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Heavy Ion Therapy Research Integration

HADRON THERAPY SYMPOSIUM

STATUS AND PERSPECTIVES, PLANS FOR NEXT GENERATION FACILITIES

18 - 21 October 2024
Thessaloniki

Radiobiology of Hadron Therapy

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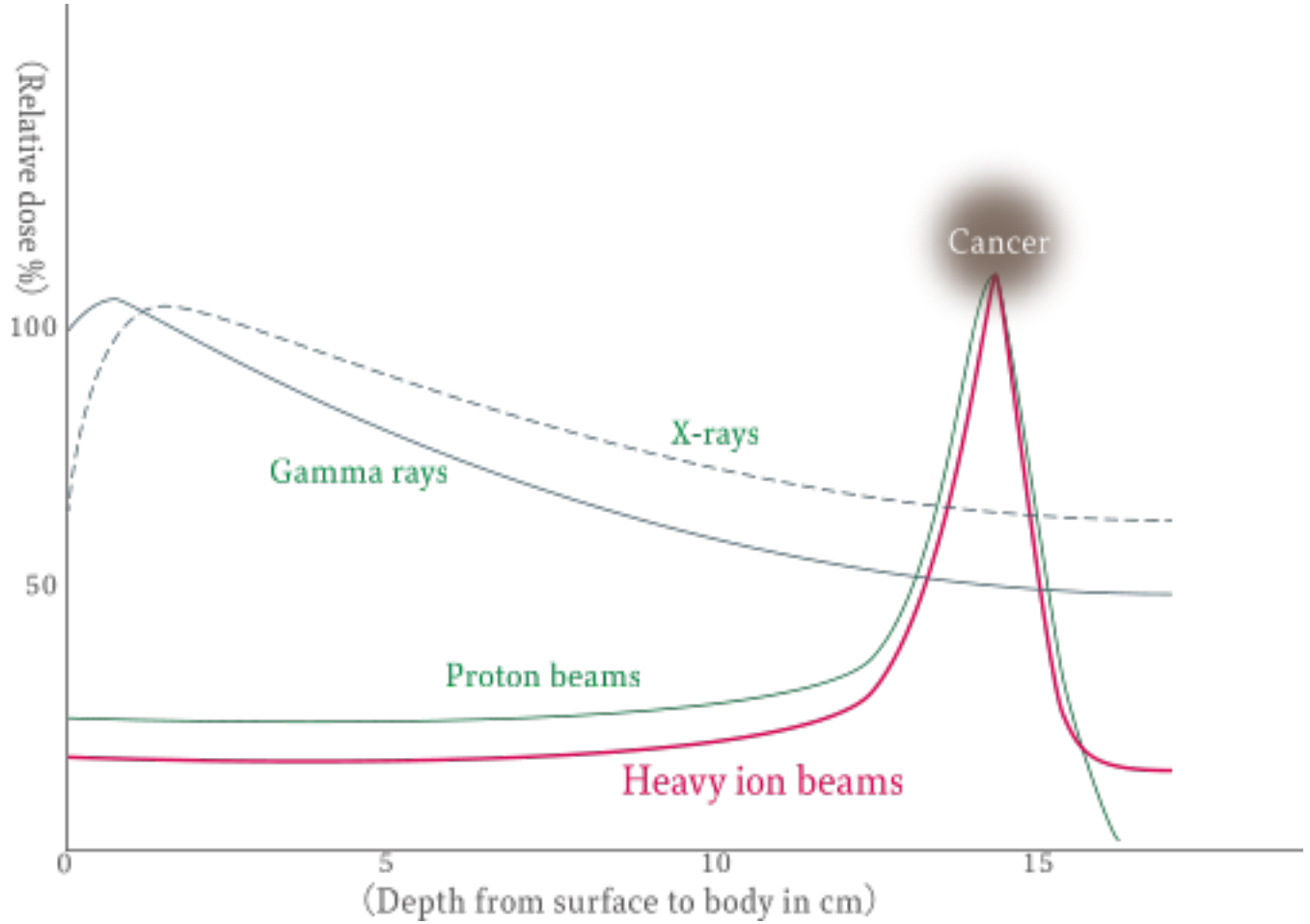
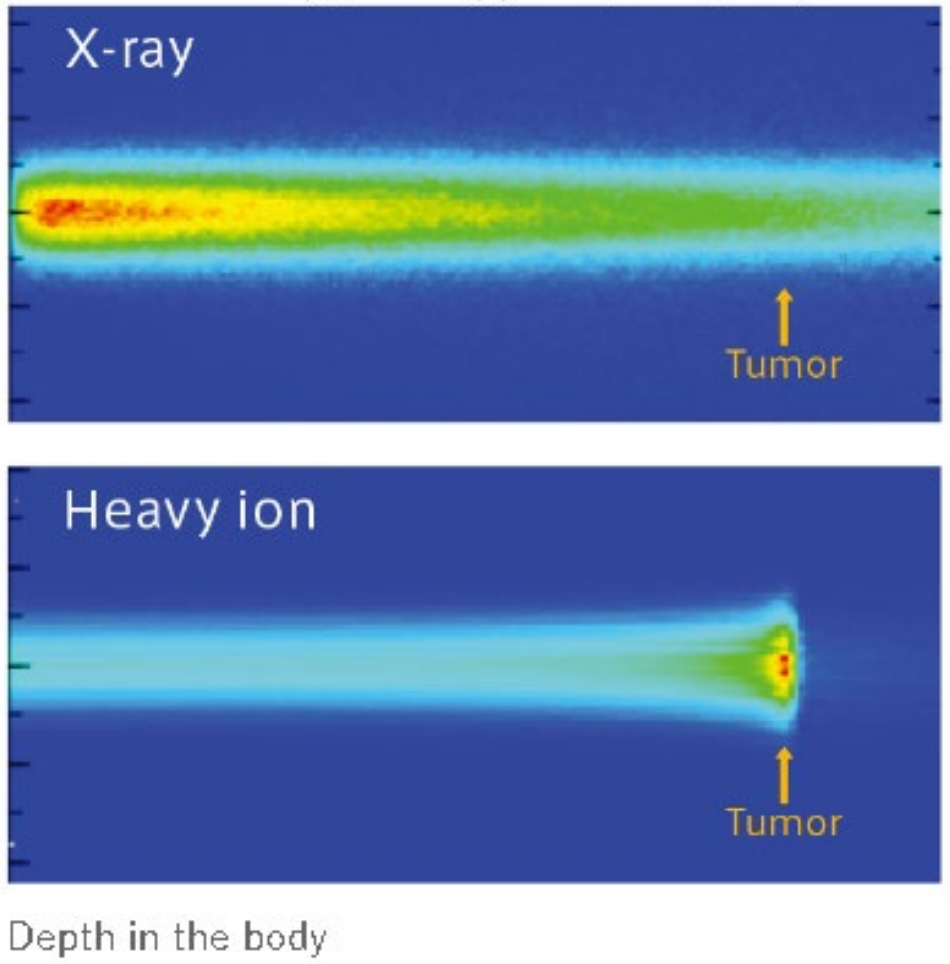
Radiobiology

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

X-rays used in conventional radiotherapy are most effective near the surface of the body and emit energy as they penetrate deeper into the tissue.

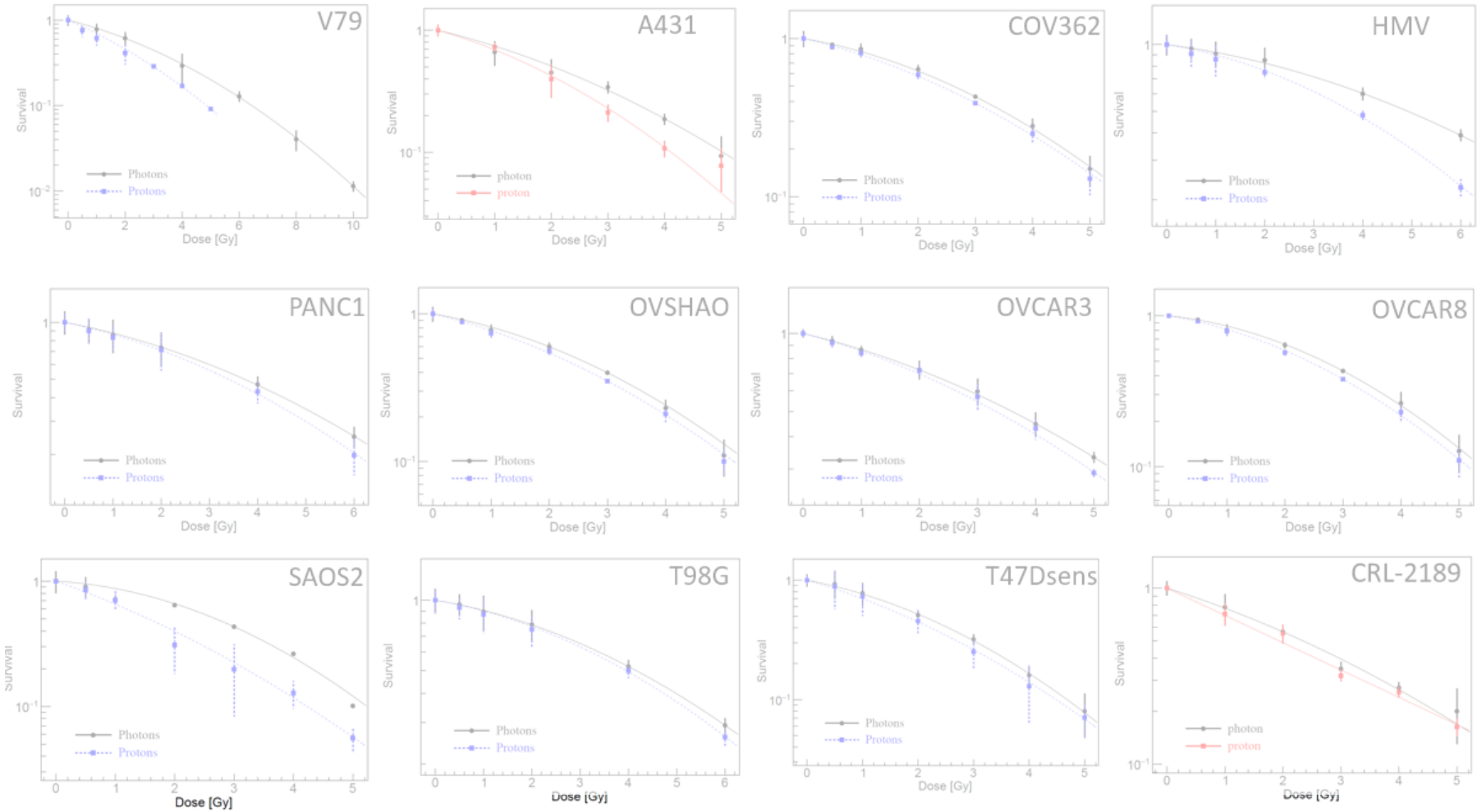
Charged particle beams, however, cause an energy peak at a fixed depth within the body, and emit considerably lower levels of energy before and after this point →**Side effects minimized**





