



Reduction of radiotoxicity by ultra-high dose rate protontherapy in zebrafish embryos

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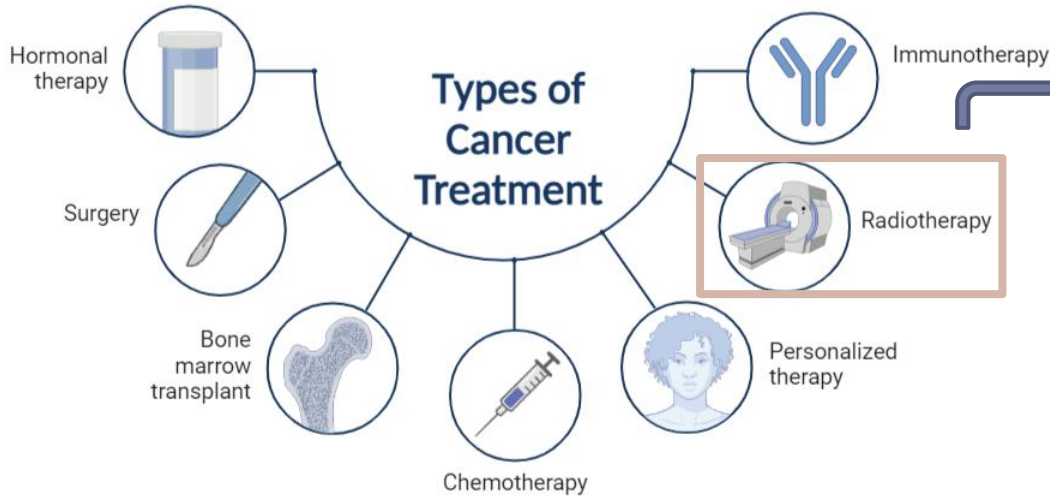
Team 3- Unit in Biological Sciences and Biotechnologies – Institut de Cancérologie de l'Ouest – René Gauducheau- Saint Herblain

Workshop : New Modalities in Cancer Imaging and Therapy
October 5th - 8th , 2022 - Erquy, France

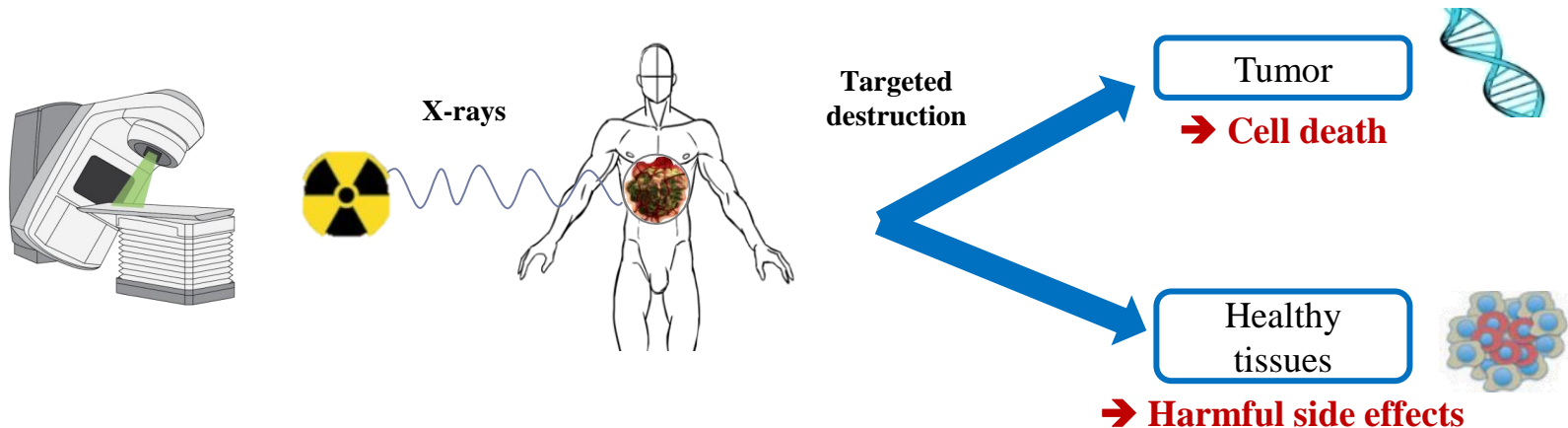
Introduction



What is radiotherapy ?

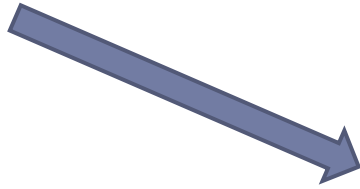


- > 50% of cancer patients are treated with radiotherapy.
- 40 sessions of 1-2 Gy/min.
- Mainly X-rays are used.

