# Hadron Therapy: Clinician's Perspective

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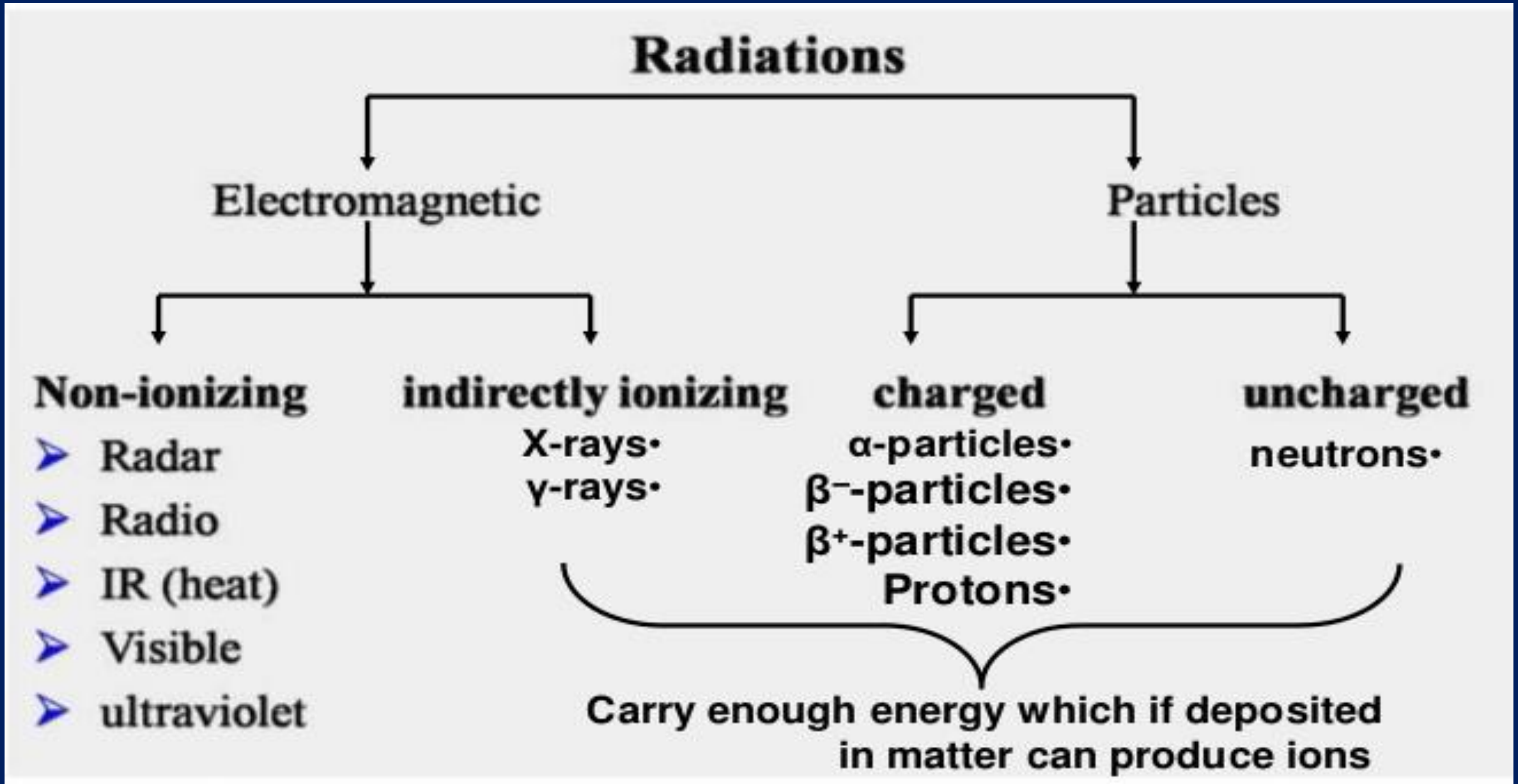
**COI: None**
**Disclosure: None**

Radiation therapy using heavy particle as source of radiation. The heavy particle can be a proton, carbon ion, neutron or meson etc

Clinician's perspective is a broad-based term

- Types of radiation
- Rationale
- Physics of particle beam
- Radiobiology of particle beam
- Clinical Utility
- Evidence and drawbacks

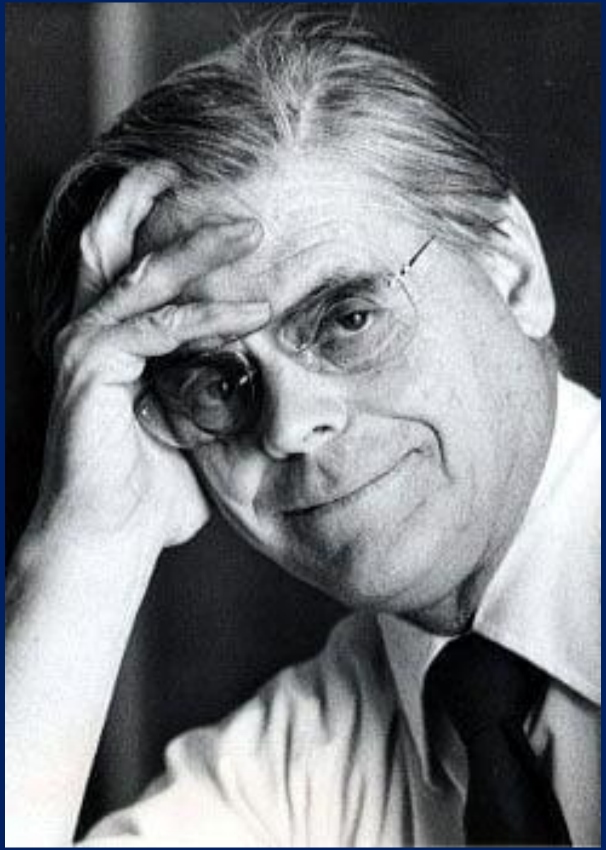
# Types of Radiation



# Shortcomings of Photon

- High entry dose
- High exit dose
- Exponential attenuation
- Lateral penumbra

# Basics of Heavy Particle Therapy

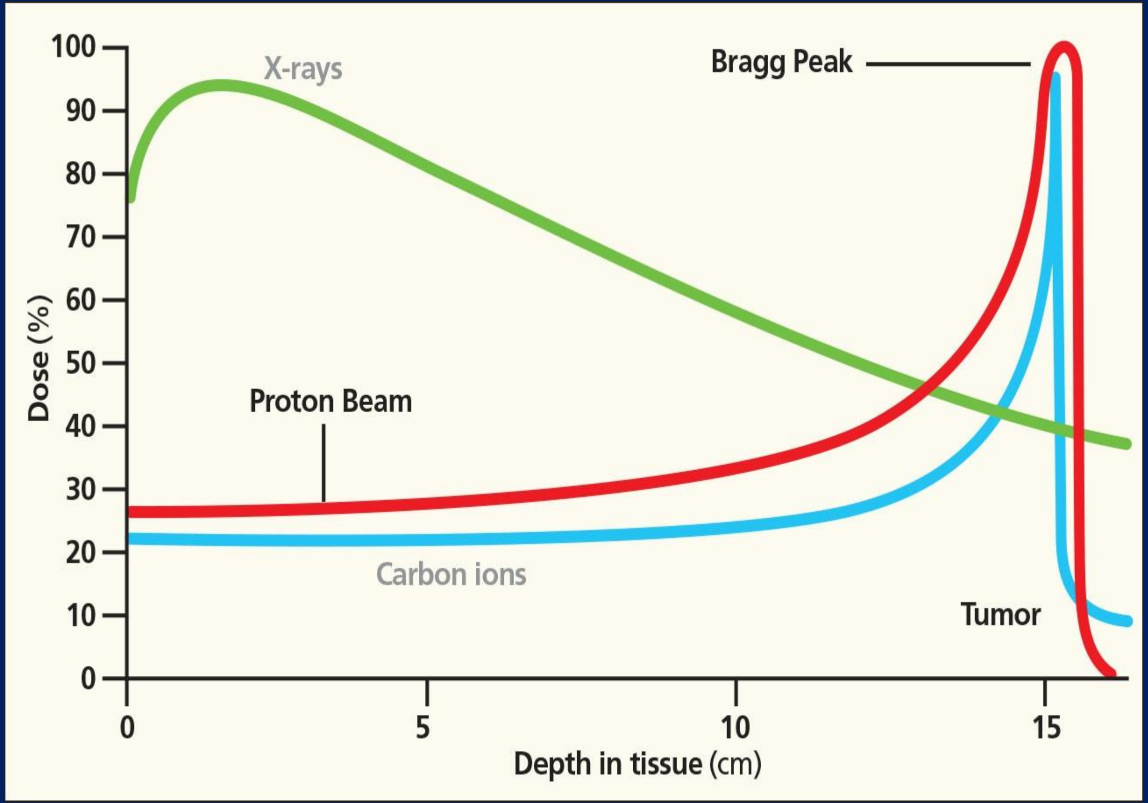


- Finite range
- Reduced lateral scattering
- Greatest potential increased relative biological effectiveness (RBE)
- Reduced oxygen enhancement ratio (OER)
- Unique effects of densely ionizing radiation
  - Reduced angiogenesis
  - Augmented immune response

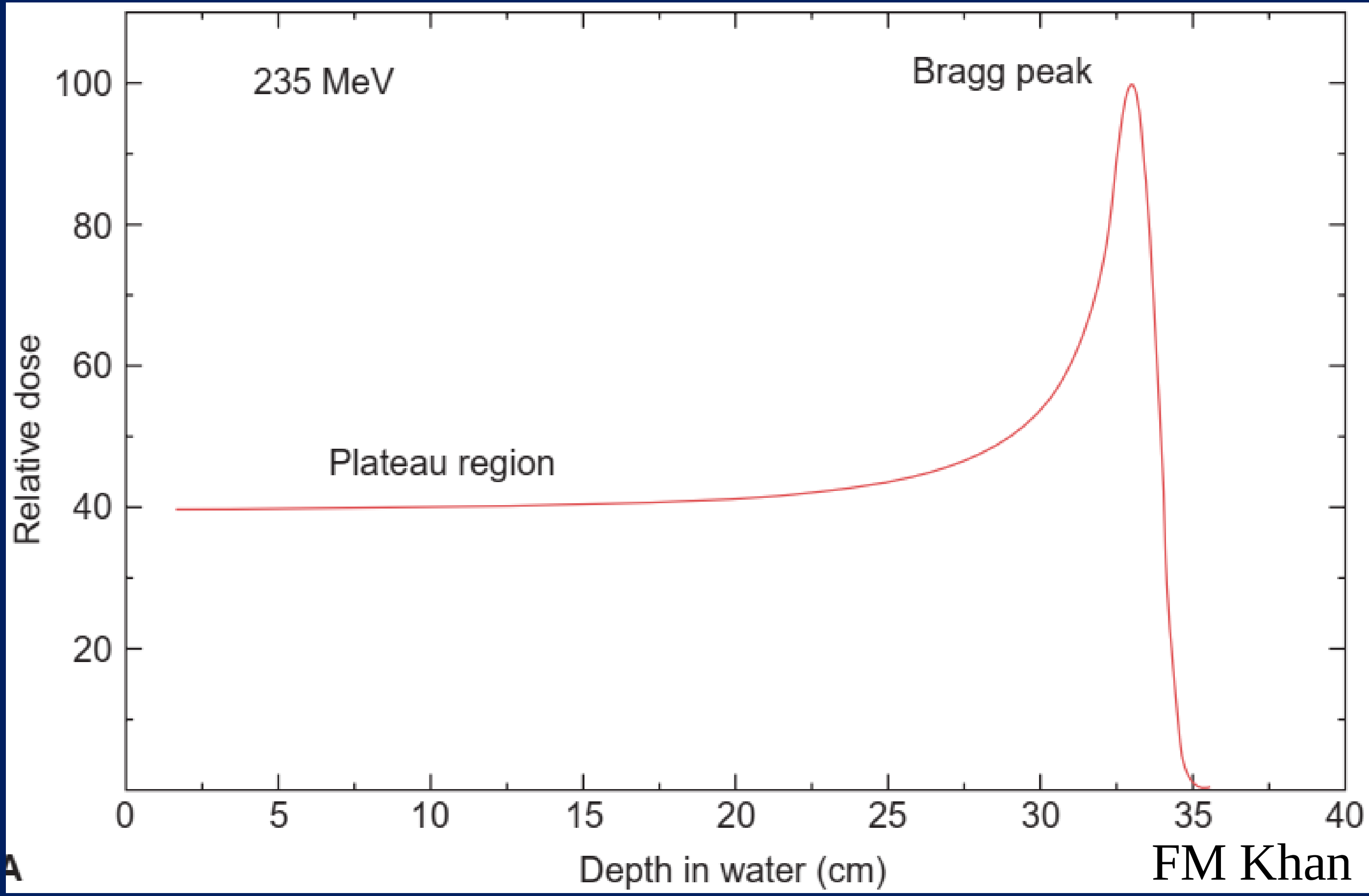
**Robert Wilson**
**Proposed proton beam for clinical use 1946**

# Advantages of Heavy Particle

- No exit dose
- Sharp Lateral penumbra
- Bragg peak
- Variable LET



# Bragg Peak




- Bragg Curve is a graph of the energy loss rate[ LET ] as a function of the distance through a stopping medium.
- Proportional to square of nuclear charge Z
- Inversely proportional to square of velocity
- This gives the Bragg Curve its familiar shape, peaking at very low energies, just before the projectile stops.

