Reducing uncertainties in particle therapy – status and perspectives

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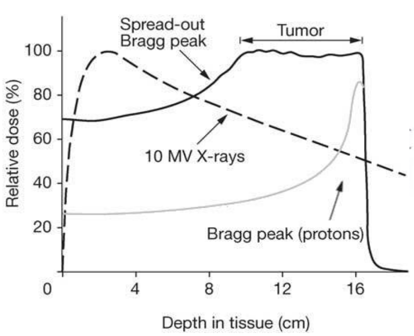
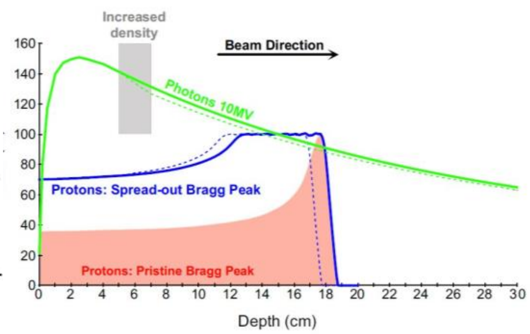
Challenges in clinical practice of ion therapy

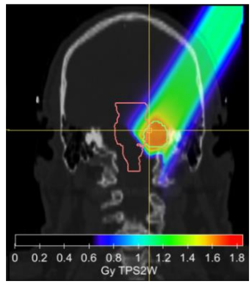
Improved physical selectivity BUT increased sensitivity to uncertainties in beam delivery
- Anatomical changes (inter- and intra-fractions)
- Tissue stopping power (relative to water, SPR)



L. Grevillot



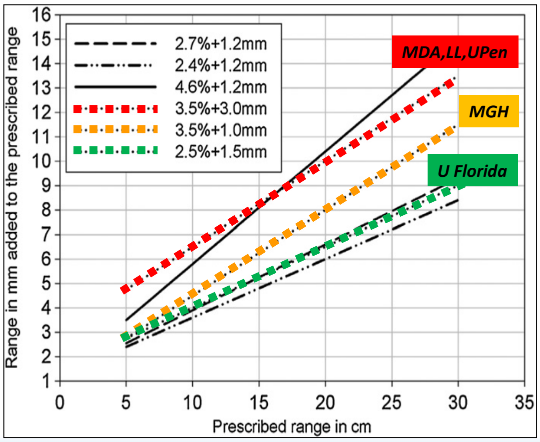
M. Engelsman et al, Seminars Rad. Onc. 2013



J. Bauer et al, HIT

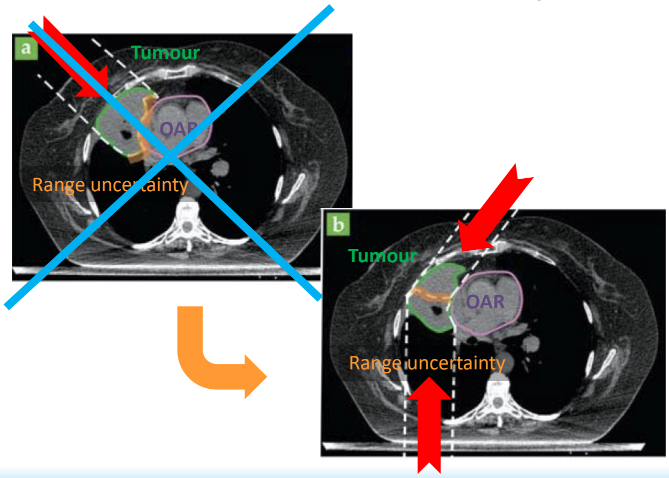
Mitigating range uncertainties in clinical practice

Usage of safety margins (non-isotropic) ≈ 2.5-3.5% + 1-3 mm



Paganetti, PMB 2012

and conservative choice of beam angles

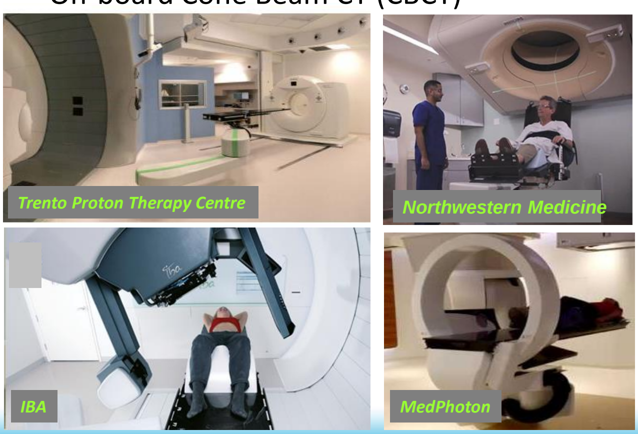


Polf and Parodi, Phys Today 2015

In-room imaging for ion beam therapy

Anatomical imaging (as in modern photon therapy)