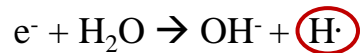
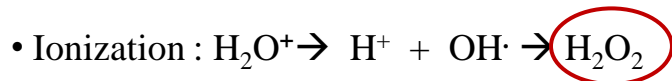
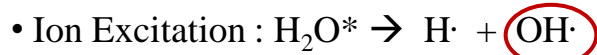
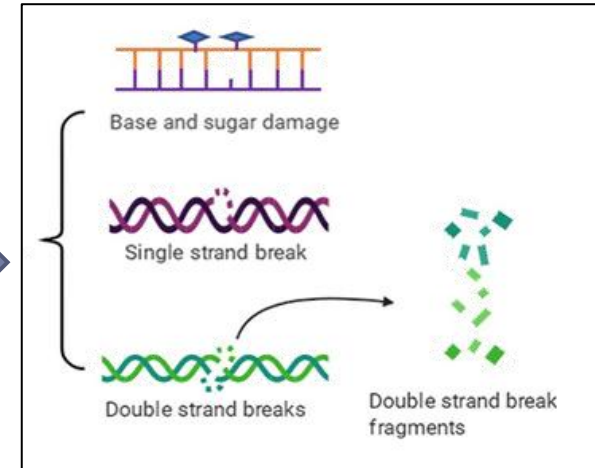
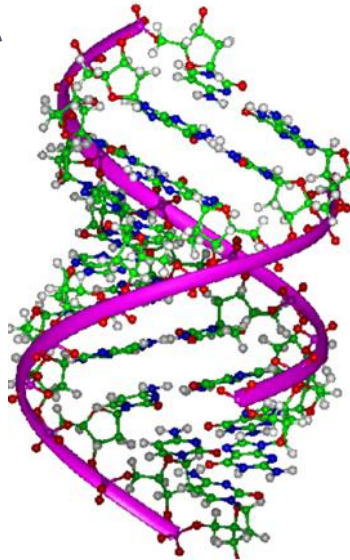
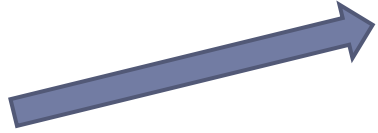


Mechanisms of damage at the molecular level

Direct effect



Indirect effect



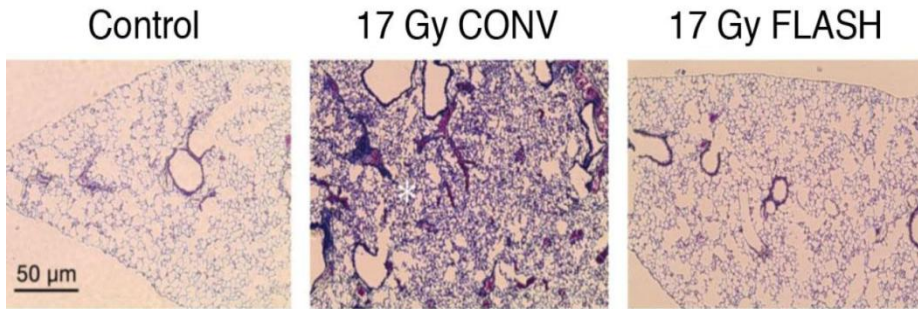
...etc

Production of H_2O_2 , $\text{OH}\cdot$, HO_2 , H_2 , $\text{H}\cdot$... in the presence of oxygen.

Ultra-High Dose Rate Radiotherapy (UHDR/FLASH-RT)

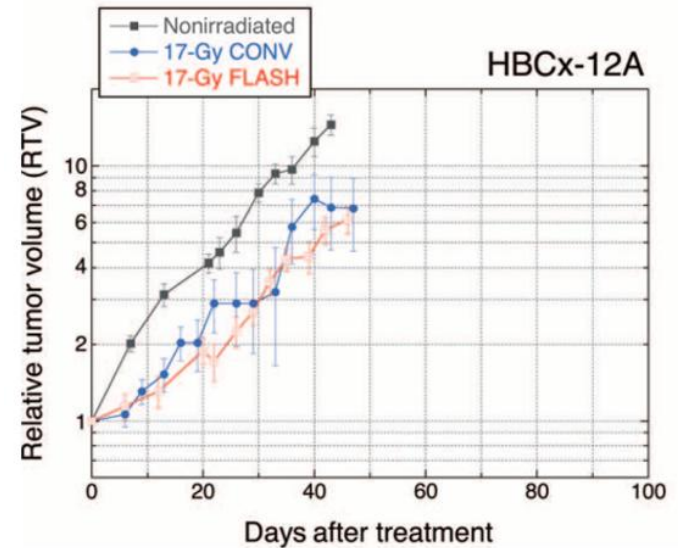
Electron UHDR-RT: $> 40 \text{ Gy/s}$ ($\leq 500 \text{ ms}$) vs conv-RT : 0.03 Gy/s .

Healthy tissue response to UHDR-RT :



Less pulmonary fibrosis with **UHDR-RT** in mice.

Tumor response to UHDR-RT :