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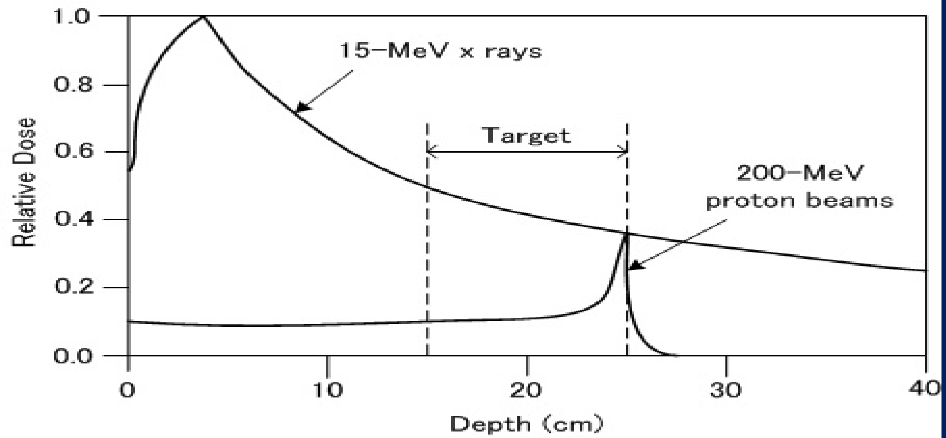
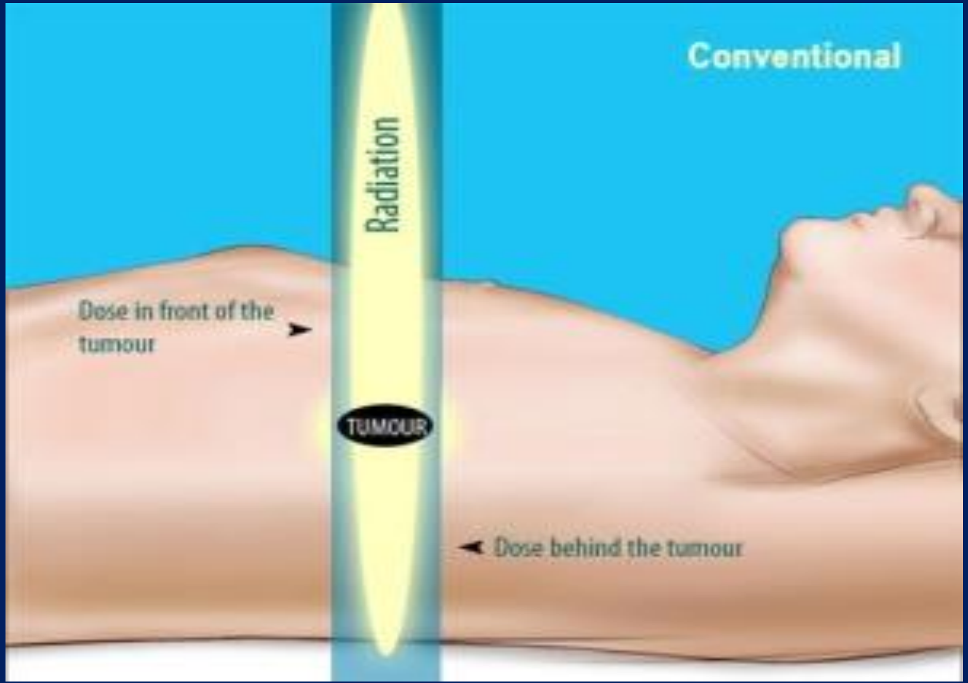
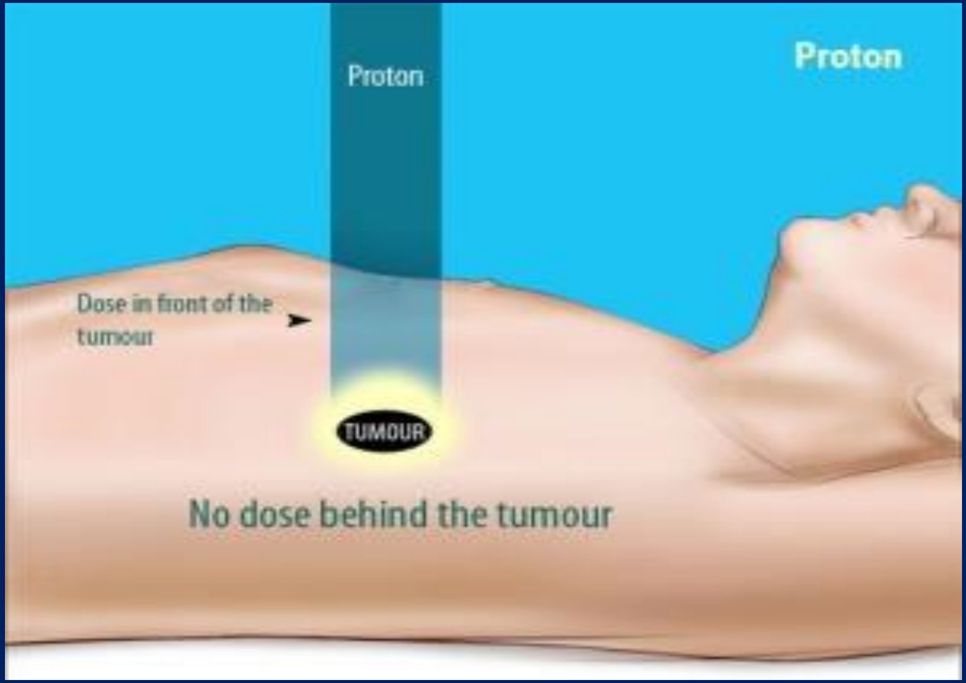
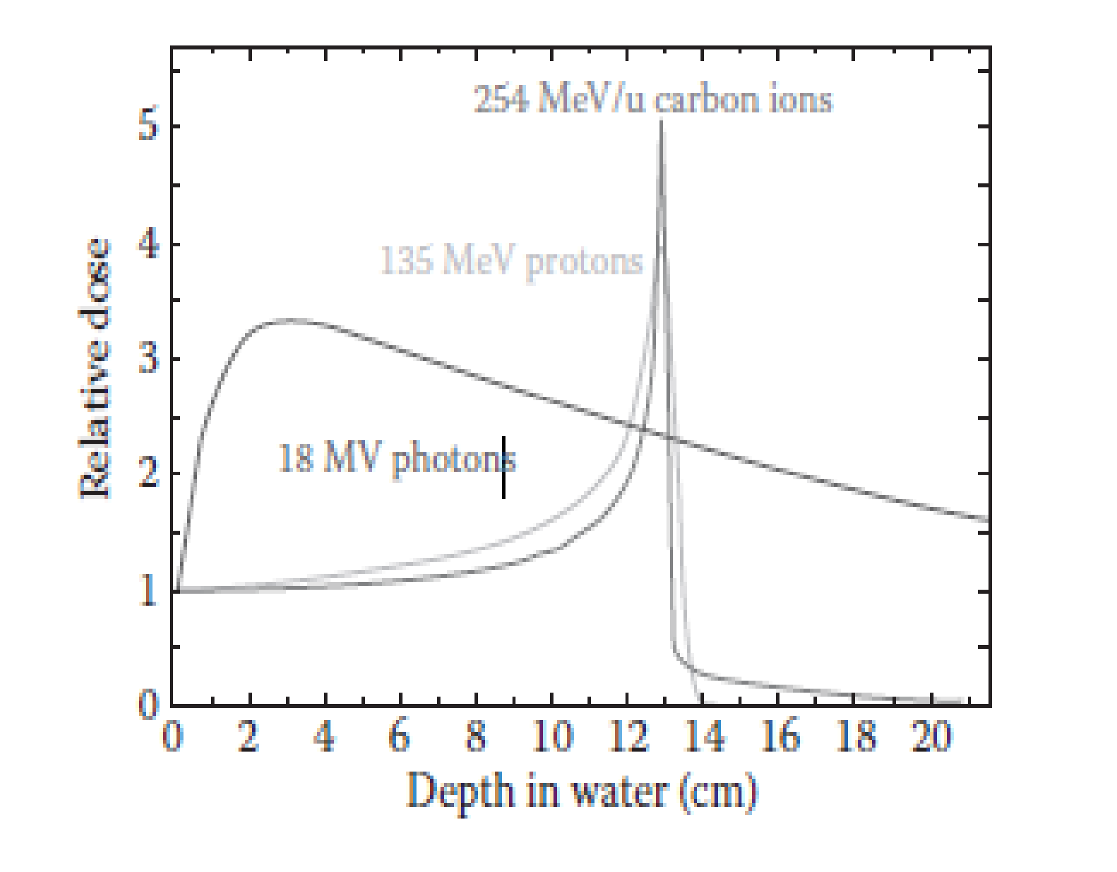


# Comparison of Pristine Bragg peak of Proton and Carbon ion

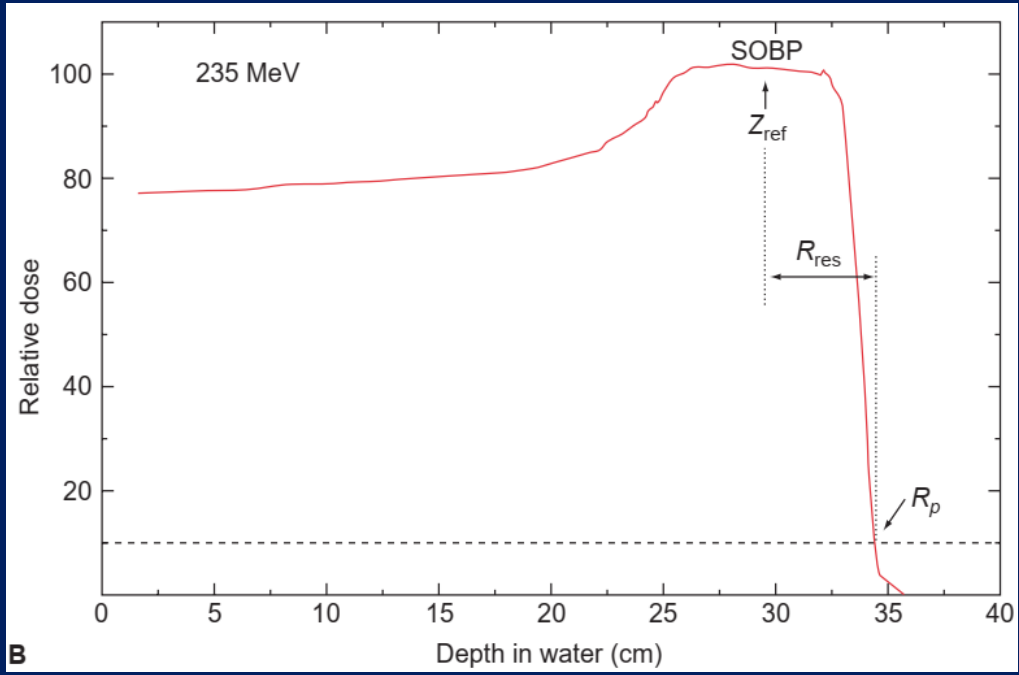
- Carbon ion is 12 times heavier than proton
- Carbon ion PBP is sharper than proton due to its rapid fall off



