LABORATÓRIO DE INSTRUMENTAÇÃO
E FÍSICA EXPERIMENTAL DE PARTÍCULAS
partículas e tecnologia

First ProtoTera PhD Students Workshop

Coimbra, 28-29th November 2022

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ProtoTera Grants (started in October 2021)

PhD Thesis:

”Dosimetry evaluation to advance charged particle minibeam radiotherapy”

PhD Student:

Maria Giorgi

Supervisors:

Prof. Jorge Sampaio (FCUL-LIP)

Dr. Yolanda Prezado (Insitut Curie)

OUTLINE

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- **SPATIALLY FRACTIONATED RADIATION THERAPY (SFRT)**

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- MINIBEAM RADIATION THERAPY (MBRT) WITH CHARGED PARTICLES AND ITS CHALLENGES IN DOSIMETRY

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- WORK DEVELOPED DURING THE FIRST YEAR OF MY PHD

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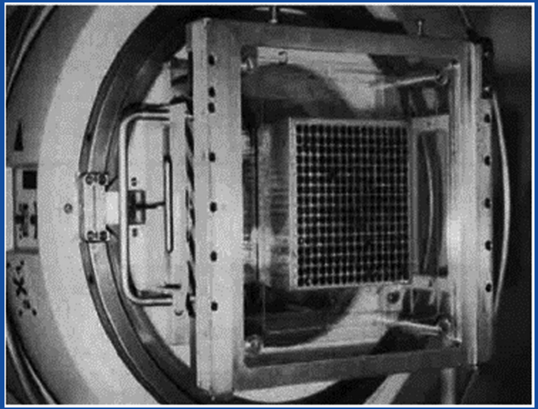
- FUTURE STEPS

SPATIALLY FRACTIONATED RADIATION THERAPY

In 1909 Alban Kohler used a "**perforated screen**" in orthovoltage X-rays machine

→ GRID Therapy: first attempt of **skin toxicity reduction with spatially fractionation of the dose**



Prezado, Molec Med 2022

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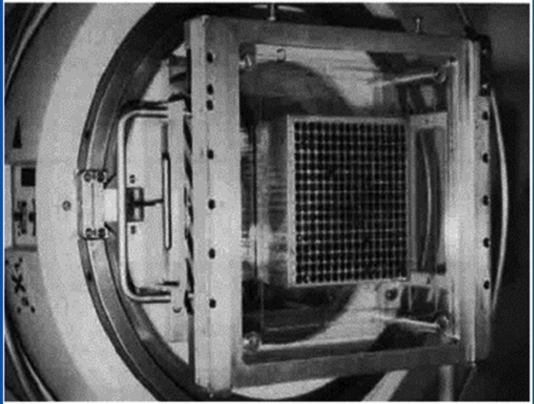

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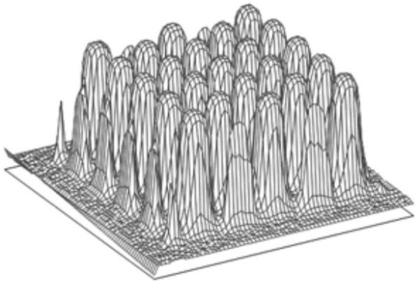
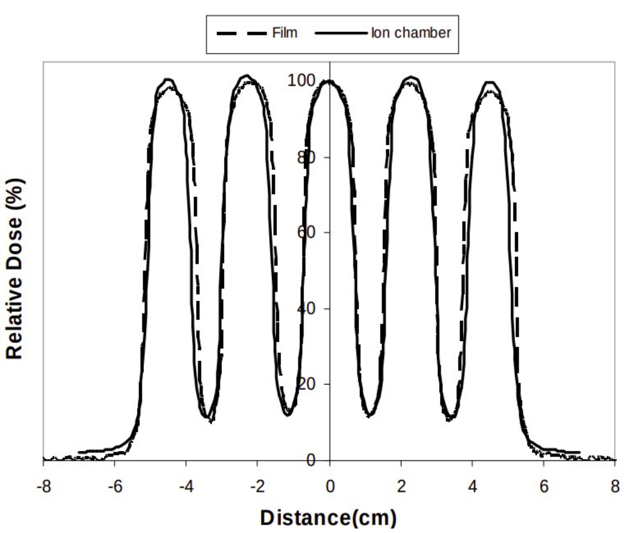


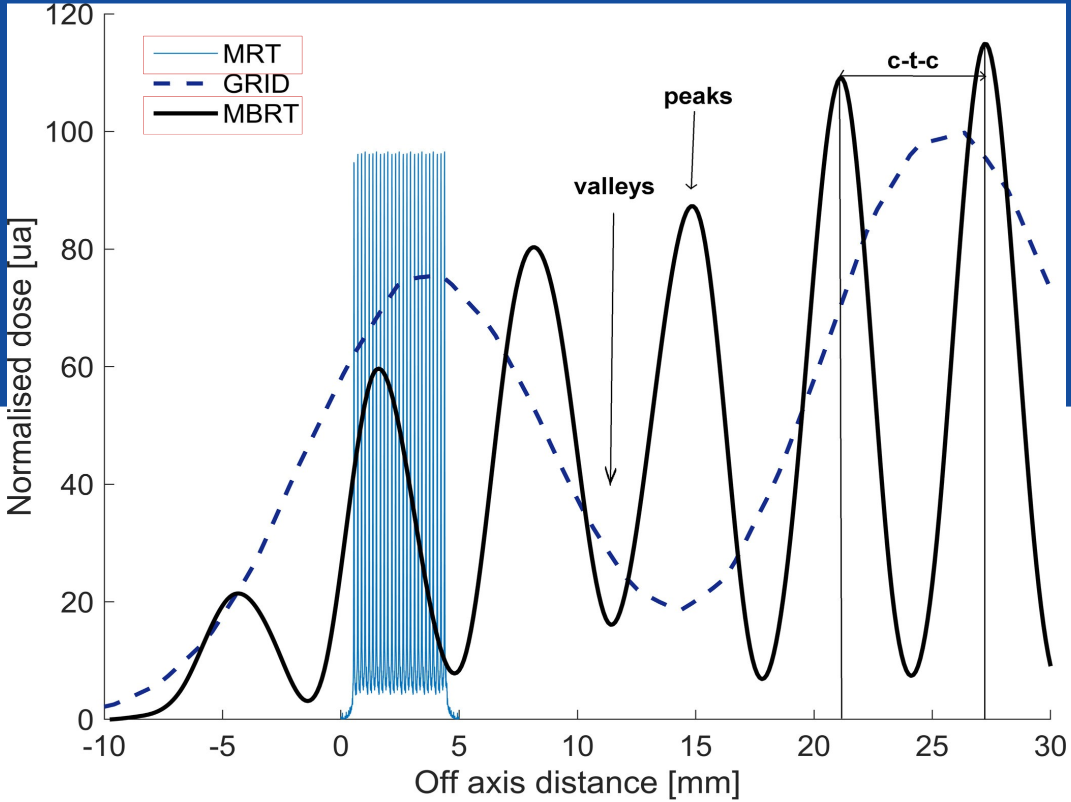


Meigooni et al, Med. Phys 2006

$$PVDR = \frac{Dose_{peak}}{Dose_{valley}}$$

High PVDR values and low valley doses are assumed to ensure **normal tissue sparing**