https://www.saga-himat.jp/library/en/treatment/

Biological effect - protons



Charalampopoulou et al, in preparation

Radiation and children

The cellular and subcellular effects of radiations are identical in adults and children **HOWEVER** the **tissue remodelling** and **functional consequences** of radiation injury differ markedly

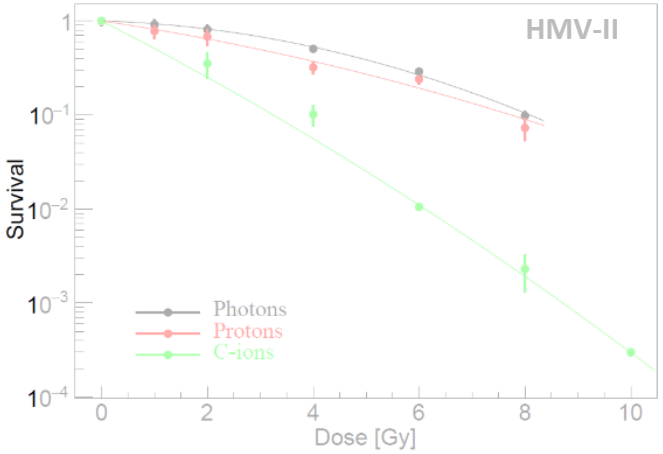
The **fibrotic-atrophic pathway** is the main cause of late normal tissue damage after radiation in all ages. In **children**, this pathway **impairs growth and organ development**, leading to conditions like hypoplasia and hypofunction (particularly in critical areas such as the brain, heart, and lungs)

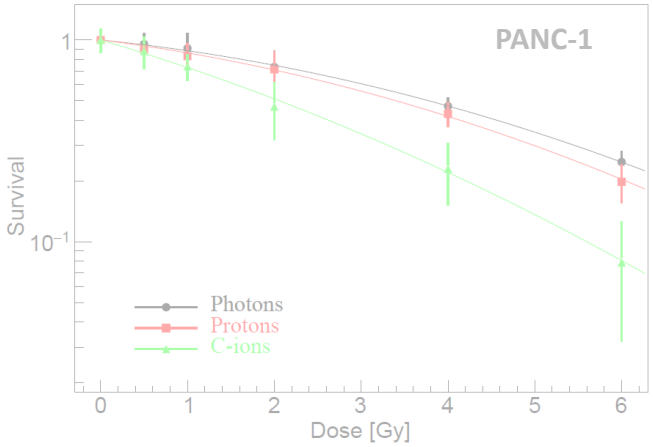
The younger the child is during radiation, the higher the risk and severity of these effects.

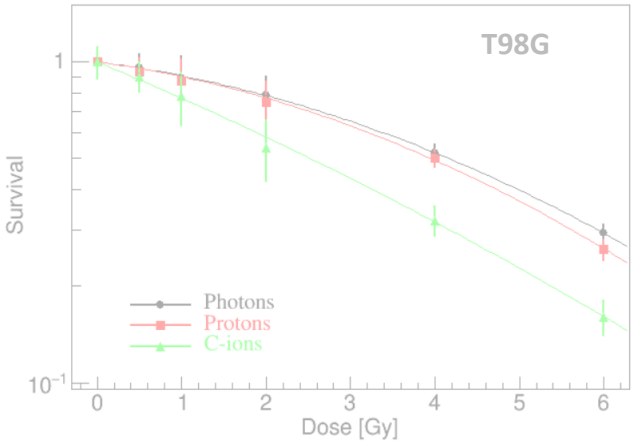
Since these effects often take a long time to appear, the risk increases as the child grows older.

The physical effects of radiotherapy can also have psychosocial implications, impacting a child's quality of life, and social interactions.

Carbon ions - Biological effect







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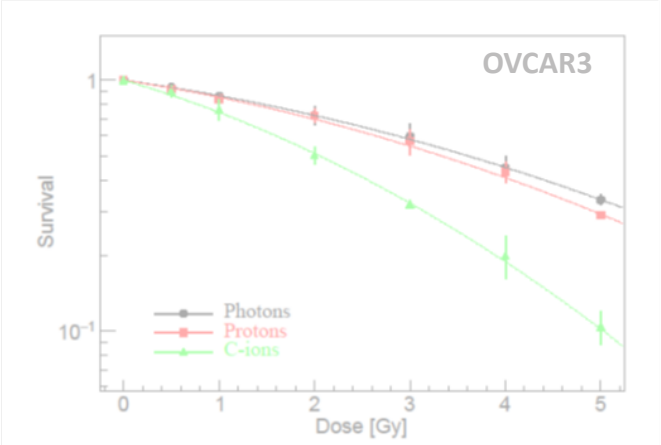
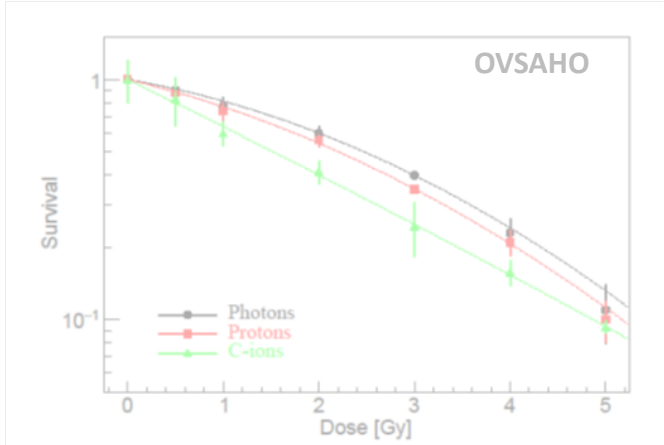
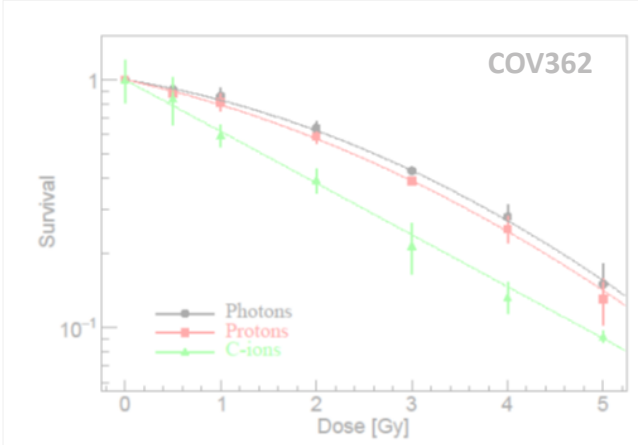
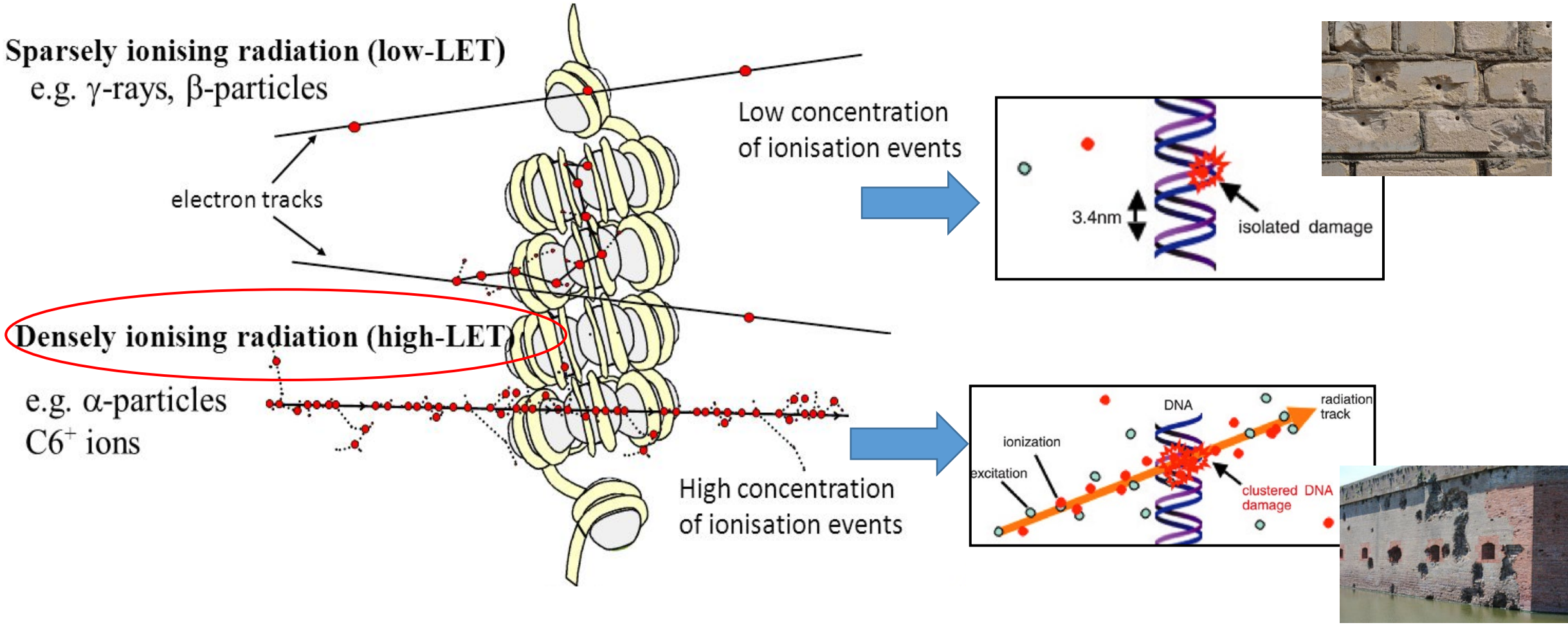




