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Imperial College London

Advancing proton minibeam radiation therapy with magnetic focussing

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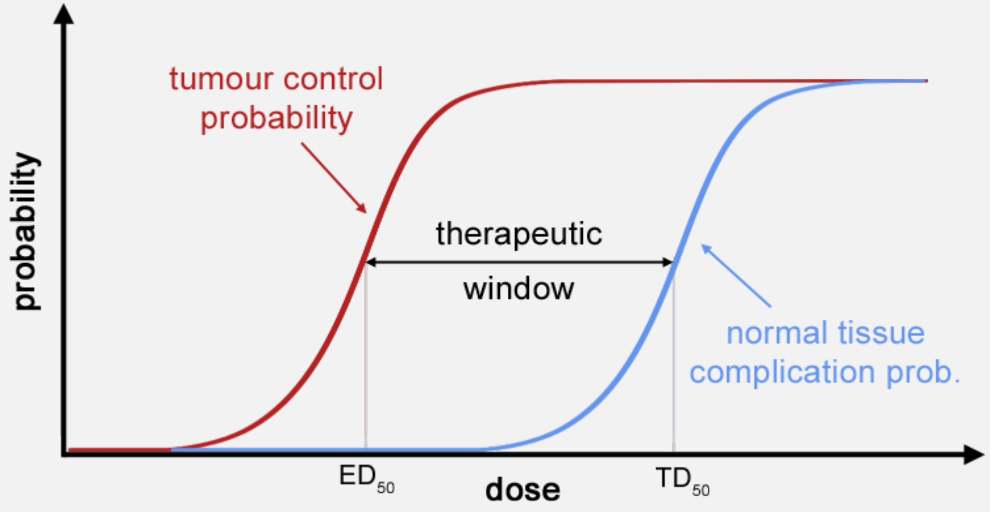
Presentation overview

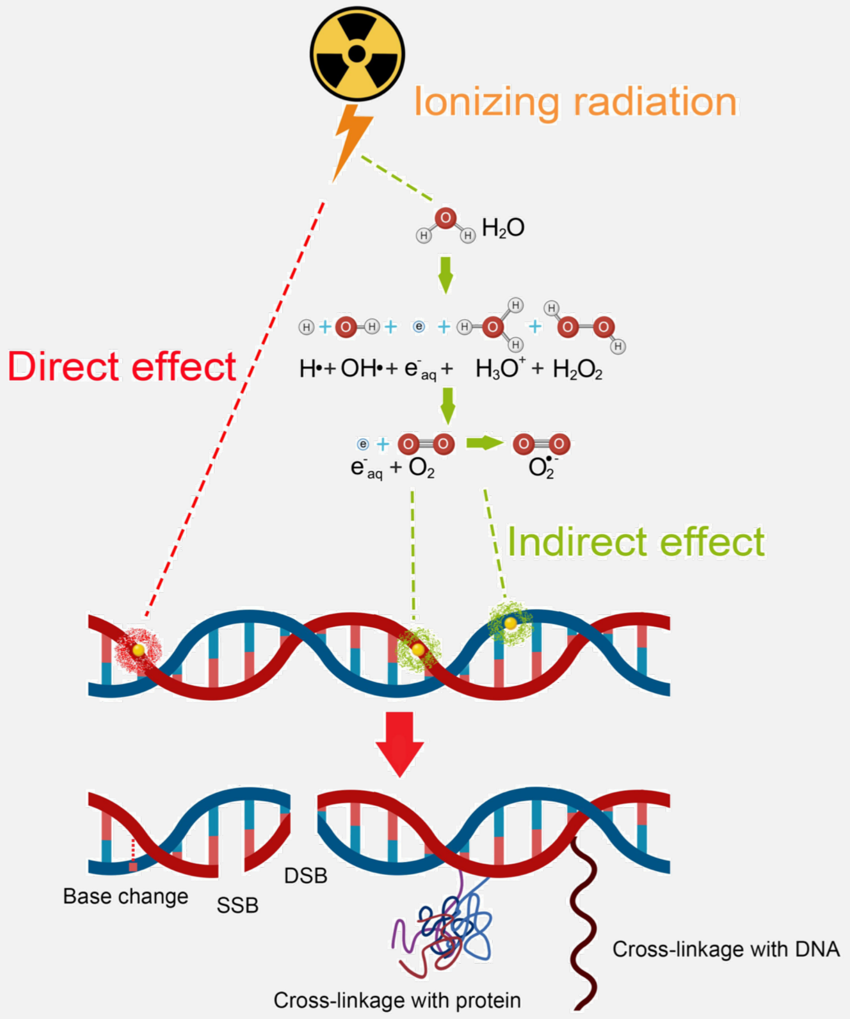
Advancing proton minibeam radiation therapy
with magnetic focussing

1. **Radiation therapy**
2. **Proton** therapy
3. Proton **minibeam** radiation therapy
4. Minibeam **generation**
5. Minibeam generation through **magnetic focussing**
6. Conclusions and perspectives

Radiation therapy (RT)

- RT = medical use (curative or palliative) of ionising radiation
- 50% of cancer patients worldwide (67% in Western countries) receive RT
- ionising radiation causes cellular damage through *direct* and *indirect effects* (main target DNA)

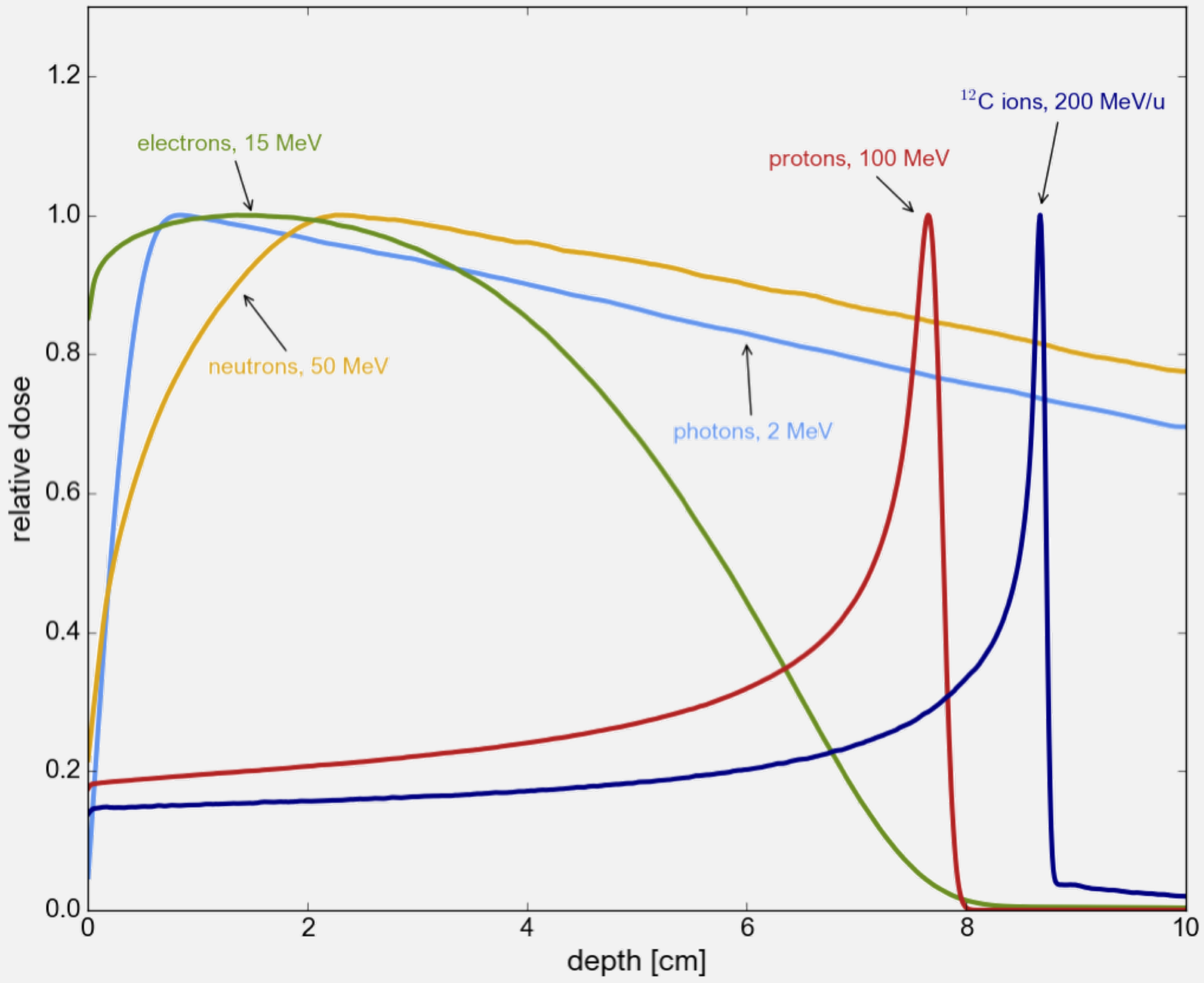




Gong et al, Int J Nanomedicine, 2021

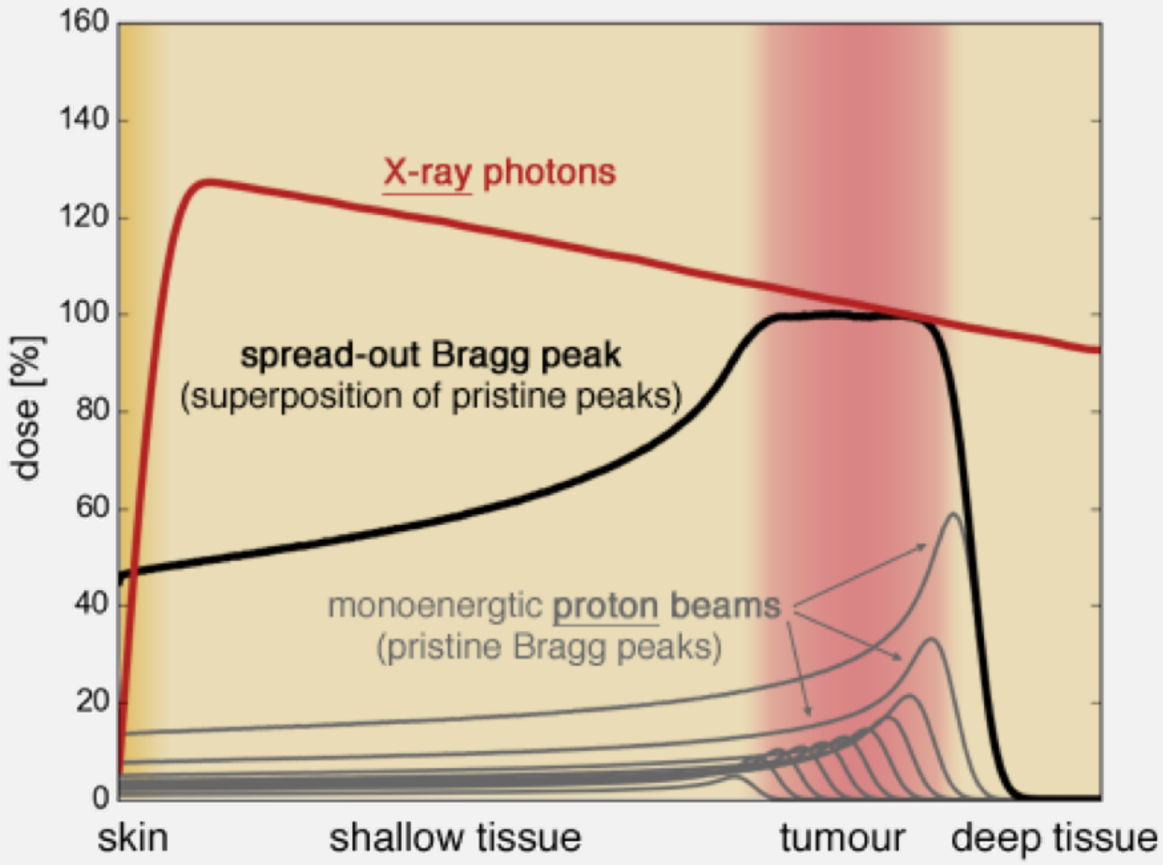
From X-rays to protons

- 1896: first treatment with X-rays
- today: vast majority of treatments is external beam RT with MV X-rays
- various types of ionising radiation used in RT (X-ray photons, electrons, protons, other ions, neutrons, …)
- proton therapy (PT):
  - proposed 1946, first treatment 1954
  - < 1% of RT treatments
  - ≈ 220,000 patients until 2019 (source: PTCOG.ch)
  - 99 clinical centres worldwide (as of Sep 2021, source: PTCOG.ch)

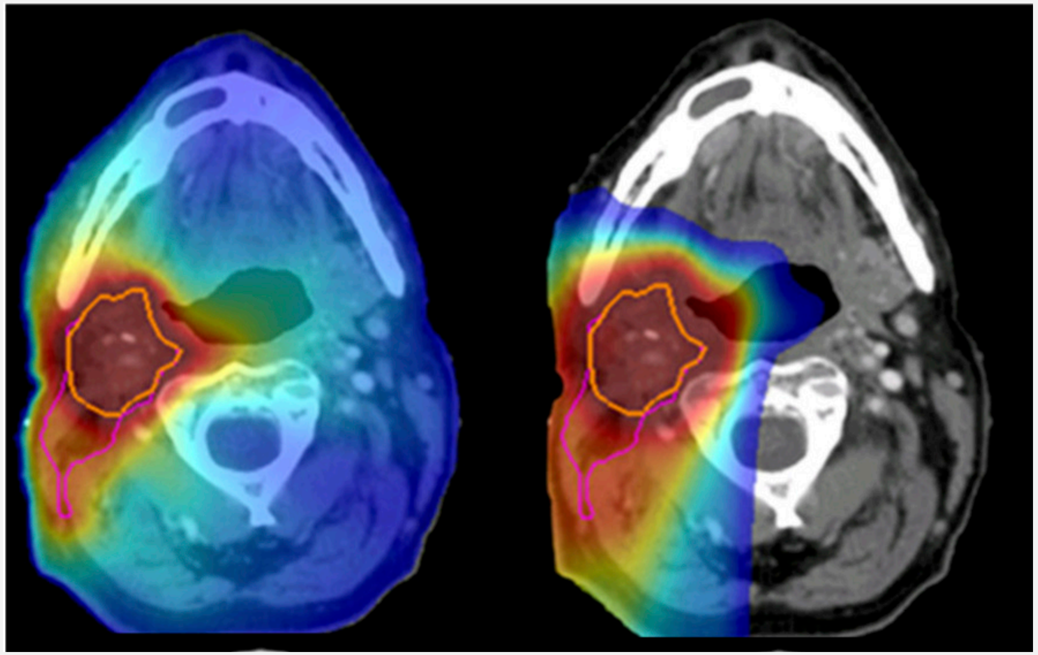


X-rays vs protons

Main rationale for PT: better dose targeting due to **Bragg peak**



X-ray photons (VMAT) | **protons** (IMPT)

