rate 0.075 Gy/s.

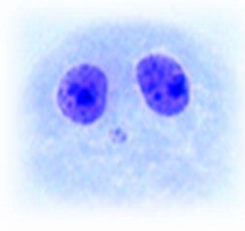
The radiation was delivered at a dose rate of 0.15 Gy/s by a Philips X-ray machine (MCN 323 model, Philips) at 250 kV. The vials were placed in a polyethylene box; radiation field-size was 20x20 cm^2, and the source to surface distance was 34.8 cm.

The new, leading edge laboratory

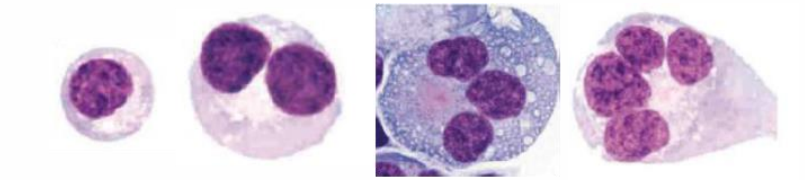
"Development and optimization of PCC (*Premature Chromosome Condensation*) method for the purposes of proton radiotherapy at the Cyclotron Center Bronowice", SONATA, the National Science Centre.

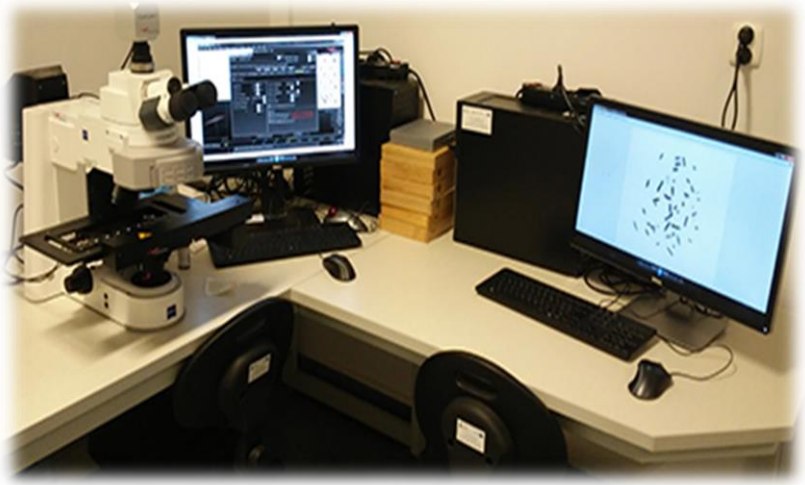


PCC, G2/M phase



CBMN





High-performance slide scanning Metafer platform (AxioImager.Z2 microscop with specimen holder for 8 slides (76x26 mm) with two independent Ikaros software modules for automatic cells detection and analysis.

Multimodal approach for ionizing radiation damage investigation, Kwiatek W. et al.
https://los.ifj.edu.pl/en/index.html
HUMN project: detailed description of the scoring criteria…, Fenech M. et al.

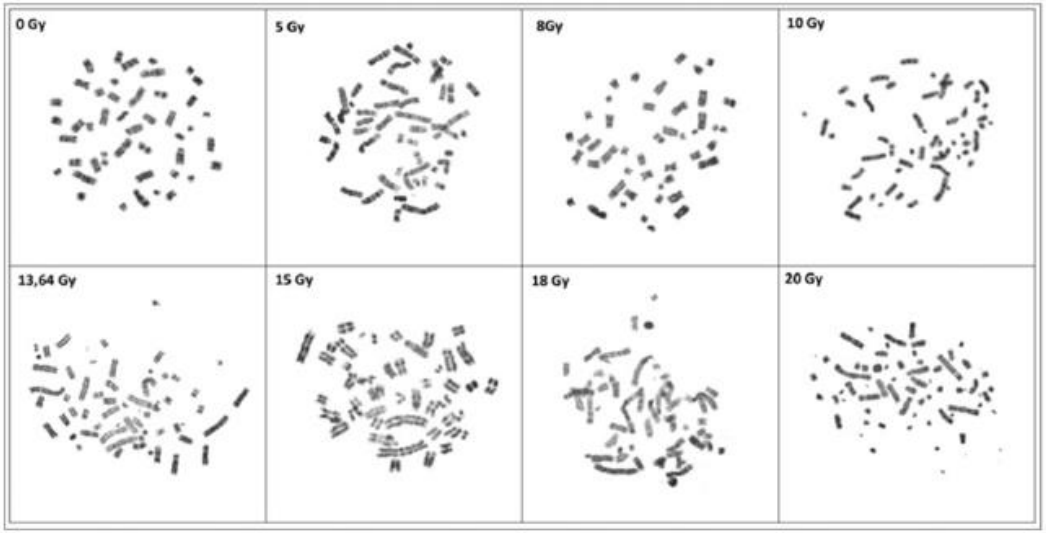
Protocols and triage modes

International Journal of Radiation Biology

ISSN: 0955-3002 (Print) 1362-3095 (Online) Journal homepage: https://www.tandfonline.com/loi/irab20

Evaluation of the premature chromosome condensation scoring protocol after proton and X-ray irradiation of human peripheral blood lymphocytes at high doses range

K. Rawojć, J. Miszczyk, A. Możdżeń, J. Swakoń & A. Sowa-Staszczak



PCC micrographs in G2/M phase post proton irradiation

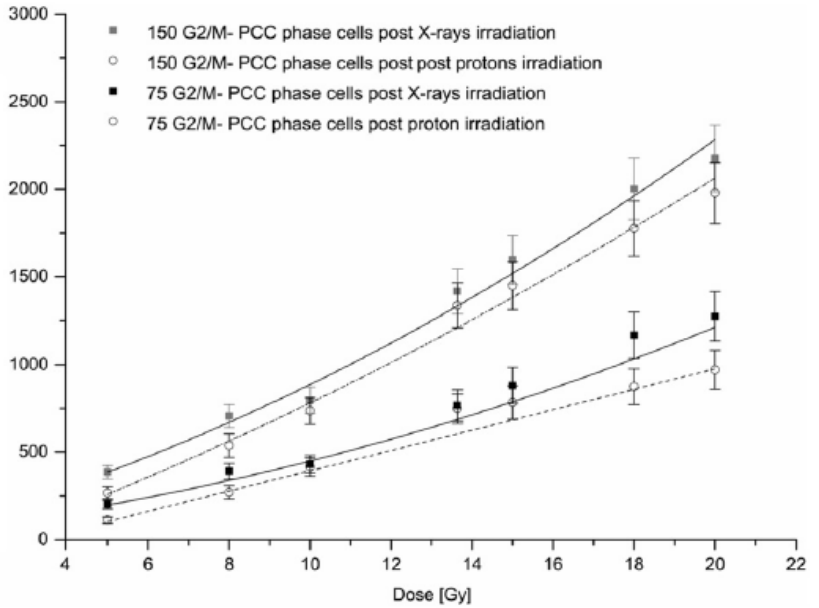


Fig. 9. Comparison between 150 vs. 75 G2/M cells scoring modes for all scorers and both types of radiation.

Similar distribution trends for both scoring modes were observed.

Protocols and triage modes

International Journal of Radiation Biology

ISSN: 0955-3002 (Print) 1362-3095 (Online) Journal homepage: https://www.tandfonline.com/loi/irab20

Effects of culturing technique on human peripheral blood lymphocytes response to proton and X-ray radiation

Justyna Miszczyk & Kamila Rawojć

The isolation process did not significantly influence the cell proliferation ability after irradiation.

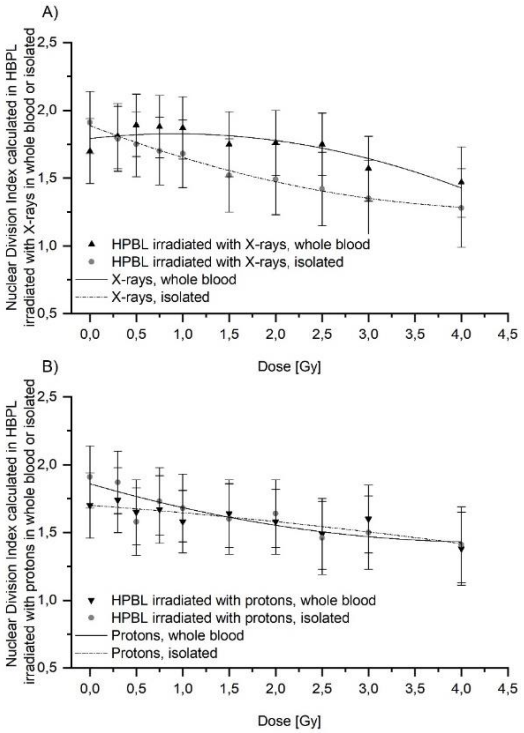


Fig. 10. Proliferation index (NDI) in irradiated cells with X-rays and protons, blood vs. isolated cells.

Significant differences in DNA damage are evident and affected by the radiation type.