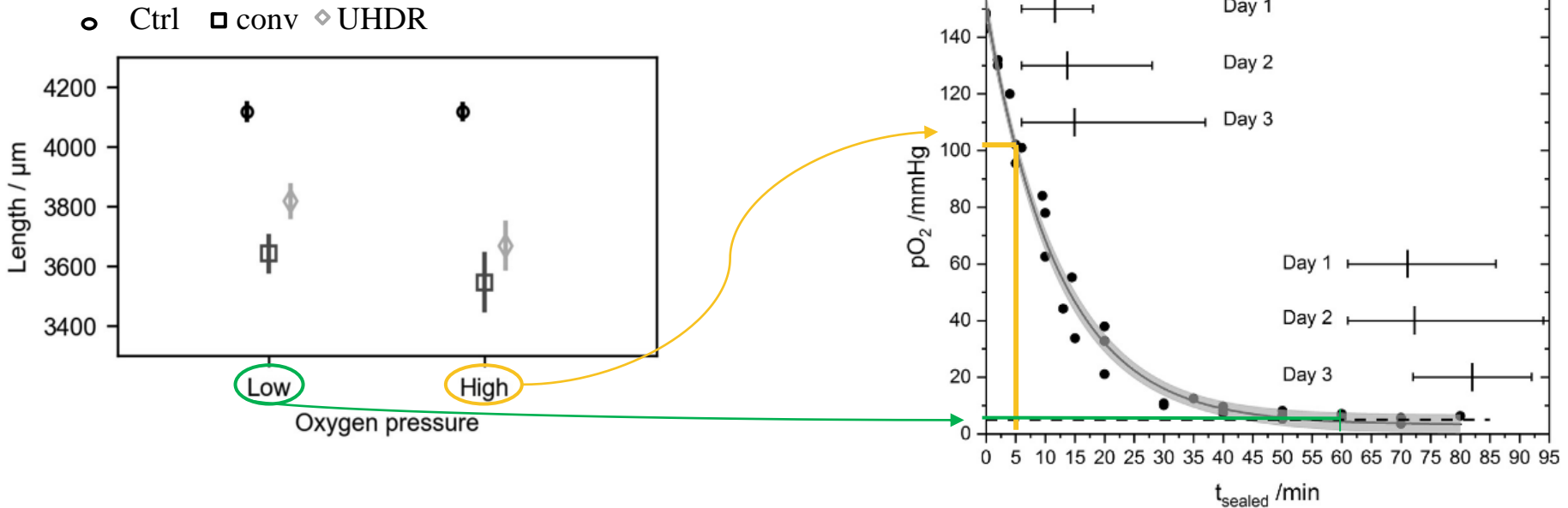


Antitumor **isoeffectiveness**.

(Favaudon et al., 2014)

Oxygen is one of the parameters involved in the response of UHDR-RT

- Zebrafish embryos irradiated at 24 hours post-fertilization (hpf).
- Electron Ultra-high dose-rate : 10^5 Gy/s vs conv-RT: 0.11 Gy/s.



Reduction of pO₂ → higher protection

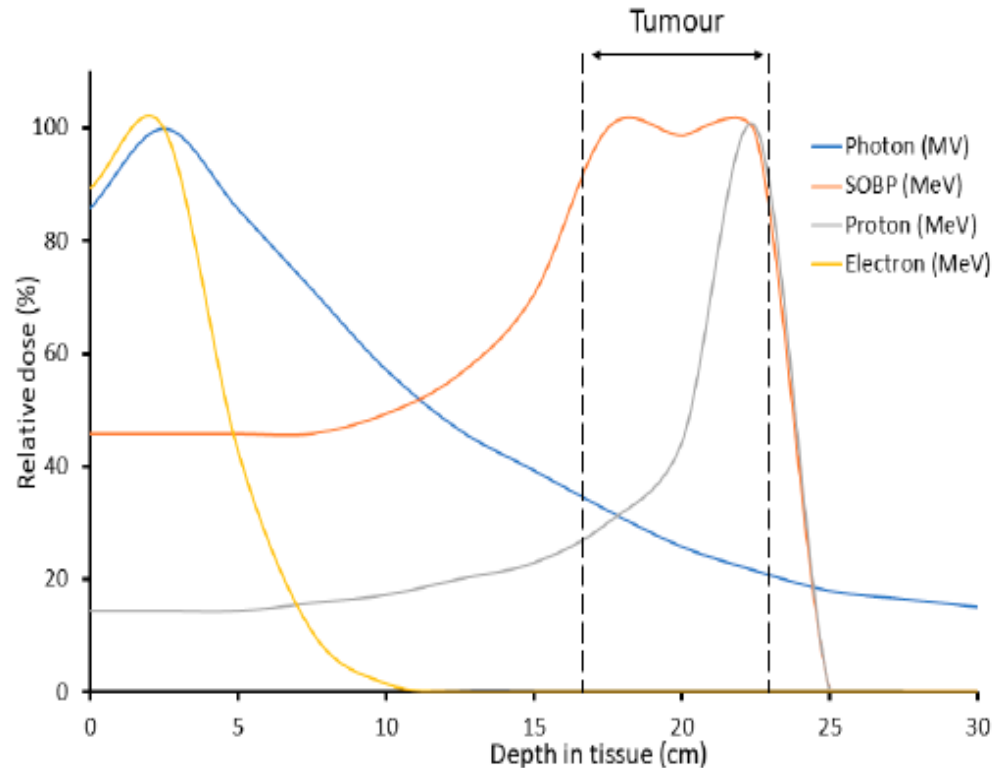
Role of the oxygen?

(Pawelke et al., 2021)

Type of particles or radiations for irradiation

Protons :

1. Spread a little along the trajectory.
2. Have a precise targeting.
3. Deposit of all the energy at the end of the trajectory.



