THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Proton Therapy Clinical Results and Perspectives

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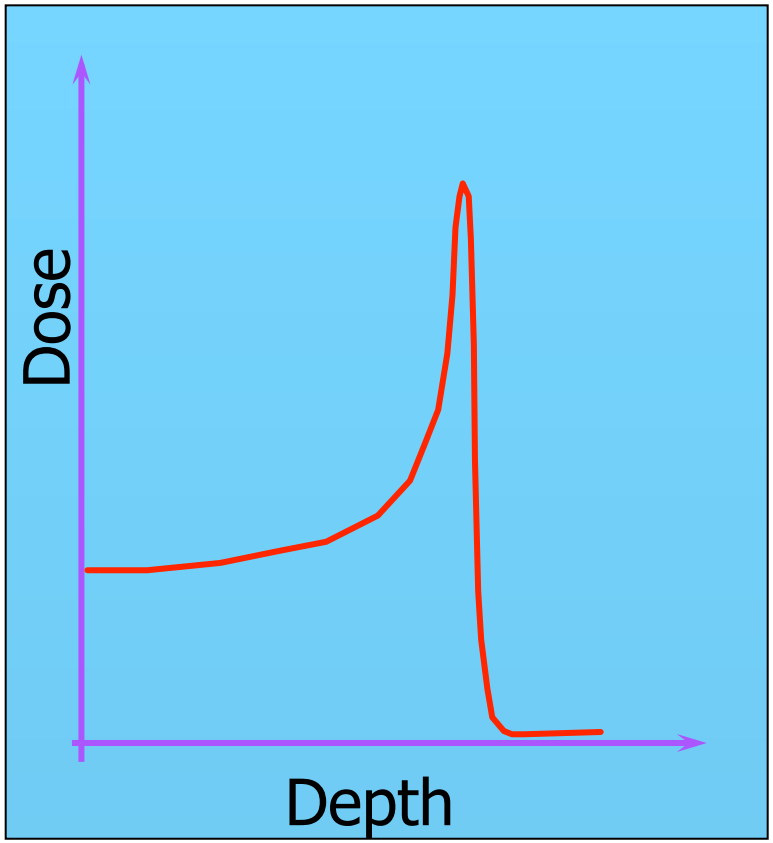
CERN MEDICAL APPLICATIONS WORKSHOP
Feb. 15-16, 2004

