Perils of Proton Therapy

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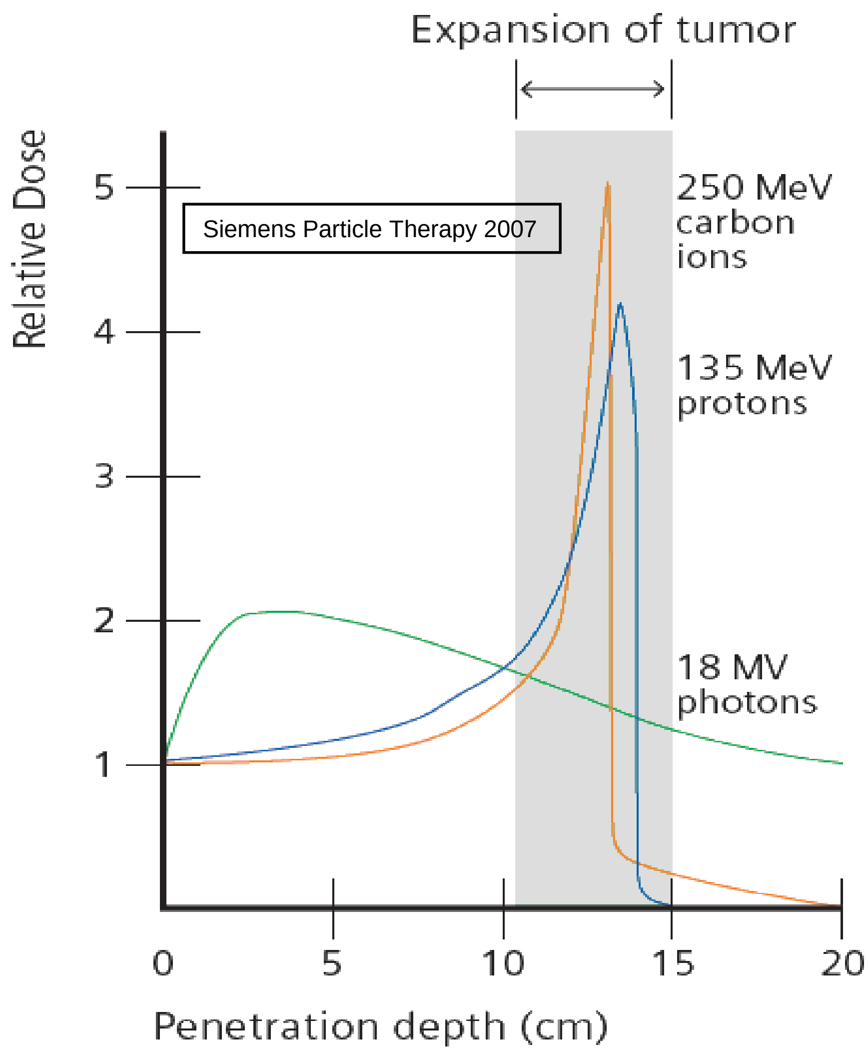
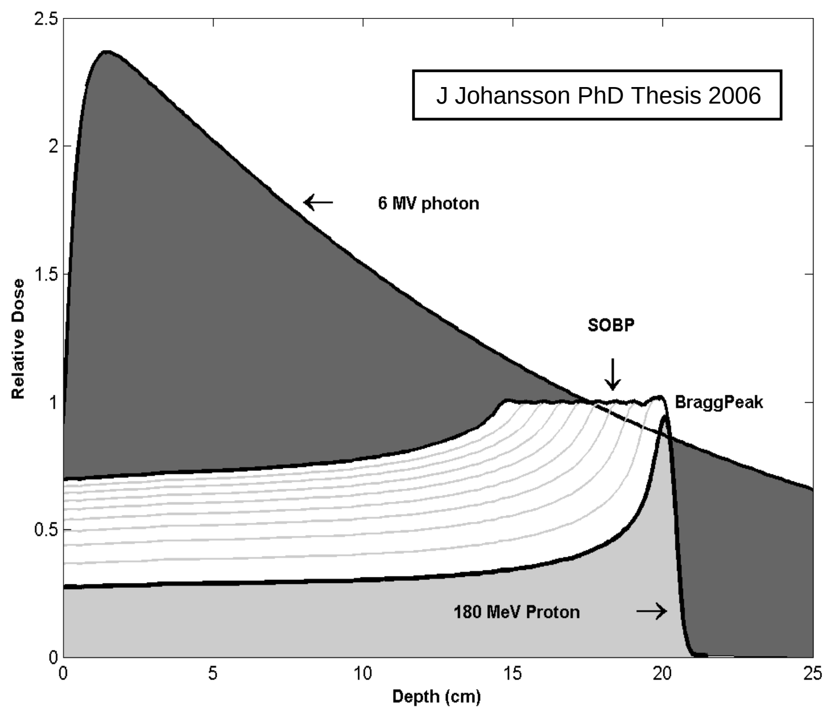
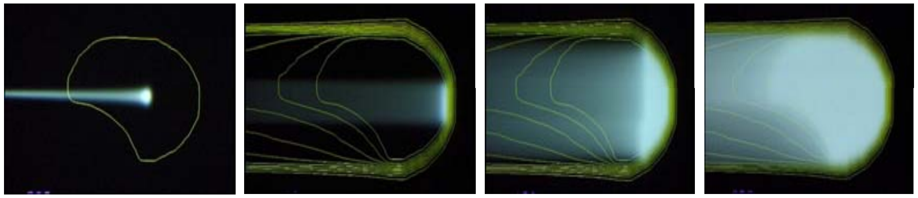
Are there any issues with these illustrations?







Proton spot scanning (from PSI home page, Pedroni *et al*)

Yes, they have made Proton Therapy <u>prone to hyperbole</u>

“Proton therapy can strike a tumor with **millimeter accuracy, yet spare healthy tissue around the tumor and cause very few, if any, side effects.** In the Proton Therapy Center, we’re able to deliver energy like never before.”

“It sounds like power belonging only to a superhero: a high-powered beam that is able to **zap a millimeter area within someone’s body, and yet not harm the surrounding healthy cells.** Heroic — yes, but this is not in comic books. It’s happening in real life, in nearby XXXXXX.”

“When treated with Proton Beam Therapy, **radiation is controlled while inside the body, that enables the physician to deliver full or higher doses while sparing surrounding healthy tissues and organs.** It allows to deliver necessary dose of radiation without causing damage to healthy tissues.”

“With protons.. **energy can be very precisely controlled to place the Bragg peak within a tumor** or other tissues that are targeted to receive the radiation dose. Because the protons are absorbed at this point, normal tissues beyond the target receive very little or no radiation”.

Promises of Proton Therapy

Compared to external beam photon therapy, proton therapy:

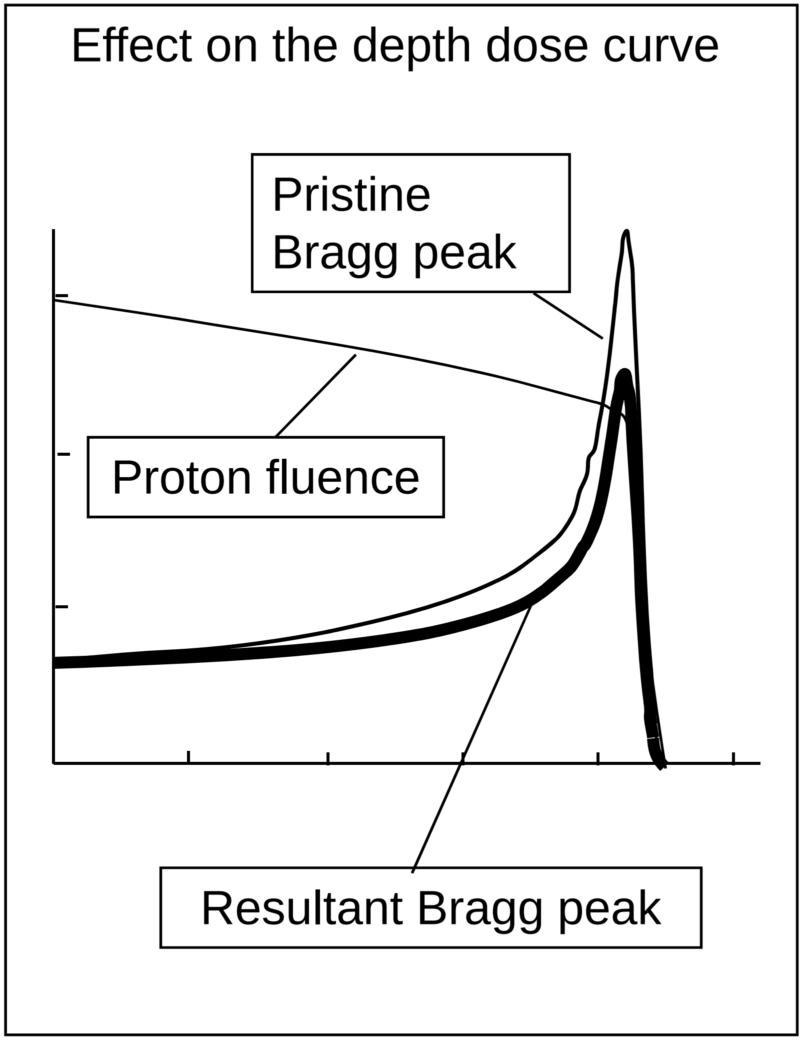
- Decreases the integral dose due to the “finite range” of protons
- Reduces the volume of normal tissue exposed to low doses, potentially lowering the risk of second malignancies. This risk is notably higher for young patients, as they are more at risk to future radiation induced cancers.
- Has demonstrated advantage for treating small tumor volumes at shallow depths (eye tumors and CNS such as chordomas and chondrosarcomas)
- Has demonstrated advantage for treating a few select cases in almost all disease site

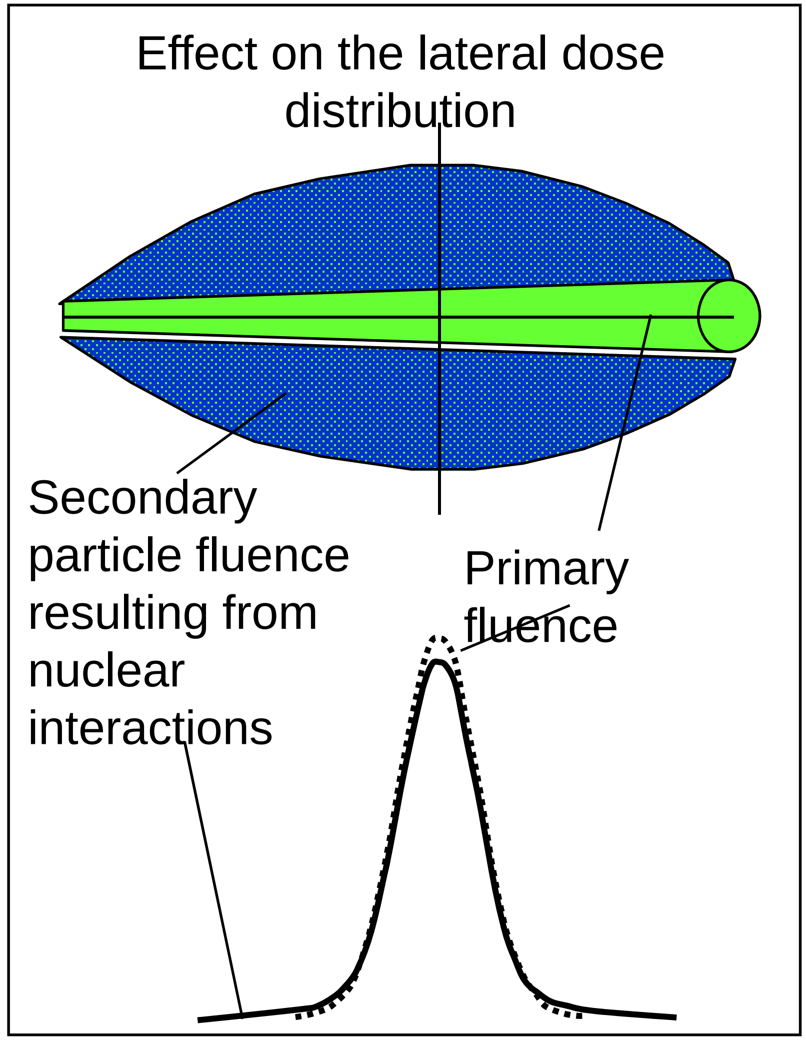
Perils of Proton Therapy

1. Uncertainties:
   - Consequences of nuclear interactions (neutrons)
   - Multiple Coulomb scattering (lateral penumbra)
   - Intrinsic basic physics uncertainty (I-values)
   - CT numbers (stopping powers; range),
   - Dose calculation errors due to complex inhomogeneities,
   - Intra-fractional organ motion,
   - Inter-fractional changes in anatomy and motion patterns,
   - Mis-registration of tissue compensators (passively scattered proton beams,
   - Uncertainties in immobilization devices and patient support devices
2. Evaluation of proton plans
   - How to evaluate a proton plan in the presence of various uncertainties?
     - PTV?
     - Error bars of dose distributions?