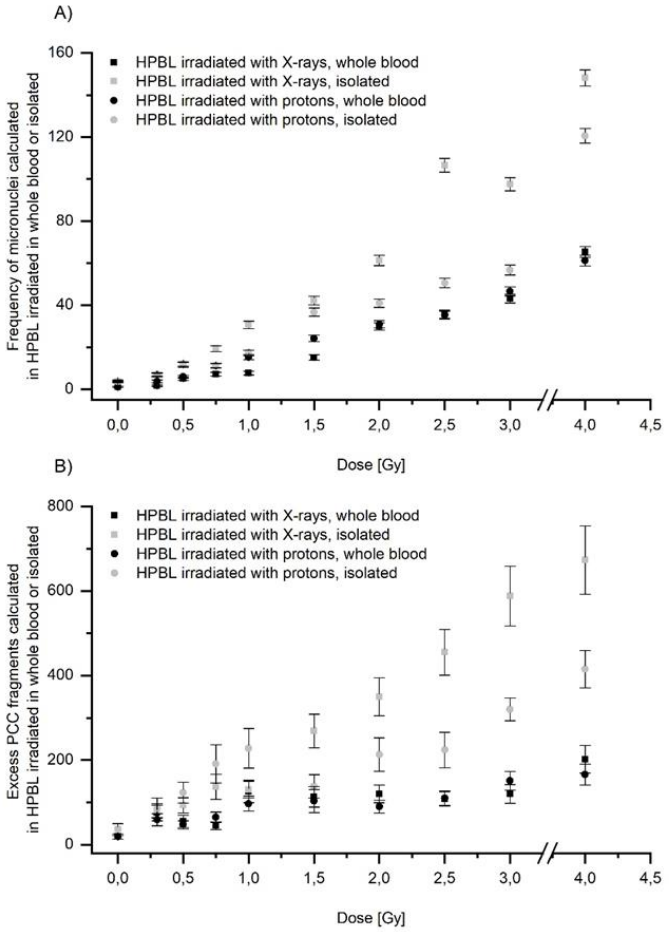


Fig. 11. DNA damage in irradiated cells with protons and X-rays, cultured in two different techniques.

Protocols and triage modes

Similar trends in estimated biomarkers between different treatment conditions were observed.

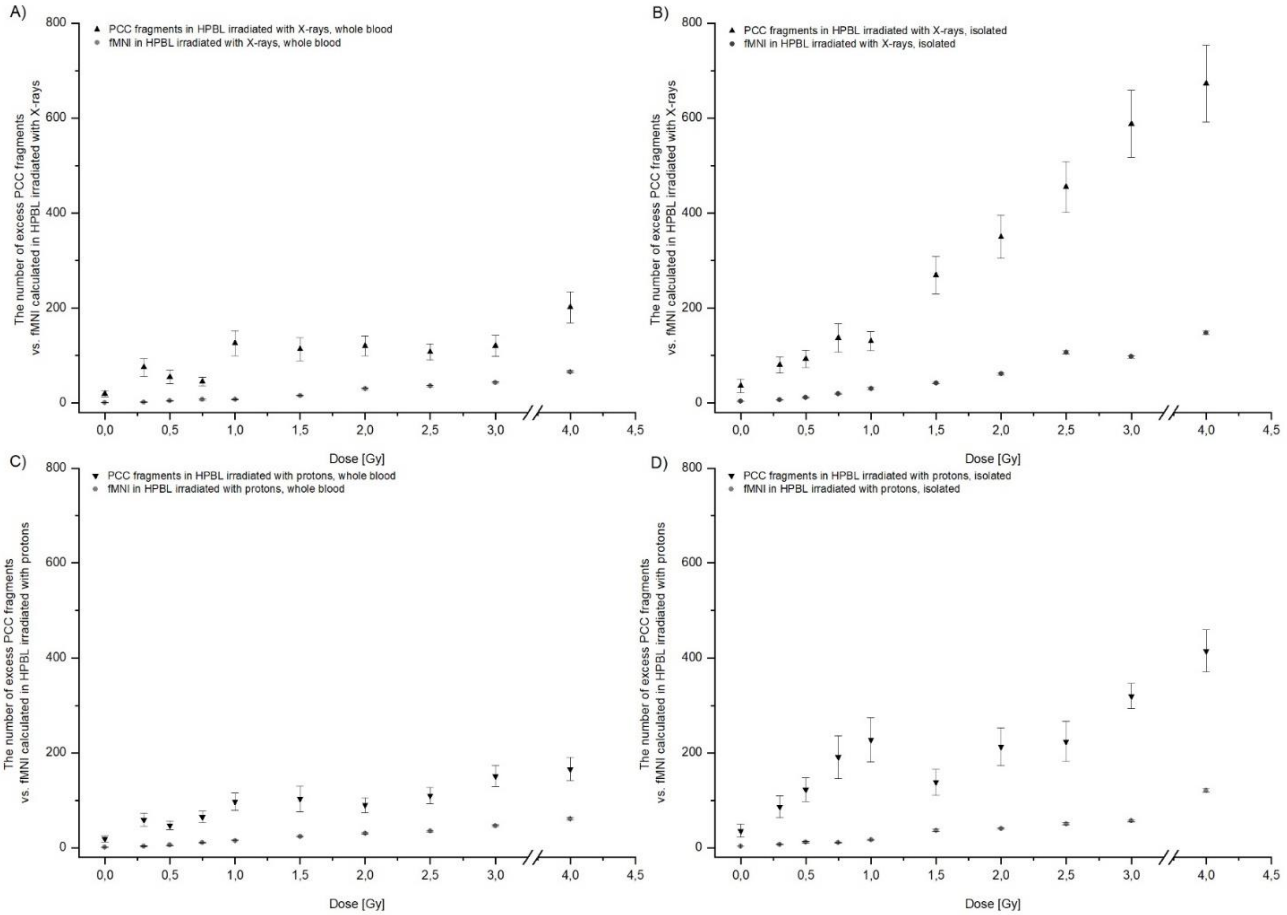
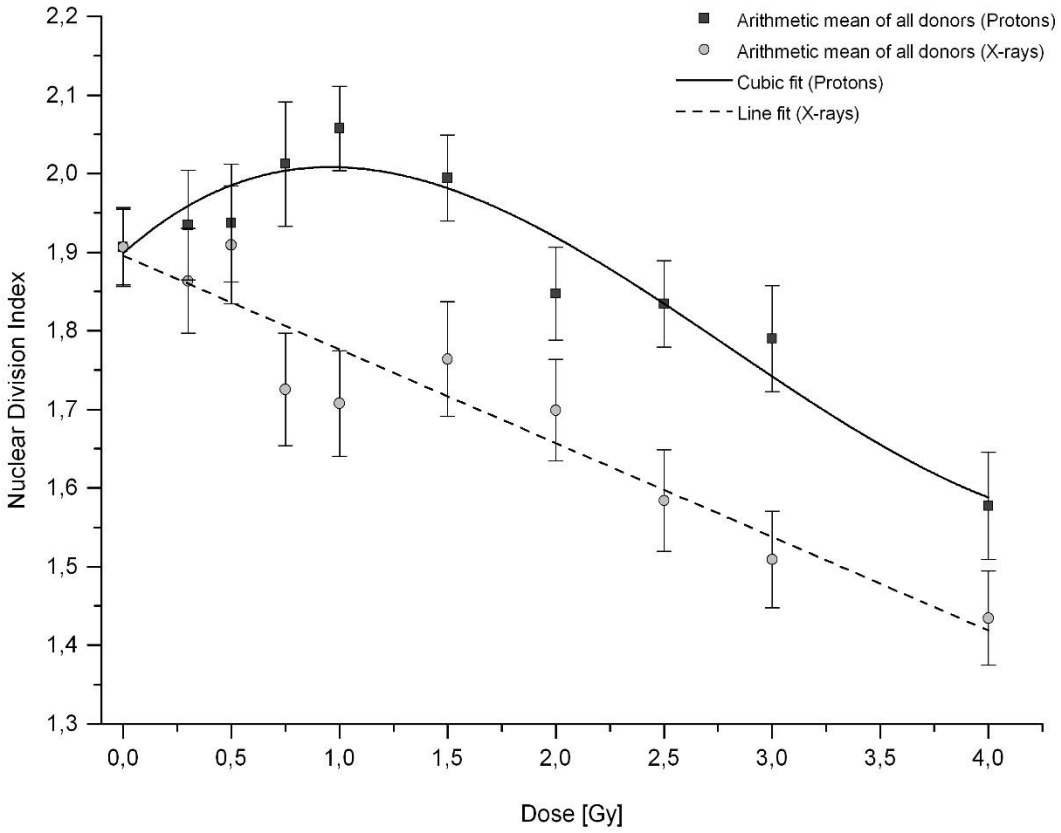


Fig. 12. Comparison of biomarkers in isolated or whole blood cultured lymphocytes post X-ray and proton irradiation.

Normal tissue response - cellular proliferation 0.3-4.0 Gy



Compared to X-rays, cellular proliferation after irradiation with protons was significantly higher in HPBL for all doses within the range of 0.75-4.0 Gy.

At dose above 1.0 Gy for both radiation types a gradual and progressive decline was seen.