- Horizonzal/vertical CT
- On-board Cone Beam CT (CBCT)



- *Magnetic Resonance Imaging ?*

Source: TPC, Northwestern Medicine, Oncoray Dresden, MGH Boston, IBA, MedPhoton; Hoffmann …Parodi, RadOnc 2020

Beyond (CB)CT/MR imaging for ion therapy planning

Theory:

$$\mathrm{SPR} \propto \rho_e \frac{\ln\left(\frac{2m_e c^2\beta^2}{I(1-\beta^2)}\right)-\beta^2}{\ln\left(\frac{2m_e c^2\beta^2}{I_{water}(1-\beta^2)}\right)-\beta^2}$$

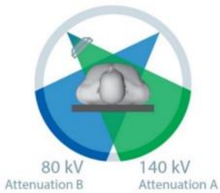
Imaging of tissue stopping power properties (SPR, specific to ion beam therapy)

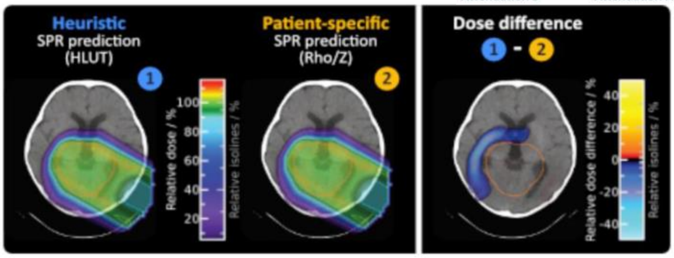
Dual Energy X-ray CT (DECT)

Commercially available

Enables patient-specific calibration

Improves SPR estimation accuracy



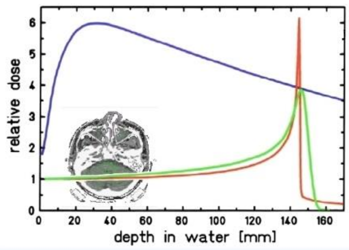


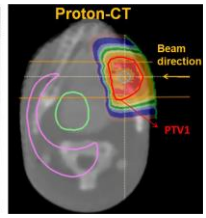
Ion transmission imaging

Under development

Enables direct SPR estimation

Low-dose imaging





Oancea&Schulte, IEEE MIC 2018

Wolfahrt et al, IJROBP 2017;
Niepel…Landry, Parodi, PMB 2020, Berthold et al, IJROBP 2021

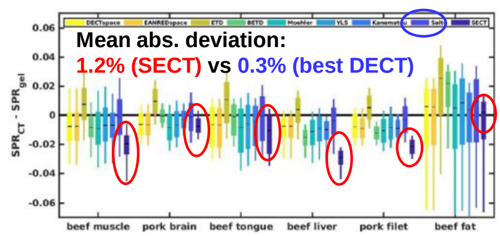
Dickmann,…Parodi, Dedes, Landry, PMB 2021

In-room imaging for ion beam therapy

Imaging of tissue stopping power properties (SPR, specific to ion beam therapy)

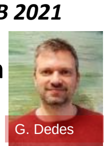
Confirmation of promising DECT SPR-based estimation in tissue samples regardless of used conversion method

GRK 2274 DFG

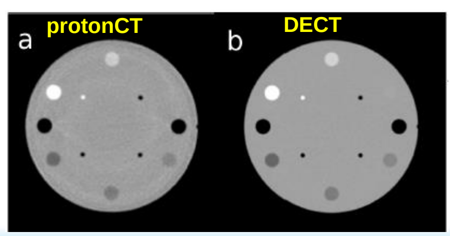


Niepel, Stanislawski…, Landry, Parodi, PMB 2021

Competitive performance of proton CT prototype vs dual-source DECT



MAPE: 0.55% vs 0.67% at ~20 reduced dose
(though not yet dose-optimized)