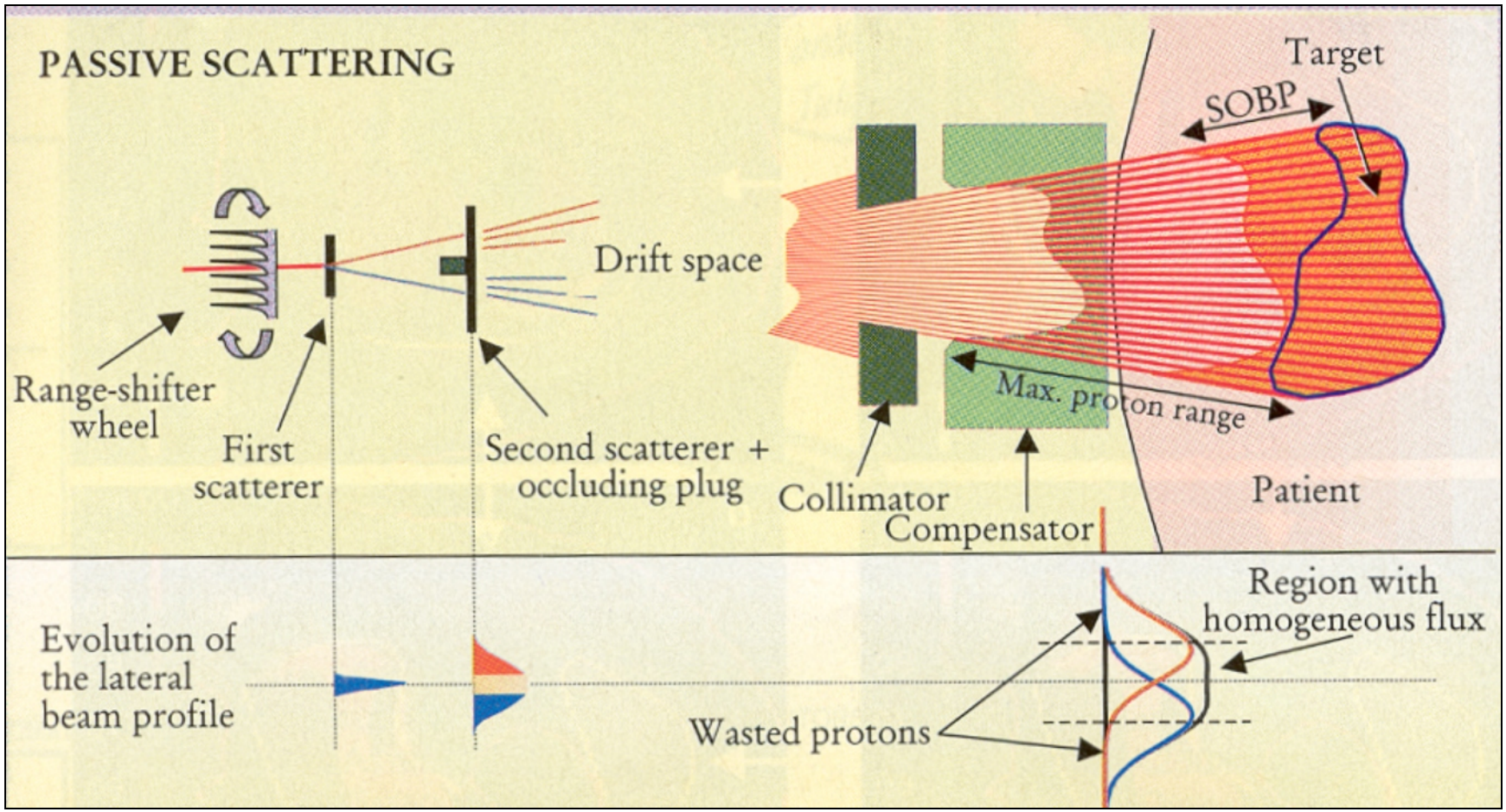
The Attraction of Protons



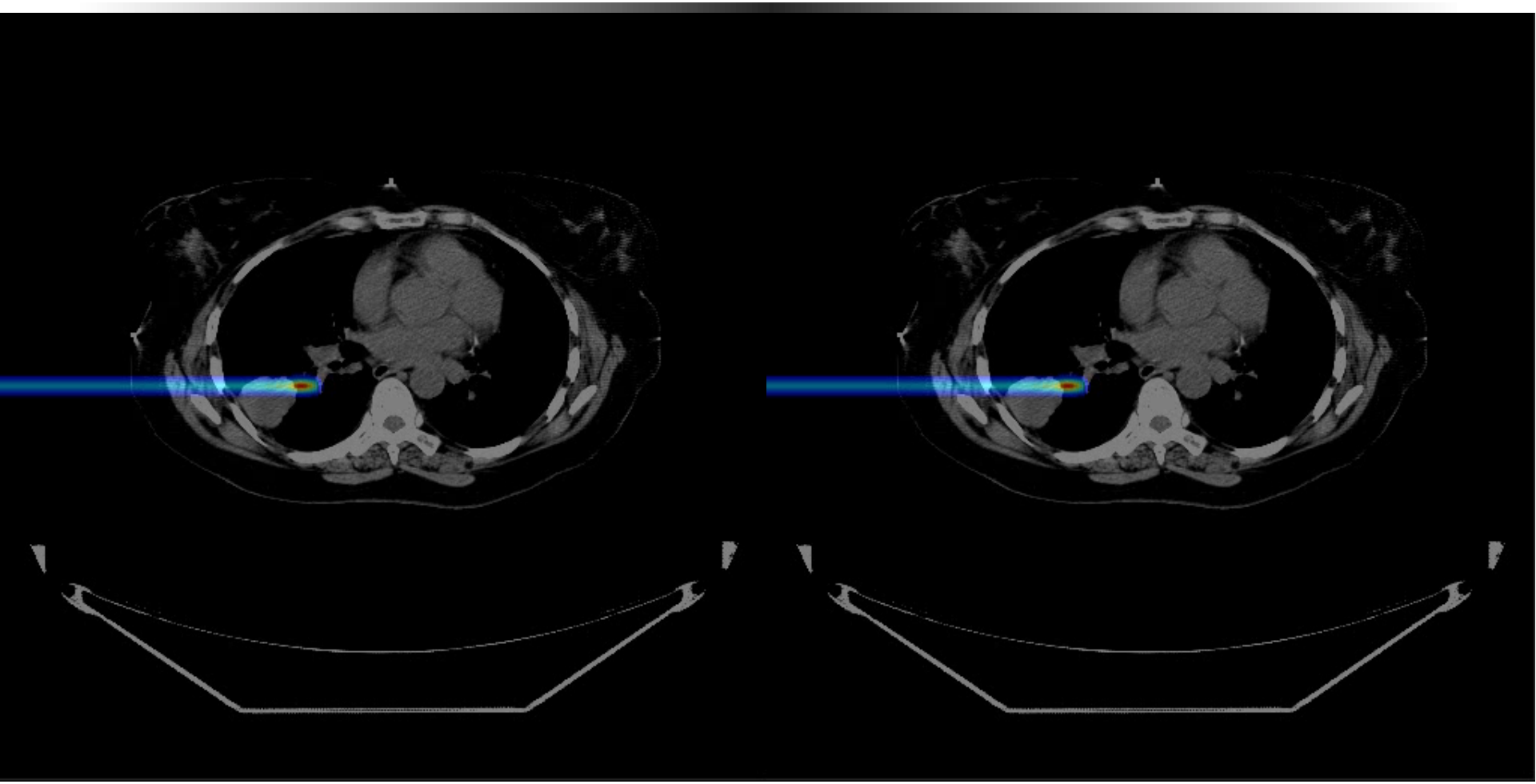
Proton Therapy – Main Delivery Modes

- **Passive scattering**
- **Scanning beams – intensity modulated**

The Passive Scattering Mode of Proton Beam Delivery



Layer-by-Layer Magnetic Scanning of Proton Beamlets for IMPT

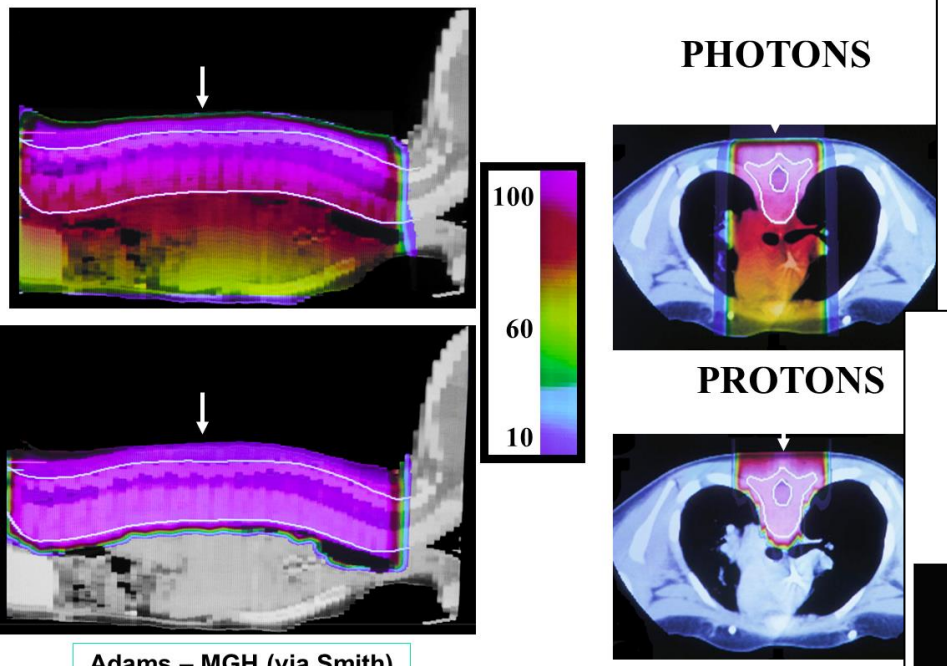


Spot position

Cumulative dose

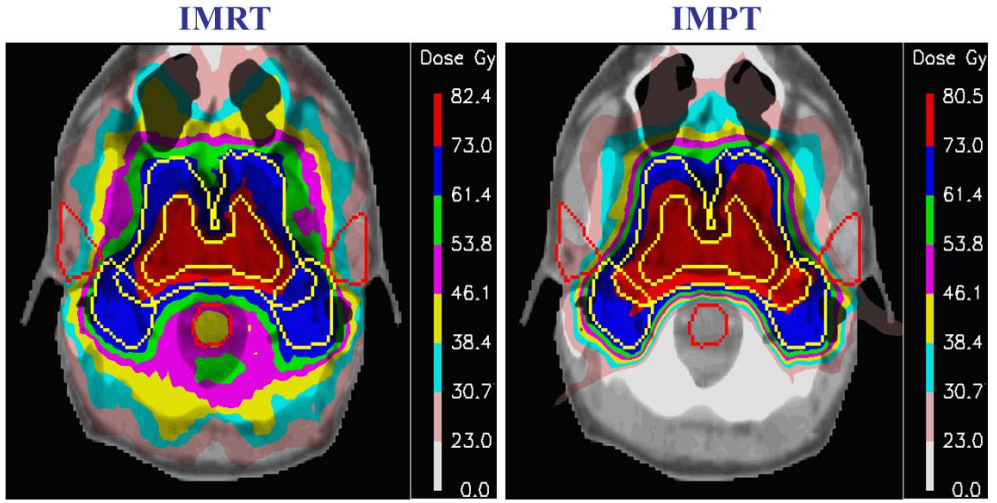
Exquisite Particle Therapy
Dose Distributions

MEDULLOBLASTOMA



Adams – MGH (via Smith)

Nasopharynx Treatment Plans
IMRT vs. IMPT



Lomax - PSI, Smith - MGH

>50 Year History of Particle Therapy - Clinical Evidence To-Date?