Nuclear Interactions

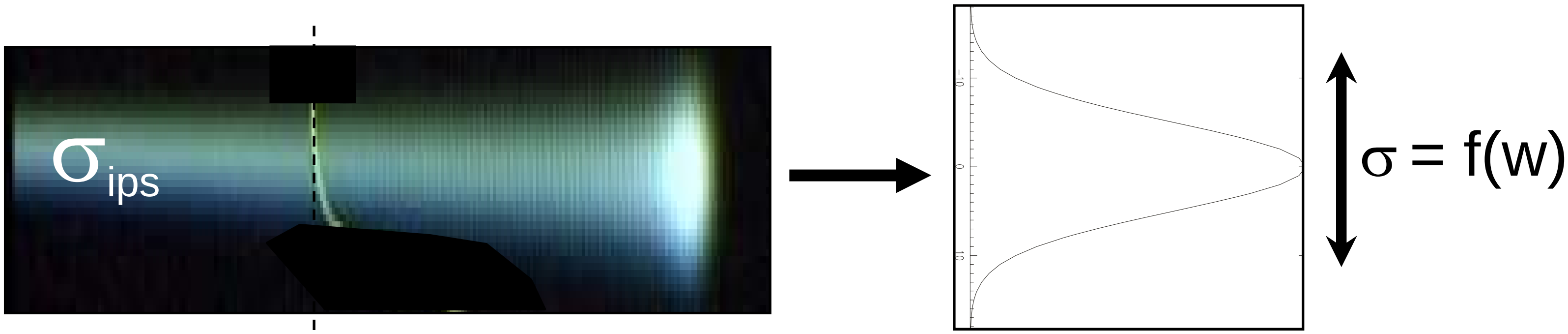
About 20% (~1%/g.cm^{-2})of primary protons lost to interactions with atomic nuclei

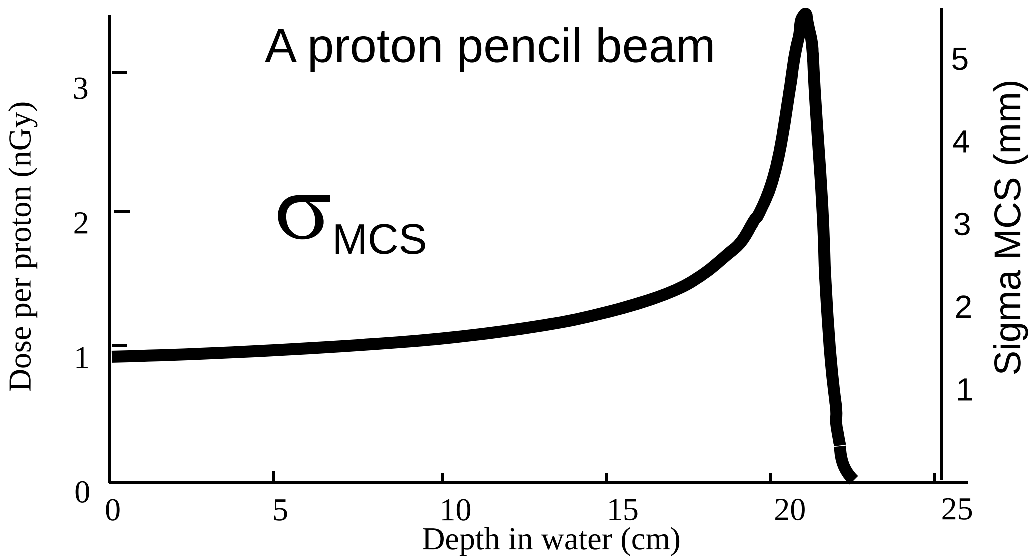




Lomax : AAPM SS 2003

Proton Scattering





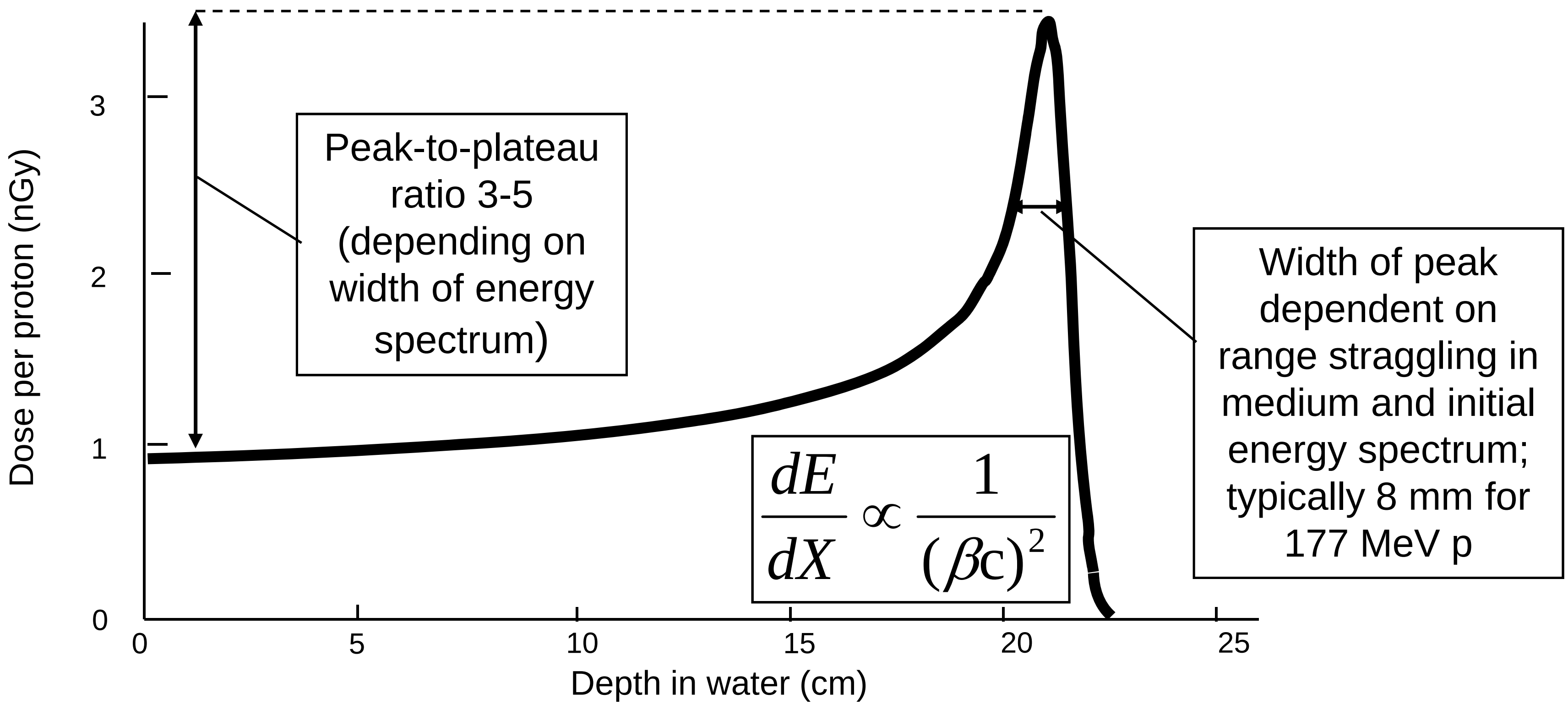
$$\sigma_{tot} = f(\sigma_{ips}, \sigma_{MCS})$$

(80-20%) lateral dose fall-offs at 10cm depth

Protons	– 5-8mm
6MV photons	– 6mm

Lomax : AAPM SS 2003

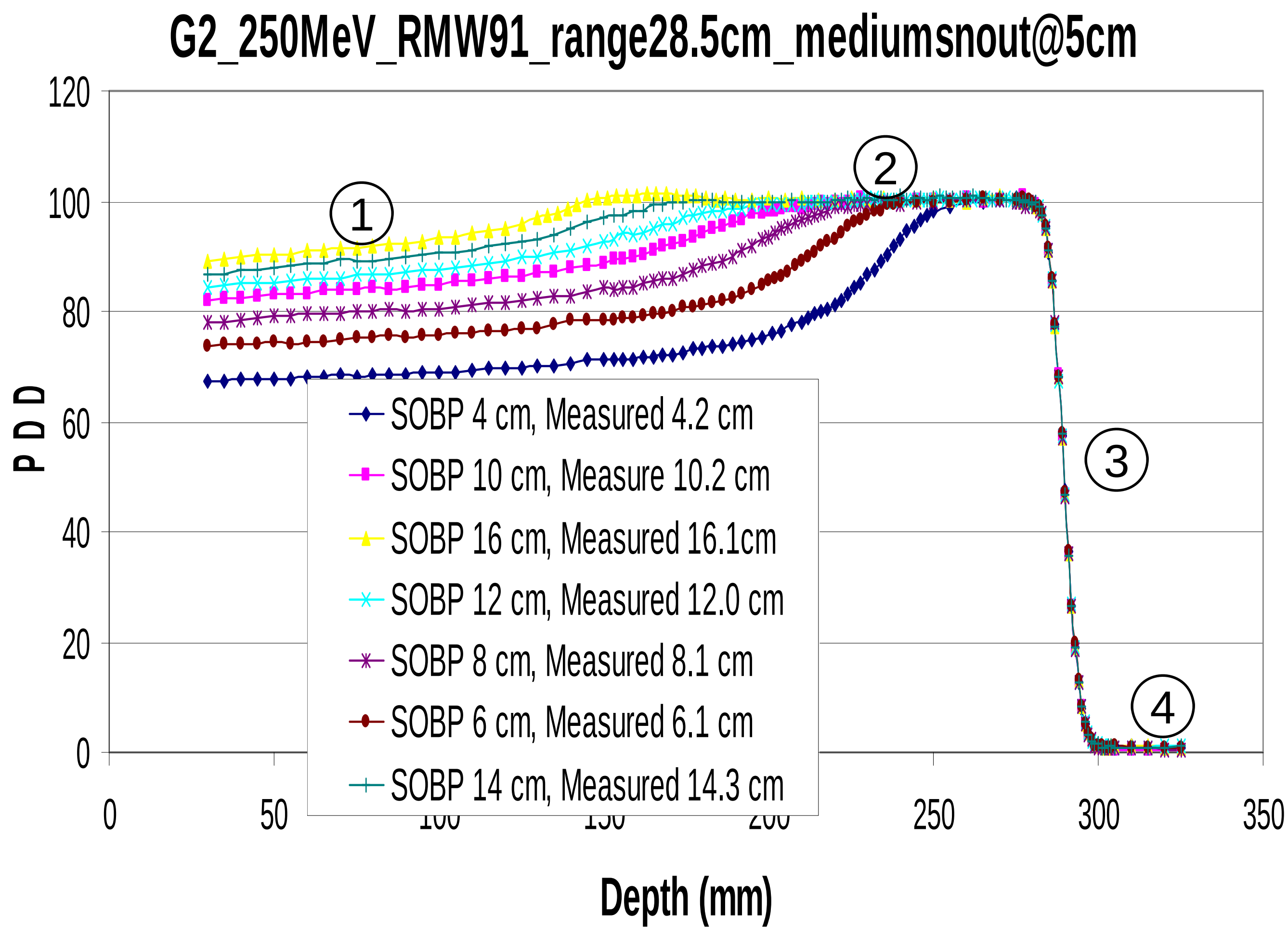
Proton Depth Dose (PDD)



Depth-dose curve for 177 MeV protons

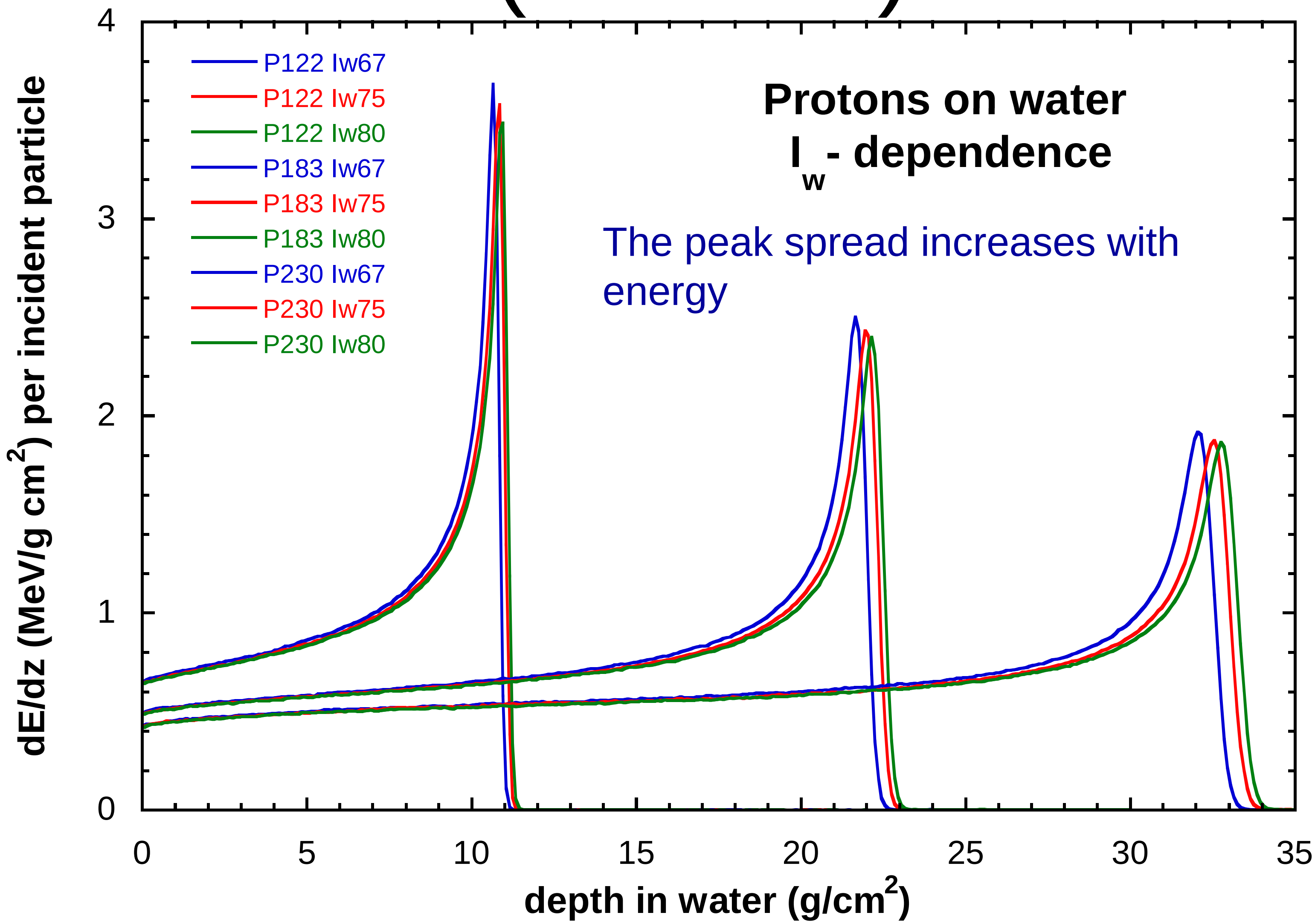
PDD as a function of SOBP widths

1. Excitation/ionization; Nuclear interaction
2. Excitation/ionization (Bragg Peaks); Nuclear interaction
3. Range straggling and energy spread
4. Neutrons from nuclear interactions