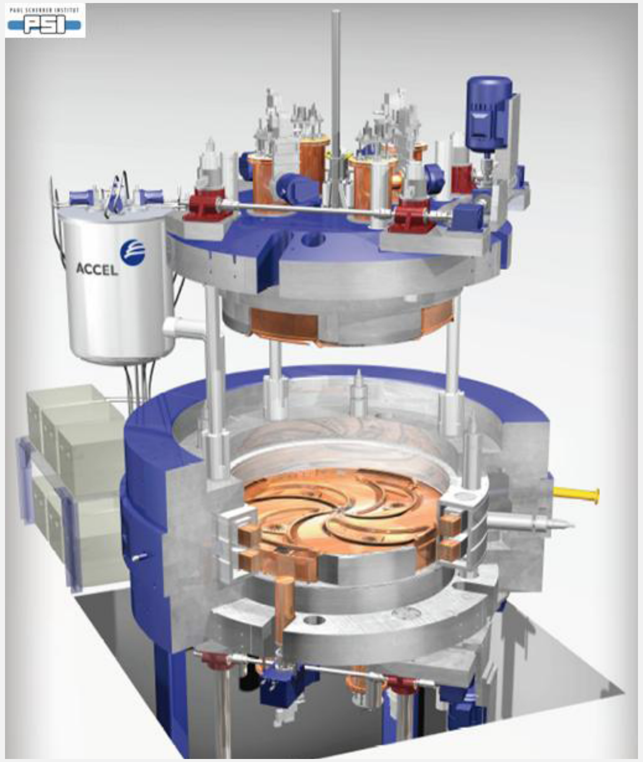


Eekers et al, Radiother Oncol, 2016

PT accelerators today

- PT requires proton beams with energies from 70 to 230/250 MeV
- cyclotrons (70%) and synchrotrons (30%)

Cyclotron at PSI (ACCEL, Varian)



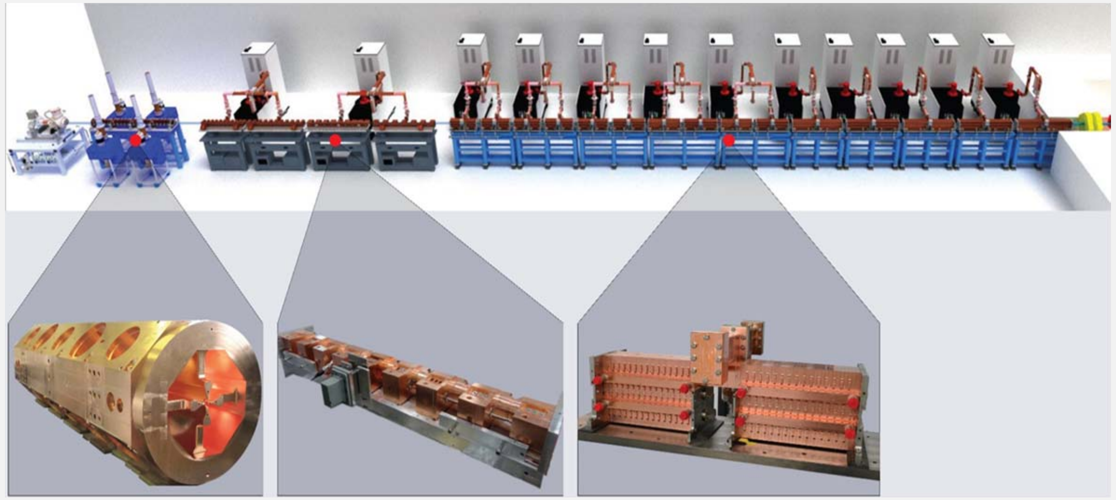
Synchrotron in Tsukuba (HITACHI)

Schippers, Cyclotrons for Proton Therapy,
CERN-CNAO-PARTNER accel. school, 2012

PT accelerators tomorrow

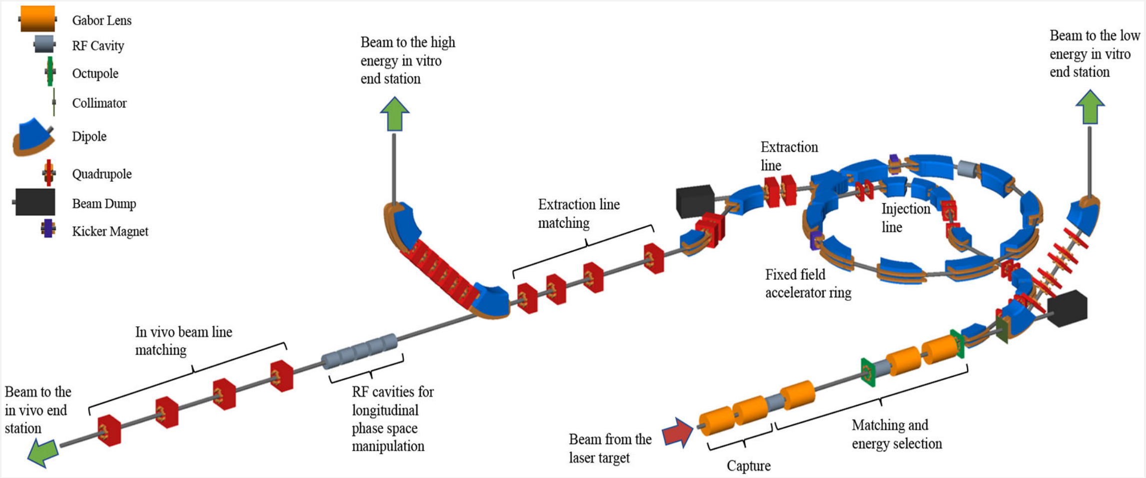
- linacs (LIGHT, TOP-IMPLART, TULIP, …)
- laser-driven accelerators (LhARA)
- FFAGs (also LhARA)

Linac LIGHT (AVO-ADAM)



Degiovanni et al, *Proceedings of NAPAC 2016*

Laser-hybrid Accelerator for Radiobiological Applications (LhARA)

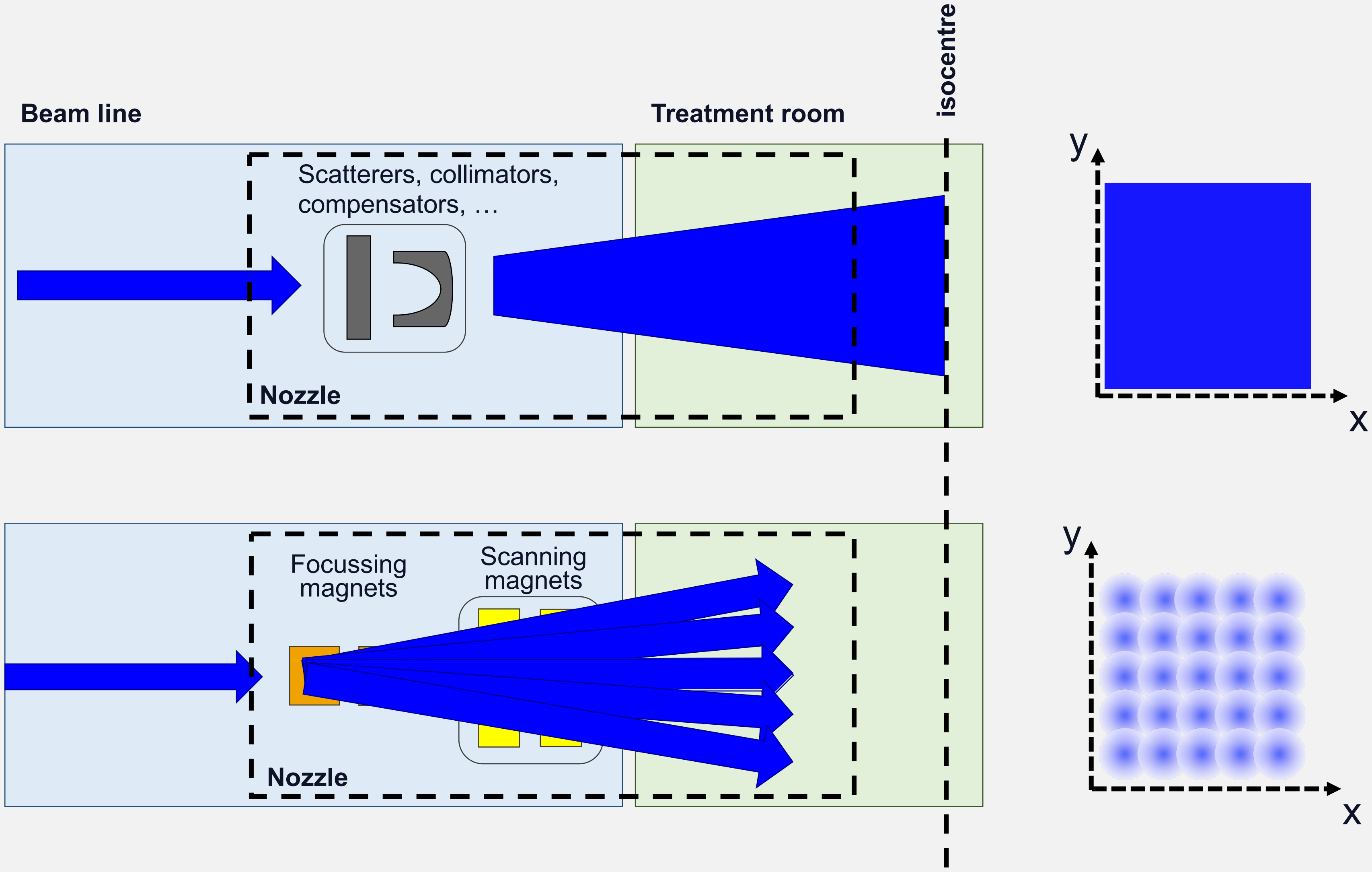


Aymar et al, *Front Phys,* 2020

PT delivery methods

Passive scattering

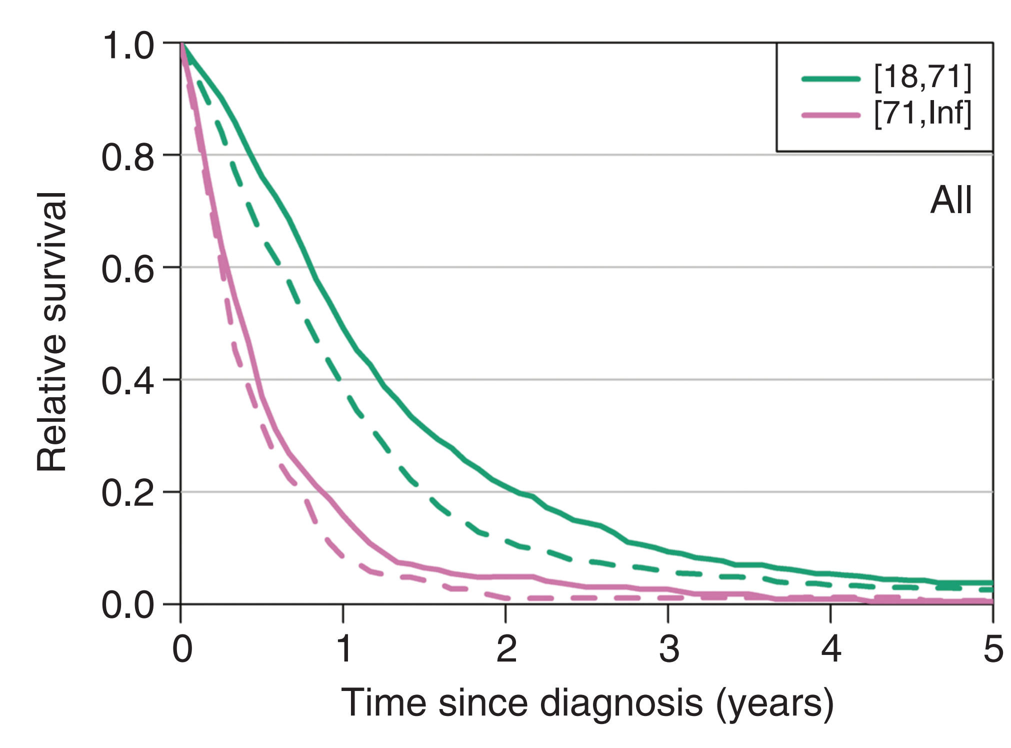
Pencil beam scanning (PBS)