A Mixed Bag

and

Not High Level

Phase 2 Study of High-Dose Proton Therapy With Concurrent Chemotherapy for Unresectable Stage III Nonsmall Cell Lung Cancer

Joe Y. Chang, MD, PhD[1]; Ritsuko Komaki, MD[1]; Charles Lu, MD[2]; Hong Y. Wen, MS[1]; Pamela K. Allen, PhD[1]; Anne Tsao, MD[2]; Michael Gillin, PhD[3]; Radhe Mohan, PhD[3]; and James D. Cox, MD[1]

Cancer, 2012:44 patients with stage III NSCLC, proton chemo-radiotherapy @74 Gy (RBE) - Median overall survival: 29 months, grade 3 pneumonitis: 3%, grade 3 esophagitis 12%

IMPT of Oropharyngeal CA - Feeding Tube Incidence and Duration

	Entire IMRT Cohort (N = 998) No. (%)	IMPT (N = 25) No. (%)	Matched IMRT (N = 25) No. (%)	p-value (IMPT v. Matched IMRT)
Feeding Tube Incidence	475 (48%)	5 (20%)	12 (48%)	0.037

>50% Reduction in Gastrostomy Tubes with IMPT over IMRT

- **For the IMPT group:**
  - **Median duration was 4.2 (2.6-11.3) months**
- **For the IMRT matched case control group:**
  - **Median duration was 4.7 (1.4-20) months**

Steven Frank (MDACC) at ASTRO 2013

Proton Clinical Results : Local control

- Ocular Melanoma (70 GyRBE in 5 fractions)
  - 95% at 15 years (Harvard Cyclotron Lab)
- Skull base chondrosarcoma (69.6 GyRBE/ 37 fx)
  - 95% at 10 years (Harvard Cyclotron Lab)
- Prostate CA T1-2B (75 GCE in 46 fractions)
  - 88% PSA disease-free 5 year survival – LLUMC
- Similar results for these diseases from proton centers around the world

Proton Clinical Results

- **Hepatocellular carcinoma**
  - 94% Local control, Tsukuba (72 CGE in 18 fx)
- **Non Small Cell Lung Cancer**
  - **Medically inoperable, early stage (Stage I)**
    - **22 pts: 51 Gy/10 fx 46 pts: 60 Gy/10 fx**
      - **Local control (3 year) 74%**
        - **T1 87% • T2 49%**
      - **Disease Free Survival: 72%**
        - **Bush et al, Chest 2004 (Loma Linda)**

MASSACHUSETTS GENERAL HOSPITAL Harvard Medical School

Courtesy Delaney

Adult Sites Treated With Protons

- Chordomas
  - Skull base: LC 42% at 10 years [MGH]
  - Spine [MGH]
    - Pre-op photon/proton 1° tumors: 100%/100% 5 y/8 y LC
    - Definitive photon/proton 1° tumors: 80% 5 y LC
- Skull base chondrosarcomas: LC 98% (10 y) [MGH]
- Spine Sarcomas
  - Local control (1° tumors: 94% 5 year/84% 10 y) [MGH]
- Prostate
  - Biochem DFS (79.2 Gy: 83% at 10 y, Zietman et al)
  - Biochem DFS with 3-D, IMRT, BrachyRx: 75-85%

Randomized Trials - Only two up until recently

- **Shipley et al: IJROBP 1995**
  - **50.4 Gy photons + 16.8 Gy photons or 25.2 CGE protons**
  - **T3 – T4, N2, M0**
  - **No increase in survival**
  - **Increased toxicity at higher dose.**
- **Zietman, et al JAMA 2005**
  - **50.4 Gy photons + 19.8 or 28.8 CGE protons.**
  - **T1b-T2b, PSA < 15**
- **No head-to-head photon vs. proton trials**
- **Very few critical comparisons with historical controls**

In Spite of the Apparent Superiority of Proton Therapy

Questions are Being Raised About its Value

Ronald Chen (UNC) Presentation at the SF ASCO GU Cancer Symposium, Feb. 2012

- **SEER-Medicare analysis of men diagnosed with localized prostate ca during 2002 – 2006**
- **IMRT resulted in less GI morbidity and hip fractures**
- **Currently, no clear evidence that proton therapy is better than IMRT**

Courtesy – R. Chen

An evidence based review of proton beam therapy: The report of ASTRO's emerging technology committee - Radiotherapy and Oncology 2012

- **Current data do not provide sufficient evidence to recommend PBT in lung, H&N, GI, and non-CNS pediatric malignancies.**
- **In hepatocellular carcinoma and prostate cancer, there is evidence for the efficacy of PBT but no suggestion of superiority.**
- **In pediatric CNS malignancies PBT appears superior but more data are needed**
- **In large ocular melanomas and chordomas, there is evidence for a benefit of PBT …**

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REVIEW ARTICLE

Proton Therapy in Clinical Practice: Current Clinical Evidence

Michael Brada, Madelon Pijls-Johannesma, and Dirk De Ruysscher

Found no convincing evidence that protons are superior to photons

Proton and other particle therapies need to be explored as potentially more effective and less toxic RT techniques. A passionate belief in the superiority of particle therapy and commercially driven acquisition and running of proton centers provide little confidence that appropriate information will become available. Objective outcome data from prospective studies is only likely to come from fully supported academic activity away from commercial influence. An uncontrolled expansion of clinical units offering as yet unproven and expensive proton therapy is unlikely to advance the field of radiation oncology or be of benefit to cancer patients.

De Ruysscher D, Mark Lodge M, Jones B, Brada M, Munro A, Jefferson T, Pijls-Johannesma M. Charged particles in radiotherapy: a 5-year update of a systematic review. *Radiotherapy and Oncology 2012*;103:5-7.

NY Times January 3, 2012
(E. J. Emanuel and S. D. Pearson)

- **"… a medical arms race for proton beam machines, which could cost taxpayers billions of dollars for a treatment that, in many cases, appears to be no better than cheaper alternatives …**
- **… Medicare should pay no more than the cheaper alternatives unless studies were done showing that proton beam therapy was better than other treatments"**

High Cost of Proton Therapy

A Major Factor

"If protons and photons were equal in cost, talk about need to demonstrate superiority of protons would end"

Why has the clear advantage of protons (particles) on paper not translated into practice?

- **Immature technology or limited experience up to now**
- **Greater vulnerability of particles to uncertainties**
  - **Inter-fractional changes, intra-fractional motion, set up**
- **Accuracy of computed dose distributions**
- **Uncertainty in relative biological effectiveness (RBE)**
- **No proton (particles) vs. photons randomized trials (until recently)**