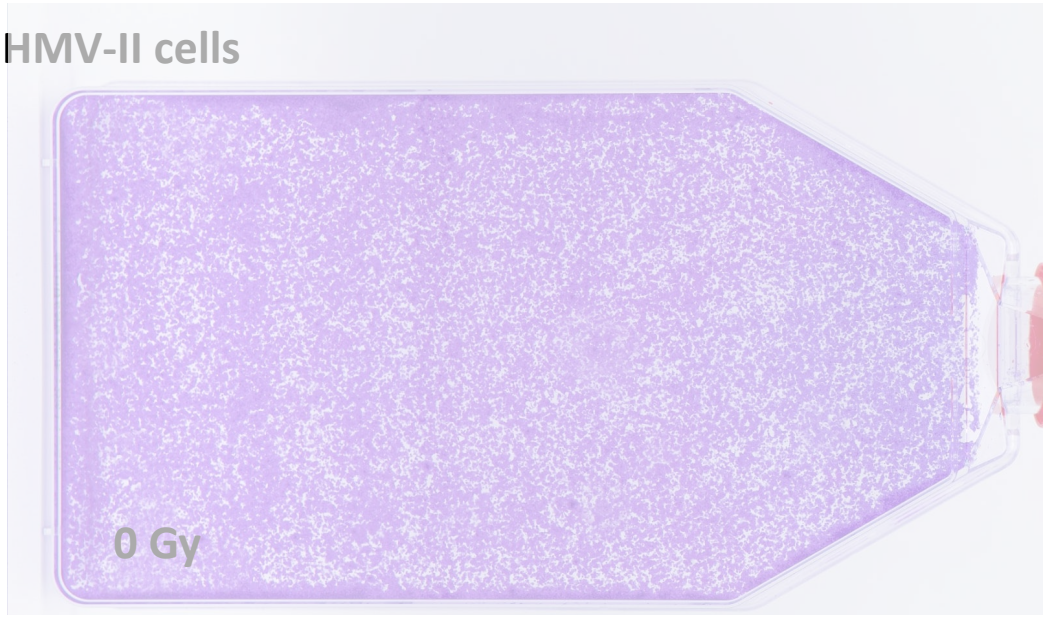


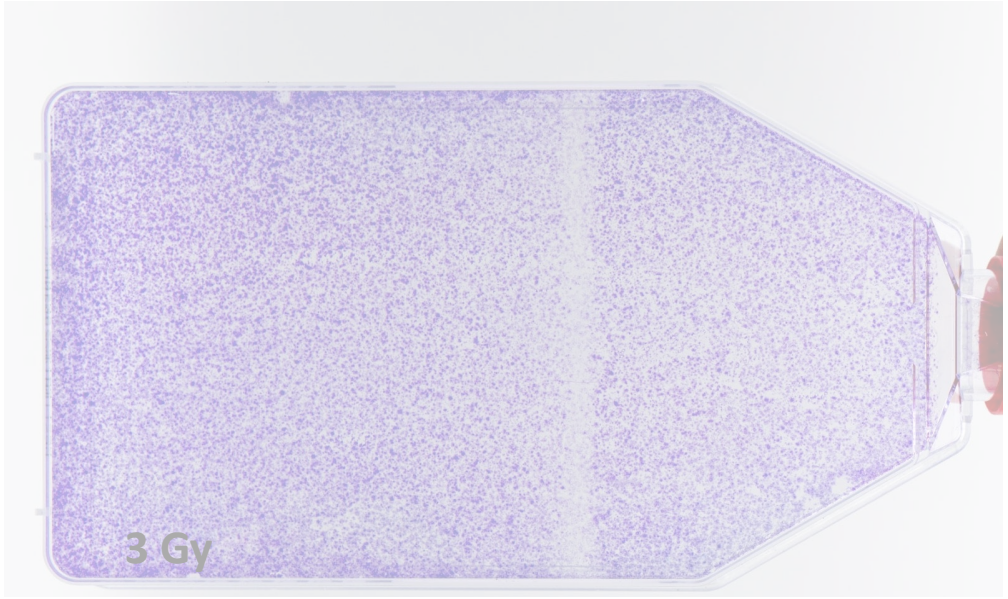
Charalampopoulou et al, in preparation

Carbon ions are densely ionising radiations inducing complex DNA damage

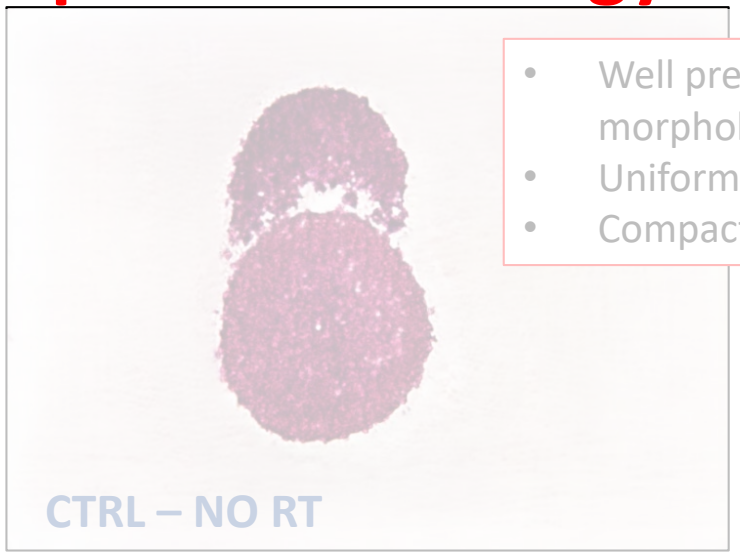


Physics + Biology



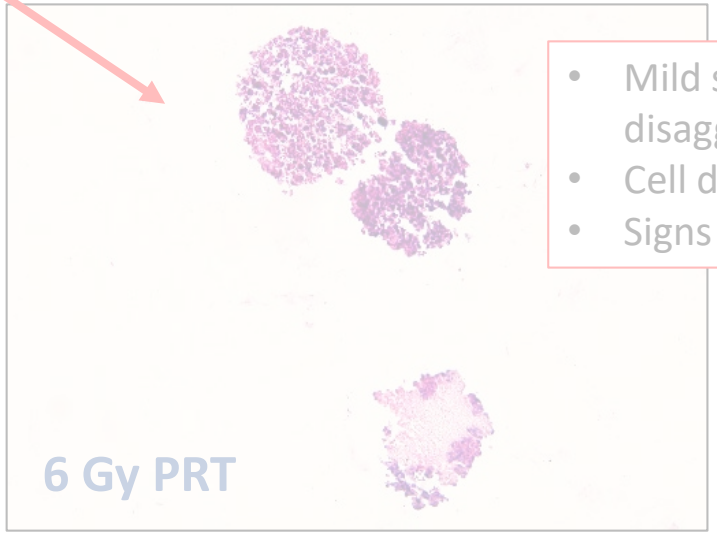


Spheroid histology – T98G

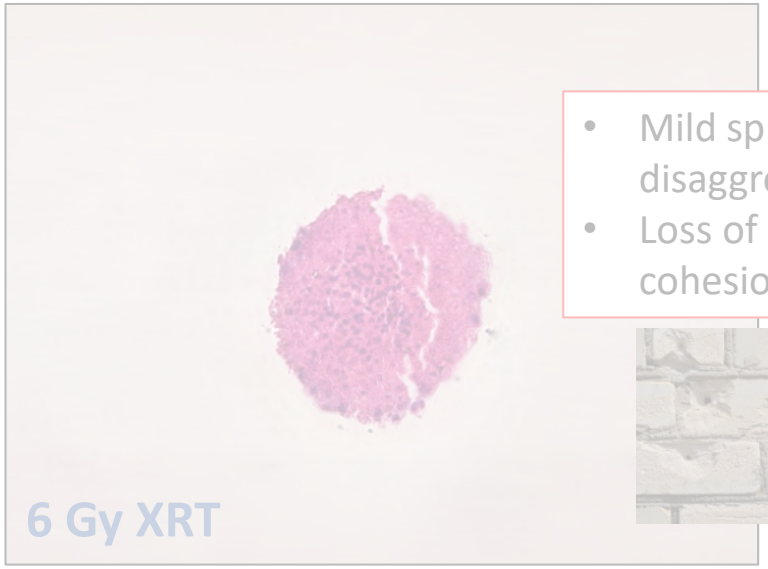


- Well preserved spheroid morphology
- Uniform cell distribution
- Compact morphology