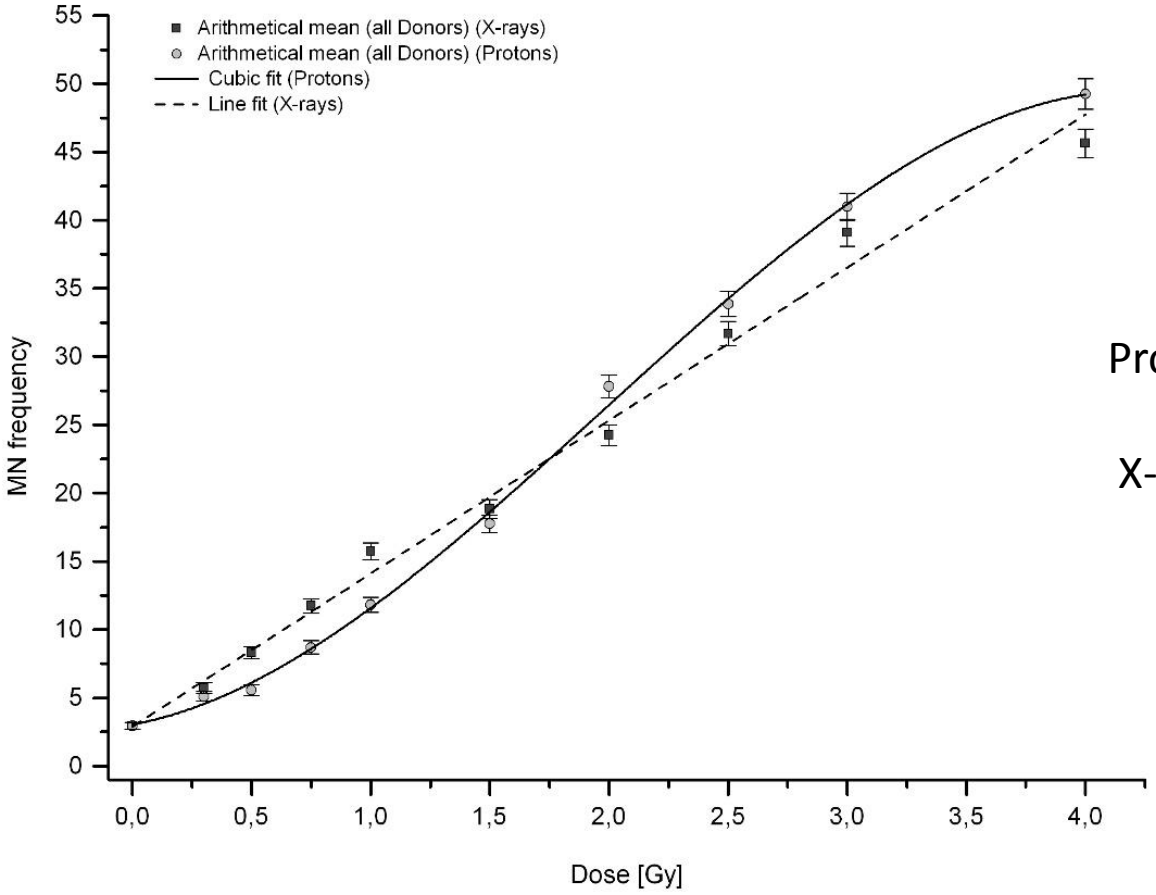
Fig. 13. Dose-effect relationship for NDI in HPBLs following irradiation with protons and X-rays.

Protons and X-rays influence HPBL cellular proliferation to different degrees.

Response of human lymphocytes to proton radiation of 60 MeV…, Miszczyk et al., Radiotherapy and Oncology, 2015.

Normal tissue response - DNA damage 0.3-4.0 Gy

Most likely, protons and photons induce DNA damage in HPBL by different mechanisms.



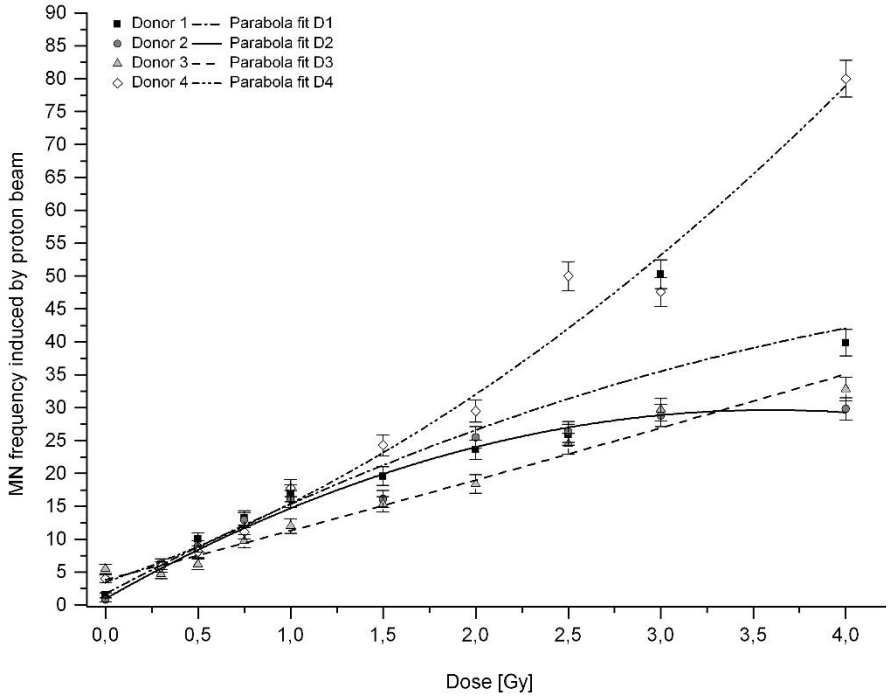
Protons were significantly less effective as compared to X-rays at doses below 1.5 Gy.

Fig. 14. Dose-response curves for DNA damage for both radiation types.

Response of human lymphocytes to proton radiation of 60 MeV…, Miszczyk et al., Radiotherapy and Oncology, 2015.

Inter-individual variability 0.3-4.0 Gy

Extent of difference varies among donors without correlation with radiation type.



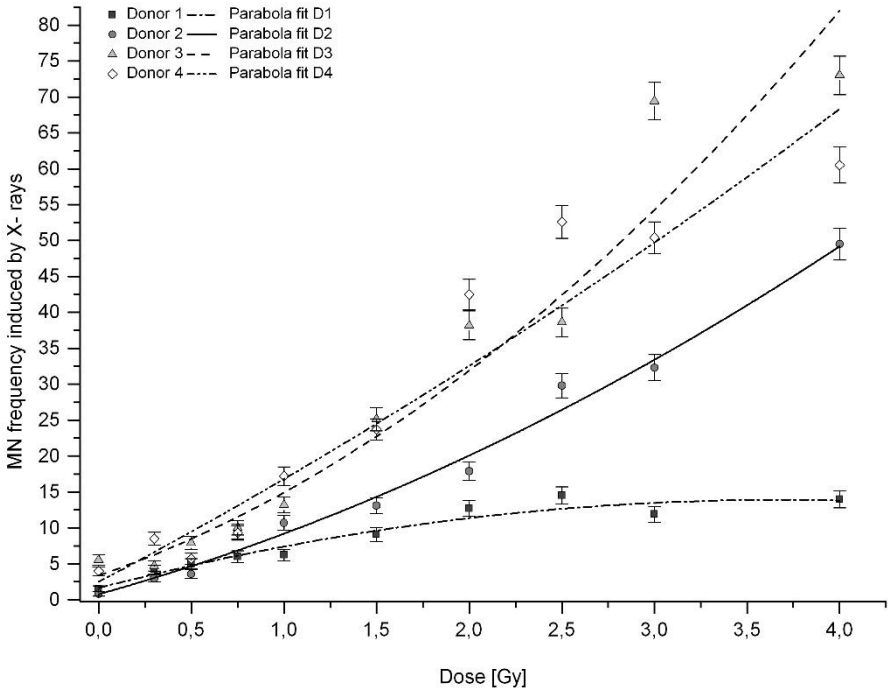


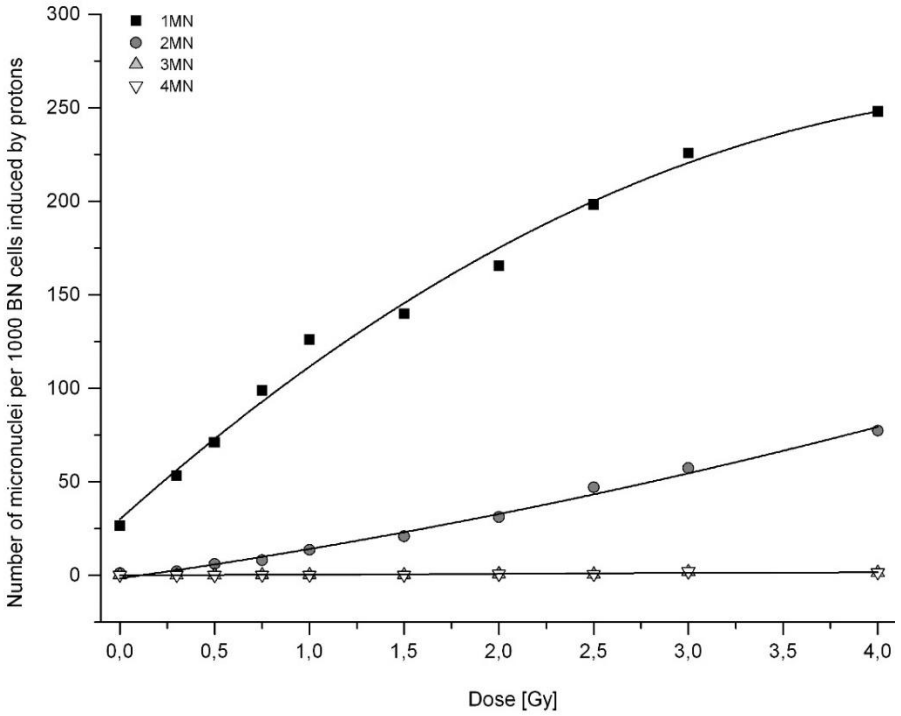
Fig. 15. The dose-dependent relationship between DNA damage for the proton beam and X-rays among individuals.

At lower proton doses curves overlapped with each other, differences were more pronounced at doses above 1.0 Gy.

Response of human lymphocytes to proton radiation of 60 MeV…, Miszczyk et al., Radiotherapy and Oncology, 2015.

