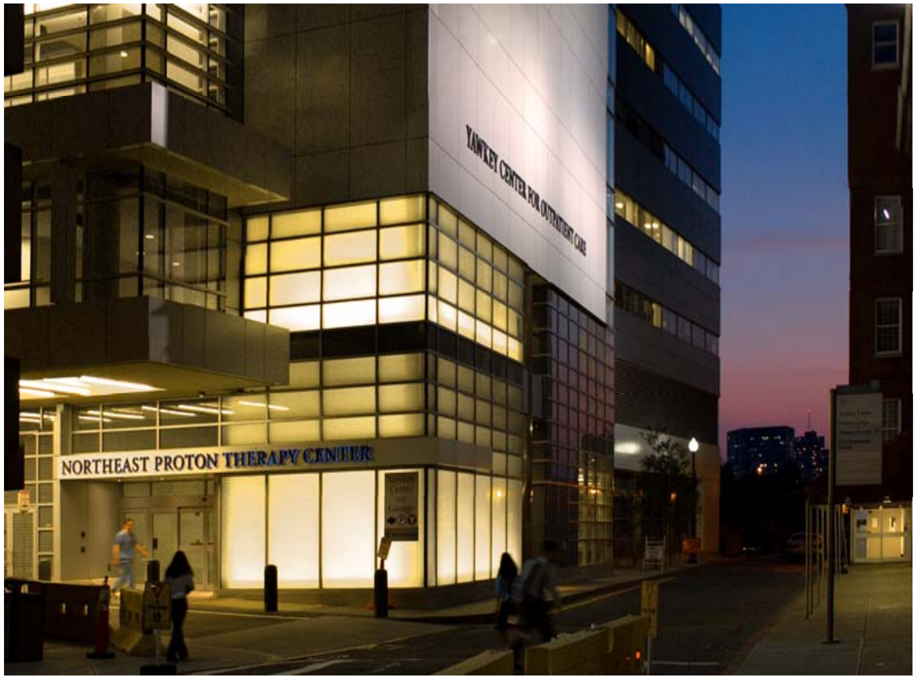
CONNECTICUT AREA MEDICAL PHYSICS SOCIETY
a chapter of the
AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE

Remaining physics challenges in proton therapy



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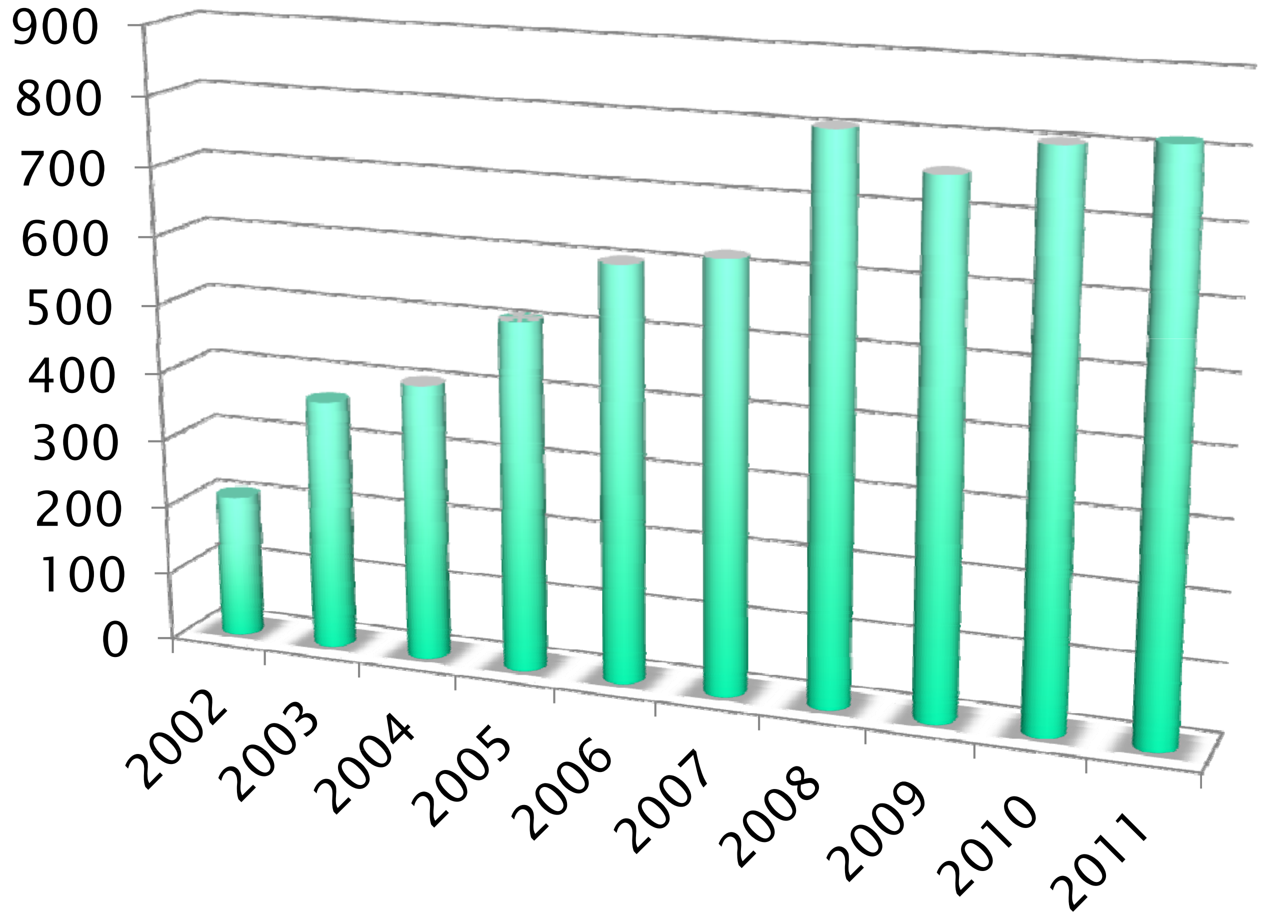
Disclosures

Work funded by the National Cancer Institute

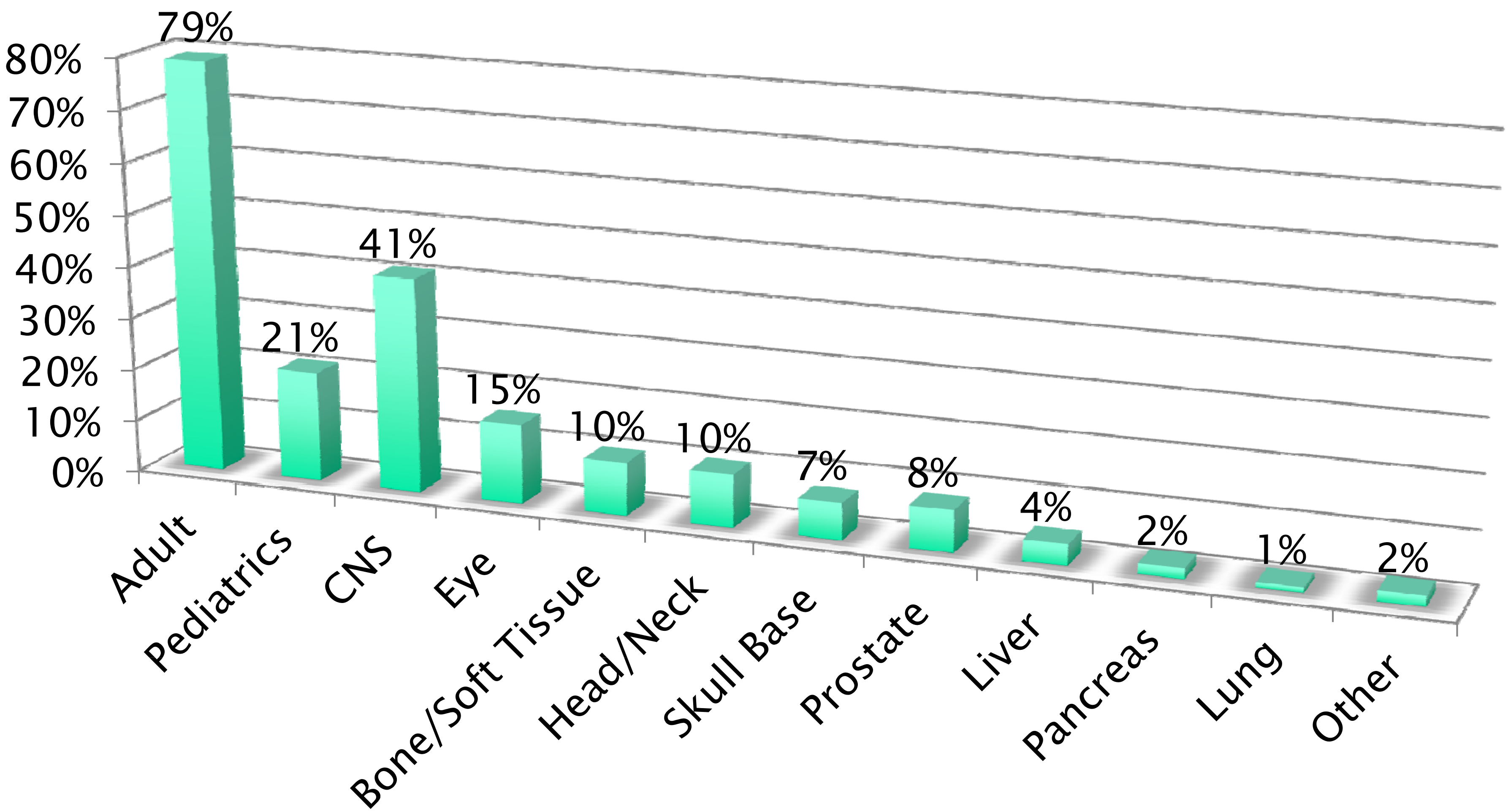
P01 CA 02139
R01 CA 111590
R01 CA 140735
C06 CA 059267

Massachusetts General Hospital, Boston

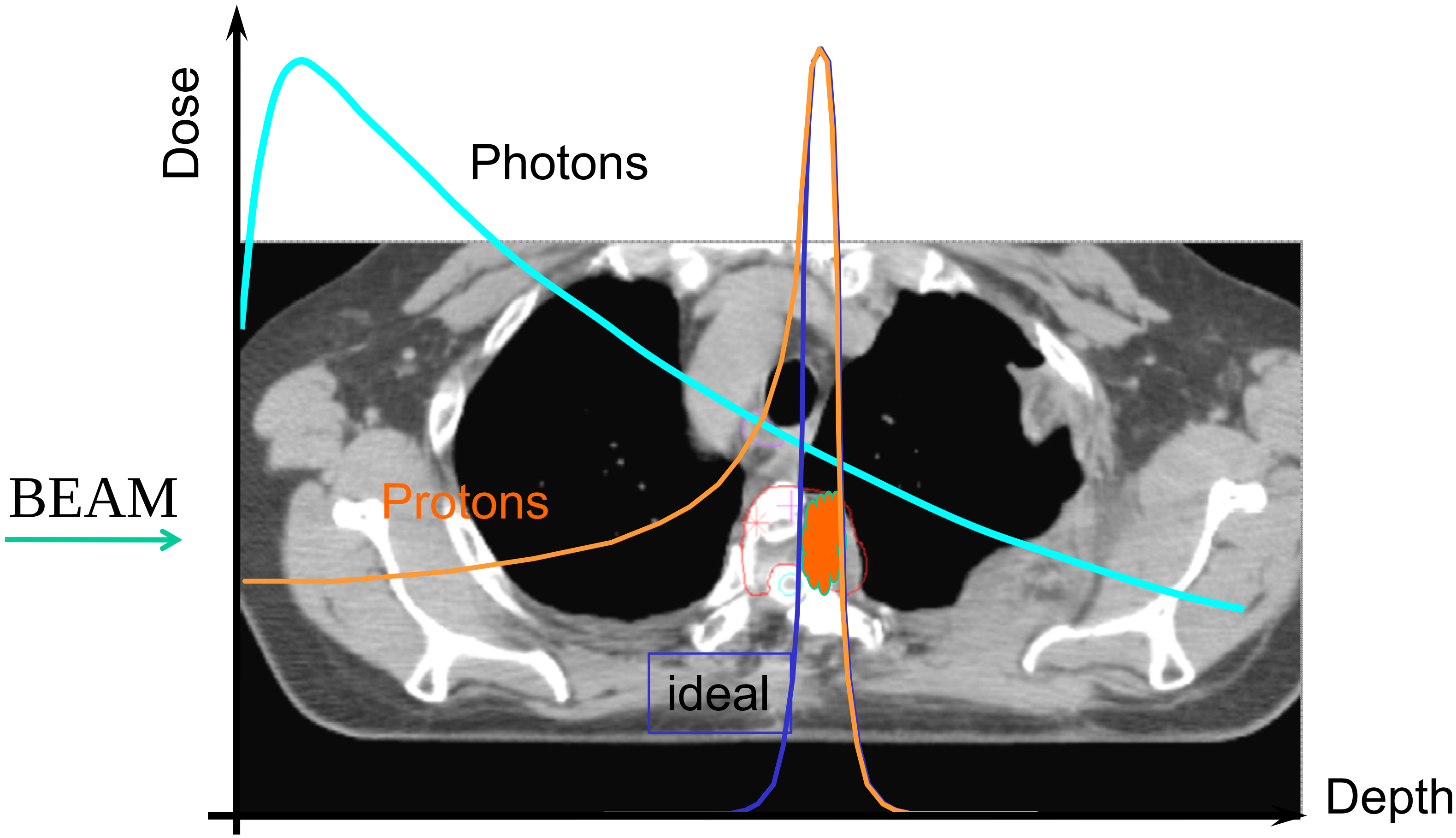


~800 patients per year

Massachusetts General Hospital, Boston

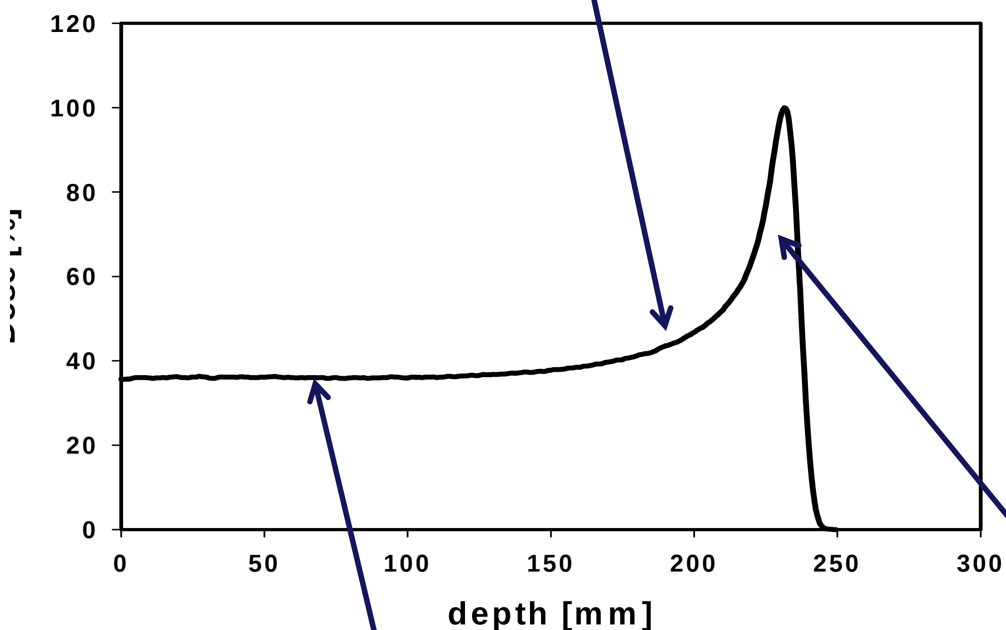


The Ideal Dose Distribution



Proton physics - The Bragg curve

increase in dE/dx as proton slows down



1) Energy loss

collisions with atomic electrons

2) Energy loss; fluence reduction

nuclear interactions

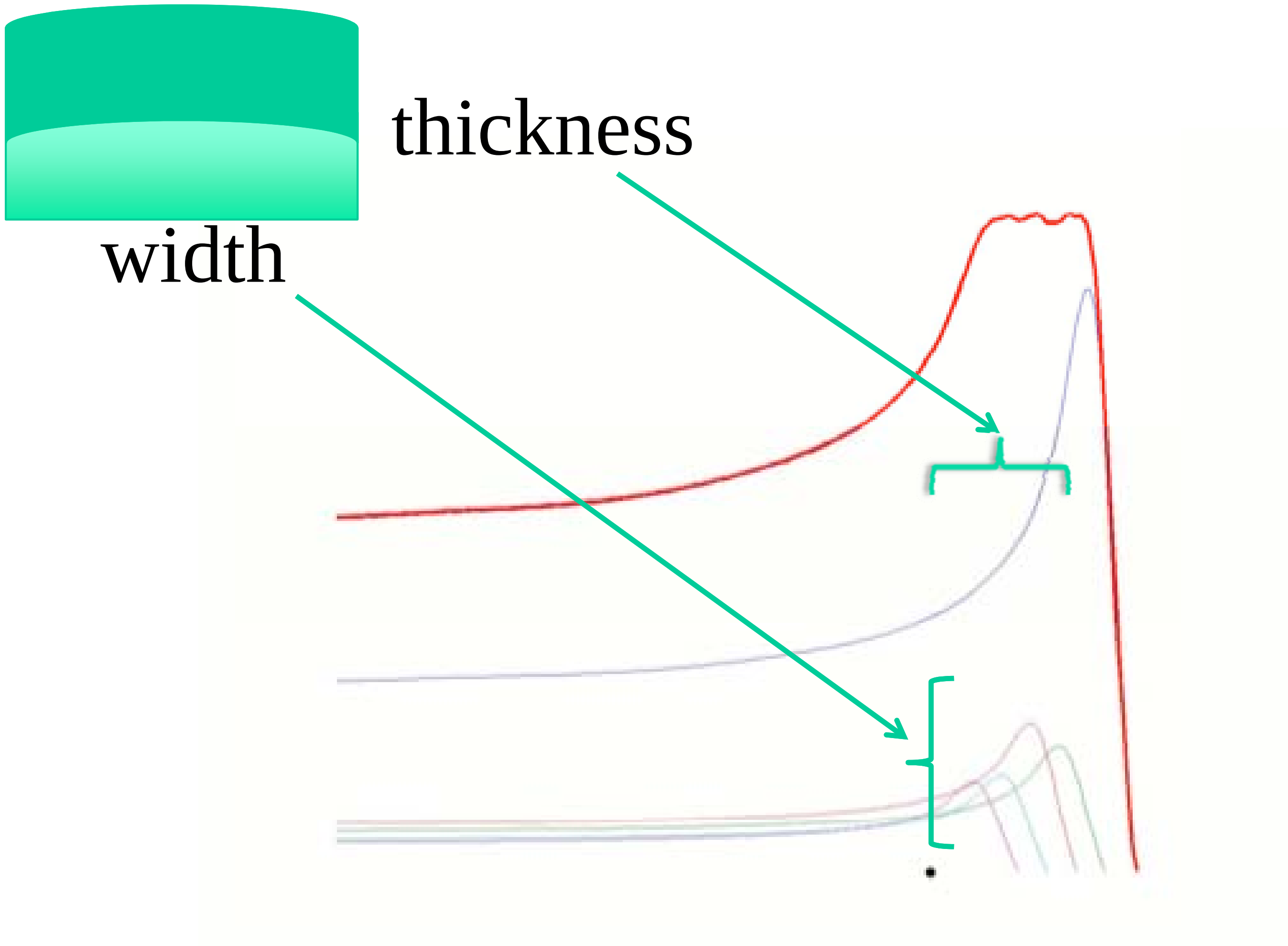
3) Scattering

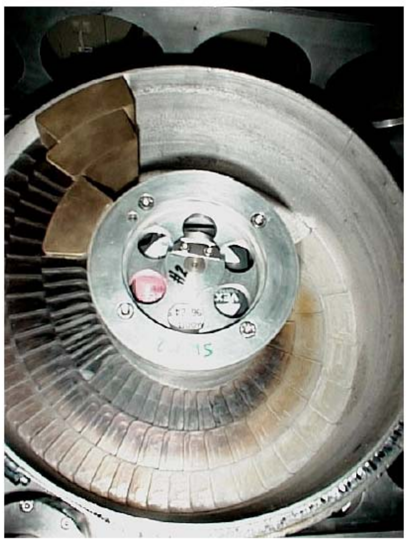
multiple Coulomb scattering

width due to range straggling

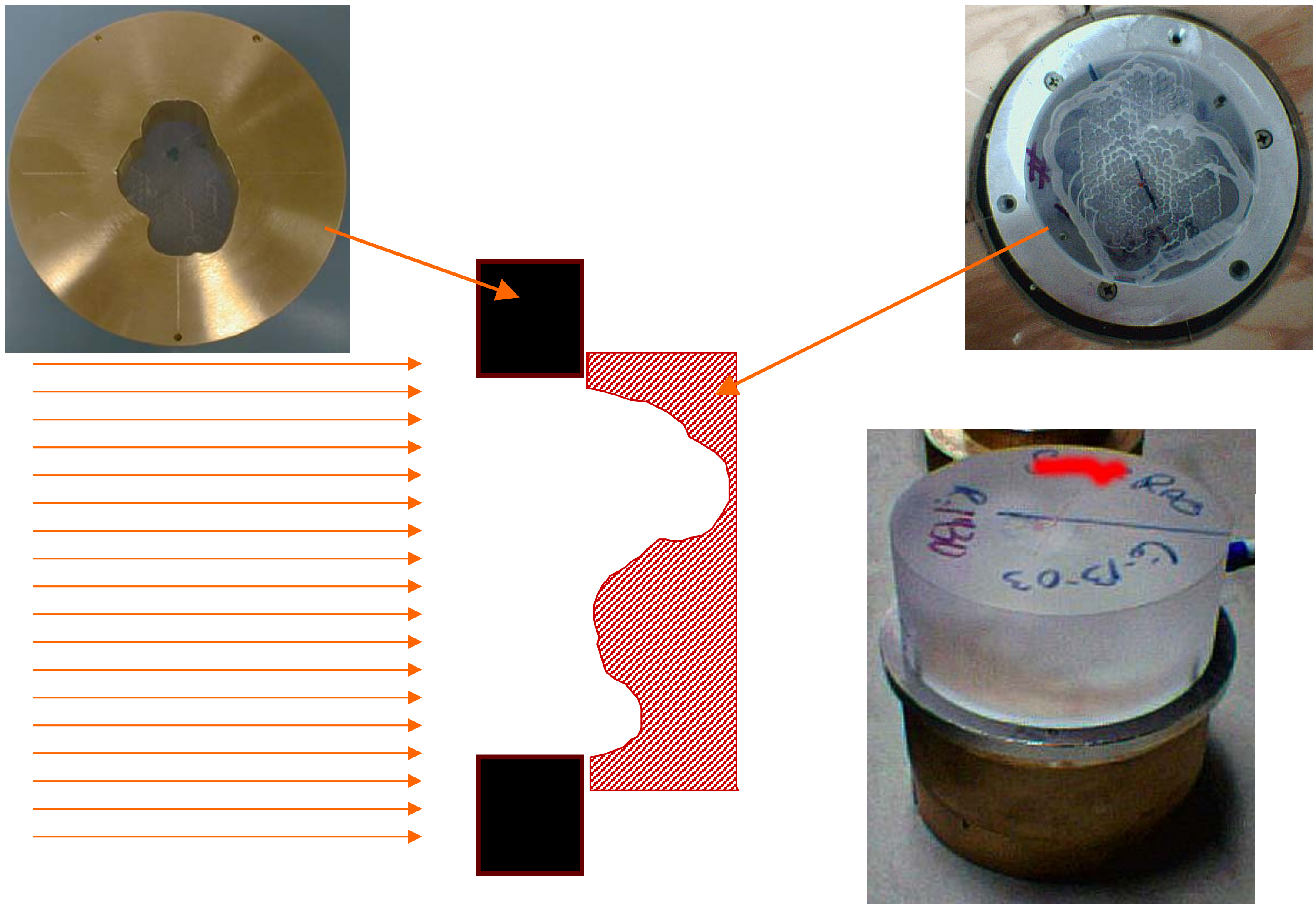
includes contribution from secondary protons