Challenges in modern RT

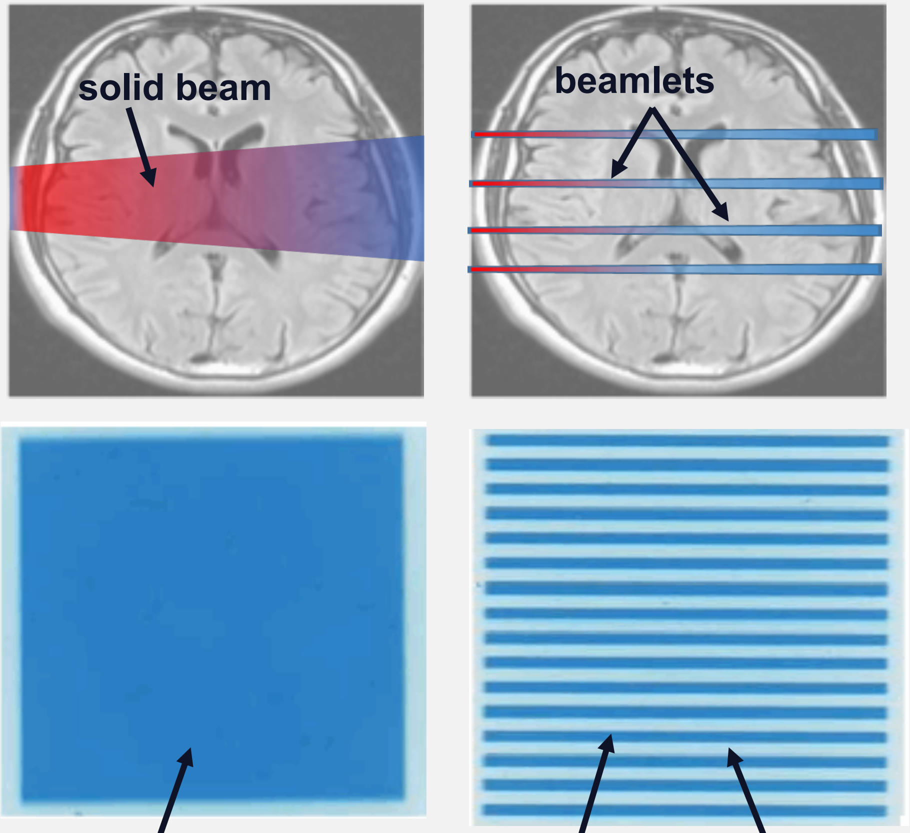
- several types of **radioresistant** cancers:
  - hypoxic tumours
  - osteosarcomas
  - chordomas
  - chondrosarcomas
  - glioblastomas
- **normal tissue tolerance** remains important **limiting factor** in RT
- new approaches needed to **widen therapeutic window**

Survival rate of glioblastoma patients in Finland



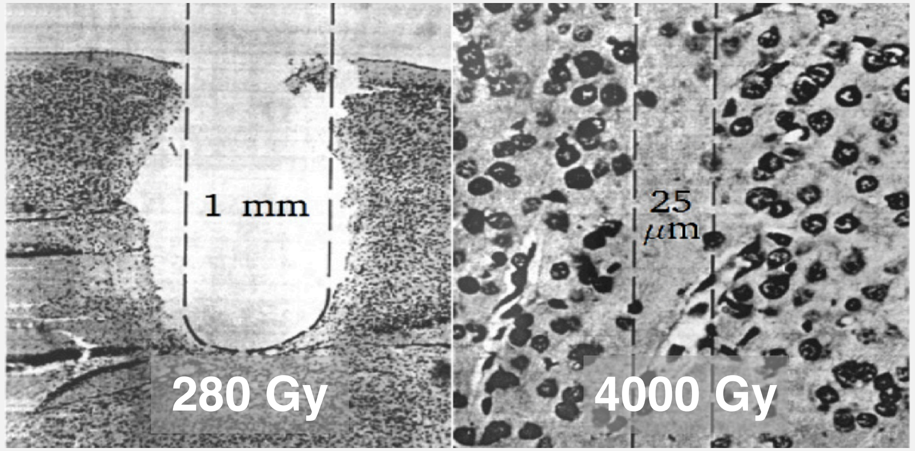
Korja et al, *Neuro-Oncology*, 2018

Spatially fractionated radiation therapy (SFRT)



- **spatial fractionation** of the dose → laterally **heterogeneous** dose
→ **increase** of **normal tissue tolerance**
→ **dose escalation** in target becomes possible

Murine brain tissue irradiated with deuteron beams



Zeman et al,
Rad Res, 1961

- smaller beamlet size → higher tissue tolerance

4 main types of SFRT

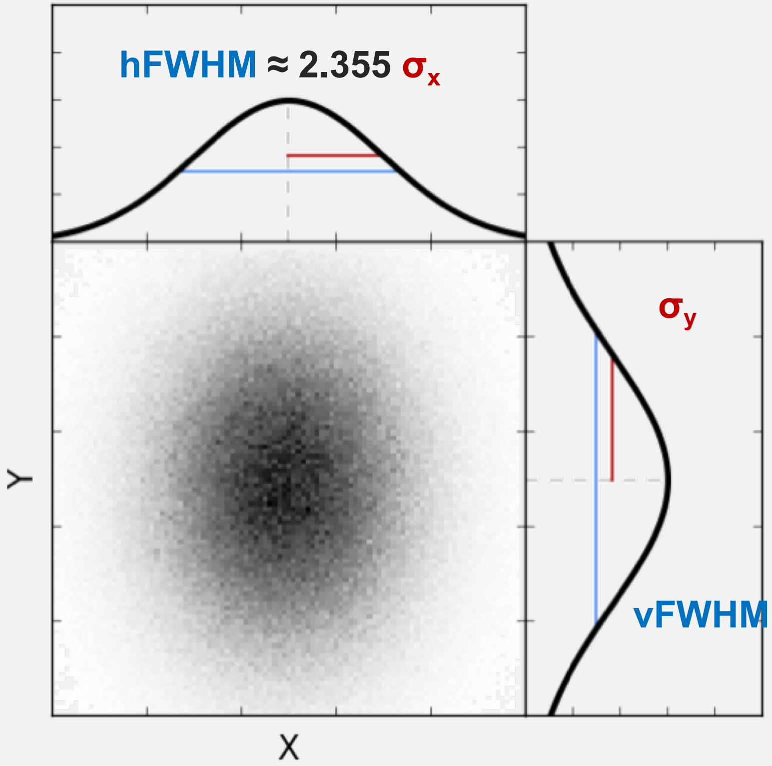
	GRID	Lattice	Microbeams	Minibeams
Beamlet size	~1-2 cm	~1-2 cm	25-100 μm	0.1-1 mm
Spacing	~2-4 cm	~2-4 cm	200-400 μm	~1-4 mm

Minibeam vocabulary

- beams usually well-described by **Gaussian spatial distribution**

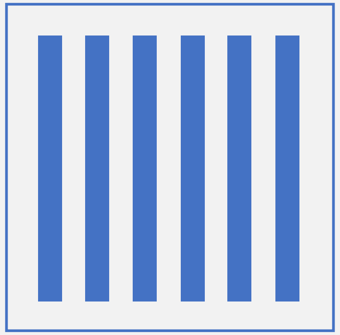
→ beam size stated as **σ** or full width at half maximum (**FWHM**) of Gaussian

hFWHM: horizontal FWHM
vFWHM: vertical FWHM



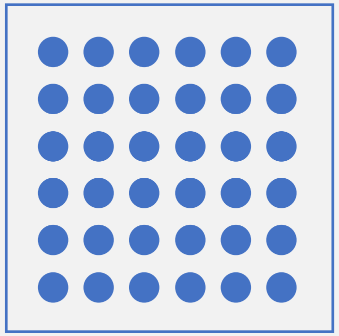
A **minibeam** (MB) satisfies:

0.1 mm ≤ min(hFWHM, vFWHM) ≤ 1 mm



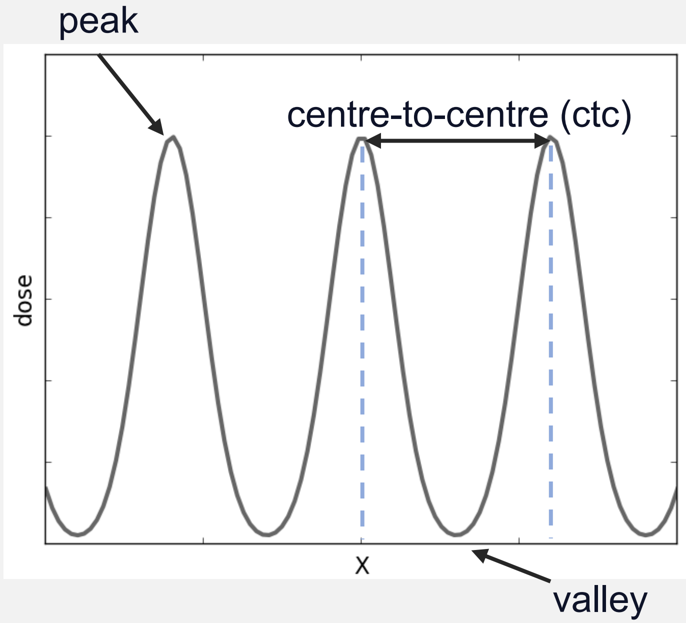
planar MBs

- strongly elongated
- clustered in 1D **arrays**



pencil-shaped MBs

- roughly circular
- clustered in 2D **grids**

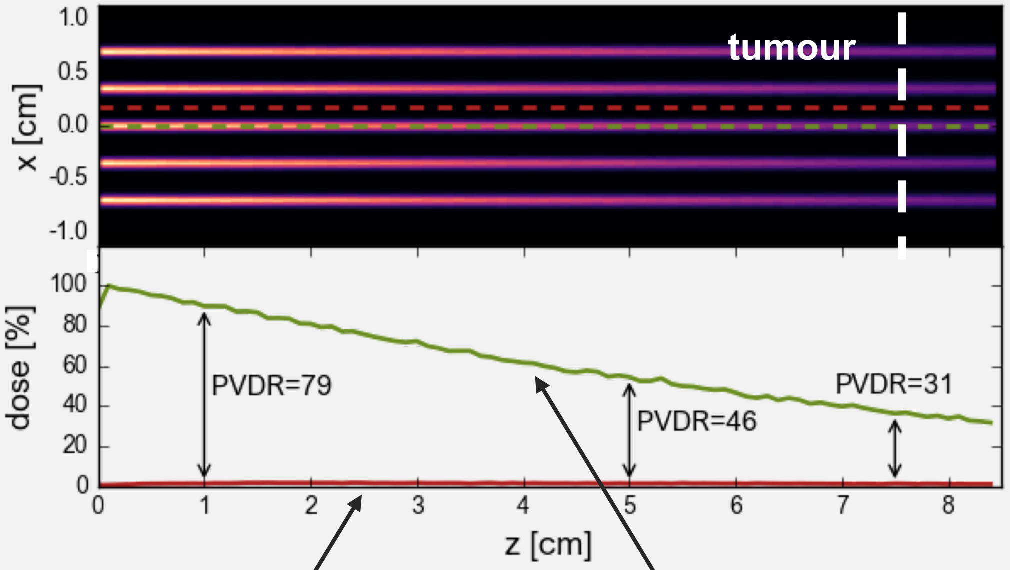


peak-to-valley dose ratio: $\mathbf{PVDR} = \frac{\mathbf{D_{peak}}}{\mathbf{D_{valley}}}$

A **high PVDR** combined with **low valley doses** improves normal tissue **sparing**.

Proton minibeam radiation therapy (pMBRT)

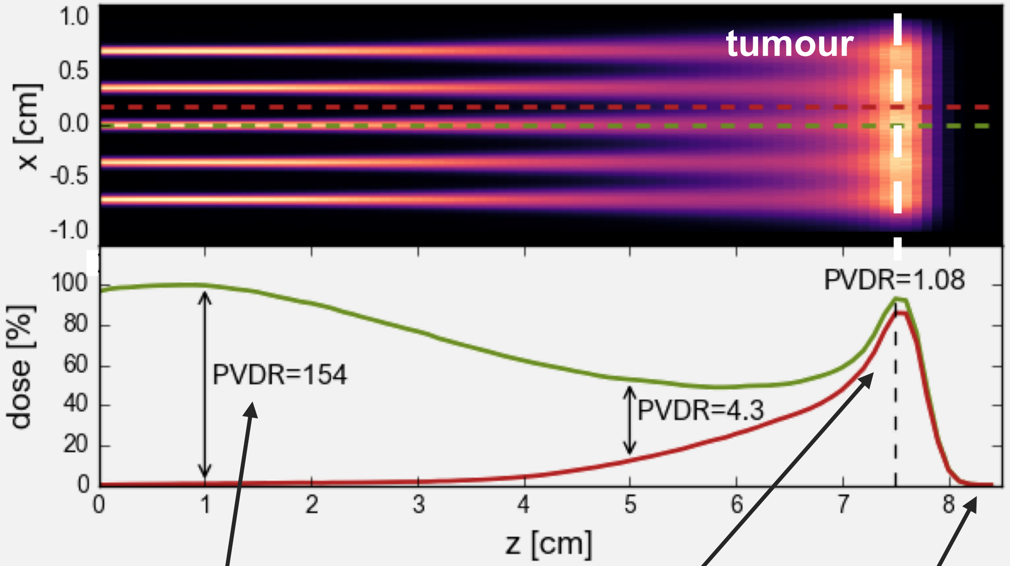
X-ray minibeams (375 keV)



valley dose
stays low

peak dose
slow, exponential decay

Proton minibeams (100 MeV)



high PVDR

no dose beyond
Bragg peak

homogenisation of **peak**
and **valley** doses

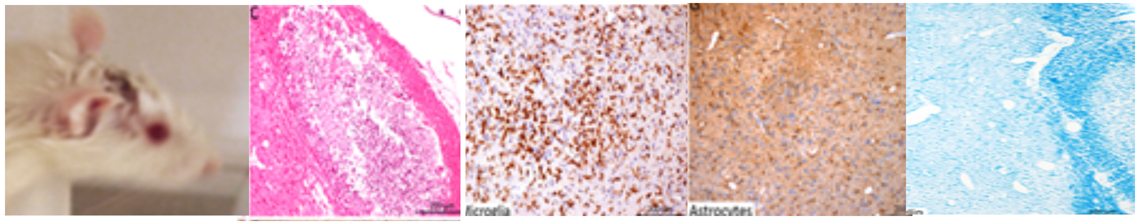
→ **proton minibeam radiation therapy** (Prezado and Fois, *Med Phys*, 2013)

Experimental evidence for pMBRT (1/4)

pMBRT **spares skin** and **brain tissue** and **preserves cognitive functions** in rodents.