DNA damage distribution
0.3-4.0 Gy

Distribution of DNA damage following irradiation with protons and photons is different.



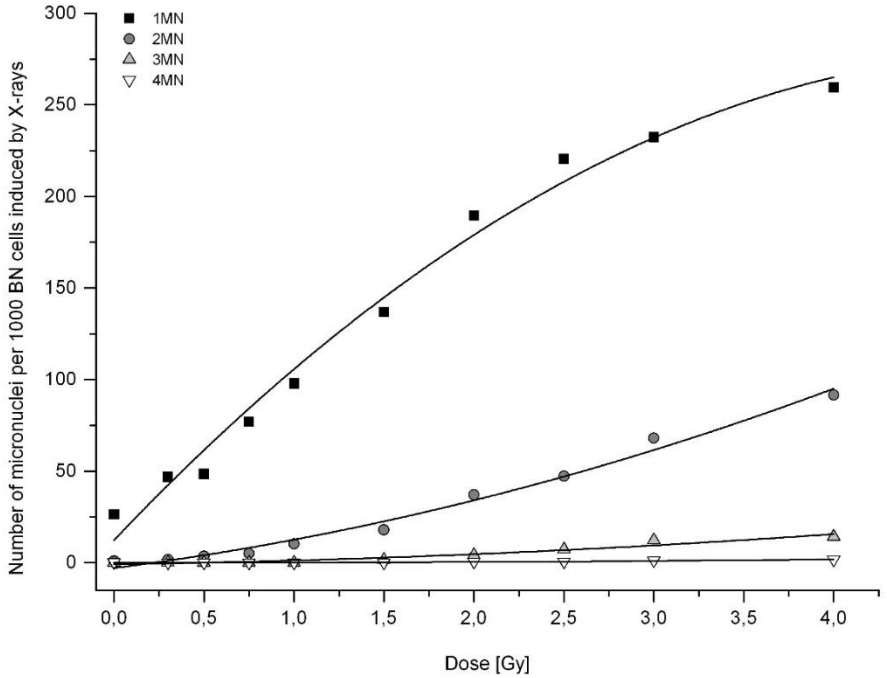
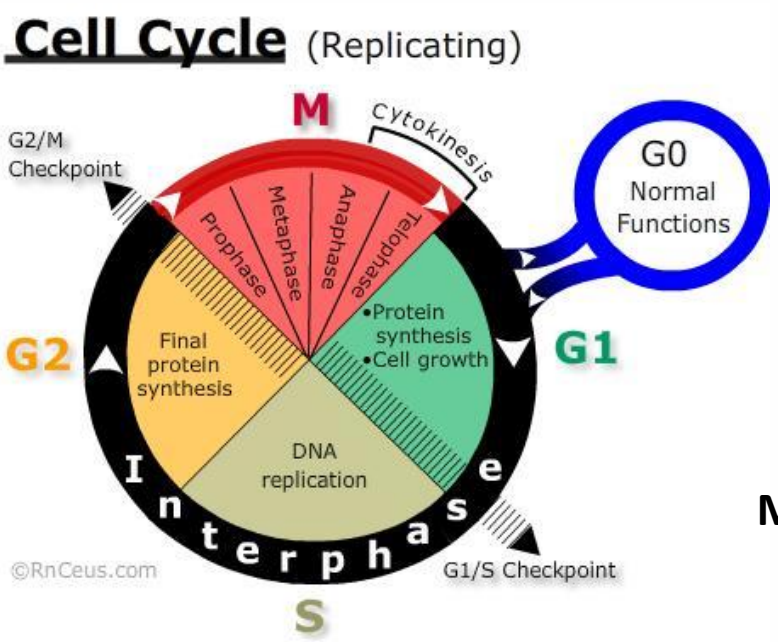


Fig. 16. The dose-response relationships for the protons and X-rays and various number of micronuclei (1, 2, 3 and 4) in 1000 BN cells as an average for all donors.

Locally multiply damaged sites or clustered DNA damage?

Response of human lymphocytes to proton radiation of 60 MeV…, Miszczyk et al., Radiotherapy and Oncology, 2015.

Normal tissue response following exposure to high doses



biology

This article belongs to the Special Issue
Applied Physics in Cancer Cells

MDPI

Article

Investigation of DNA Damage and Cell-Cycle Distribution in Human Peripheral Blood Lymphocytes under Exposure to High Doses of Proton Radiotherapy

Justyna Miszczyk

Cell death

Mitotic delay

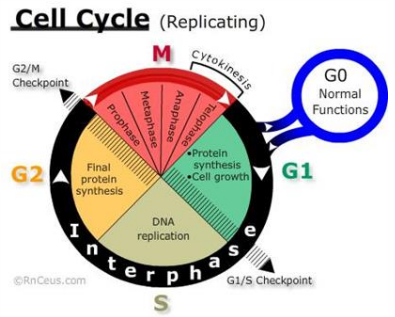
The effects and mechanisms of a single high-dose delivery remain unclear.

Pre-clinical studies have suggested that RT, especially higher doses of 20-25 Gy can substantially stimulate anti-tumor T-cell immunity and increase the T-cell response to help control tumor growth.

Cellular proliferation
8.0-20.0 Gy

X-rays	G1	S	G2	M	A	Nucleated
8.00	0.05	1.90	4.45	0.05	0.25	93.30
13.64	0.05	1.60	2.20	0.00	0.00	96.15
15.00	0.00	1.50	2.00	0.00	0.00	96.50
20.00	0.00	1.25	1.45	0.00	0.00	97.30

Protons [Gy]	G1	S	G2	M	A	Nucleated
8.00	0.00	1.65	2.80	0.05	0.70	94.80
13.64	0.00	1.85	1.35	0.00	0.20	96.60
15.00	0.05	1.40	1.10	0.00	0.30	97.15
20.00	0.10	1.25	0.90	0.00	0.20	97.55

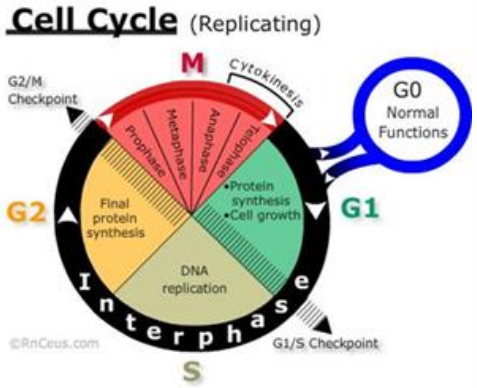


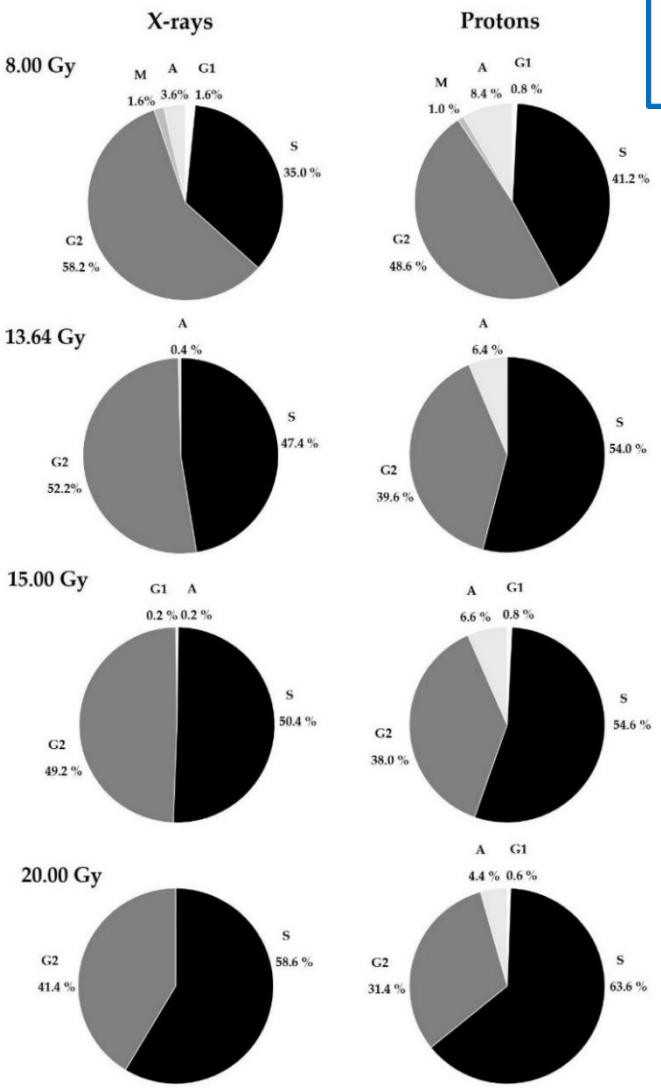
Percentages of G1, S, G2, M, A phases and nucleated cells at each dose of X-rays or protons.

As the dose increases, the number of nucleated cells for both studied types of radiation increases to comperable values.

The largest proportion of cells were in the S and G2 phases.

For both types of radiation, as the dose increased, the number of S-phase cells also increased and was higher for each dose after proton radiotherapy.





Percentages of cells in the G1, S, G2, M, A phases at each dose after X-rays or protons.

Normal tissue response - DNA damage 8.00-20.00 Gy

High doses of protons induce DNA damage in the G2/M differently than X-rays.