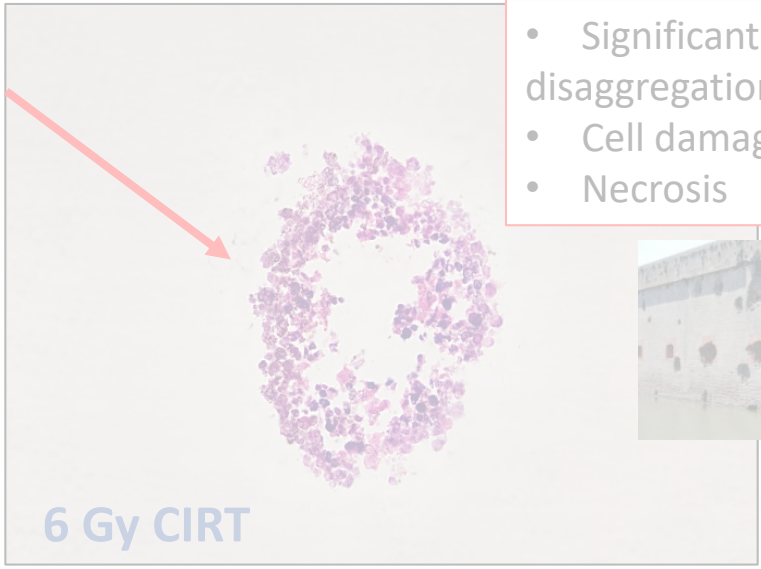
5 days post RT



- Mild spheroid disaggregation
- Cell damage
- Signs of necrosis



- Mild spheroid disaggregation
- Loss of cellular cohesion

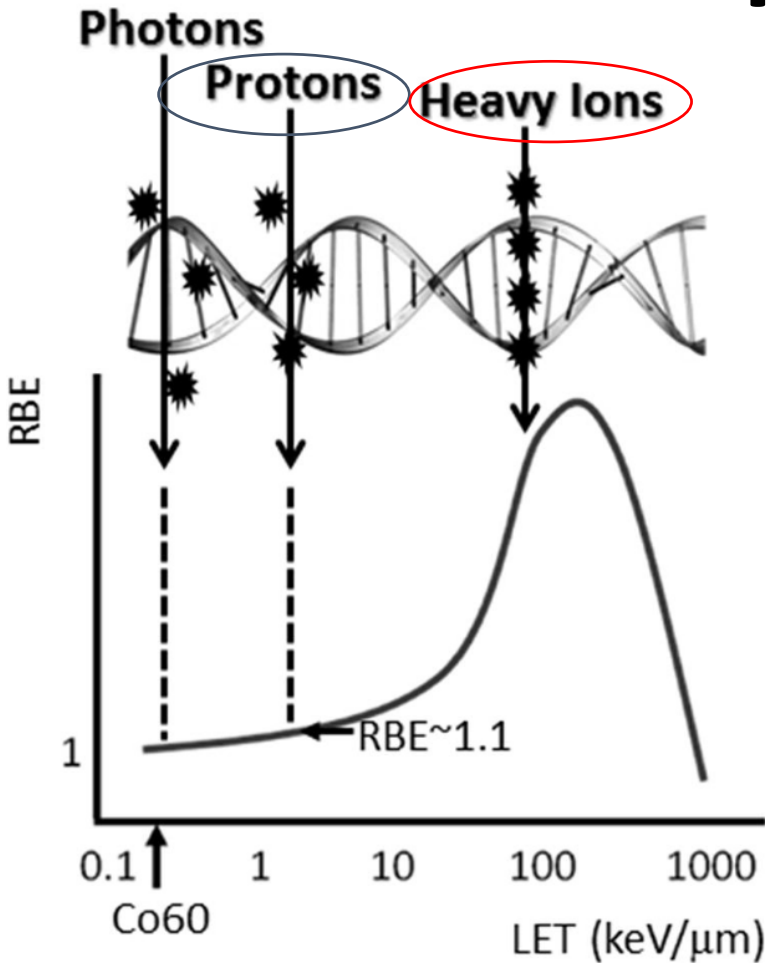


- Significant spheroid disaggregation
- Cell damage
- Necrosis

Charalampopoulou et al, in preparation

LET: the higher the better???

The optimal Linear Energy Transfer



Henning Willers et al, 2018

LET of about **100 keV/µm** is optimal in terms of producing a biologic effect.

→ At this density of ionization, **the average separation in ionizing events is equal to the diameter of DNA double helix** which causes significant DSBs.

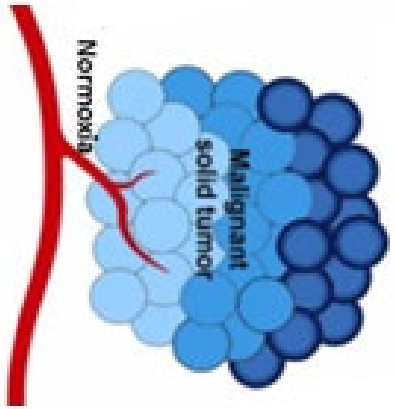
→ Beyond this value, the energy is wasted as events coincide with each other.

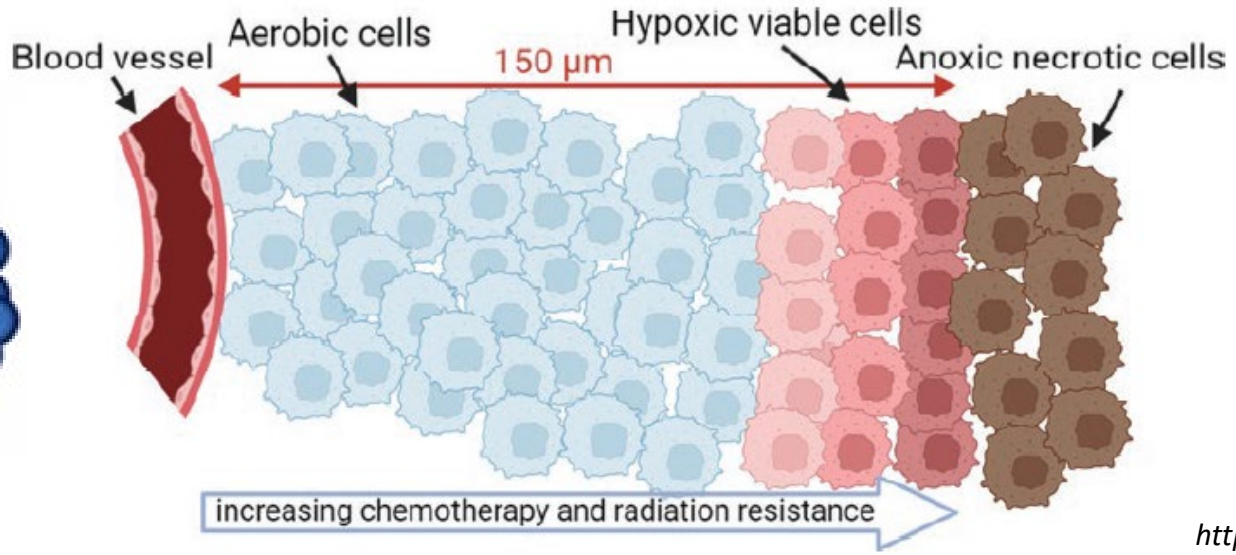
Assumption: DSBs are the basis of most biologic effects (**Cell killing, mutagenesis or oncogenic trasformation)**

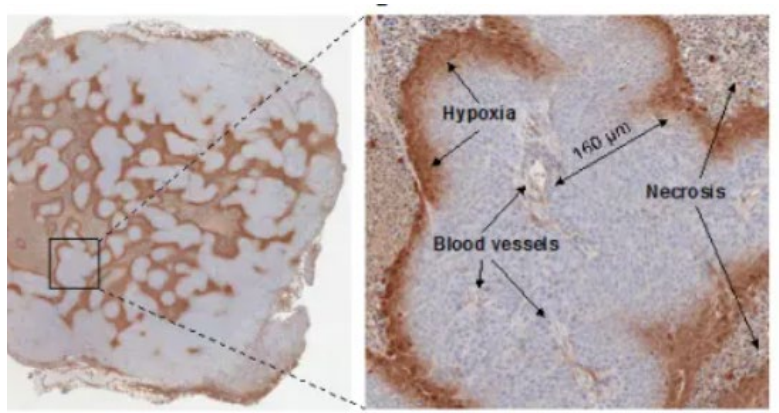
What about other biological effects???