SPATIALLY FRACTIONATED RADIATION THERAPY



De Marzi et al, Cancer 2019

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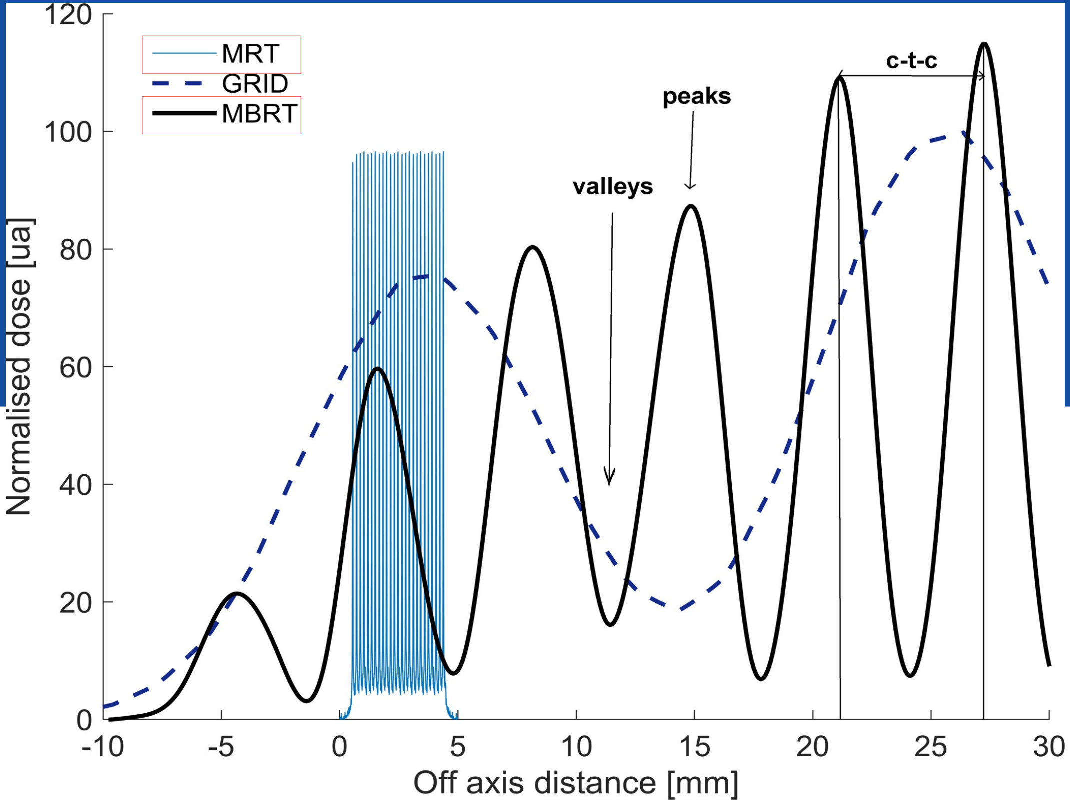

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The narrower the beamlets are
the **higher the tolerances** of normal tissues

MICROBEAM VS MINIBEAM RADIATION THERAPY

MRT

Very narrow beamlets (0.05 – 0.1 mm)

Normal tissue tolerance scaled up to ~ 300 Gy/fraction

Tumor control effectivness significantly increased

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Possible low cost implementation
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To be translated into clinical practice:

- deeper understanding of radiobiological mechanisms
- development of accurate dosimetry protocols

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Some advantages may arise using heavier ions in MBRT:

- less subjected to Multiple Coulomb Scattering → **lower valley dose**
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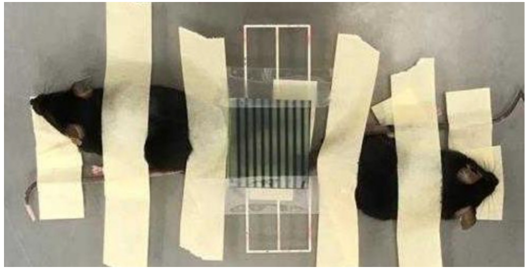
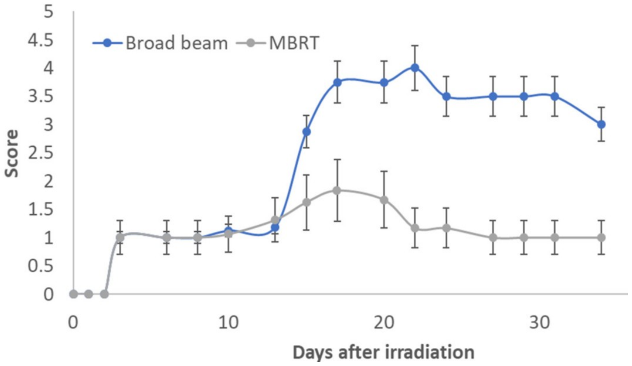
Ne MBRT experiment was realized in 2020 at HIMAC (Japan)



Prezado et al, Cancers 2021



DOSIMETRY IN MBRT

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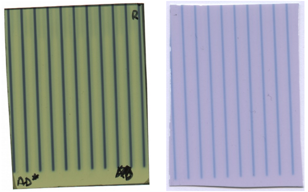
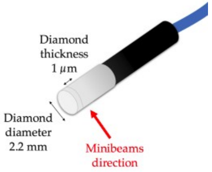
Among the suitable types of commercialised dosimeters, those I used are:

- Gafchromic **films** EBT-3 and Orthochromic films OC-1

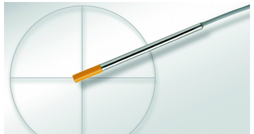


- PTW 60019 **microDiamond**



C. Peucelle's Thesis, 2016

- IBA **Razor Diode**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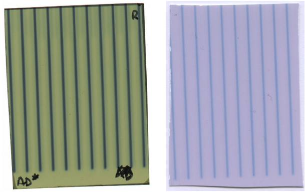

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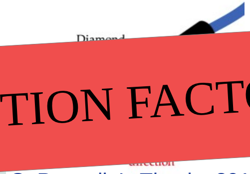

PERTURBATION CORRECTION FACTOR

C. Peucelle's Thesis, 2016

IBA's website

DOSIMETRY IN MBRT

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Sotiropoulos et al (Med Phys 2022) proposed a formalism to evaluate this correction through Monte Carlo simulations

$$k^{\mathrm{MB,PVDR,d}} = \frac{\dfrac{D^{\mathrm{x=valley}}{}_{\mathrm{PMMA}}}{D^{\mathrm{x=valley}}{}_{\mathrm{MD}}}}{\dfrac{D^{\mathrm{x=peak}}{}_{\mathrm{PMMA}}}{D^{\mathrm{x=peak}}{}_{\mathrm{MD}}}}$$

$$PVDR^{1\ \mathrm{cm}}{}_{\mathrm{corr}} = \frac{D^{\mathrm{x=peak}}{}_{\mathrm{PMMA}}}{D^{\mathrm{x=valley}}{}_{\mathrm{PMMA}}} = \frac{D^{\mathrm{x=peak}}{}_{\mathrm{MD}}}{D^{\mathrm{x=valley}}{}_{\mathrm{MD}}} * \frac{1}{k^{\mathrm{MB,\ PVDR,\ 1\ cm}}}$$

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It has to be evaluated for each different experimental setup

WORK DEVELOPED DURING THE FIRST YEAR OF MY PHD

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- Implementation of **simulations** with the Monte Carlo code TOPAS to obtain **crucial irradiation parameters in carbon ions MBRT**

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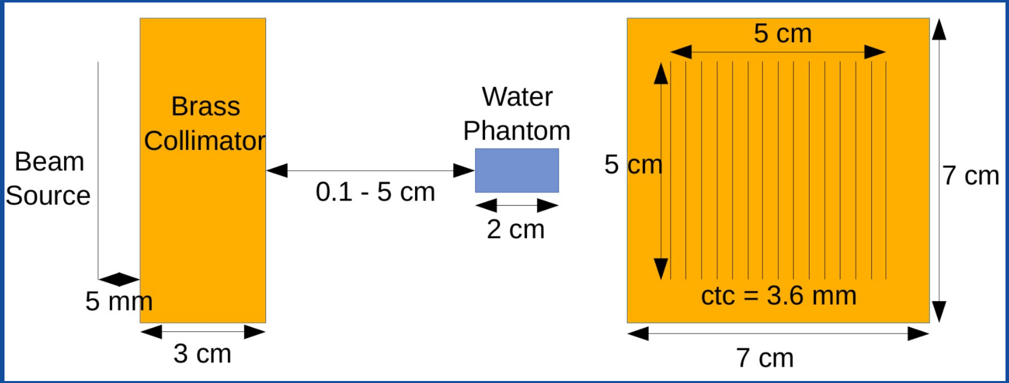
- Implementation of **simulations** with the Monte Carlo code TOPAS to obtain **crucial irradiation parameters in carbon ions MBRT**

- Experimental **dosimetric characterisation of the carbon beam** at GSI (Darmstadt) used for MBRT

- Monte Carlo evaluation of **perturbation correction factors** in MBRT dosimetry for carbon at GSI and for proton at institut Curie (Paris)