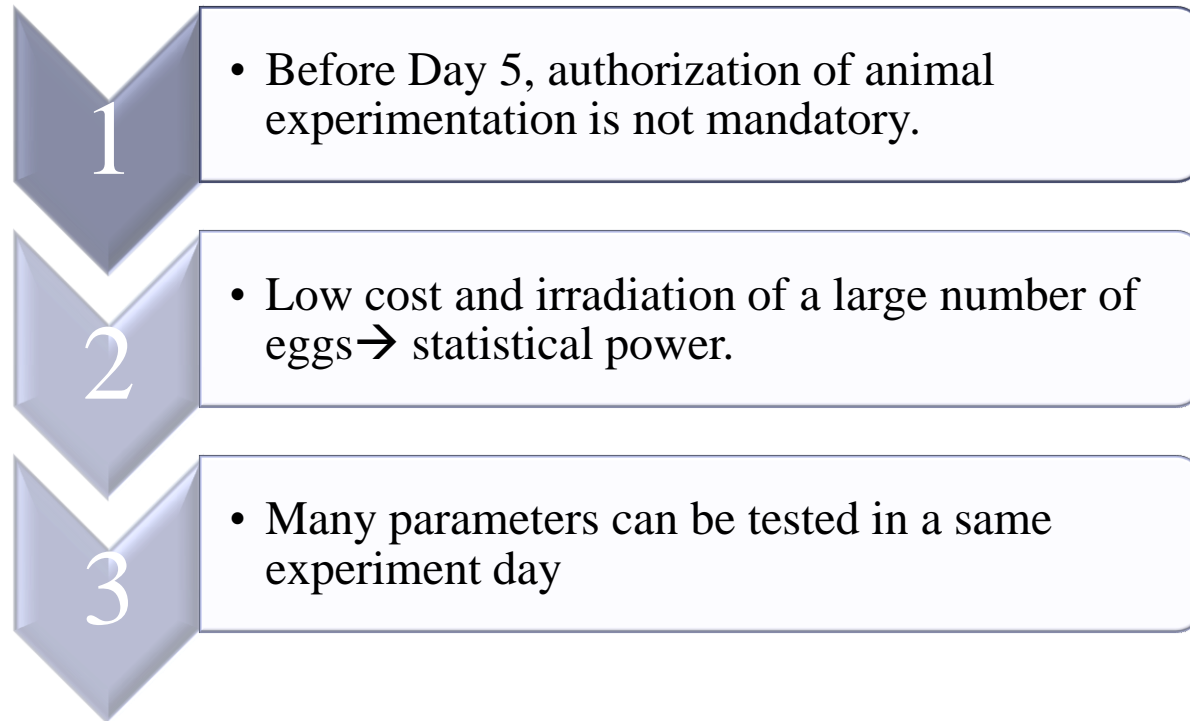
(Hughes and Parsons, 2020)

Does **proton-UHDR radiotherapy reduce toxicity** compared to conventional dose-rate irradiation?