Spread-out Bragg Peak

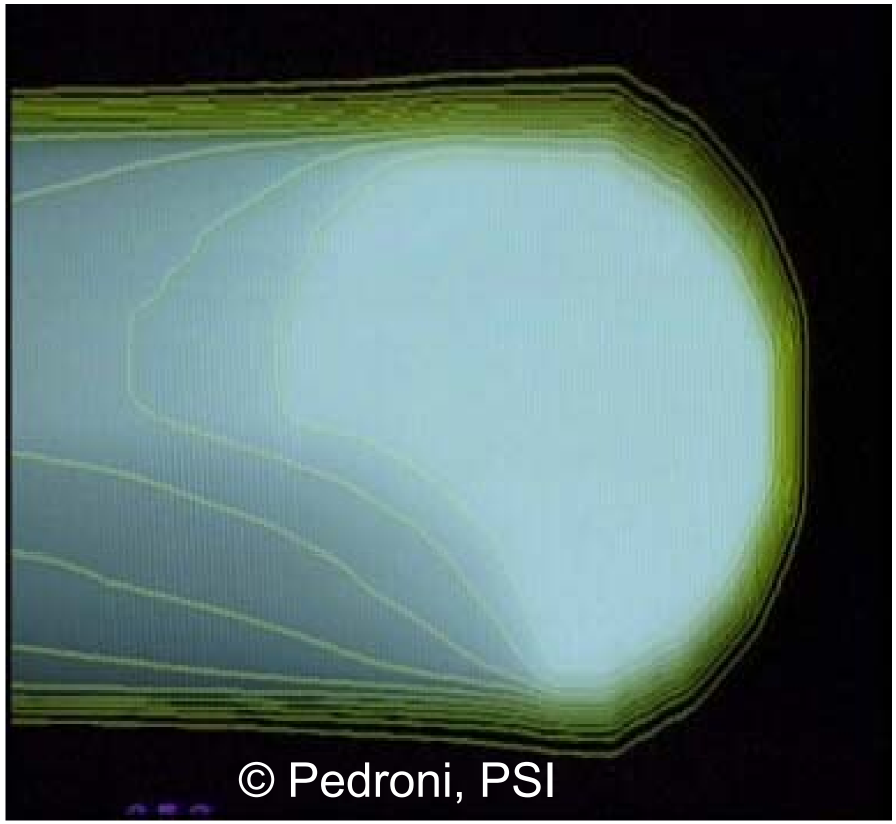




Aperture and Compensator

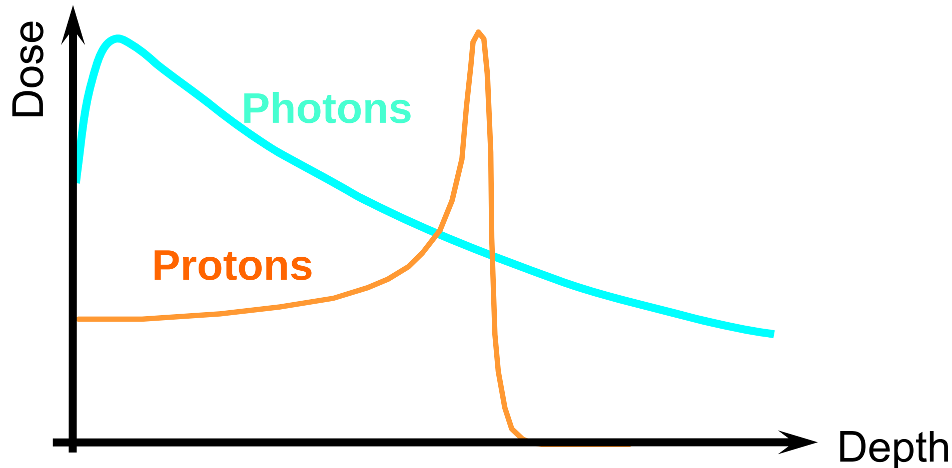


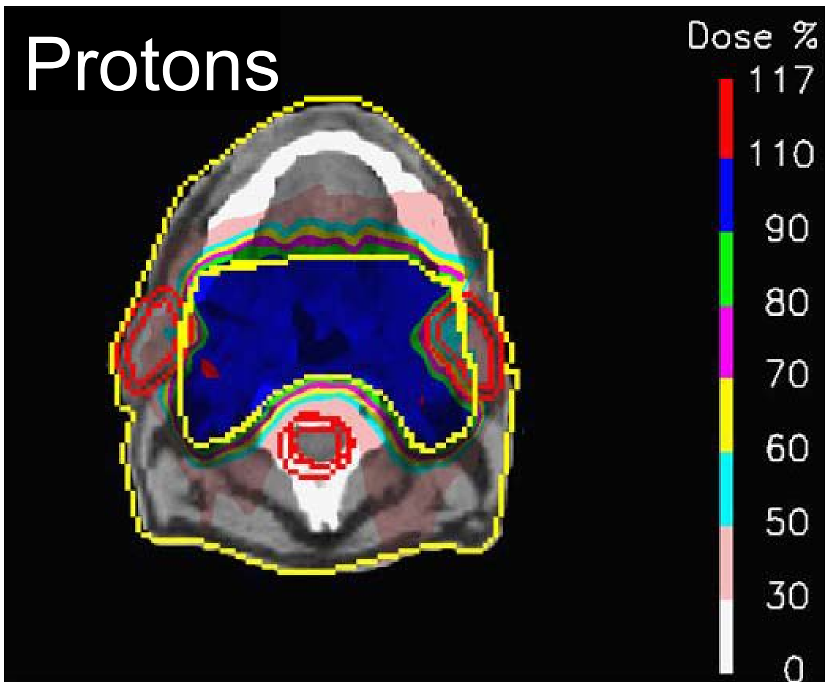
Pencil Beam Scanning

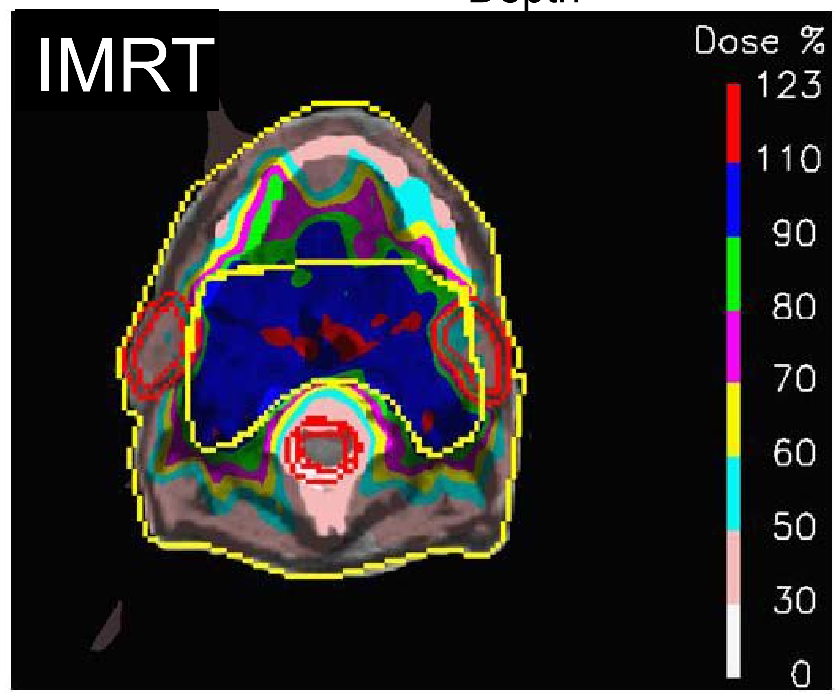


potential for intensity-modulated proton therapy (IMPT)

Introduction







Main proton advantage 1: The 'integral dose' difference : 2-3
Main proton advantage 2: The end of range

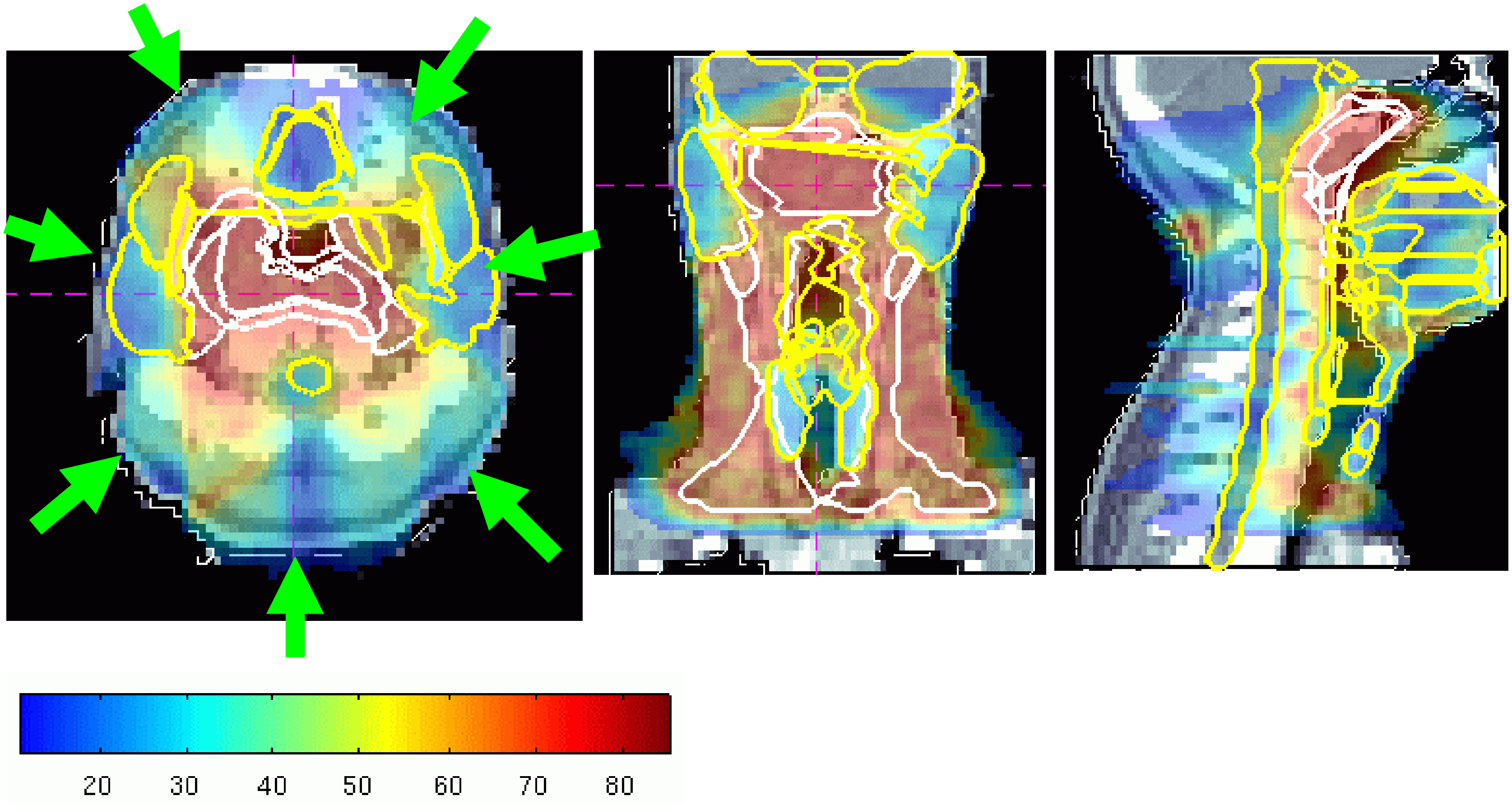
Remaining physics challenges in proton therapy

- Utilizing the integral dose advantage
- Predicting the range in the patient to within 1-3 mm
- Validating the dose in the patient

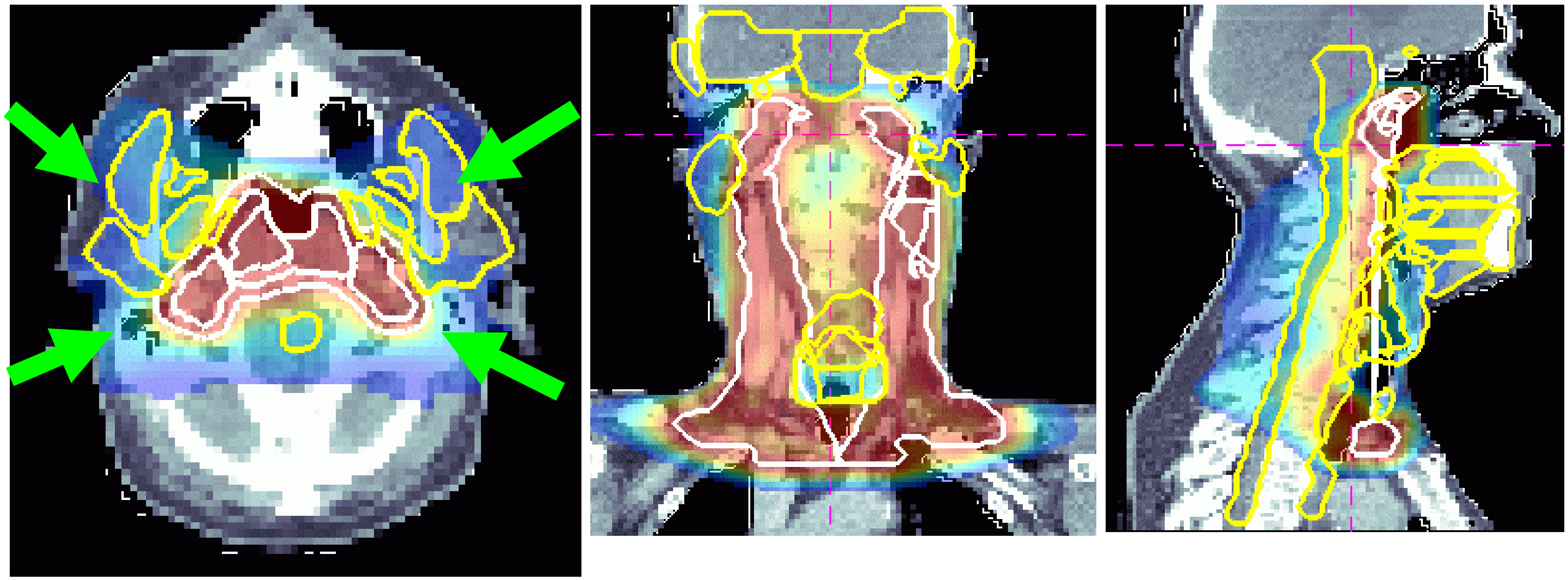
Integral dose

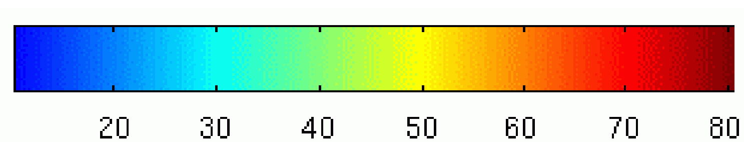
IMRT plan

(7 coplanar photon beams)



IMPT plan
(4 coplanar proton beams)



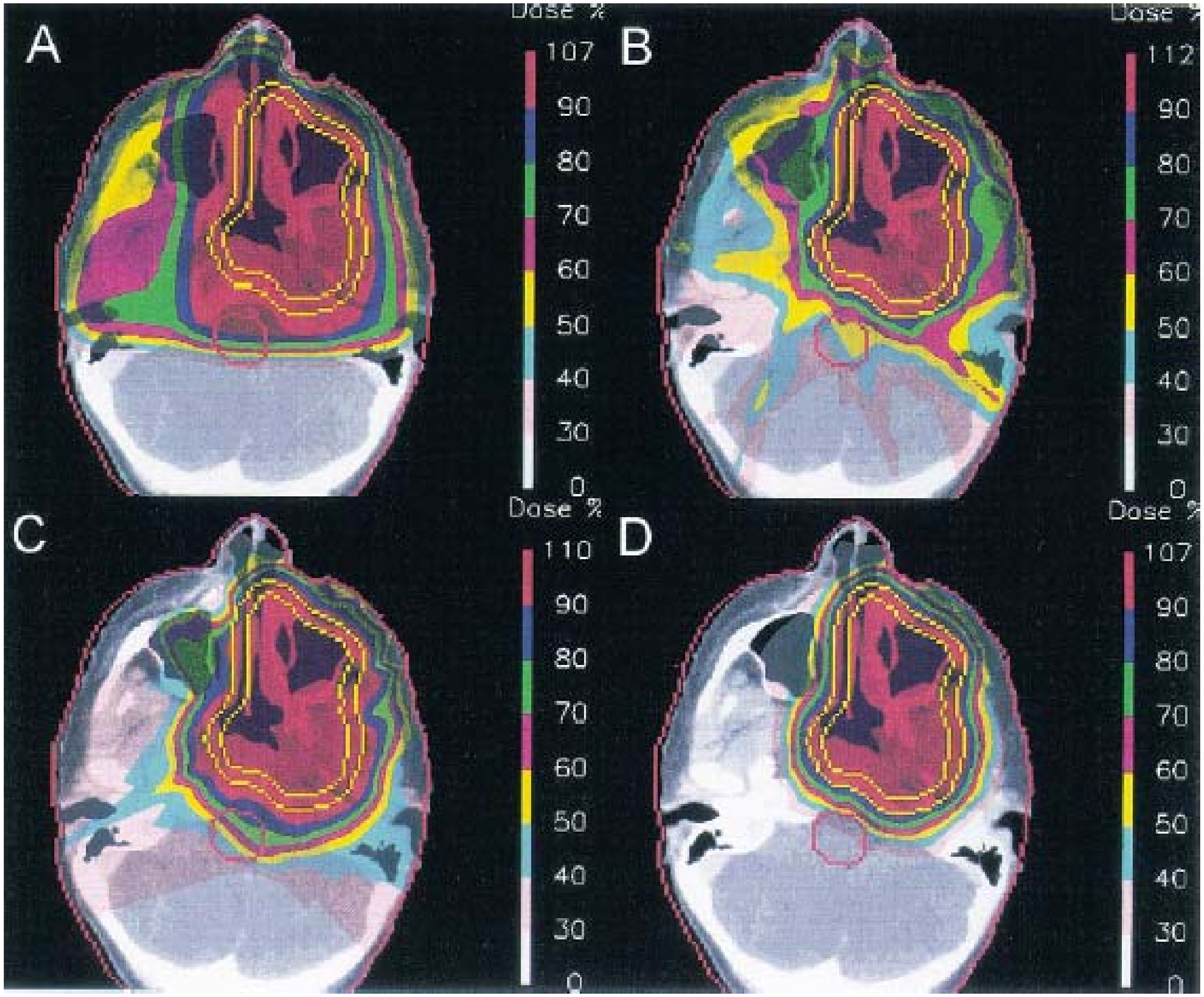


Integral dose

Rhabdomyosarcoma of Paranasal Sinus (7 y old boy)

6 MV Photons (3 field)

160 MeV Protons (2 field)

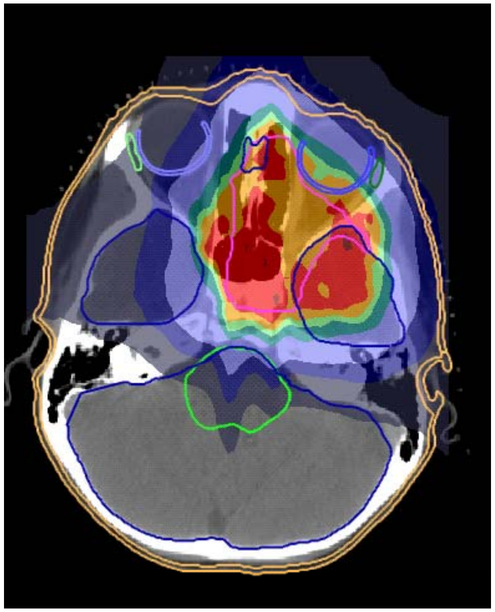


Photon IMRT (9 field)

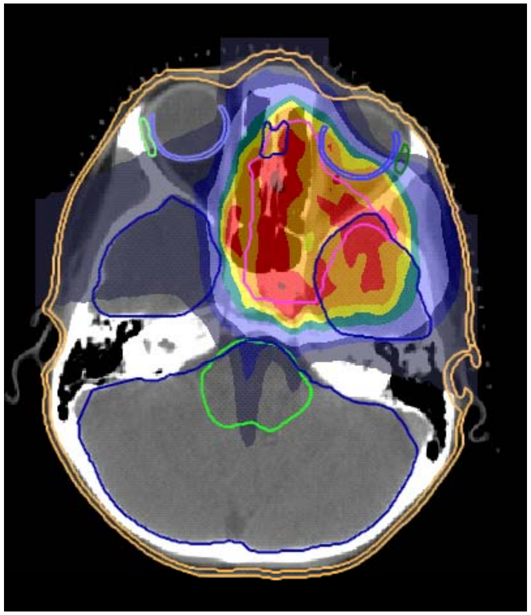
Proton IMPT (9 field)

Integral dose

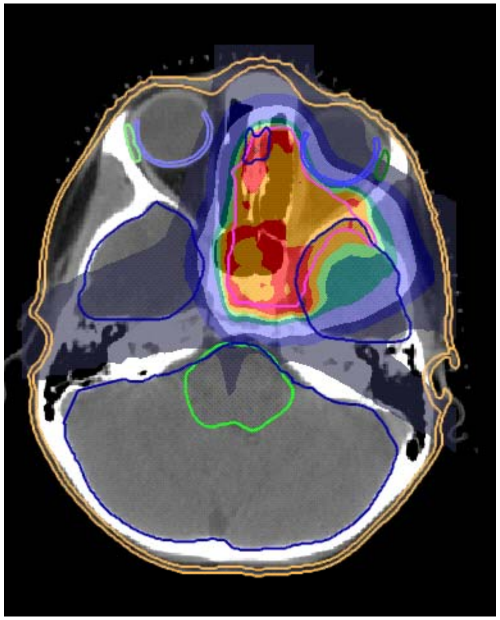
In beam scanning, spot size matters !



σ=12mm



σ=12mm
+aperture

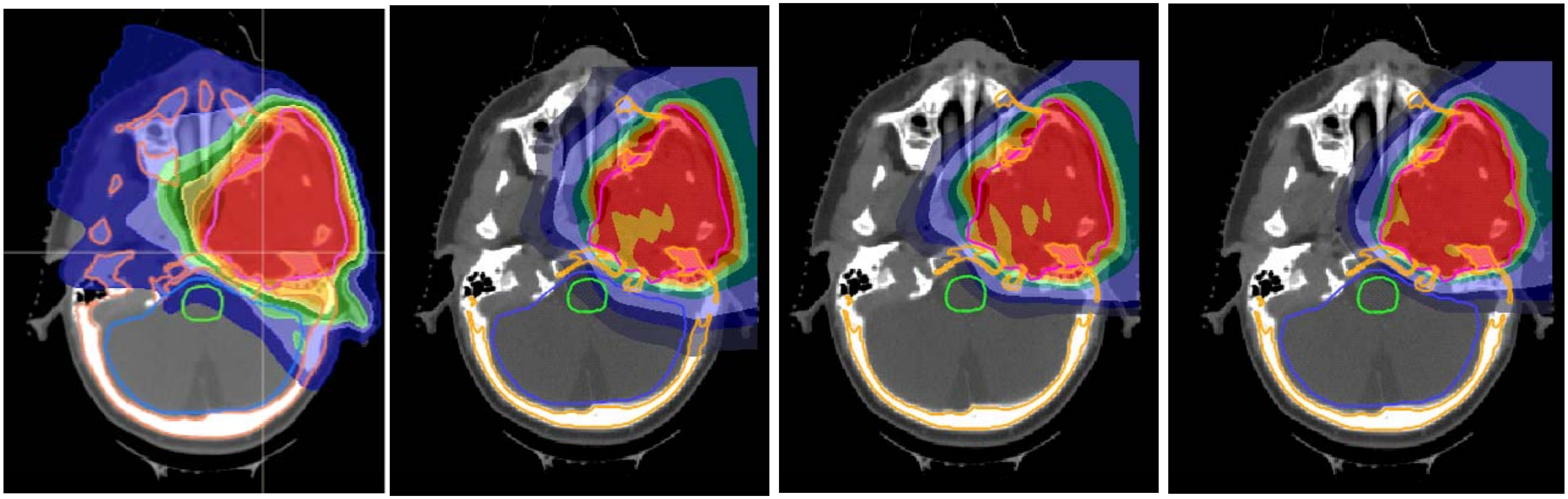


σ=3mm

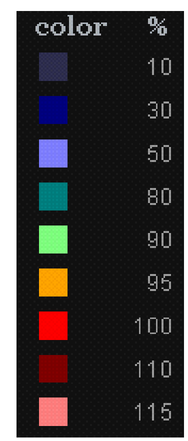
Depending on the beam characteristics, there are considerable differences between different proton beams (potentially showing inferiority compared to photon treatments)

Integral dose

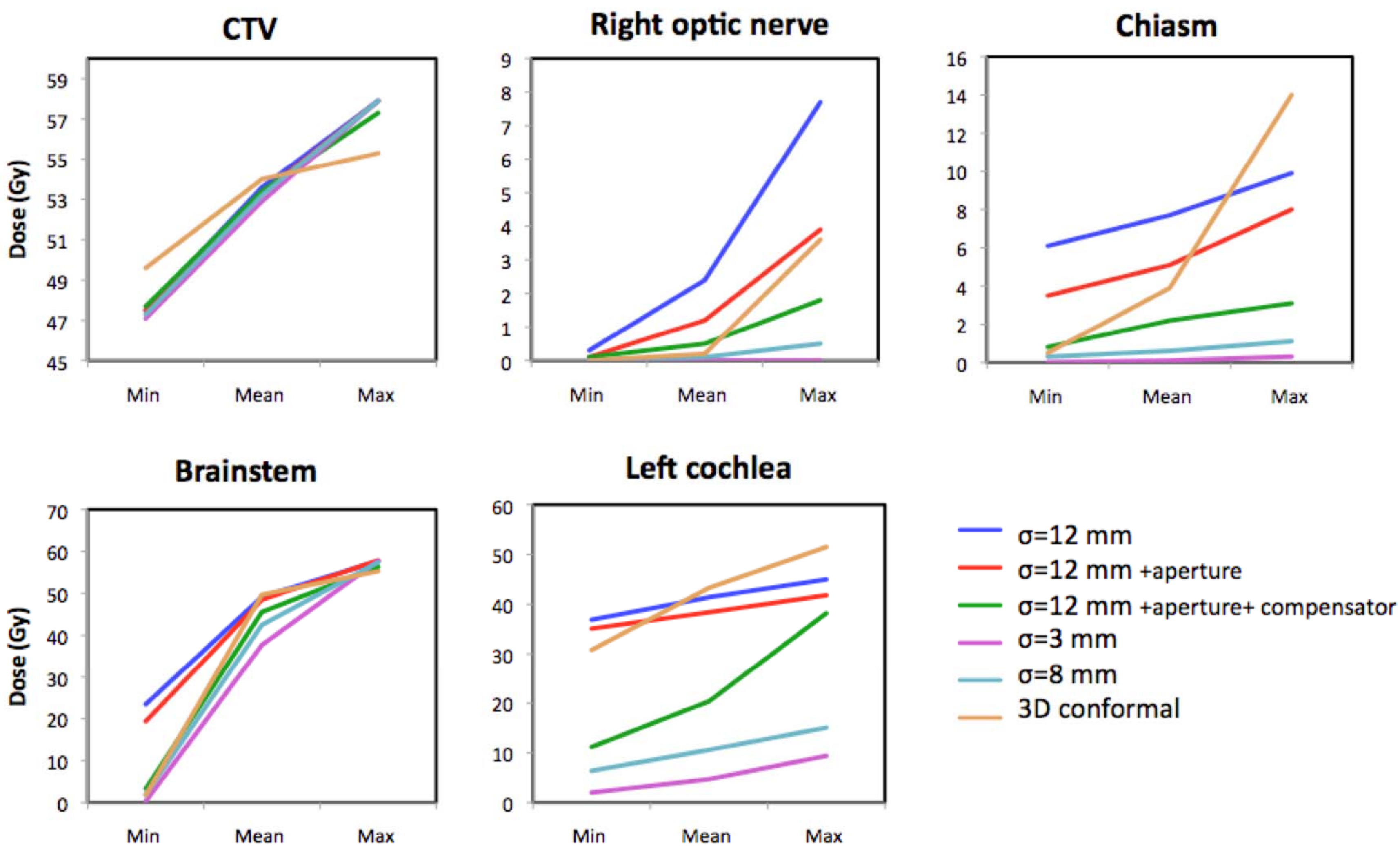
IMRT PBS 12mm PBS 12mm+AP PBS 3mm



Rhabdomyosarcoma
Total dose = 50.4 Gy
Number of proton fields = 2
Number of IMRT fields = 5