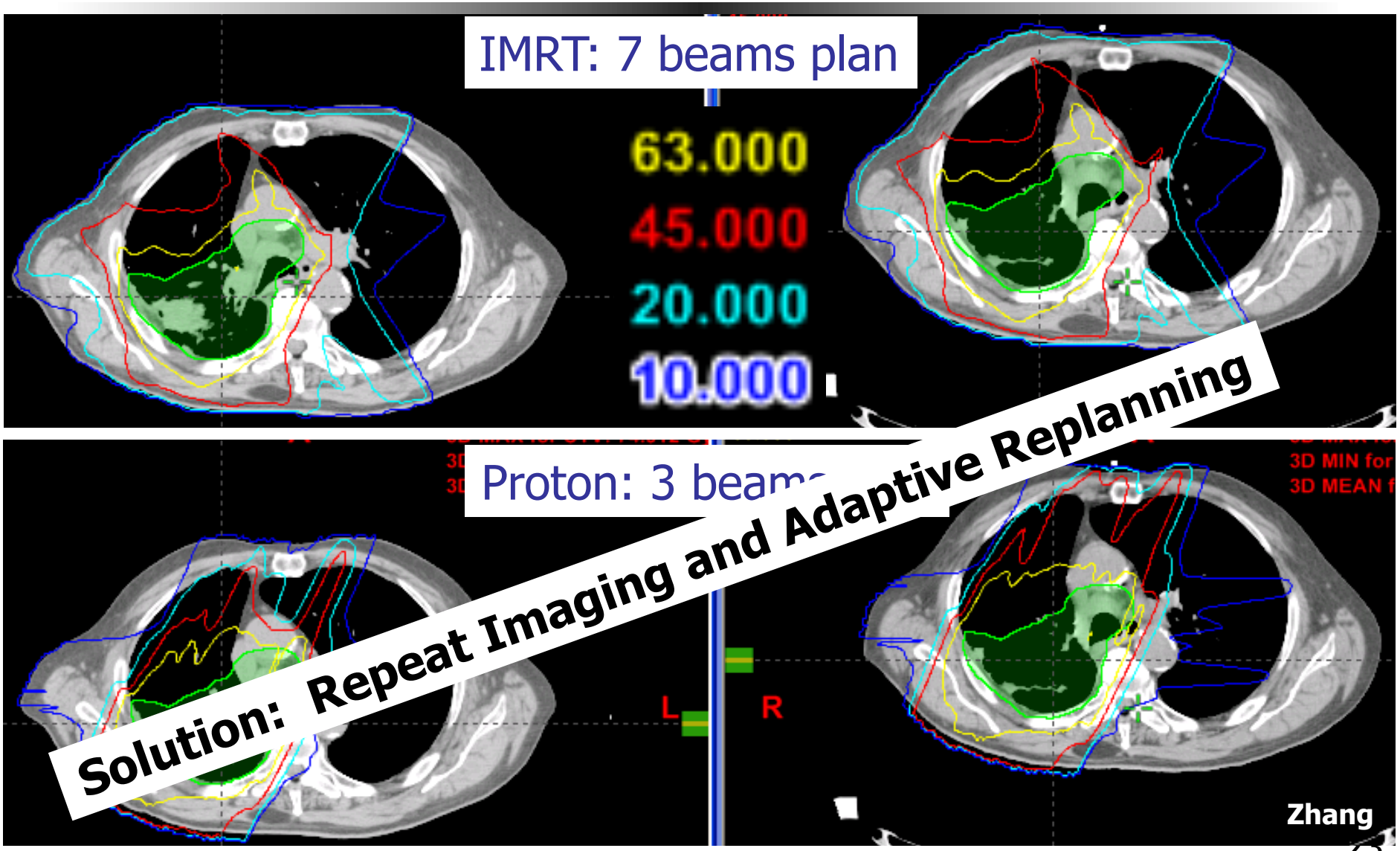
Illustrative Examples

Limitations, Ongoing Research to Overcome Them and Further Opportunities

PSPT

Inter-Fractional Variations

Original Plan **After Two weeks of Radiotherapy**



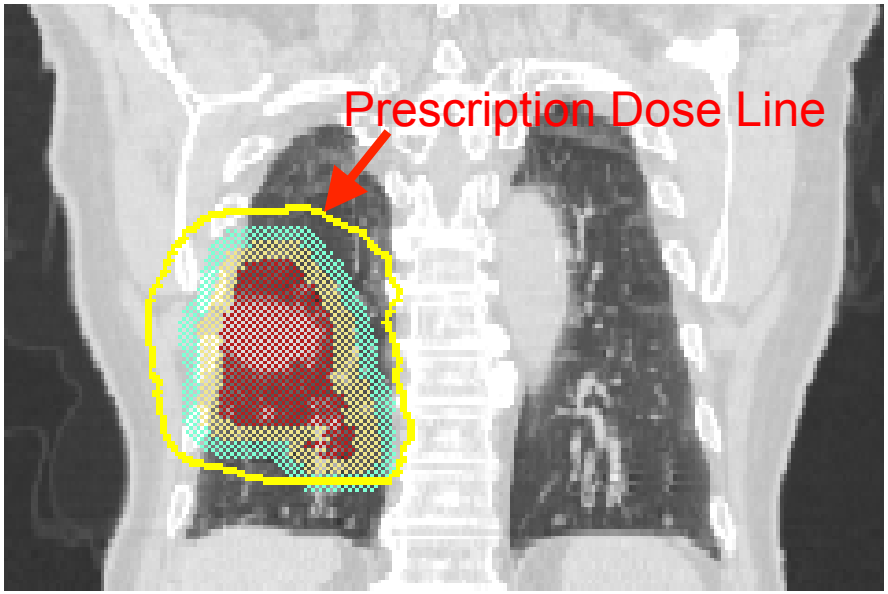
Solution: Repeat Imaging and Adaptive Replanning

Impact of Inter- fractional Variations on Dose Distributions for Lung Patients

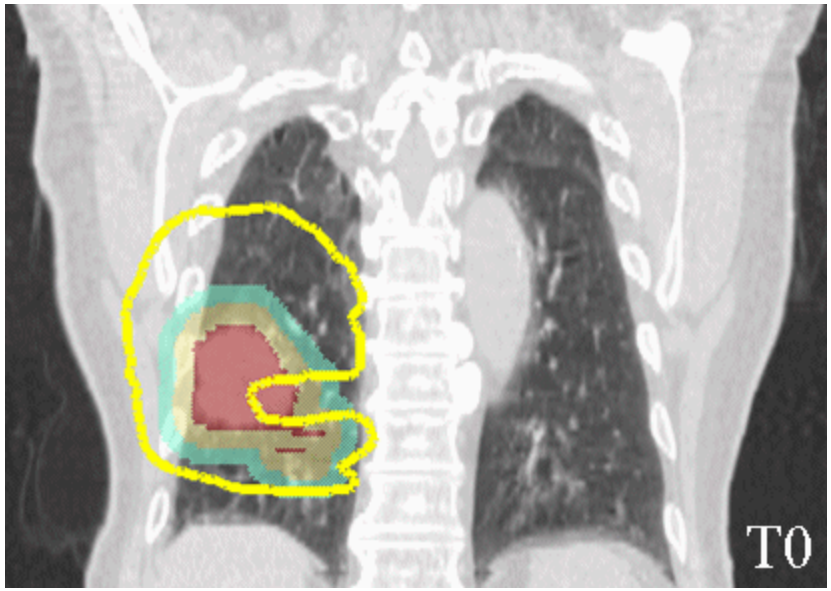
Relative Importance of Adaptive Re-Planning

The first 93 patients on a phase II Randomized IMRT vs. PSPT trial for stage III NSCLC	
53 randomized to IMRT	40 randomized to PSPT
10 required adaptive plans	21 required adaptive plans
18.9%	52.5%

Impact of Respiratory Motion on Proton Dose Distributions



Treatment planned based on single free-breathing CT image (perceived dose distribution)



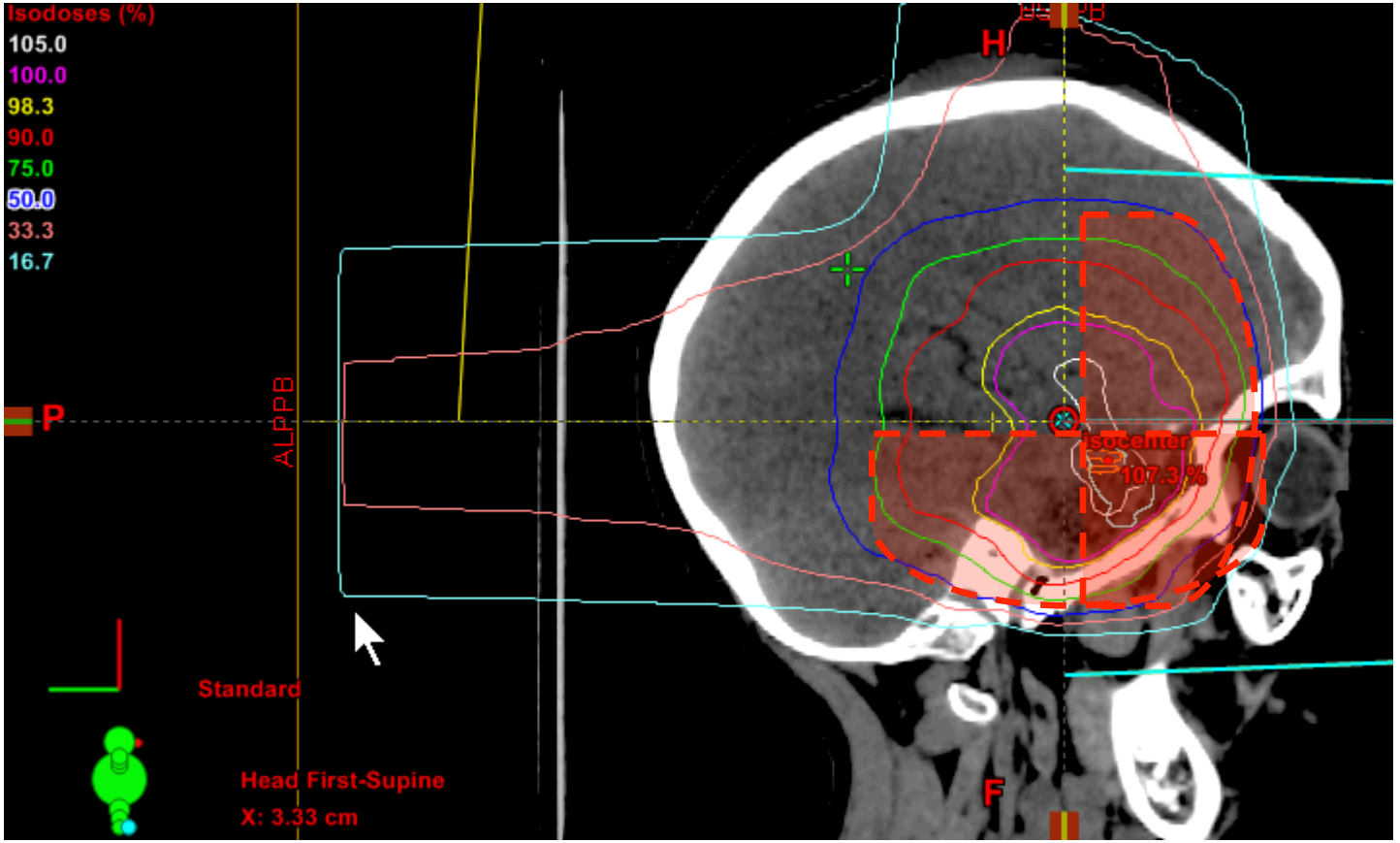
The same treatment plan calculated on 10 phases of the 4D CT image