Radiobiological advantagies of carbon ions

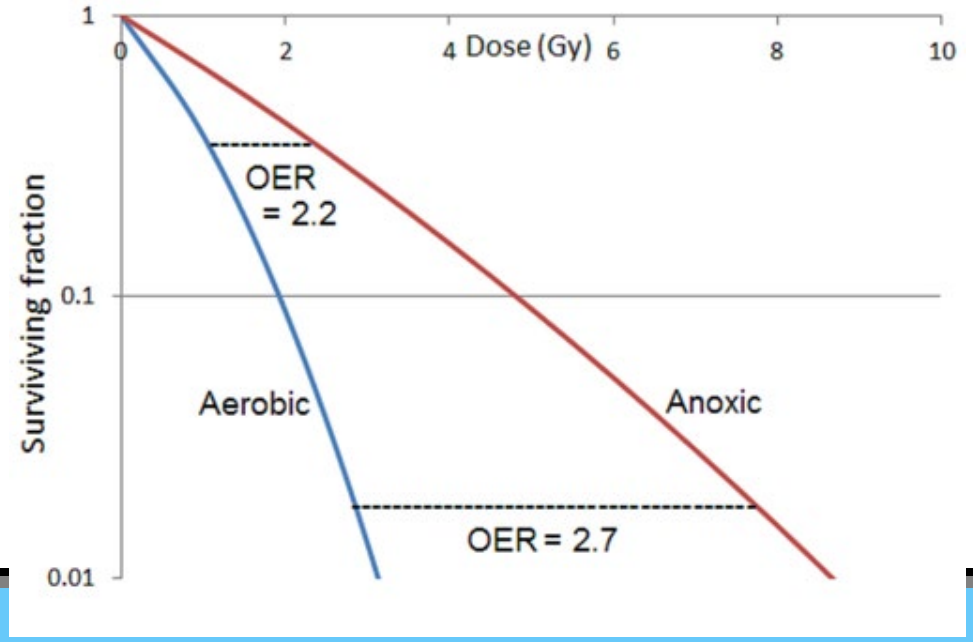
Hypoxia-induced radioresistance



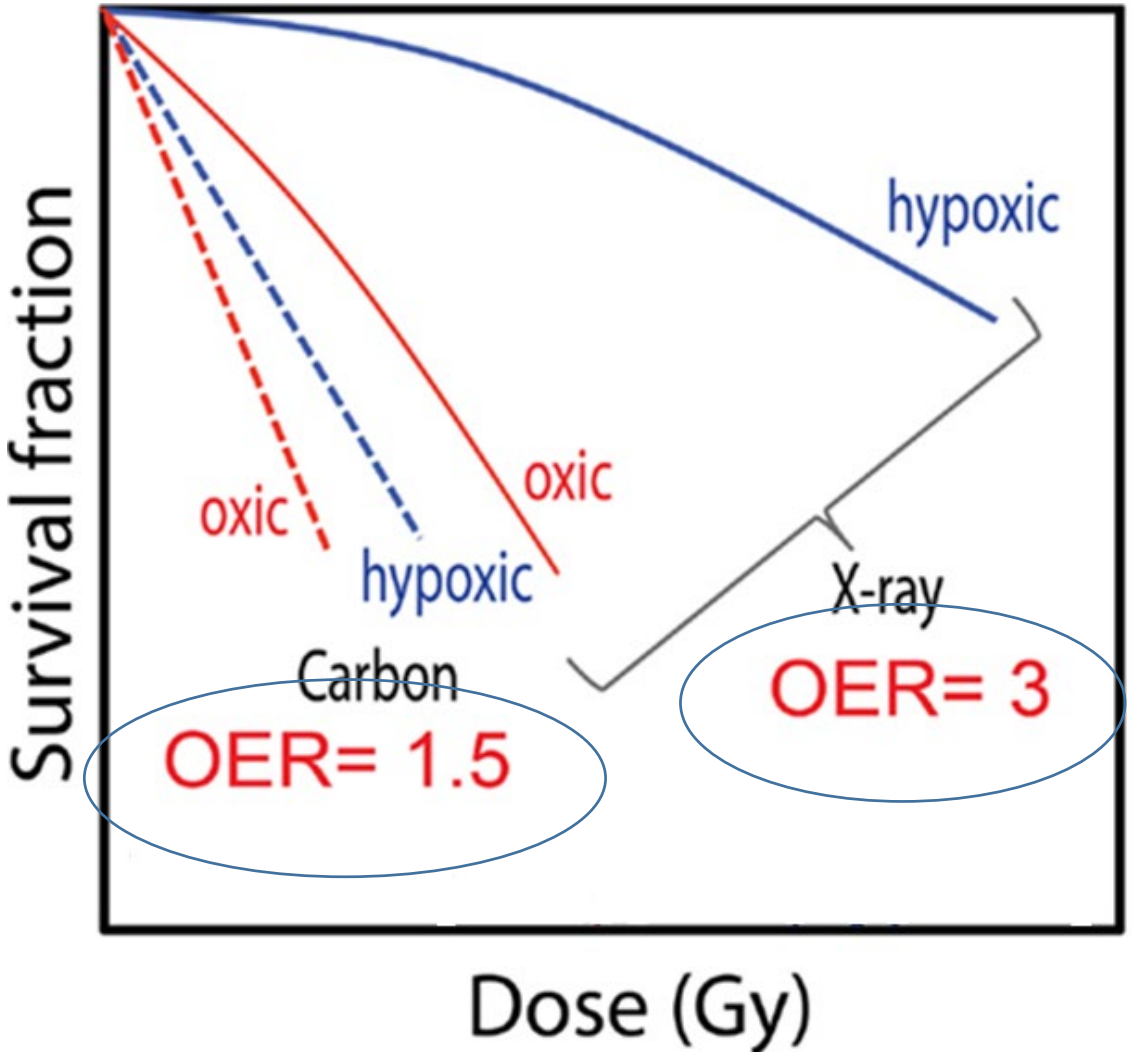




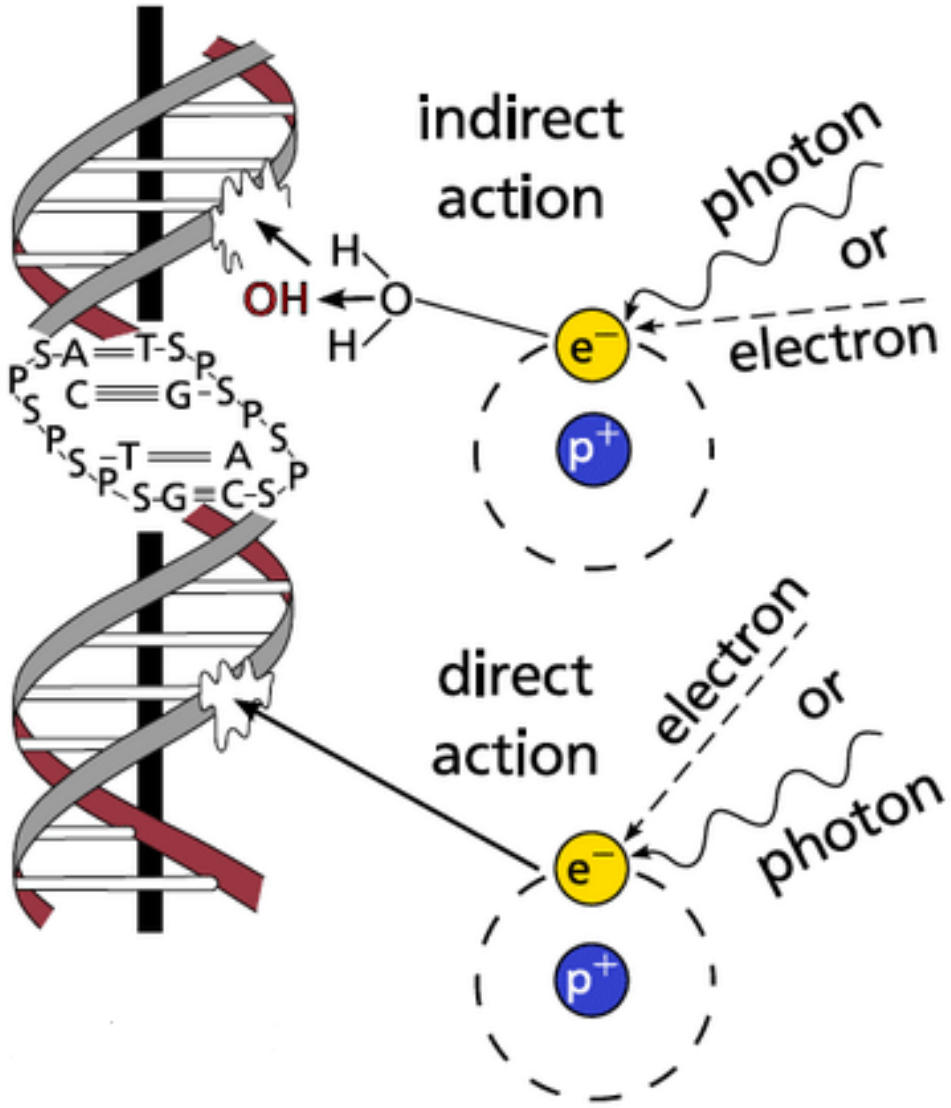
https://www.oncology.ox.ac.uk/research/research-group/tumour-hypoxia



Carbon-ion irradiation is able to reduce hypoxia-induced radioresistance



The oxygen effect is reduced with carbon-ion irradiation



Dominant for low LET radiation

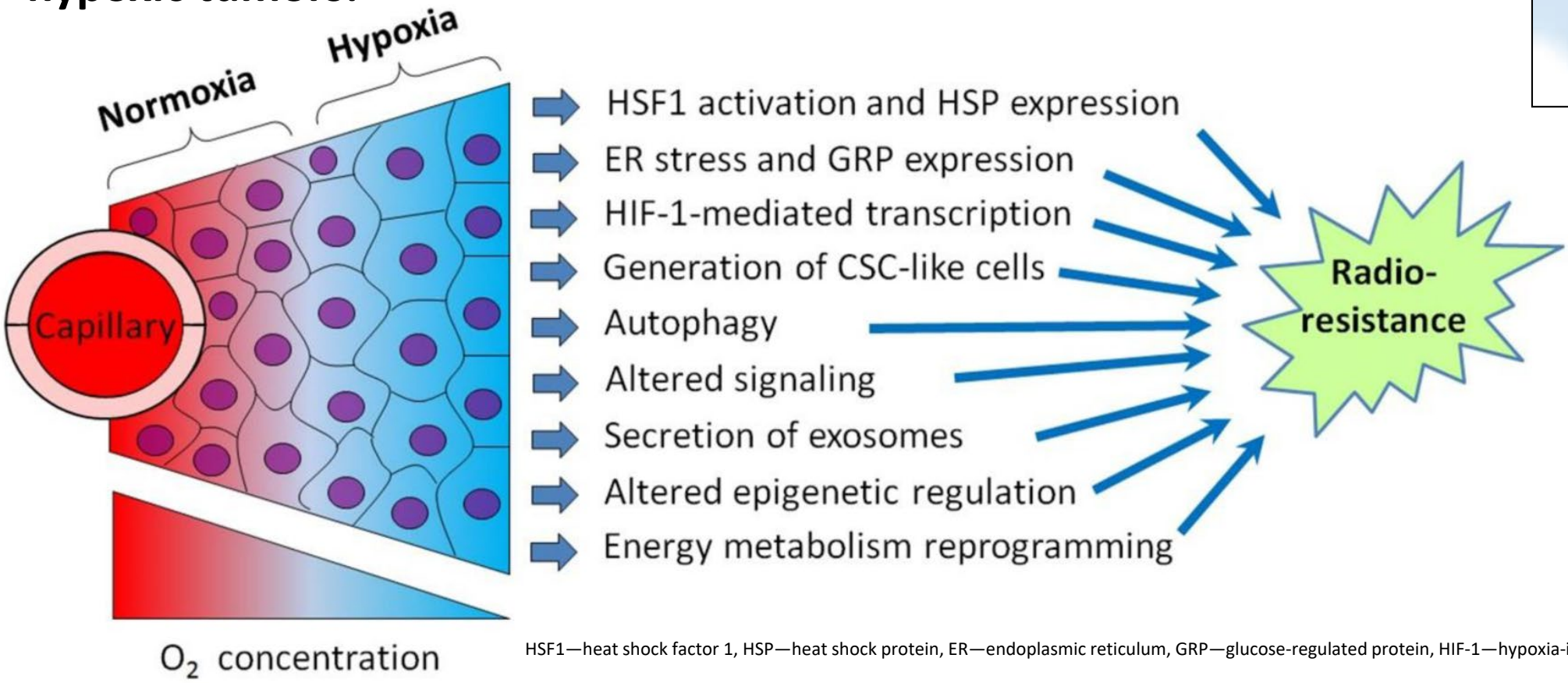
Radiation interacts with other molecules in the cells, particularly water, to produce **free radicals** such as hydrogen atoms (H^+), hydroxyl radicals (HO), and superoxide radical anion (O2 −), which in turn induce the damage to the DNA.