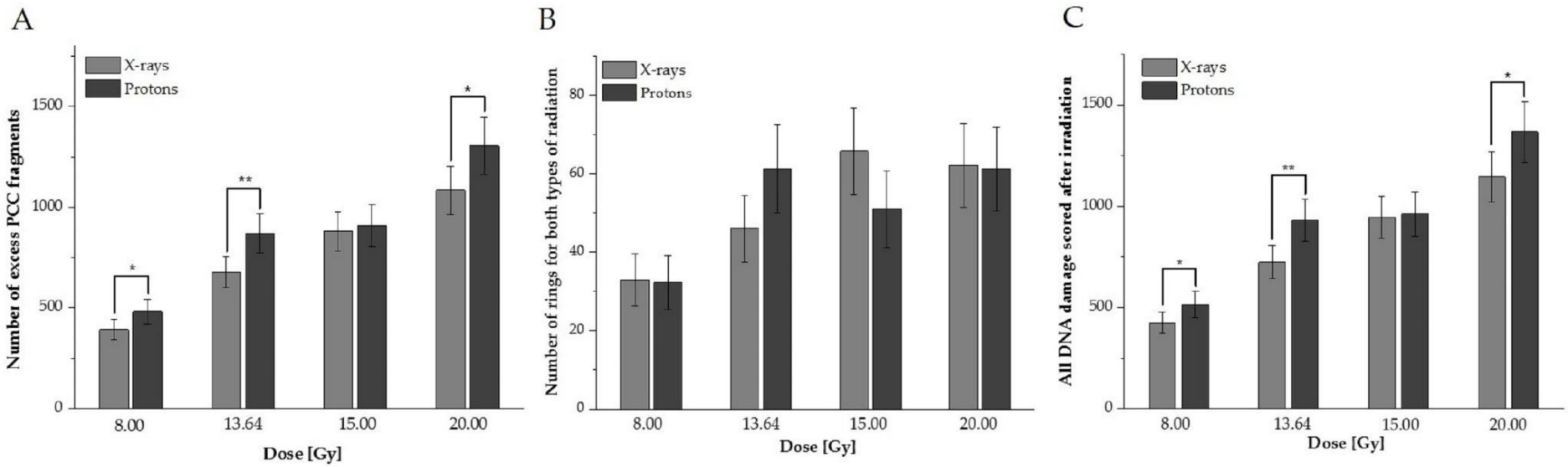


Fig. 17. Average values of DNA damage for HPBLs irradiated with high doses.

For all doses except 15.00 Gy, a higher DNA damage value after proton therapy was observed.

Inter-individual variability
8.00-20.00 Gy

The distribution of DNA damage following high doses of irradiation with protons vs. photons differs between donors, types of radiation, and doses.

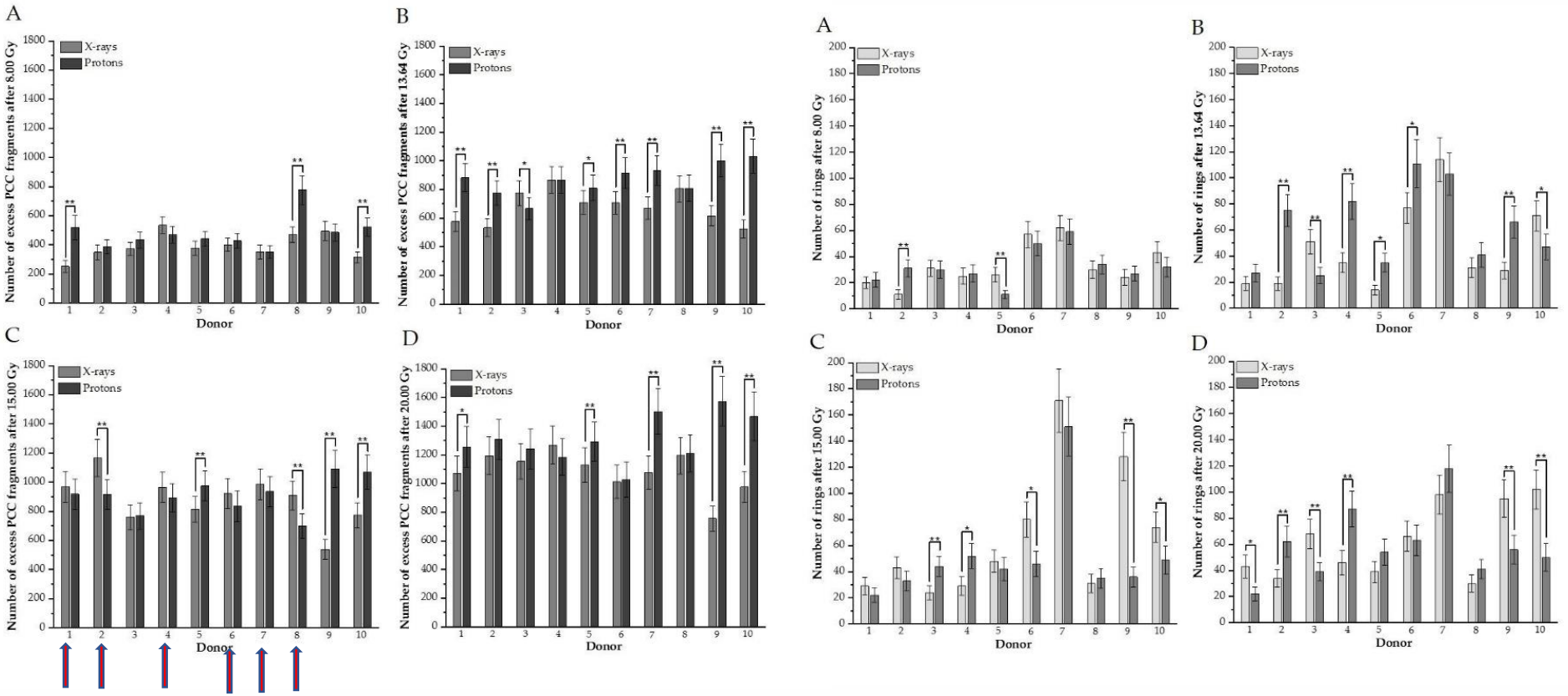


Fig. 18. An individual number of DNA damage for donors irradiated with different doses of protons vs. X-rays.

More scattered distribution for protons vs. X-rays was observed.

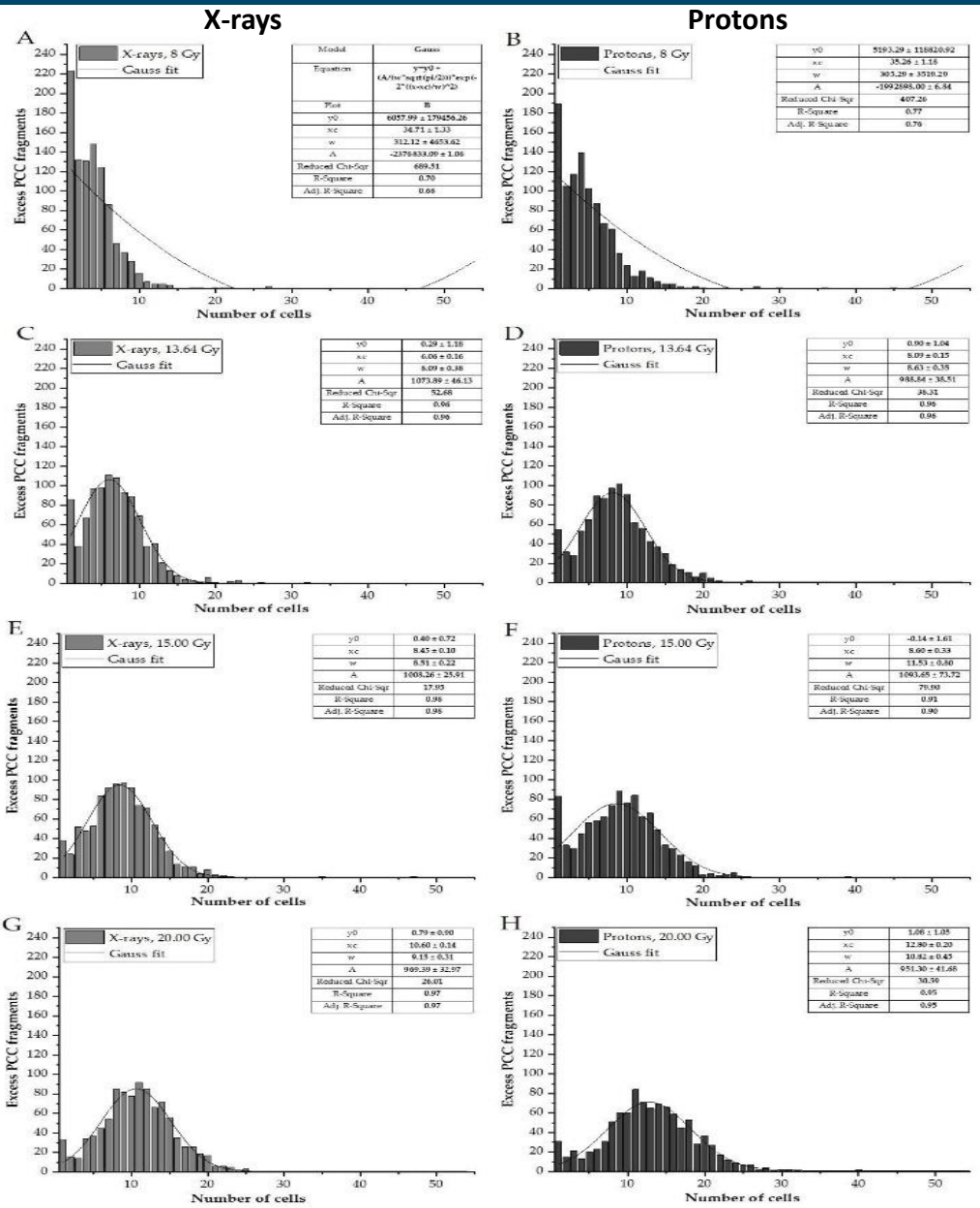
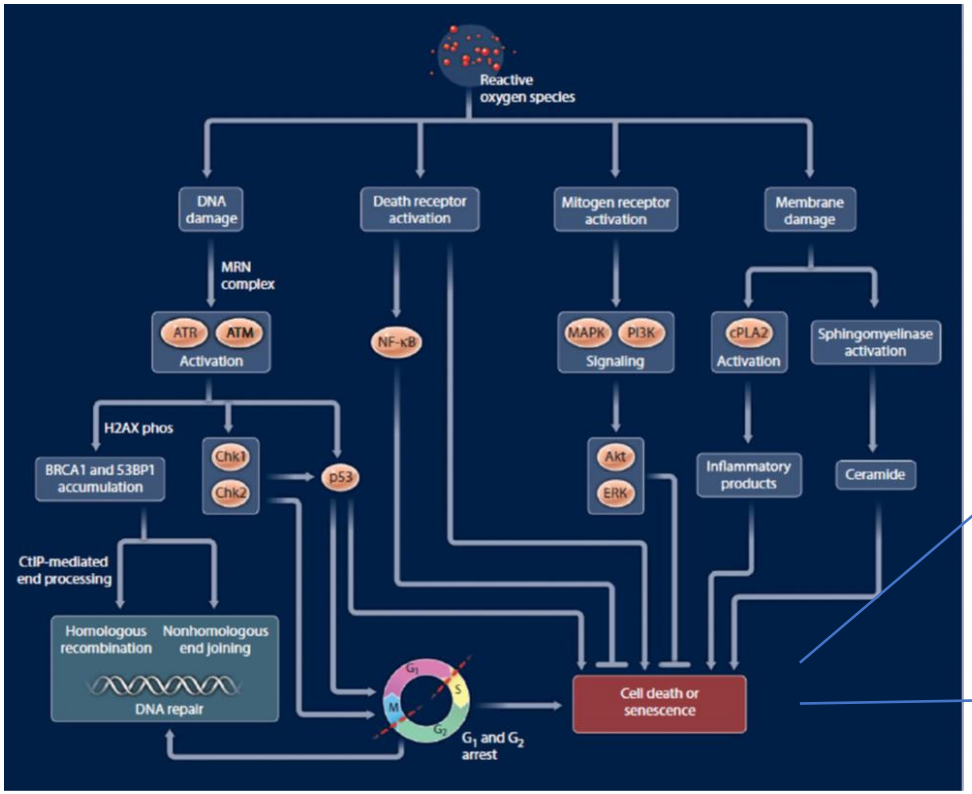