Dedes, …, Landry, Parodi, PMB 2019

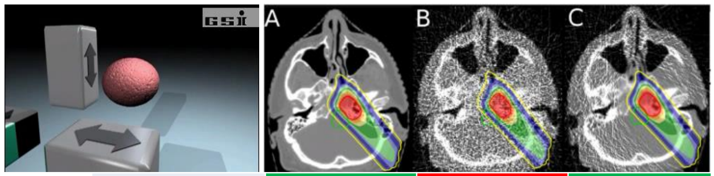
In-room imaging for ion beam therapy

Imaging of tissue stopping power properties (SPR, specific to ion beam therapy)

Further dose reduction possibilities in combination with fluence modulation

Dedes…Parodi, Landry Med Phys 2018

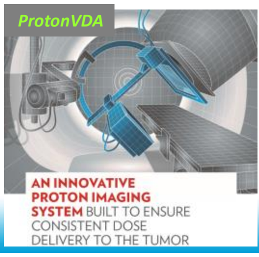
Dickmann,…Parodi, Landry, Dedes PMB 2020



	A	B	C
noise in beam	Low	High	Low
dose outside beam	High	Low	Low

First commercial prototype close to clinical translation for proton radiography

Dedes et al SU-J-207-1 (Sunday, 7/10/2022)



Enhancement of in-room CBCT with proton/ion radiography or dual energy/spectral imaging capabilities?

DFG Project HIGH-ART
(PI: C. Gianoli & K. Parodi)

Gianoli…Parodi, PMB 2019&2020

GRK 2274 DFG

PhD project G. Hu

(in collaboration with LMU Klinikum, Manuscript submitted to Front Oncol)

PET/PG imaging for on-site treatment verification

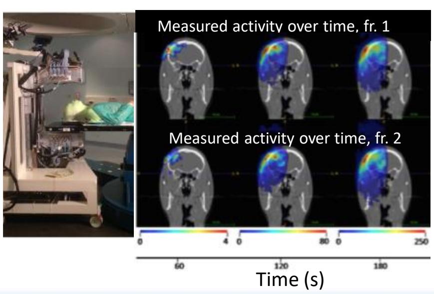
Detection of energetic photons resulting from nuclear interactions

In-beam PET

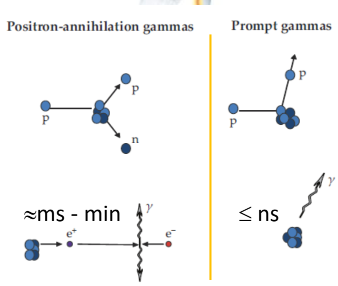
3D imaging of irradiation-induced β^+-activity ideally during irradiation, integrating signal over ≈ s – min

PG imaging

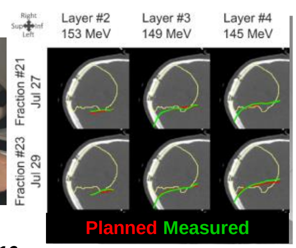
So far 1-2D detection of irradiation induced PG after mechanical collimation, integrating signal of a few pencil beams (≈ ms – s)



Ferraro et al, Sci Rep 2018



Richter et al, Radiother Oncol 2016



Xie et al, IJROBP 2017

Tattenberg et al, WE-E-BRA-5 (Wednesday 7/13/2022)

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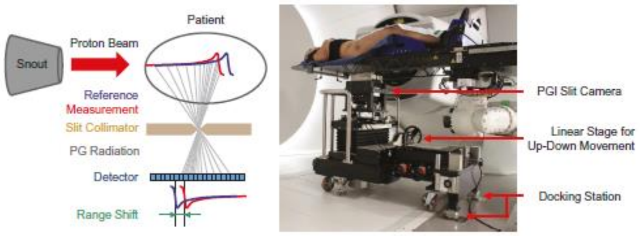
Confirmation of improved SPR determination



Int J Radiation Oncol Biol Phys, Vol. 111, No. 4, pp. 1033–1043, 2021

First-In-Human Validation of CT-Based Proton Range Prediction Using Prompt Gamma Imaging in Prostate Cancer Treatments

Jonathan Berthold, MSc,*,† Chirasak Khamfongkhruea, MSc,*,‡ Johannes Petzoldt, PhD,§ Julia Thiele,‖ Tobias Hölscher, MD,‖ Patrick Wohlfahrt, PhD,*,† Nils Peters, MSc,*,† Angelina Jost, BSc,*,# Christian Hofmann, PhD,** Guillaume Janssens, PhD,§ Julien Smeets, PhD,§ and Christian Richter, PhD*,†,‖,††

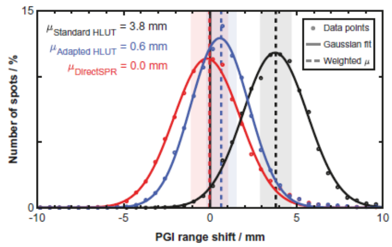


Fig. 3. Weighted histogram of prompt gamma imaging (PGI) range shifts for the 3 investigated range prediction approaches combining all fractions and patients. The shaded regions correspond to $\pm u_{\mu_{PGI}}$ (2σ) of the respective mean values. The Gaussian fit serves as visual guidance and highlights the normal distribution of the data.