Dominant for high LET radiation

Radiation directly interacts with DNA resulting in DNA damage.

Hypoxia-induced radioresistance: biological point of view

Hypoxia-induced cancer cell responses promoting the radioresistance of hypoxic tumors:



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C-ions?

HSF1—heat shock factor 1, HSP—heat shock protein, ER—endoplasmic reticulum, GRP—glucose-regulated protein, HIF-1—hypoxia-inducible factor-1, CSC—cancer stem cell

→ Radiation induces HIF-1 activity and production of survival factors linked to radioresistance

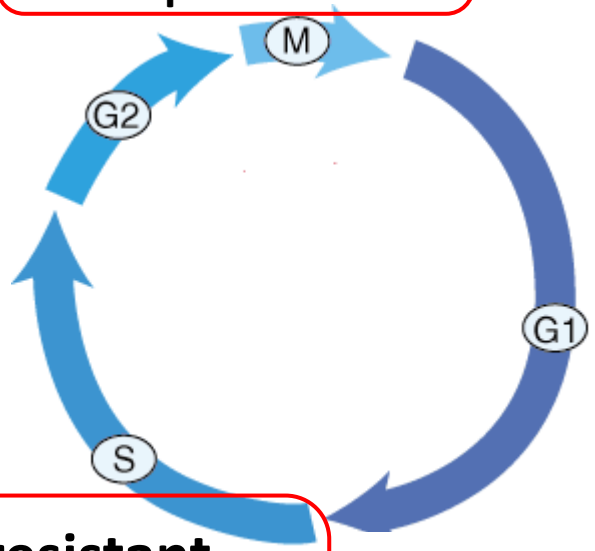
→ C- ion irradiation is able to decrease the expression of the HIF-1a subunit in hypoxic conditions, both *in vitro* and *in vivo*

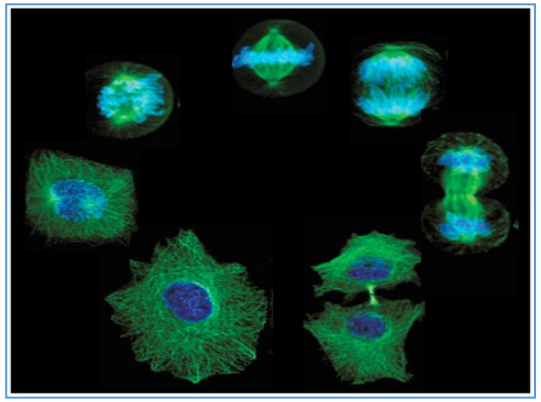
Kabakov A.E and Yakimova AO, 2021

The cell cycle dependence

PHOTONS

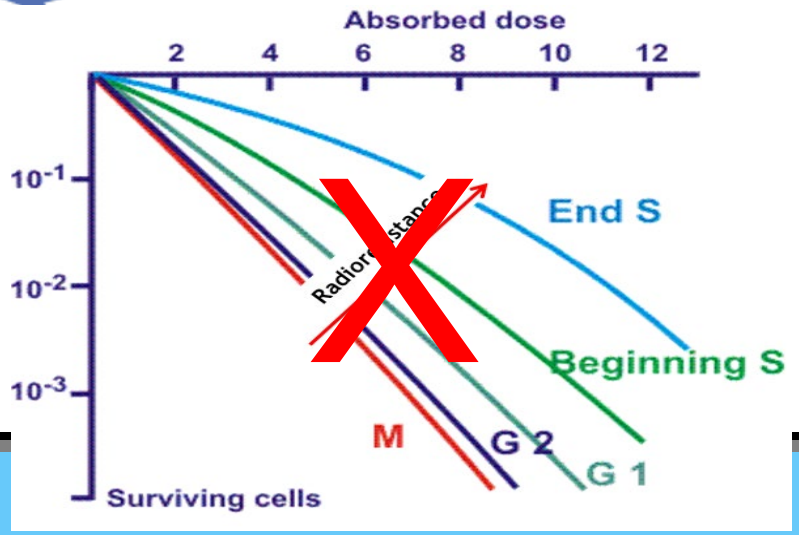
Radiosensitive
DNA repair difficult





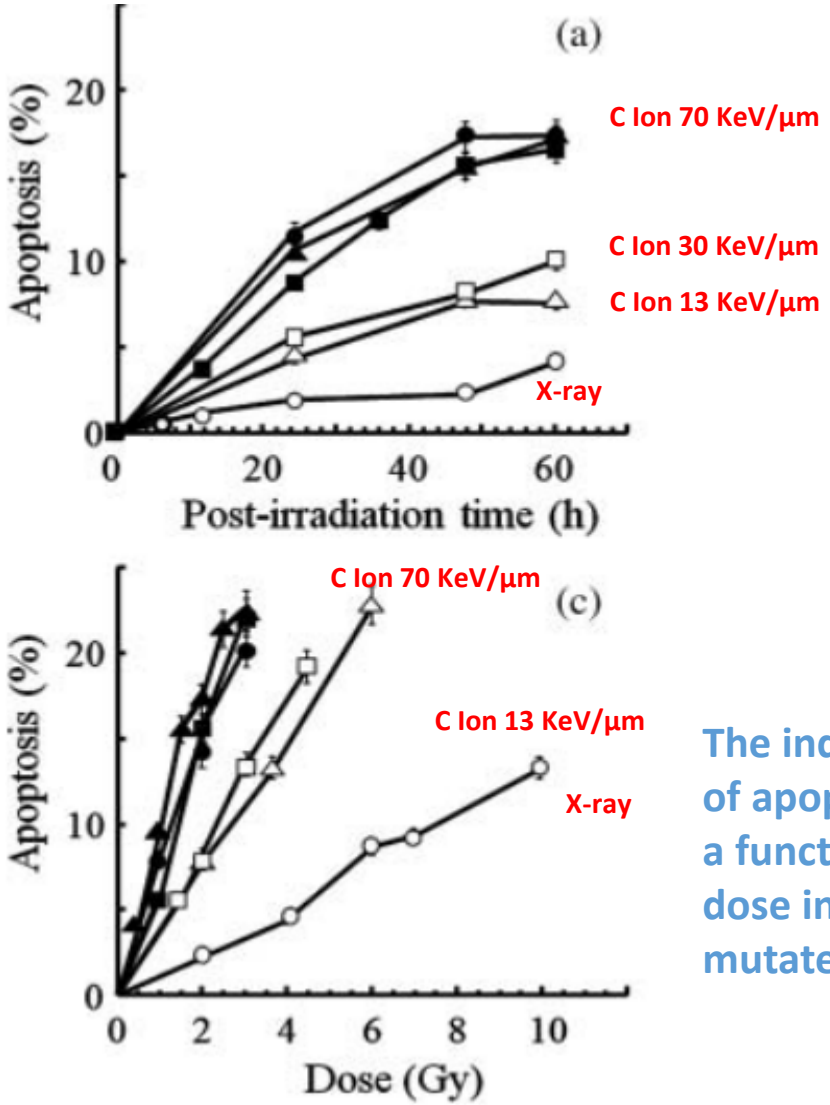
Cells are most sensitive to photon irradiation in the G2/M phases of the cell cycle, and most resistant in late S phase

Radioresistant
Duplicated DNA strands provide template for repair



No significant effects on radiosensitivity through the cell cycle when delivering high LET radiation

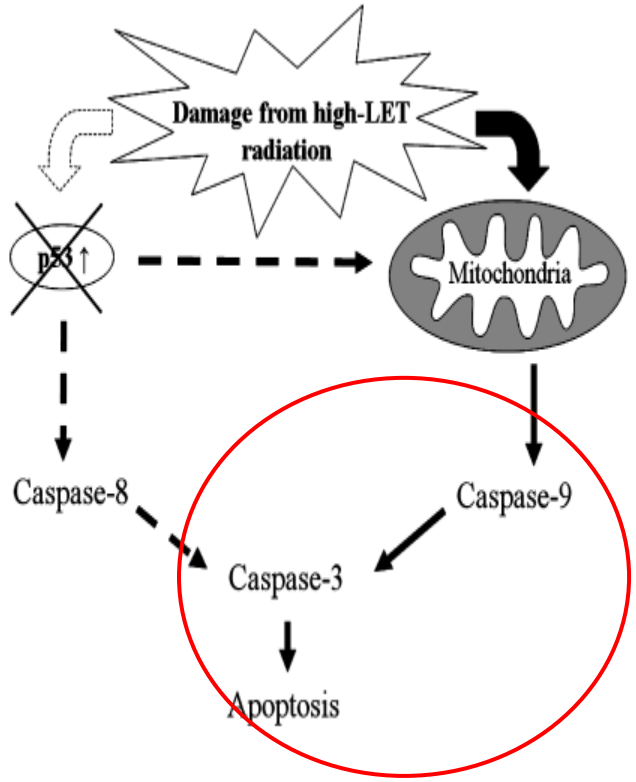
P53-independent apoptosis induced by high LET radiation



Time course of apoptosis induced by X-ray and heavy-ion beam irradiation with 2 Gy in p53 mutated cells

The induction of apoptosis as a function of dose in p53 mutated cells.