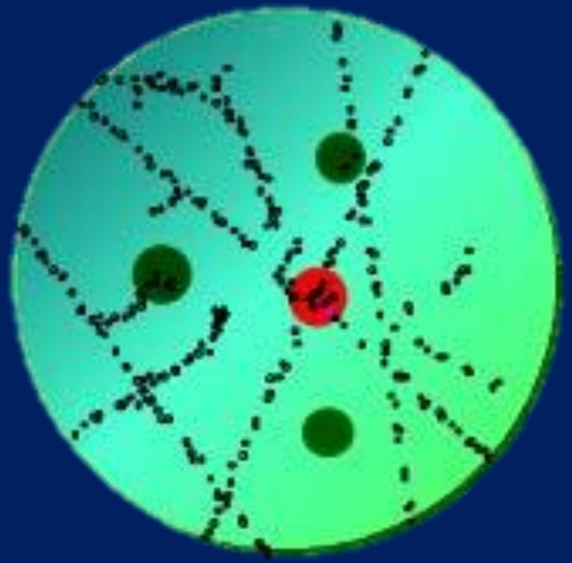

Courtesy: Proton and Carbon Ion Therapy, CRC press

# SOBP

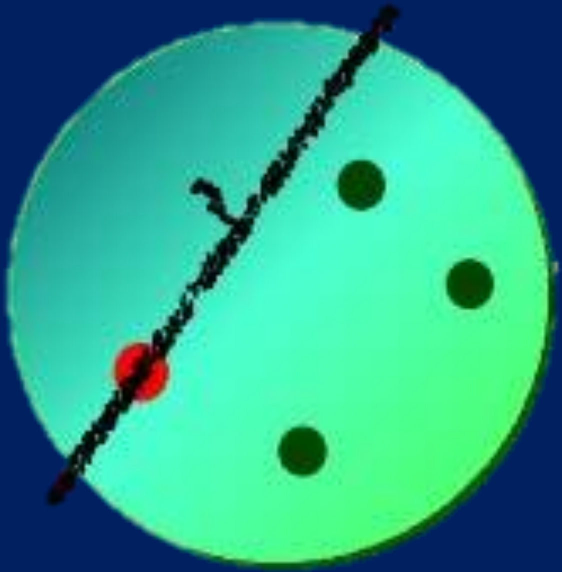
- A single proton in a proton beam→ very narrow Bragg peak
- A mono energetic proton beam → range straggling at the very end→ slight broadening of Bragg peak→ not enough
- Plastic or graphite material with different thickness rotated in front of continuous proton beam→ pull back of each ray → different depth of penetration → summation of all Bragg peaks at different depth→ SOBP



# Ionization Density (LET)

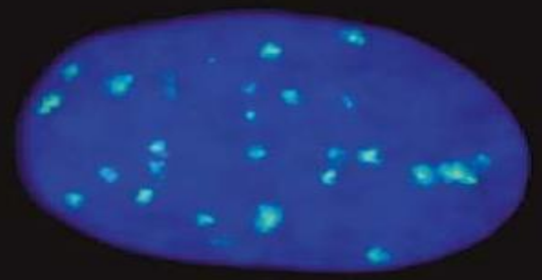


Low LET (Protons)



High LET [(Neutrons)

DNA breaks after high LET beam



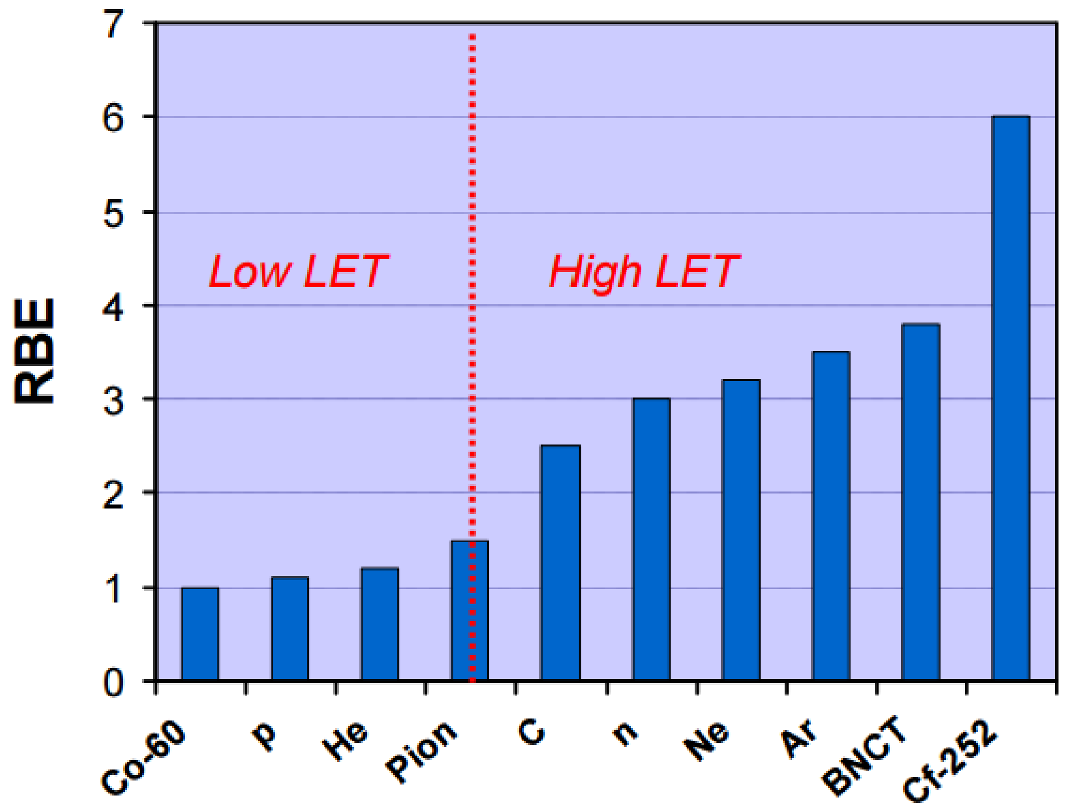
DNA breaks after X Rays

# LET and RBE

## TYPICAL LET VALUES IN TISSUE

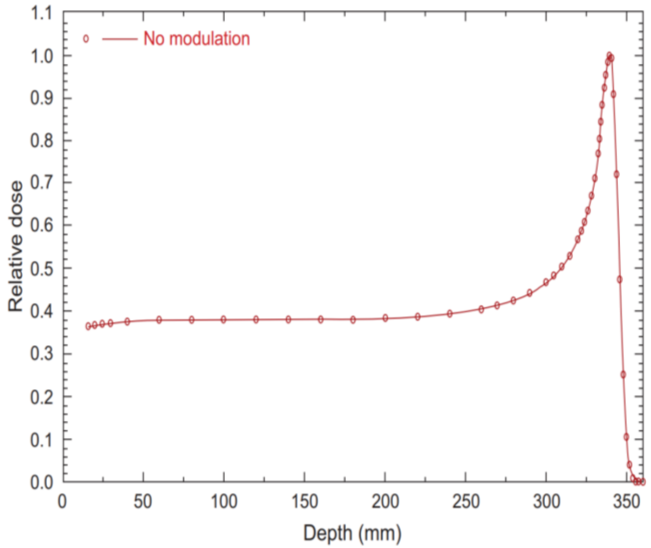
| RADIATION | LET (keV μm$^{-1}$) |
|---|---|
| $^{60}$Co γ-rays<br>MV x-rays | 7 |
| Electrons | 7 |
| 250 kV x-rays | 10 |
| Protons | 10 |
| $^{4}$He ions | 15 |
| $\pi^{-}$ mesons | 20 |
| $^{12}$C ions | 75 |
| Fast neutrons | 75 |
| $^{252}$Cf | 100 |
| $^{40}$Ar ions | 120 |
| Boron neutron capture<br>$^{4}$He<br>$^{7}$Li | <br>200<br>160 |

## RELATIVE BIOLOGICAL EFFECTIVENESS

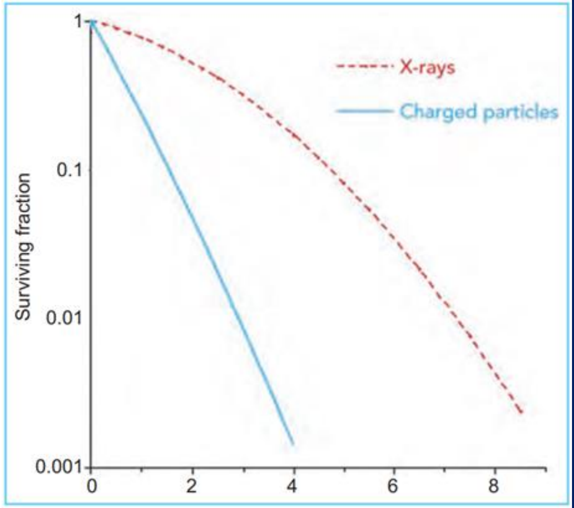


- Charged heavy particle having finite range
- Nucleus of the hydrogen atom, or a hydrogen atom without electron

- ➢ Sharp peak at the end of particle range
- ➢ Depends on particle and medium property
  - ➢ Square of particle charge
  - ➢ Inversely proportional to velocity
- ➢ Monoenergetic
- ➢ SOBP



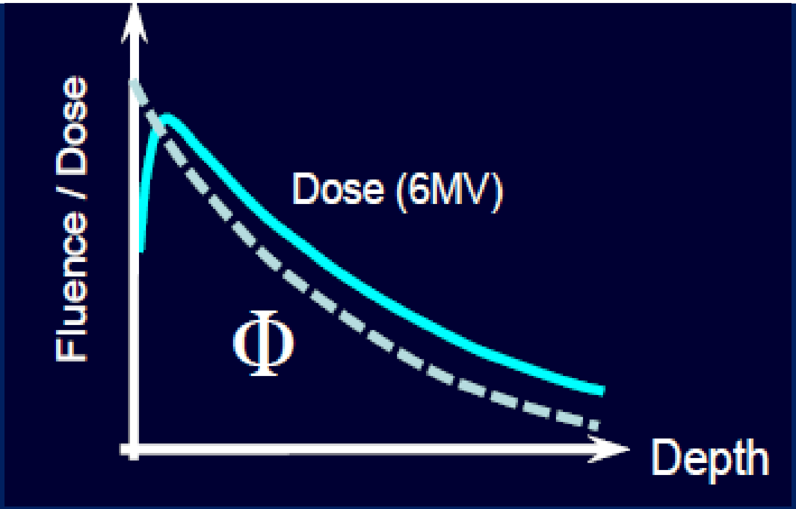

- ➢ RBE
- ➢ Related to LET
- ➢ Uniform RBE 1.1
- ➢ Reference: 250 kV Xray / 60-Co γ ray



# Energy loss: Photon vs Proton

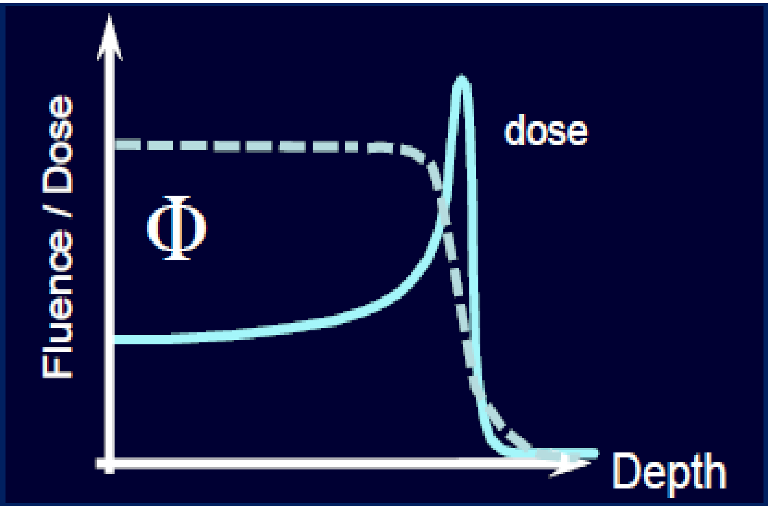
## Photon

- Attenuation since beginning
- Fluence decreases since beginning
- No substantially change in energy spectrum
- No change in ion pair production per unit length