Materials and Methods

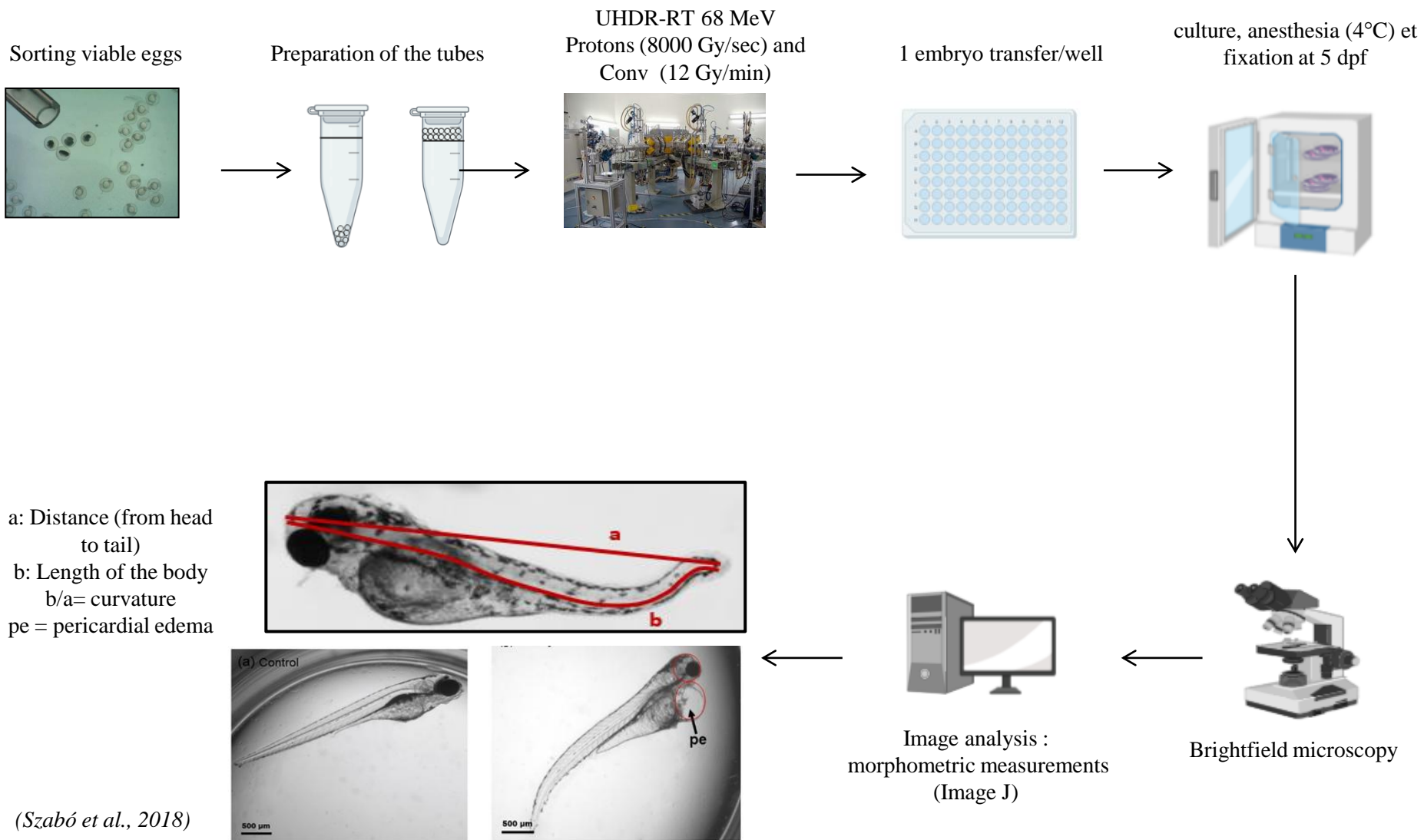


Zebrafish embryos :



(Geiger et al., 2006)

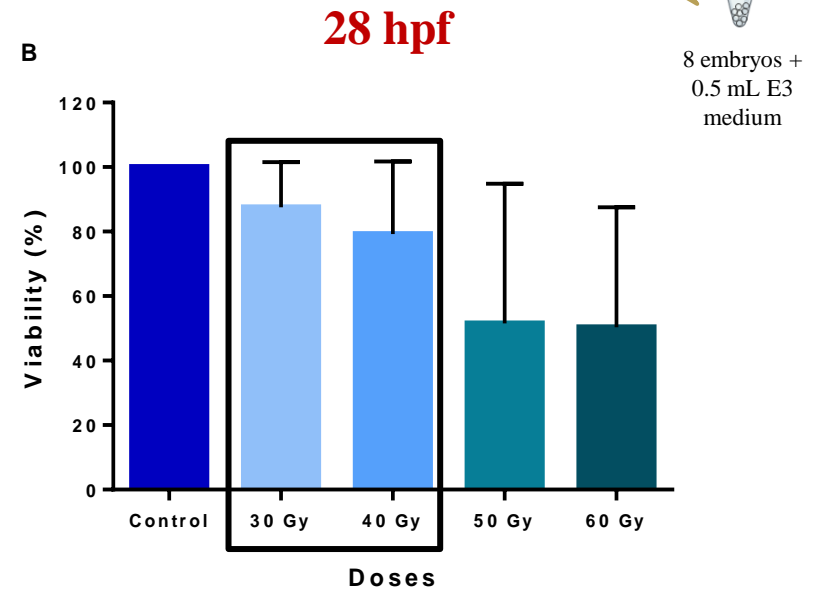
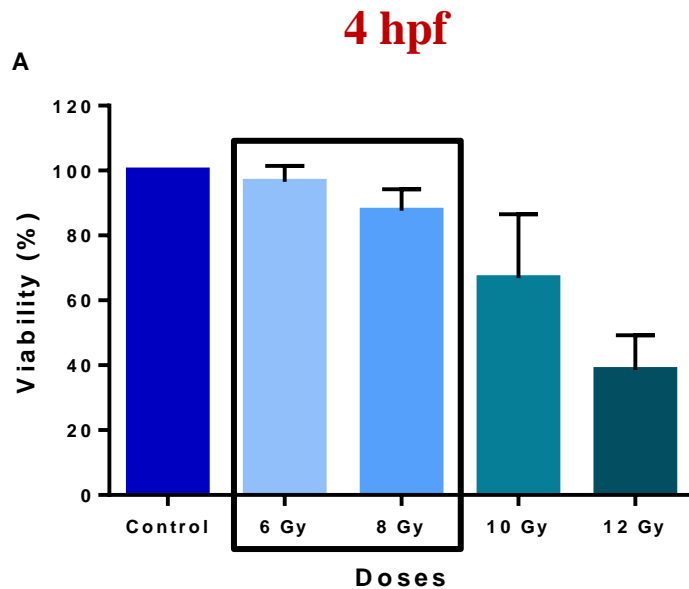
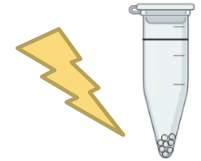
Method



Results

Determination of optimal irradiation doses

- Zebrafish irradiated at 4 and 28 hpf.
- X-rays : Dose-rate = 3,25 Gy/min.