Uncertainty in Radiobiological Effectiveness of Protons (Particles)

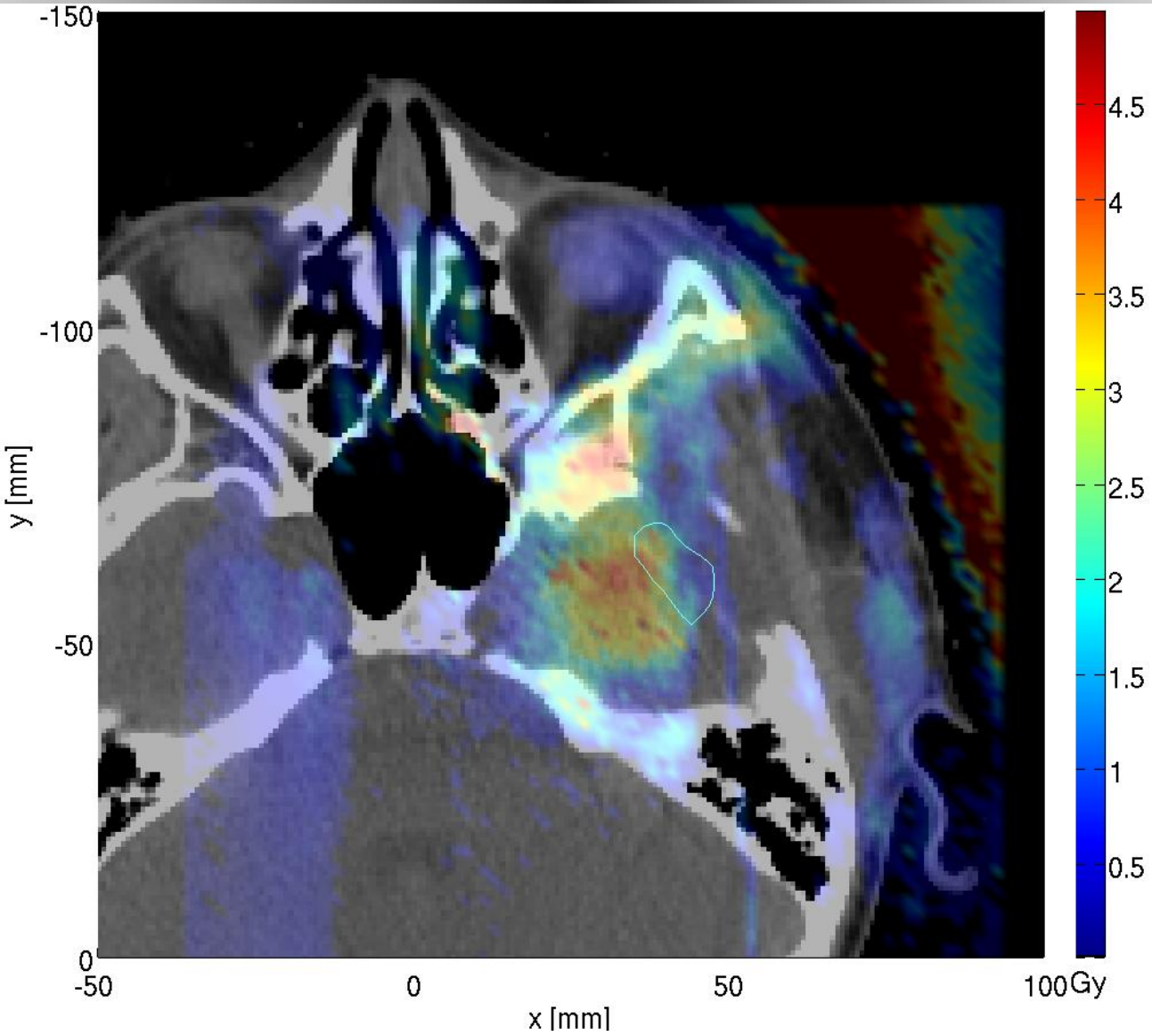
- **Proton RBE is assumed to be 1.1**
- **Claim: Clinical data do not suggest that RBE is different from 1.1**
- **In reality, RBE is a complex function of**
  - **Energy (LET)**
  - **Dose per fraction**
  - **Tissue/cell type, alpha/beta ratio**
  - **End point**
- **Another claim: Proton RBE is high in very narrow region and, thus inconsequential**

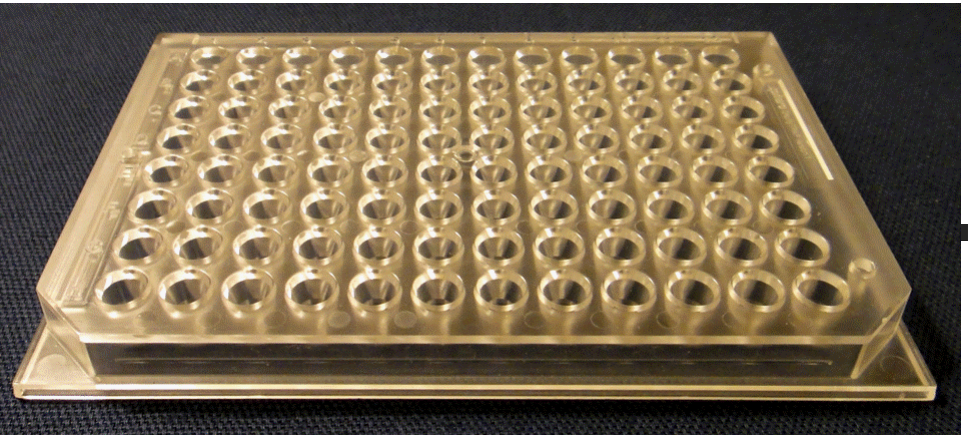
Variable RBE-Weighted Dose Effect for a CNS Patient