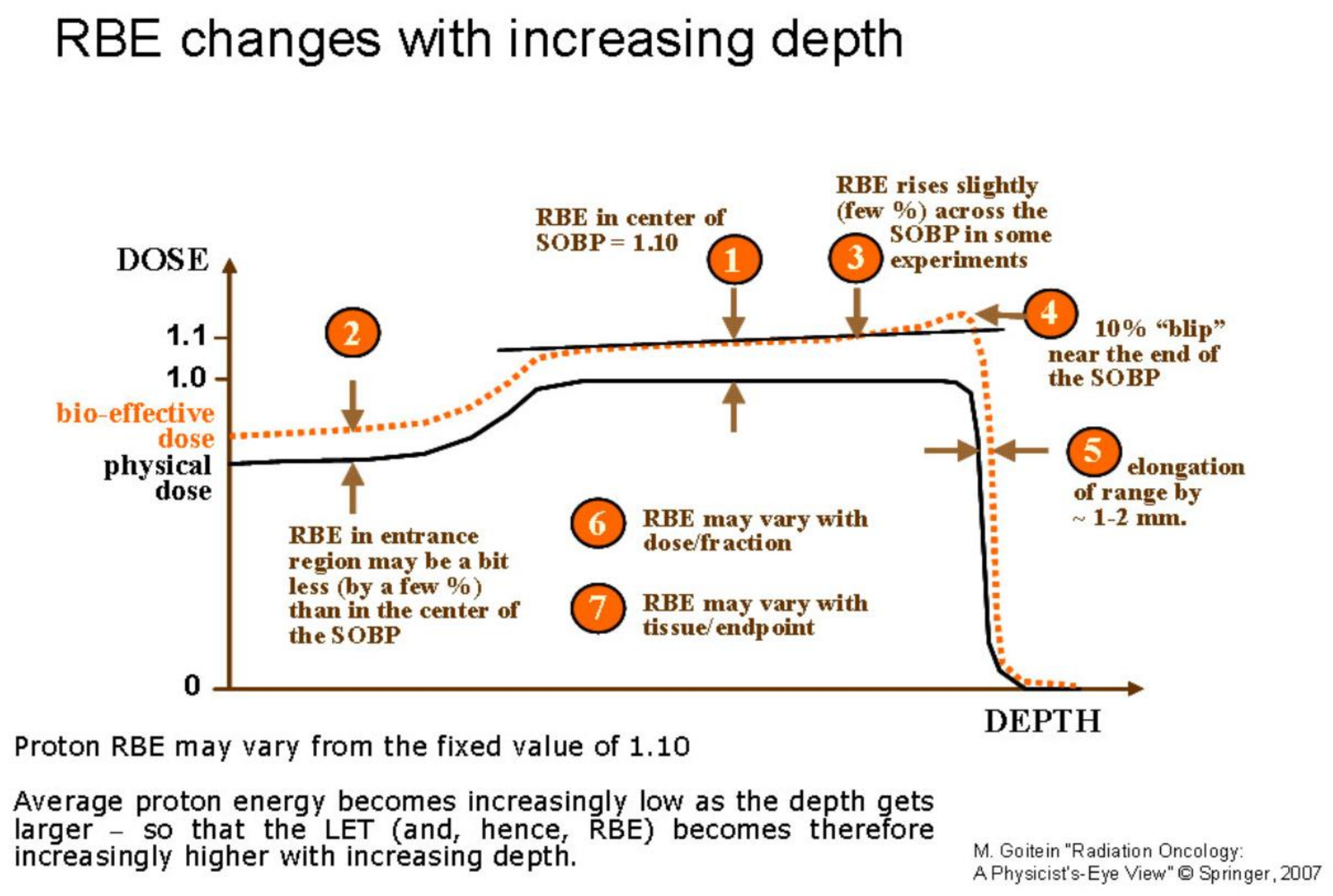

## Proton

- No attenuation till bragg peak
- No change in fluence except near the end
- Particle losses its energy gradually
- Production of ion pair gradually increase



# RBE for Proton therapy

- Measured as CGE (cobalt gray equivalent)
- Biological effective dose= RBE x physical proton dose {Gy(RBE)}
- Though common practice to use a constant generic RBE of 1.1(ICRU Report 78 )
- But proton RBE is not same along the the SOBP



# Characteristics of carbon ion and proton ions

| Proton | Carbon Ion |
|---|---|
| • Low LET particle<br>• Deposition of energy along the track is similar to that of photon before reaching Bragg peak where it becomes denser<br>• Double strand break is higher than photon therapy | • High LET particle<br>• Deposition of energy is dense which becomes denser at Bragg peak<br>• More clustered DNA damage<br>• Double strand break is much higher than proton |

# Main difference between proton and photon

| | Factors | Protons | Photons |
|---|---|---|---|
| 1 | CT # and stopping powers accuracy | Sensitive - affect range, distal target coverage or distal normal tissue sparing | Not sensitive |
| 2 | Target motion normal to beam | Affects margin, may affect dose distribution distal to target | Affects margin |
| 3 | Normal structure motion orthogonal to beam | Affects range, dose distribution distal to structure | Minimal effect |
| 4 | Target motion along beam direction | No effect | Affects margin |
| 5 | Normal structure motion along beam direction | No effect | Minimal effect |
| 6 | Complex inhomogeneities | Not well characterized, perturb dose distributions, degrade distal edge | Well understood, effect not strong |
| 7 | Anatomy changes over course of RT | Affect dose distribution | Minimal effect |
| 8 | Plan Evaluation | Impact of uncertainties significant, PTV concept not valid, validity of initial nominal plan questionable | PTV concept valid, dose distributions relatively invariant to uncertainties, initial plan acceptable approximations |

# Uncertainties and Problems with heavy Particles

**Physics Uncertainty: Range uncertainty**

Related to physical dose distribution

Planning CT image: Daily patient geometry may be different

CT number /Hounsfield Unit – Represent photon attenuation power

Proton stopping power require HU conversion

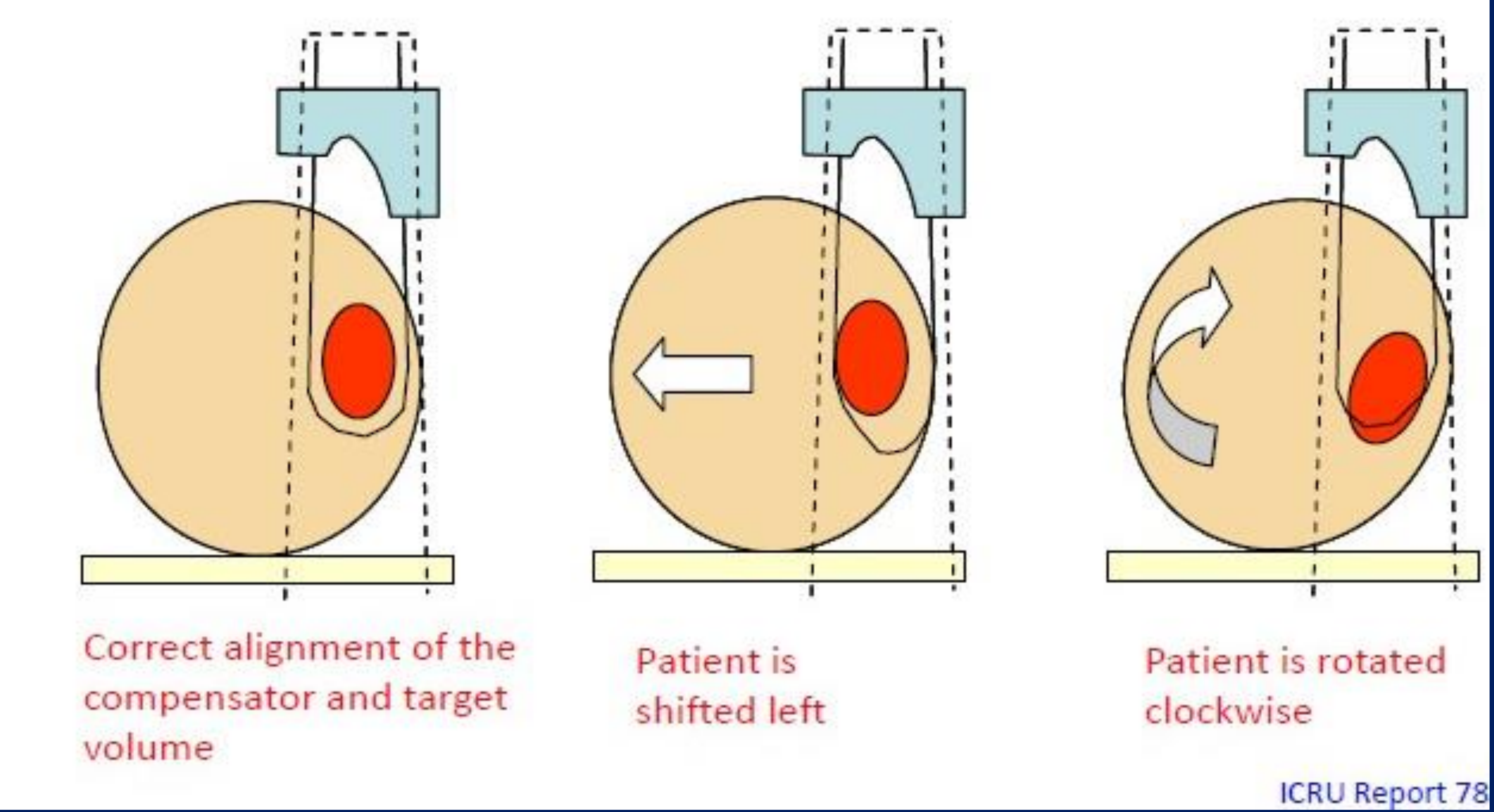
CT artefacts

**Biologic Uncertainty**

- 1.1 is a close approximation
- RBE increased by 5% at 4 mm from the distal edge
- RBE increased by 10% at 2 mm from the distal edge
- Varies with type of tissue (low or high $\alpha/\beta$)
- Varies with dose

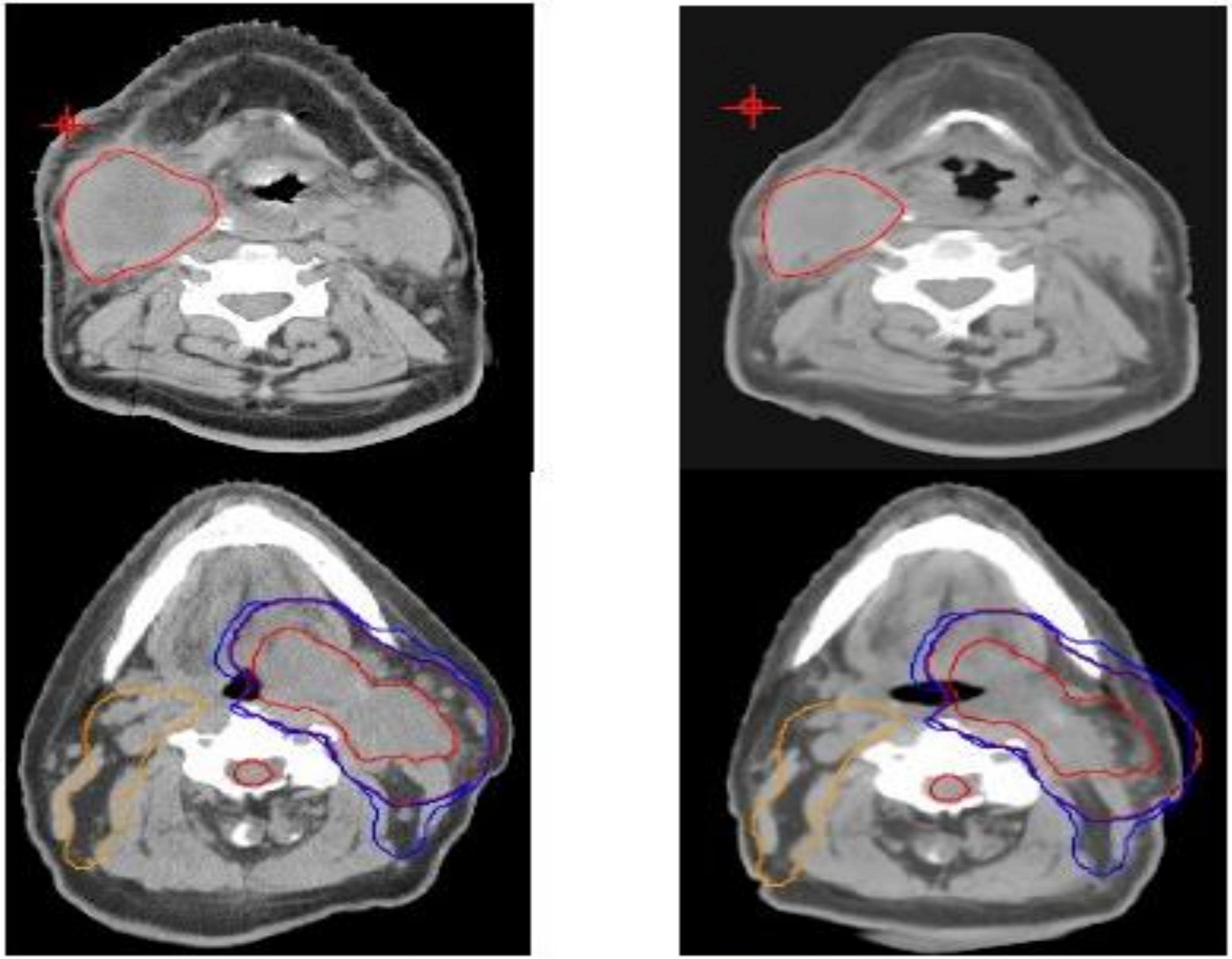
- Limitations of CT data (beam hardening, noise, resolution etc)
- Uncertainty in energy dependent RBE Calibration of CT to stopping power
- CT artifacts
- Variations in patient anatomy
  - Variations in proton beam energy Variations in patient positioning