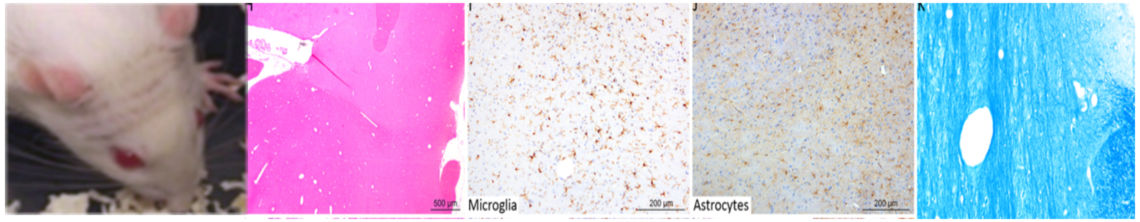
Whole-brain irradiations (normal rats, 7-weeks old) with long-term follow up (6 months)

Standard PT (25 Gy, 1 fraction)



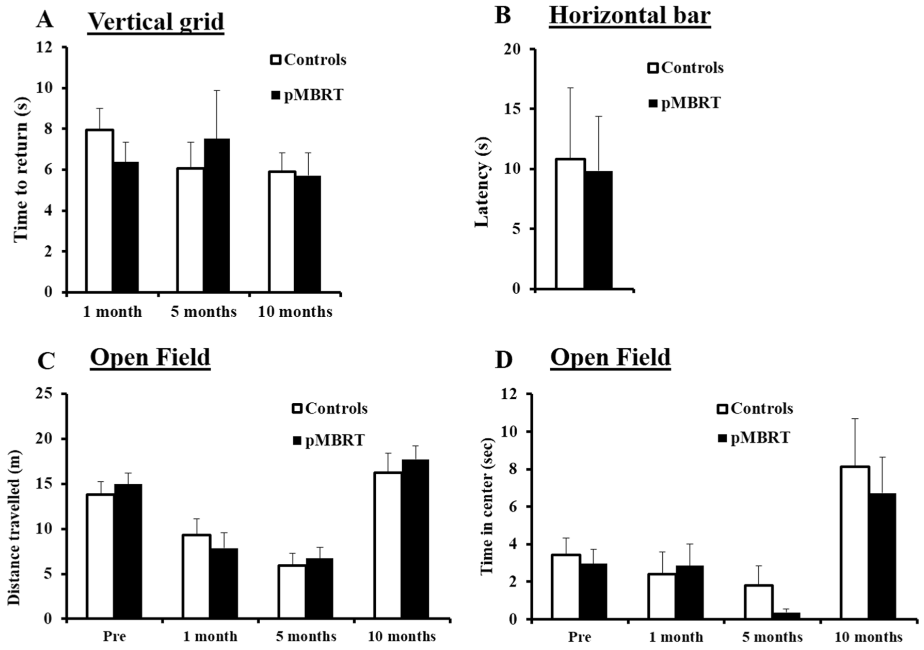
necrosis *inflammation* *astrogliosis* *demyelination*

pMBRT (25 Gy mean, 58 Gy peaks, 1 fraction)



Prezado et al, *Sci Rep*, 2017

Behavioural tests
Motor and anxiety assessment

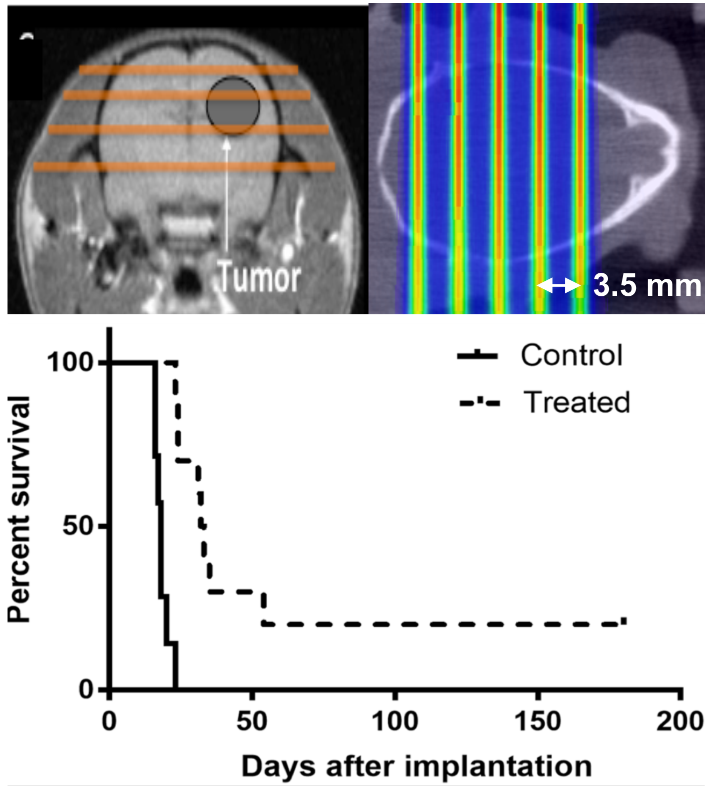


Lamirault et al, *Sci Rep*, 2020

Experimental evidence for pMBRT (2/4)

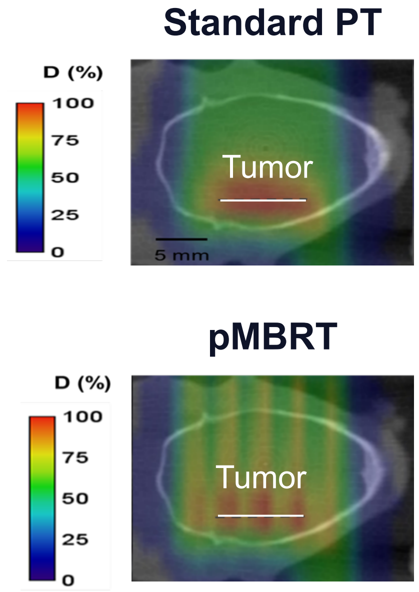
pMBRT **significantly increases** the **therapeutic index** for rat glioma.

Plateau irradiation of RG2-glioma-bearing rats

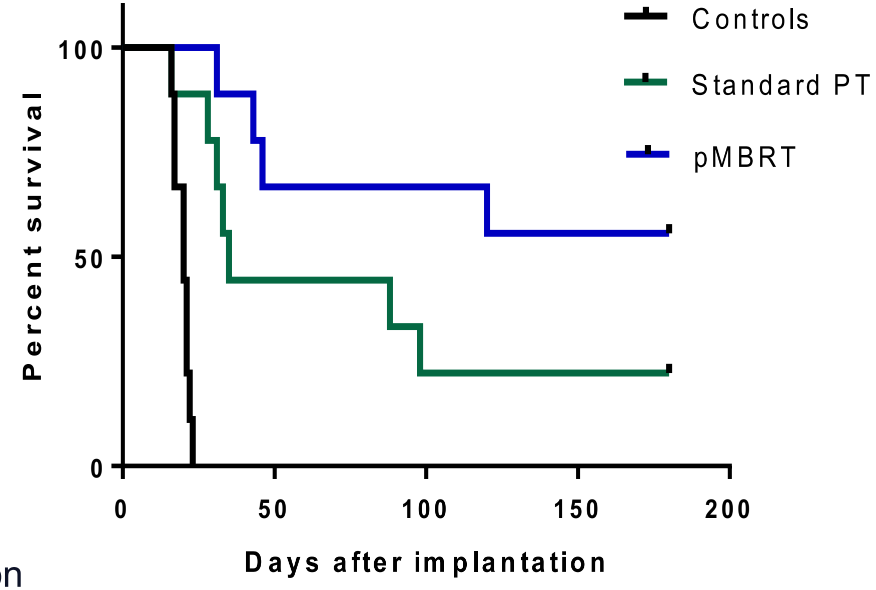


Prezado et al, *Sci Rep*, 2018

Bragg Peak irradiation of RG2-glioma-bearing rats



25 Gy mean, 1 fraction

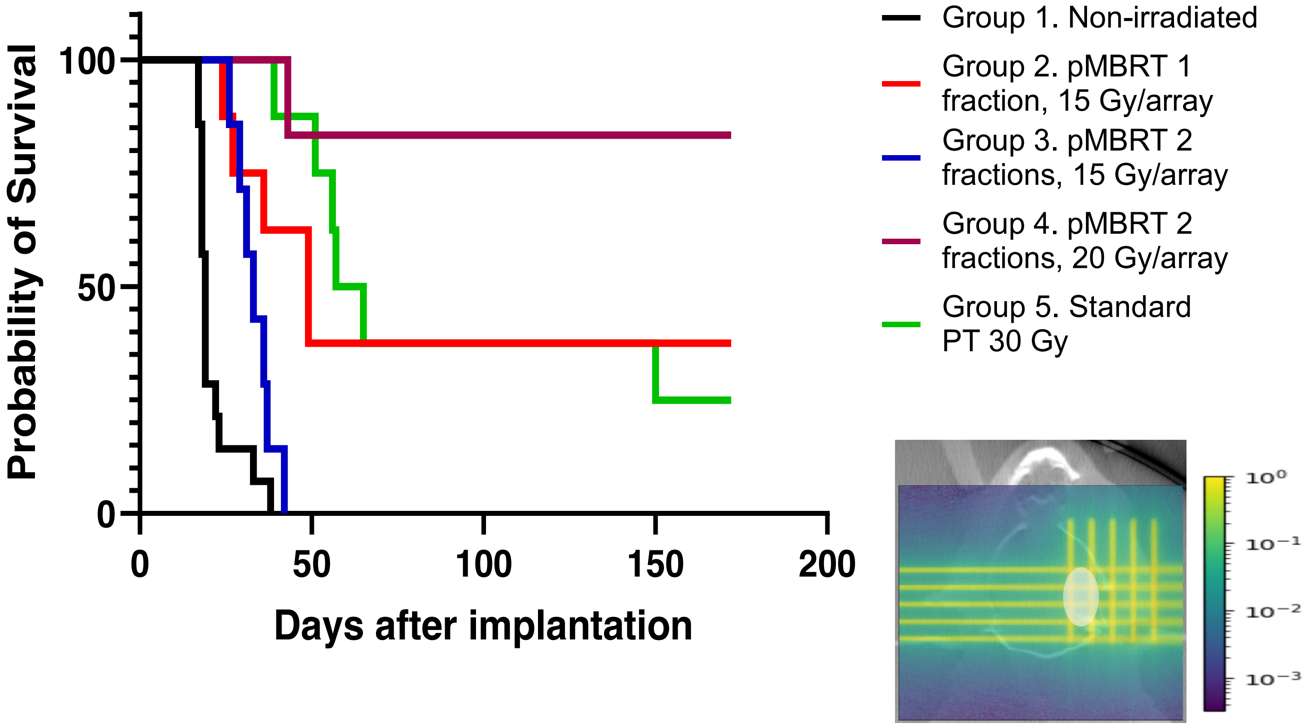


pMBRT irradiation: **67% of long-term survivals (free of tumor)**

Prezado et al, *IJROBP*, 2019

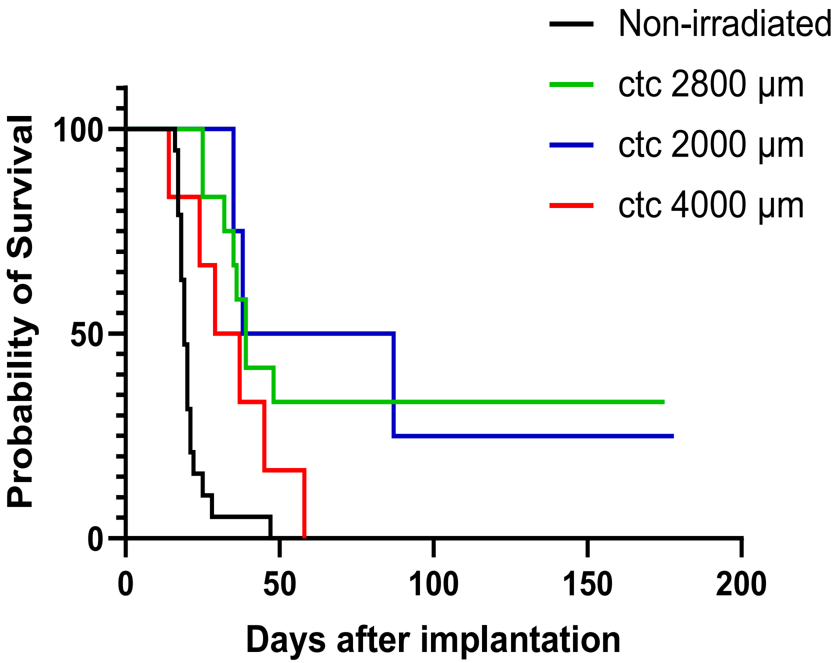
Experimental evidence for pMBRT (3/4)

Minibeams and temporal fractionation



Bertho et al, *Cancers*, 2021

Influence of minibeam spacing

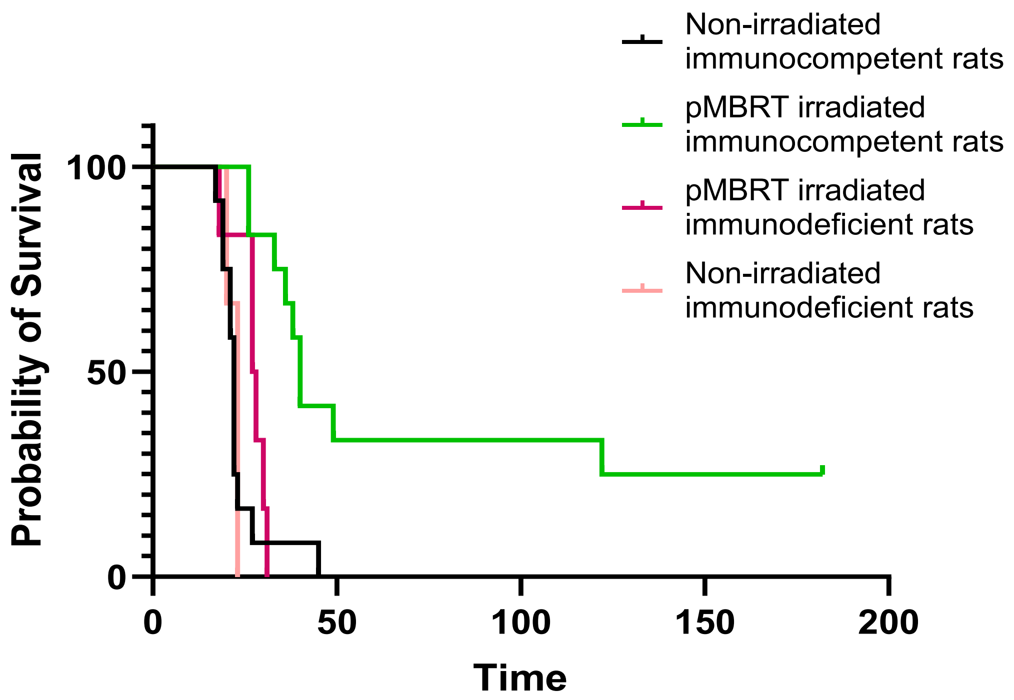


ongoing research

Experimental evidence for pMBRT (4/4)