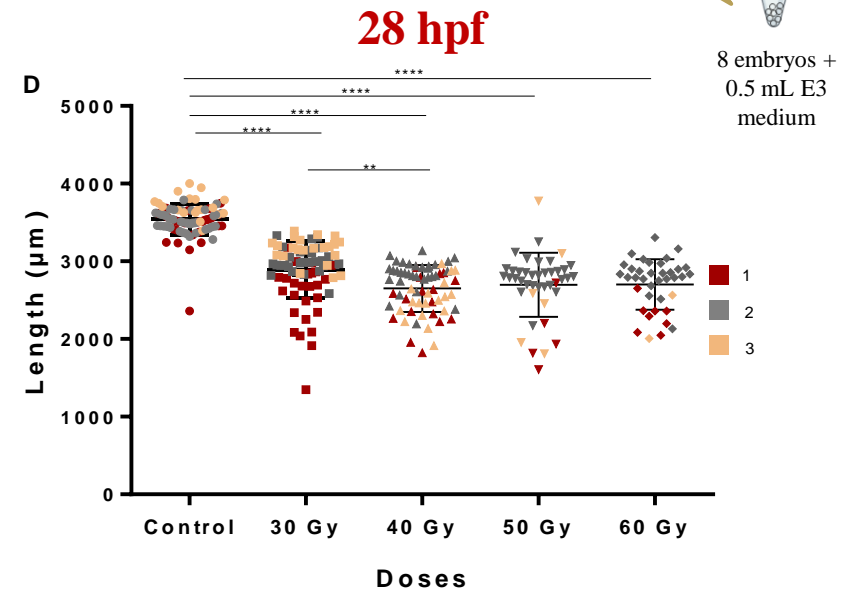
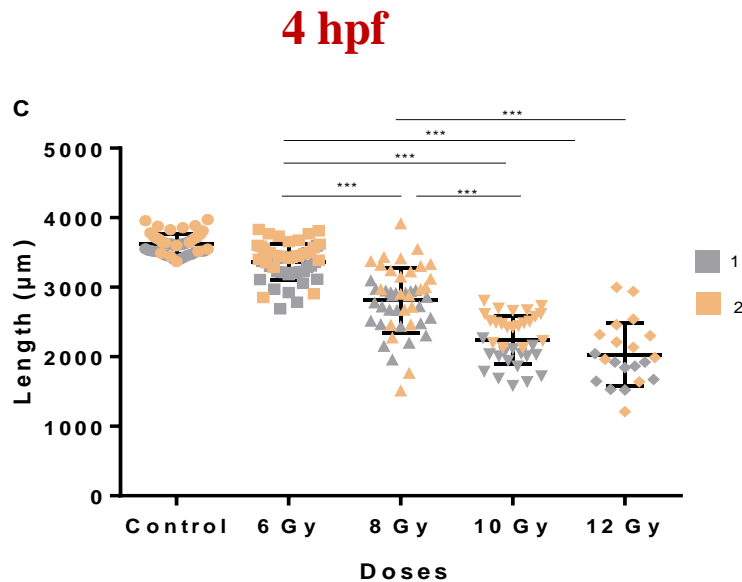
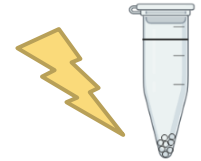


The higher the dose is, the more sensitive the embryos are at the same age

2 and 3 experiments were done at 4 hpf and 28 hpf respectively.

Determination of optimal irradiation doses

- Zebrafish irradiated at 4 and 28 hpf.
- X-rays : Dose-rate = 3,25 Gy/min.



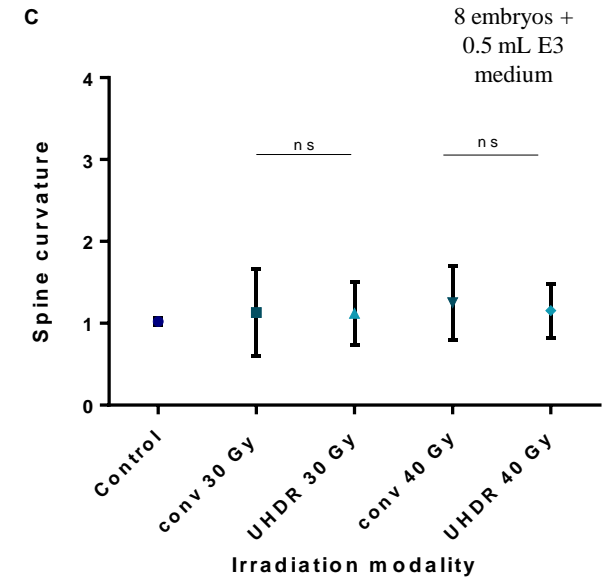
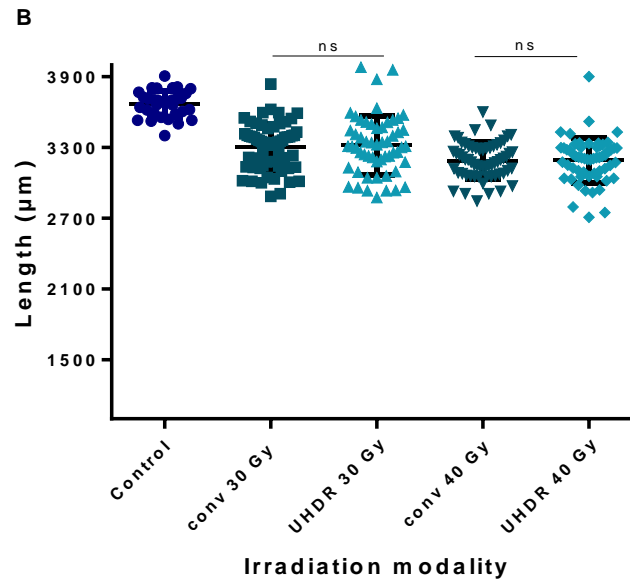
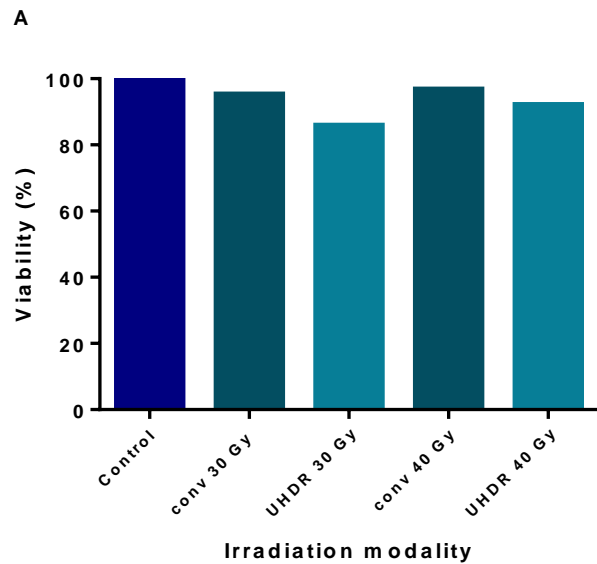
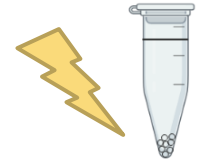
✓ The higher the dose is, the shorter is the body of the embryos.