CARBON ION MBRT: Pre-Experiment Simulations



Beam source parameters

Label	E [MeV/u]	ΔE [%]	σ_x [mm]	σ_y [mm]	$\sigma_{x'}$ [$mrad$]	$\sigma_{y'}$ [$mrad$]	$r_{xx'}$	$r_{yy'}$
Param1	180	0.1	4.8	5.4	3.6	1.6	0	0
Param2	180	0.1	4.8	5.4	0.1	0.1	0	0
Param3	180	0.1	4.8	5.4	10	10	0	0
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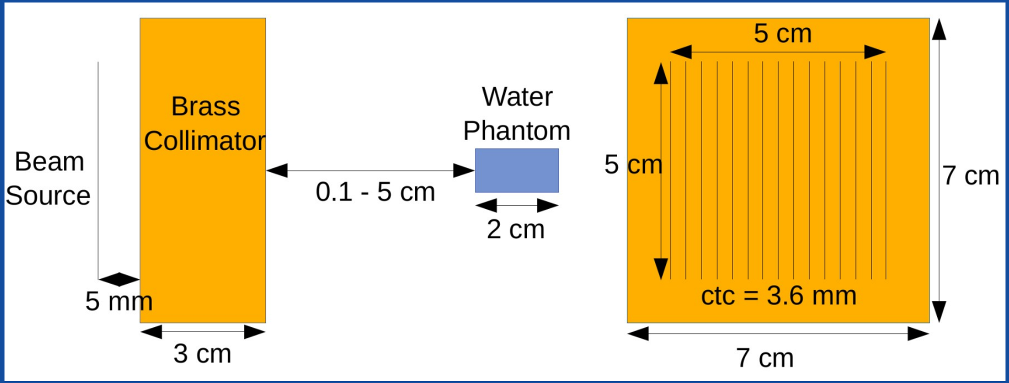

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$$OF_1 = \frac{D_{MBRT,average}}{D_{BB,average}} \qquad PVDR = \frac{D_{MBRT,peak}}{D_{MBRT,valley}}$$

	$D_{BB,aver}$ [Gy]		$D_{MBRT,aver}$ [Gy]		OF_1		OF_2		PADR		PVDR	
	1 cm	2 cm	1 cm	2 cm	1 cm	2 cm	1 cm	2 cm	1 cm	2 cm	1 cm	2 cm
*Param*1 *Air gap* 0.1 cm	0.1043	0.1089	0.0231	0.0226	0.22	0.21	1.14	1.00	5.14	4.80	73.7	64.1
*Param*1 *Air gap* 1 cm	0.1043	0.1089	0.0230	0.0225	0.22	0.21	1.04	0.92	4.71	4.45	63.8	50.3
*Param*1 *Air gap* 5 cm	0.1043	0.1089	0.0225	0.0221	0.22	0.20	0.72	0.65	3.35	3.20	8.5	9.4
*Param*2 *Air gap* 1 cm	0.1043	0.1089	0.0231	0.0228	0.22	0.21	1.08	1.03	4.90	4.91	72.9	63.8
*Param*3 *Air gap* 1 cm	0.1043	0.1089	0.0223	0.0212	0.21	0.19	0.64	0.51	2.97	2.62	25.8	16.1
*Param*4 *Air gap* 1 cm	0.1045	0.1093	0.0231	0.0226	0.22	0.21	1.04	0.92	4.72	4.43	64.2	52.6

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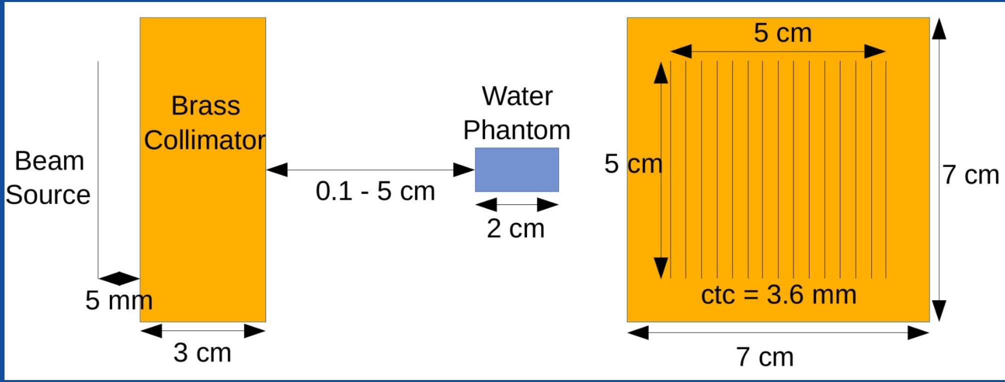

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SPOILER

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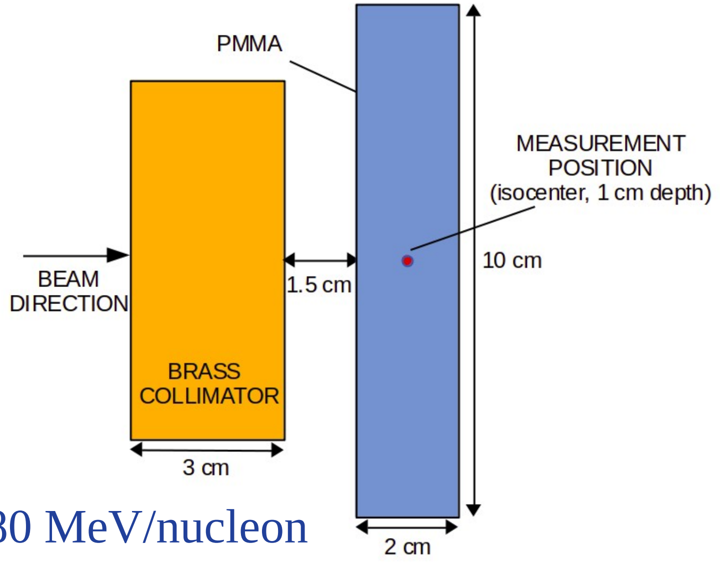

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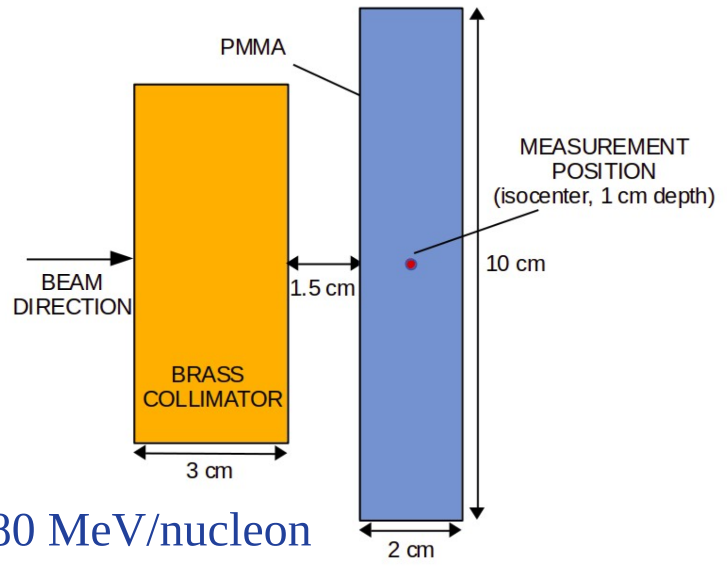

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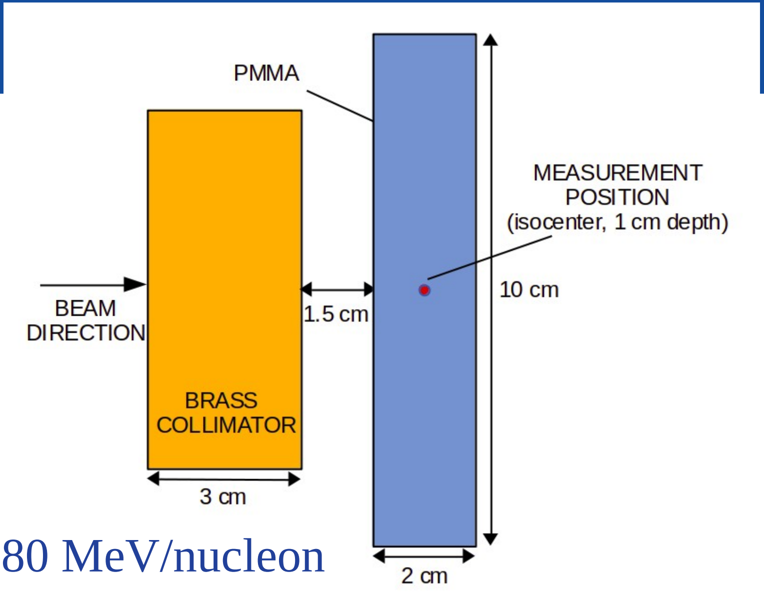