# Misalignment of Compensator with Target



# Anatomic Variation During Treatment



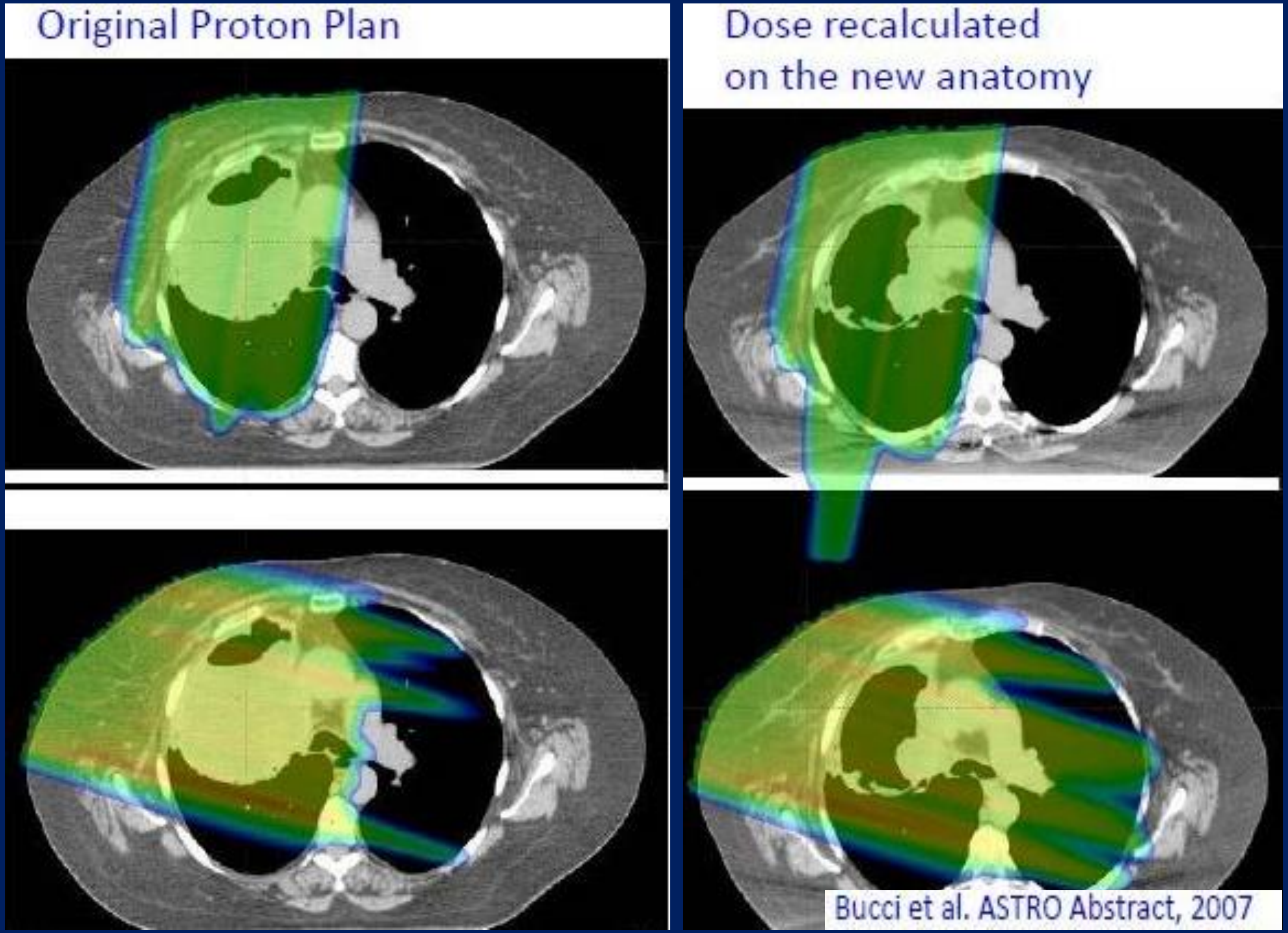


Planning CT

Three Weeks into RT

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

# Impact of Tumor Shrinkage on Dose Distribution



# How to mitigate uncertainties

- Rigorous Quality assurance
- Proper patient selection
- Better image registration and site specific treatment
- Immobilization etc

**Solution to range uncertainty:**

- The depth of the Bragg peak (Distal 90%)
- Modulation: The spread of the Bragg peak
- Apertures: Shaping the beam perpendicular to the path
- Compensators: Distal Shaping

# The Place of Ion Beams in Clinical Applications

- Better organ sparing (Skull base tumors)
- Better local control needed (Ca Prostate)
- Late morbidity (Pediatric malignancies)
- Complex geometry (Ocular melanoma)
- Large target volume (Childhood Medulloblastoma)

# Improving Particle Therapy

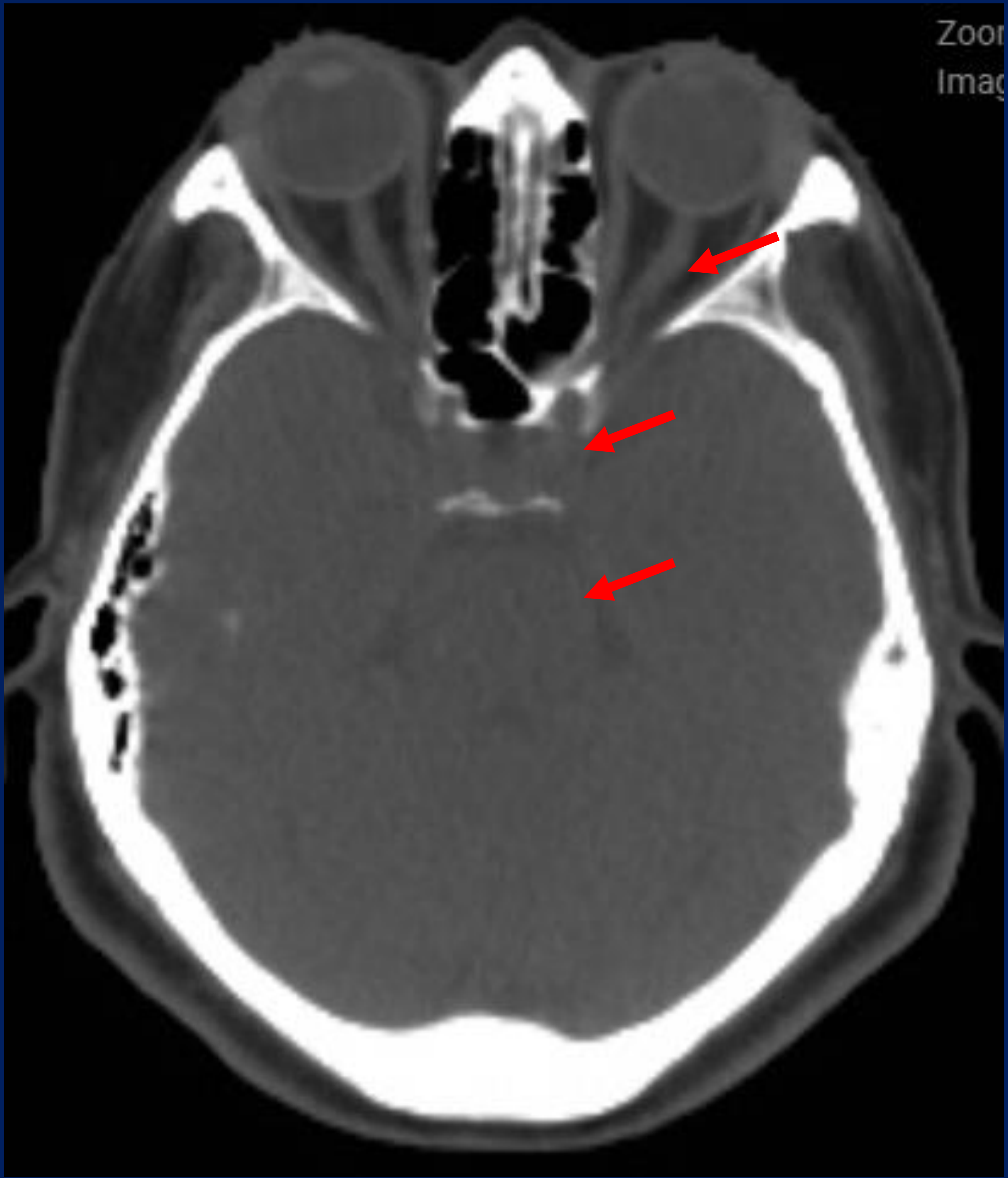
- Anatomy variations
  - IGRT/adaptive radiotherapy
  - Robust optimization
- Intra-fractional motion
  - Gating, coaching, tracking…
- Accurate stopping power ratios (CT number conversion)
- Scanning pencil beams (IMPT) with beam angle optimization.

# Clinical Aspect

# Planning Difficulties with Photon

# Difficulties in HNC radiation planning

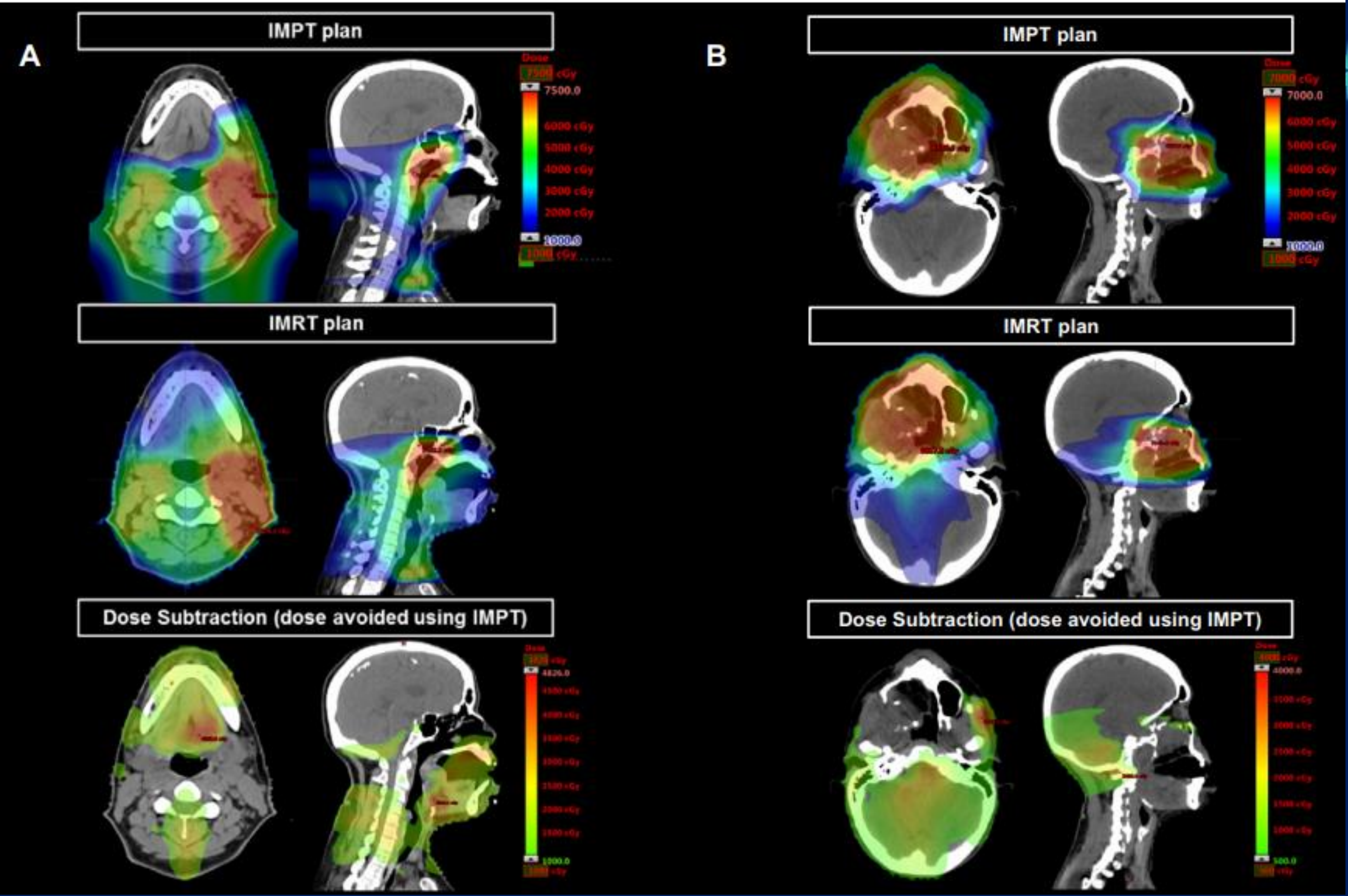
| | | | | | |
|---|---|---|---|---|---|
| Salivary gland (one side) | Each parotid gland separately | <7 cc<br>Mean dose | 20 Gy<br><26 Gy | 32 Gy | xerostomia |
| Larynx | Starting 1 cm above first appearance of true vocal cord include entire cord, arytenoid muscles, corniculate and arytenoid cartilages and portions of thyroid cartilage abutting these structures ending at the first appearance of the cricothyroid ligament. | <3 cc | 39 Gy | 63 Gy | necrosis/edema |
| TM joint | Each side separately starting at the superior articular surface near the zygoma bone and ending at the notch at the superior part of the ramus of the mandible. | <1cc | 60 Gy | 65 Gy | inflammation |