✓ 6 and 8 Gy, 30 and 40 Gy = doses creating morphological alterations without altering the viability.

2 and 3 experiments were done at 4 hpf and 28 hpf respectively.

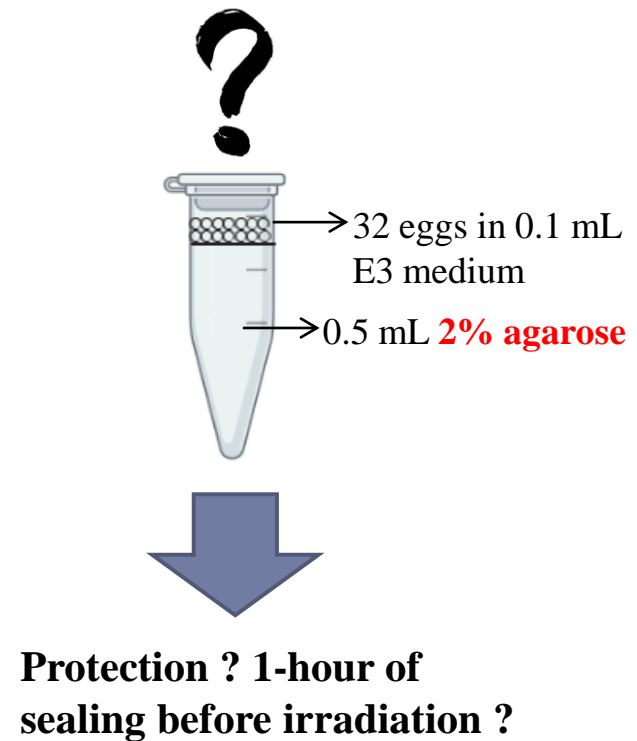
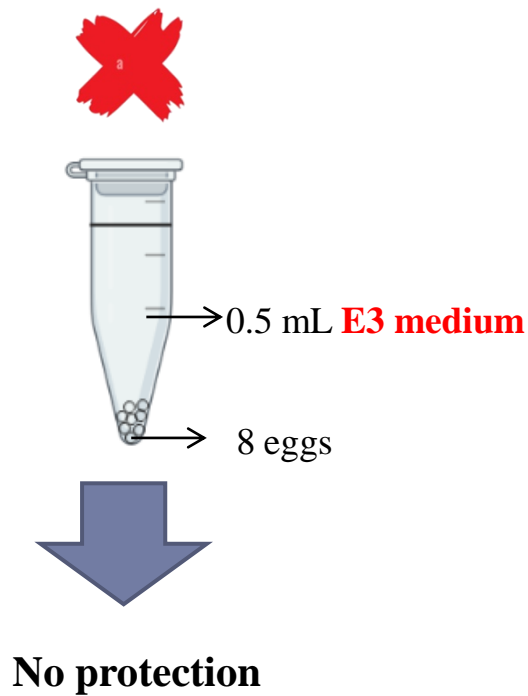
Proton - UHDR radiotherapy

Dose	Age	IR modality
30-40 Gy	29 hpf	conv-UHDR (protons) Dose-rate: 10 Gy/min and 7000 Gy/sec