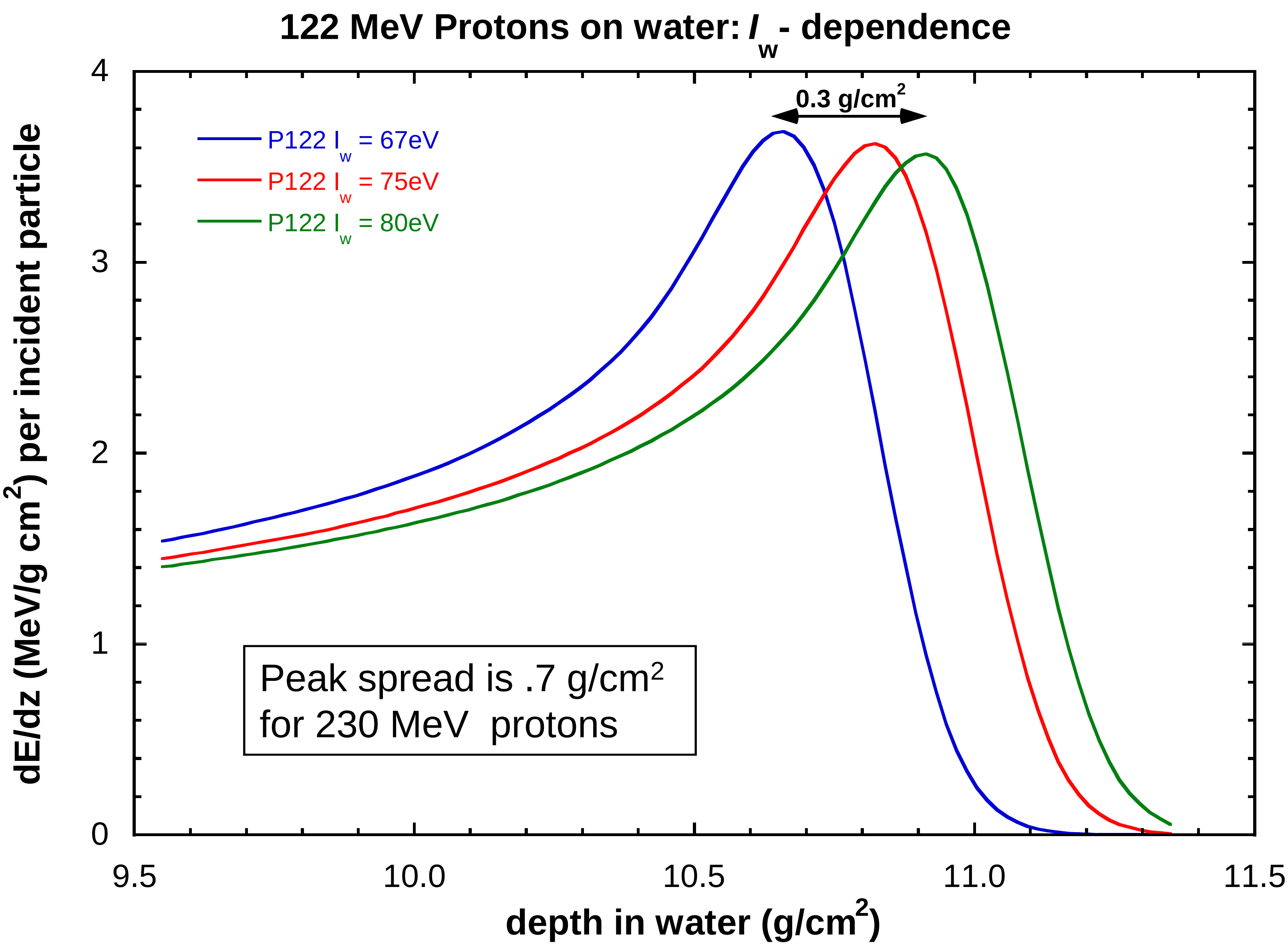


Note increase in entrance dose with increase in modulation.

Intrinsic basic physics uncertainty (I-values)



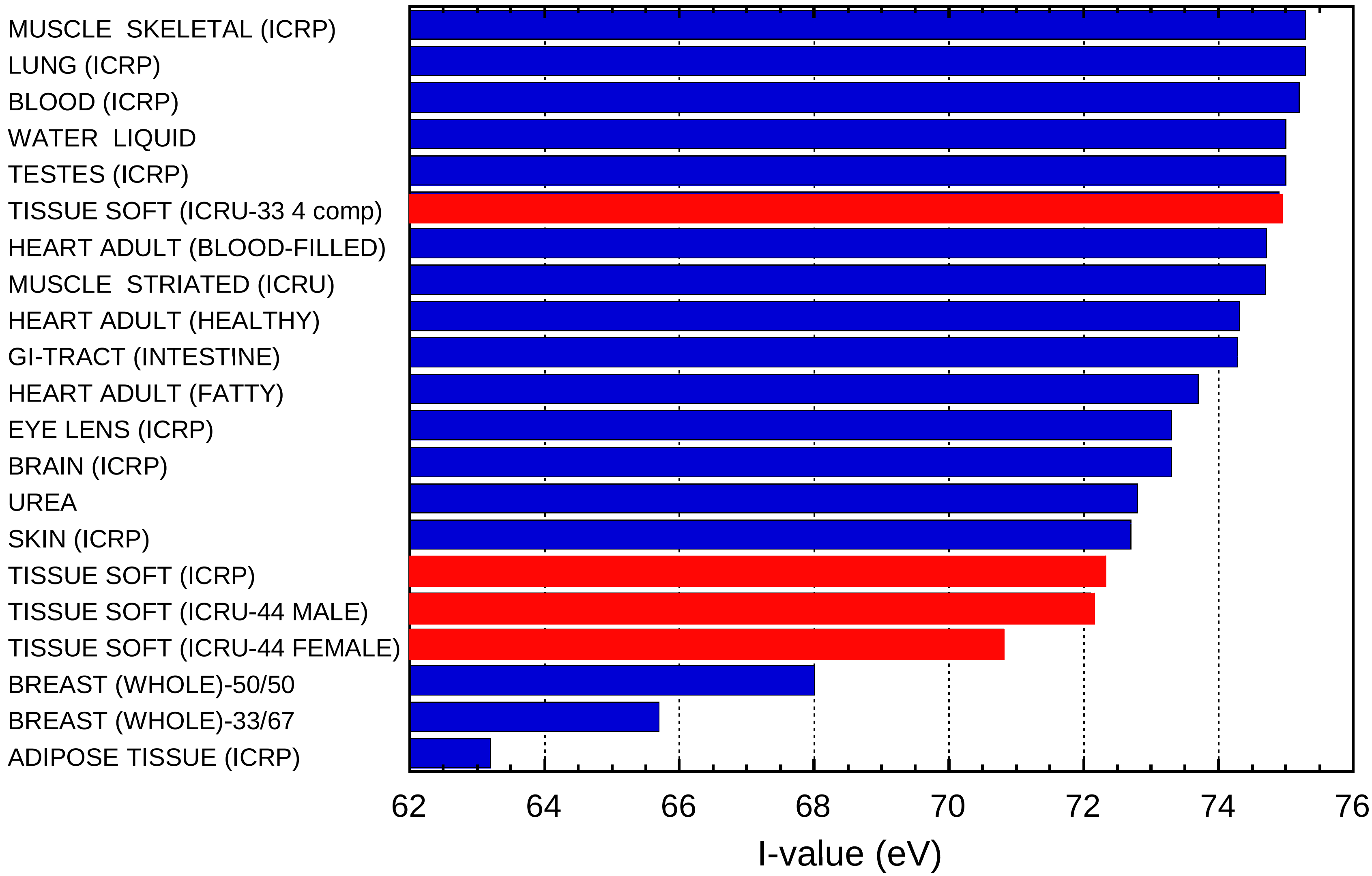
P Andreo, Phys Med Biol, 2009



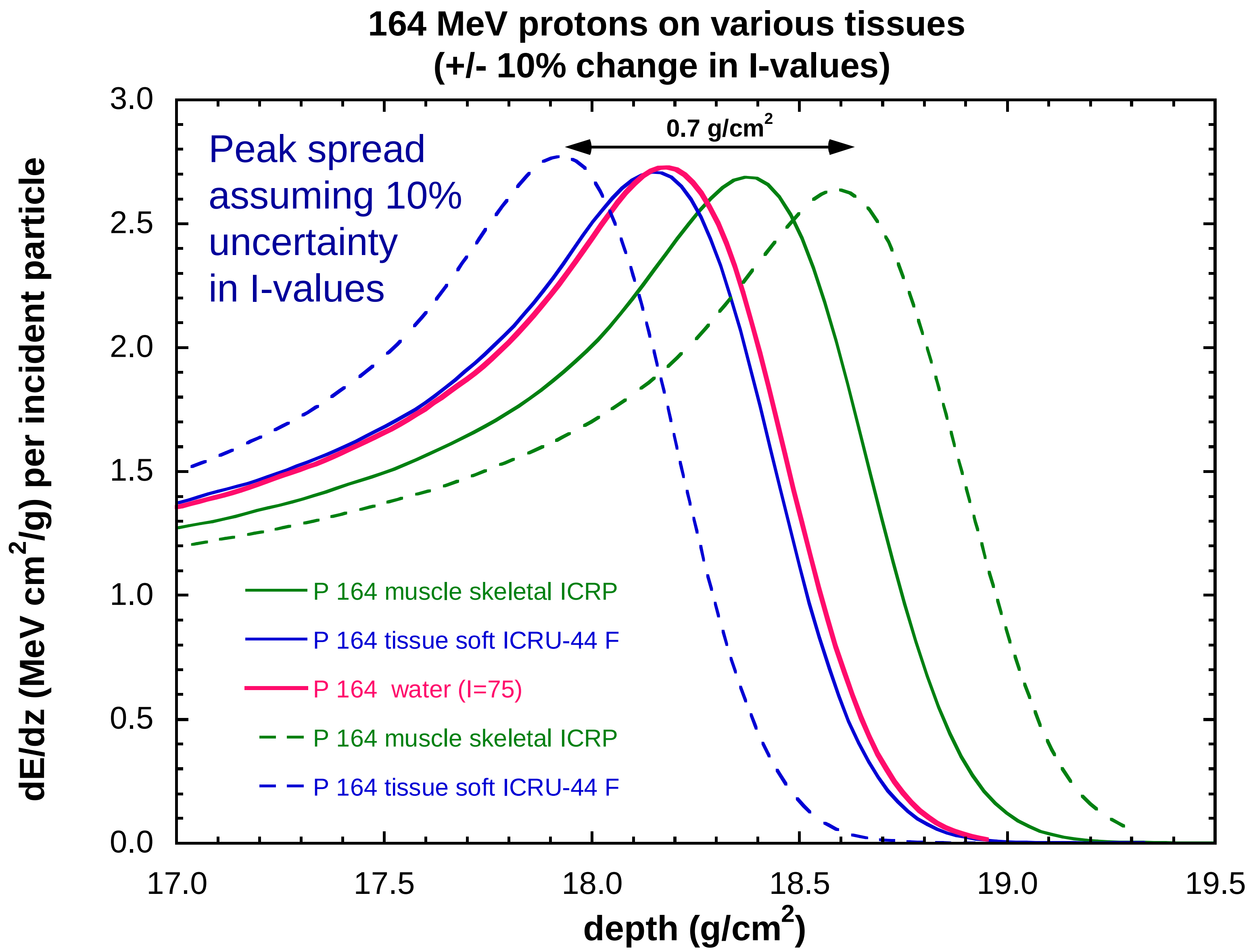
Intrinsic basic physics uncertainty makes the argument of "sub-millimeter precision" an issue, which deserves careful consideration