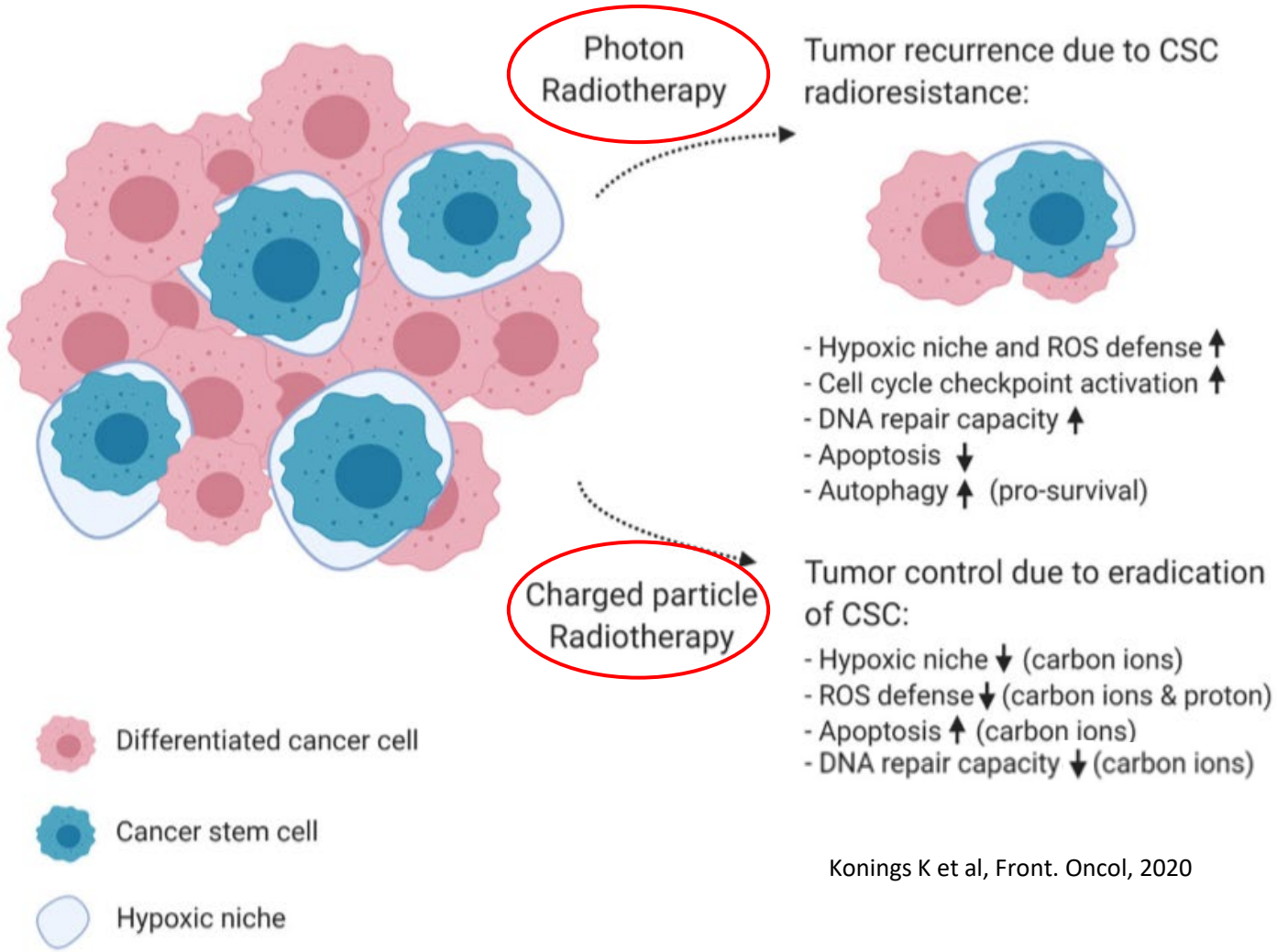
Apoptotic pathways triggered by high LET radiation do not require *p53*.



Yamakawa N et al Cancer Sci, 2008

TUMOR RADIORESISTANCE: Cancer Stem Cells

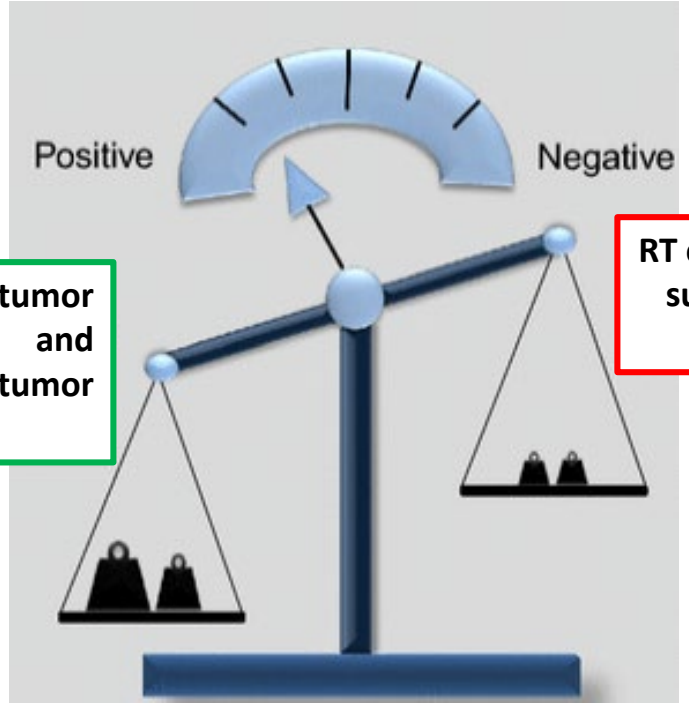
Several studies have already demonstrated a better efficacy of heavy ions to overcome pro-survival signaling (such as AKT survival signaling), suggesting that carbon ions could enhance apoptosis in radioresistant CSCs



Konings K et al, Front. Oncol, 2020

Combined treatments - immunotherapy

RT can promote immunity through the release of tumor antigens, induction of type I interferon, and modification of the immunosuppressive tumor microenvironment

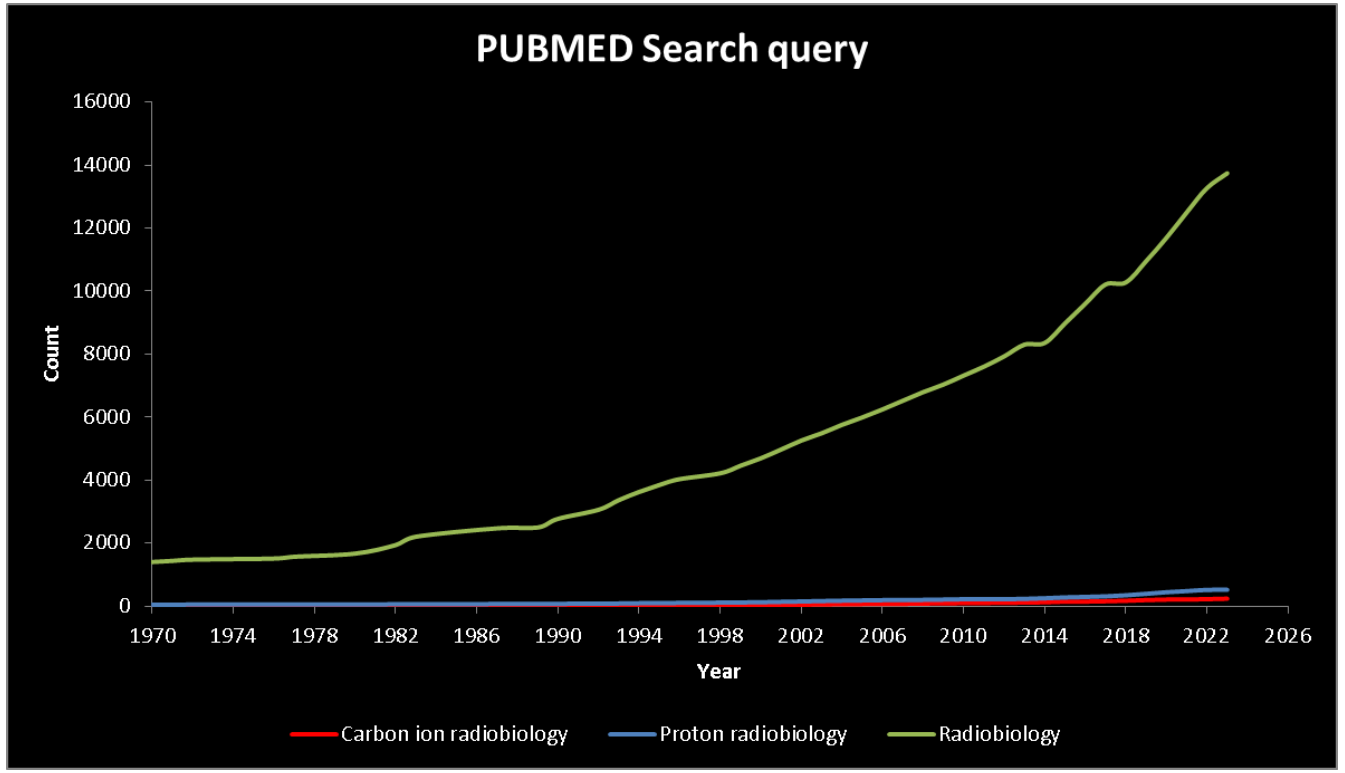


RT can activates immunosuppressive pathways such as upregulation of PD-L1 expression in tumor cells