# Can proton overcome the difficulties

Difficulties with proton planning:

- Highly sensitive to tissue type
- Uncertainties are more
- HU to stopping power conversion
- Overshoot or undershoot
- Complex local anatomy
  - Skin
  - Soft tissue, fat, muscle
  - Bone
  - Air cavities
  - Nerves
  - Brain
- Lack of trained manpower




Blanchard P, 2018

# Can we predict radiation toxicity with proton beam therapy using photon data?

- NTCP models
- Radiobiological model
  - Xerostomia
  - Dysphagia or feeding tube dependence
  - Hypothyroidism
  - Laryngeal edema
  - Nausea
  - Acute mucositis

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biology • physics

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Clinical Investigation

**A Model-Based Approach to Predict Short-Term Toxicity Benefits With Proton Therapy for Oropharyngeal Cancer**

Jean-Claude M. Rwigema, MD,[*,†] Johannes A. Langendijk, MD, PhD,[‡]
Hans Paul van der Laan, PhD,[‡] John N. Lukens, MD,[*]
Samuel D. Swisher-McClure, MD,[*] and Alexander Lin, MD[*]

*Perelman School of Medicine, University of Pennsylvania, Department of Radiation Oncology,

- Statistically significant reductions in the mean NTCP values
- Largest difference in grade ≥2 dysphagia and grade ≥2 xerostomia

# Clinical Utility

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Cancer Res Treat. 2021;53(3):621-634

Special Article

## Who Will Benefit from Charged-Particle Therapy?

**Kyung Su Kim**[1], **Hong-Gyun Wu**[2,3,4,5]

*[1]Department of Radiation Oncology, Ewha Womans University College of Medicine, Seoul, [2]Department of Radiation Oncology, Seoul National University Hospital, Seoul, [3]Institute of Radiation Medicine, Seoul National University Medical Research Center, Seoul, [4]Cancer Research Institute, Seoul National University College of Medicine, Seoul, [5]Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, Korea*

| California, PBT (2003-2016) [11] | | Japan, PBT (1979-2013) [77] | | Japan, CIRT (1994-2017) [78] | | UK (Christie), PBT (2018-2019) [8] | | |
|---|---|---|---|---|---|---|---|---|
| Site | Percentage | Site | Percentage | Site | Percentage | Population | Site | Percentage |
| Prostate | 41.3 | Prostate | 30.0 | Prostate | 24.7 | Pediatric and | CNS | 38.9 |
| Breast | 14.0 | Liver | 19.0 | Bone and soft tissue | 11.5 | young adult | H&N | 15.7 |
| Eye/orbit | 11.8 | H&N | 13.0 | H&N | 9.6 | (~24 yr) | Body | 10.2 |
| Lung | 6.1 | Lung | 12.0 | Lung | 9.2 | | Spine | 6.5 |
| CNS | 6.0 | GI | 6.0 | Pancreas | 5.4 | | CSI | 1.9 |
| Lymphoma/leukemia | 2.9 | Pancreas | 4.0 | Liver | 5.3 | Adult | CNS | 8.3 |
| Liver | 2.4 | Sarcoma | 3.0 | Rectum (recur) | 4.9 | | H&N | 3.7 |
| H&N | 2.3 | CNS | 3.0 | Uterus | 2.5 | | Body | 0.9 |
| Female genital | 2.1 | Others | 10.0 | Uveal melanoma | 1.8 | | Spine | 13.9 |
| Colon and rectum | 3.0 | | | Abdominal LN | 1.2 | | | |
| Others | 9.1 | | | CNS | 0.9 | | | |
| | | | | GI tract | 0.8 | | | |
| | | | | Re-irradiation | 9.2 | | | |
| | | | | Others | 13.0 | | | |
| Total | 100 (n=8,609) | Total | 100 (n=15,000 approximately) | Total | 100 (n=11,580) | Total | | 100 (n=108) |

Table 1. Recommended or public health insurance covered indications for charged particle therapy from several countries

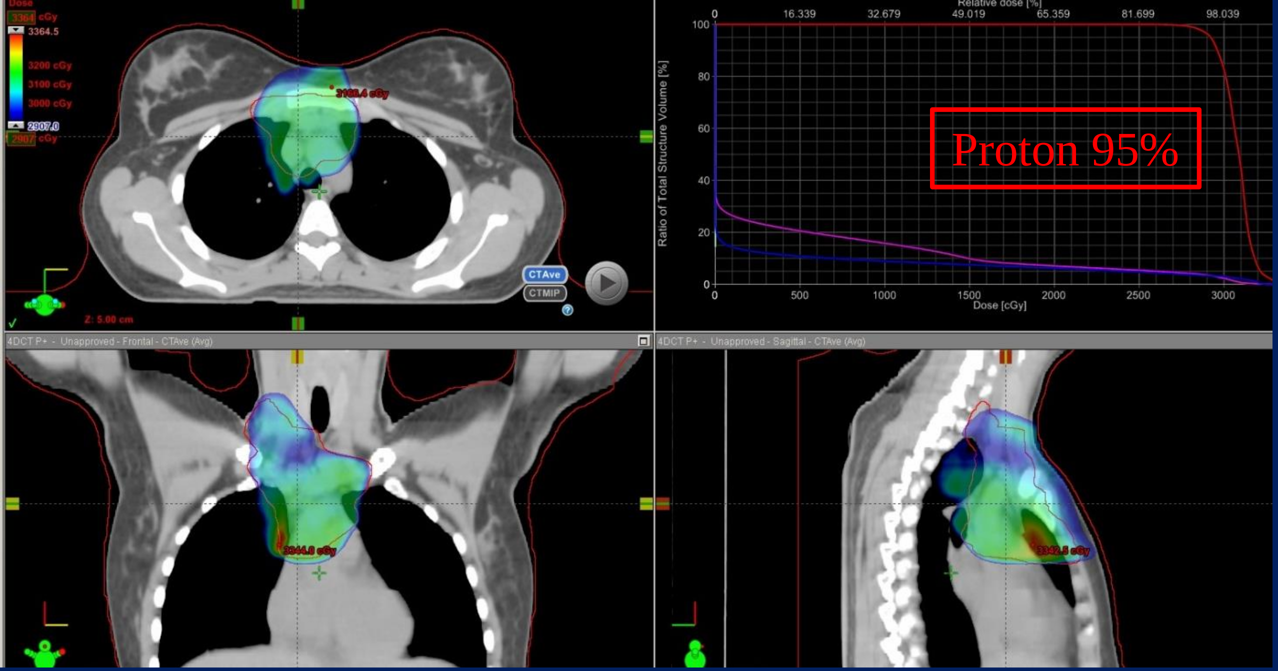
| Country | |
|---|---|
| United States [7] | Astro Model P[...] including intr[...] |
| | Tumors that [...] or chondros[...] |
| | Primary or m[...] treatment o[...] |
| | Hepatocellul[...] |
| | Primary or b[...] childhood t[...] |
| | Patients with[...] to NF-1 pati[...] |
| | Malignant ar[...] |
| | Advanced (e[...] |
| | Cancers of th[...] |
| | Non-metasta[...] |
| | Re-irradiatio[...] |

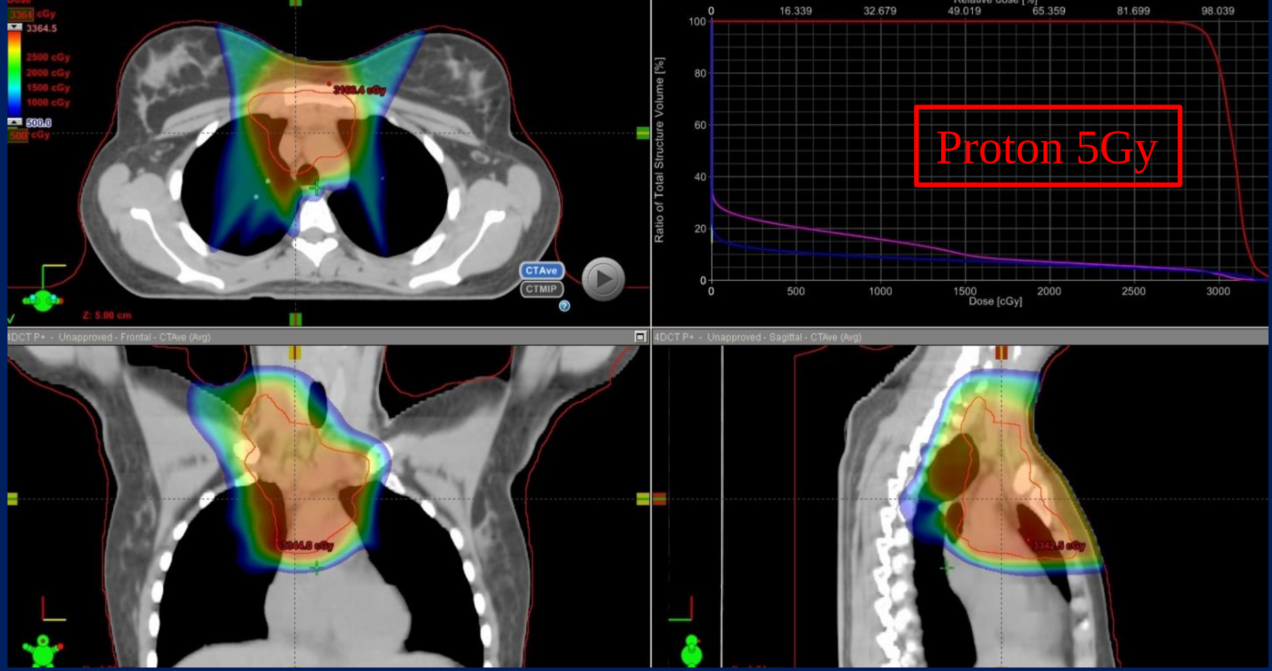
| | |
|---|---|
| United Kingdom [8] | NHS England Indications of PBT |
| | Pediatric tumor |
| | Most pediatric tumors, malignant and benign |
| | Adult |
| | Base of skull tumors (radioresistant) |
| | Spinal and paraspinal tumors (radioresistant) |
| | Paranasal sinus tumors with base of skull involvement |
| Netherlands [9] | Health Council of the Netherlands. Proton Radiotherapy |
| | Standard indication |
| | Skull base or spinal chordoma and chondrosarcoma |
| | Other intracranial, spinal, and paraspinal tumors, including meningioma |
| | Pediatric tumors, including bone tumors, soft-tissue sarcoma, low-grade glioma, meningioma, medulloblastoma, ependymoma, and neuroblastoma |
| | Potential indications (cases for which protons may be specifically utilized to improve local control) |
| | Re-irradiation (malignant brain tumors, head and neck cancer) |
| | Paranasal sinus tumors, nasopharyngeal carcinoma, prostate, NSCLC, retroperitoneal sarcoma |
| | Model based indication (cases where proton will be utilized to reduce side effect) |
| | Re-irradiation (meningioma, head and neck cancer) |
| | Head and neck cancers, prostate |
| | Reduction of secondary cancer |
| | Breast cancer |
| | Lymphoma |
| | Testis |

