6th Proton Physics Research and Implementation Group Workshop
9th - 10th November 2023
National Physics Laboratory, Teddington, UK

Optimization of a PET cyclotron-based proton beam line facility for radiobiological *in vitro* studies

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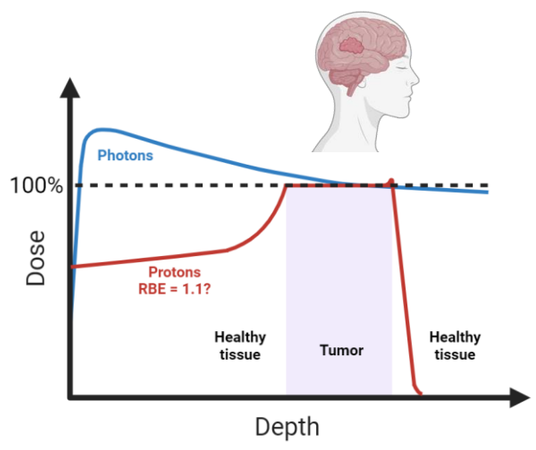
Introduction

Proton therapy as a radiotherapy alternative

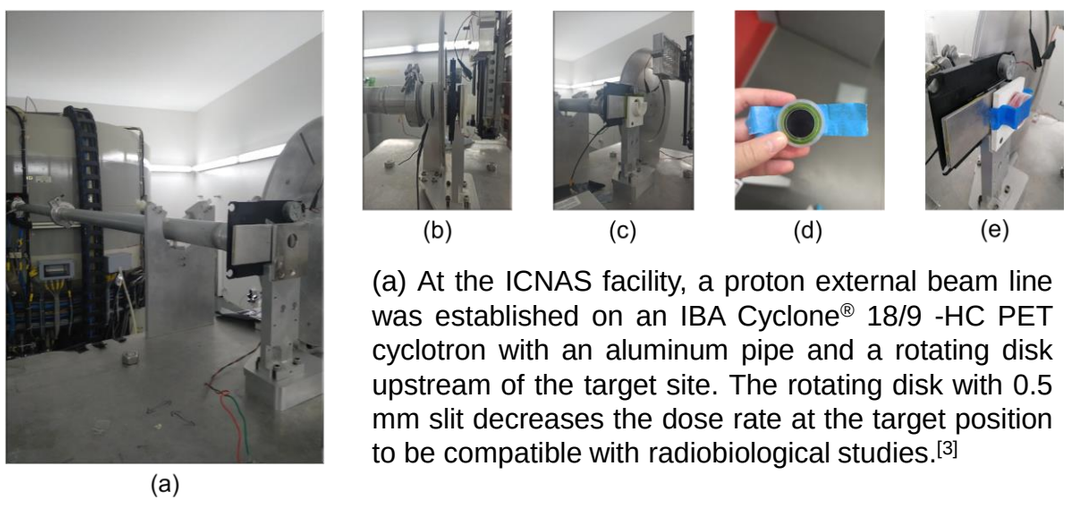
Proton therapy has emerged as an alternative to conventional radiotherapy in oncology, since the adjustment of the Bragg peak to the tumor's depth can lead to an efficient tumor eradication while minimizing undesired exposure of the adjacent healthy tissues. Clinical proton treatment planning is based on a constant value of Relative Biological Effectiveness (RBE) of 1.1. However, as proton biological interactions may be linked to a variable RBE, further preclinical studies are urgently needed to provide a better insight on RBE dependencies and, consequently, ensure the effectiveness of proton therapy.[1]



Glioblastoma multiforme, a type of brain cancer, is a malignancy that will strongly benefit from a proton treatment modality as it is still associated with a poor prognosis under standard therapeutics (surgery followed by combined radiotherapy and chemotherapy). Moreover, proton therapy is forecasted to reduce neurotoxicity when compared to conventional radiotherapy techniques.[2]

Methodology

PET cyclotron-based proton beam line

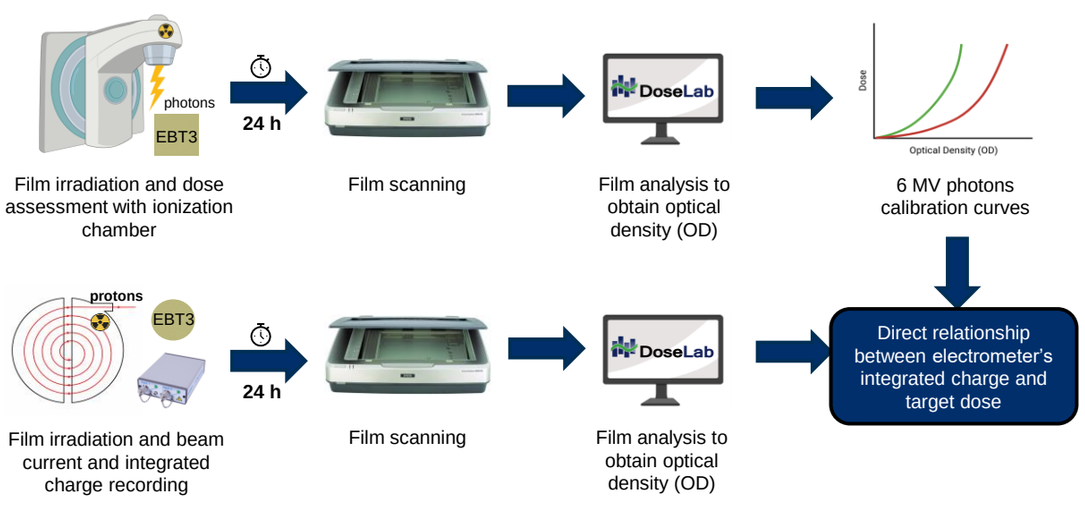


(a) (b) (c) (d) (e)