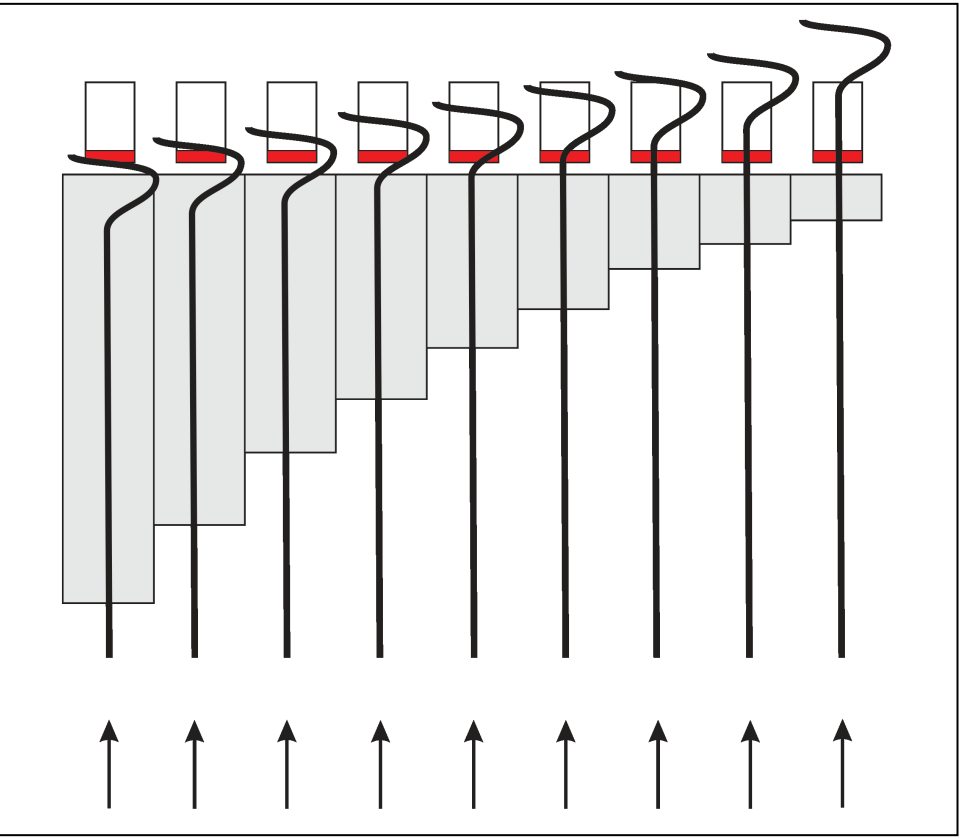
13 year old male with malignant meningioma