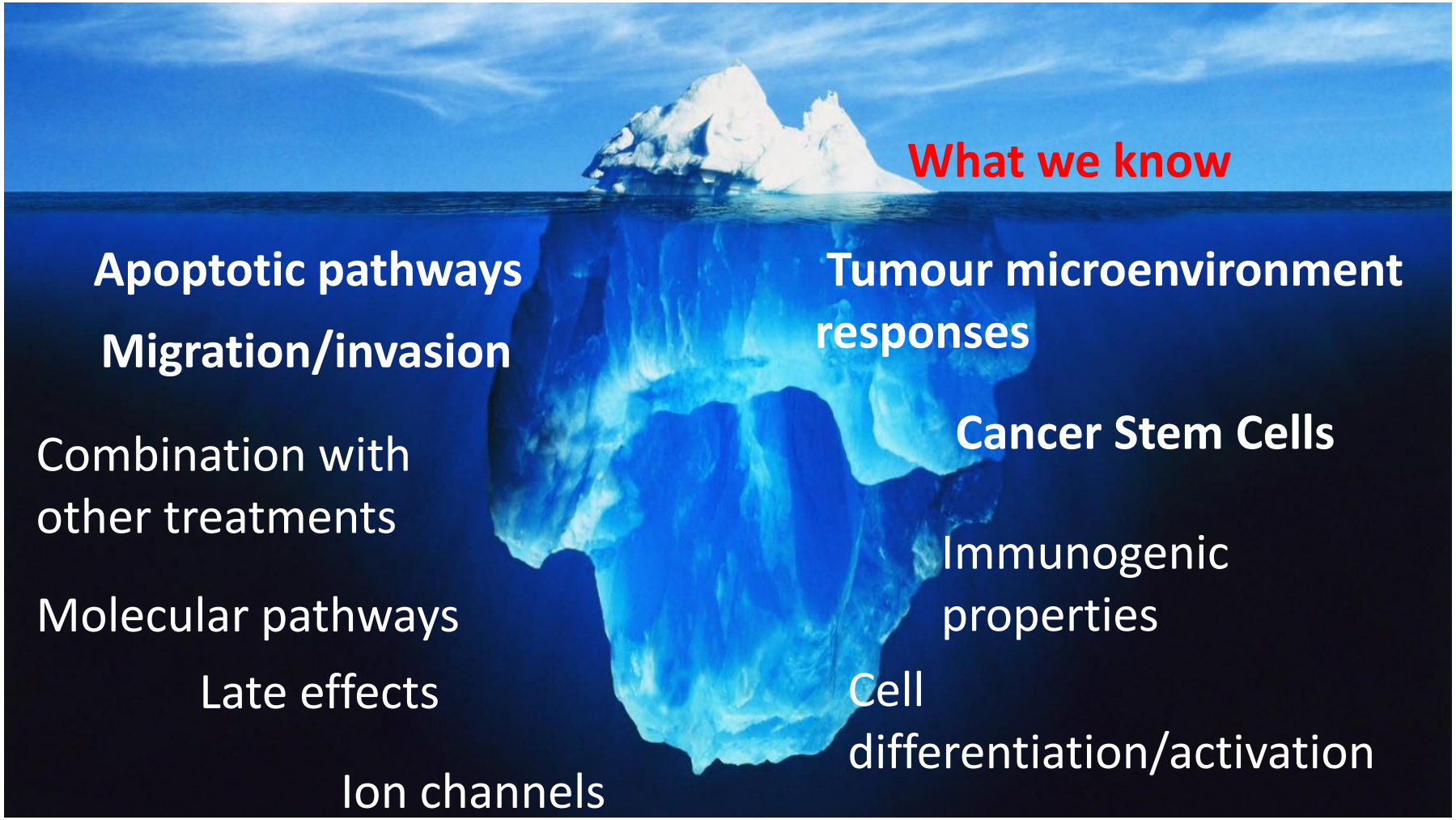
The synergistic effects of carbon ion beam irradiation combined with immunotherapy may be more effective than those observed with conventional radiation therapy.

- ✓ Classic protracted regimens of fractionated radiation therapy induce some degree of lasting l**ymphopenia**, by exposure of circulating blood during treatment and inclusion of active hematopoietic organs within relevant dose volumes. The more favorable integral dose of particle therapy likely **reduces this effect** *(Durante M et al, 2016)*
- ✓ Increased induction of **radiation-induced immunogenic cell death** with the activation of tumor-specific T cells
- ✓ Clustered DNA lesions trigger different **DNA damage repair signals strongly related to the immune response**
- ✓ Carbon ion radiation increased the levels of **high mobility group box 1** (HMGB1) in the culture supernatants of different human cancer cell lines *(Yoshimoto Y et al, 2015).*
- ✓ Preliminary *in vitro* studies showed an increased release of **immune-stimulating cytokines** after heavy ion exposure *(Durante M & Formenti S. 2019).*
- ✓ Carbon ions, may **distinctly affect cell death pathways**, leading to increased immunogenicity.

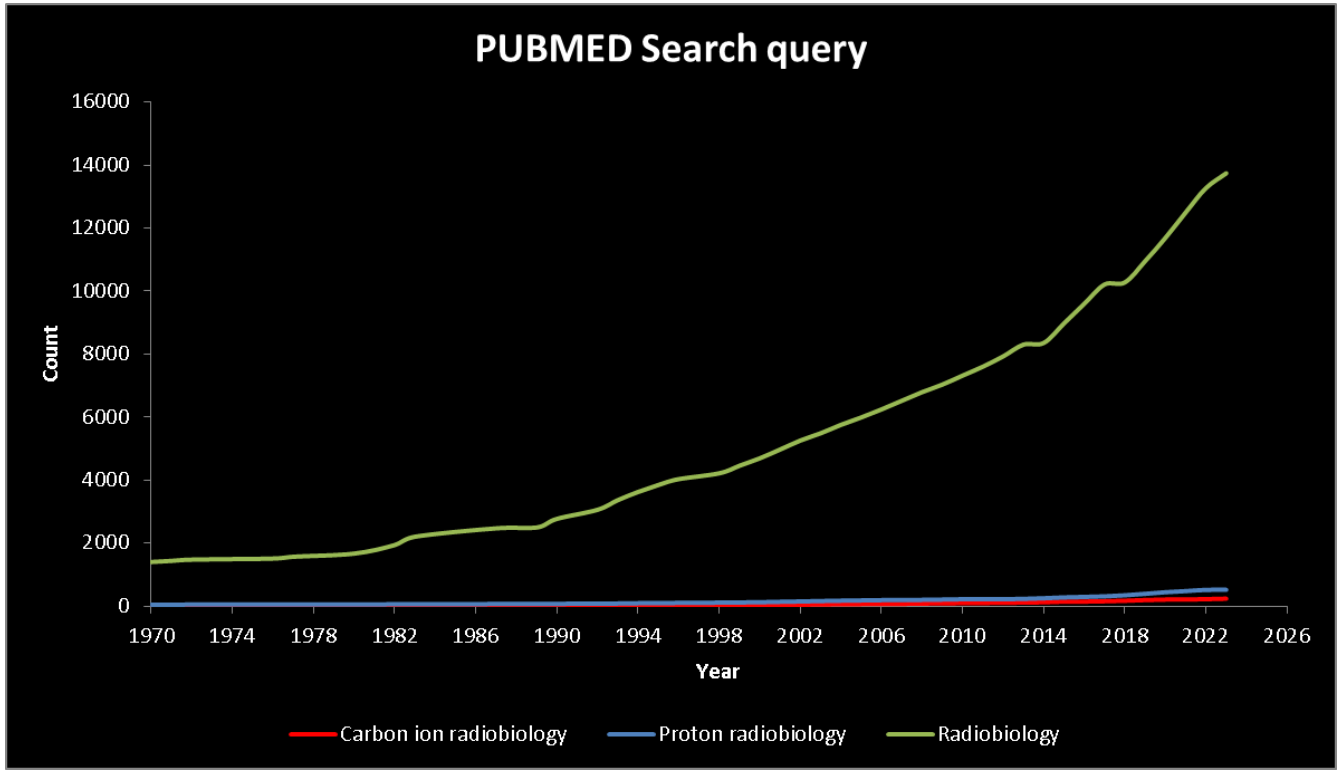
Hadrontherapy radiobiology…where are we??

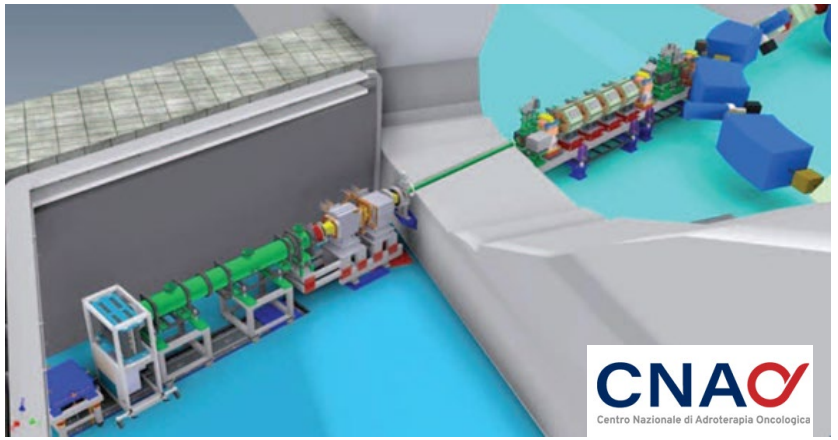


C-ion radiobiology



Hadrontherapy radiobiology…where are we??





Thank you!

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