Patient with posterior fossa ependymoma



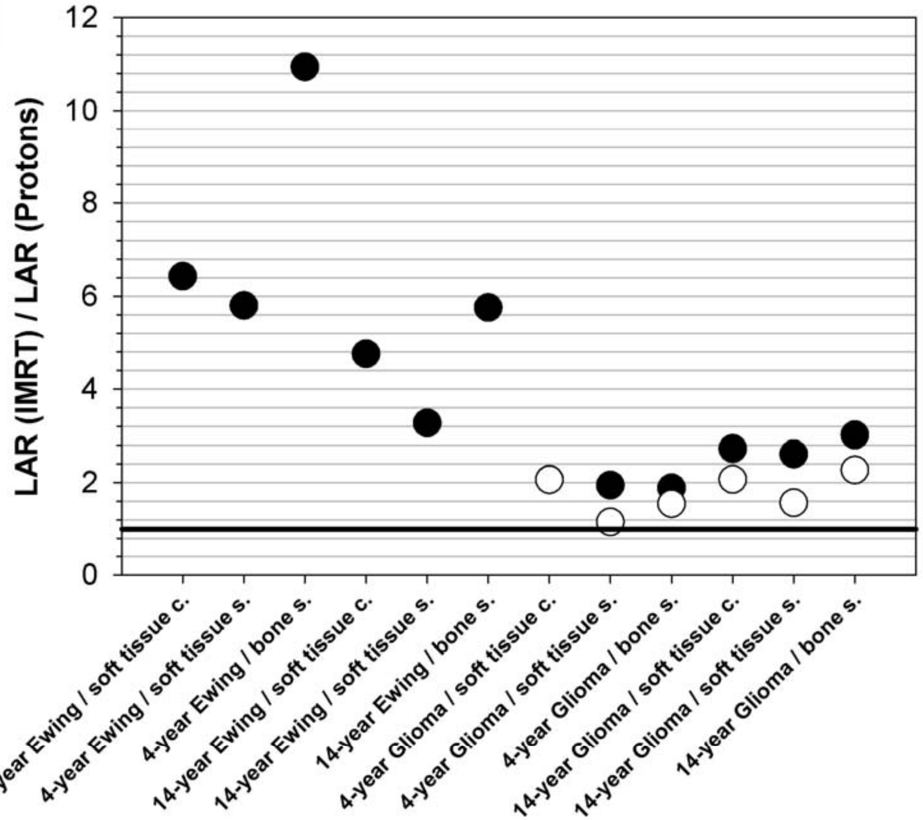
Is the integral dose the decisive parameter?

Is a small volume of high dose 'better' compared to a large volume of low dose?

second cancer induction

cognitive development in children (!)

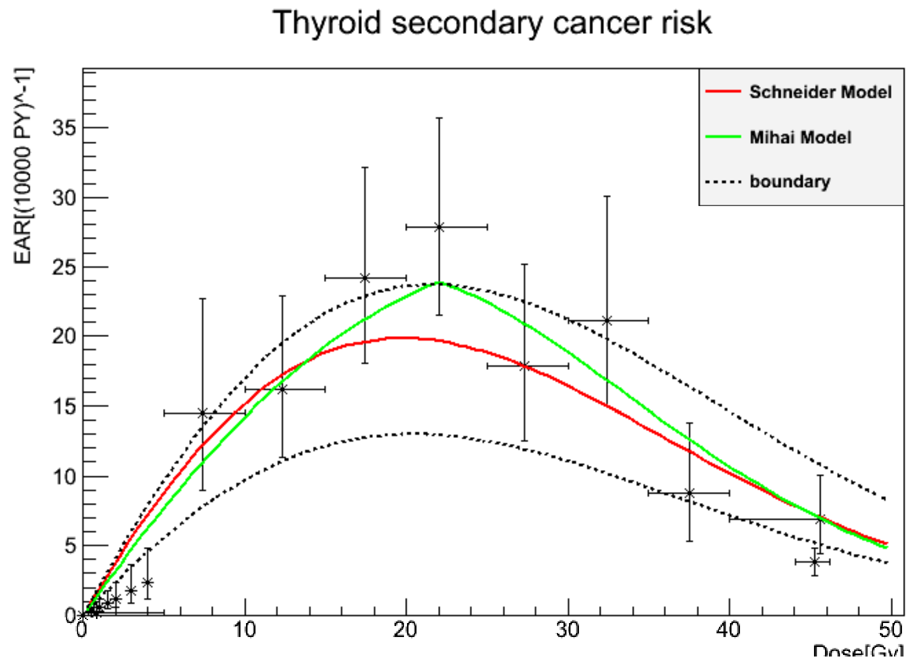
Integral dose

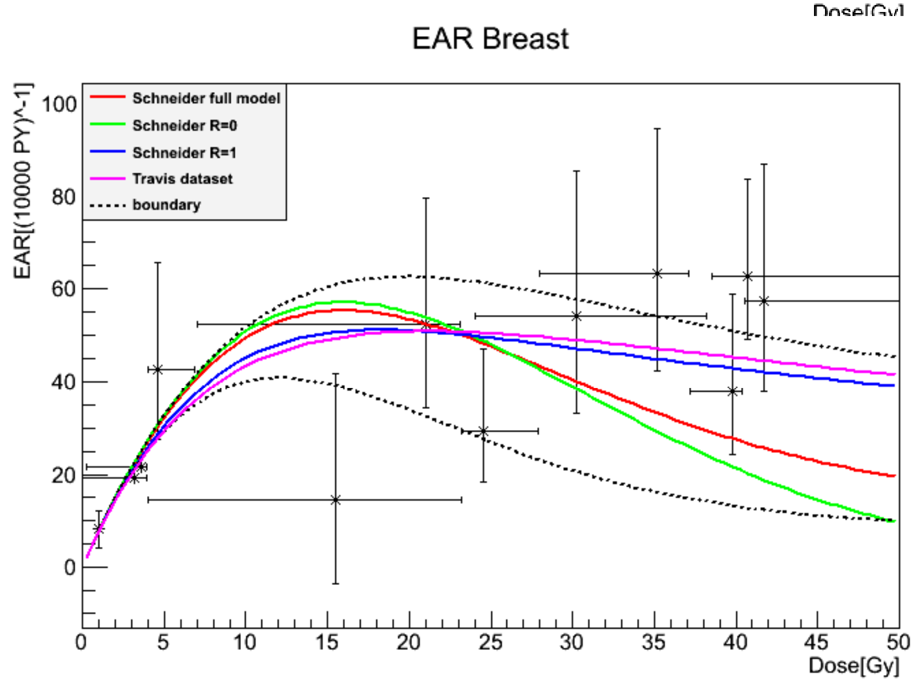


Total energy deposited (in Joules) in the patient for the treatment plans considered.

	Optic glioma			Ewing's sarcoma	
	Protons (3 fields)	Protons (4 fields)	IMRT	Protons	IMRT
4-year old	10.98	11.64	36.04	24.04	47.70
14-year old	10.73	12.05	29.57	75.48	148.00

Integral dose





Integral dose

Note:

- NTCP considerations in treatment planning are based on photon dose distributions
- Organ doses in proton therapy are more heterogeneous. There are no proton specific normal tissue constraints

Integral dose

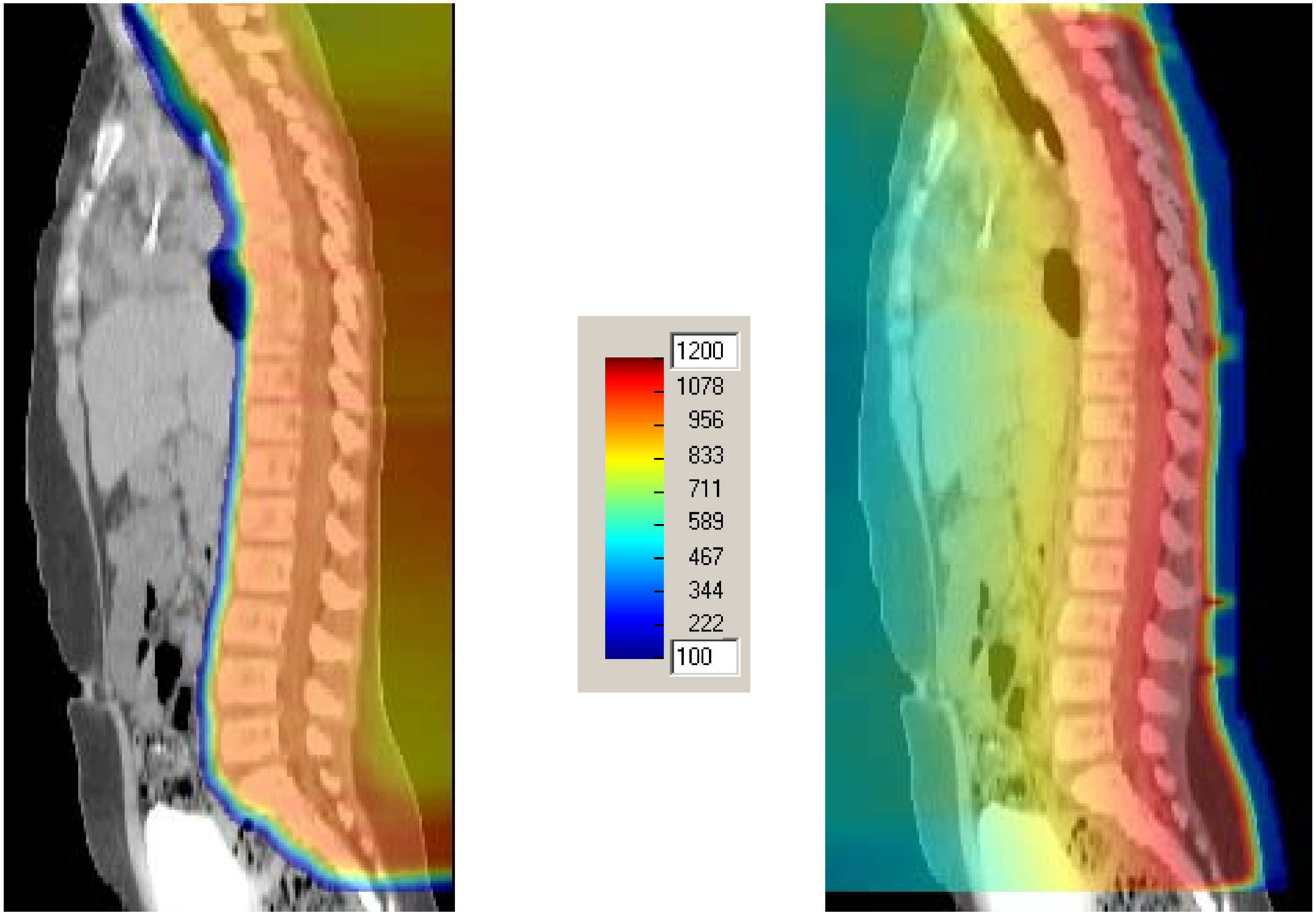
Conclusion I:

The total energy deposited in a patient ("integral dose") is always lower when treating with protons. This, theoretically, should always result in an advantage for proton treatments. However,

- the dose distribution matters
- this may not always result in a significant clinical gain (site dependent; clinical trials?)
- the delivery system matters

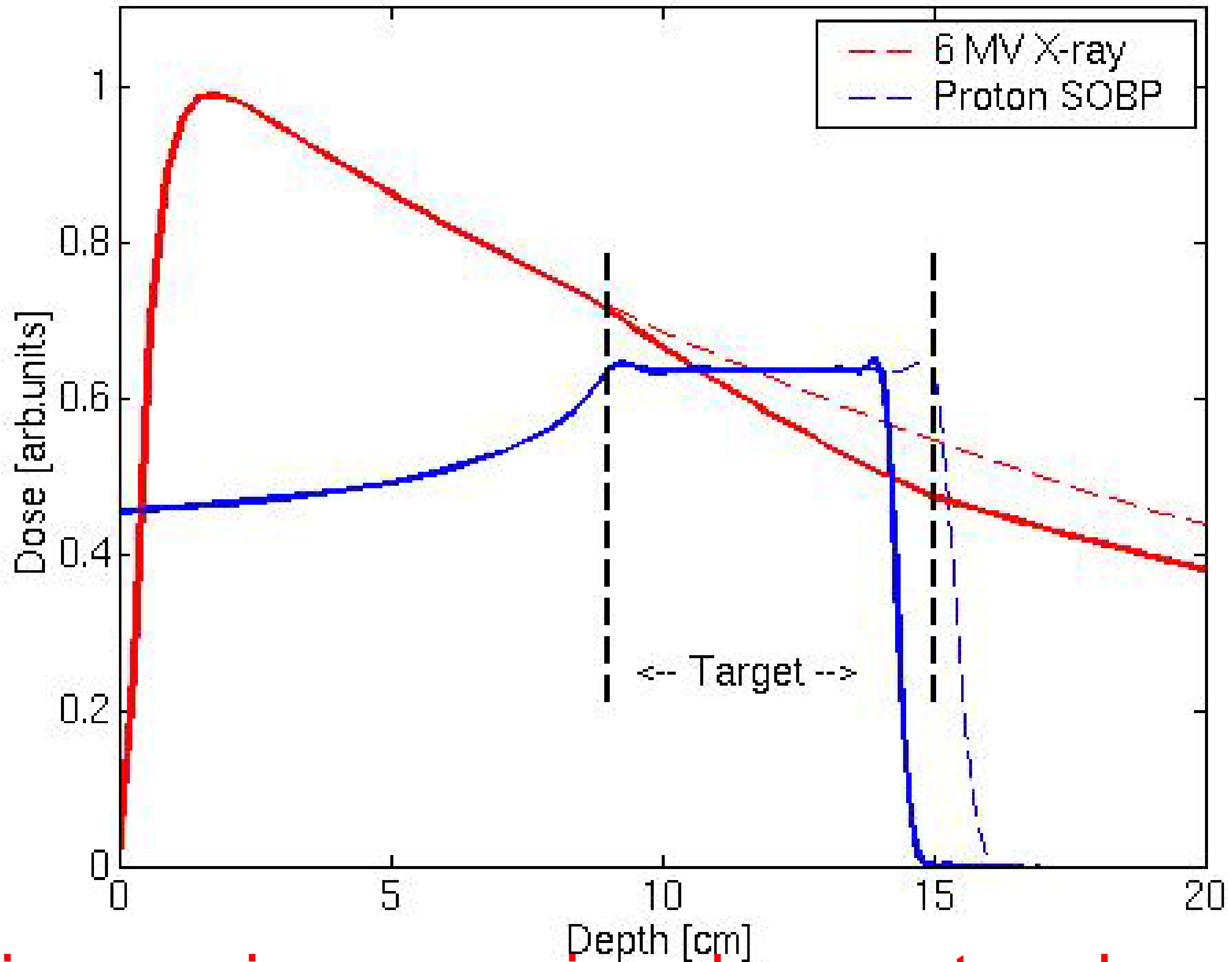
Medulloblastoma

Protons **Photons**



Predicting the range

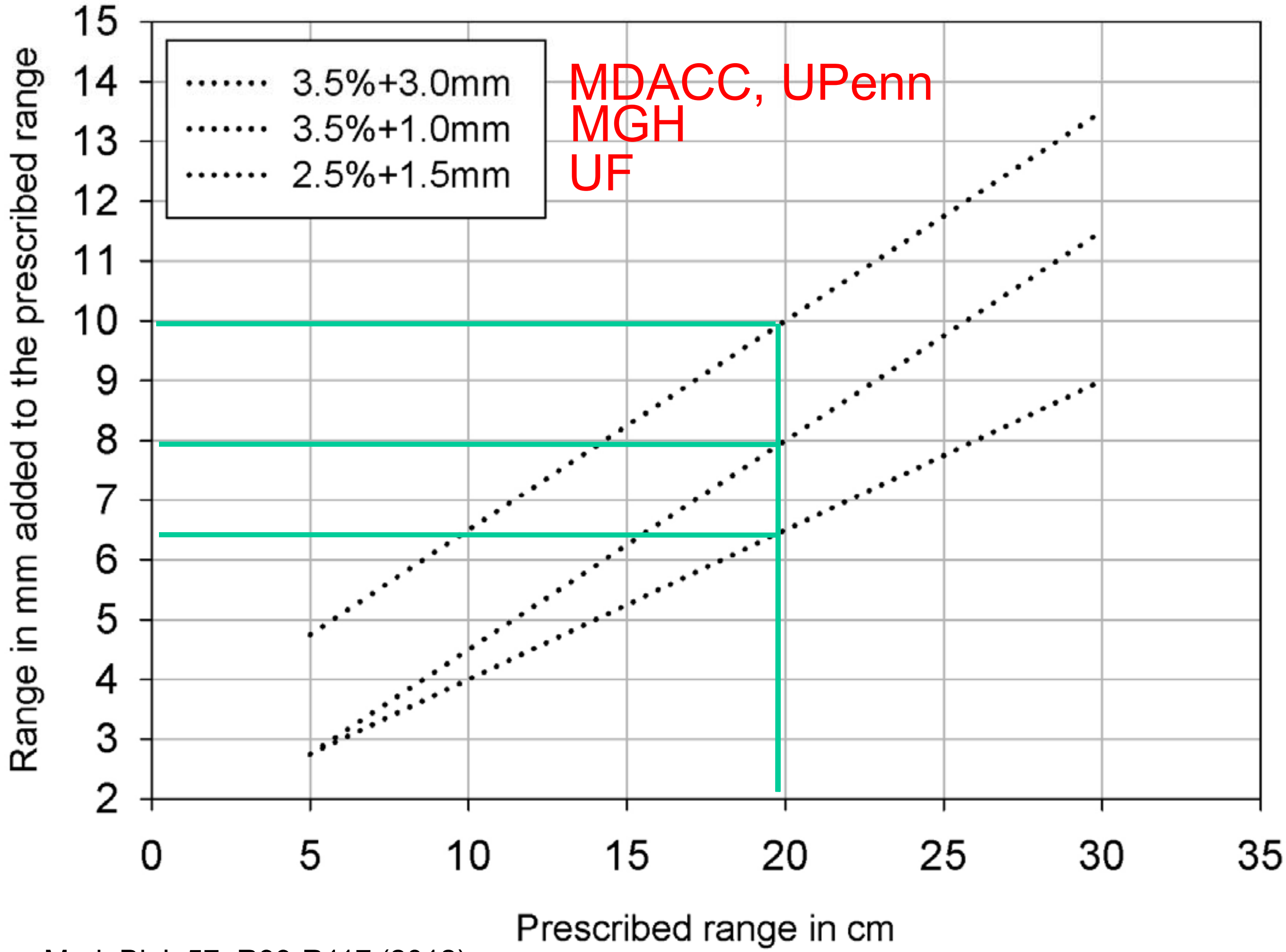
The difference compared to photon therapy: range uncertainties



symmetric margin expansion does not make sense !

Predicting the range

Applied range uncertainty margins for non-moving targets



H. Paganetti: Phys. Med. Biol. 57, R99-R117 (2012)

Predicting the range

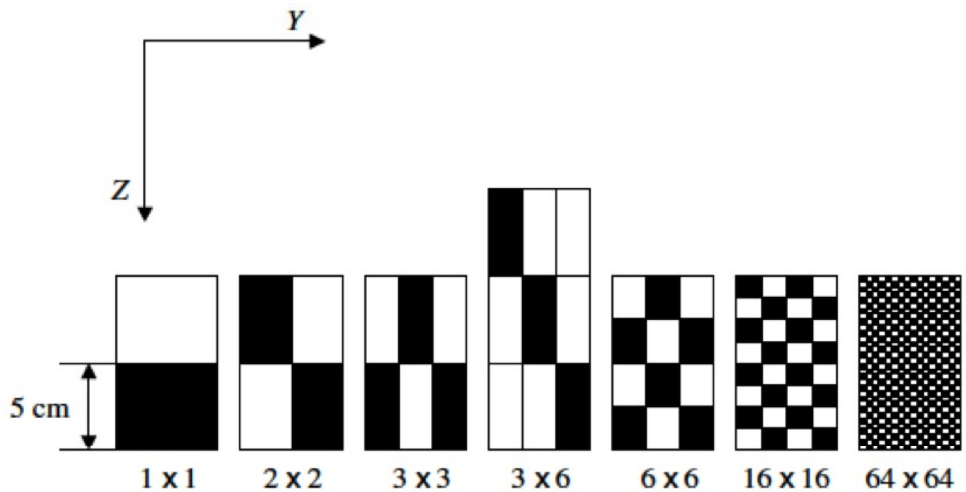
Applied range uncertainty margins for non-moving targets

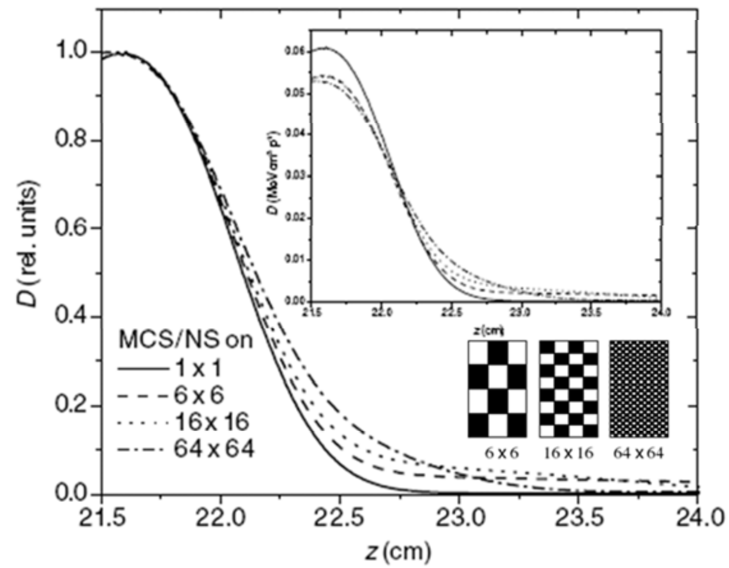
Source of range uncertainty in the patient	Range uncertainty
Independent of dose calculation:	
Measurement uncertainty in water for commissioning	± 0.3 mm
Compensator design	± 0.2 mm
Beam reproducibility	± 0.2 mm
Patient setup	± 0.7 mm
Dose calculation:	
Biology (always positive)	+ 0.8 %
CT imaging and calibration	± 0.5 %
CT conversion to tissue (excluding I-values)	± 0.5 %
CT grid size	± 0.3 %
Mean excitation energies (I-values) in tissue	± 1.5 %
Range degradation; complex inhomogeneities	- 0.7 %
Range degradation; local lateral inhomogeneities *	± 2.5 %
Total (excluding *)	**2.7% + 1.2 mm**
Total	**4.6% + 1.2 mm**