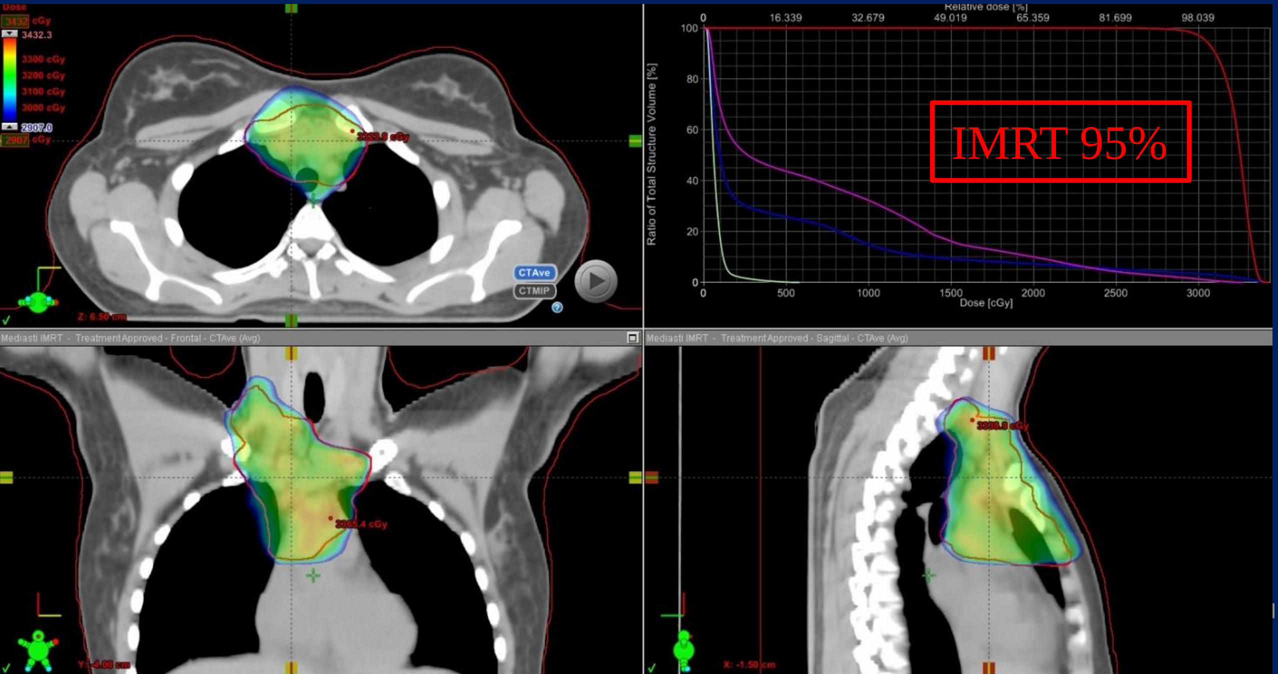
| | |
|---|---|
| | Testis |
| Japan [10] | Public Health Insurance of Particle Therapy |
| | PBT |
| | Pediatric cancer |
| | Bone and soft tissue sarcoma |
| | Head and neck |
| | Prostate |
| | CIRT |
| | Bone and soft tissue sarcoma |
| | Head and neck |
| | Prostate |

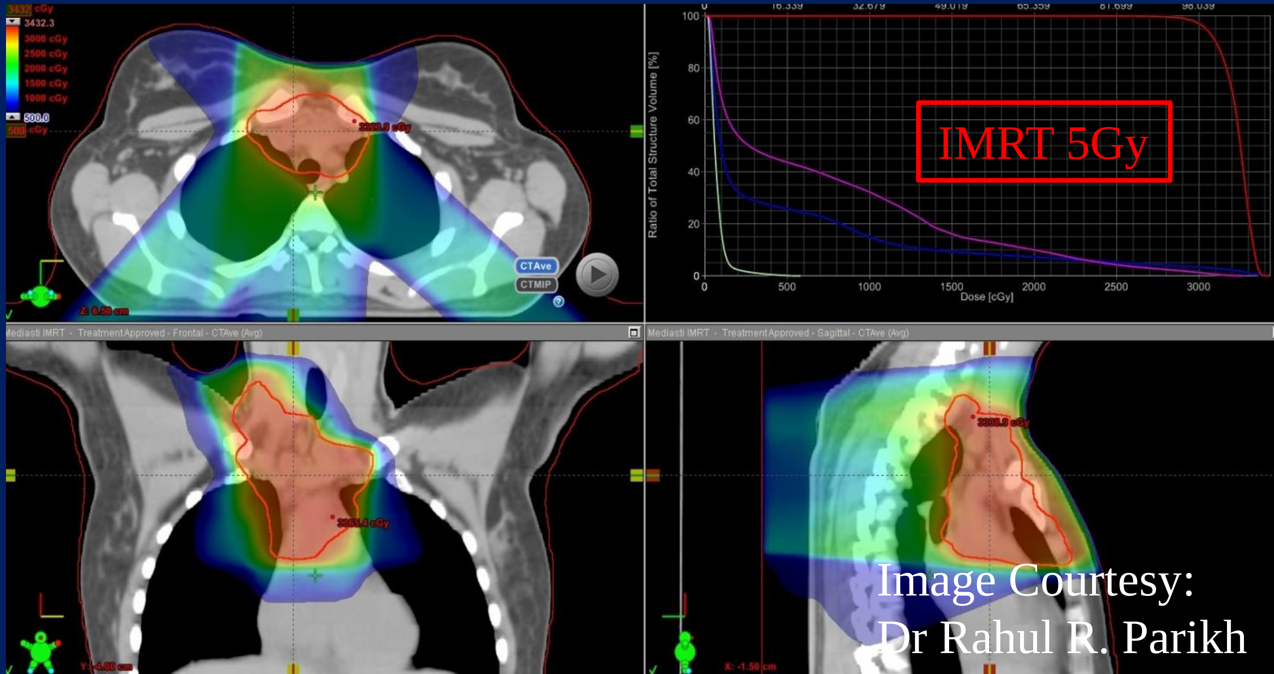
| | |
|---|---|
| Korea [10] | Public Health Insurance of PBT |
| | Pediatric cancer |
| | Re-RT |
| | Brain, skull base, and spinal tumors |
| | Head and neck cancer including orbit |
| | Thorax tumor (lung, esophagus, and mediastinum except breast cancer) |
| | Abdominal tumors (hepatobiliary, pancreas, and retroperitoneum |