(a) At the ICNAS facility, a proton external beam line was established on an IBA Cyclone® 18/9 -HC PET cyclotron with an aluminum pipe and a rotating disk upstream of the target site. The rotating disk with 0.5 mm slit decreases the dose rate at the target position to be compatible with radiobiological studies.[3]

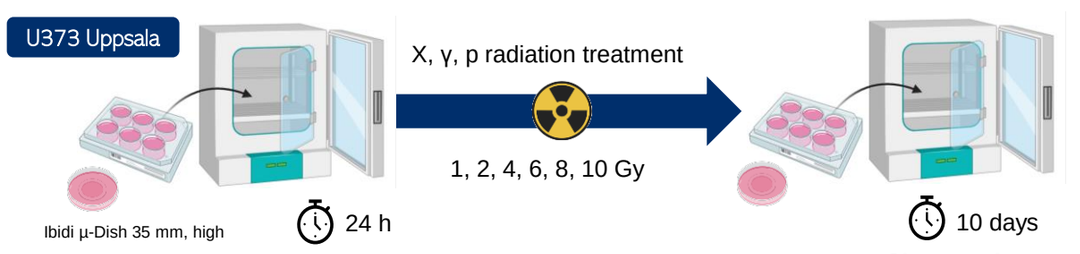
(b) At the end of the pipe, an aluminum foil was positioned for measurement of beam current and correspondent integrated charge and was connected to a PC electrometer with appropriate software (Sun Nuclear).
(c) A dish holder was assembled at the target location.
(d) For calibration purposes, EBT3 films were irradiated inside a cell culture dish (Ibidi® µ-Dish 35 mm) ensuring that all cell growth area is uniformly exposed.
(e) Illustration of cell irradiation with protons. The proton beam reaches the cells with an energy of 13.5 MeV.

Cross-calibration method



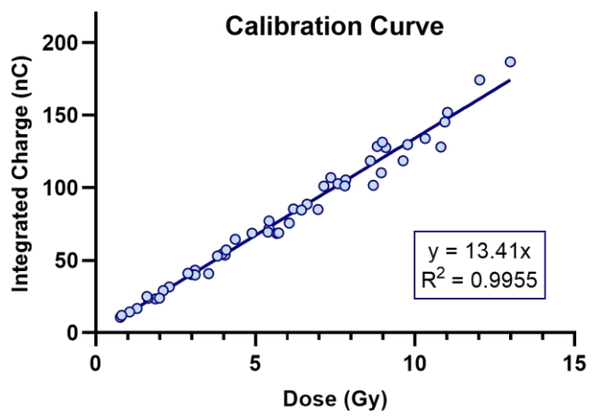
The proton irradiation set-up was calibrated by irradiating EBT3 films which were further analyzed with calibration curves obtained at IPO-Porto from a 6 MV LINAC according to the IAEA Technical Report Series (TRS) No. 398.[4] A direct relationship between integrated beam charge and absorbed dose at the target region was established from the optical density of the proton irradiated films.[5]

Quantification of cell survival



U373 Uppsala cells were exposed to gamma radiation (^{60}Co), to X-rays (160 kVp) and to protons (13.5 MeV) under the same experimental conditions. Cell survival was assessed with a clonogenic assay 10 days post-irradiation.

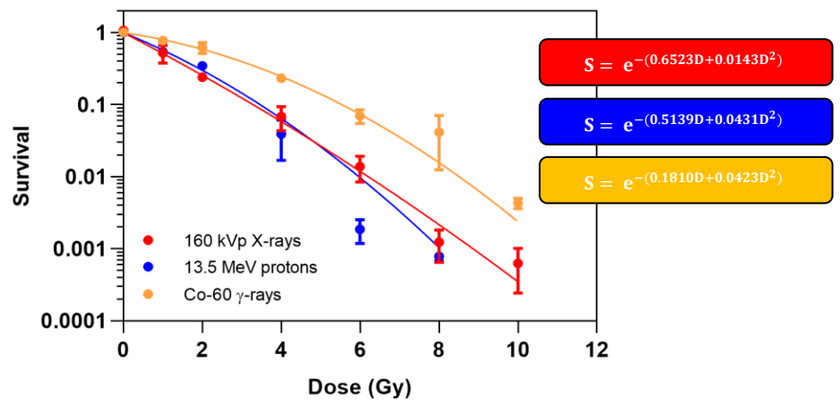
Results



Dose (Gy)	Charge (nC)
1	13,4
2	26,8
4	53,6
6	80,5
8	107,3
10	134,1

Maximum error: 11,4%

A calibration curve correlating the proton dose at the target to the integrated beam charge for the PET cyclotron-based set-up was successfully collected. This curve is valid for cell irradiation with dose rates between 2 and 3.5 Gy/min (n=3).



Irradiation experiments showed that U373 cells are less radiosensitive to γ radiation than to X-rays and protons. In addition, exposure to X-rays and protons produced identical survival curves for U373 cells (n=3 for each radiation treatment).

Conclusion

A PET cyclotron-based proton beam line was optimized for radiobiological *in vitro* research. Future work will include validation of proton beam dosimetry with Monte Carlo simulations and quantification of additional radiobiological effects in glioblastoma cells such as ROS production and DNA damage.

References

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Acknowledgments

This work was supported by CENTRO2020 and FCT (LISBOA-01-0247-FEDER-045904).