P Andreo, Phys Med Biol, 2009

average I-values of various soft tissues

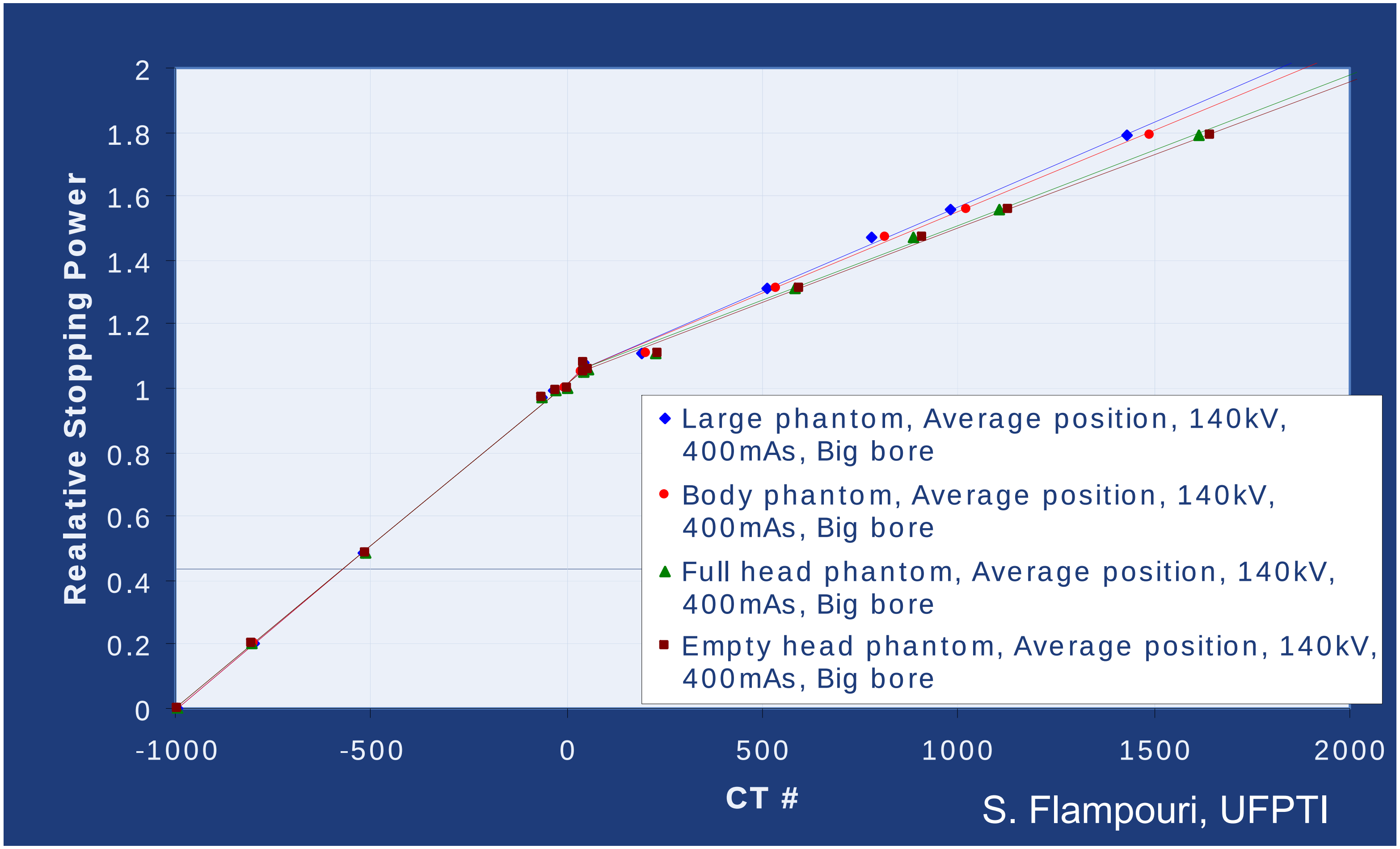


P Andreo, Phys Med Biol, 2009



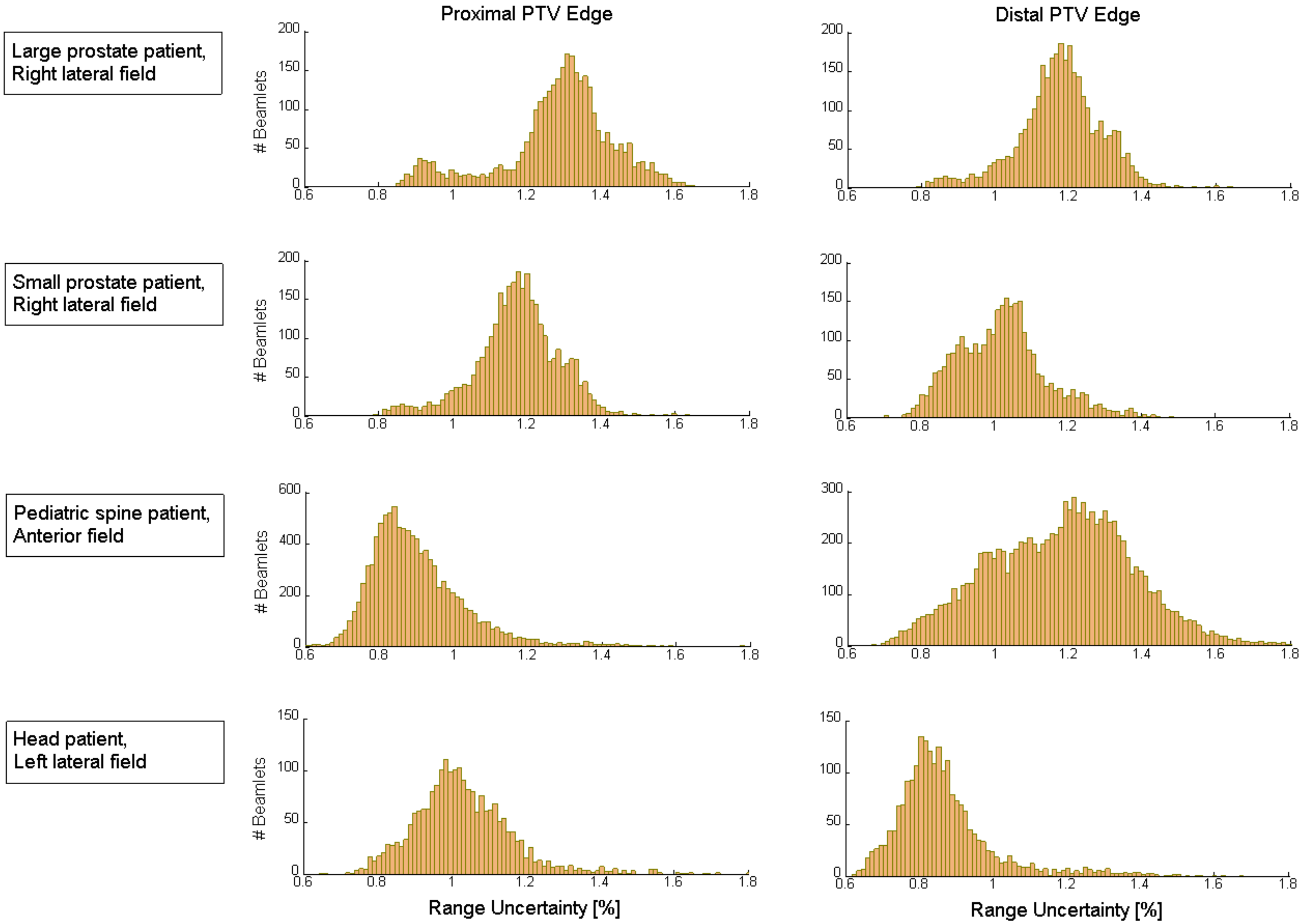
P Andreo, Phys Med Biol, 2009

HU-Stopping Power Calibration Curve



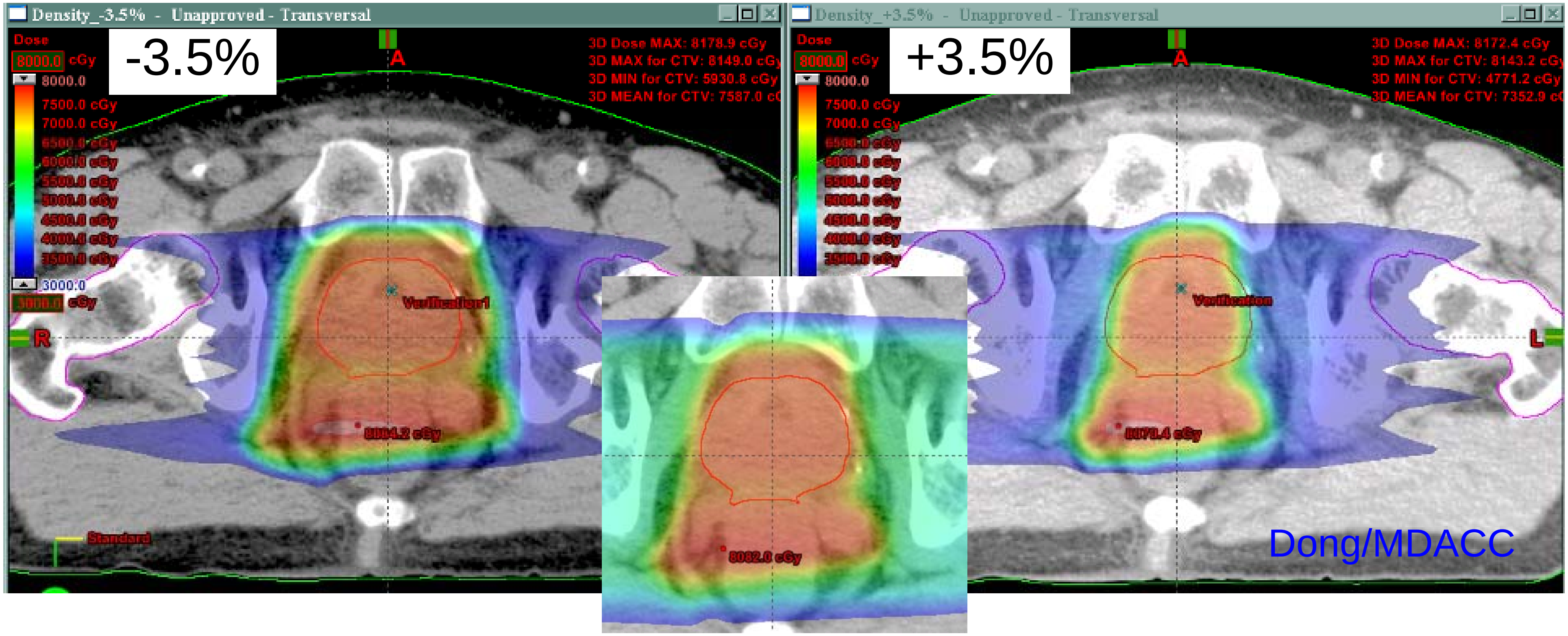
Range uncertainty due to CT calibration is generally taken as 3.5%. However, it can be minimized with better calibration techniques.

HU-Stopping Power Conversion Uncertainties Results in Range Uncertainties



S Flampouri, UFPTI, 2007

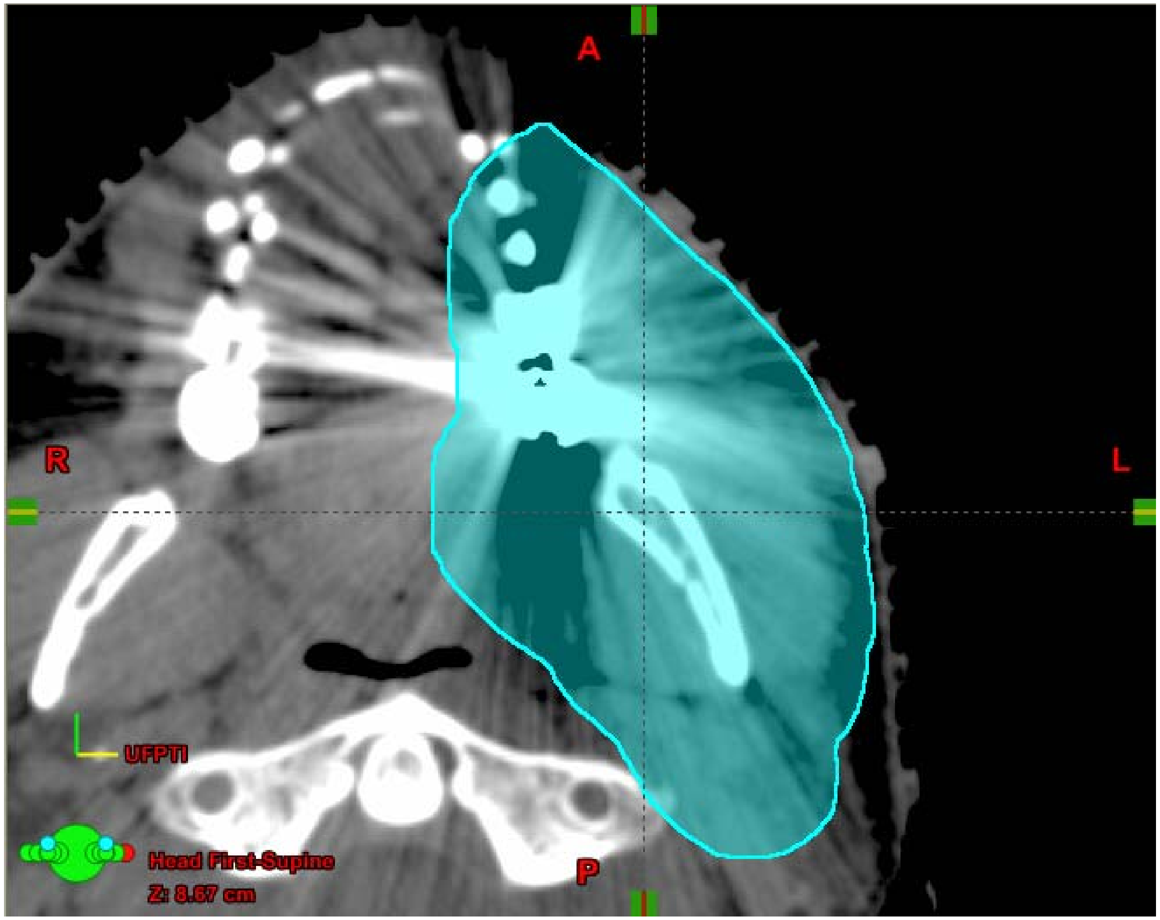
Impact of CT Hounsfield number uncertainties on dose distributions



0% uncertainty

Individualized patient determination of tissue composition along the complete beam path, rather than CT Hounsfield numbers alone, would probably be required even to reach “sub-centimeter precision”