Niepel et al, TH-F-201-6 (Thursday, 7/14/2022)

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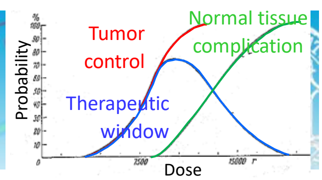
Expected clinical impact of range uncertainty reductions…



S. Tattenberg PhD project, MGH & LMU

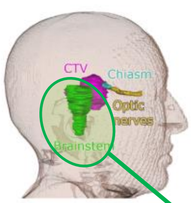
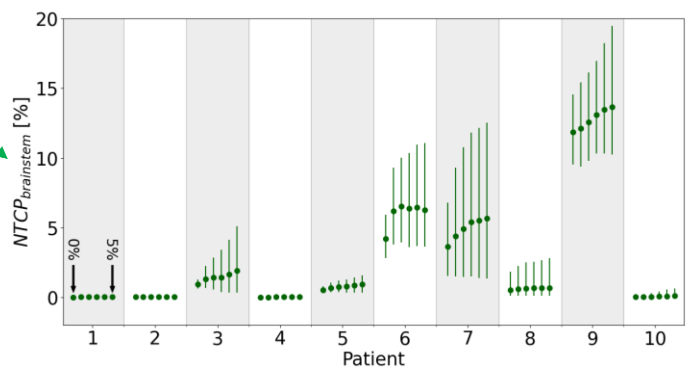


FIGURE 1 The relevant structures for one of the studied skull base cases (patient 5). The brainstem abutted the CTV in all cases while the distance between CTV and optic chiasm varied between patients

NTCPs have been quantified as a function of range uncertainty



Received: 21 February 2021 | Revised: 4 July 2021 | Accepted: 7 July 2021
DOI: 10.1002/mp.15097

RESEARCH ARTICLE

MEDICAL PHYSICS

Proton range uncertainty reduction benefits for skull base tumors in terms of normal tissue complication probability (NTCP) and healthy tissue doses

Sebastian Tattenberg[1,2] | Thomas M. Madden[2] | Bram L. Gorissen[3] | Thomas Bortfeld[2] | Katia Parodi[1] | Joost Verburg[2]

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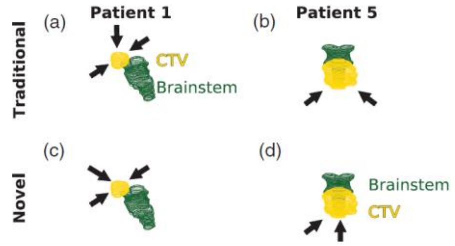
…and novel beam arrangements



MEDICAL PHYSICS

The International Journal of Medical Physics Research and Practice

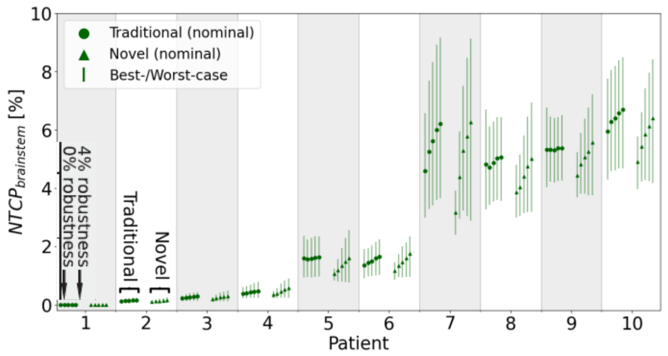
RESEARCH ARTICLE | Open Access

Range uncertainty reductions in proton therapy may lead to the feasibility of novel beam arrangements which improve organ at risk sparing

Sebastian Tattenberg, Thomas M. Madden, Thomas Bortfeld, Katia Parodi, Joost Verburg