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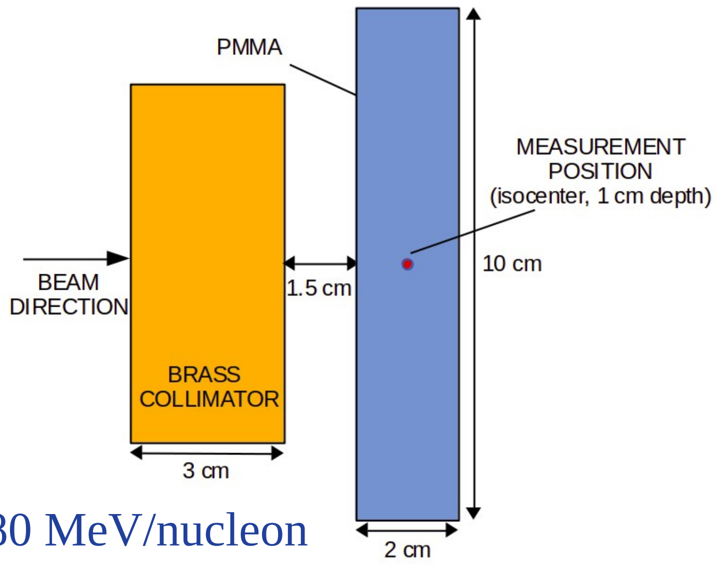

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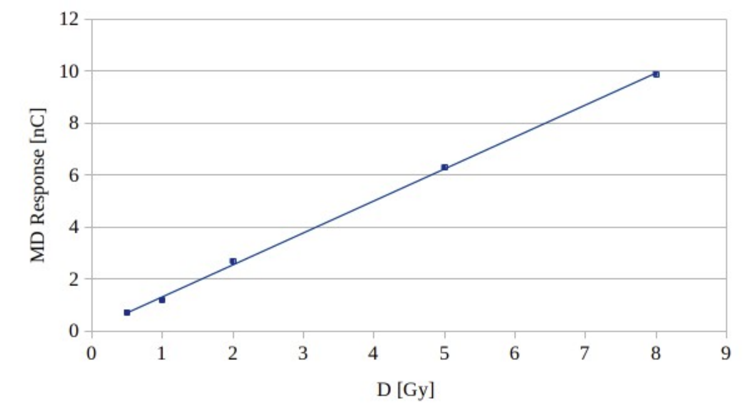
Dosimetry with microDiamond



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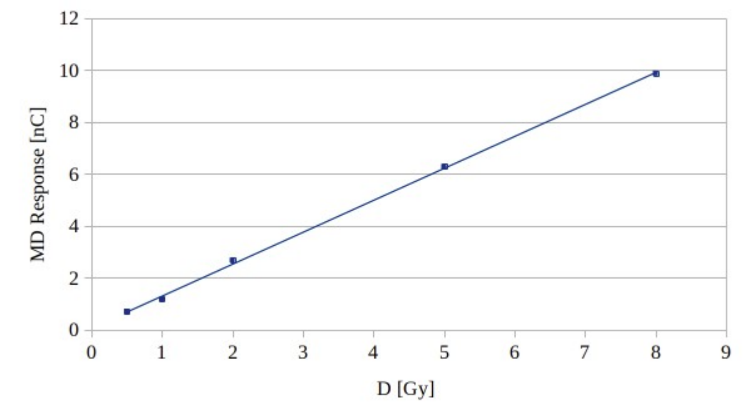
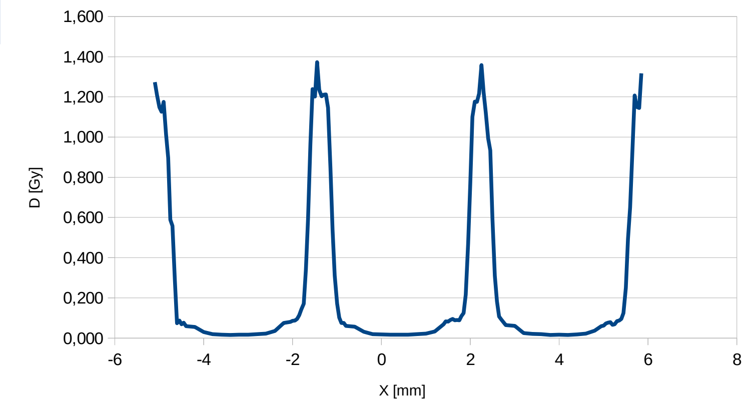


- Peak regions: 2 Gy plan dose and 0.05 mm MD step size
- Valley regions: 5 Gy plan dose and 0.2 mm MD step size



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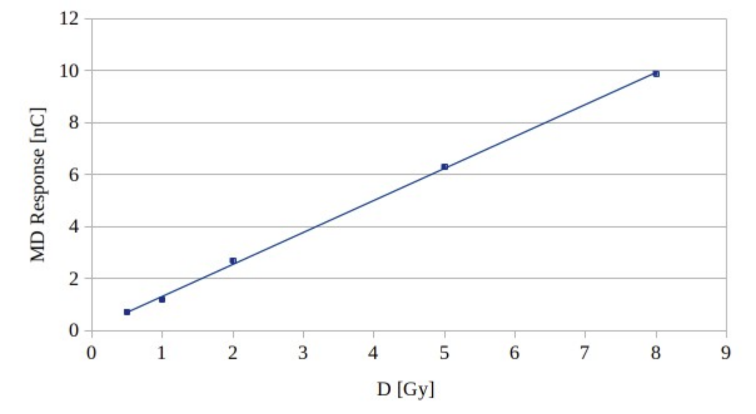

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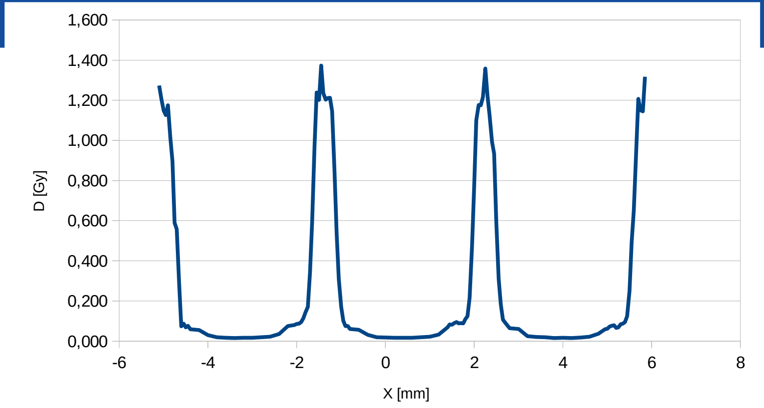
	PVDR	PADR	FWHM [mm]	OF_1	OF_2
MD	69 ± 3 *	6.1 ± 0.3	0.51 ± 0.05	0.21 ± 0.01	1.30 ± 0.04



OF_1 was used **to prescribe the dose** for the mice irradiations, which was chosen equal to 95 Gy to get a MB average dose around 20 Gy.

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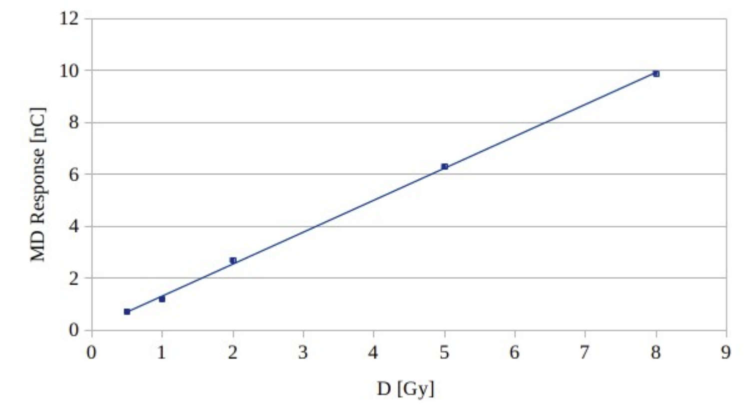
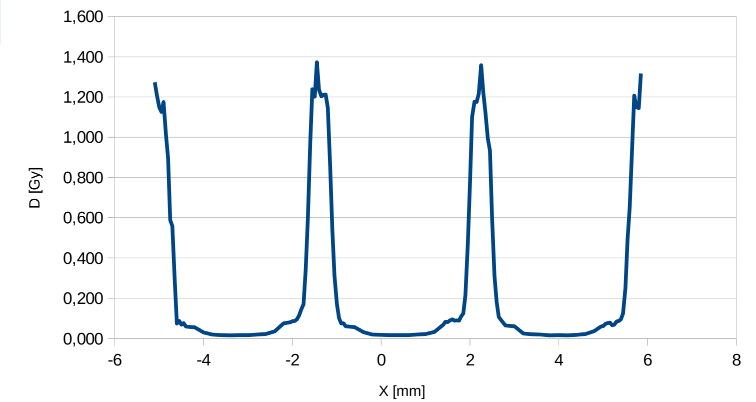


- Peak regions: 2 Gy plan dose and 0.05 mm MD step size
- Valley regions: 5 Gy plan dose and 0.2 mm MD step size



	PVDR	PADR	FWHM [mm]	OF_1	OF_2
MD	69 ± 3 *	6.1 ± 0.3	0.51 ± 0.05	0.21 ± 0.01	1.30 ± 0.04

OF_1 was used **to prescribe the dose** for the mice irradiations, which was chosen equal to 95 Gy to get a MB average dose around 20 Gy.