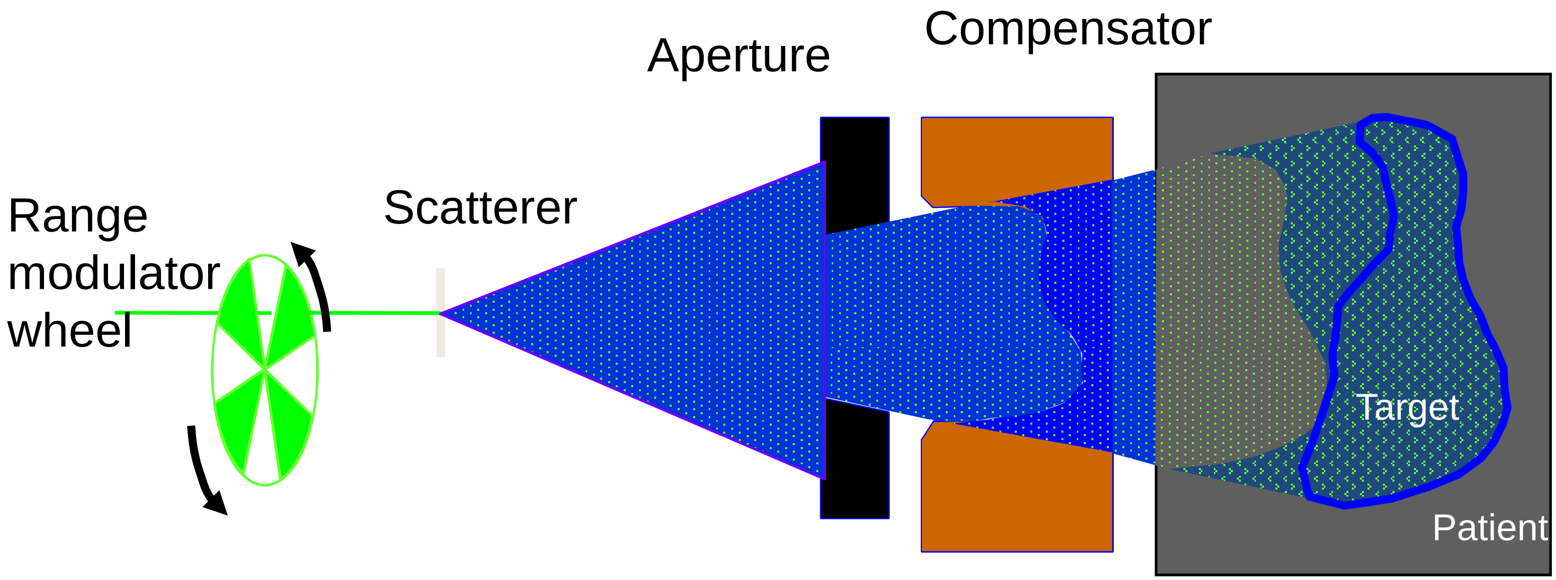
CT Artifacts and Hounsfield Numbers



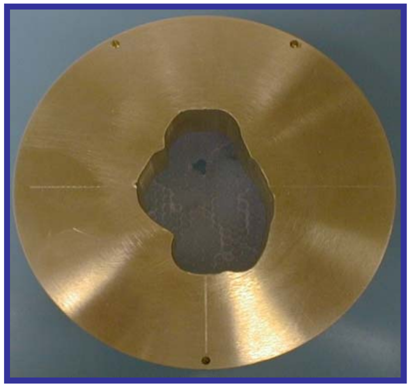
“It is imperative that body-tissue compositions are not given the standing of physical constants and their reported variability is always taken into account” (ICRU-44, 1989).

Proton treatment delivery

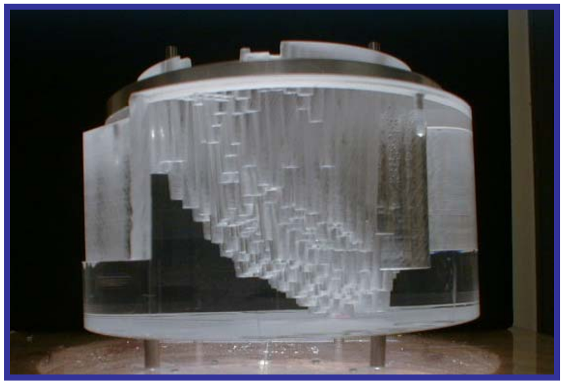
Passive scattering in practice



Range compensator conforms dose to distal edge target volume; the aperture shapes field in lateral direction.