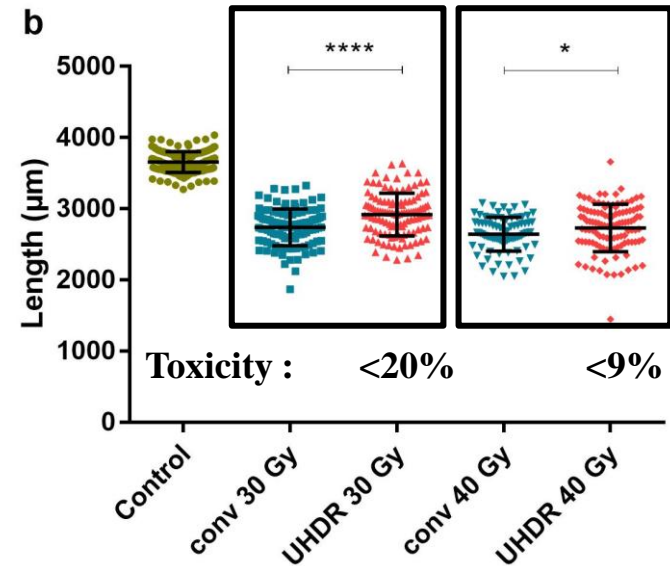
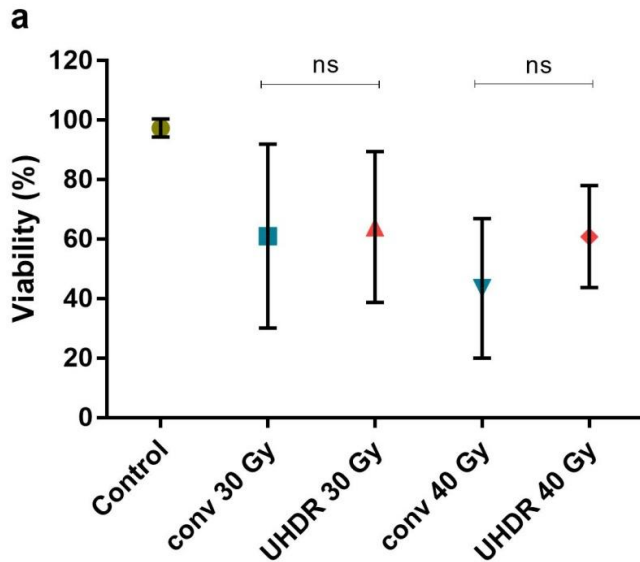
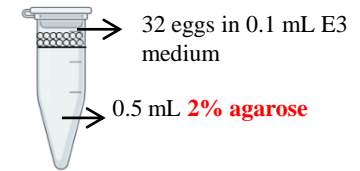
✓ No protection of the length and the spine curvature after UHDR-RT.

Proton - UHDR radiotherapy



Proton - UHDR radiotherapy

Dose	Age	IR modality
30-40 Gy	28 hpf	conv-UHDR (protons) Dose-rate: 12 Gy/min and 8000 Gy/sec



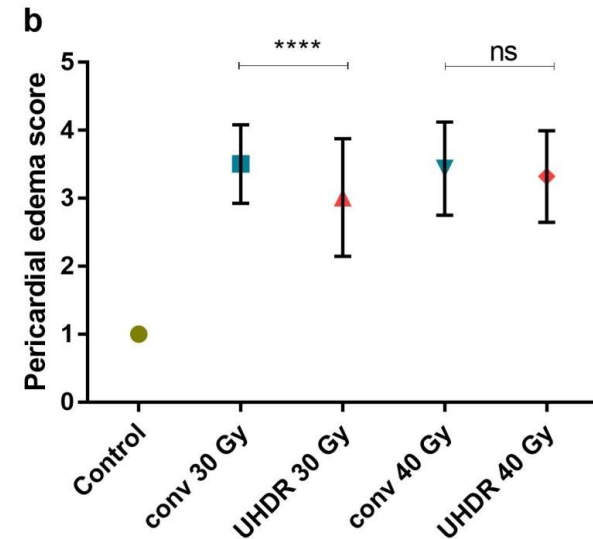
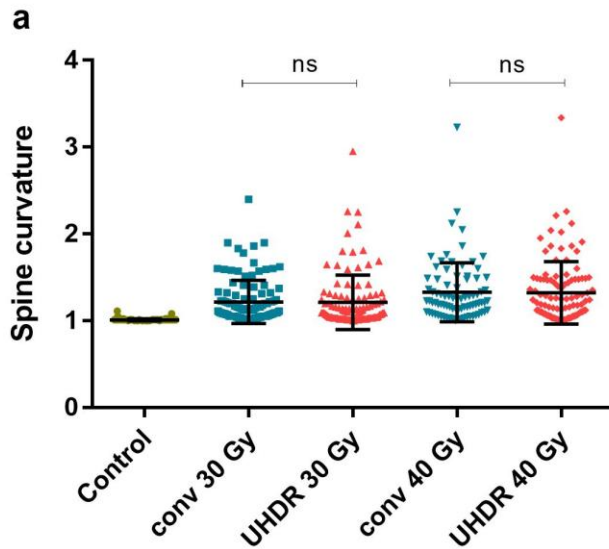
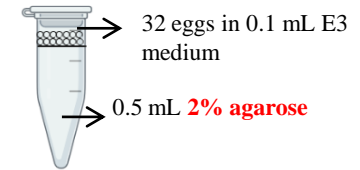
✓ Longer body length of embryos between UHDR-RT and conv-RT at 30 Gy and 40 Gy.

3 independent experiments were done at 28 hpf.

(Saade et al., 2022, *Advances in Radiation Oncology*, in review)

Proton - UHDR radiotherapy

Dose	Age	IR modality
30-40 Gy	28 hpf	conv-UHDR (protons) Dose-rate: 12 Gy/min and 8000 Gy/sec



✓ No significant difference in the spine curvature after UHDR-RT.

✓ Significant reduction of the score of pericardial edema only at 30 Gy after UHDR-RT.

3 independent experiments were done at 28 hpf.

(Saade et al., 2022, *Advances in Radiation Oncology*, in review)

Conclusion

- The protection of the length of zebrafish embryos was observed after UHDR-RT at 30 and 40 Gy.
- The score of pericardial edema was only reduced at 30 Gy.

Thank you for your attention !
Any question ?