H. Paganetti: Phys. Med. Biol. 57, R99-R107 (2012)

Predicting the range

Range degradation Type I



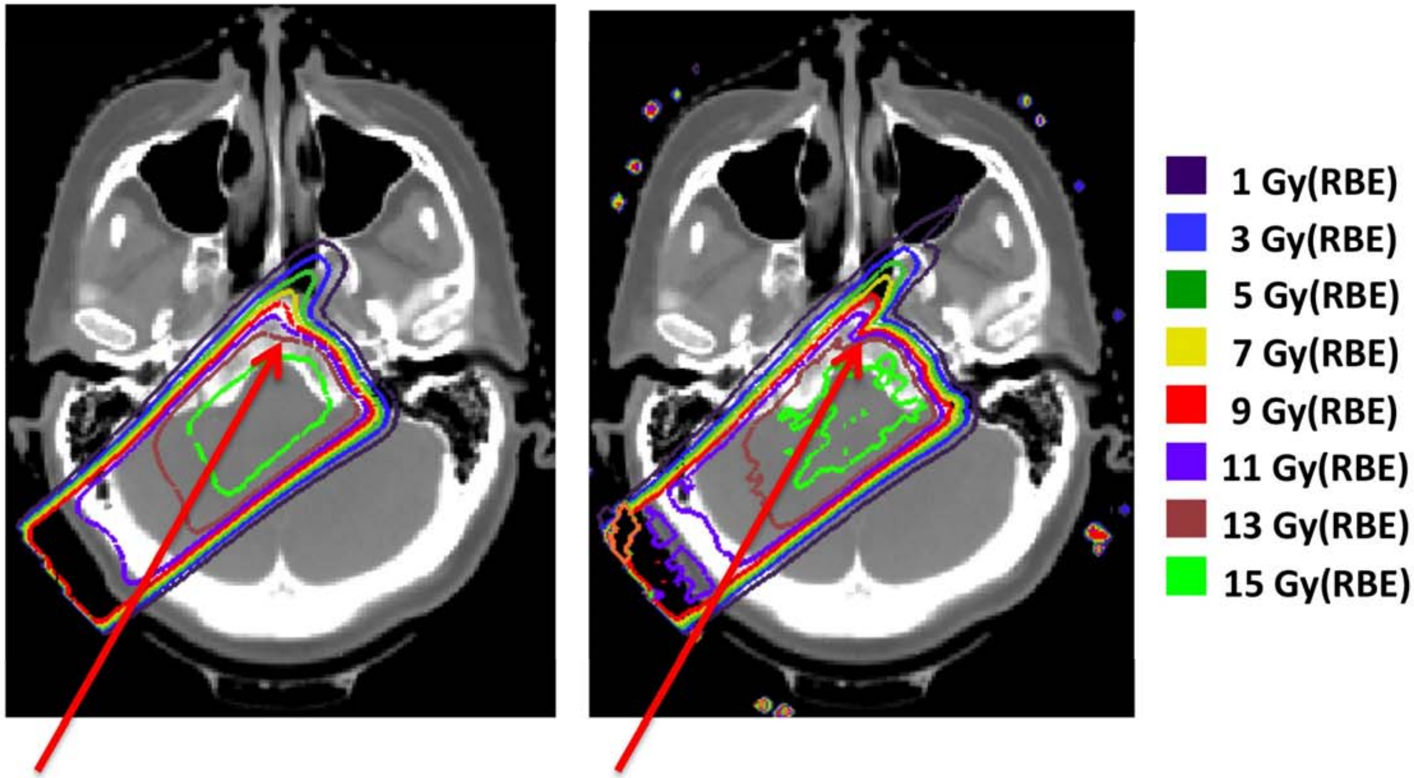


(Sawakuchi *et al.*, 2008)

Predicting the range

Range degradation Type II

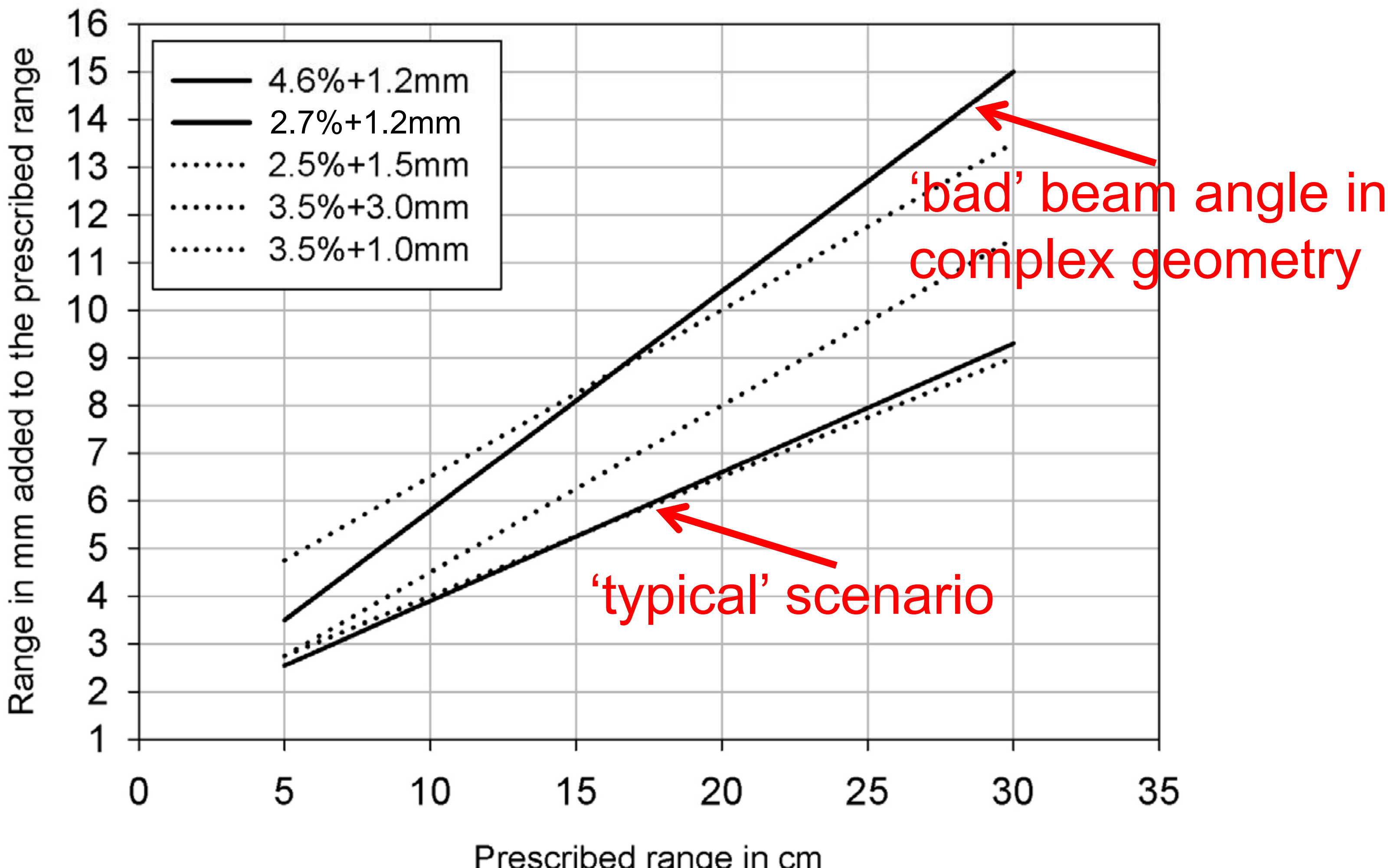
analytical | Monte Carlo



(Paganetti *et al.*, 2008)

Predicting the range

Applied range uncertainty margins for non-moving targets



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Predicting the range

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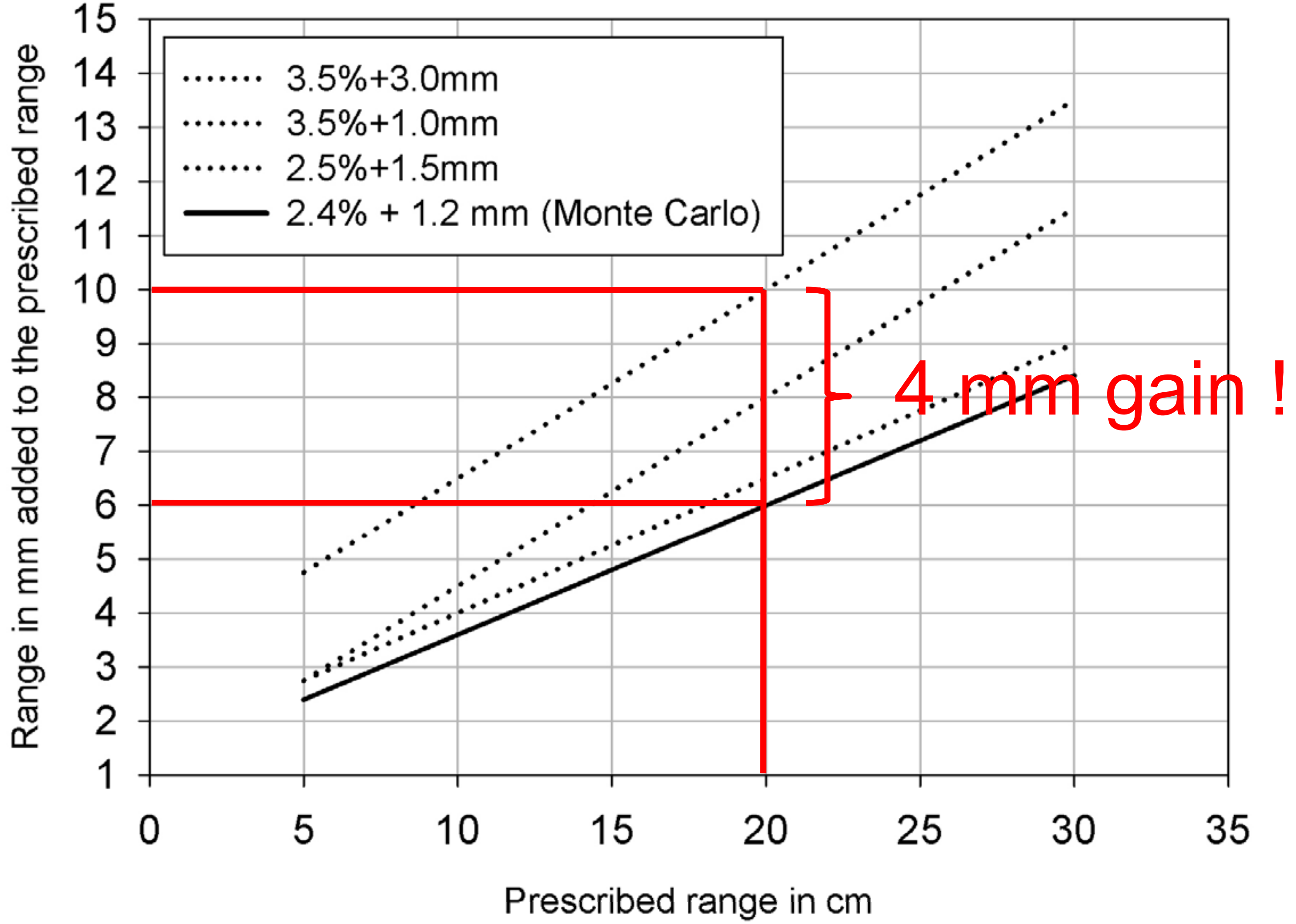
H. Paganetti: Range uncertainties in proton beam therapy and the impact of Monte Carlo simulations
Phys. Med. Biol. 57: R99-R117 (2012)

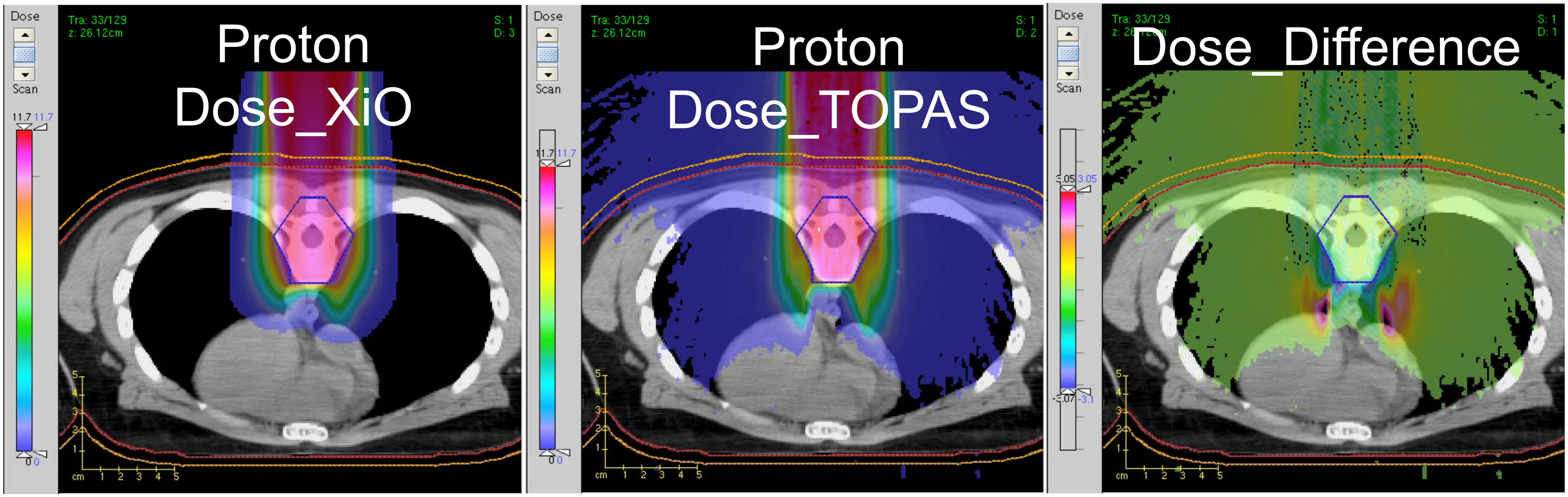
Predicting the range

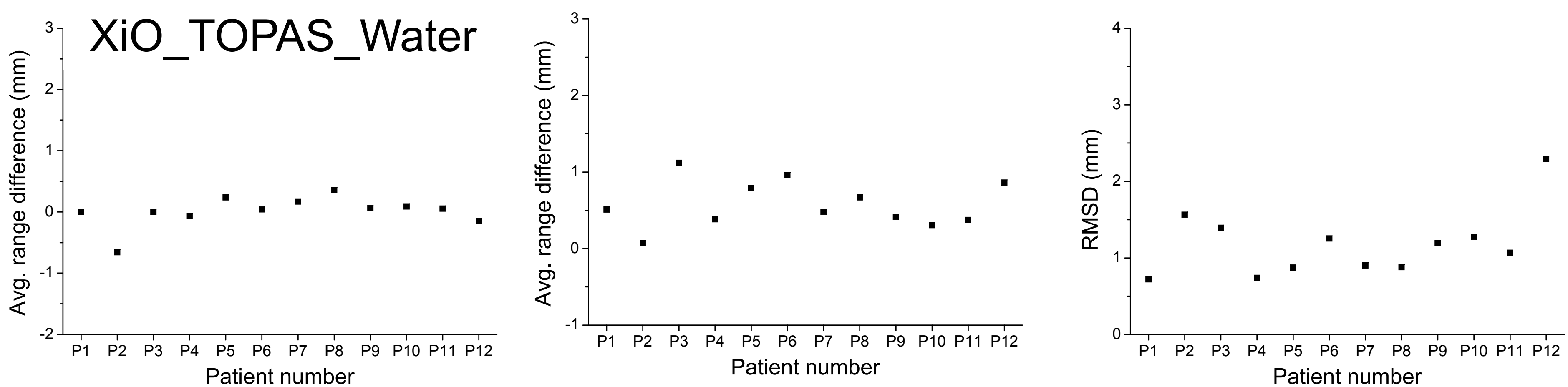


H. Paganetti: Range uncertainties in proton beam therapy and the impact of Monte Carlo simulations
Phys. Med. Biol. 57: R99-R117 (2012)

Predicting the range

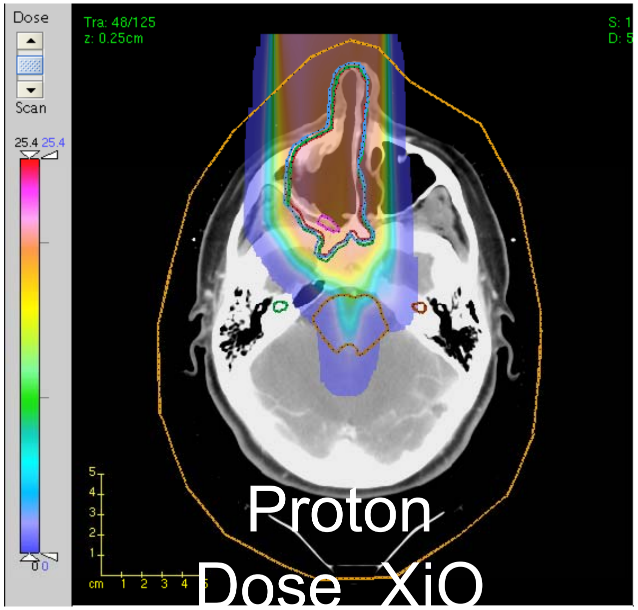
Medduloblastoma Patient

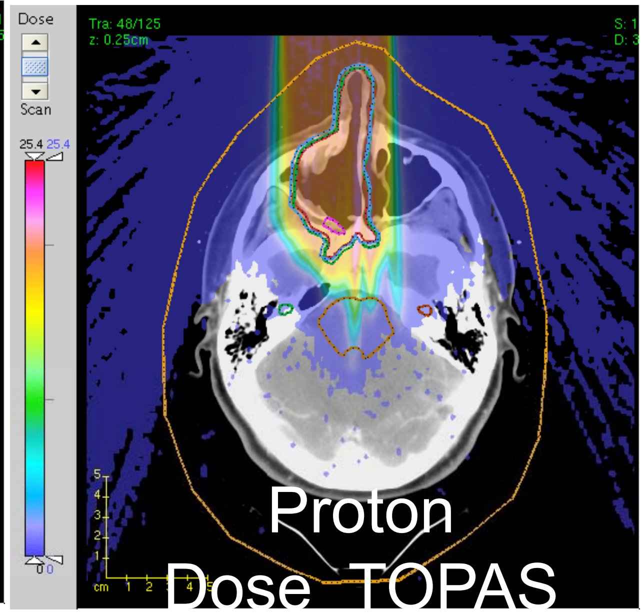


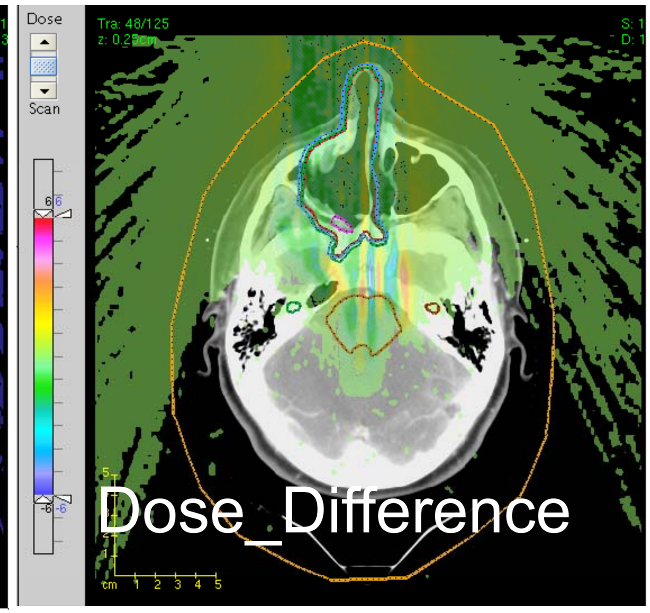


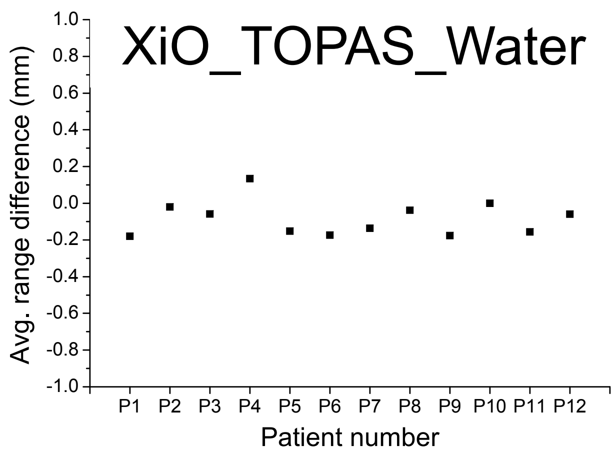
Predicting the range

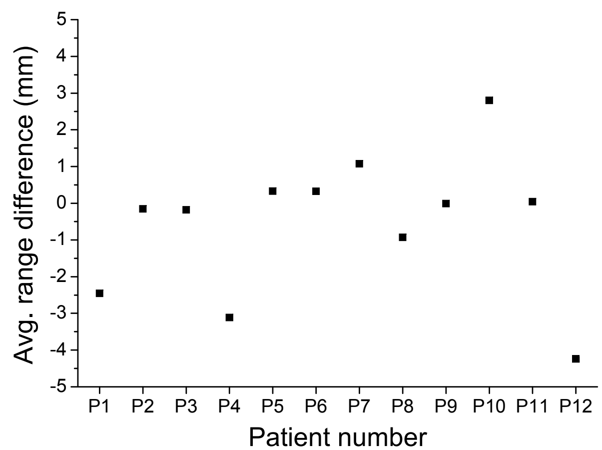
Head & Neck Patient

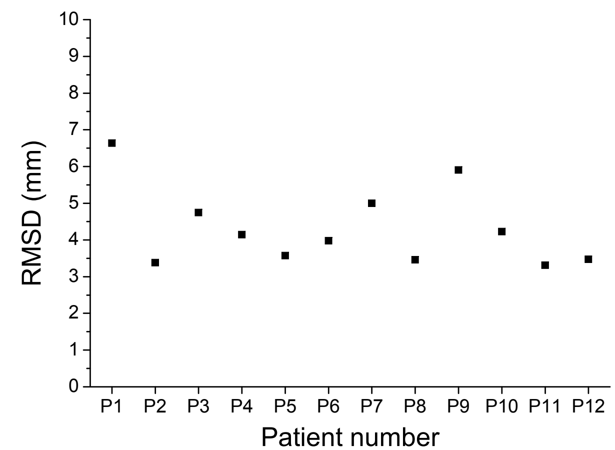












Predicting the range

Note:

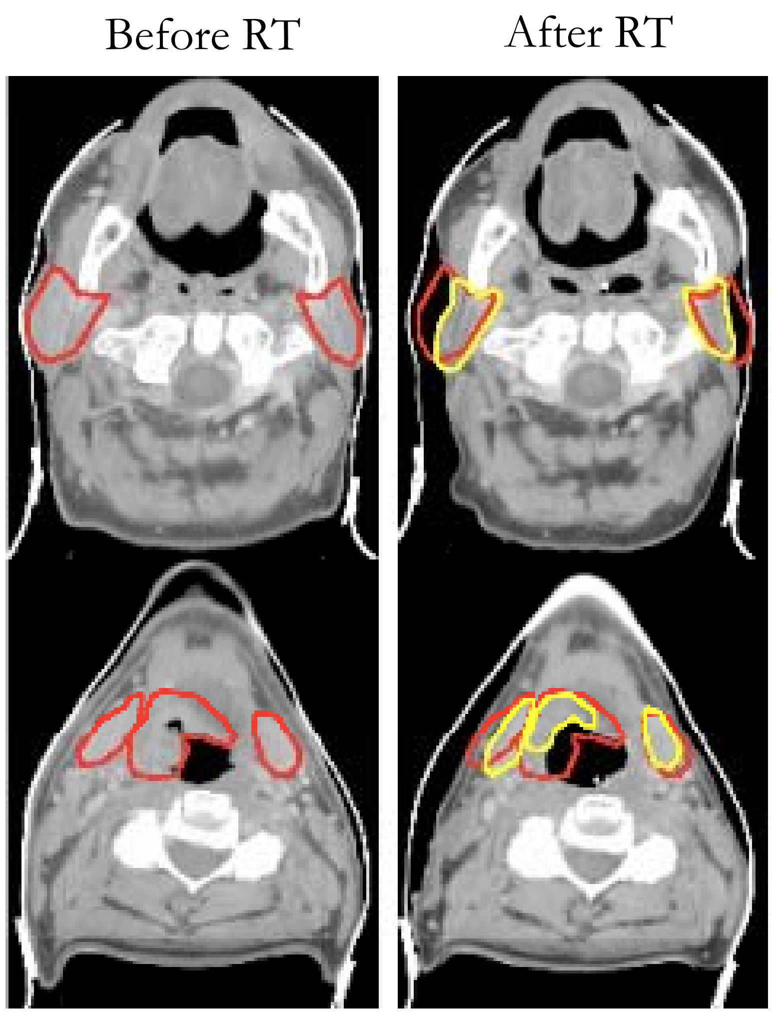
In proton therapy, generic margin recipes are not sufficient !