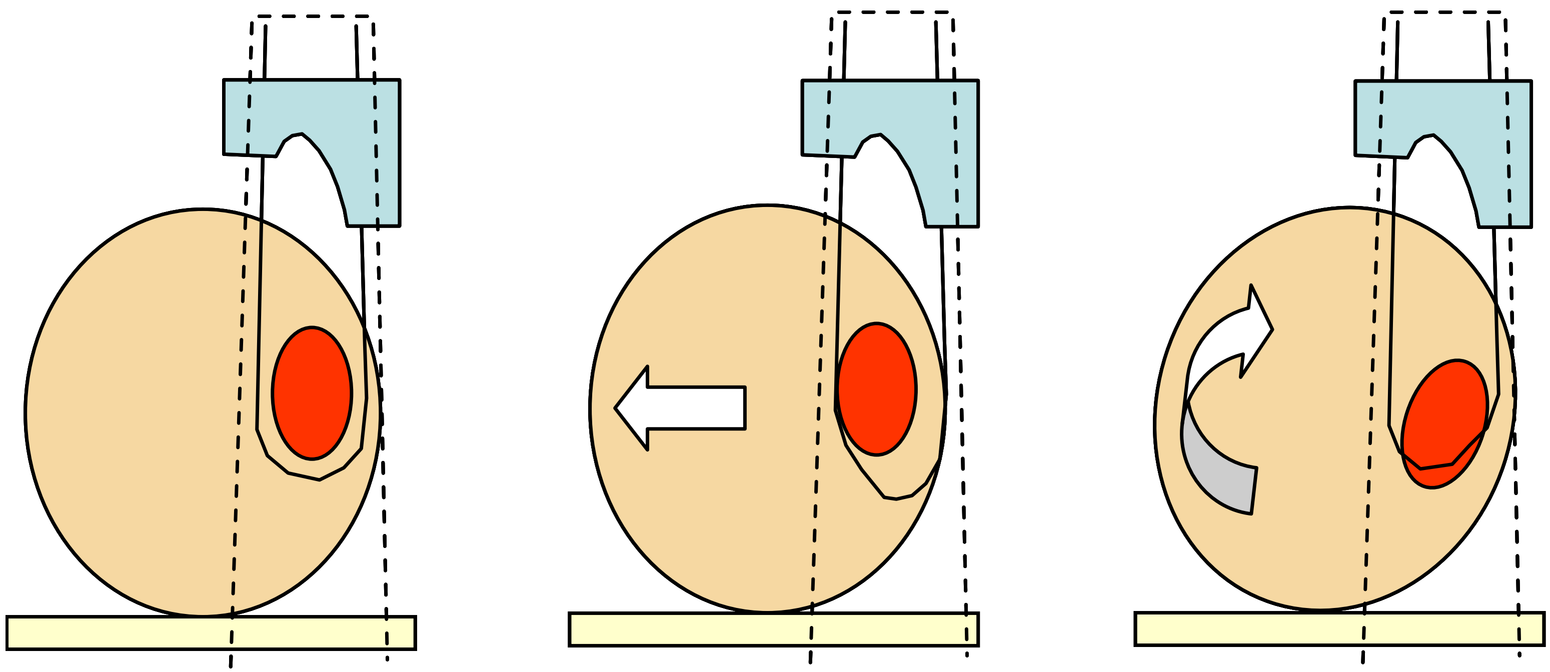


Brass aperture



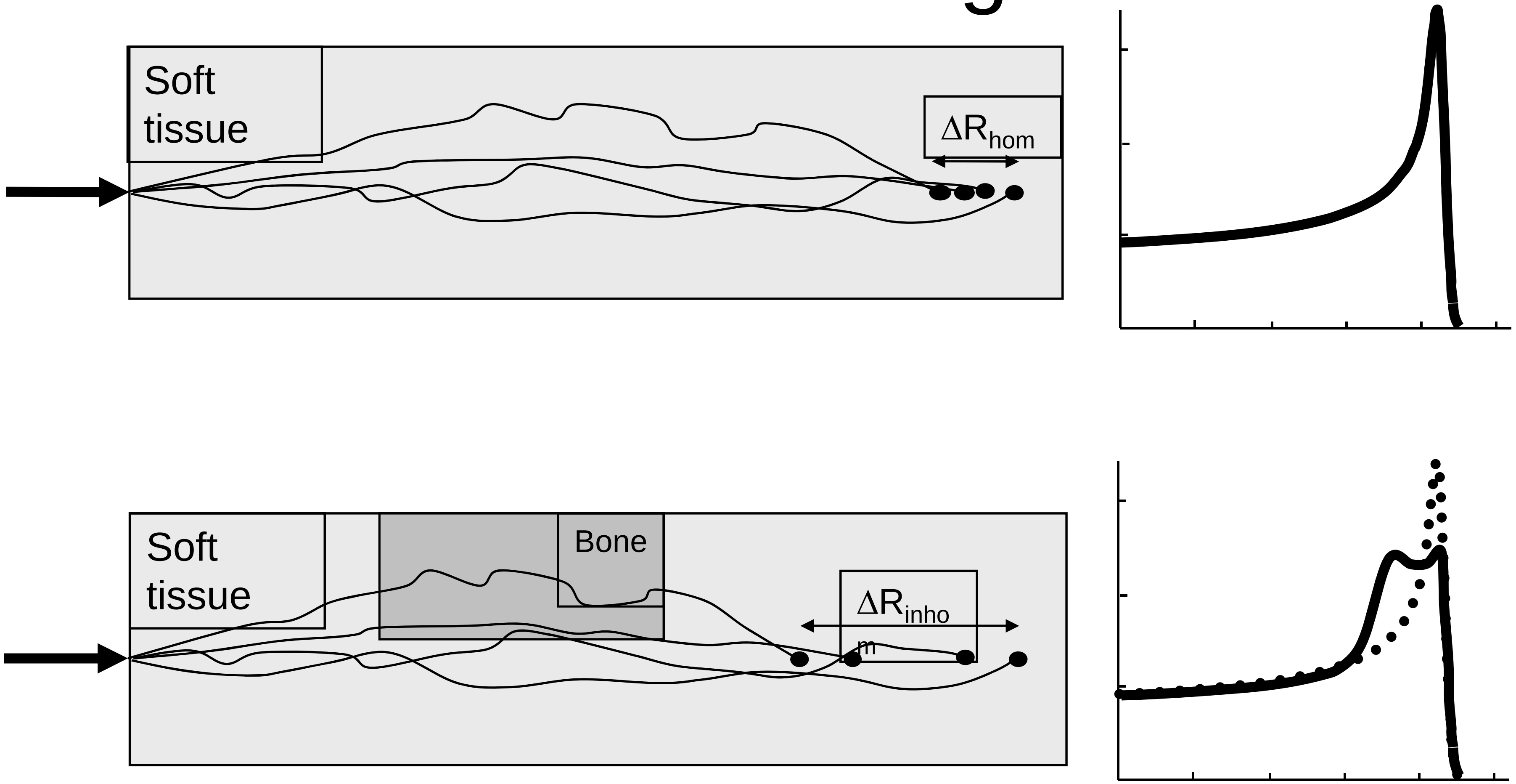
Lucite range compensator

Misalignment of the compensator with Target Volume



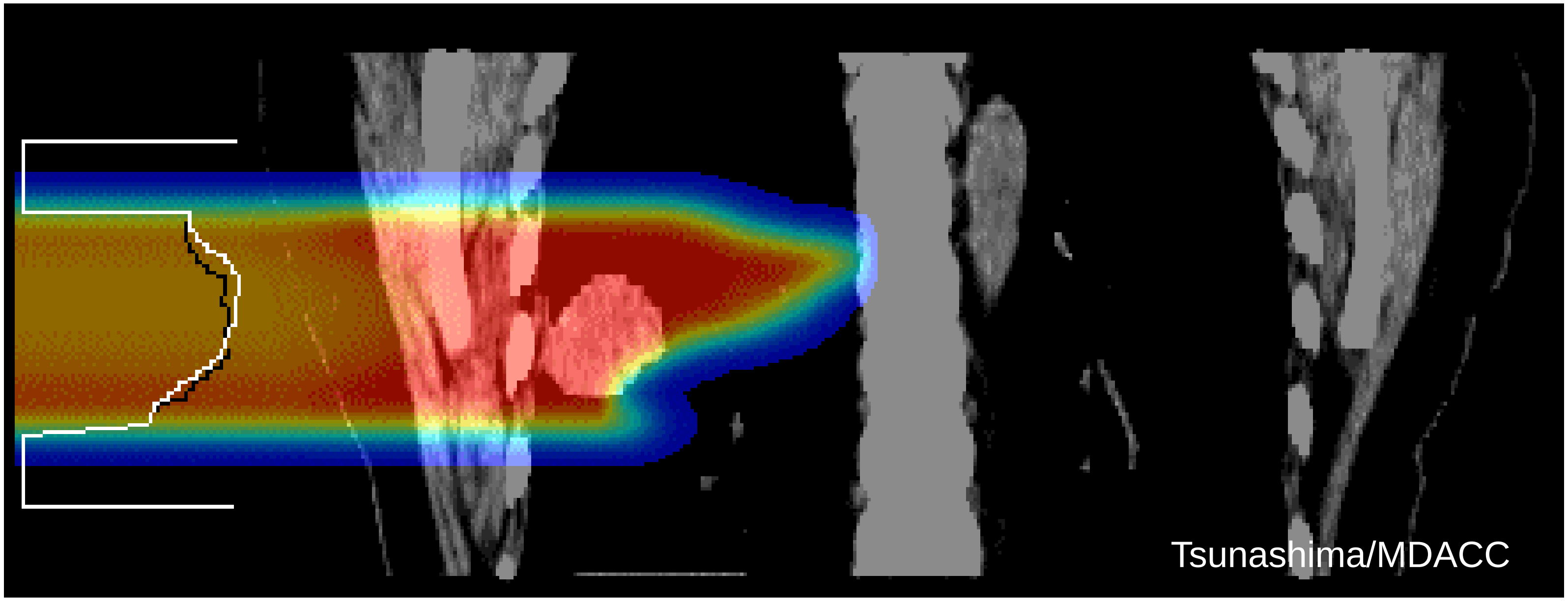
ICRU Report 78

Proton Range Uncertainty in the Presence of heterogeneities



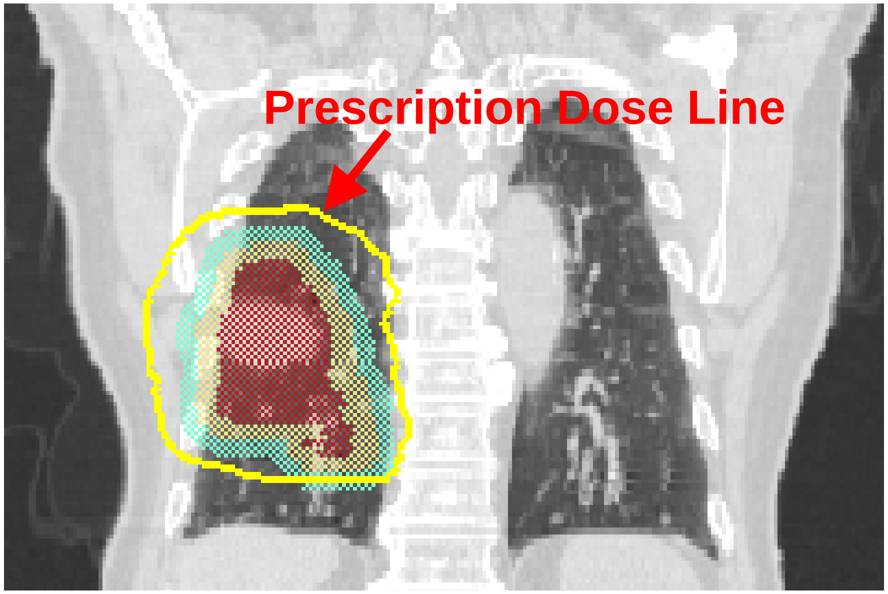
Lomax : AAPM SS 2003

Impact of Organ Motion on Proton Dose Distributions

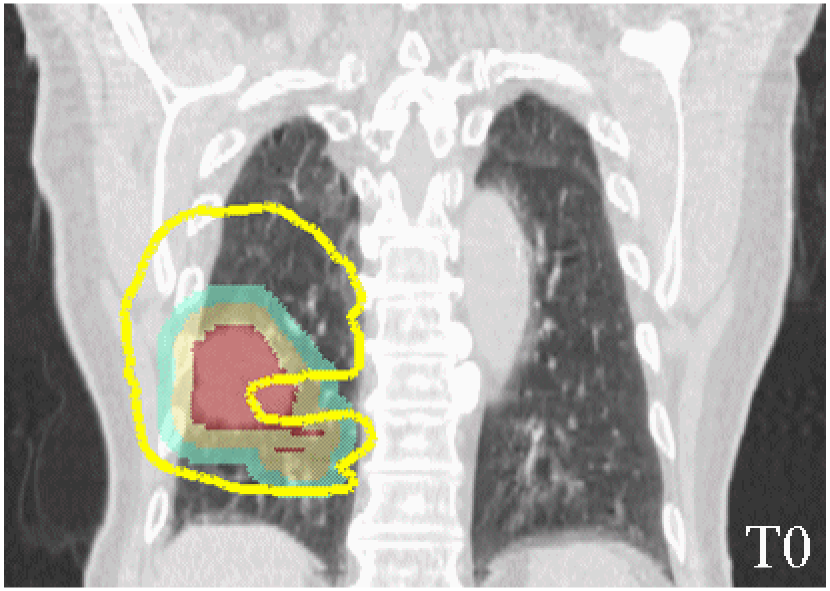


Dong: ASTRO 2008

Impact of Organ Motion on Proton Dose Distributions



Treatment planned based on single Free-breathing (FB) CT image (conventional approach)



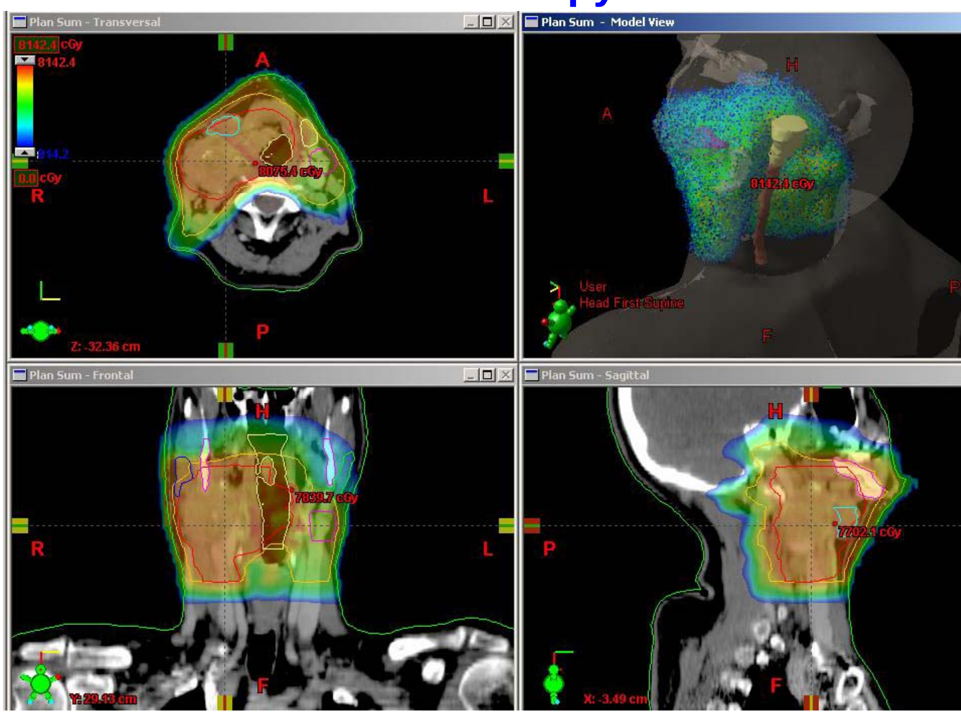
The same treatment plan calculated on 4D CT images

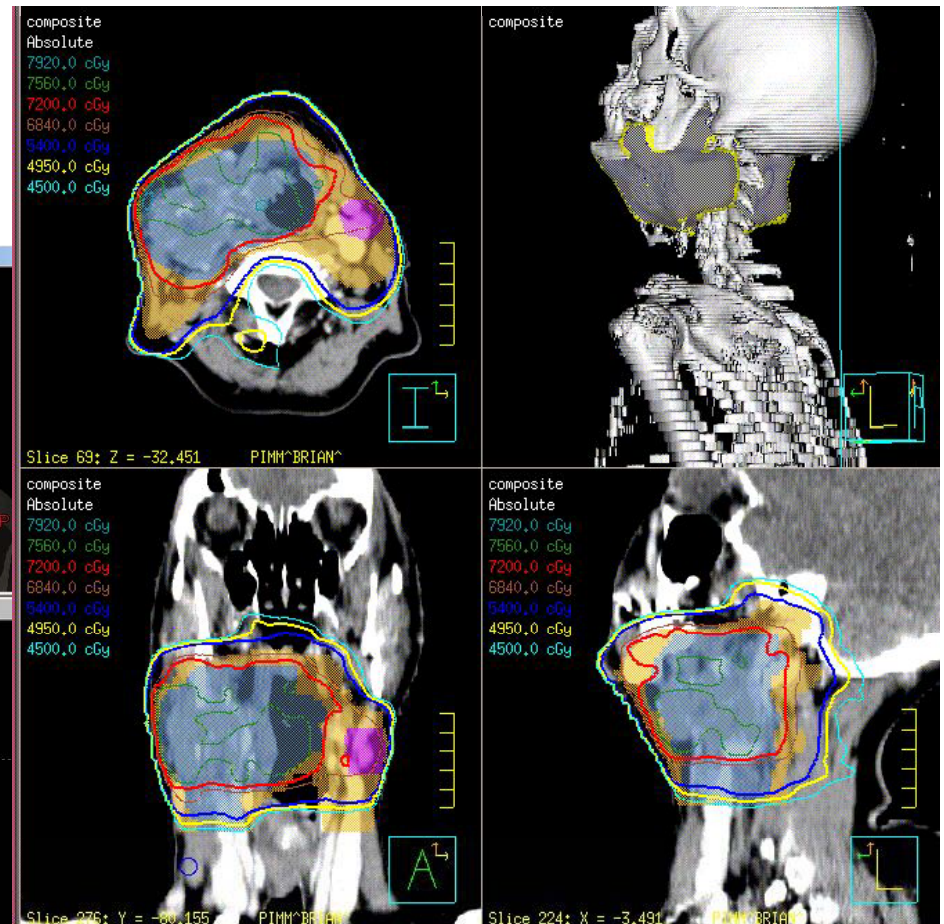
Y. Kang et al. IJROBP. **67**, 906-914 (2007)

Comparing Proton Therapy with IMRT

It is incontrovertible
that dose distributions of
protons can be theoretically
superior to those of high
energy photons

Protons Therapy





Ca Oropharynx

Photon IMRT

Yeung UFPTI

Ca Oropharynx

Concomitant Boost (7200 cGy)

(95% PTV receives prescription dose, 99% PTV receives 93% of prescription dose and 20% PTV receives <110% of prescription dose)

Tumor Coverage	Photon IMRT	PROTONS
95% of PTV 5400/7200	7320 (101.6%)	7178 (99.7%)
99% of PTV 5400/7200	7221 (100.3%)	6975 (96.7%)
20% of PTV 5400/7200	7722 (107.3%)	7243 cGy (106%)

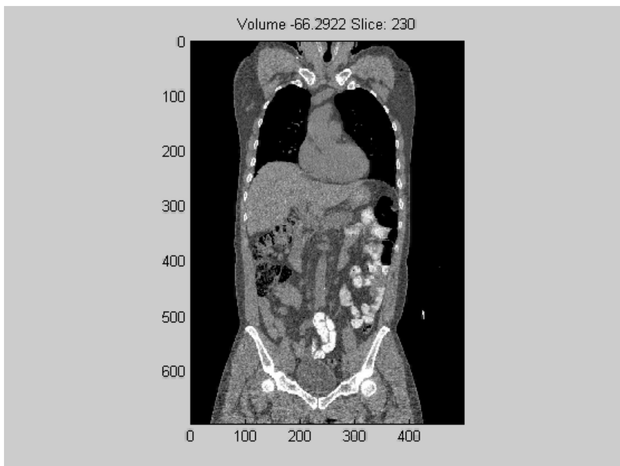
Brain stem (0.1 c.c.)	5020	2685
Spinal cord (0.1 c.c.)	4400	546
Contralateral parotid (mean dose ≤ 2600)	2529	1482
Contralateral submandibular gland (mean dose ≤ 2600)	6928	6148

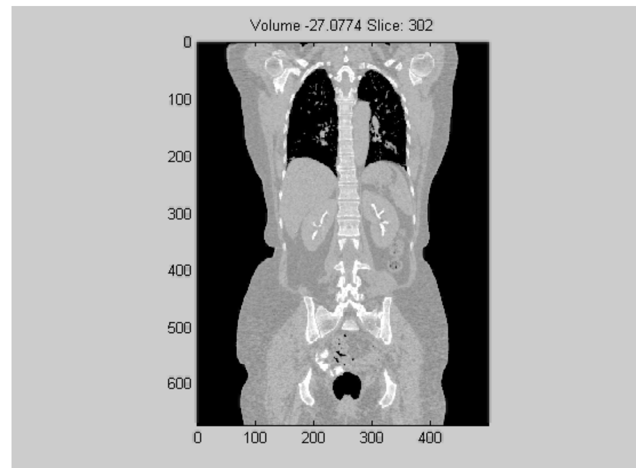
Please note that this is **ONLY** a synthetic comparison of two modalities of treatment