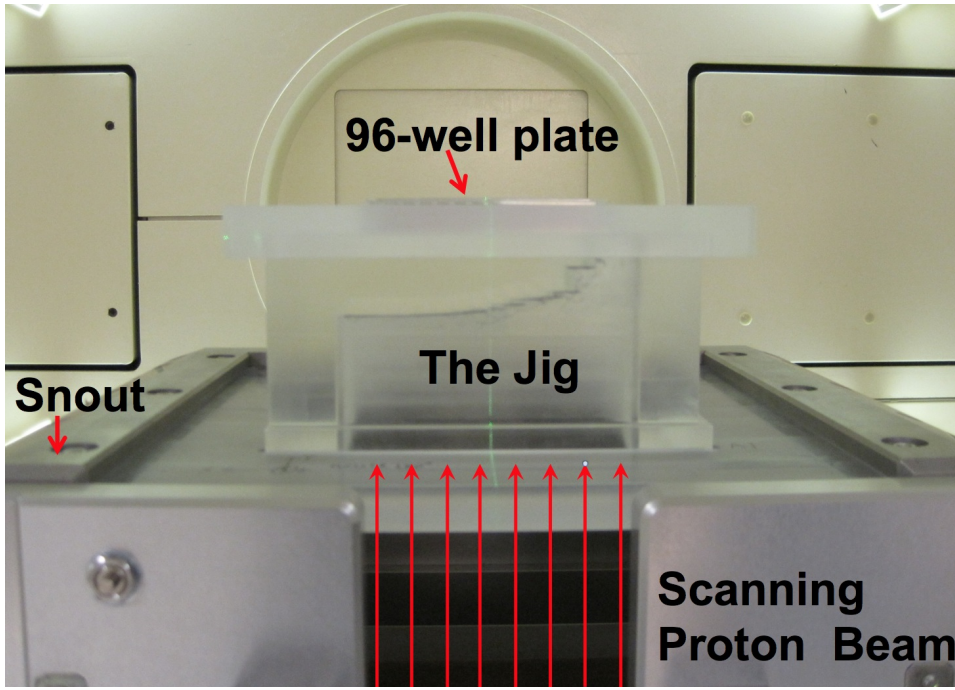


Possible Effect of Variable RBE-Weighted Dose - Brain Necrosis in CNS Patients

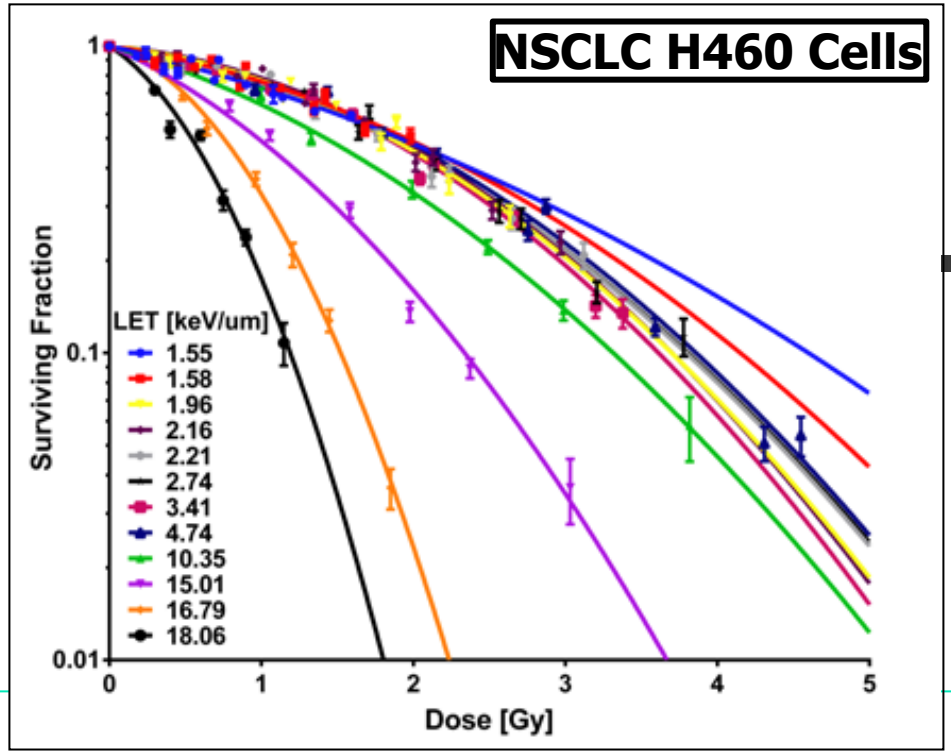


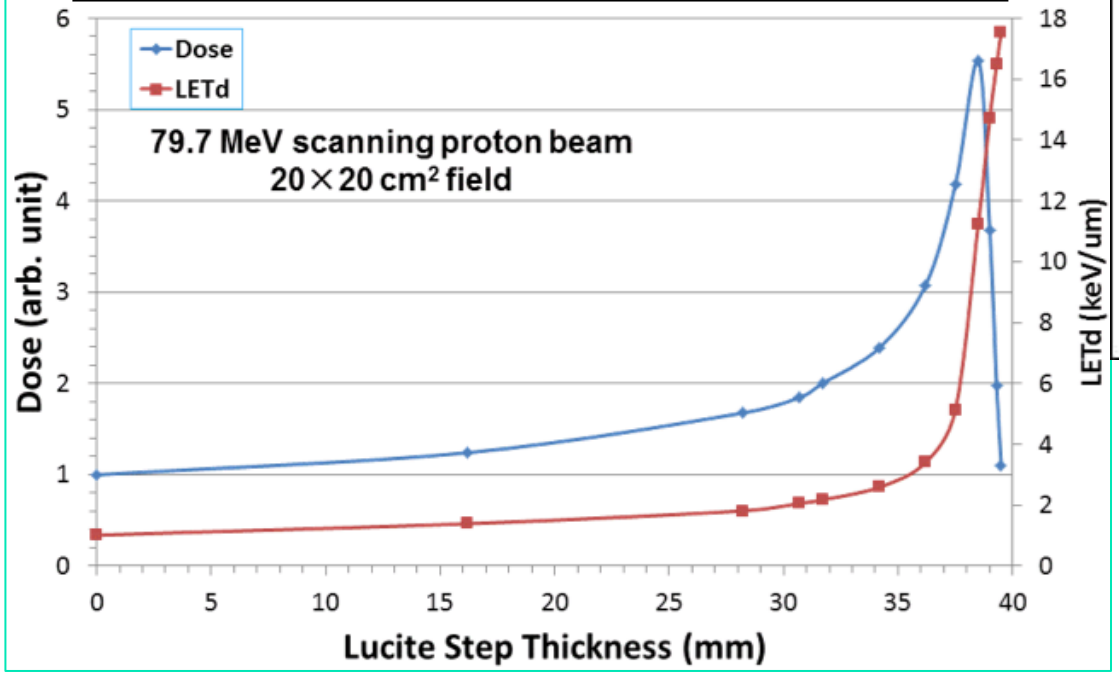


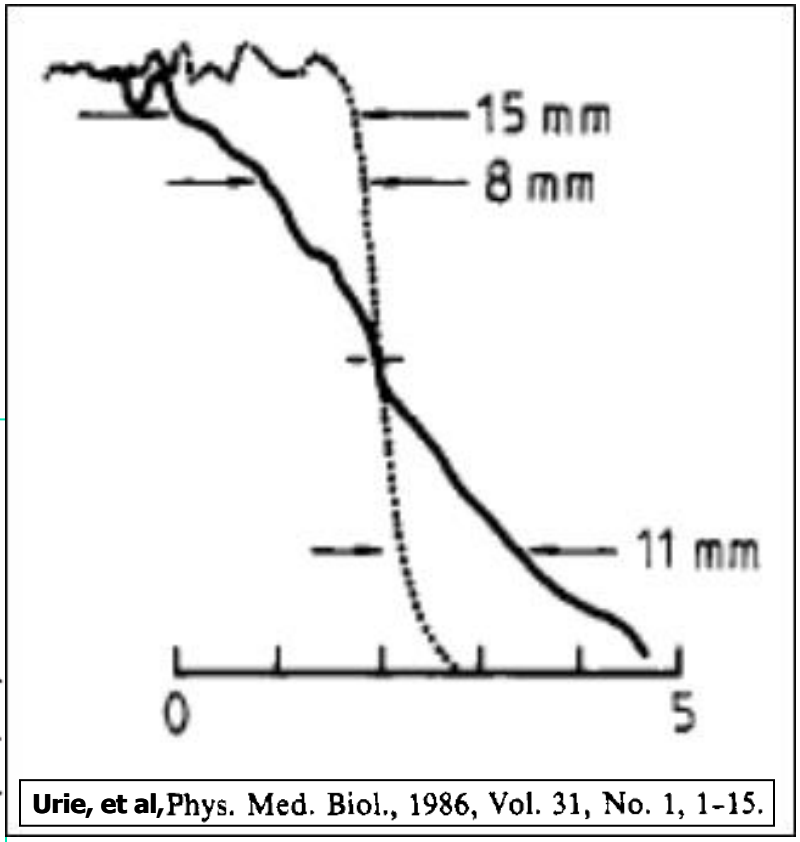



96-well plate
The Jig
Snout
Scanning
Proton Beam

RBE of Protons







Urie, et al, Phys. Med. Biol., 1986, Vol. 31, No. 1, 1-15.

What is being done? - Examples

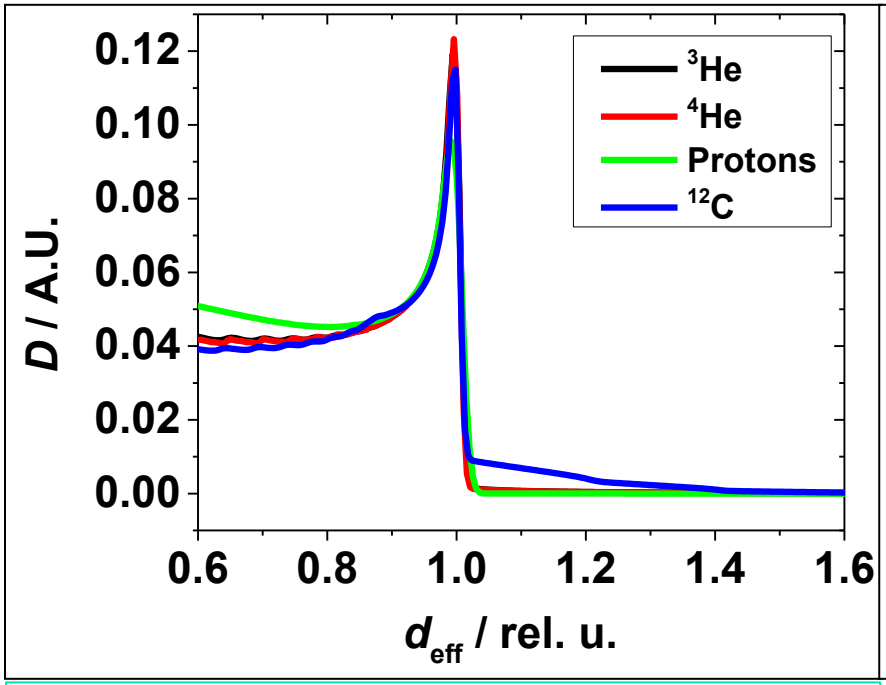
- **Further development of IMPT planning and delivery methods**
- **Reduction in uncertainties through advanced image guidance**
- **Improvement in accuracy of computed dose distributions (MC & others)**
- **Determination of dose distributions "actually delivered"**
- **Improvement in understanding of RBE and its incorporation in IMPT optimization**
- **Robust optimization of IMPT**