Advanced dose calculation only solves part of the problem

Predicting the range

In addition(!): patient geometry changes

Example: Intra-fractional geometry changes



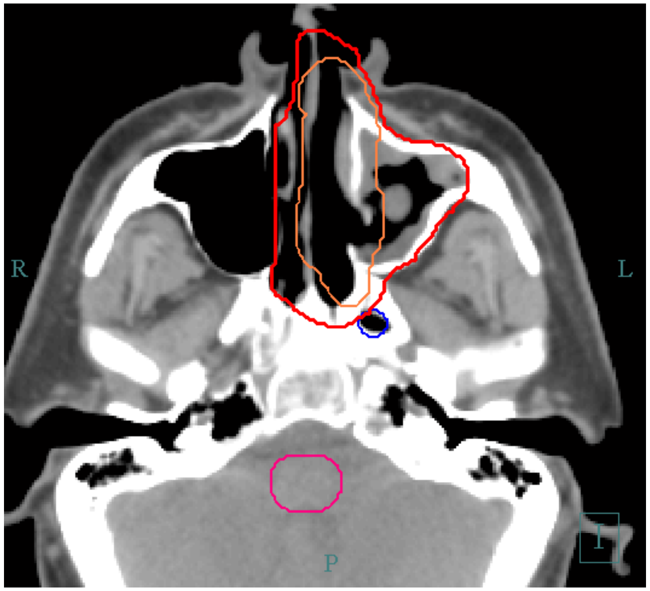
- Parotid glands
- Subm.glands
- Tumor

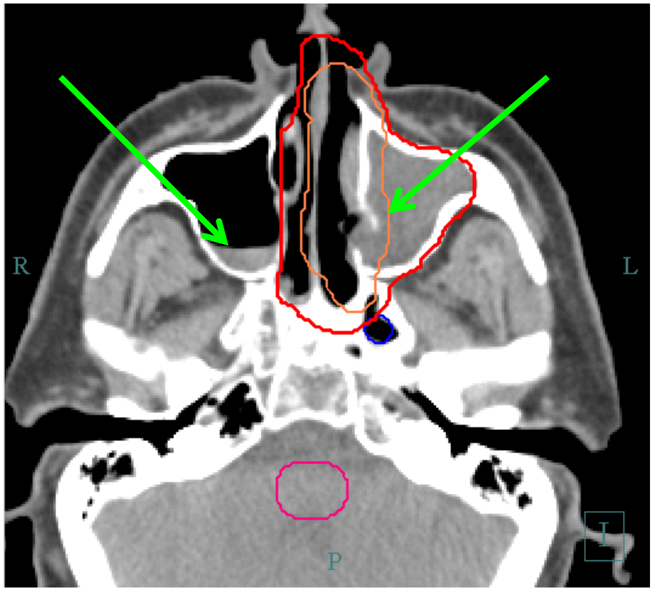
E. M. Vasques Osorio *et al.*
IJROBP 70: 875-82

Predicting the range

In addition(!): patient geometry changes

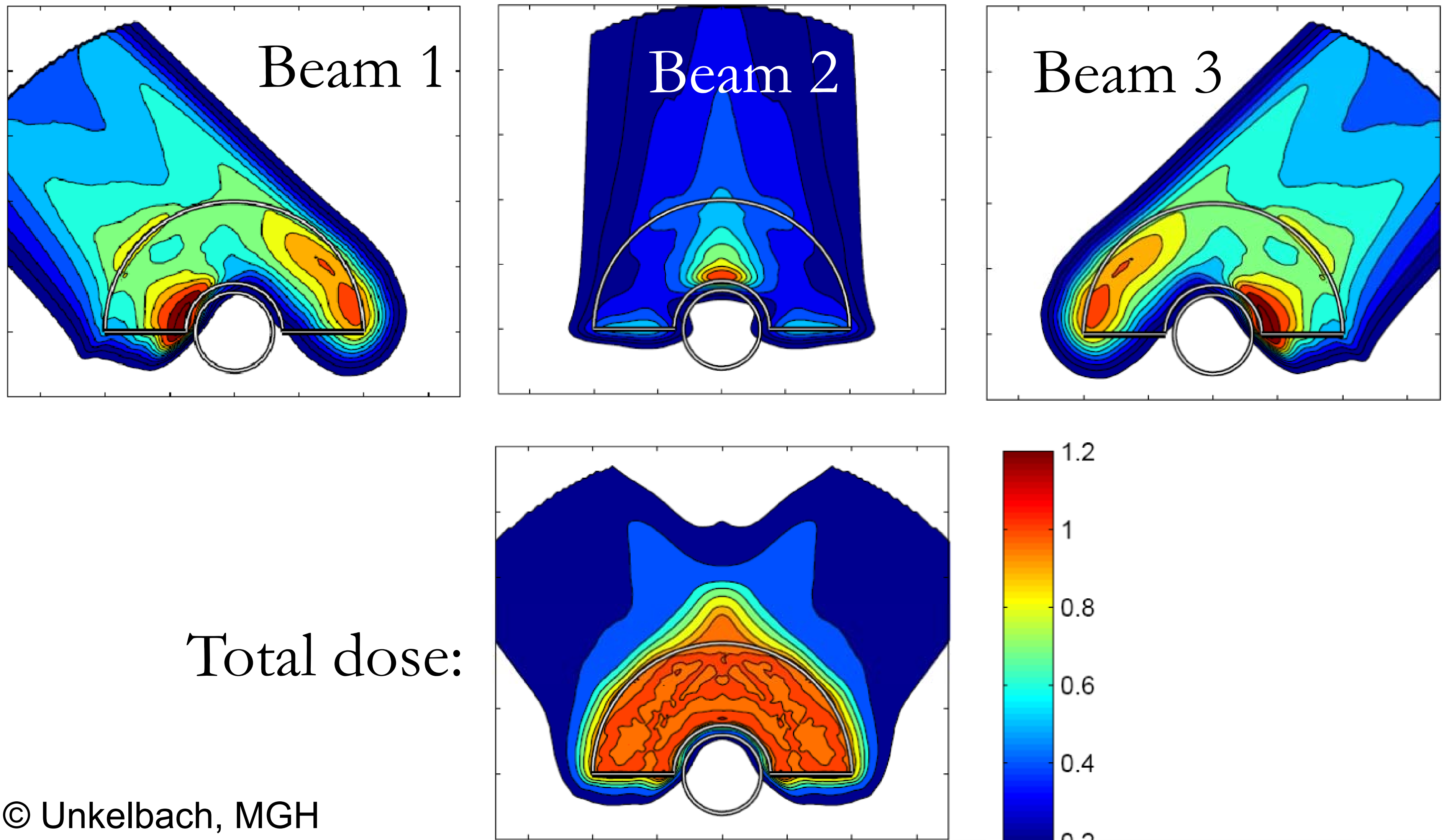
- Patient weight gain / loss
- Filling up of sinuses
- (Sub-clinical) pneumonia
- Wet hair / gel / hairspray





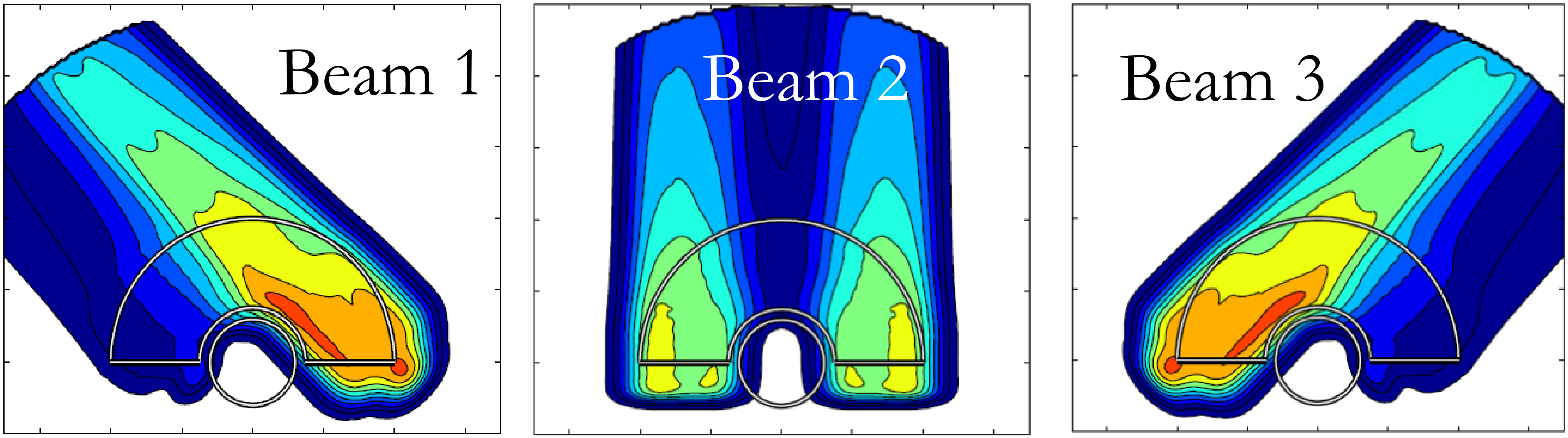
Predicting the range

Mitigating range uncertainties using robust planning in IMPT

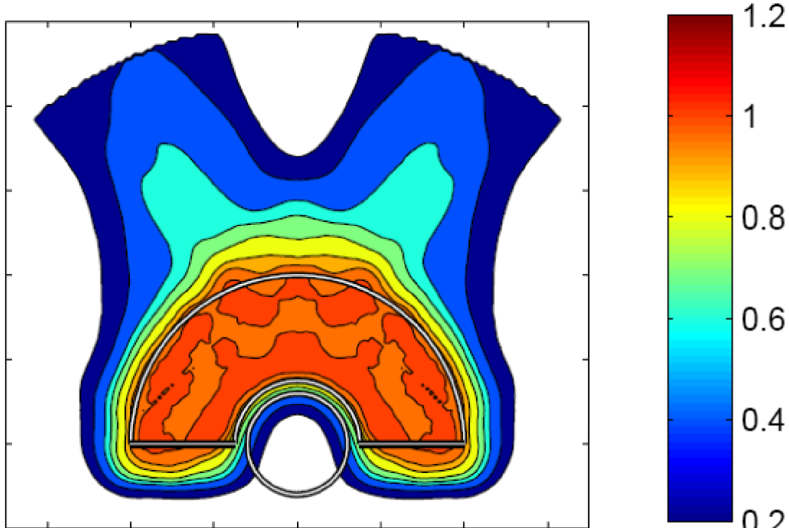


Predicting the range

Mitigating range uncertainties using robust planning in IMPT

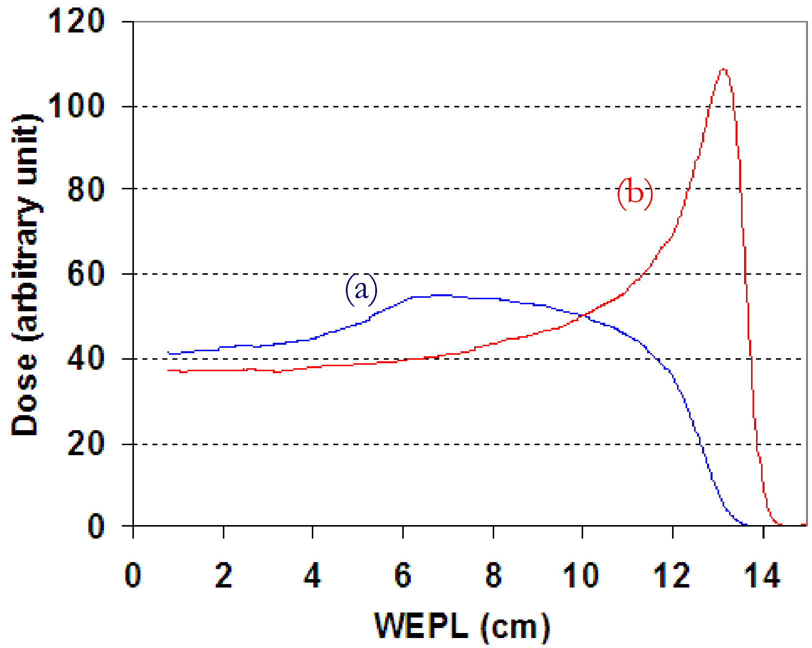


Total dose:

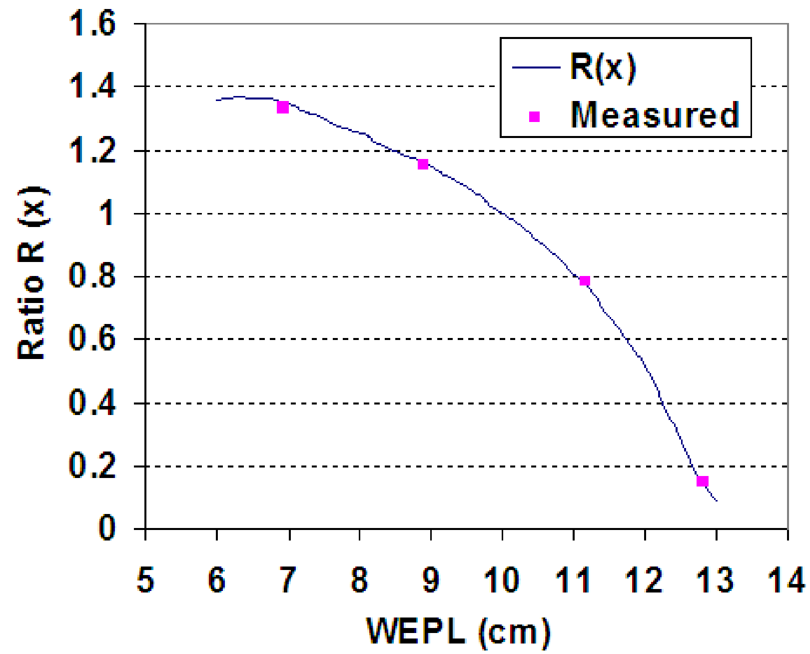


Measuring range using the ratio of two point doses

Partial distributions for field pair

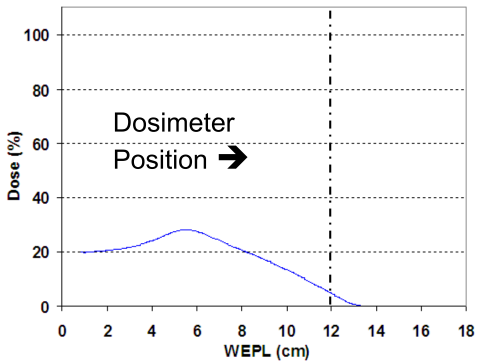


Ratio function



Range adjustment for adaptive delivery

$$\mathbf{D\,(x) = D_a\,(x) + D_b\,(x) + D_c\,(x)}$$



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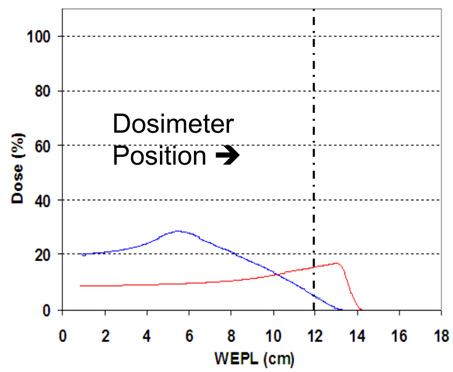

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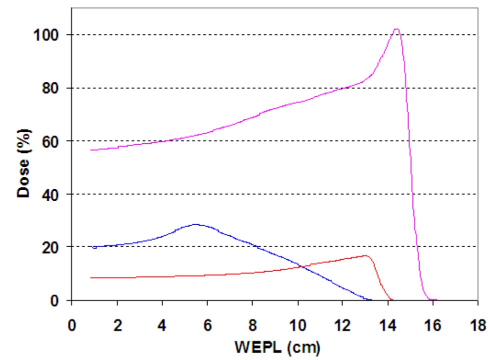
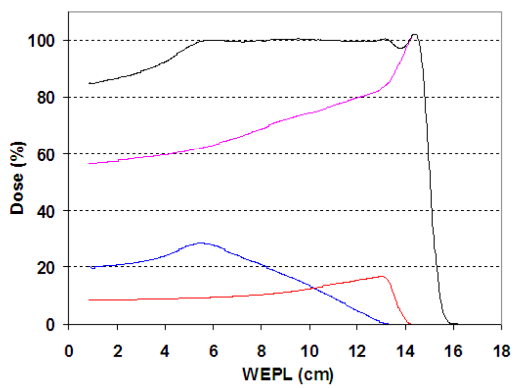


- Deliver field **a**
- Measure dose $\mathbf{D_a}$

- Deliver field **b**
- Measure dose $\mathbf{D_b}$

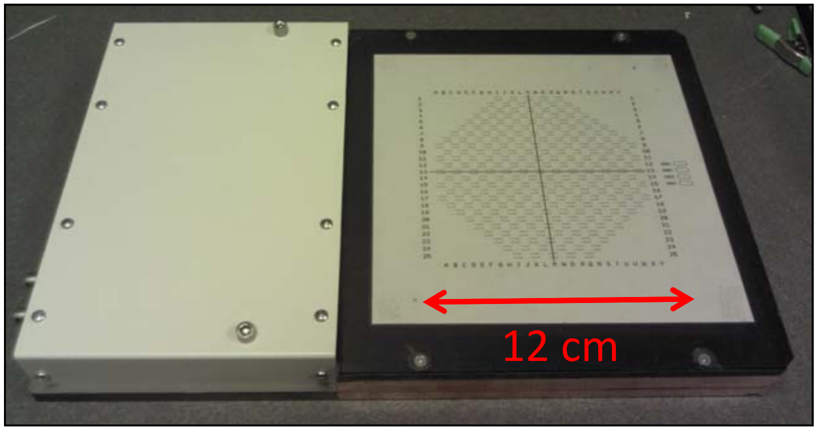
- Calculate ratio $\mathbf{R=D_a/D_b}$
- Drive WEPL of dosimeter
- Design subfield **c** (magenta)
- Deliver **c**.

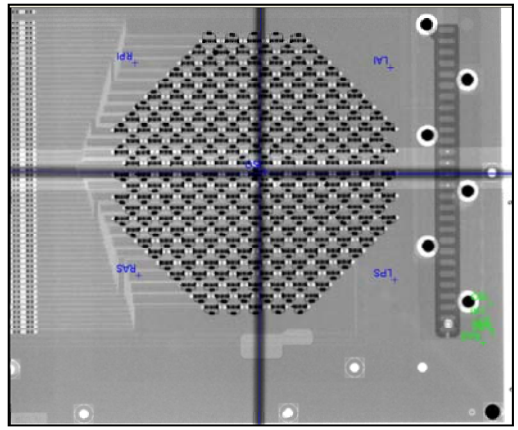
=>



Total distribution (black) has the correct range

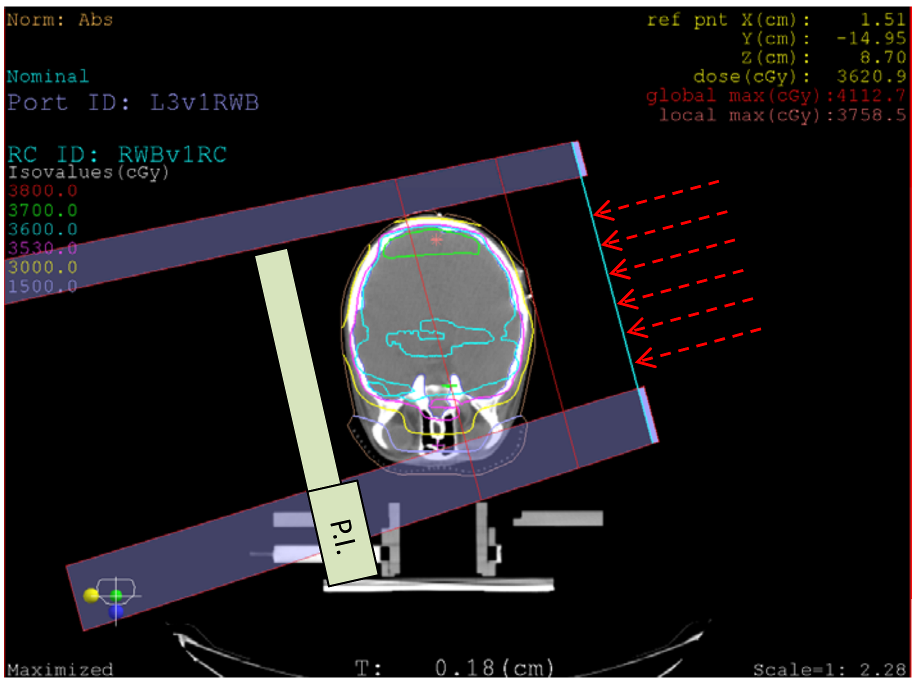
Predicting the range





Technical Characteristics

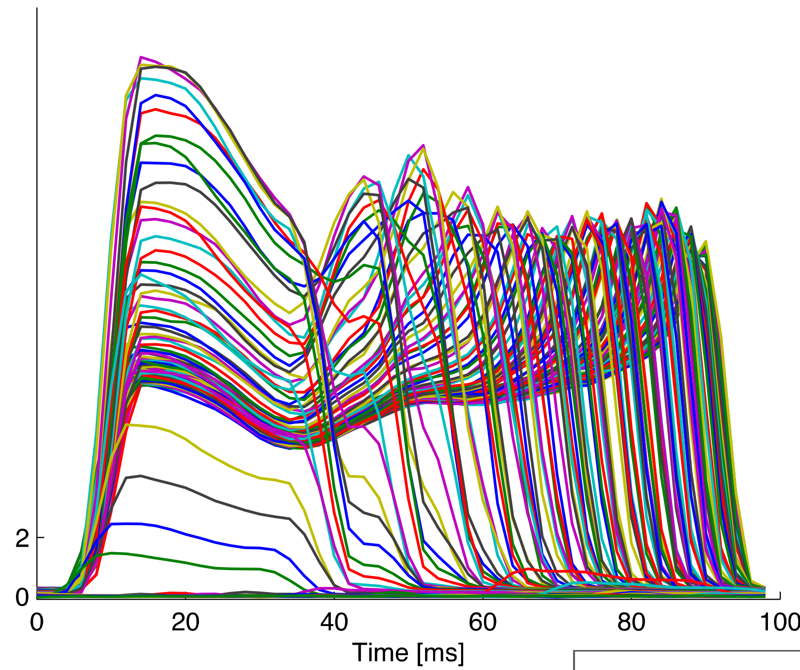
Number of diodes: 249
Time resolution: ~ 2 msec
Pitch: ~ 10 mm
Manufacturer: Sun Nuclear



Applications

- Check the patient positioning
- Monitor patient morphological change (Range verification)
- Pre-treatment Range Tuning (Cranial field Medulloblastoma)

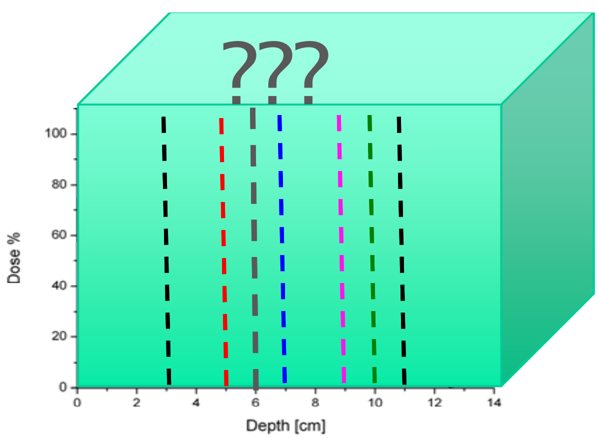
Pr

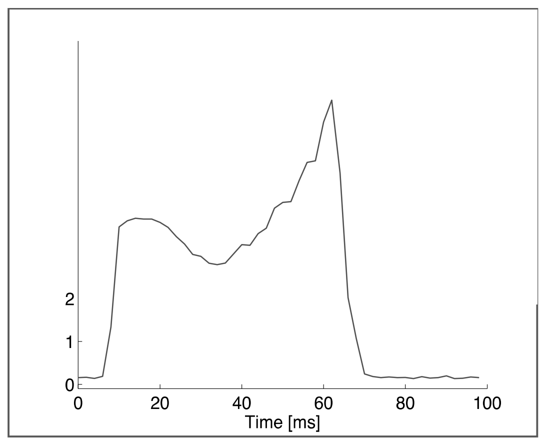


1. **Pattern Matching Technique**
   Minimization of the least-squares difference between measured profiles and 'Data Base'
2. **rms-width (σ_t) fitting technique**

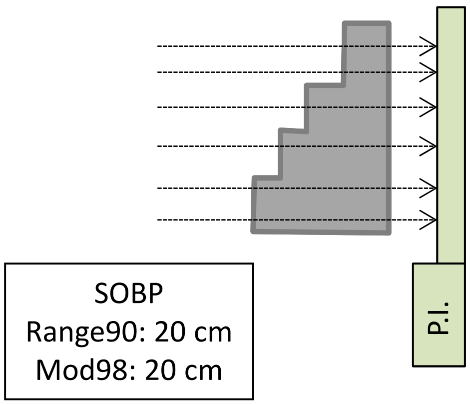
$$S = \sum_{i=i_1}^{i_N} v_i \quad (\mathrm{V}),$$