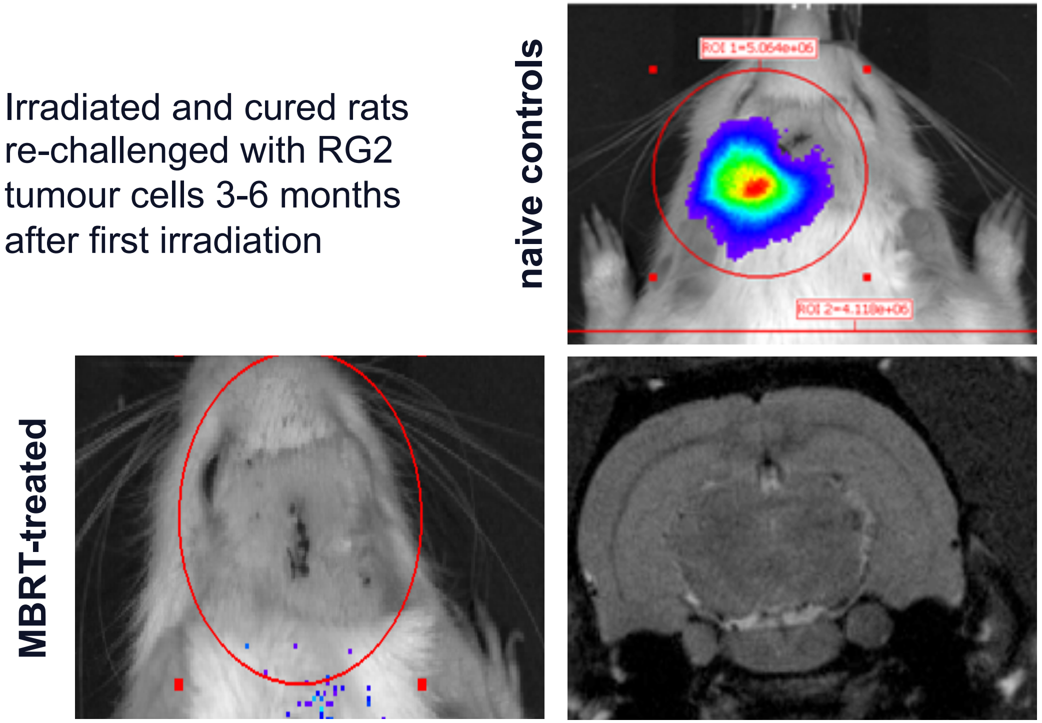
Ongoing research…

Determinant role of immune system in pMBRT irradiations



Possible long-term anti-tumour immunity after MBRT treatment (X-rays)

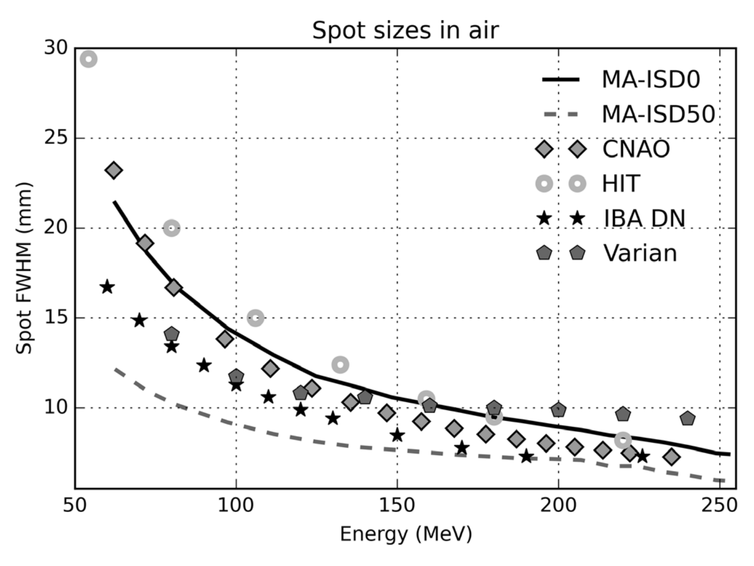
Irradiated and cured rats re-challenged with RG2 tumour cells 3-6 months after first irradiation



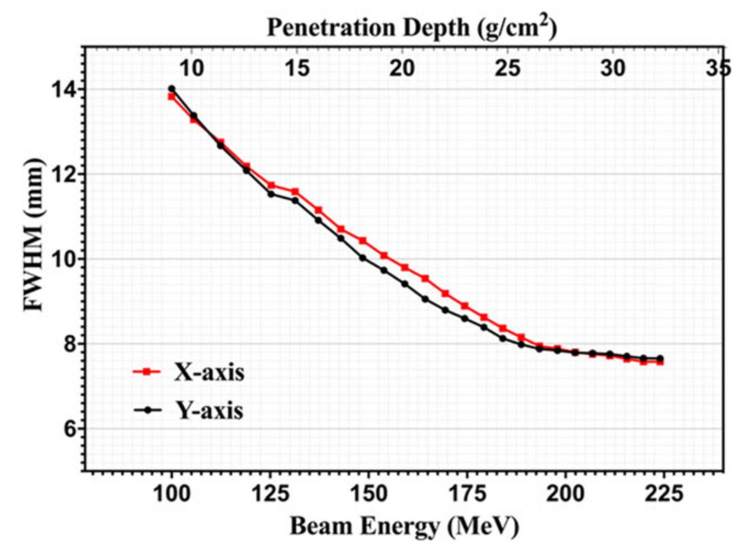
Generation of proton minibeams

- current PT facilities **not designed** for delivery of **minibeams**
- typical beam sizes:
  - Passive scattering: > 1 cm
  - PBS: FWHM 8-20 mm (smallest ≈ 4-5 mm)
- minibeams: **FWHM ≤ 1 mm**

→use **mechanical collimators** to reduce beam size

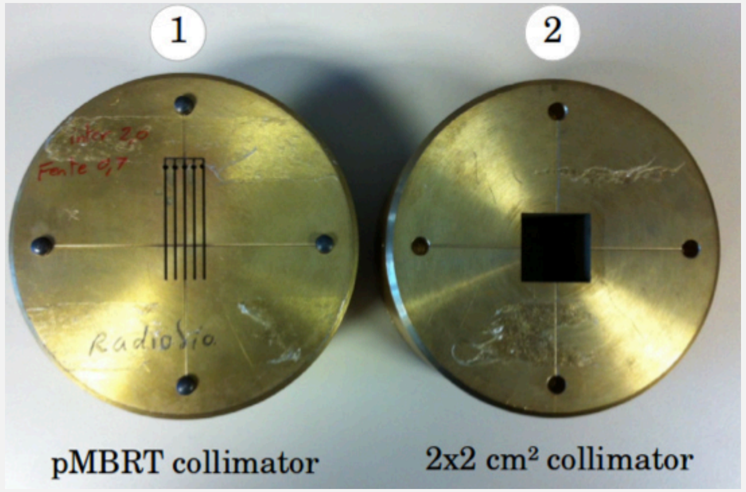


Grevillot et al,
Med Phys, 2020

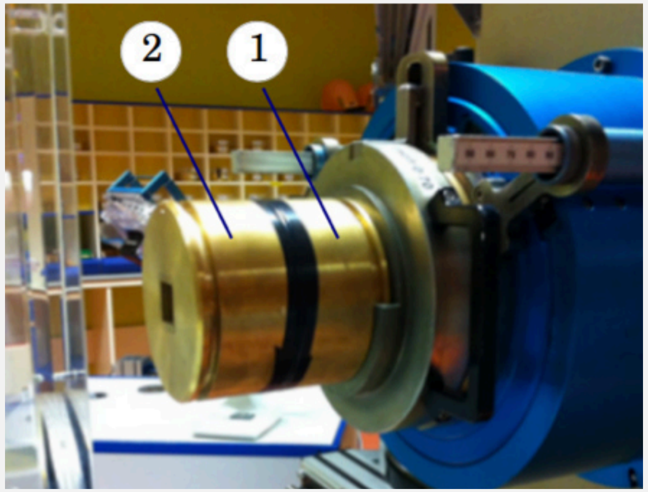


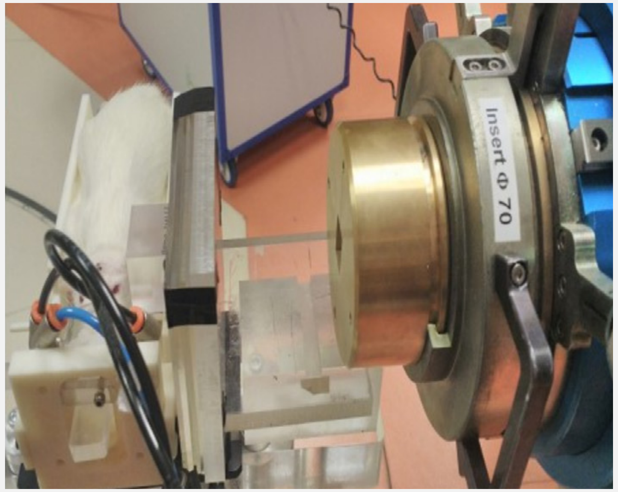
Pidikiti et al,
J Appl Clin Med Phys, 2018

Static collimators



Peucelle, *PhD thesis*, 2016





Prezado et al, *IJROBP*, 2019

Pros and cons:

compatible with current systems

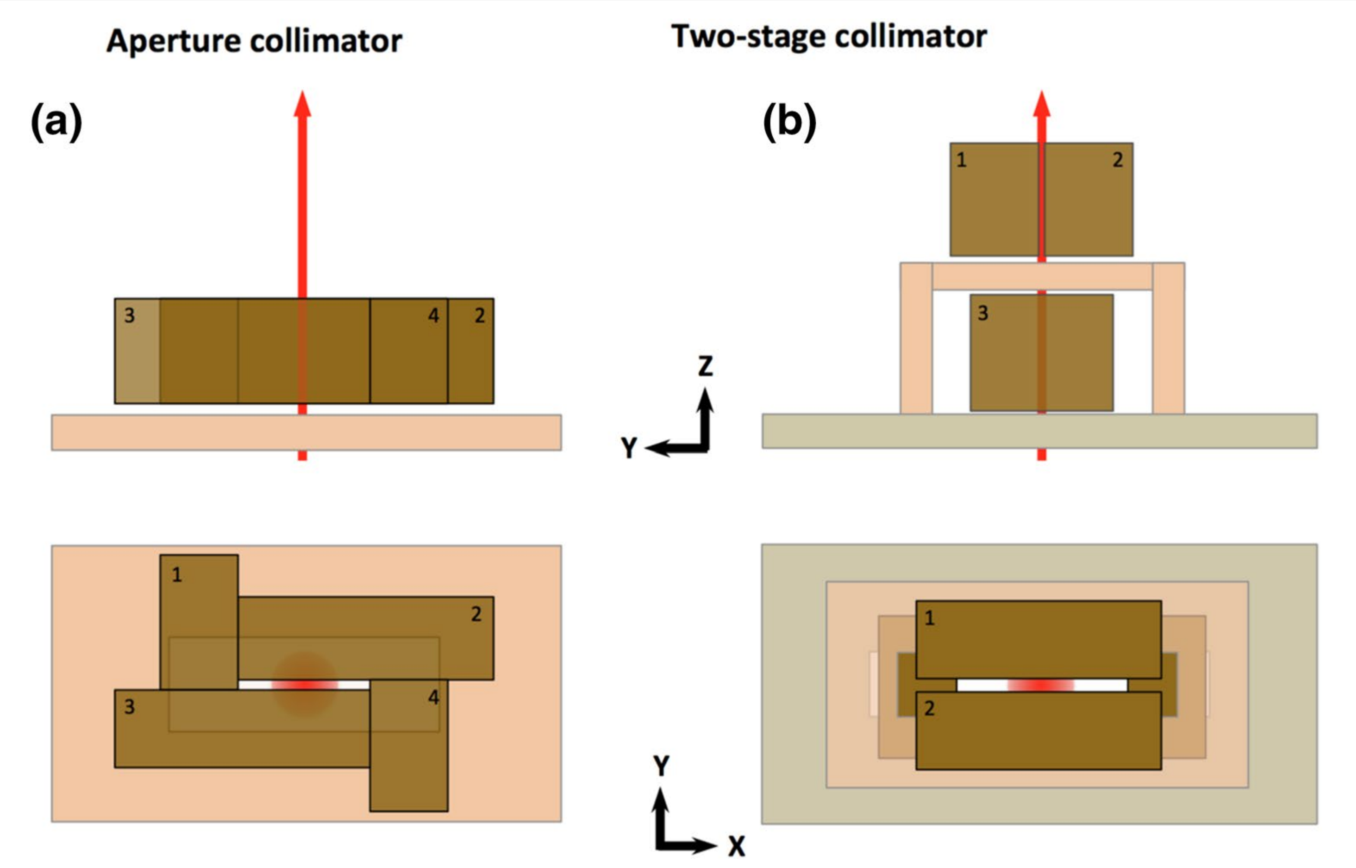
successfully used in experiments

inherently inefficient

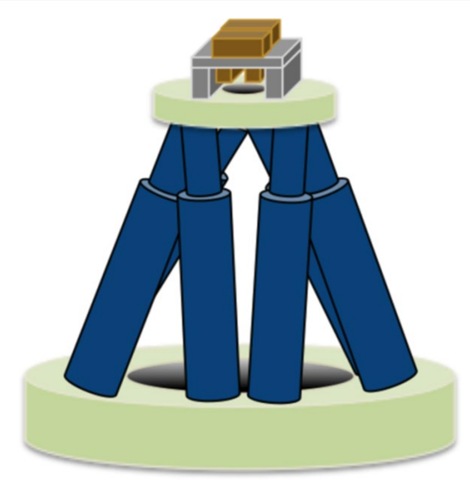
inflexible

production of secondaries (neutrons)