First published: 31 March 2022 | https://doi.org/10.1002/mp.15644

Novel beam arrangements will have additional benefits



S. Tattenberg PhD project, MGH & LMU

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Study	Site	NTCP	ΔRange uncertainty [pp]	ΔNTCP [pp]
Van de Water et al.[1]	Oropharynx	Various	2 (3%-1%)	μ = 0.4
Wagenaar et al.[2]	H&N	Various	1	μ = 0.9
Tattenberg et al.[3,4]	Clivus	Optic chiasm (blindness)	3 (4%-1%)	≤0.9 (nominal) ≤2.2 (worst-case)
	Clivus	Brainstem necrosis		≤1.3 (nominal) ≤2.9 (worst-case)
	Brain & skull base	Brainstem necrosis		≤1.8 (nominal) ≤3.2 (worst-case)

1: Van de Water S, van Dam I, Schaart D, Al-Mamgani A, Heijmen B, Hoogeman M. The price of robustness; impact of worst-case optimization on organ-at-risk dose and complication probability in intensity-modulated proton therapy for orpharyngeal cancer patients. *Radiother Oncol.* 2016;120(1):56-62.
2: Wagenaar D, Kierkels R, Van der Schaaf A, Meijers A, Scandurra D, Sijtsema N, Korevaar E, Steenbakkers R, Knopf A, Langendijk J, Both S. Head and neck IMPT probabilistic dose accumulation: Feasibility of a 2 mm setup uncertainty setting. *Radiother Oncol.* 2020;54:45-52.
3: Tattenberg S, Madden T, Gorissen, B L, Bortfeld T, Parodi K, Verburg J. Proton range uncertainty reduction benefits for skull base tumors in terms of normal tissue complication probability (NTCP) and healthy tissue doses. *Med Phys.* 2021;48(9):5356-5366.
4: Tattenberg S, Madden T, Bortfeld T, Parodi K, Verburg J. Range uncertainty reductions in proton therapy may lead to the feasibility of novel beam arrangements which improve organ-at-risk sparing . *Med Phys.* 2022; in print.

Courtesy S. Tattenberg

But biological implications have to be considered…

Can We Advance Proton Therapy for Prostate? Considering Alternative Beam Angles and Relative Biological Effectiveness Variations When Comparing Against Intensity Modulated Radiation Therapy

Tracy Underwood, DPhil, Drosoula Giantsoudi, PhD, Maryam Moteabbed, PhD, Anthony Zietman, MD, Jason Efstathiou, MD, DPhil, Harald Paganetti, PhD

International Journal of Radiation Oncology biology • physics
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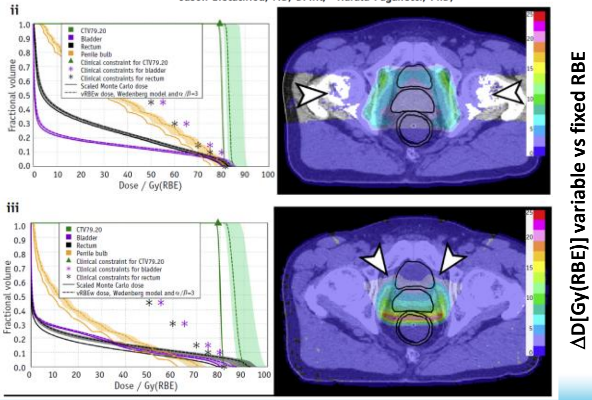


Int J Radiation Oncol Biol Phys, Vol. 95, No. 1, pp. 454–464, 2016

RESEARCH ARTICLE | Open Access

Range uncertainty reductions in proton therapy may lead to the feasibility of novel beam arrangements which improve organ at risk sparing

Sebastian Tattenberg, Thomas M. Madden, Thomas Bortfeld, Katia Parodi, Joost Verburg

First published: 31 March 2022 | https://doi.org/10.1002/mp.15644
MEDICAL PHYSICS
The International Journal of Medical Physics Research and Practice

TABLE 3 The mean dose-averaged linear energy transfer (LET_d) within the brainstem for all 10 cases

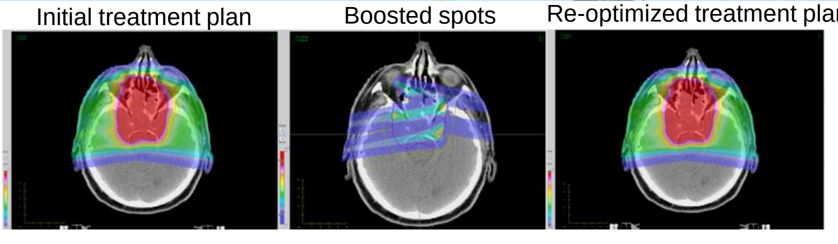
Patient #	LET_d [keV/μm] Traditional	Novel
1	5.5	5.2
2	3.3	3.3
3	3.1	3.7
4	5.2	5.1
5	4.6	6.1
6	2.7	3.1
7	2.5	2.7
8	4.0	5.7
9	4.0	5.7
10	4.0	4.3