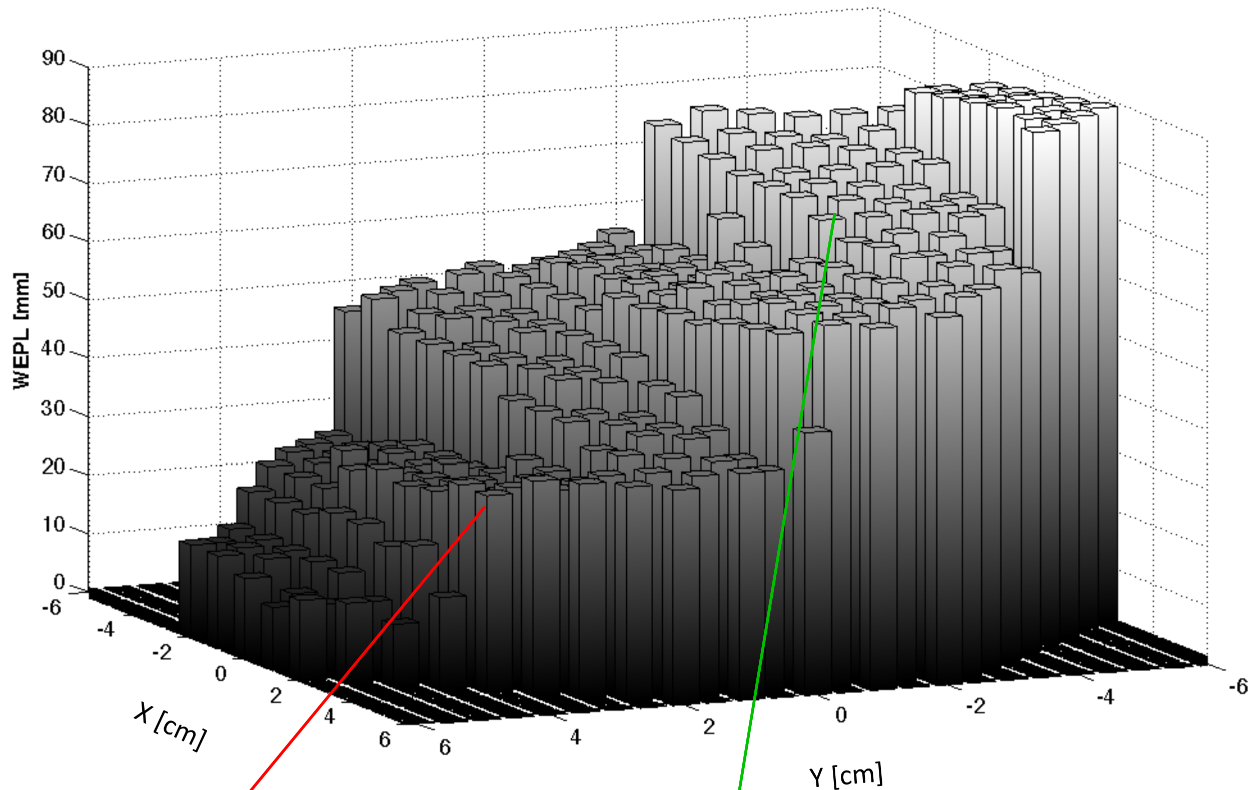
$$m = \frac{1}{S} \sum_{i=i_1}^{i_N} v_i t_i \quad (\mathrm{ms}),$$

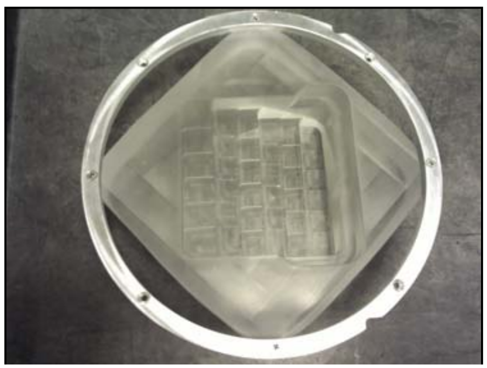


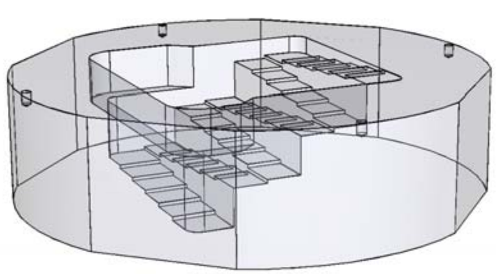


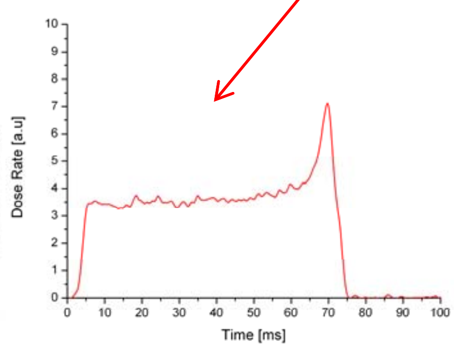
Predicting the range

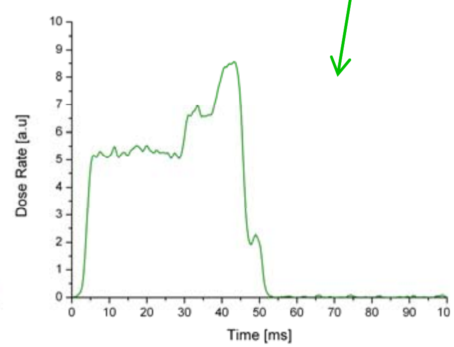


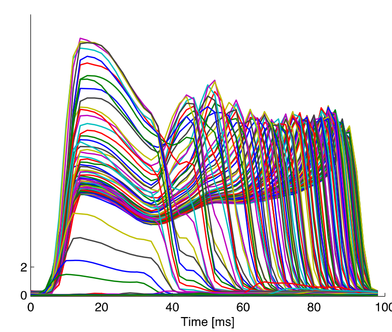




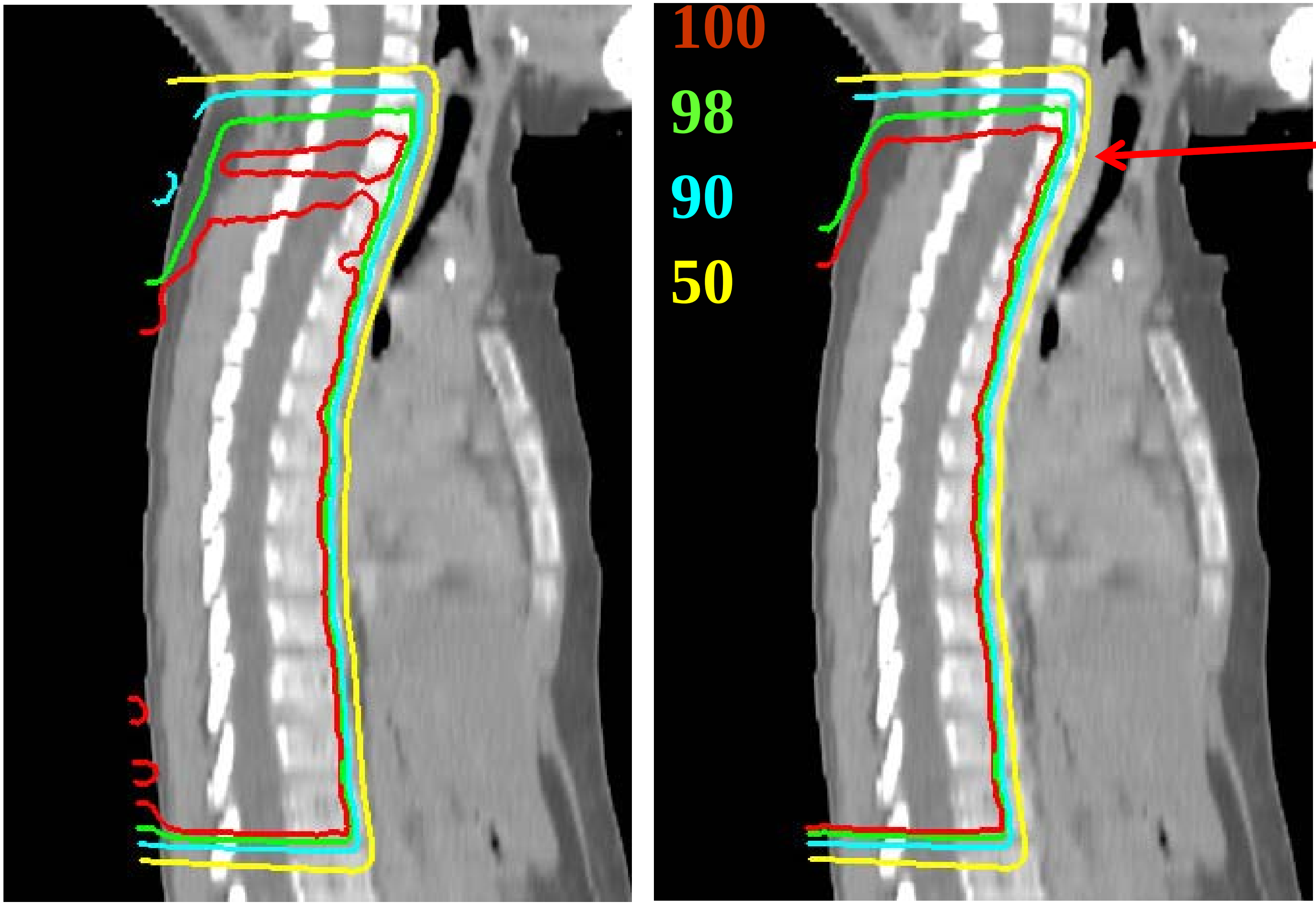






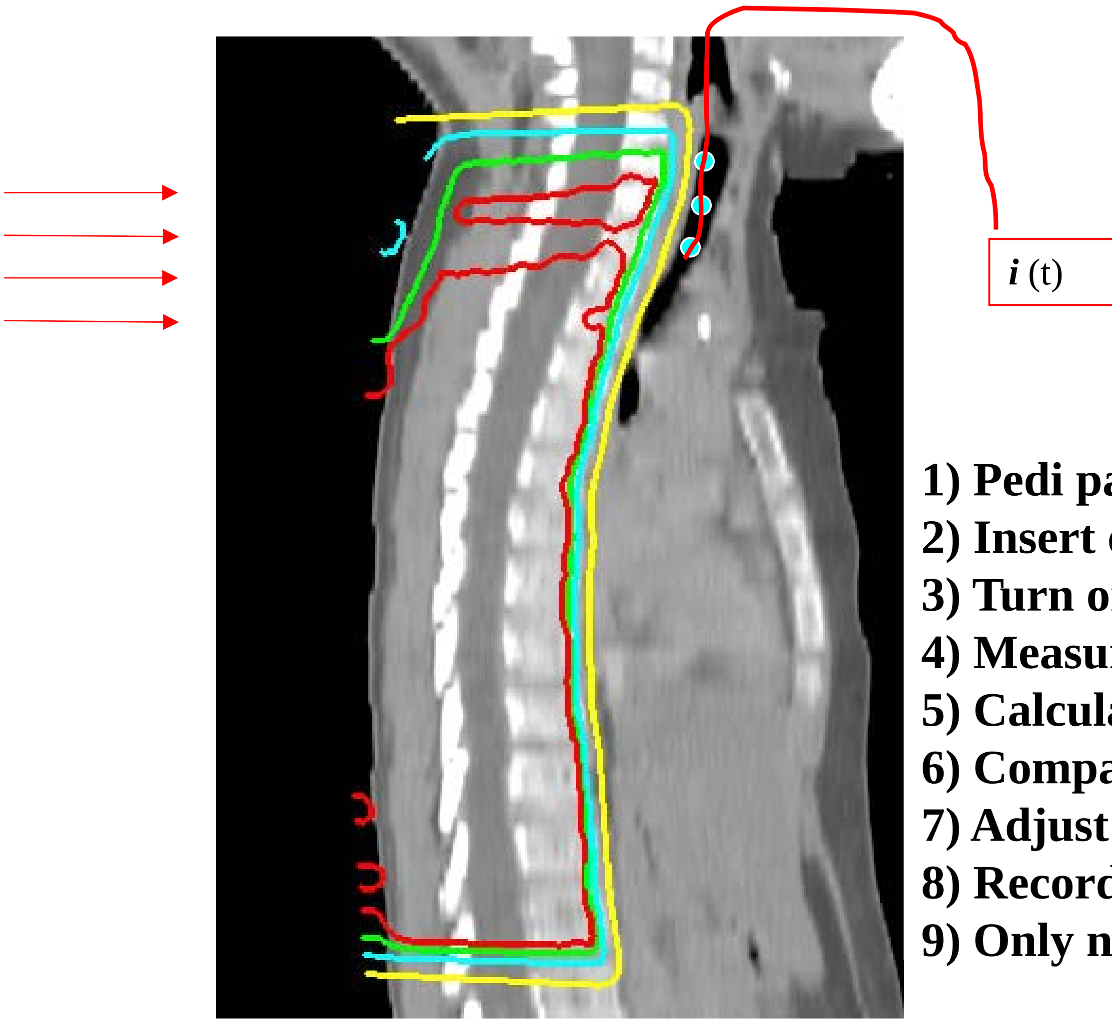


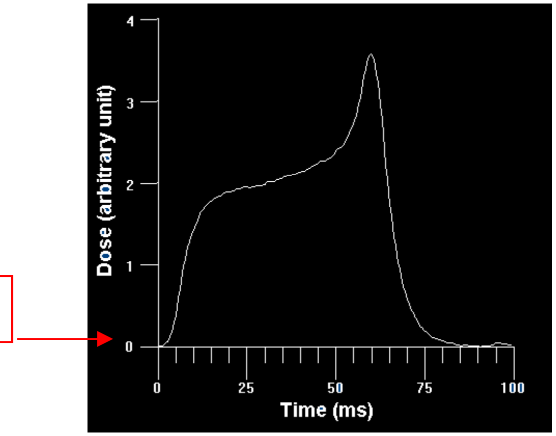
Esophagus sparing



Range pullback of 4 mm for all patients

In-Vivo Range Check





1) Pedi patient under anesthesia
2) Insert esophageal dosimeter (diodes)
3) Turn on range check beam for < 1 cGy
4) Measure dose rate as function of time
5) Calculate water equivalent path length
6) Compare with treatment planning
7) Adjust beam range for treatment
8) Record dose delivered to esophagus
9) Only needed during 1st treatment

Predicting the range

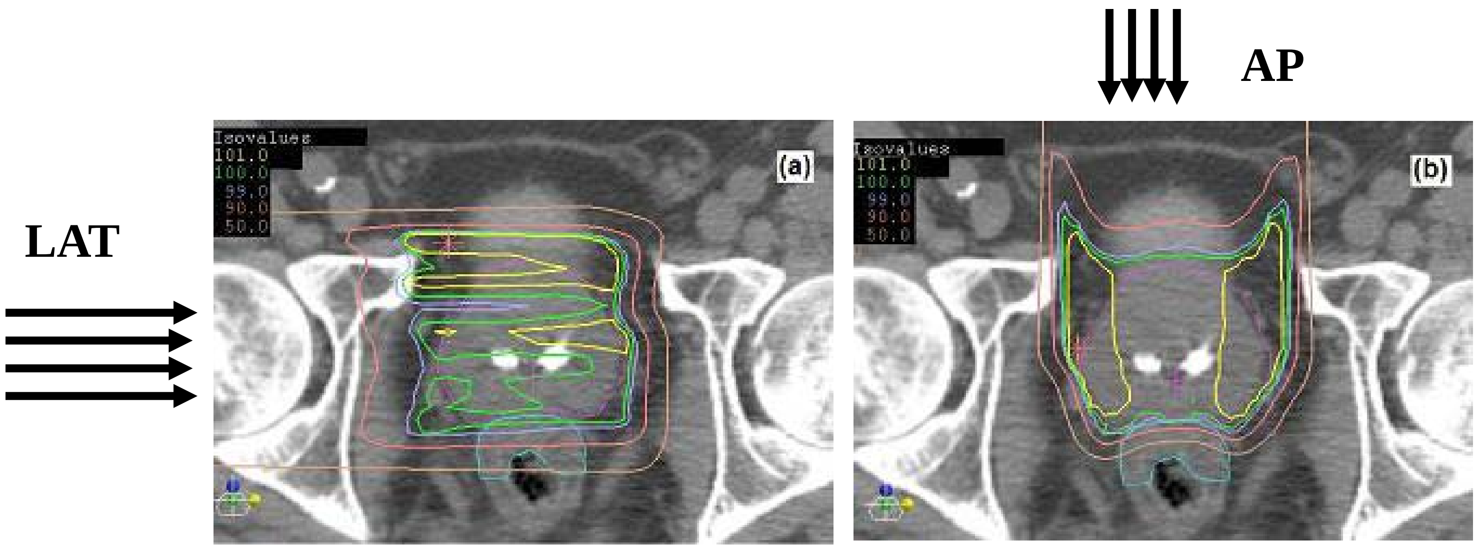
Range uncertainties sometimes limit our ability to exploit the end of range and thus negate some of the potential advantages of proton therapy

Example: Prostate treatments

Protons and Prostate Treatments

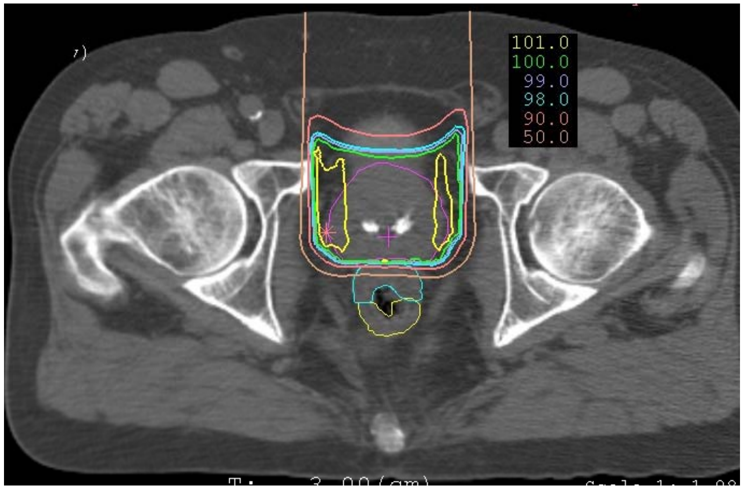
Current technique: Lateral fields
Use lateral penumbra (10 mm, 50-95%) to spare rectum
(penumbra not better than 15 MV photon fields)

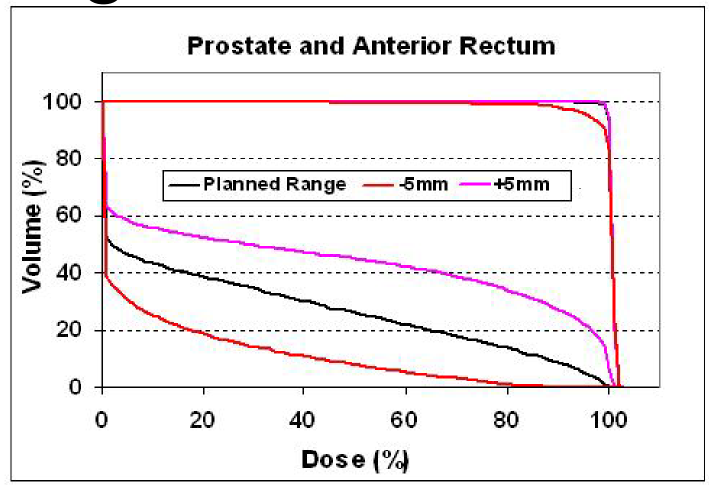
Why not AP fields?
Use much sharper distal penumbra (~ 4 mm, 50-95%)

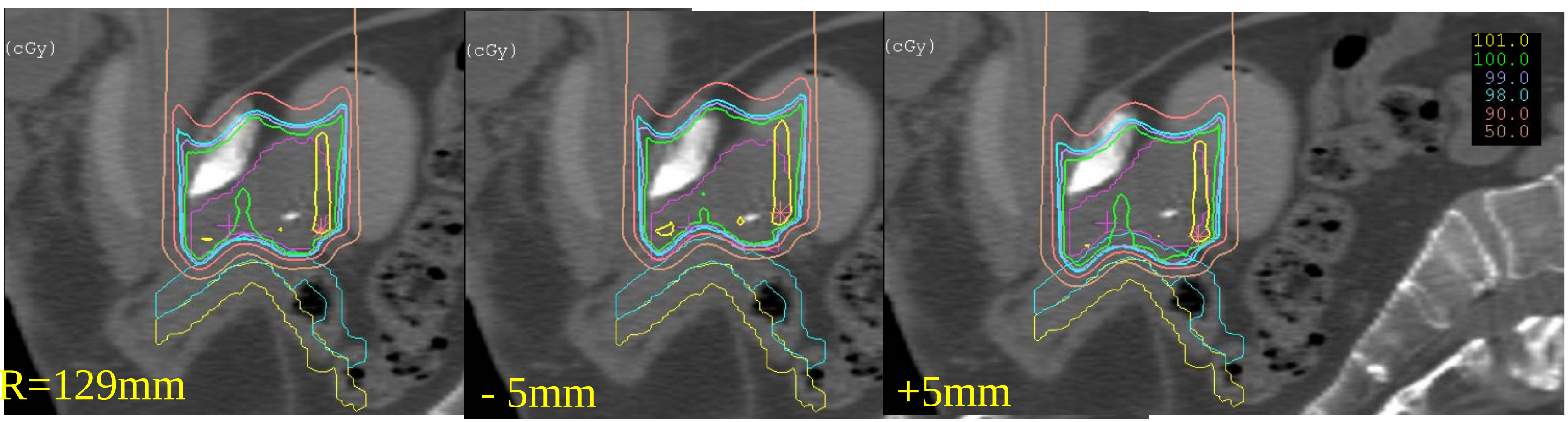


Predicting the range

Effect of 5 mm Range Variation



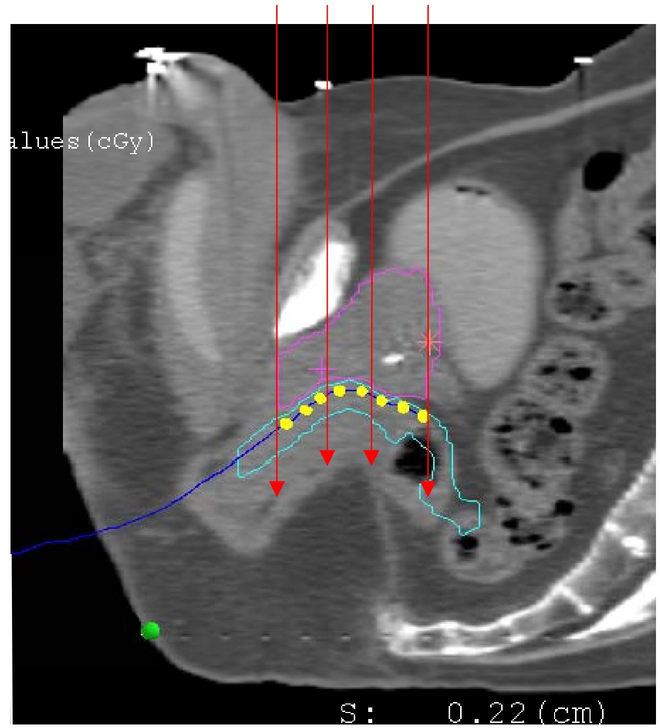


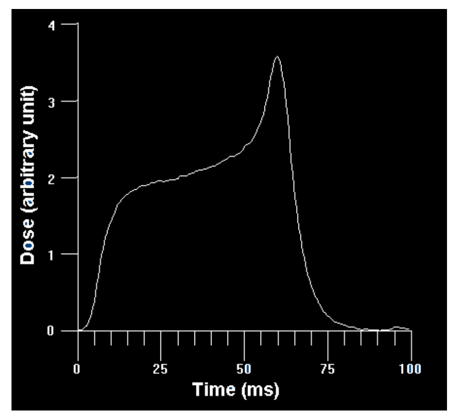


Correct Range Undershooting Overshooting

Predicting the range

1) Use balloon with detector array embedded on the surface
2) Deliver dose (< 1 cGy) for 500 ms using a few cm of extra beam range to cover dosimeters
3) Measure dose rate functions by a multi-channel electrometer
4) Match data with “ruler” to determine WEPL at dosimeters
5) Compare with planning calculations to adjust beam range
6) Commence treatment and measure distal tail dose by dosimeters as verification

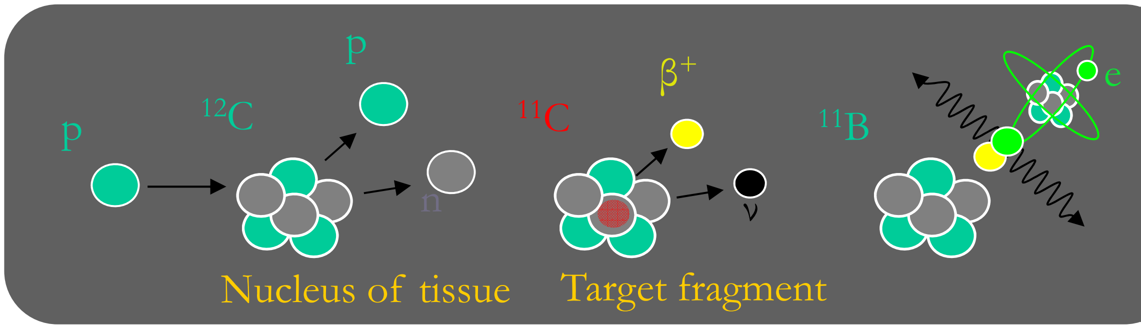




Conclusion II:

- Proton treatment planning needs to be done by experienced planners who understand the impact of range uncertainties.
- For some sites (e.g. prostate) range uncertainties prevent us from exploiting the full potential of proton therapy.
- In vivo systems can potentially be used to validate the range

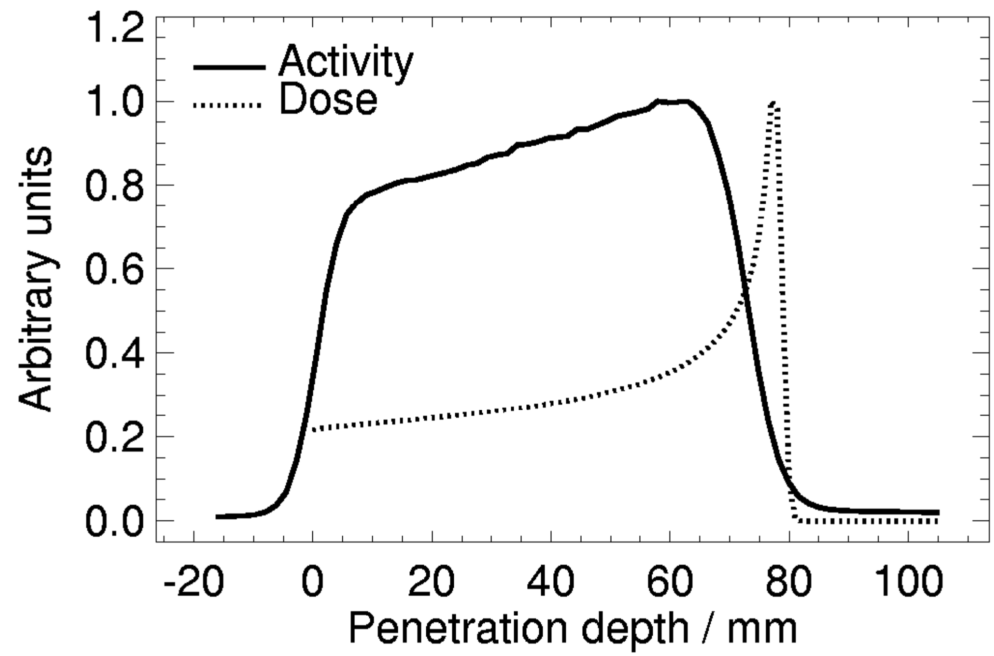
Validating the range



$^{16}O(p,3p3n)^{11}C$
$^{16}O(p,pn)^{15}O$
$^{16}O(p,2p2n)^{13}N$
$^{12}C(p,pn)^{11}C$