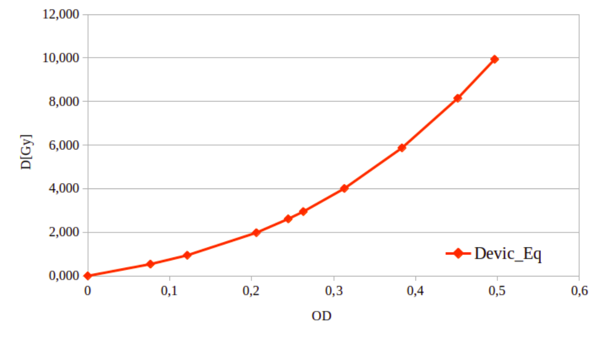
! *corrected with a **perturbation correction factor** of 1.03 ± 0.02

CARBON ION MBRT: Experimental Measurements

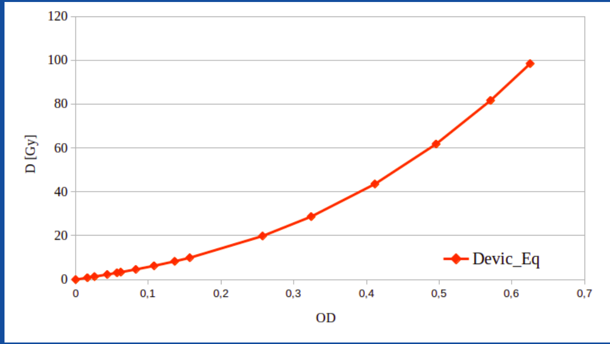
Dosimetry with films

$$OD = -\log_{10}\frac{I}{I_0}$$

$$D = a * OD + b * OD^c$$



EBT-3



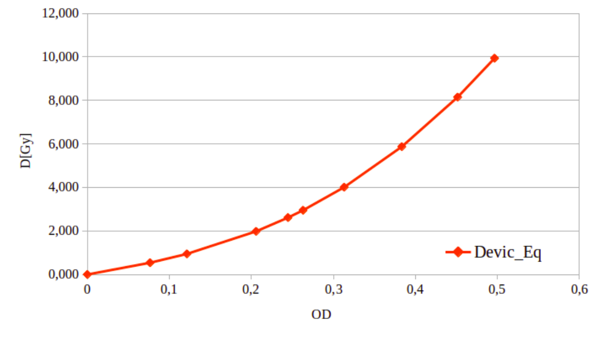
OC-1

CARBON ION MBRT: Experimental Measurements

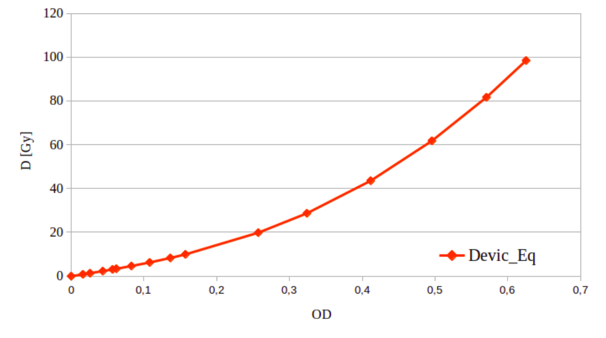
Dosimetry with films

$$OD = -\log_{10} \frac{I}{I_0}$$

$$D = a * OD + b * OD^c$$

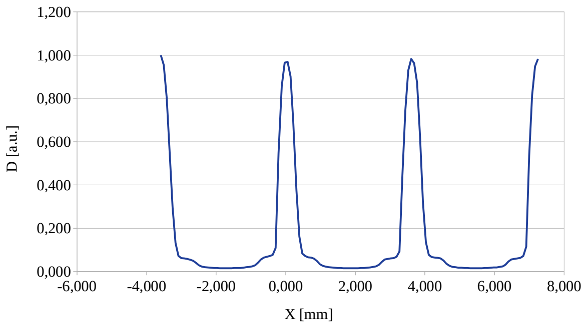


EBT-3



OC-1

Irradiation field 6 x 6 cm^2 - Plan dose 40 Gy



Type	Dynamic Dose Range [Gy]
EBT-3	0.2 – 10
OC-1	0.1 - 100

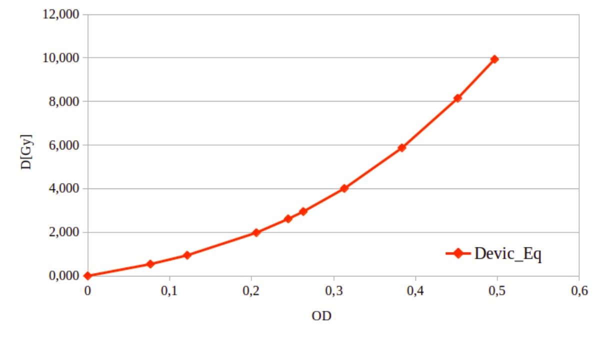
	PVDR	PADR	FWHM [mm]	OF_1	OF_2
Films without correction	53 ± 4	5.5 ± 0.4	0.50 ± 0.05	0.18 ± 0.01	0.99 ± 0.05
Films with correction	64 ± 5	5.8 ± 0.4	0.50 ± 0.05	0.20 ± 0.01	1.18 ± 0.06

CARBON ION MBRT: Experimental Measurements

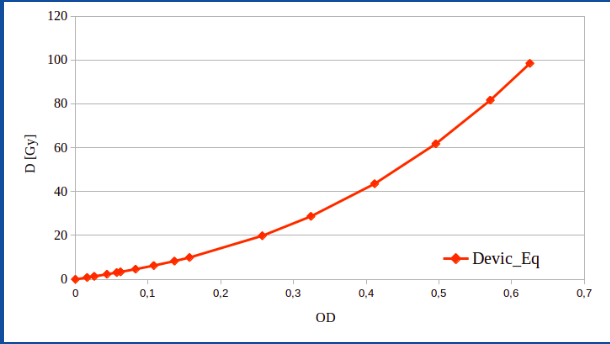
Dosimetry with films

$$OD = -\log_{10}\frac{I}{I_0}$$

$$D = a * OD + b * OD^c$$



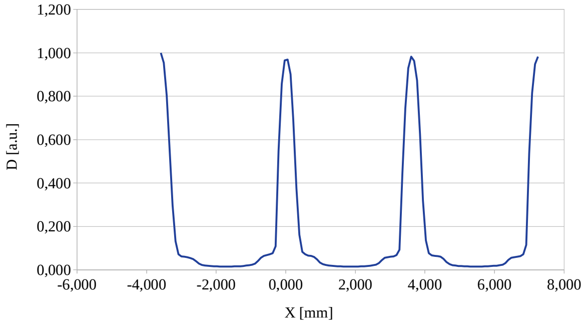
EBT-3



OC-1

Irradiation field 6 x 6 cm² - Plan dose 40 Gy

Type	Dynamic Dose Range [Gy]
EBT-3	0.2 – 10
OC-1	0.1 - 100



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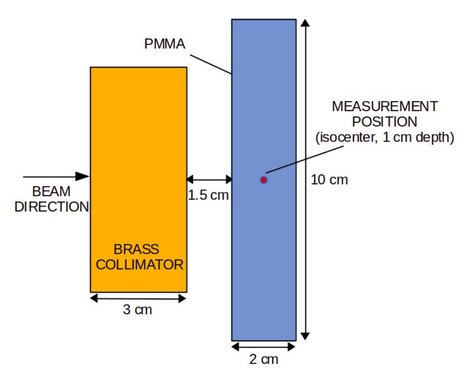
Films with correction	64 ± 5	5.8 ± 0.4	0.50 ± 0.05	0.20 ± 0.01	1.18 ± 0.06