Fig. 19. Frequency distribution of the number of DNA damage after X-rays or protons.

Cell-killing process after radiotherapy

Apoptosis and necrosis are controlled by different molecular pathways.



Cell memebrane remains intact, cell breaks into apoptotic bodies. No inflammation.

Apoptosis (programmed cell death)

Necrosis

Loss of cell membrane integrity, resulted in an uncontrolled release of products into the extracellular space. Inflammation.

New paradigms and future challenges in radiation oncology…, Liauw SL, Connell PP&Weichselbaum RR.
http://www.radiologyandphysicalmedicine.es/radiation-induced-lesions-in-dna/
https://www.istockphoto.com/pl/wektor/apoptoz%C4%99-i-martwica-r%C3%B3%C5%BCnica-gm528240983-53538844

Cell death visualisation and quantification

Clinical and Translational Radiation Oncology 9 (2018) 23–29

Contents lists available at ScienceDirect

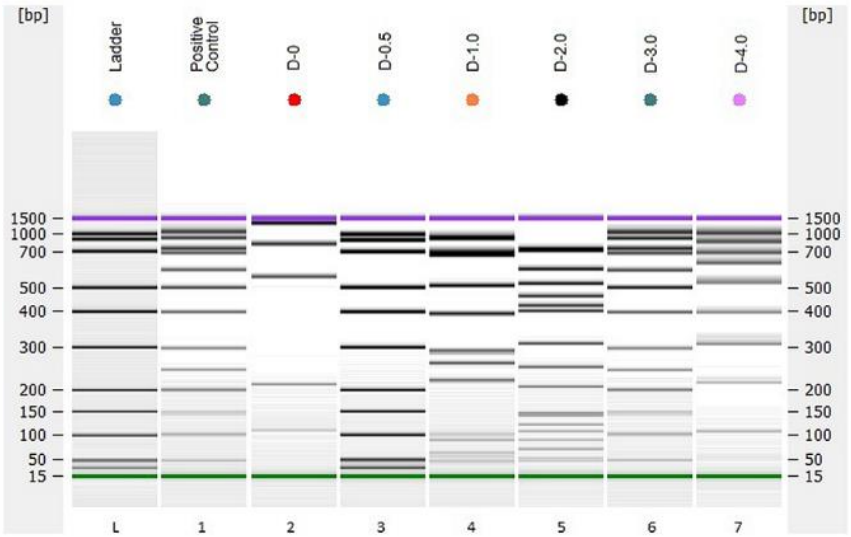
Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

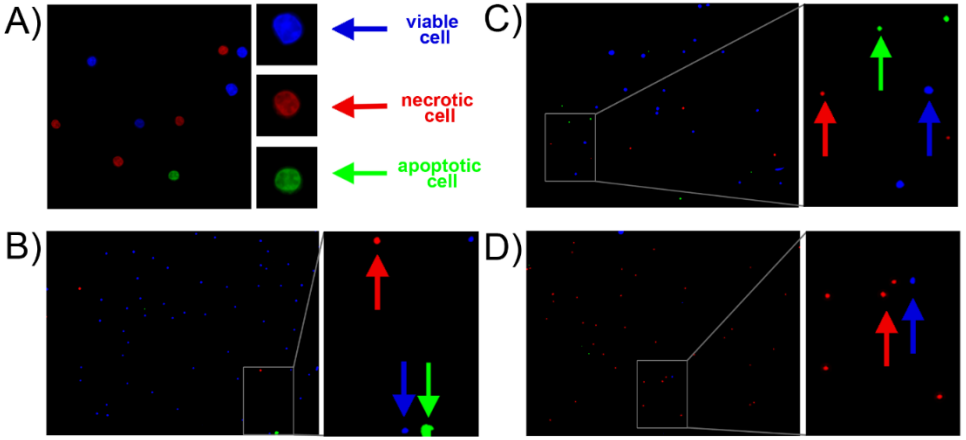
Original Research Article

Do protons and X-rays induce cell-killing in human peripheral blood lymphocytes by different mechanisms?

J. Miszczyk [a,*], K. Rawojć [b], A. Panek [a], A. Borkowska [a], P.G.S. Prasanna [c], M.M. Ahmed [c], J. Swakoń [a], A. Gałaś [d]



DNA (chip) fragmentation assay confirmed various degrees of DNA fragmentation. Lanes showed apoptosis, as well as smearing indicative of necrosis.



Cells after ex vivo irradiation with 3 Gy protons following staining with Apoptotic, Necrotic and Healthy Cells Kit, (Biotium, Hayward, USA).

Quantification studies of apoptosis 0.3-4.0 Gy

Proton irradiation resulted in higher apoptotic activity.

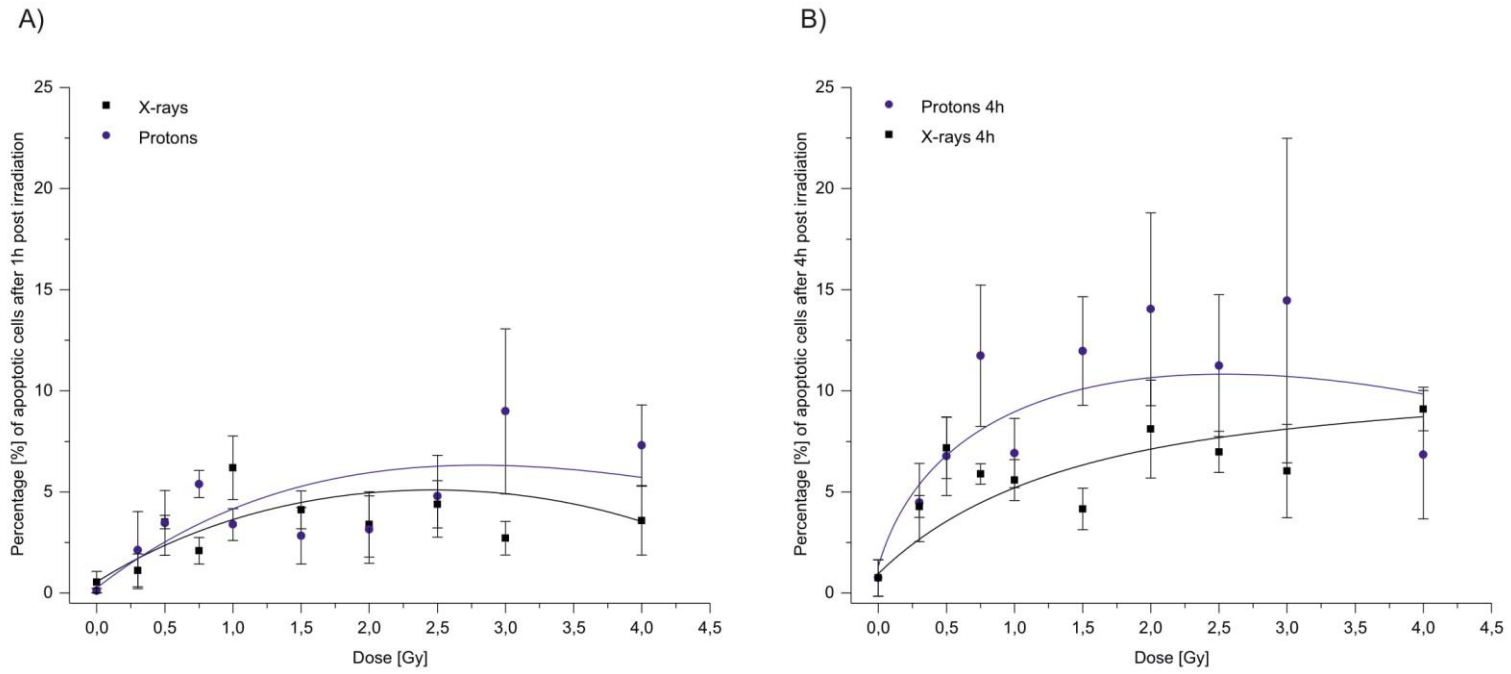


Fig. 20. Percentage of apoptotic cells after irradiation with X-rays vs. protons (1 and 4 h after irradiation).