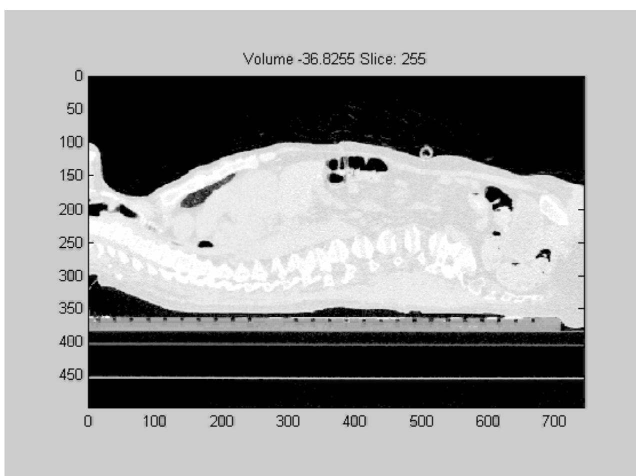
Yeung UFPTI

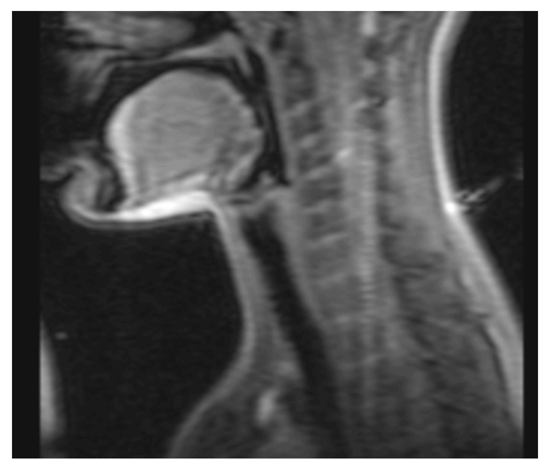
The Clinical Challenge

Accurately deliver ionizing radiation to the real dynamic patient





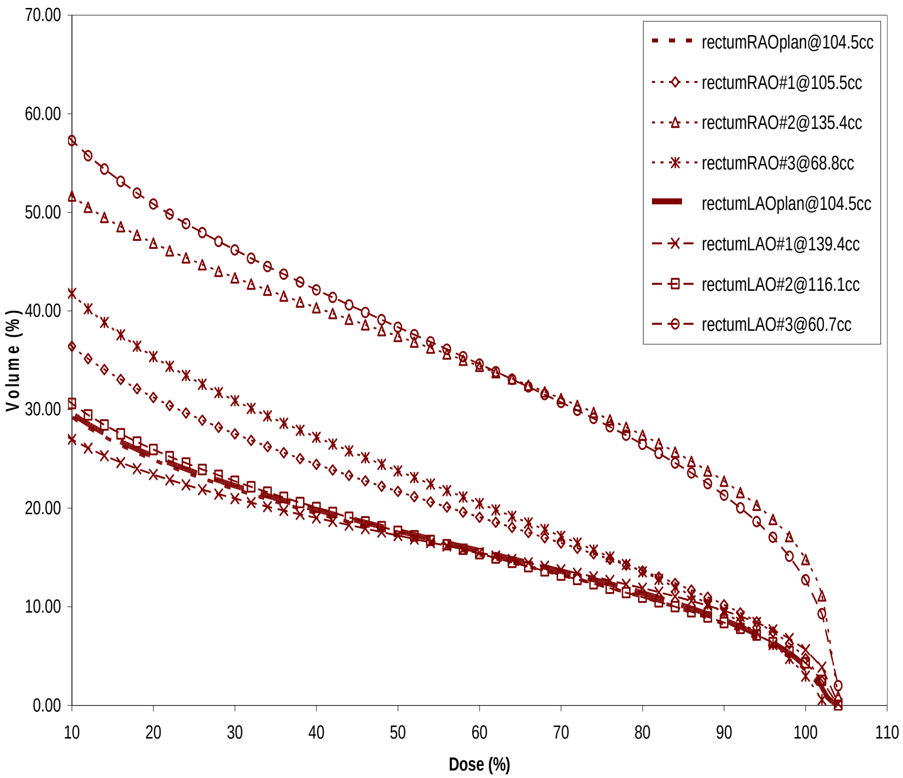




Intra-Fraction Prostate Motion

Due to Breathing and Bladder Filling

Rectal DVH from multiple post treatment PET/CT

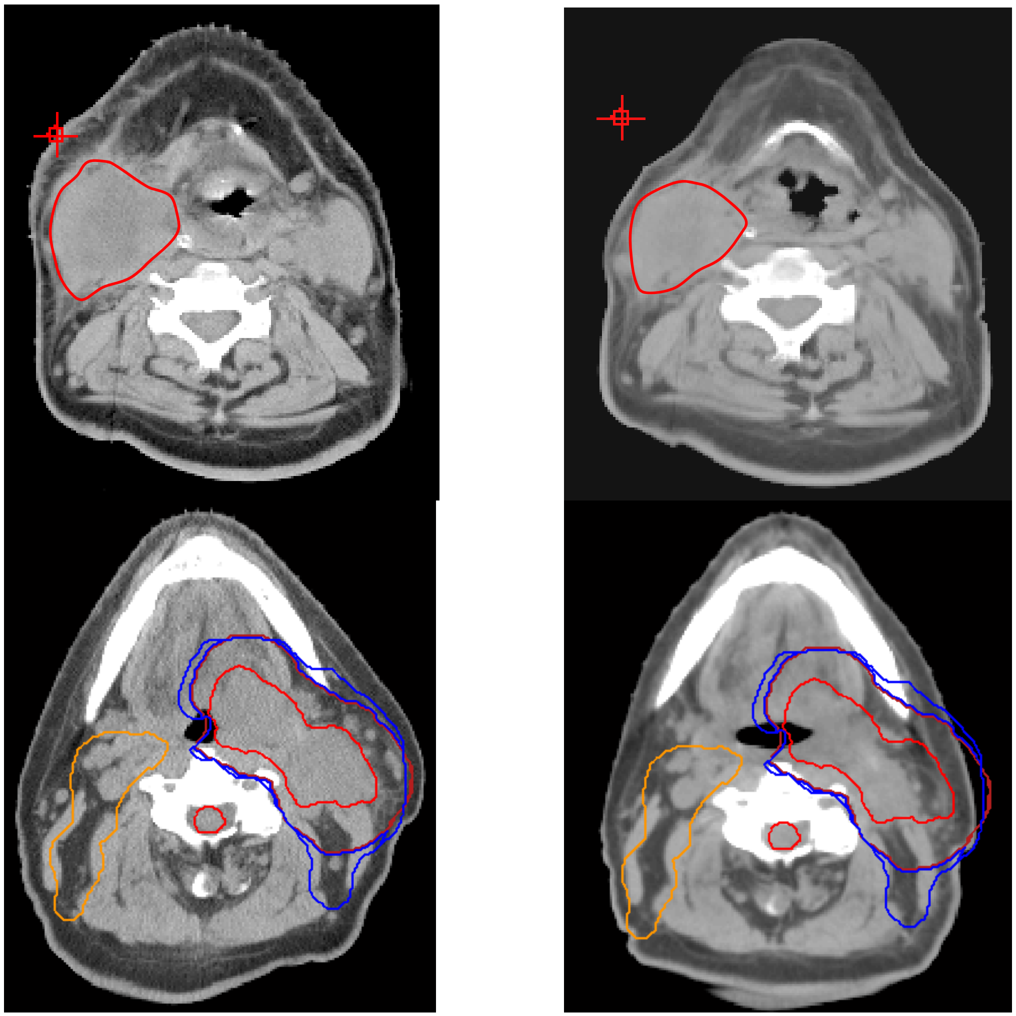


Uncertainties in Rectal V_{74} and V_{39}

	Mean ± Dev.	Rel. Dev. ± Dev.
V_{74}	9.6%±7.2%	**73.9%±20.5%**
V_{39}	25.2%±11.4%	**42.1%±15.3%**

Yin: UFPTI, 2008

Anatomic Variations During Course of RT



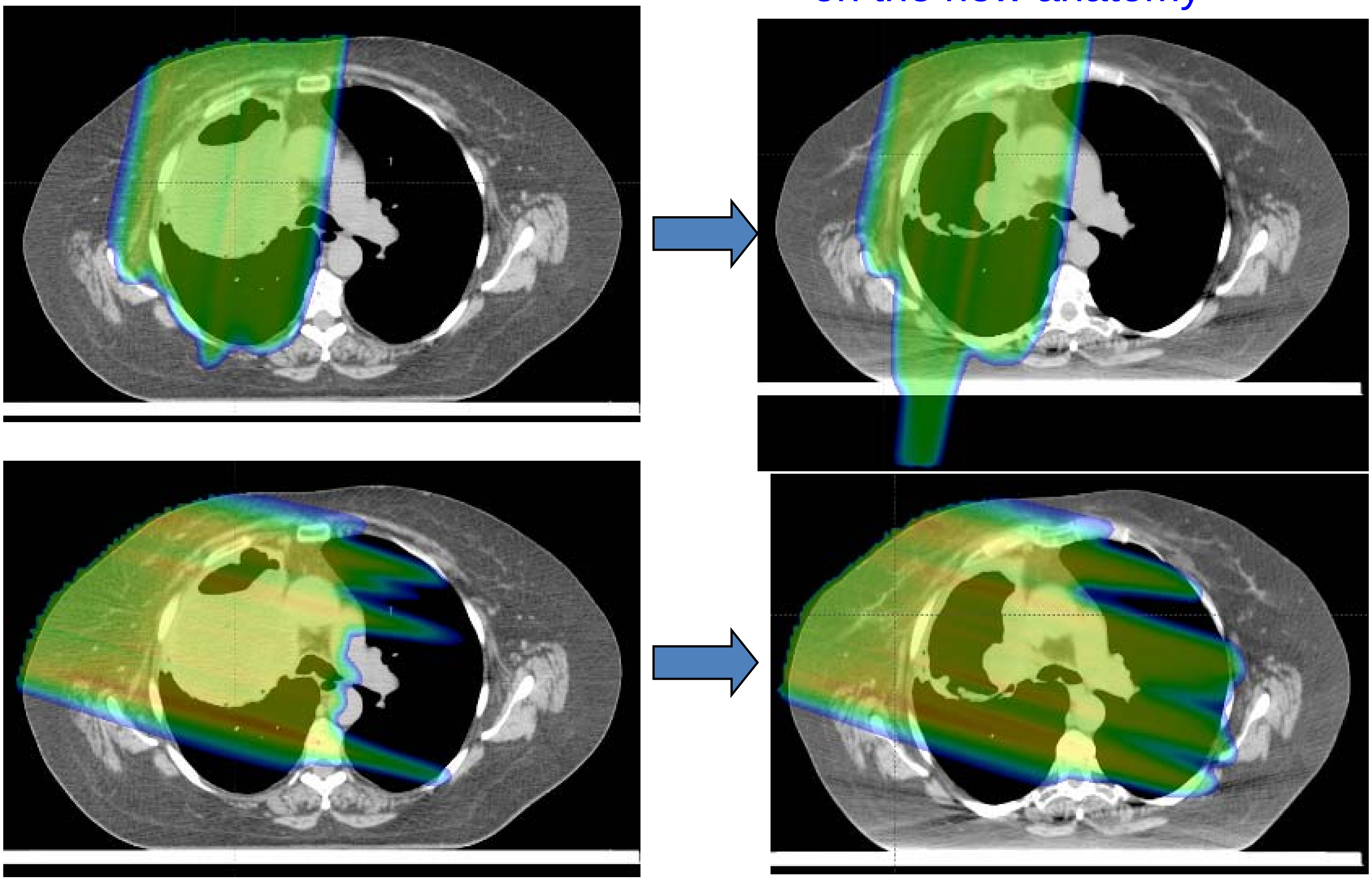
Planning CT   Three Weeks into RT

Barker et al. *Int J Radiat Oncol Biol Phys* 2004;59:960-970.