! **OC-1 data corrected by a factor 1.2** to compensate the limited spatial resolution, which does not allow **to resolve the peak** due its thickness (∼0.5 mm)

CARBON ION MBRT: Experimental Measurements

Monte Carlo Simulations

$Label$	E $[MeV/u]$	ΔE $[\%]$	σ_x $[mm]$	σ_y $[mm]$	$\sigma_{x'}$ $[mrad]$	$\sigma_{y'}$ $[mrad]$	$r_{xx'}$	$r_{yy'}$
$Param2$	180	0.1	4.8	5.4	0.1	0.1	0	0



- **Brass collimator** with 15 slits of 0.5 mm x 5 cm with center-to-center spacing of 3.6 mm
- **PMMA Phantom** of 10 x 10 x 2 cm^2 placed 1.5 cm far from the collimator
- Topas scorer **DoseToWater** at 1 cm depth in voxels of 0.005 x 0.2 x 0.1 cm^3
- Irradiation with **61 x 61 spots** pattern **covering 6 x 6 cm^2** (spaced by 1 mm^2)
- **Topas Modular Physics Lists**: g4em-standard opt3, g4h-phy QGSP BIC HP, g4decay, g4ion-binarycascade, g4h-elastic HP, g4stopping and g4radioactivedecay
- **Range Cut Value**: 0.01 mm (0.005 mm was used for gamma, electron, positron and proton to account for the small voxel sizes in the phantom)

CARBON ION MBRT: Experimental Measurements

Monte Carlo Simulations

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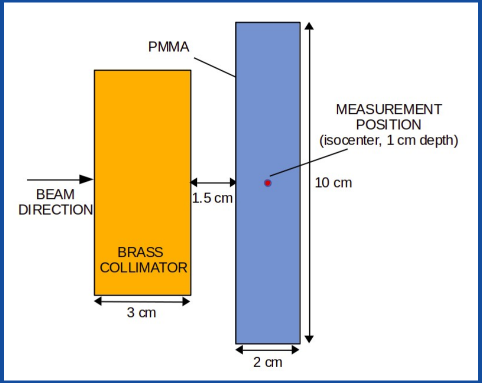
Param2	180	0.1	4.8	5.4	0.1	0.1	0	0



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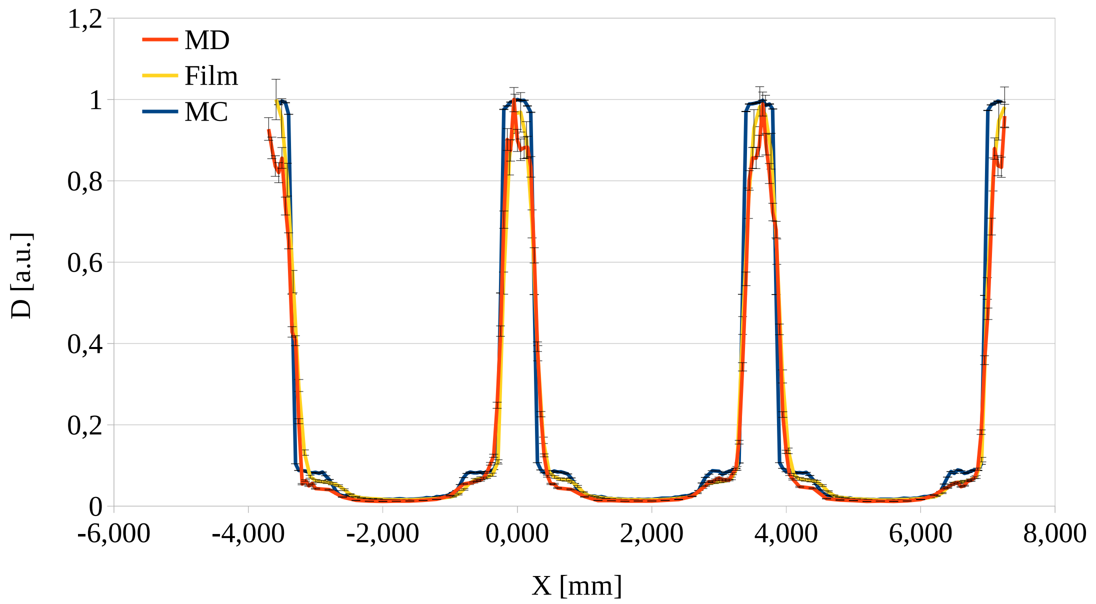
MORE REALISTIC SIMULATIONS

CARBON ION MBRT: Experimental Measurements



	PVDR	PADR	FWHM [mm]	OF_1	OF_2
MD	69 ± 3	6.1 ± 0.3	0.51 ± 0.05	0.21 ± 0.01	1.30 ± 0.04
Films with correction	64 ± 5	5.8 ± 0.4	0.50 ± 0.05	0.20 ± 0.01	1.18 ± 0.06
MC	64.5 ± 0.9	5.67 ± 0.09	0.50 ± 0.05	0.184 ± 0.003	1.04 ± 0.02

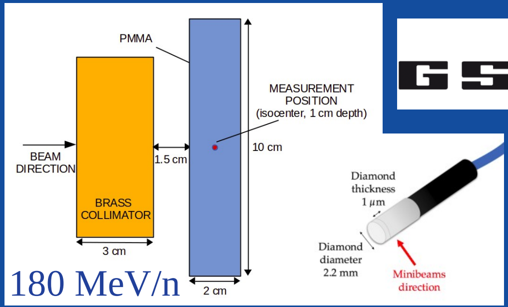
PERTURBATION CORRECTION FACTOR IN MBRT

Perturbation correction factor for PVDR evaluated through MC simulations

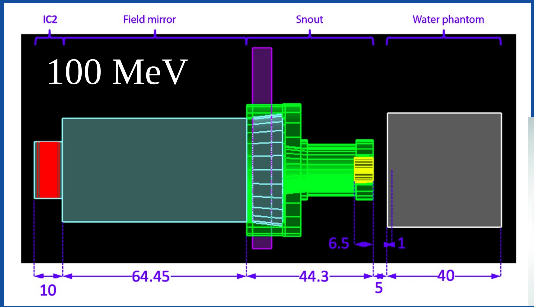
180 MeV/n

PERTURBATION CORRECTION FACTOR IN MBRT

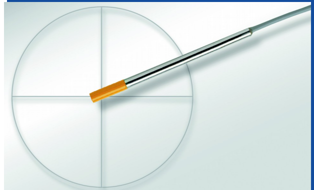
Perturbation correction factor for PVDR evaluated through MC simulations



C. Peucelle's Thesis, 2016



Sotiropoulos et al, Med Phys 2022



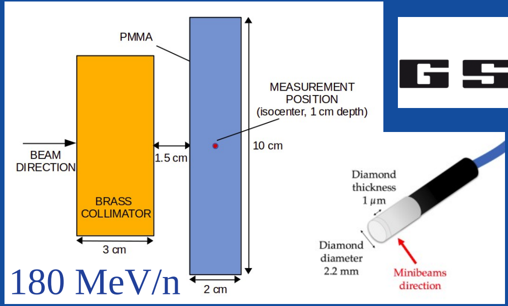
IBA's website

Two different collimators:

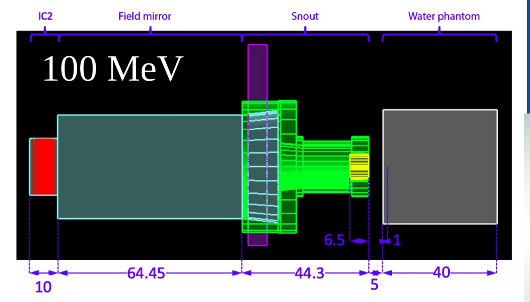
- 6.5 cm thick brass
- 5 divergent slits of 400 um width and 20 mm length
- center-to-center distances of 2.8 and 4 mm