Quantitative determination of apoptosis 0.3-4.0 Gy

Original Article

Translational Cancer Research 2018;
7(4):879-889.

Therapeutic proton irradiation results in apoptosis and caspase-3 activation in human peripheral blood lymphocytes

Justyna Miszczyk[1], Kamila Rawojć[2], Anna Maria Borkowska[1], Agnieszka Panek[1], Jan Swakoń[1], Aleksander Gałaś[3], Mansoor M. Ahmed[4], Pataje G. S. Prasanna[4]

Variability between donors and types of radiation is observed.

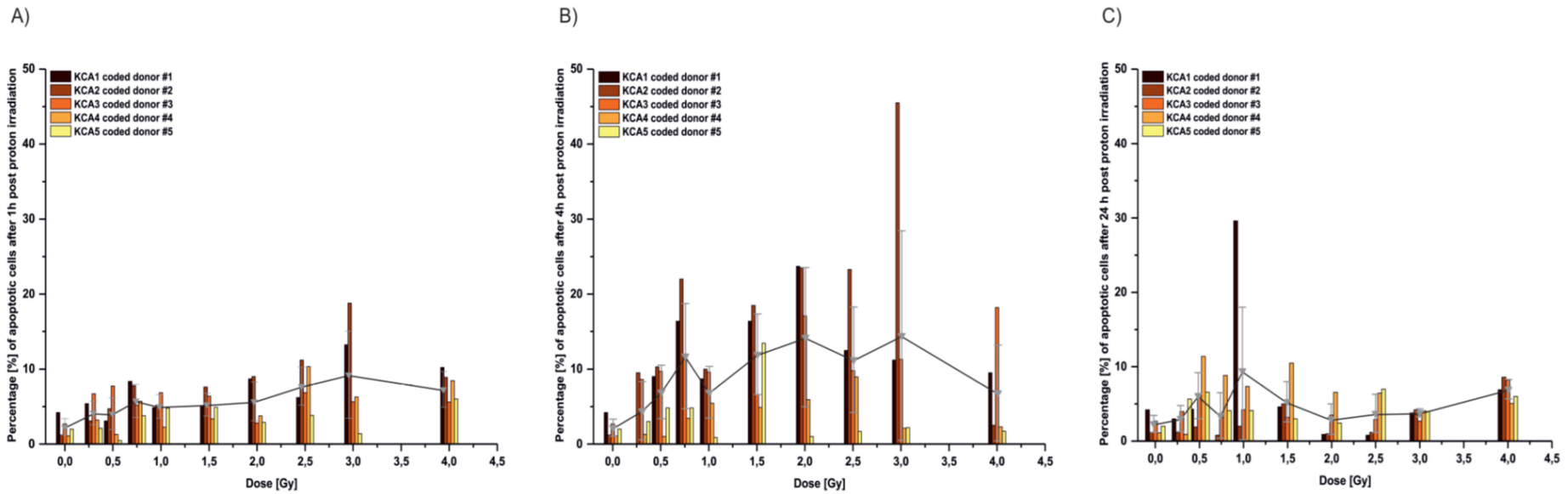


Fig. 21. Apoptotic cells percentage for individuals determined with Annexin V-FITC fluorescent staining in *ex vivo* HPBL model after 1 h, 4 h and 24 h post-proton treatment.

Quantitative determination of apoptosis by caspase-3 activation

After proton irradiation apoptosis is mediated through caspase-3,

activity is mostly observed at 6 h proton-irradiation, decreased significantly after 24h.

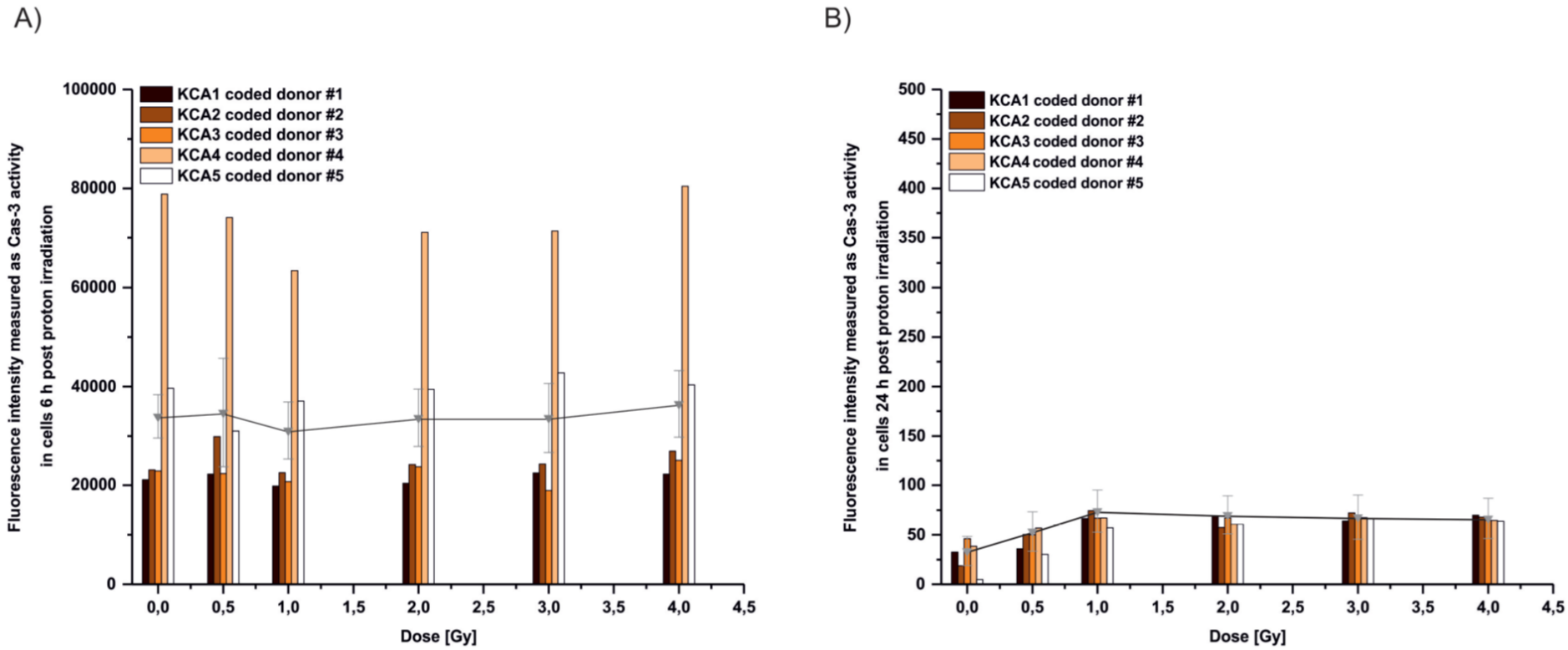


Fig. 22. Differences in caspase-3 activity among donors at 6 and 24 h post proton treatment (HTS assay kit, Biotium).

Therapeutic proton irradiation results in apoptosis and caspase-3 activation…, Miszczyk J et al., 2018.

Quantification studies of necrosis 0.3-4.0 Gy

Protons are more efficient in cell-killing due to their potential to cause necrosis in addition to apoptosis, especially at higher doses!