What more needs to be done? - Examples

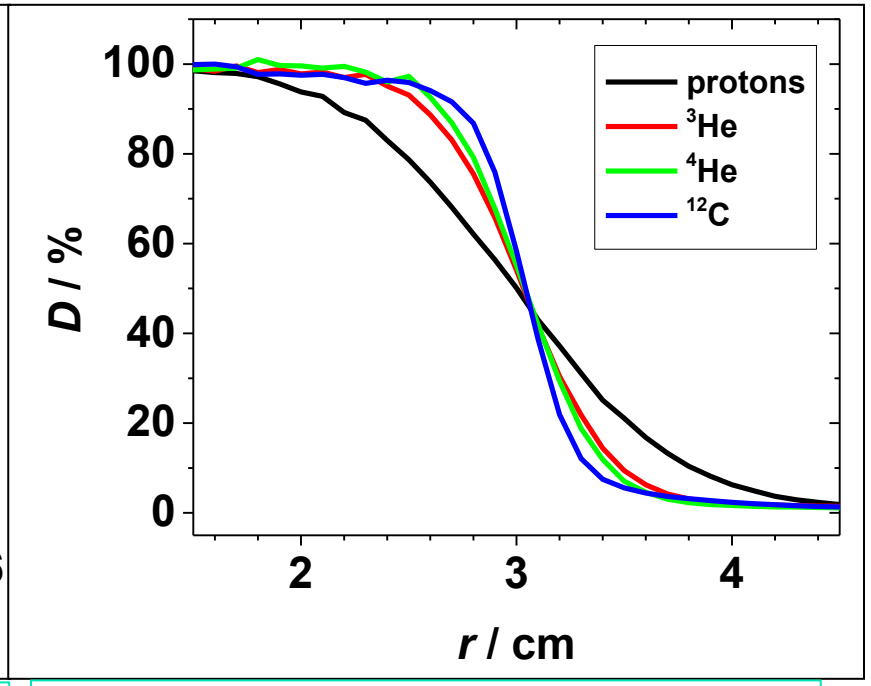
- A LOT more of the same, but better
- Reduction in cost
- Automation of planning
- More efficient optimization and (accurate) dose calculation algorithms
- More in-vitro and in-vivo biology experiments and biological model development
- "Smart" clinical trial
- Particles other than protons and carbon

The Optimum Ion

Proton, Carbon or something else

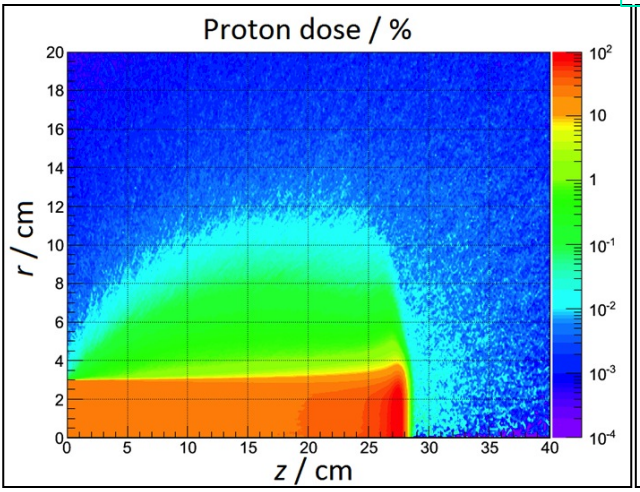


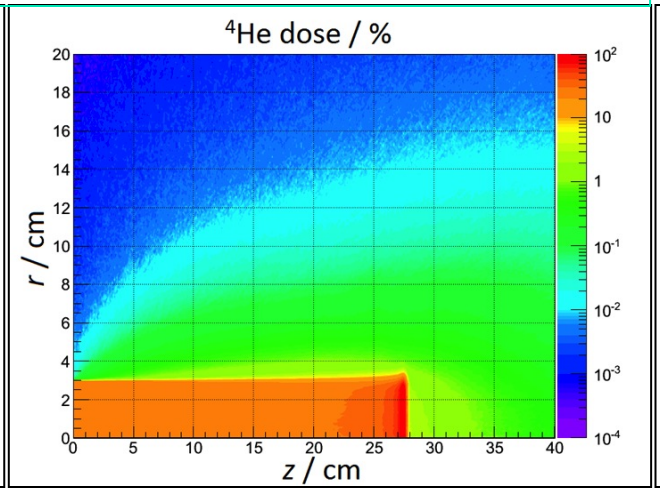
Beamlet Integral Depth Dose

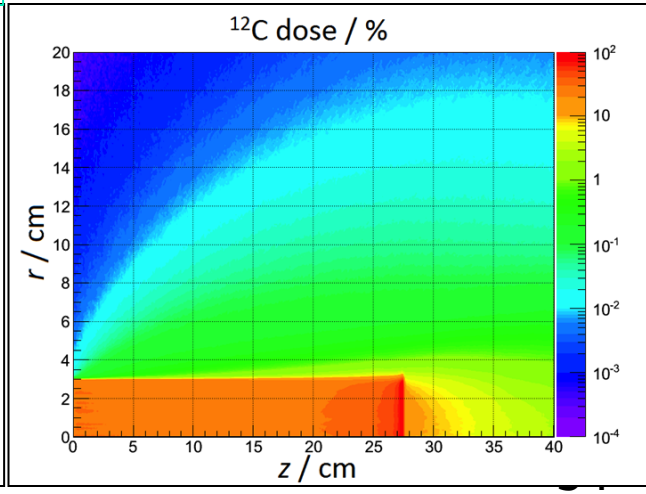


Profiles of 6 cm dia field

Out-of-Field Dose







A Few Words About Clinical Trials Comparing Technologies

Perhaps all trials involving technologies

"Trial of the 21st century"

A Bayesian Randomized Trial of Image-Guided Adaptive Conformal Photon vs. Proton Therapy with Concurrent Chemotherapy, for Locally Advanced NSCLC

http://clinicaltrials.gov/ct2/show/NCT00915005

Randomized IMRT vs. Protons LA NSCLC
Initial Reaction: "You AreCrazy"

- Randomized trials comparing technologies have never been done
- Would it be ethical?
- Would patients consent to be randomized?
- …

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials – Smith et al, BMJ 2003;327:1459-1461

Objective: To determine whether parachutes are effective in preventing major trauma or death related to gravitational challenge.

Other Randomized Trials

- **RTOG 1308 randomized protons vs. photon trial for locally advanced lung cancers (Liao)**
  - **Prescription dose 70 Gy (RBE)**
  - **Endpoint – Overall survival**
- **Phase III Randomized Clinical Trial of Proton vs. IMRT for Low or Low-intermediate Risk Prostate Cancer (MGH, U Penn, MDACC, …)**
  - **Endpoints: efficacy and bowel/bladder/erectile toxicity**
- **Oropharynx Phase II/III IMPT vs. IMRT (Frank)**
  - **Endpoints: late Grade 3-5 toxicity and PROs**
- **…**

Randomized IMRT vs. Protons LA NSCLC How We Did It

- Adaptive randomization
- P01 application: "… we are directing our research effort at perhaps the hardest outstanding problems in proton beam therapy"
- But really, there was an air of over confidence
  - Protons will easily beat out IMRT
  - "It will be over in no time"

Challenges of Conducting Technology-Based Trials – Randomized or Not

- **Dependence on user expertise and experience**
- **Differences in products of different vendors**
- **Ongoing changes in technologies and techniques**
- **Large variability in multi-institutional trials**
- **…**

Therefore “Smart” Design and High Quality of Conduct of Trials are Critical

Quality of Trials

- **Current sources of quality problems**
  - **Compliance with protocol**
  - **Weak requirements – Example**
    - **85% of the points measured in a phantom must be within +/-5% or 5 mm – one institution may give 10% different dose than another**
    - **What about the dose to the remaining 15% of the points?**
    - **What about the dose to normal tissues?**
    - **What about the actual dose delivered to the patient?**

What can be done to raise the bar?

- **Make requirements more restrictive**
- **Contra-arguments - Not enough participants and patients**
- **Well done trial with smaller sample vs. poorly done trial with large sample**
- **Explore the possibility of two tiers of trials**
  - **To answer the scientific question**
  - **To determine the feasibility of the new technology / technique in the community setting**
- **Why obscure the answer and deny better treatment if it can be done by some institutions and not by all?**

Message

- **Proton therapy has been around for more than 50 years**
- **Theoretically, it has significant clinical potential over photon therapy**
- **This potential has not been clearly demonstrated to date**
- **The reasons may be technological immaturity, sensitivity to uncertainties, inadequate understanding biology of protons (particles), …**
- **Protons are costly, questions are being raised about their cost effectiveness**
- **Considerable more R&D and "smart" clinical trials re needed**

Thank You