PERTURBATION CORRECTION FACTOR IN MBRT

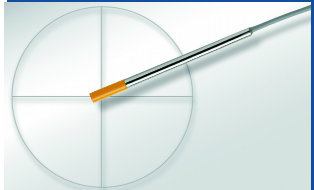
Perturbation correction factor for PVDR evaluated through MC simulations



C. Peucelle's Thesis, 2016



Sotiropoulos et al, Med Phys 2022



IBA's website

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- center-to-center distances of 2.8 and 4 mm

TOPAS scorer **DoseToWater** was used to assess the **absorbed dose in a voxelized scorer** (0.005 x 0.2 x 0.1 cm ^{3}) and **in the active volume of the detectors**, whose models provide **realistic dimensions and material compositions**.

$$k^{\mathrm{MB,PVDR,d}} = \frac{\dfrac{D^{x=\mathrm{valley}}_{\mathrm{PMMA}}}{D^{x=\mathrm{valley}}_{\mathrm{MD}}}}{\dfrac{D^{x=\mathrm{peak}}_{\mathrm{PMMA}}}{D^{x=\mathrm{peak}}_{\mathrm{MD}}}}$$

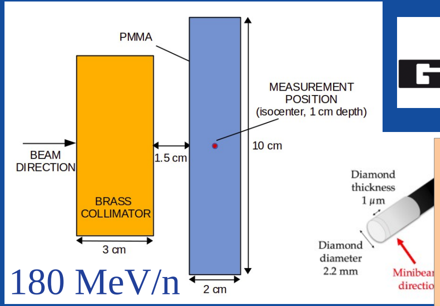
GSI/Carbon/MD → **k^{PVDR}= 1.03 ± 0.02**

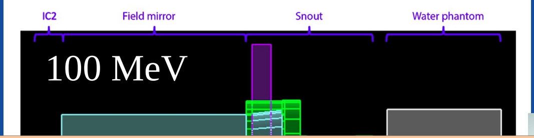
ICPO/Proton/RD/ctc2.8mm → **k^{PVDR}= 1.02 ± 0.01**

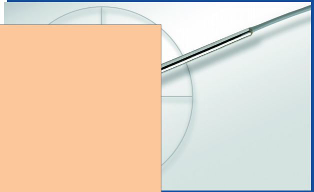
ICPO/Proton/RD/ctc4mm → **k^{PVDR}= 1.02 ± 0.01**

PERTURBATION CORRECTION FACTOR IN MBRT

Perturbation correction factor for PVDR evaluated through MC simulations







Two different collimators:

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- center-to-center distances of 2.8 and 4 mm

C. Peucelle's Thesis, … A's website

TOPAS scorer **DoseTo**… **voxelized scorer** (0.005 x 0.2 x 0.1 cm ^{3})… e models provide **realistic dimensions a**…

Not influenced by **ctc distance**

Correction <2%

But…
it is important to evaluate it **for each different experimental scenario**

$$k^{\mathrm{MB,PVDR,d}} = \frac{\frac{D^{x=\mathrm{valley}}_{\mathrm{PMMA}}}{D^{x=\mathrm{valley}}_{\mathrm{MD}}}}{\frac{D^{x=\mathrm{peak}}_{\mathrm{PMMA}}}{D^{x=\mathrm{peak}}_{\mathrm{MD}}}}$$

GSI/Carbon/MD → $\mathbf{k^{PVDR}= 1.03 \pm 0.02}$

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FUTURE STEPS

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- **MC evaluation of a proton MBRT treatment** plan for cardiac radioablation in CT images of an anonymized patient

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- Test of moqui, the new **GPU-based MC code** for proton dose calculation

FUTURE STEPS

- **MC evaluation of a proton MBRT treatment** plan for cardiac radioablation in CT images of an anonymized patient

- Test of , the new **GPU-based MC code** for proton dose calculation

- **Implementation of proton MBRT simulations** in

Thank

This PhD project is supported by the ProtoTera grant ref PRT/BD/151548/2021

WE HAVE A PROBLEM

ACCORDING TO THE WORLD HEALTH ORGANIZATION, **CANCER** IS AMONG THE LEADING CAUSES OF **DEATH** IN THE WORLD

RADIOTHERAPY IS ONE OF THE **POWERFUL WEAPONS** WE HAVE TO FIGHT AGAINST IT

HITTING CANCER CELLS WITH IONISING RADIATION, TRYING TO **PRESERVE** AS BEST AS POSSIBLE THE SURROUNDING **HEALTHY TISSUES**

SPATIALLY FRACTIONATED RADIATION THERAPY

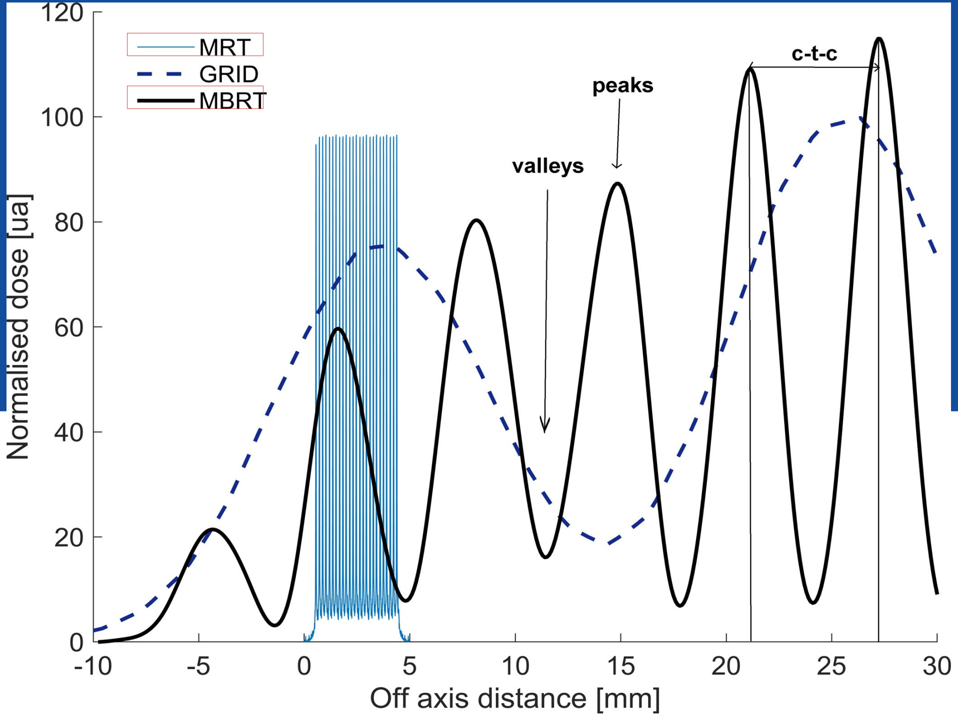
NOWDAYS...

GRID Therapy with megavoltage X-rays beams (LINACS) is used mainly **for palliative treatment** of bulky tumor due to:

- Beam widths ≥ 1 cm^2
- Photons scattering in tissues → Small Peak-to-Valley Dose Ratio (PVDR) (between 2 to 5)

BUT…

Other potential techniques of SFRT **to treat radioresistent tumors** are in **preclinical phases**



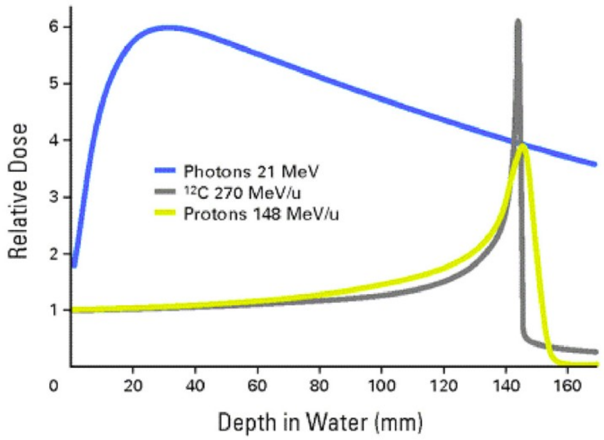
De Marzi et al, Cancer 2019

The narrower the beamlets are the **higher the tolerances** of normal tissues

MBRT WITH CHARGED PARTICLES

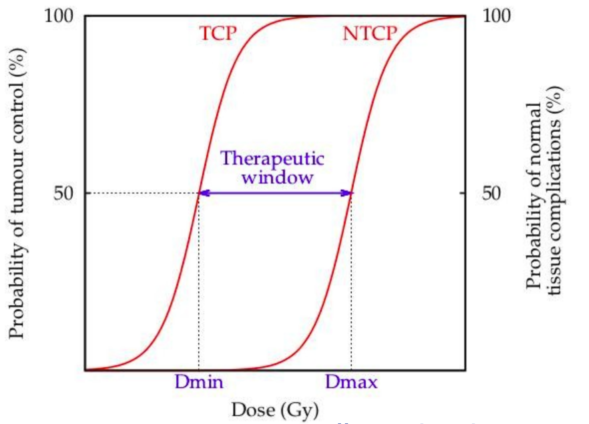
The use of charged particles presents **several benefits both in terms of physics and radiobiology**:

- localized release of energy in matter (**Bragg Peak**)
- dose profiles **shaped more precisely** thanks to the small lateral and range straggling
- **strong increase of the Linear Energy Transfer** (LET) in the Bragg Peak



Dilmanian et al, Frontiers 2015

The combination of these advantages with those of MBRT can improve the therapeutic window for cancers with poor prognosis



C. Peucelle's Thesis, 2016

DOSIMETRY IN MBRT

Gafchromic films EBT-3 and Orthochromic films OC-1

Nearly tissue equivalent material

Not processing after irradiation

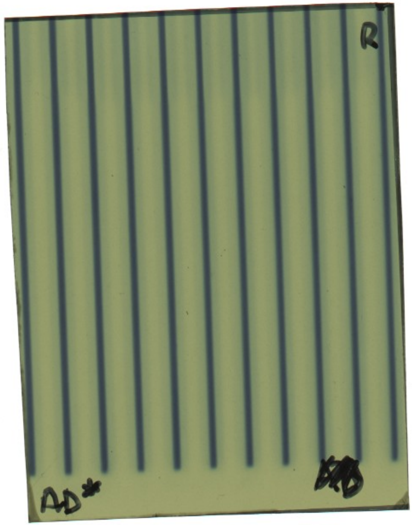
Analysed with a conventional flatbed scanner (→ spatial resolution)

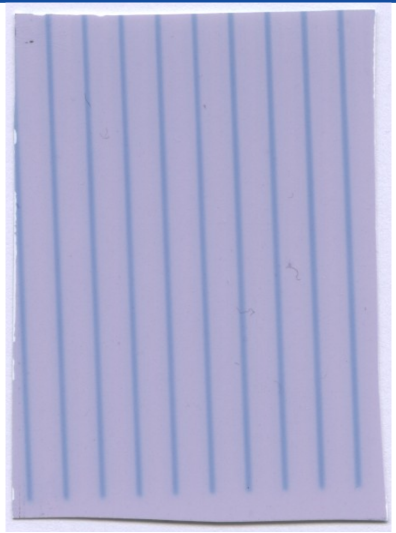
Many hours or even days to obtain the results

Different dynamic dose range

Type	Dynamic Dose Range [Gy]
EBT-3	0.2 – 10
OC-1	0.1 - 100

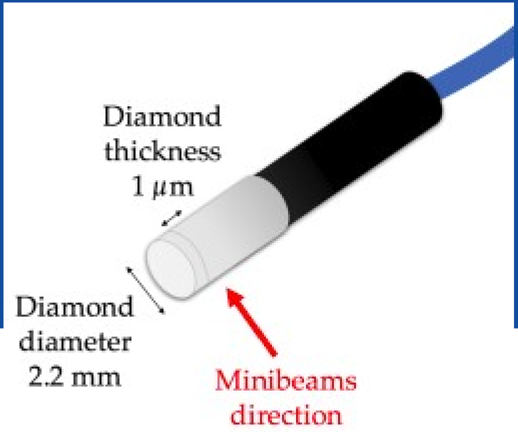
Significant uncertainty due to calibration and film positioning





DOSIMETRY IN MBRT

PTW 60019 microDiamond



C. Peucelle's Thesis, 2016

Nearly tissue equivalent material

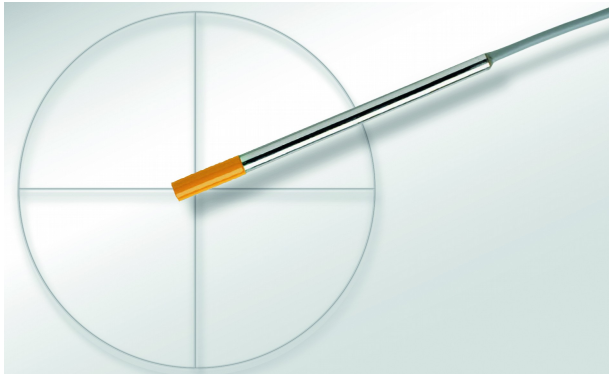
Radiation hardness

LET-independency

Active volume of 1 µm thickness (on-edge)

IBA Razor Diode

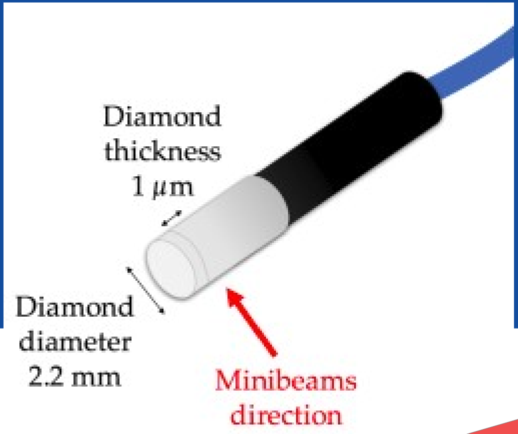
Active volume of 20 µm thickness (on-edge)



IBA's website

DOSIMETRY IN MBRT

PTW 60019 microDiamond



C. Peucelle's The

Nearly tissue equivalent material

Radiation hardness

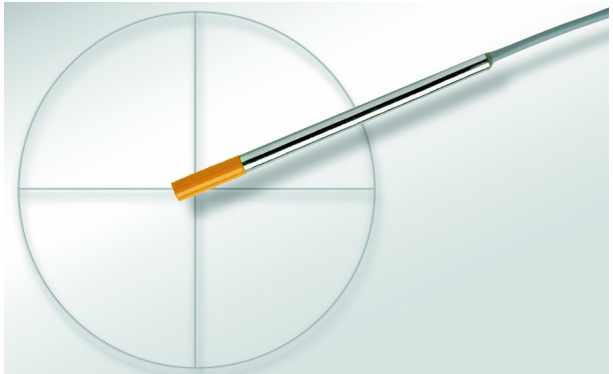
LET-in pendency

Acti n thickness (on-edge)

PERTURBATION CORRECTION FACTOR

IBA Razor Diod

Active volume of 20 μm thickness (on-edge)



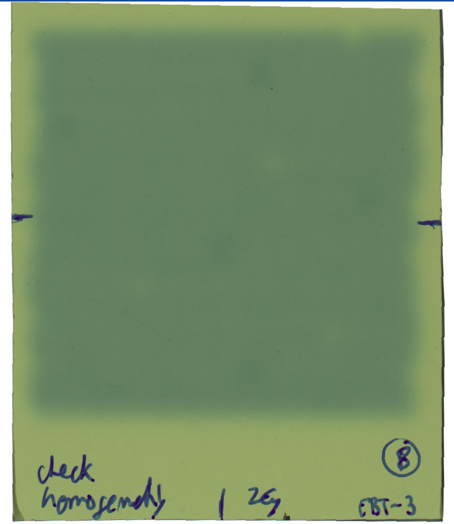
IBA's website

CARBON ION MBRT: Experimental Measurements

Reference measurement:

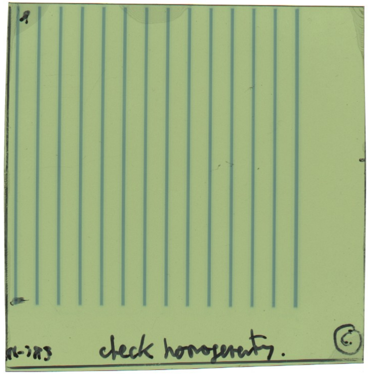
absolute dose for an irradiation field of 6 x 6 cm^2 were measured with a PTW 30013 Farmer **Ionisation Chamber placed 1 cm depth in solid water (RW3) at the isocenter of the room**

Plan dose = 2 Gy → D_{IC} = 2.019 Gy



Collimator alignment:

- two **ionisation chamber** → maximum "transmission"
- Gafchromic EBT-XD **film**



- PTW 60019 **microDiamond**