Dynamic collimators



Patent application filed (EP21306092)



Two-stage collimator mounted on hexapod

Sotiropoulos & Prezado, *Sci Rep*, 2021

Pros and cons:

compatible with current systems

more flexibility

still inefficient

production of secondaries

From collimation to magnetic focussing

- easily implementable at existing facilities
- successfully used in many experiments
- static collimators → **low flexibility** (may be improved with dynamic collimators)
- large part of beam blocked → **low efficiency** → important dose rate reduction
- production of unwanted **secondary particles** → increases valley doses/decreases PVDR

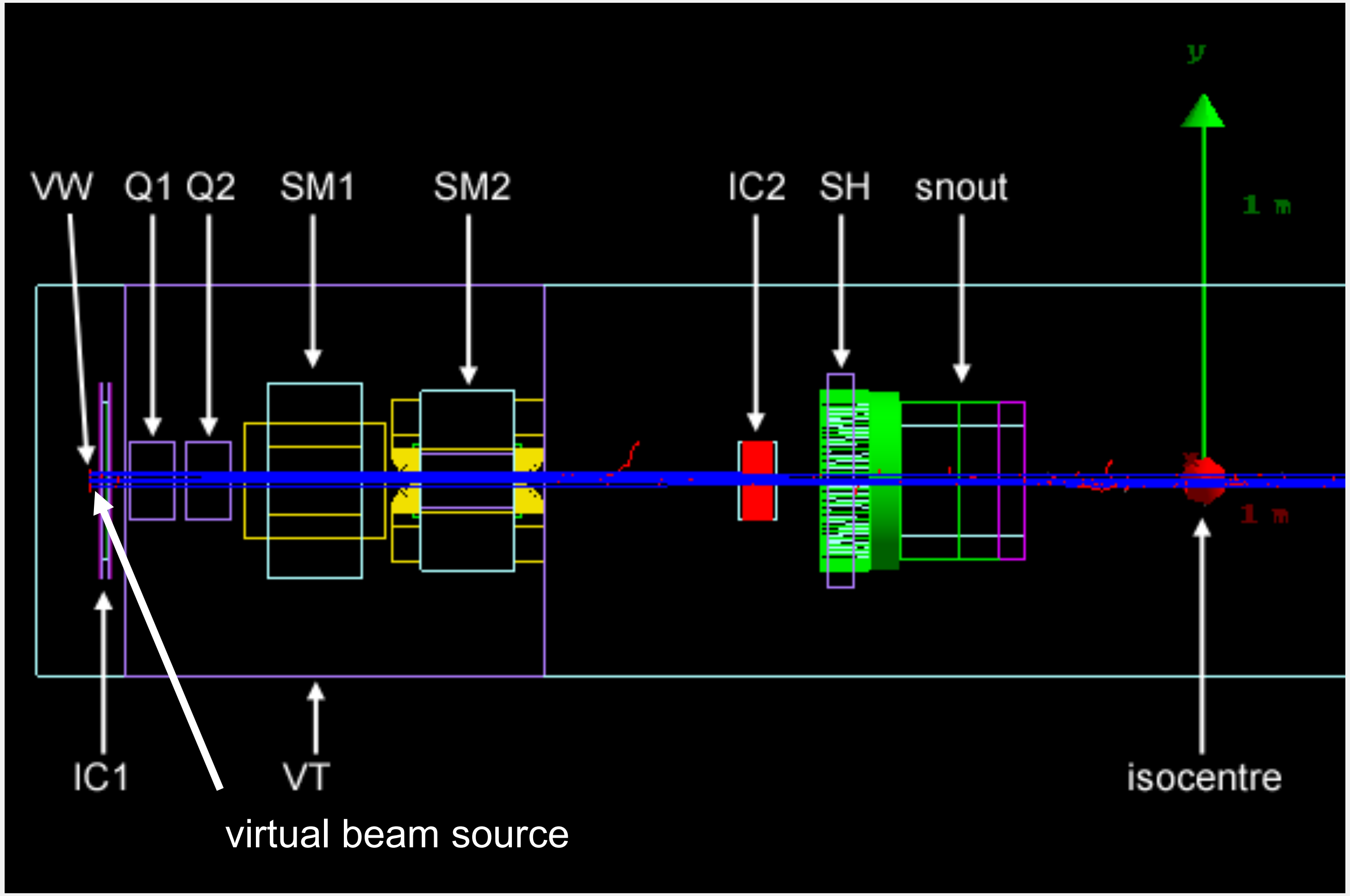
→ solution: **magnetically focussed** and **scanned** minibeams

Generation of magnetically focussed minibeams

- goal: generation of **magnetically focussed** and **scanned** proton **minibeams** at **clinically relevant energies** and in a **clinical setting**
- PBS nozzles already contain **focussing** and **scanning magnets**
- strategy:
  - investigate existing nozzle with computer model
  - MC simulation toolkit TOPAS (based on Geant4)
  - geometry and beam model of Institut Curie proton therapy centre in Orsay (ICPO)
  - assessment of minimum achievable beam size
  - consideration of clinical beam energies (100, 150 and 200 MeV)

The PBS nozzle at ICPO

Nozzle geometry in TOPAS

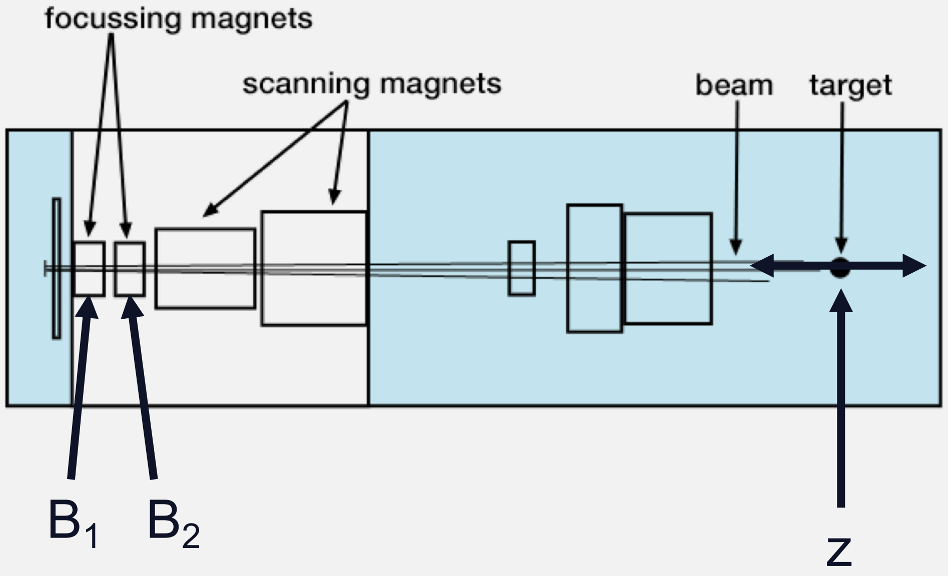


IC	ionisation chamber
Q	quadrupole magnet
SH	snout holder
SM	scanning (dipole) magnet
VT	vacuum tank
VW	vacuum window

Beam size minimisation

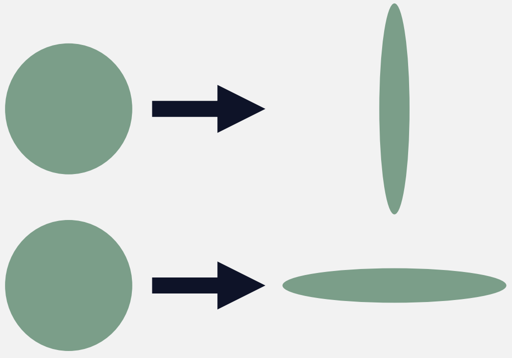
Varied parameters:

- quad field strength: $0\ T \leq B_1, B_2 \leq 2\ T$
  51x51 configs
- quad orientation: 2 configs
- target position: $-40\ cm \leq z \leq 40\ cm$
  5 positions



Different minimisation schemes:

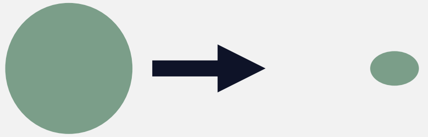
unidirectional minimisation



→ minimum hFWHM

→ minimum vFWHM

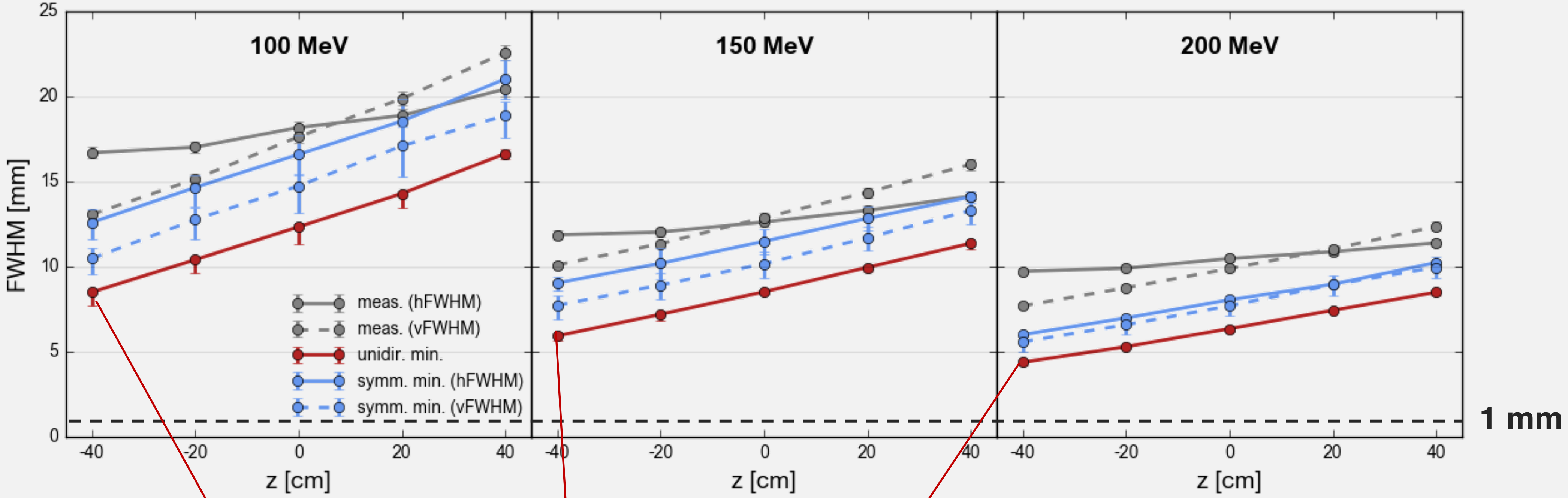
symmetric minimisation



→ minimum Ω

$$\Omega := \sigma_x \sigma_y \left(\frac{\sigma_x}{\sigma_y} + \frac{\sigma_y}{\sigma_x} \right) = \sigma_x^2 + \sigma_y^2$$

Study of the PBS nozzle at CPO (1/3)