$A(z) \neq D(z)$

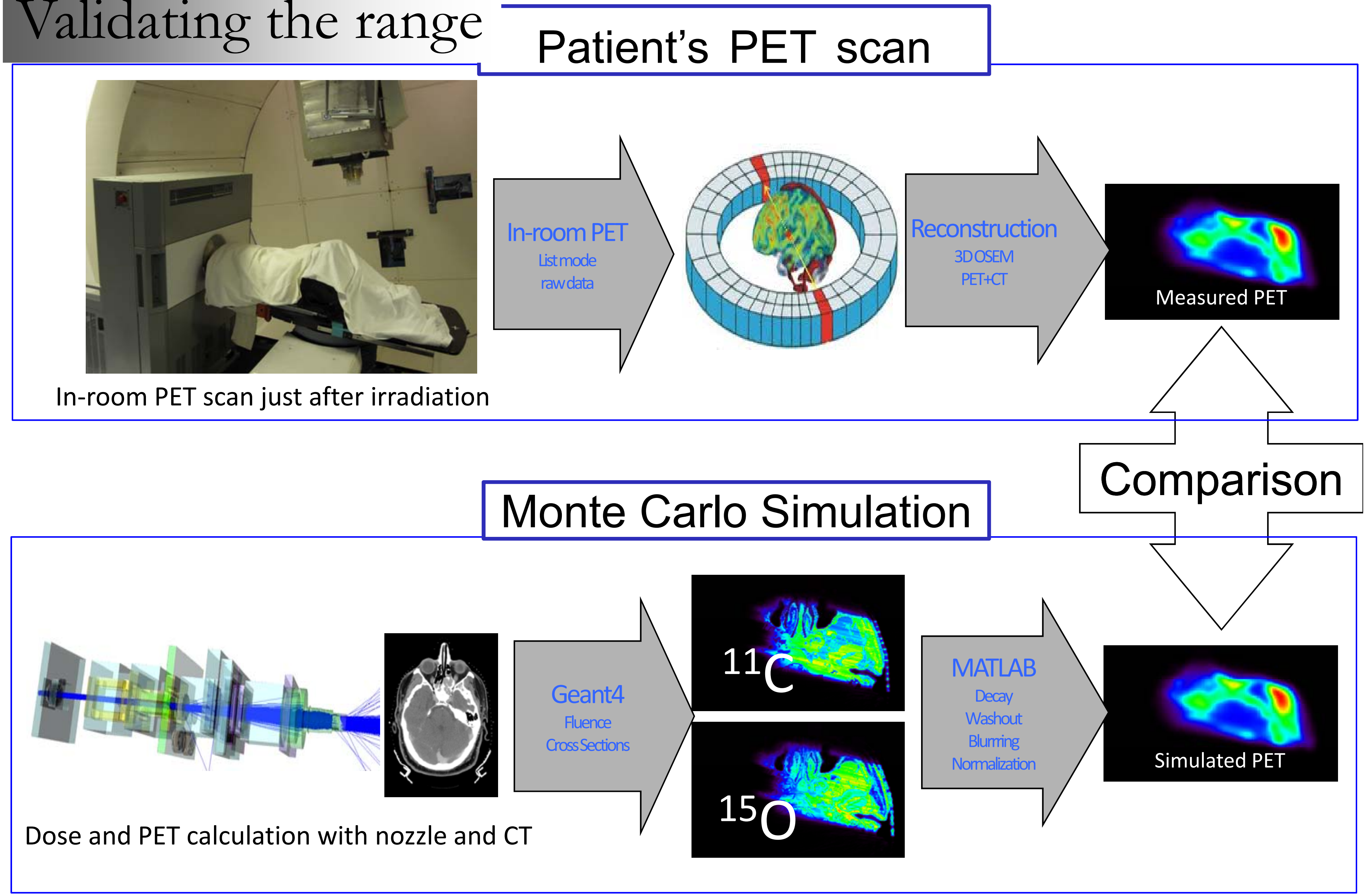
Measured Activity has to be compared with calculation



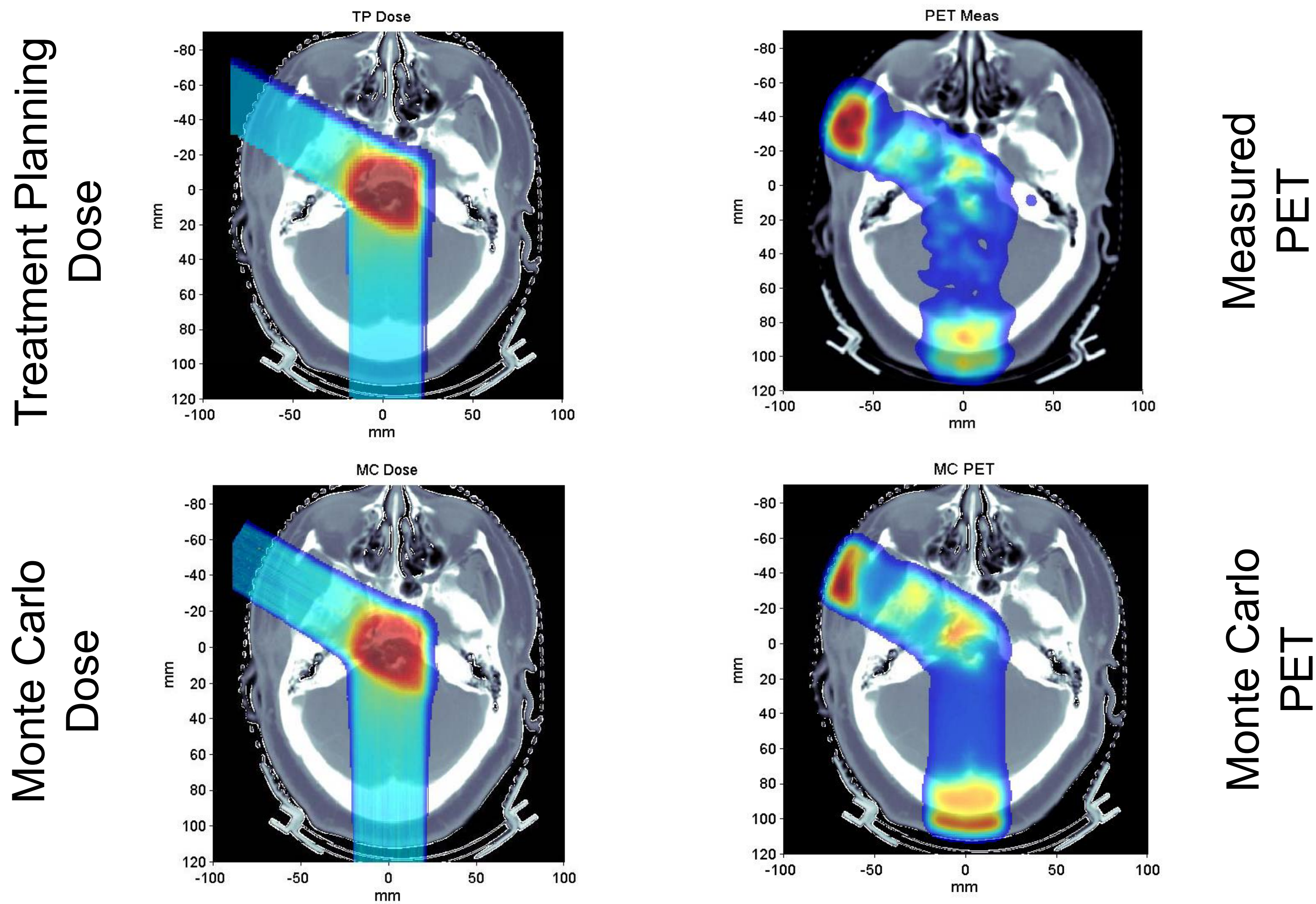
Validating the range

Isotope	Half life (min)
^{15}O	2.03
^{11}C	20.33
^{13}N	9.96

Validating the range

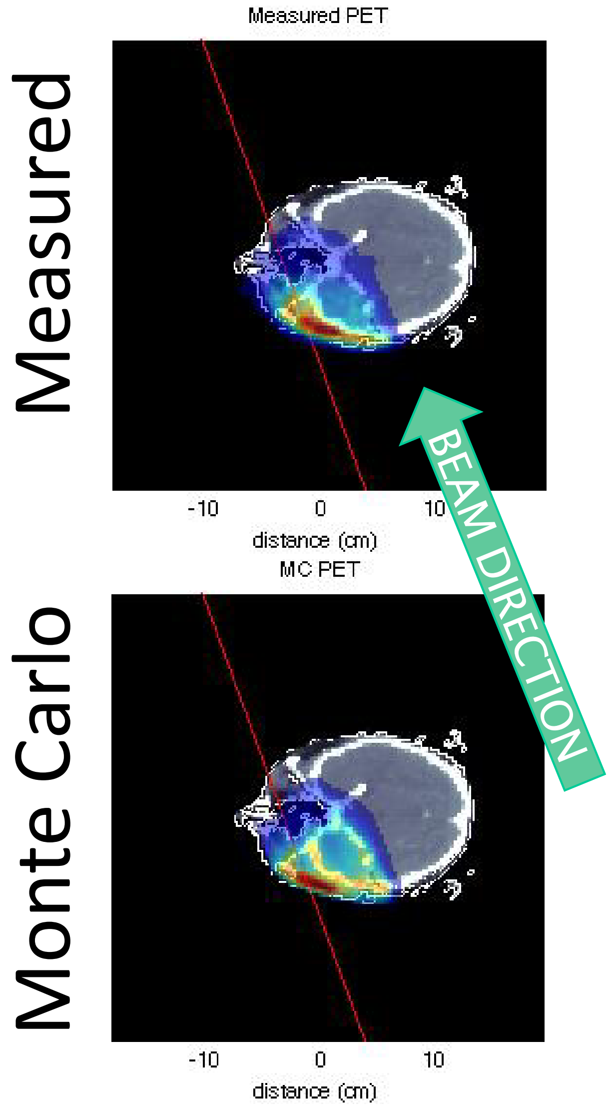


Validating the range

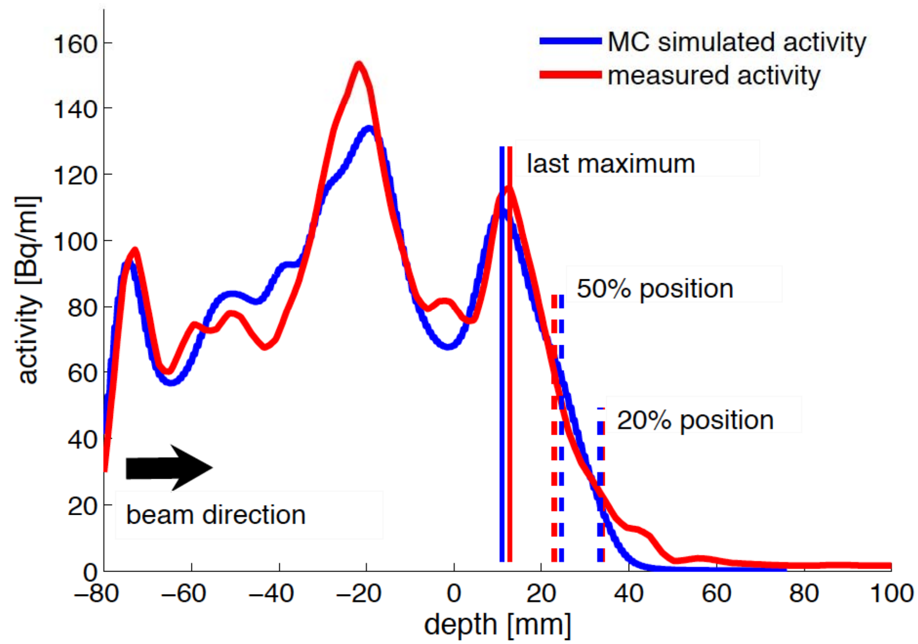


K. Parodi, H. Paganetti, H.A. Shih, et al.
Int. J. Radiat. Oncol. Biol. Phys. 68, 920-934 (2007)

Validating the range



current accuracy in soft tissue ~5mm
current accuracy in bone ~2mm

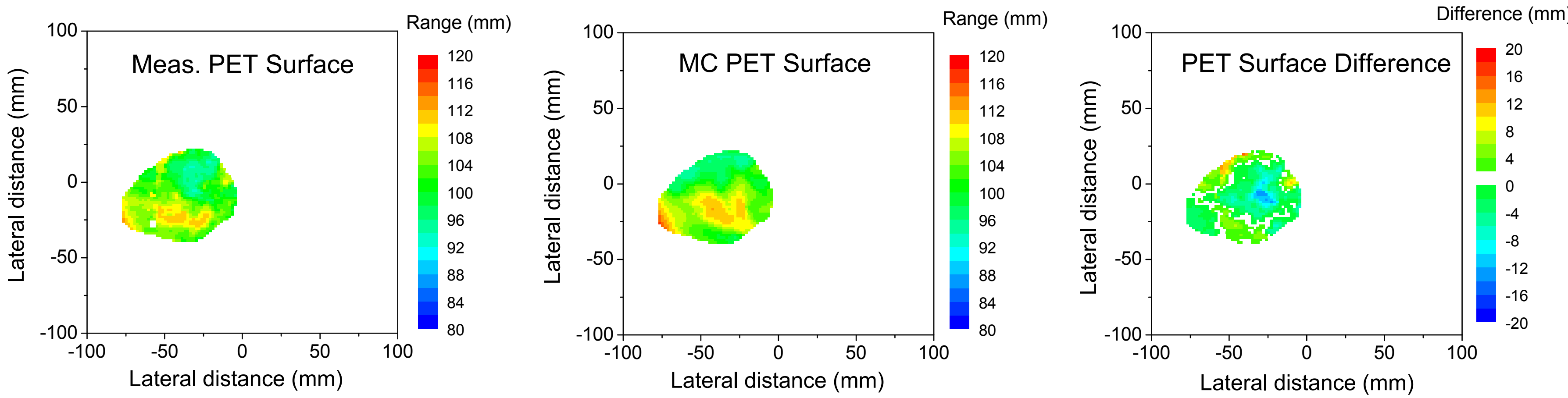


Shift

$$R_{diff} = \arg\min_{\delta}\left(\sum_{i\in M}|A_{meas}(x_i) - A_{ref}(x_i - \delta)|\right)$$

Validating the range

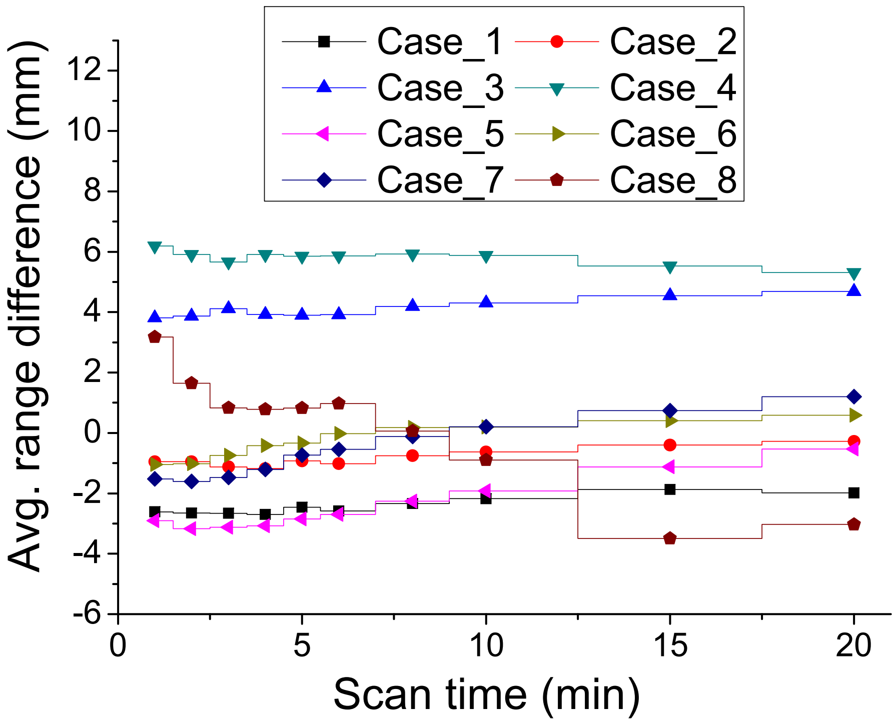
PET Surface Comparison

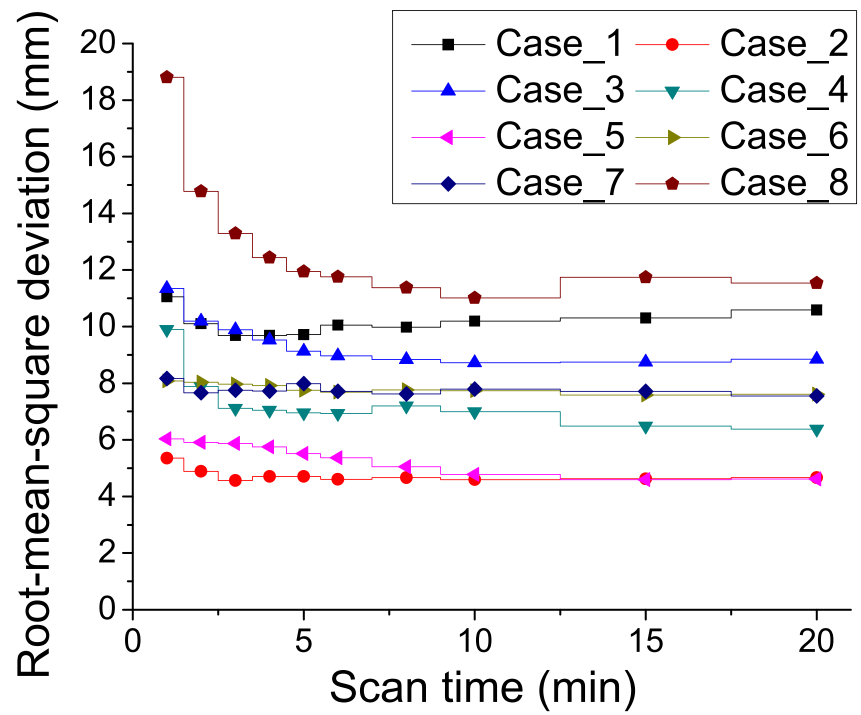


$$Avg.Difference = \frac{\sum_{i=1}^{n} (X_{meas,i} - X_{mc,i})}{n} \qquad RMSD = \sqrt{\frac{\sum_{i=1}^{n} (X_{meas,i} - X_{mc,i})^2}{n}}$$

- $X_{meas,i}$ = reference range of measured PET, $X_{mc,i}$ = reference range of MC PET
- Reference range = midpoint of 50% and 25% location of maximum PET activity.
- Avg. Difference = average difference in reference ranges of measured and simulated PET.
- RMSD = root-mean-square deviation over PET surfaces.

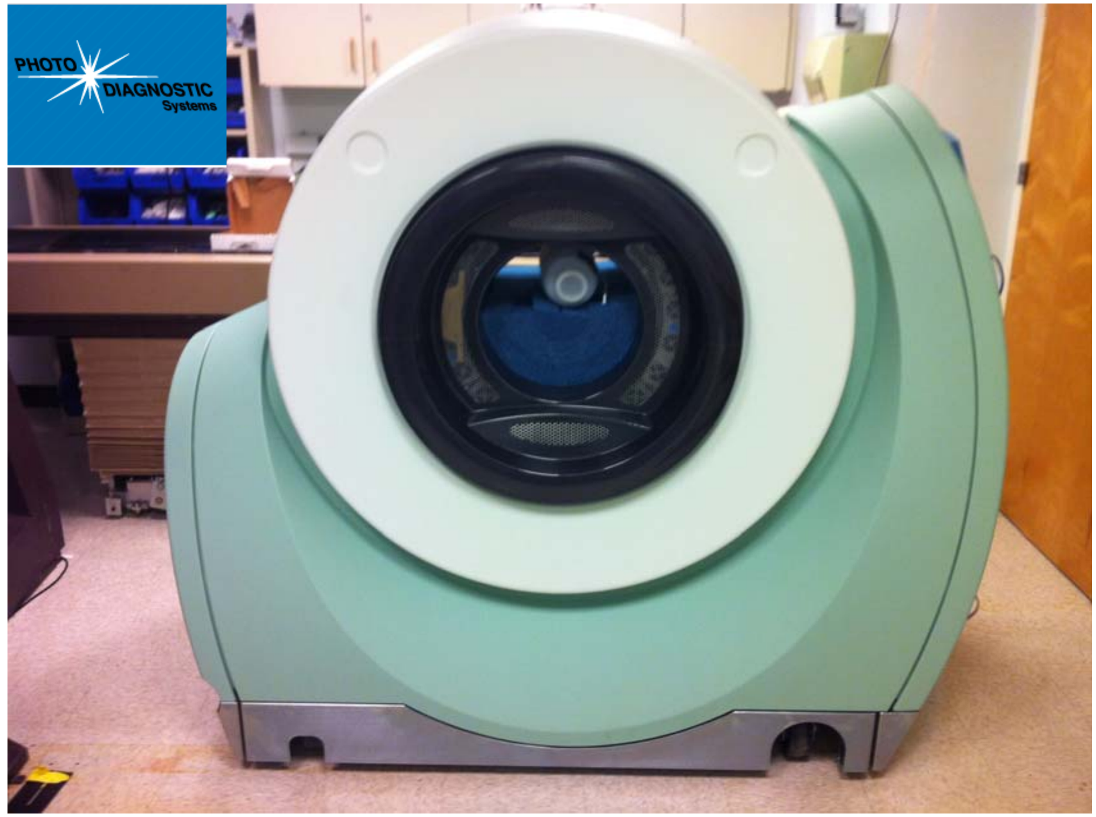
Validating the range





- The uncertainty in range verification using PET does not decrease further after ~5 min of scan time
- In-room PET scanner is currently being replaced by in-room PET/CT

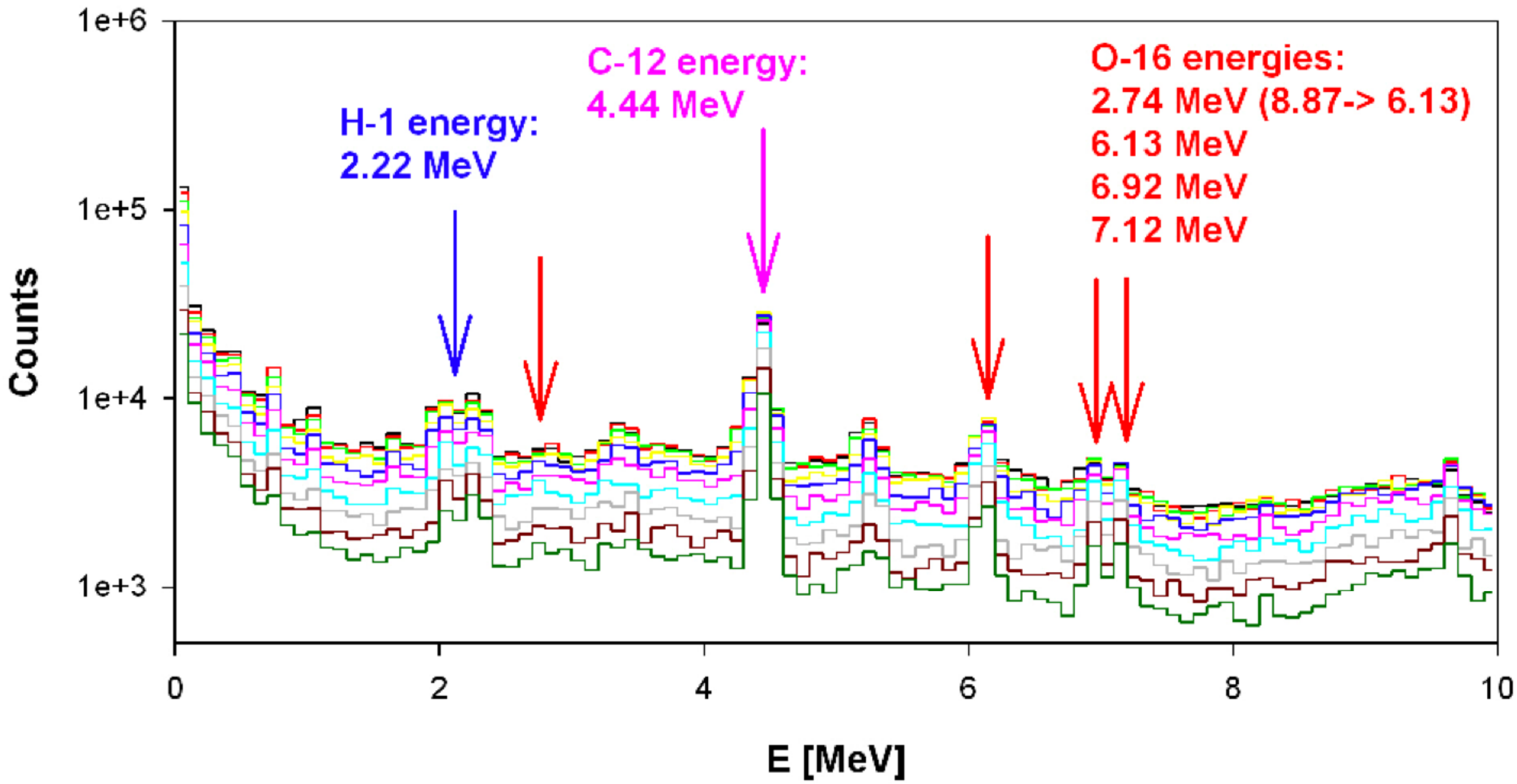
Validating the range



- ✓ Higher sensitivity - Acquisition time of 2-3 min
- ✓ Higher spatial resolution - 4.3 mm (In-room PET) vs. 2.0 mm (In-room PET/CT)
- ✓ CT component for accurate image co-registration - One of the largest technical obstacles is the co-registration accuracy between PET and CT image