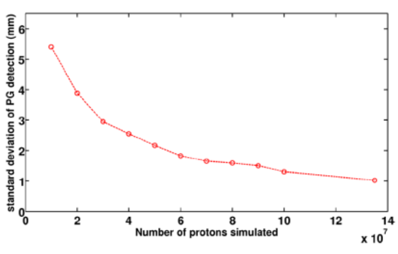
The mean dose-averaged linear energy transfer (LET_d) within the brainstem for all 10 cases included in this study. All values concern the nominal scenario of the treatment plan only robust to setup errors of ±2 mm.

Toward new treatment planning strategies accounting for range verification and biological effects

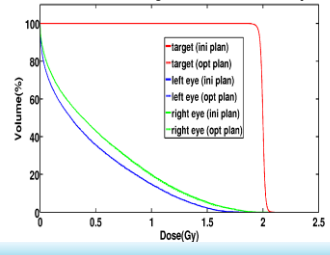
Range retrieval accuracy and precision crucially depend on PB statistics and PG-dose correlation

Initial treatment plan | Boosted spots | Re-optimized treatment plan

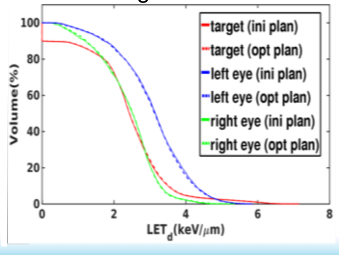




DVH of the target and nearby OARs

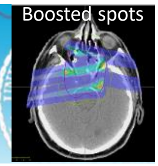


Dose average LET distribution

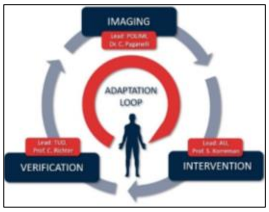


Tian, …Parodi, PMB 2018, 2019, 2020

Toward new treatment planning strategies accounting for range verification and biological effects

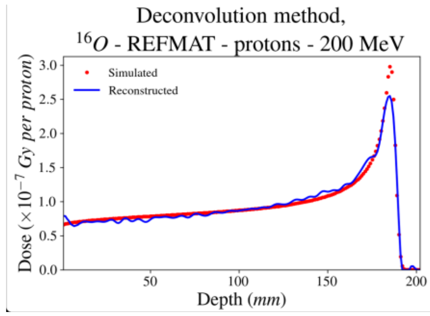


Invert prediction to estimate dose from PG for monitored high statistics PBs & put back in progressive plan adaptation



PhD project of Beatrice Foglia

Foglia…Parodi, Pinto, presented @PTCOG 2022



And explore tradeoffs in number of high statistics PB for PG monitoring and other considerations (eg. biology from LET)

DFG Deutsche Forschungsgemeinschaft

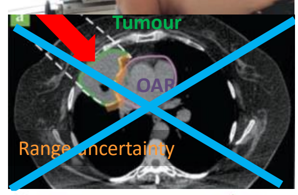
DFG Project
(PI: K. Parodi, K.H. Küfer, C. Thieke)

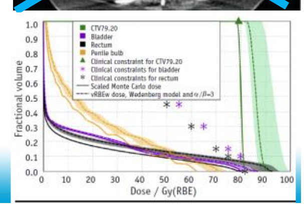
M. De Simoni

M. Pinto

Z. Huang

Conclusion & Outlook





- Promising techniques for reduction of range uncertainties in clinical practice close to or just starting clinical translation & evaluation
- Reduction of range uncertainties at planning & delivery stage will enable more accurate dose delivery and likely impact clinical outcome
- Understanding of biological uncertainties and development of reliable models is mandatory to fully exploit the benefit of range uncertainty reduction, and all information could be used in new planning strategies

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LMU Department of Experimental –Medical Physics

Collaborations

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- R. Schulte et al, Loma Linda University
- T. Bortfeld, J. Verburg, MGH
- E. Traneus, R. Nilsson, RaySearch
- F. Verhaegen, MAASTRO
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- F. Schwarz, T. Kröncke, Uniklinikum Augsburg

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