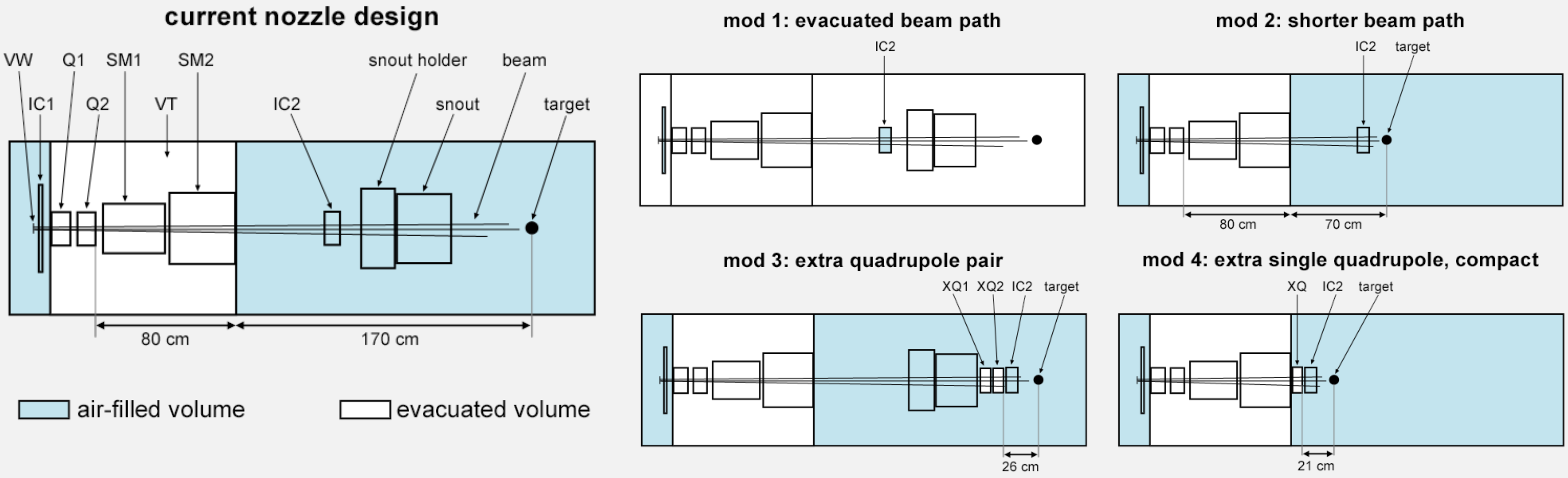
Minibeam: FWHM ≤ 1 mm

Energy	100 MeV	150 MeV	200 MeV
Min. FWHM	8.5 mm	5.9 mm	4.4 mm

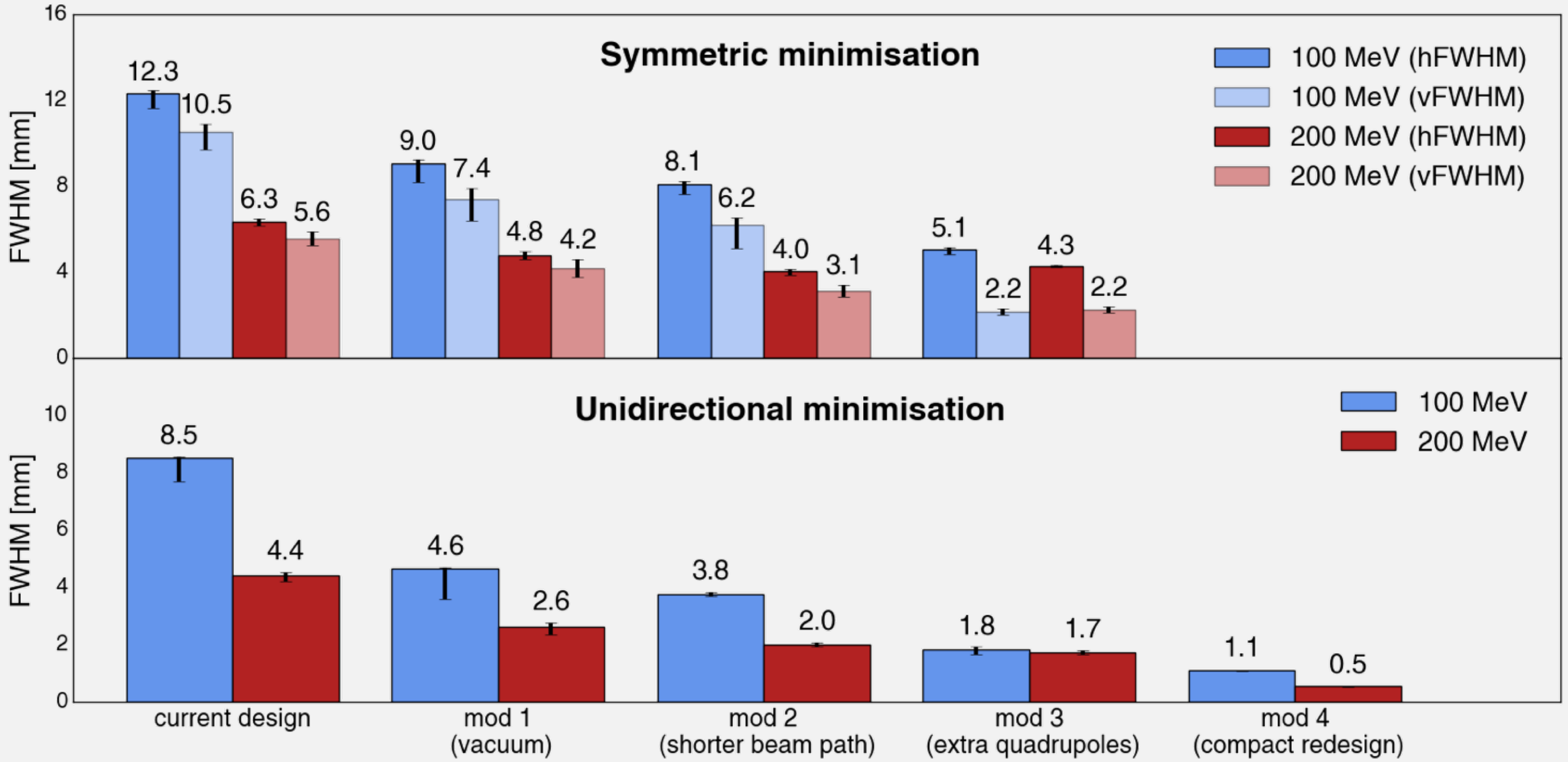
→ magnetically focussed minibeams **cannot be achieved** with **current PBS** nozzle

Study of the PBS nozzle at CPO (2/3)

→ consideration of different **geometry modifications** to find limiting factors



Study of the PBS nozzle at CPO (3/3)



Conclusions from ICPO nozzle study

1) current PBS nozzle at ICPO will **not** be **suitable** for the generation of **magnetically focussed** proton **minibeams**

2) two main limiting factors could be identified:
   - too much air in beam path
   - distance between focussing elements and target (focal length)

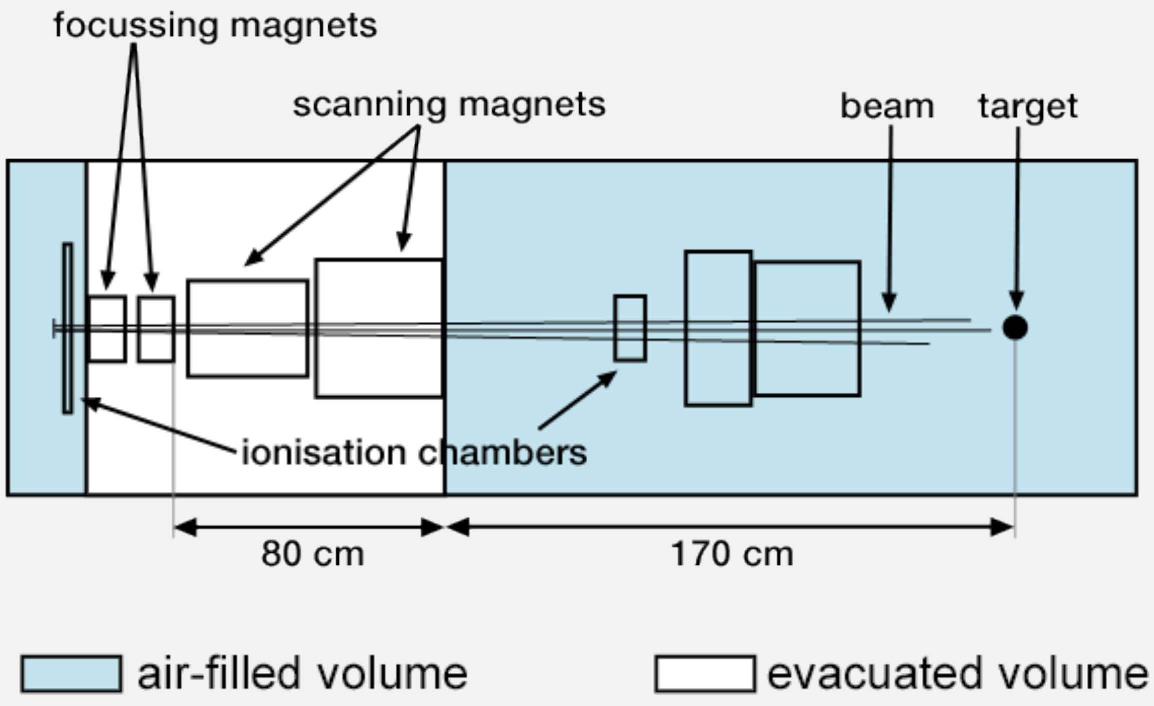
3) any **nozzle** with **similar dimensions** likely **not suitable** either

→ **new, optimised nozzle design needed**

Design of a dedicated minibeam nozzle

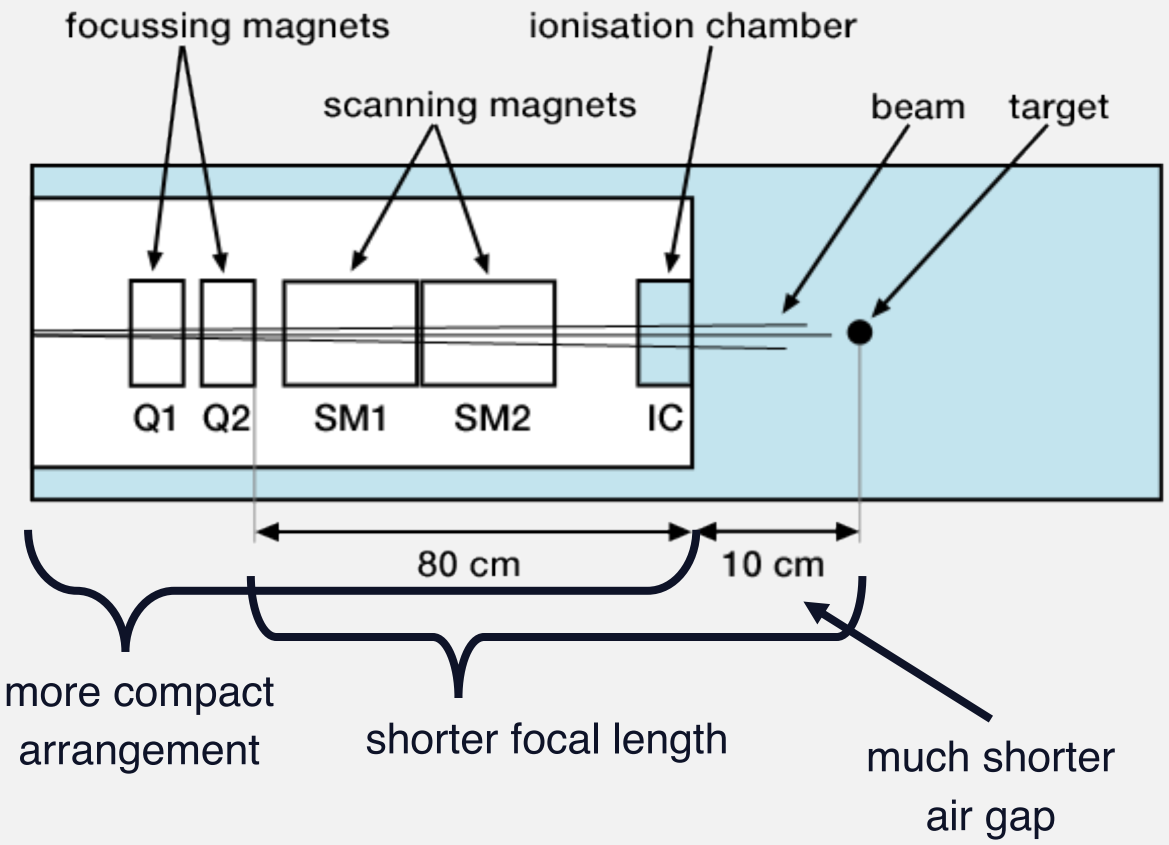
Schneider et al, *Sci Rep*, 2020

current PBS nozzle at ICPO



new minibeam nozzle

Patent application filed (PCT/EP2020/082766)



Performance evaluation

- evaluation of nozzle performance:
  - systematic benchmarking (theoretical beams)
  - beam models of different clinical facilities
- assessment of minimum beam size and target position
- varied parameters:
  - quad field strength (0 T ≤ B1,B2 ≤ 2 T, 51x51 configs)
  - quad orientation (2 configs)
- focus on symmetric minimisation

Performance of the new minibeam nozzle

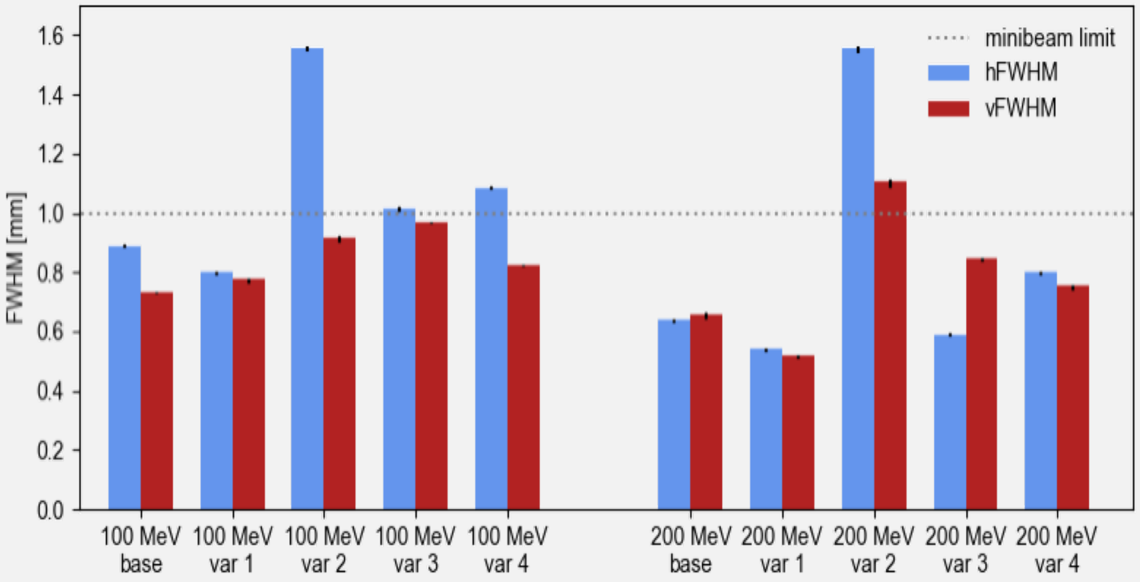
Beam model / accelerator	Energy [MeV]	Min. beam size at target [mm]		Beam model parameters		
		hFWHM	vFWHM	σ_x / σ_y [mm]	$\sigma_{x'}$ / $\sigma_{y'}$ [mrad]	$r_{xx'}$ / $r_{yy'}$
Optimised theoretical source	100	**0.66**	**0.66**	6.5 / 10.0	3.0 / 10.0	-1.0 / -1.0
	200	**0.33**	**0.35**	8.0 / 8.0	7.5 / 3.0	-1.0 / -1.0
ICPO *cyclotron*	100	2.05	1.77	8.89 / 12.99	0.75 / 2.50	-0.80 / -0.95
	200	**0.38**	1.20	3.96 / 5.65	0.20 / 1.50	1.00 / -0.90
RPTC *cyclotron*	100	10.60	4.03	3.88 / 3.29	3.13 / 3.14	0.37 / 0.41
	200	5.35	2.10	4.12 / 3.25	1.62 / 1.62	0.44 / 0.49
MedAustron *synchrotron*	100	2.10	**1.08**	2.09	0.66	0.57
	200	**1.06**	**0.61**	2.71	0.44	0.78
LIGHT *linear accelerator*	100	**0.89**	**0.73**	0.30 / 0.45	0.54 / 0.53	-0.91 / 0.98
	200	**0.64**	**0.66**	0.24 / 0.47	0.20 / 0.45	0.19 / 0.97
LhARA *laser-driven + FFAG*	127	**0.59**	**0.64**	2.5	0.05	0.0