Impact of Tumor Shrinkage on Proton Dose Distribution

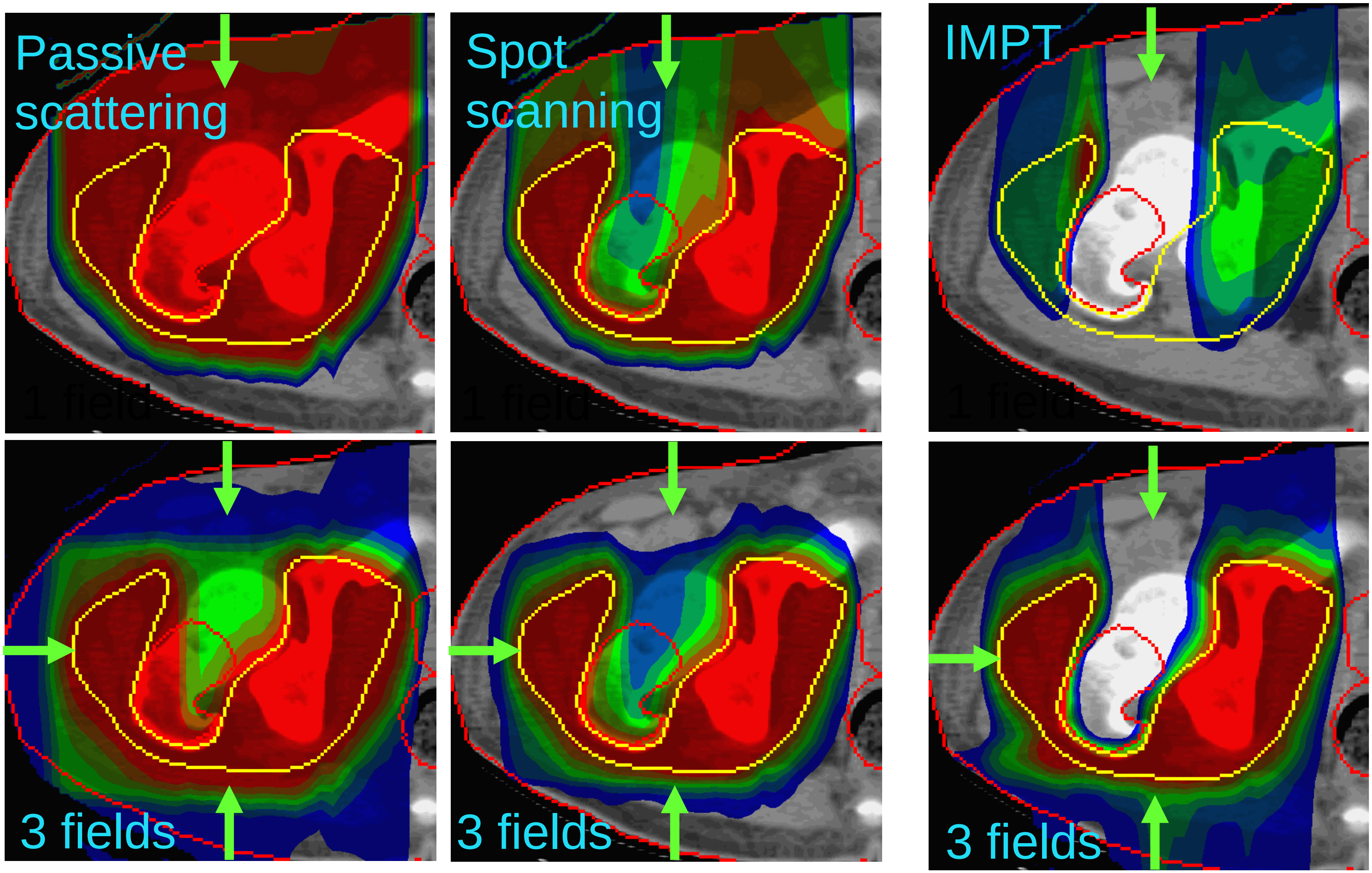
Original Proton Plan

Dose recalculated
on the new anatomy



Bucci et al. ASTRO Abstract, 2007

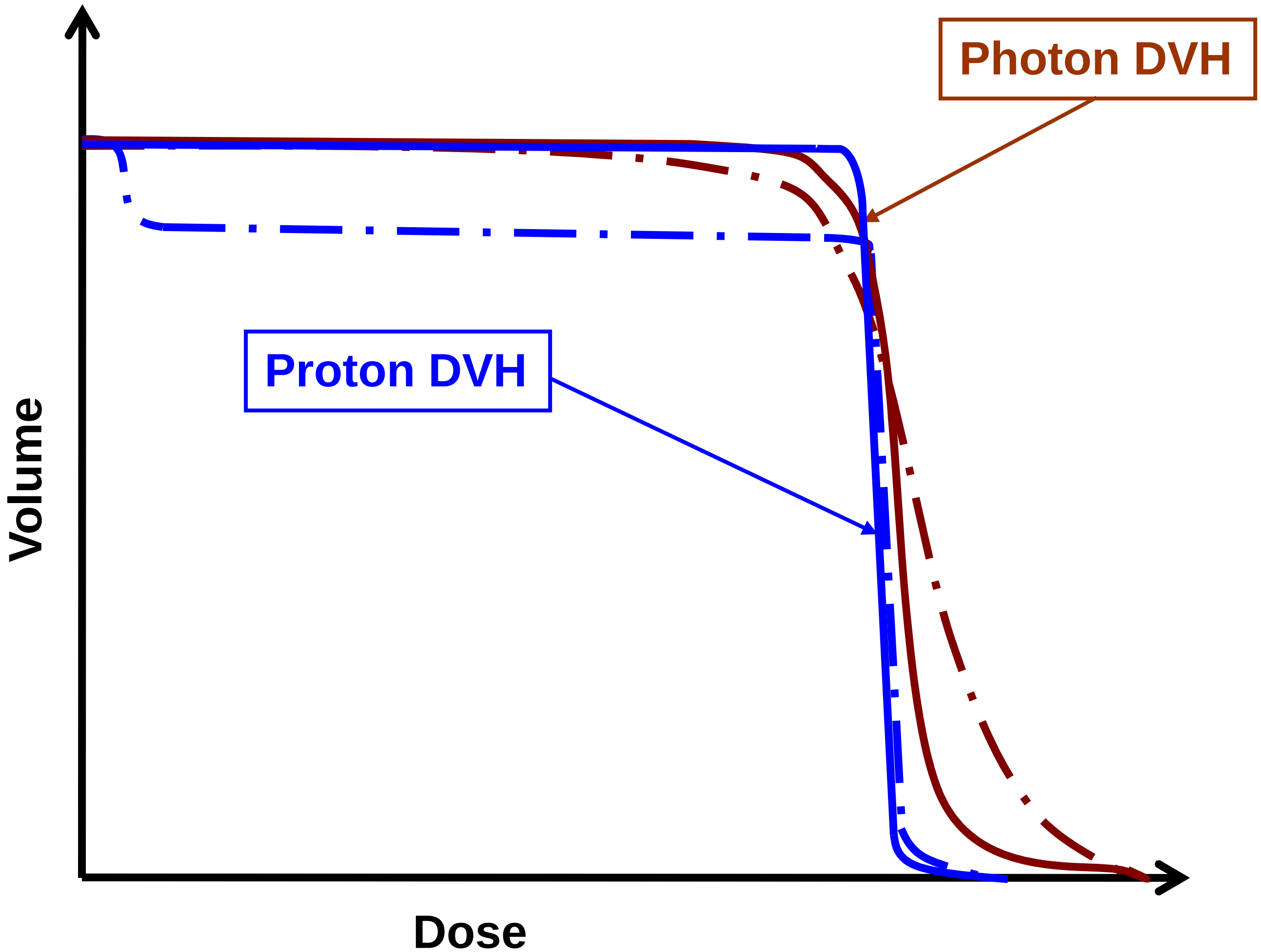
Intensity Modulated Proton Therapy (IMPT)



Lomax/PSI

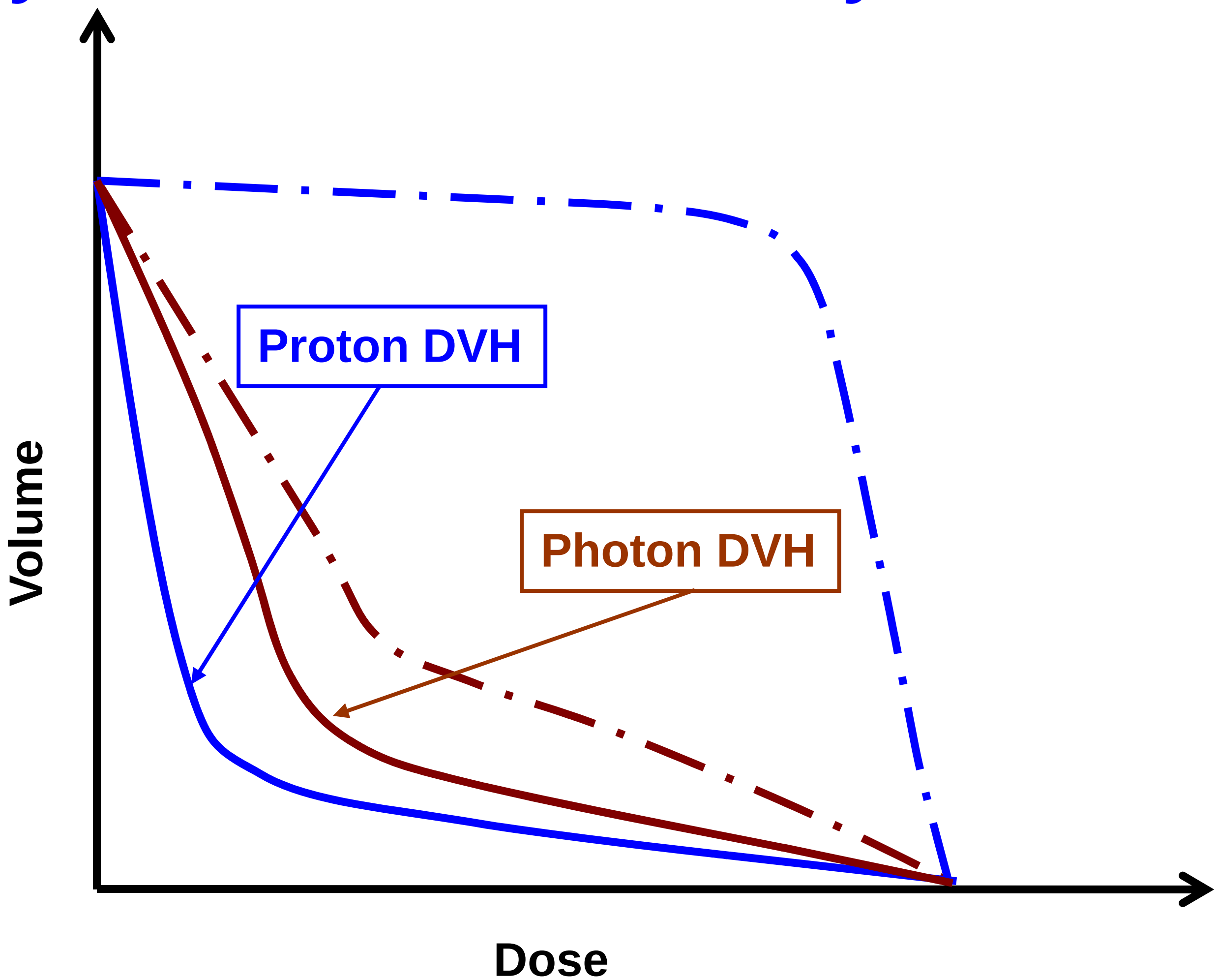
Plan DVH Evaluation (PTV)

What you see is not what you always get….



Plan DVH Evaluation (PRV)

What you see is not what you always get..

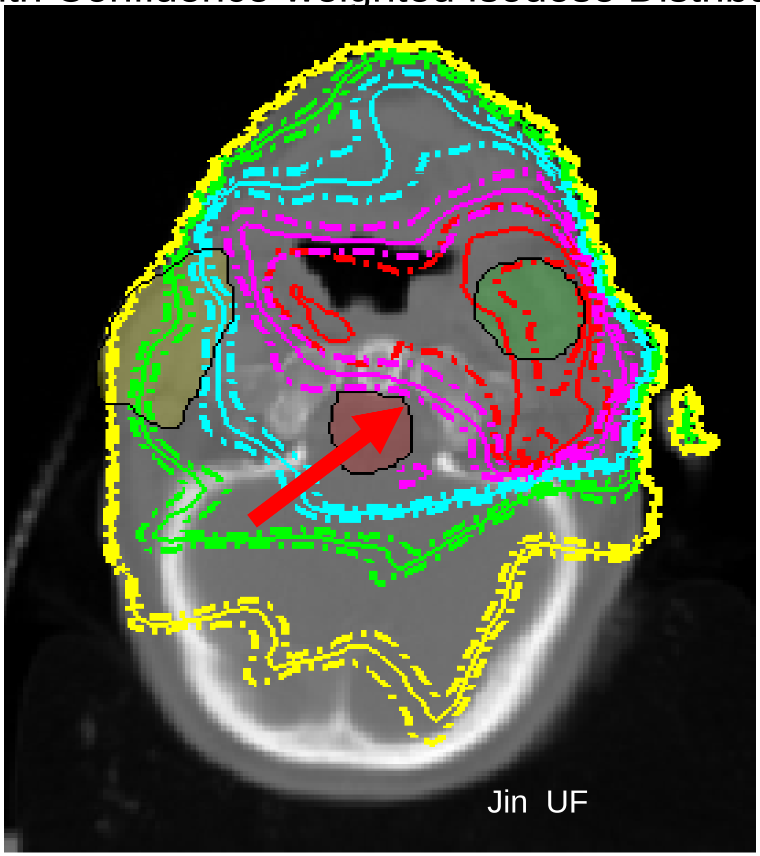


Plan Evaluation

What you see is not what you always get….

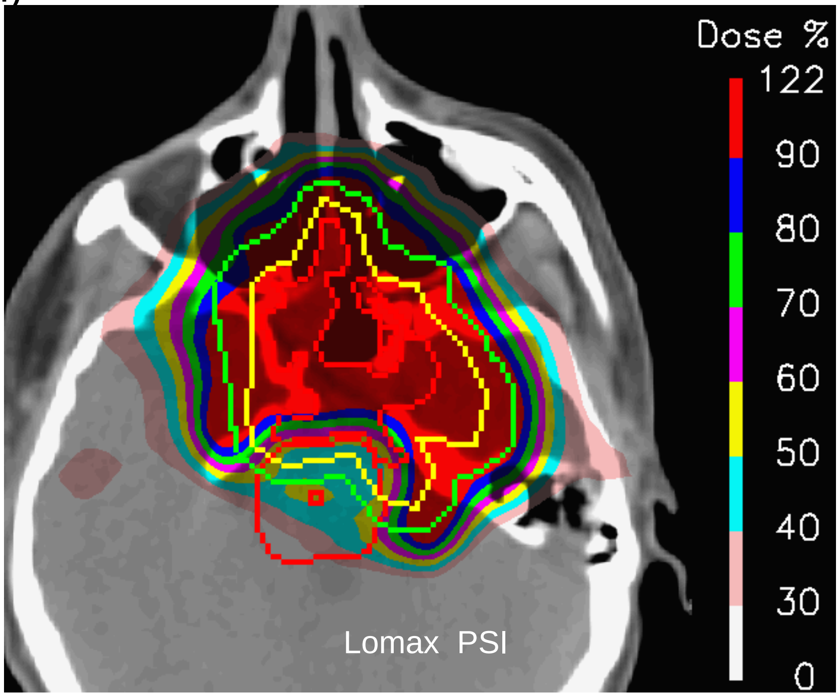
IMXT Plan

(with Confidence-weighted Isodose Distribution)



180 160 120 80 40 cGy

IMPT Plan



There is no easy way to show what patient will get in proton therapy

Summary 1

- Proton beams stop - no exit dose
  - Although we don’t know exactly where they stop
- Proton beams are more sensitive to
  - CT Hounsfield number/Stopping Power accuracy
  - Organ motion
  - Anatomy changes
- Proton plans are difficult to evaluate
  - “What you see is not what is delivered”
- Protons demonstrate excellent low dose sparing

Summary 2

- IMPT shows additional benefits both in low dose sparing and high dose conformality
- IGRT and Adaptive RT will play an important role
- Inter/Intra-fractional variations have far more significant consequences in patients treated with proton therapy
  - Approaches and data to deal with this issue is still lacking
    - Minimize it and develop strategies to deal with the residual motion

Summary 3

- Empirical approaches used in defining margins for range uncertainties, smearing, and smoothing are questionable
  - No real data exist to support any of these approaches
- Repeat imaging and reevaluation based on deformable registration may be necessary
  - In some cases repeat planning may be clinically beneficial
- Biologically Effective Dose
  - Little published data on end of range RBE

General Observations Regarding Proton Therapy Technology

- State-of the Art in Proton Therapy is still an accelerator with multi-room configuration and scattered beam delivery system. These are far from "turnkey" systems
-
  - Scanning and IMPT are still a works-in-progress.
  - Subsystem integration is far from complete
    - It impacts clinical workflow and throughput
- Development of new proton beam production technologies are being fueled by the promise of proton therapy in normal tissue sparing.
  - Developing a technology is lot simpler and quicker than its seamless and safe integration in existing clinical work flow.
    - Historically, routine application of new developments in radiation oncology has taken at least 5 years from the time its FDA approval (e.g. MLC, IMRT, IGRT, etc.)
- Promise of Proton Therapy will only hold if we take the most advantage of the state-of-the art in conventional radiation therapy
  - We must not be satisfied with less than the best in technology available for immobilization, imaging, treatment planning, patient/target position verification, and treatment delivery.