Validating the range

Prompt gamma radiation

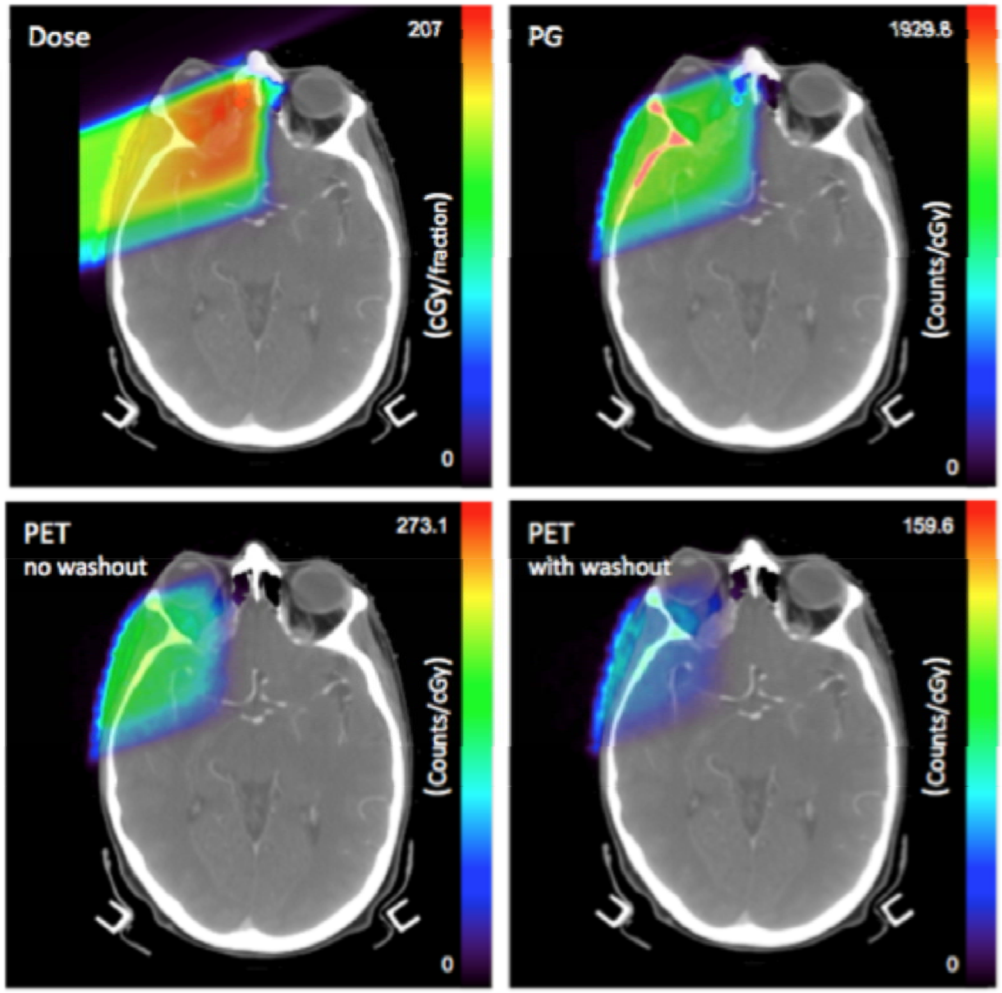


Validating the range

DOSE

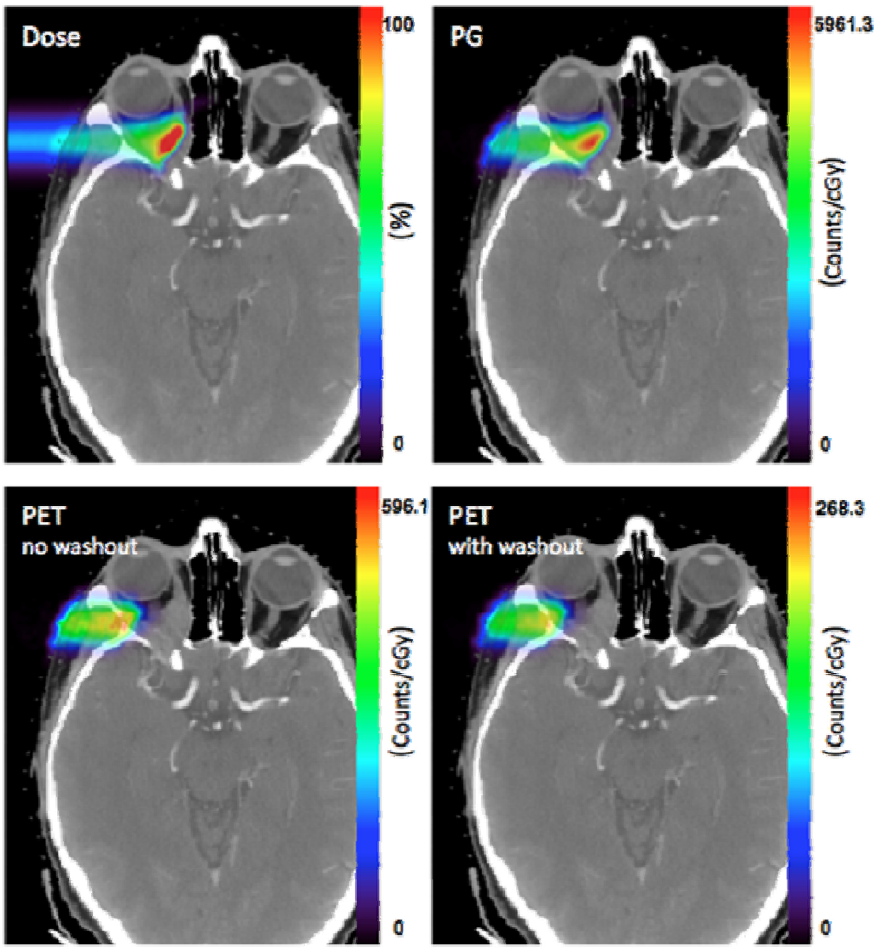
PromptGamma

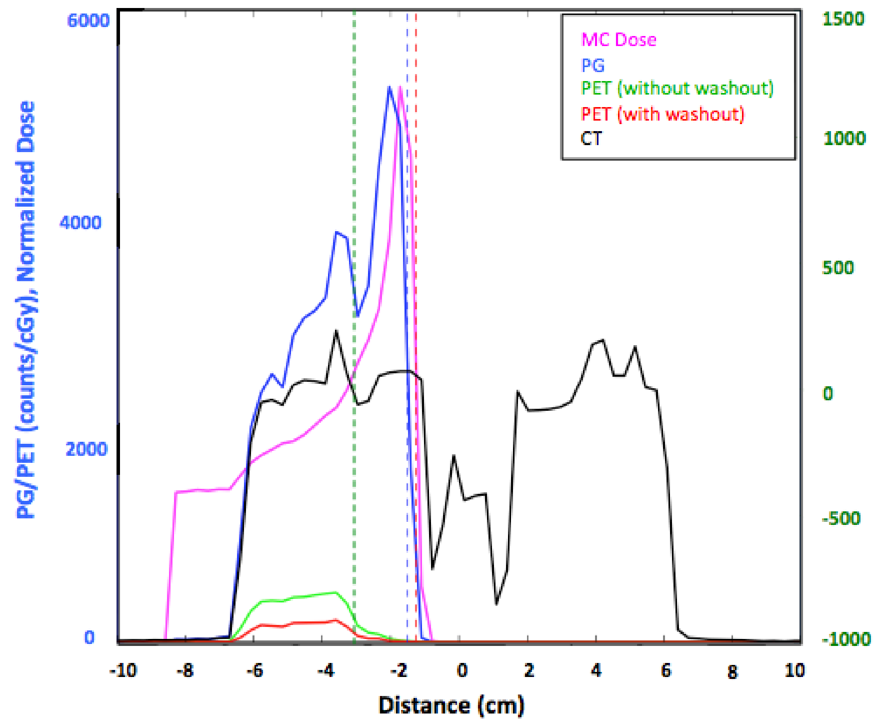
PET



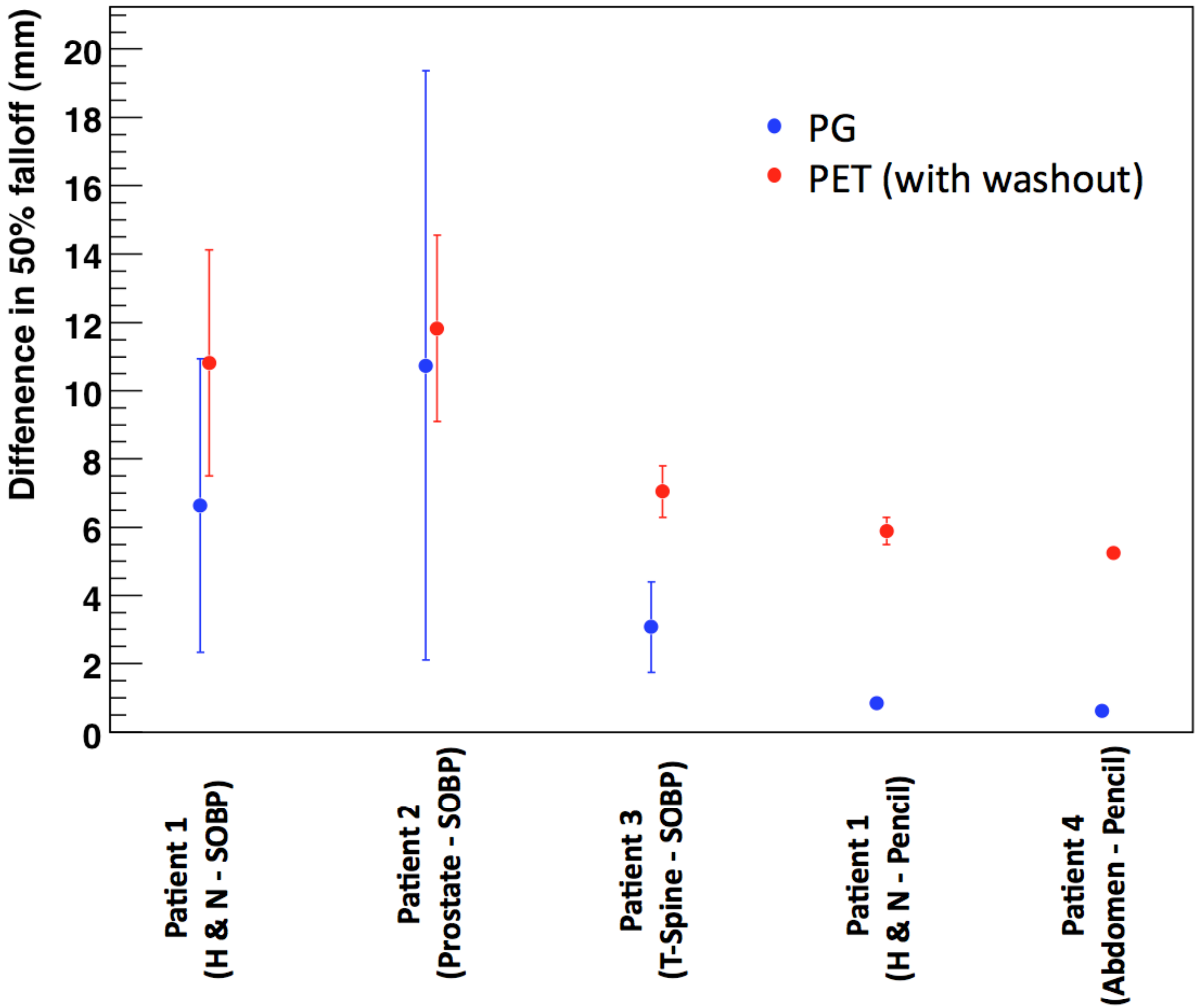
M. Moteabbed, S. España, H. Paganetti
Phys. Med. Biol. 56, 1063-1082 (2011)

Prompt Gamma analysis; Adenoid cystic c.
- Beam scanning -





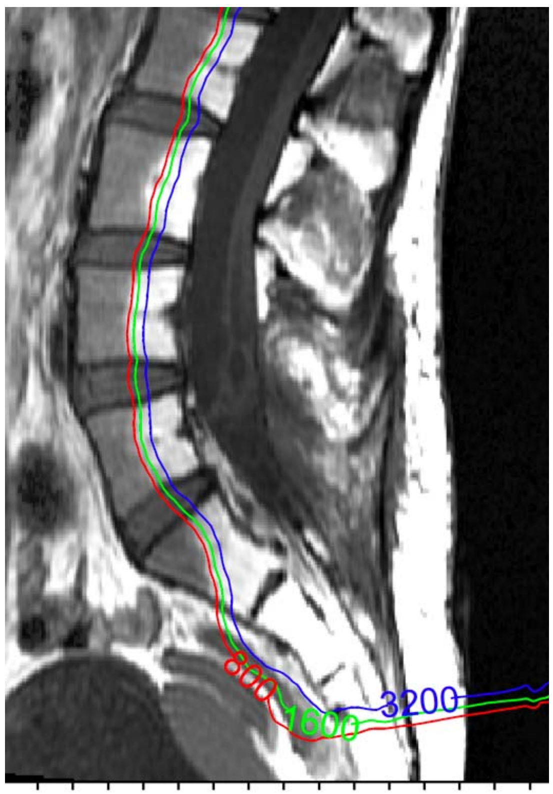
Validating the range

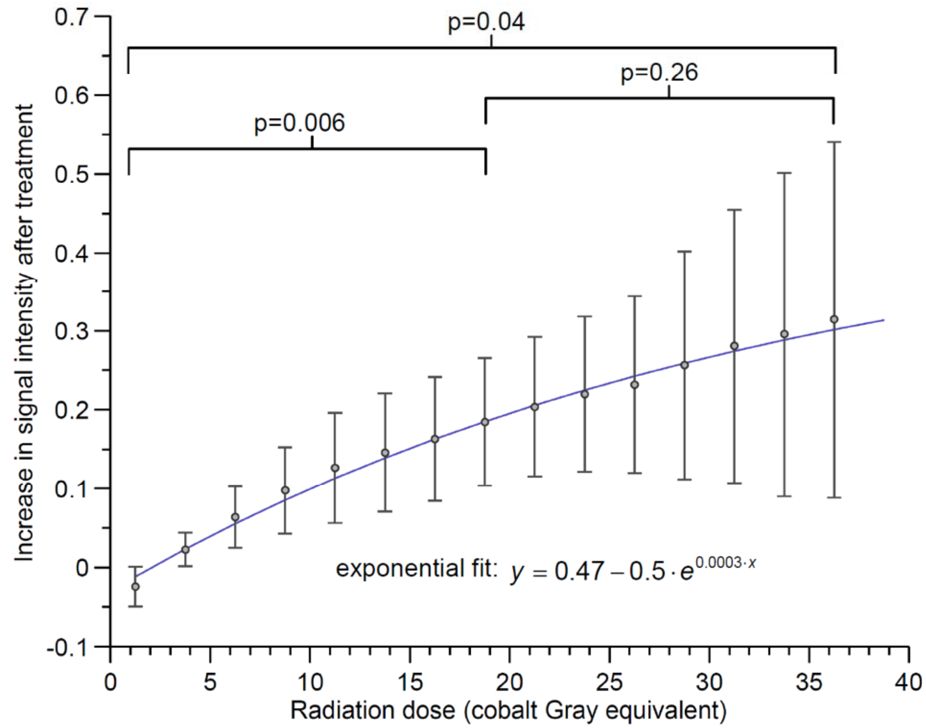


Validating the range

After radiation exposure, vertebral bone marrow undergoes fatty replacement

T-1 weighted spin-echo sequence



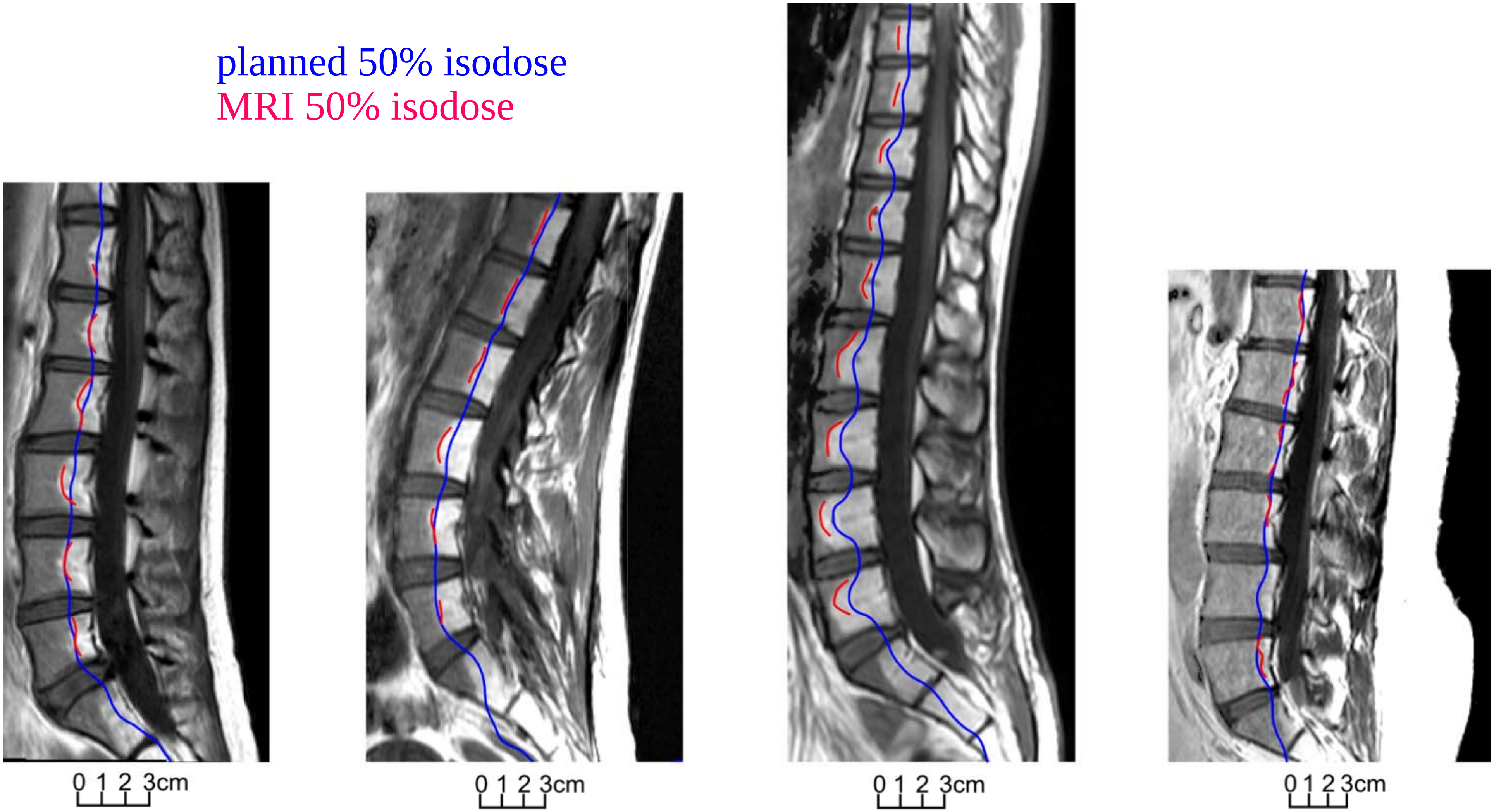


Overall dose-signal intensity derived from the lateral penumbra in the sacrum

Gensheimer M F, Yock T I, Liebsch N J, Sharp G C, Paganetti H, Madan N, Grant P E and Bortfeld T 2010
Int J Radiat Oncol Biol Phys **78** 268-75

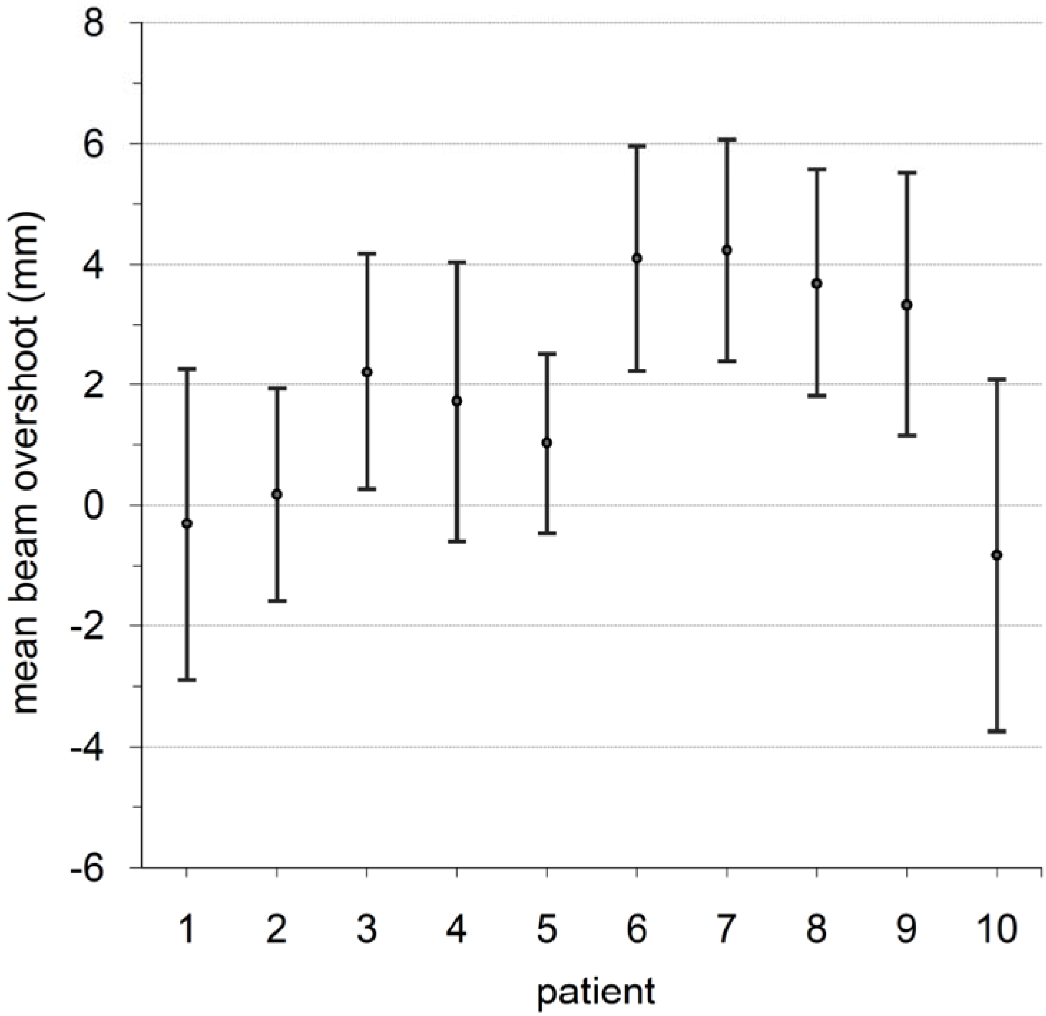
Validating the range

planned 50% isodose
MRI 50% isodose



Pt. 1, 36 Gy (RBE)   Pt. 5, 50.4 Gy (RBE)   Pt. 6, 36 Gy (RBE)   Pt. 10, 36 Gy (RBE)

Validating the range



Validating the range

Conclusion III:

- Proton therapy offers unique imaging capabilities due to nuclear interactions in tissues
- The highly conformal dose distributions in proton therapy offer the potential of outcome imaging

SUMMARY

The physical characteristics of proton beams

- … cause dosimetric advantages compared to photon beams
- … results in unique dosimetric uncertainties
- … offer unique imaging and adaptive therapy strategies

- uncertainties in predicting the proton beam range in patients are ~3-5% (~2.5% with advanced dose calculation methods)
- uncertainties can be mitigated in (robust) IMPT optimization
- In vivo detectors might allow to adjust the range
- unique in vivo dose (range) verification methods (PET, prompt-gamma, MRI) are being worked on

Acknowledgements

“Physics Research” and “Physics Translational Research” at Massachusetts General Hospital – Radiation Oncology