RPTC: Rinecker Proton Therapy Centre - *LIGHT: Linac For Image Guided Hadron Therapy* - *LhARA: Laser-hybrid Accelerator for Radiobiological Applications*

New minibeam nozzle and LIGHT linac

Schneider et al, *Cancers*, 2021

Robustness against beam variations



Different variations of beam parameters leading to emittance doubling:

var 1	beam size x2	var 3	reduced correlation
var 2	divergence x2	var 4	combined variation

Robustness against quad errors

Error type	E [MeV]	Spot position [mm] X	Spot position [mm] Y	Beam size [mm] hFWHM	Beam size [mm] vFWHM
Translational and rotational alignment	100	2.2	3.3	< 0.01	≤ 0.01
	200	2.0	3.0	< 0.01	< 0.01
Field gradient	100	< 0.01	< 0.01	< 0.01	0.02
	200	< 0.01	< 0.01	0.03	0.07

- generally **good tolerance** to **beam variations**
- divergence should be kept small
- **good tolerance** to **quadrupole magnets errors**
- alignment errors are static and can be compensated

→ **robustness** of linac-nozzle combination **demonstrated**

Focussed vs collimated minibeams (1/4)

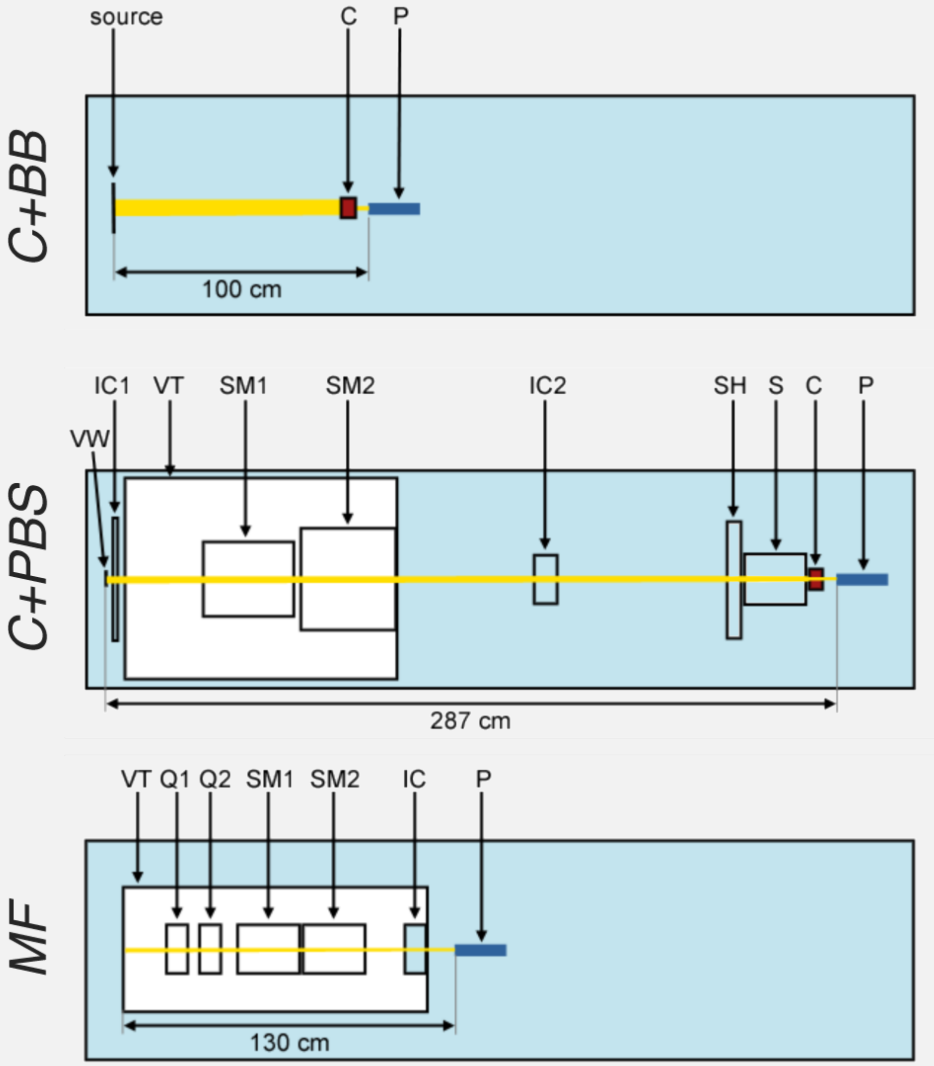
Schneider et al, *Front Phys*, 2021

Comparison of three techniques:

- **collimator** and **broad beam** (C+BB)
- **collimator** and CPO **PBS** nozzle (C+PBS)
- **magnetic focussing** with new nozzle (MF)

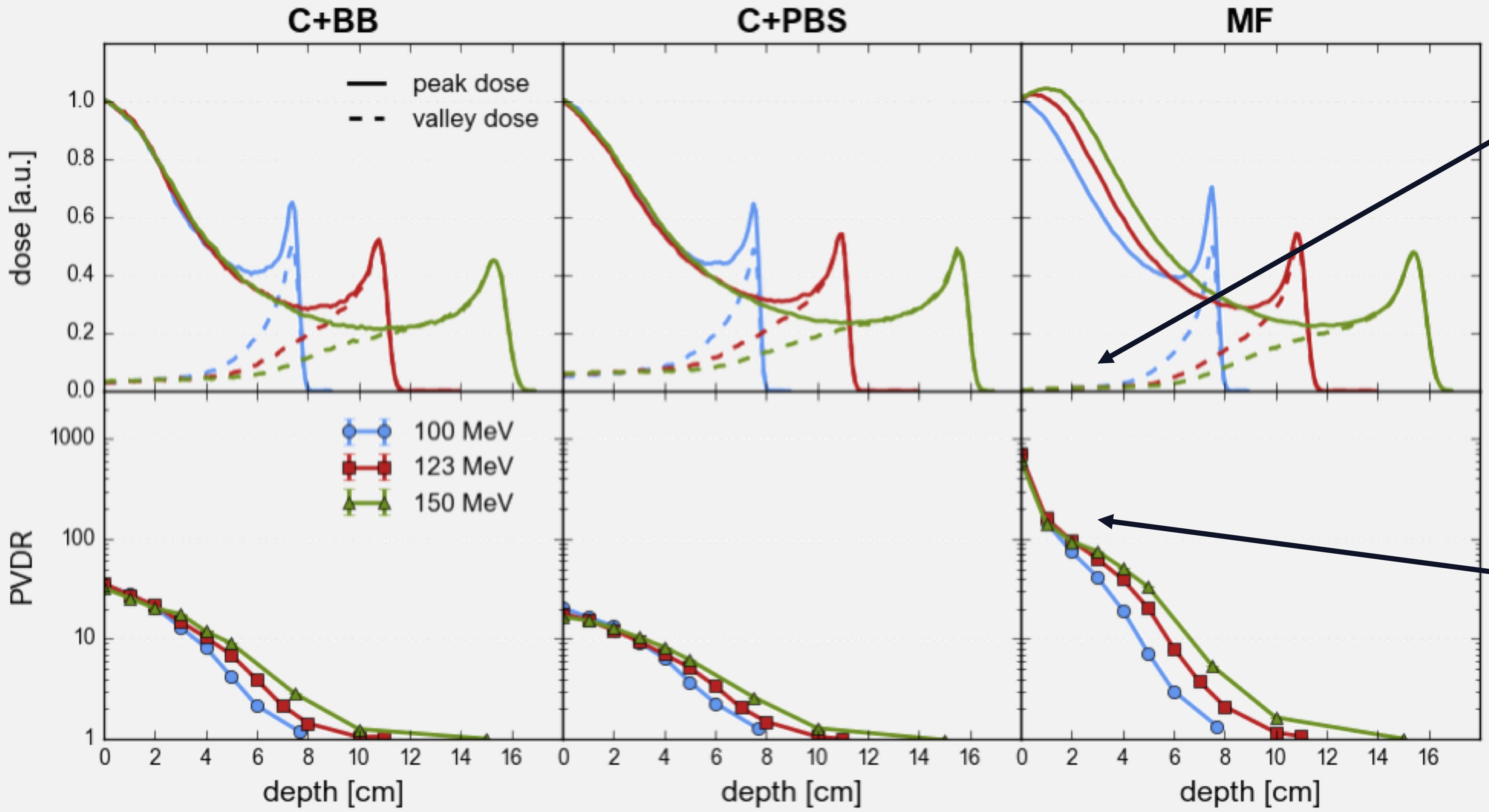
Compared quantities:

- dose distributions
- irradiation efficiency
- neutron production



Focussed vs collimated minibeams (2/4)

Dose distributions in water



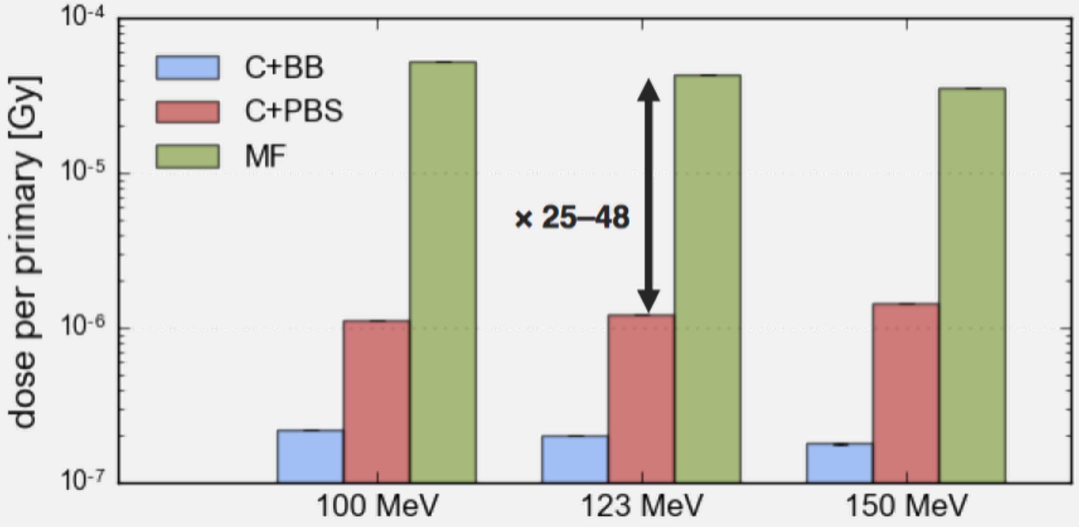
lower valley doses

results in **higher PVDR**

Focussed vs collimated minibeams (3/4)

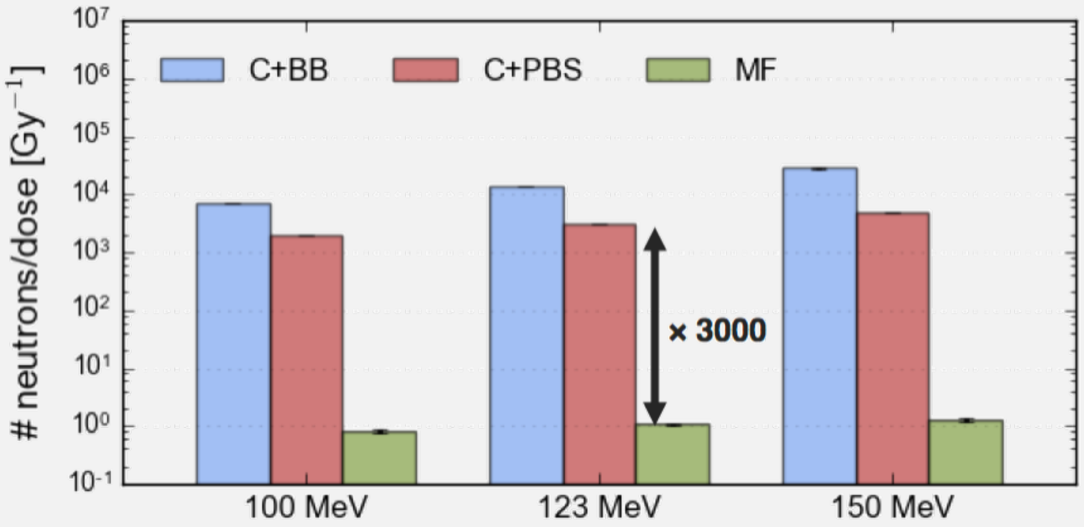
Irradiation efficiency

(dose at Bragg peak depth per primary particle)



Neutron production

(neutron yield per gray deposited at Bragg peak depth)



Focussed vs collimated minibeams (4/4)

	Mechanical collimation	Magnetic focussing
Efficiency	–	+
Flexibility	–*	+
Contamination with secondary particles	–	+
PVDR	+	++
Implementation (at existing facilities)	+	–

*) better with dynamic collimators

→ **optimal implementation** of pMBRT should use **magnetic focussing**

Conclusions (1/2)

- pMBRT very promising new technique
- conventional PT facilities not suitable for minibeam generation

- mechanical collimators:
  - **straightforward** and **universally** applicable
  - successfully implemented at ICPO used in experiments
  - poor flexibility (can be improved with dynamic collimators)
  - inherently inefficient
  - source of secondary particles (such as neutrons)

→ use magnetic focussing instead

Conclusions (2/2)

- **current** PBS nozzles **cannot deliver** magnetically focussed minibeams
- development of **new nozzle** suitable for **magnetically focussed minibeams**
- required conditions achievable with **existing technology** (synchrotrons)
- very good results with new linac LIGHT and LhARA
- maximum flexibility
- magnetic focussing → maximise dose rate → **pMBRT + FLASH**

Perspectives

Minibeam nozzle:

- technical design study on minibeam nozzle + LIGHT (→ prototype)
- further studies on minibeam nozzle + LhARA?
- studies on pMBRT + FLASH

Radiobiology and dosimetry:

- better understand radiobiological mechanisms underlying pMBRT
- determine optimal irradiation parameters (beam size, ctc, …)
- dosimetry standards and guidelines/protocols

Transition to clinical applications:

- development of treatment planning system
- move towards first clinical trials (protocol under development)

Thank you for your attention!

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