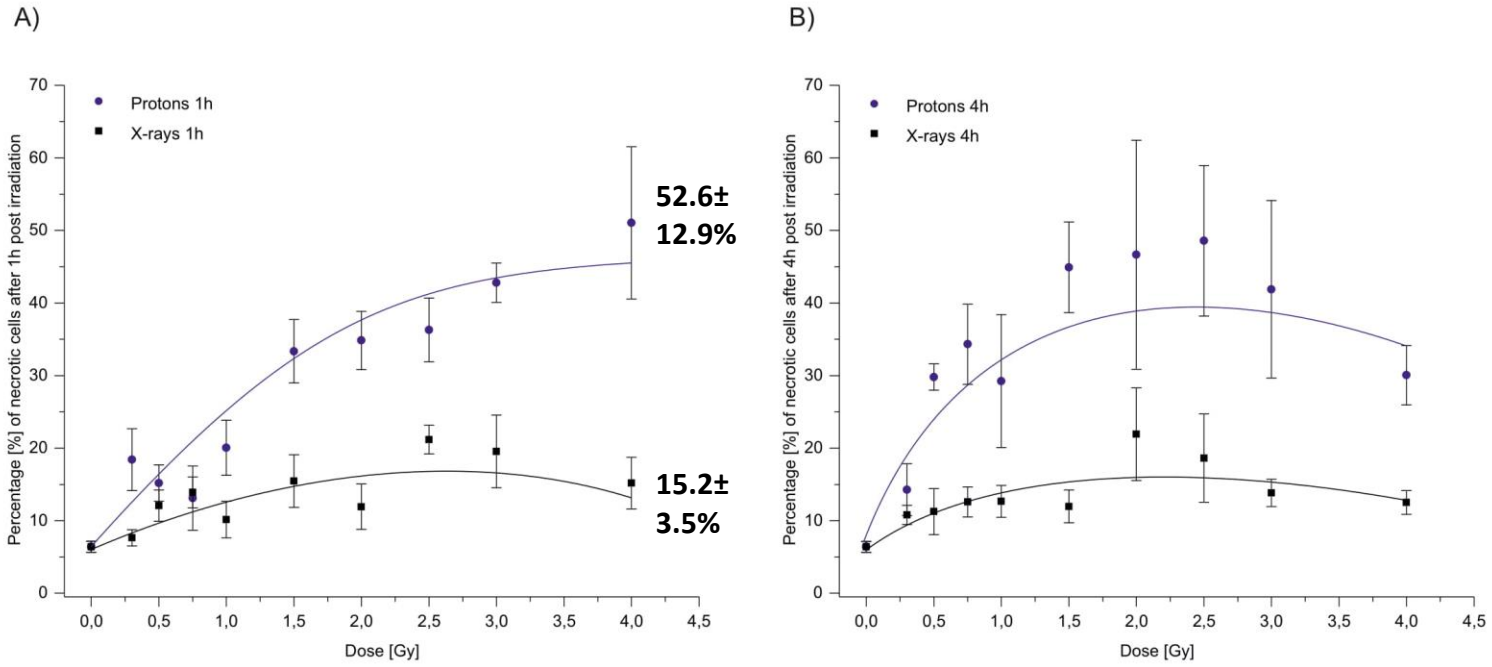


Fig. 23. Percentage of necrotic cells after irradiation with X-rays vs. protons (1 and 4 h after irradiation).

Facts, gaps and opportunities – part 2 and 3

- ✓ **HPBLs, phantom, unique position.**
- ✓ **Easy, reliable biodosimetry protocols (PCC, CBMN) and different triage modes post proton and X-rays radiation for low and high dose exposure were proposed (possibility to discriminate whole and partial body exposures).**
- ✓ **Not only radiation (dose, type, dose-rate) but also the procedural steps determined the cell response to different degrees.**
- ✓ **Normal tissue response to protons vs. X-rays for low and high doses is different (influence cellular proliferation and DNA damage to different degrees).**

Effect depend on radiation type and dose.

Inter-individual differences determine response and effect.

Therefore, potentially influence the type, incidence and itensity of the RT AEs.

Facts, gaps and opportunities – part 2 and 3

- ✓ **Protons and X-rays induce cell-killing in normal tissue by different mechanisms. Protons are more efficient by necrosis. Inter-individual differences were also observed.**

- ✓ **Apoptosis is mediated by caspase-3, but necrosis?**

THE HENRYK NIEWODNICZAŃSKI
INSTITUTE OF NUCLEAR PHYSICS
POLISH ACADEMY OF SCIENCES

Due to physical properties, protons and heavy ions deposit energy more selectively than X-rays, allowing a higher local control of the tumor.

Thus, the damage induced in normal tissues surrounding the tumor is limited.

Protons are distinct from photons not only concerning their unique dosimetry but also with their ability to invoke unique biological responses that can be differentially exploitable.

Therefore, continued studies of these differences are necessary to benefit from a given type of radiation treatment.

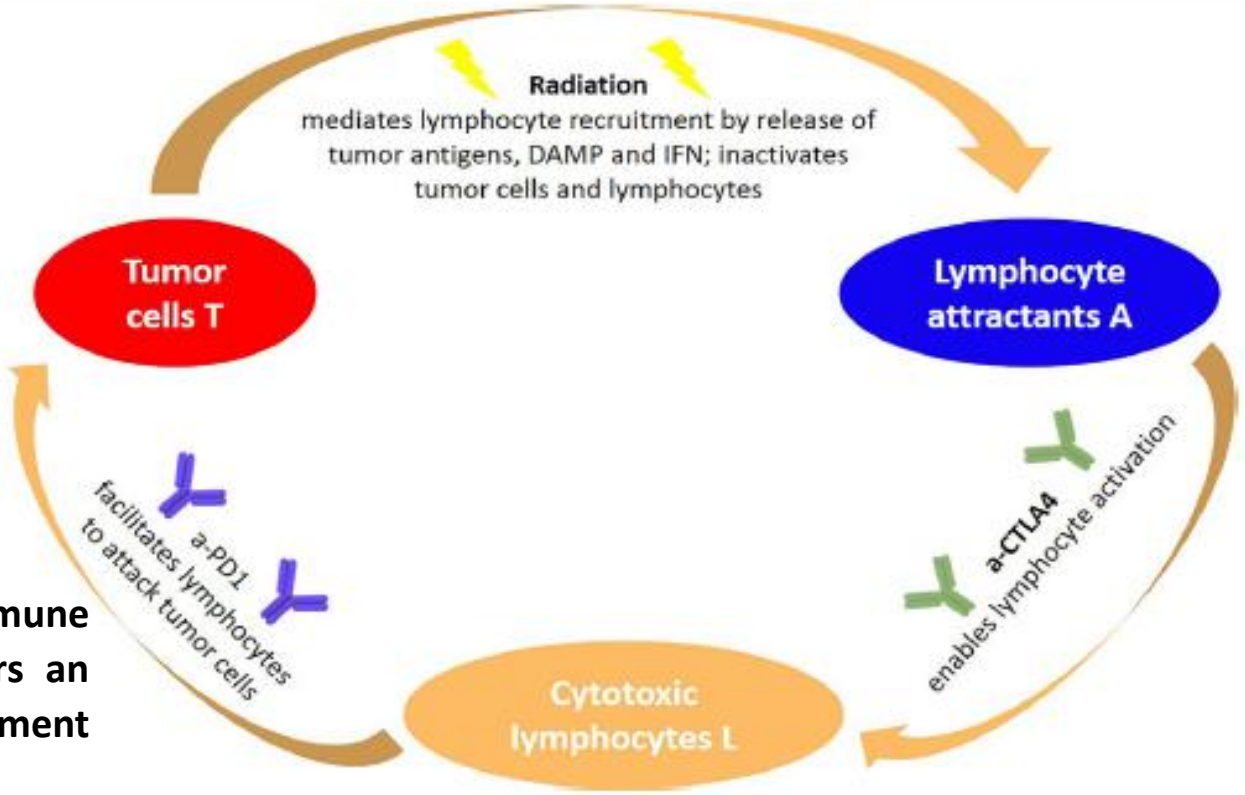
Modeling Radioimmune Response—Current Status and Perspectives

Thomas Friedrich[1], Nicholas Henthorn[2,3] and Marco Durante[1,4]*

frontiers in Oncology

REVIEW
published: 16 March 2021
doi: 10.3389/fonc.2021.647272

Potential sensitizers or radioprotectors can make tumor cells more detectable for immune system.



The combination of immune therapy with radiation offers an exciting and promising treatment modality in cancer therapy.

General paradigm underlying RT using immune checkpoint blockers.

Future issues

ELSEVIER

Cancer Treatment Reviews

Available online 16 April 2021, 102209

In Press, Journal Pre-proof

Anti-tumour Treatment

Proton beam therapy for children and adolescents and young adults (AYAs): JASTRO and JSPHO Guidelines

Masashi Mizumoto [a], Hiroshi Fuji [b], Mitsuru Miyachi [c], Toshinori Soejima [d], Tetsuya Yamamoto [e], Norihiro Aibe [f], Yusuke Demizu [d], Hiromitsu Iwata [g], Takayuki Hashimoto [h],

The Japanese Society for Radiation Oncology (JASTRO)

The Japanese Society of Pediatric Hematology/Oncology (JSPHO).

- ✓ **Careful use of PBT is recommended in adult patients, while sedation is required to maintain pediatric patients at rest.**
- ✓ **Further validation of irradiation techniques is needed for X-ray and PBT in both pediatric and adult patients.**
- ✓ **These guidelines show the superiority or equivalence of PBT in comparison with X-ray therapy for pediatric tumors.**
- ✓ **However, brainstem necrosis after PBT is still under discussion and requires further examination.**

We need continue to evaluate the long-term efficacy of proton beam therapy for pediatric and adult patients.

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Faculty of Physics and Applied Computer Science

Irradiations

Cell's counted

~0.5 mln.

Image aquisition

Methods used

7; 12

Data were analyzed separately from 3 independent repetitions, by min. 2 independent scorers.

Acknowledgments

Laboratory of spectroscopic imaging for radiobiology, treatment and research of complex systems - equipment purchased as a part of the project co-funded by the Malopolska Regional Operational Program Measure 5.1 Krakow Metropolitan Area as an important hub of the European Research Area for 2007-2013.

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DEMOKRITOS

NIH NATIONAL CANCER INSTITUTE
Cancer Prevention Fellowship Program

AACR American Association for Cancer Research

Leiden University Medical Center, Department of Toxicogenetics, Netherlands.

LUMC

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