# Some Case Studies


Proton 95%


Proton 5Gy


IMRT 95%


IMRT 5Gy
Image Courtesy:
Dr Rahul R. Parikh

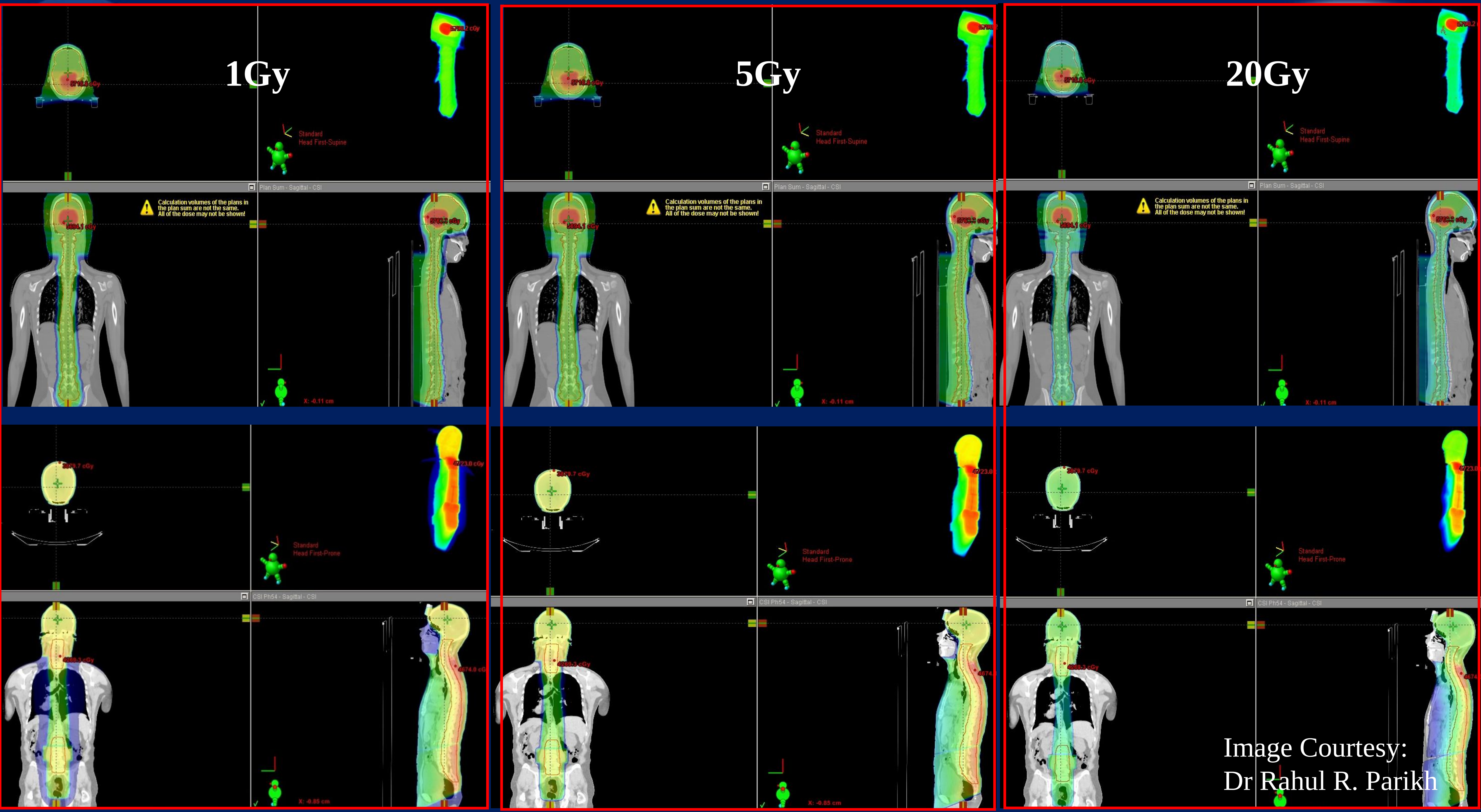



Image Courtesy:
Dr Rahul R. Parikh

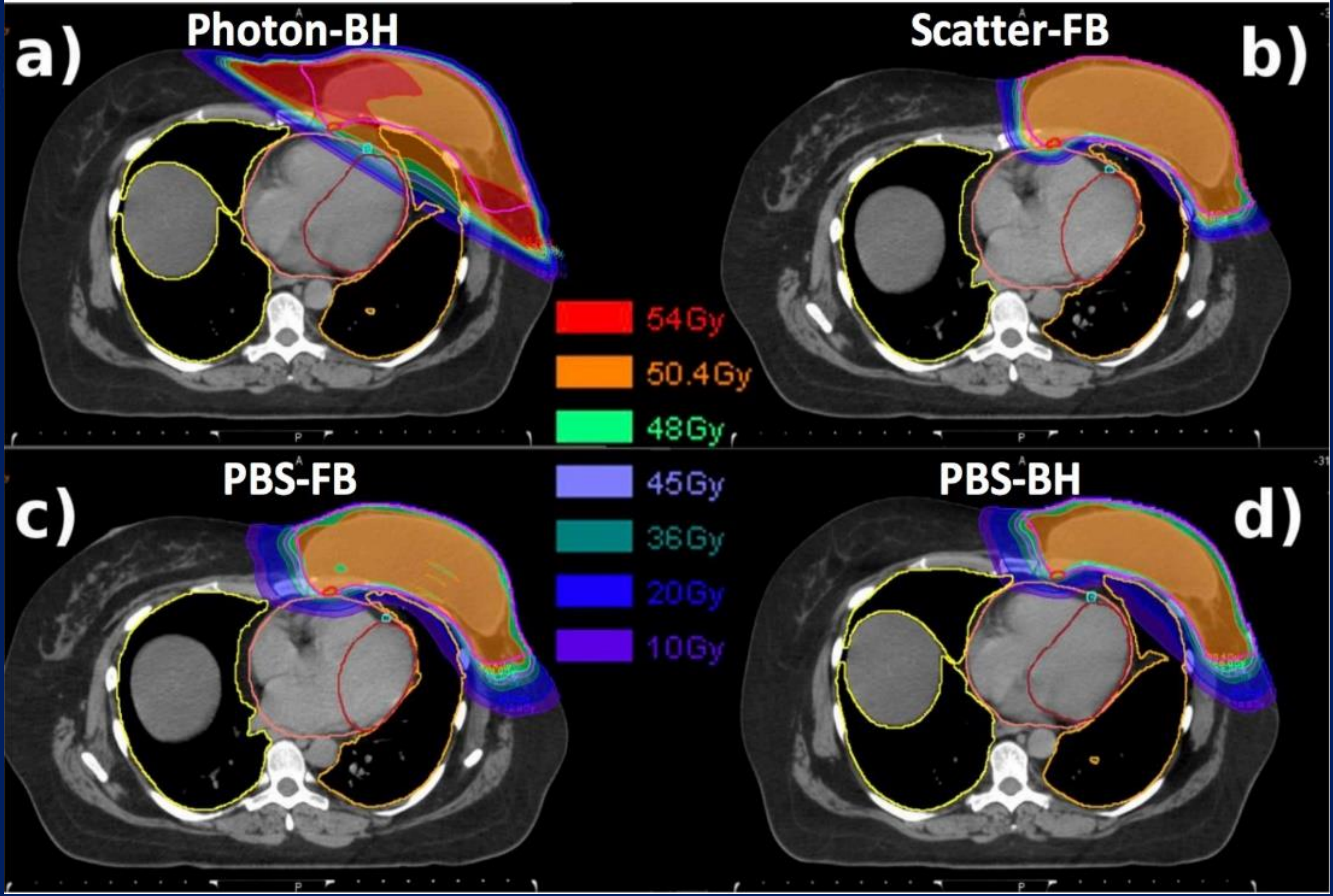
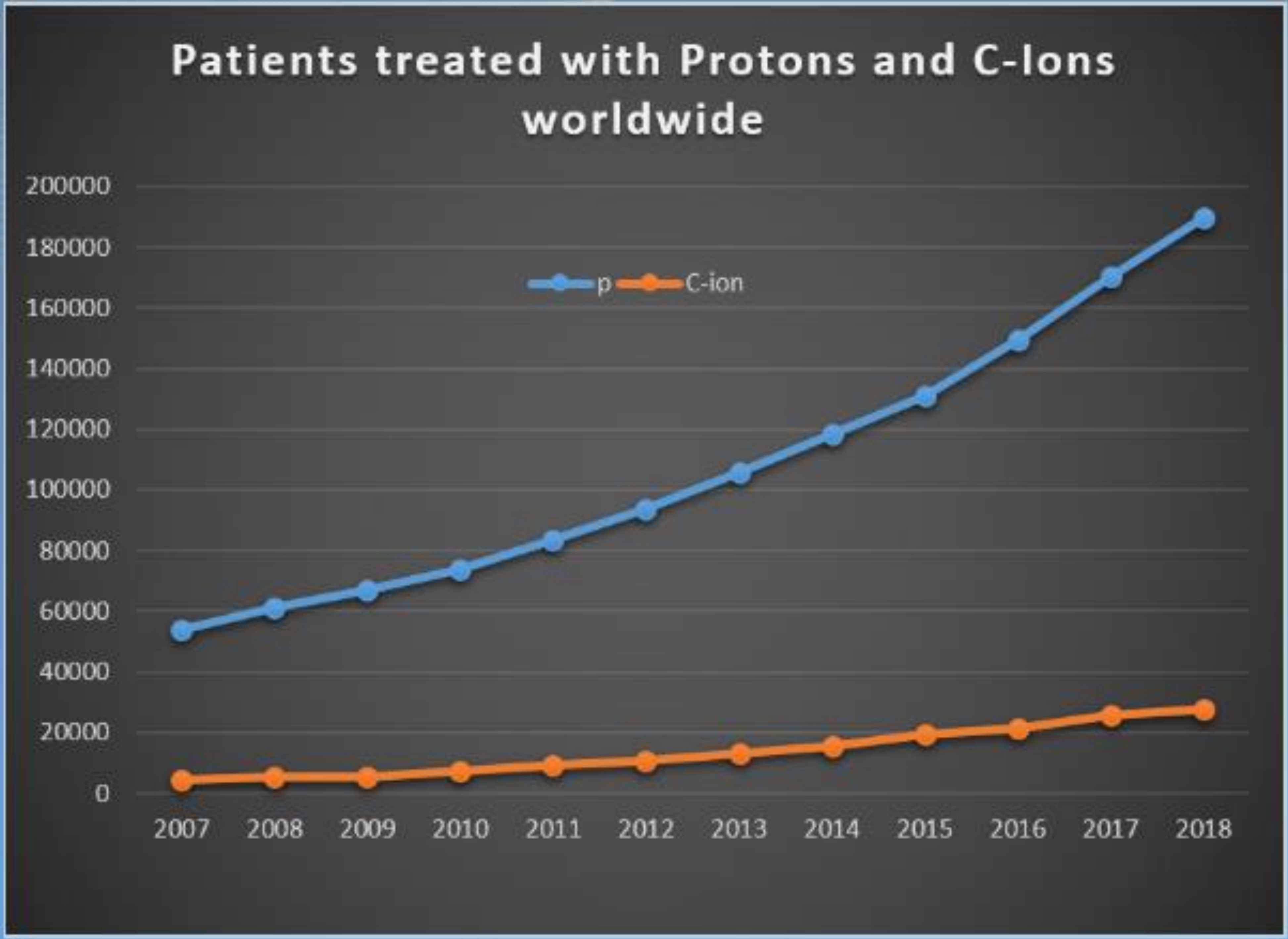



Image Courtesy:
Dr Rahul R. Parikh

# Criticism




**316 registered phase III trials, only 1 out of 38 on HNC!!!**

**Patient treated Proton:**

**2007:20000**

**2018:200000**

**10X increase**

**Patient treated Carbon Ion:**

**2007: 1000**

**2018: 25000**

**25X increase**

# Proton trials: 20 years analysis of clinical trials

INTERNATIONAL JOURNAL of PARTICLE THERAPY

## A 20-Year Analysis of Clinical Trials Involving Proton Beam Therapy

Bismarck C. L. Odei, BS[1]; Dustin Boothe, MD[2]; Sameer R. Keole, MD[3]; Carlos E. Vargas, MD[3]; Robert L. Foote, MD[4]; Steven E. Schild, MD[3]; and Jonathan B. Ashman, MD, PhD[3]

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## Abstract

**Purpose:** Clinical trials (CTs) in proton beam therapy (PBT) are important for determining its benefits relative to other treatments. An analysis of PBT trials is, thus,

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| Characteristics | No. of trials (N = 152) | Trials, % |
|---|---|---|
| Primary site | | |
| Gastrointestinal system | 32 | 21.1 |
| Central nervous system | 31 | 20.4 |
| Lung | 21 | 13.8 |
| Prostate | 19 | 12.5 |
| Breast | 10 | 6.6 |
| Sarcoma | 15 | 9.9 |
| Eye | 8 | 5.3 |
| Other | 16 | 10.5 |
| Sex | | |
| Female | 10 | 6.6 |
| Male | 21 | 13.8 |
| Both | 121 | 79.6 |
| Age | | |
| Children included | 28 | 18.4 |
| Adult Only | 124 | 81.6 |
| Location | | |
| North America | 131 | 86.2 |
| Europe | 10 | 6.6 |
| Asia | 11 | 7.2 |

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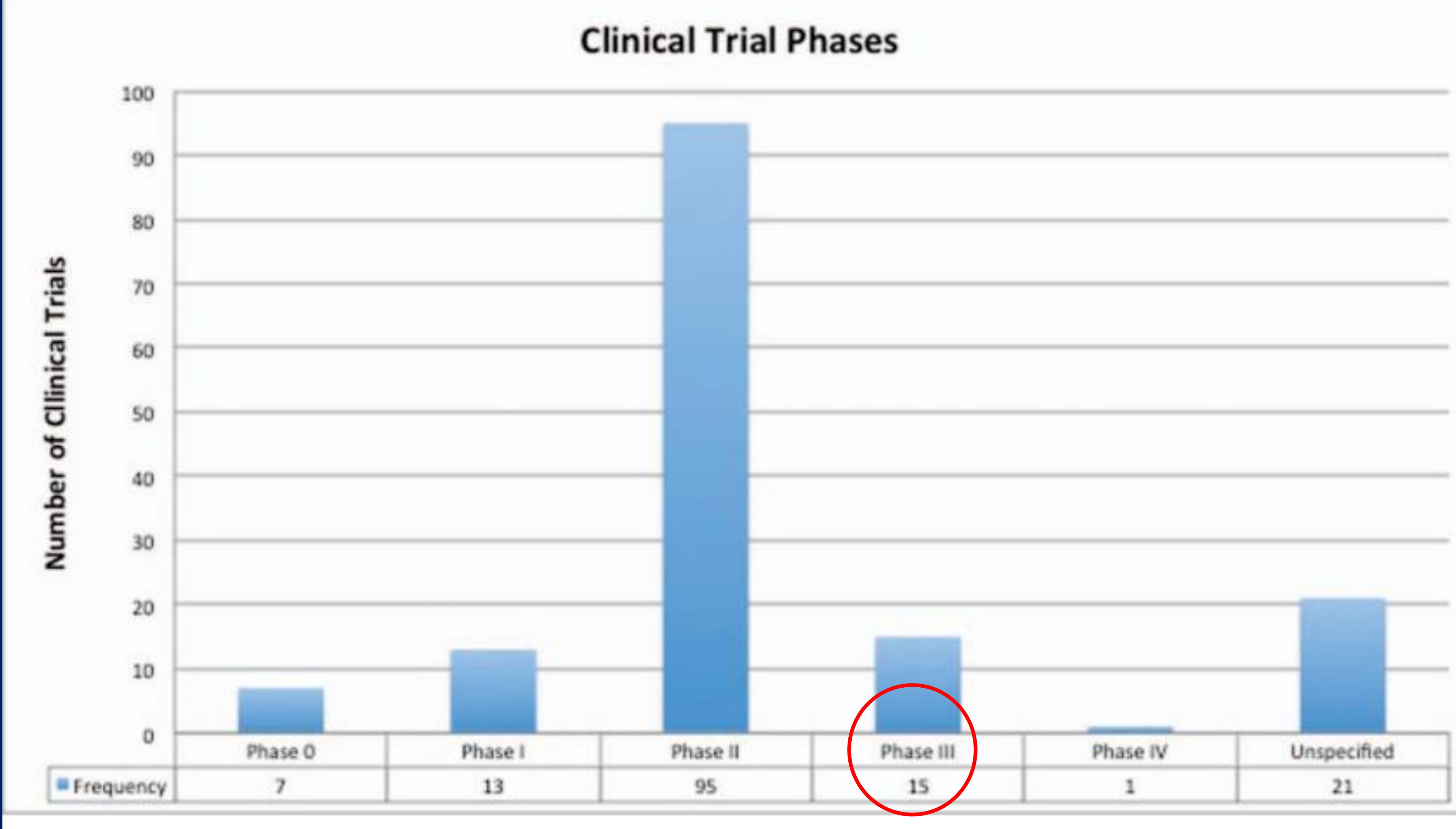
| Characteristics | No. of trials (N = 152) | Trials, % |
|---|---|---|
| Randomization | | |
| Randomized | 35 | 23.0 |
| Nonrandomized | 37 | 24.3 |
| Unspecified | 80 | 52.6 |
| Treatment endpoint | | |
| Safety and efficacy | 94 | 61.8 |
| Efficacy | 28 | 18.4 |
| Safety | 7 | 4.6 |
| Bioequivalence | 1 | 0.7 |
| Unspecified | 22 | 14.5 |
| Intervention model | | |
| Single group | 84 | 55.3 |
| Parallel group | 55 | 36.2 |
| Unspecified | 11 | 7.2 |
| Masking | | |
| Open label | 134 | 88.2 |
| Single blind | 4 | 2.6 |
| Double blind | 2 | 1.3 |
| Unspecified | 12 | 7.9 |
| Recruiting status | | |
| Active, recruiting | 79 | 52.0 |
| Active, not recruiting | 37 | 24.3 |
| Complete | 13 | 8.6 |
| Terminated | 12 | 7.9 |
| Not yet recruiting | 6 | 3.9 |

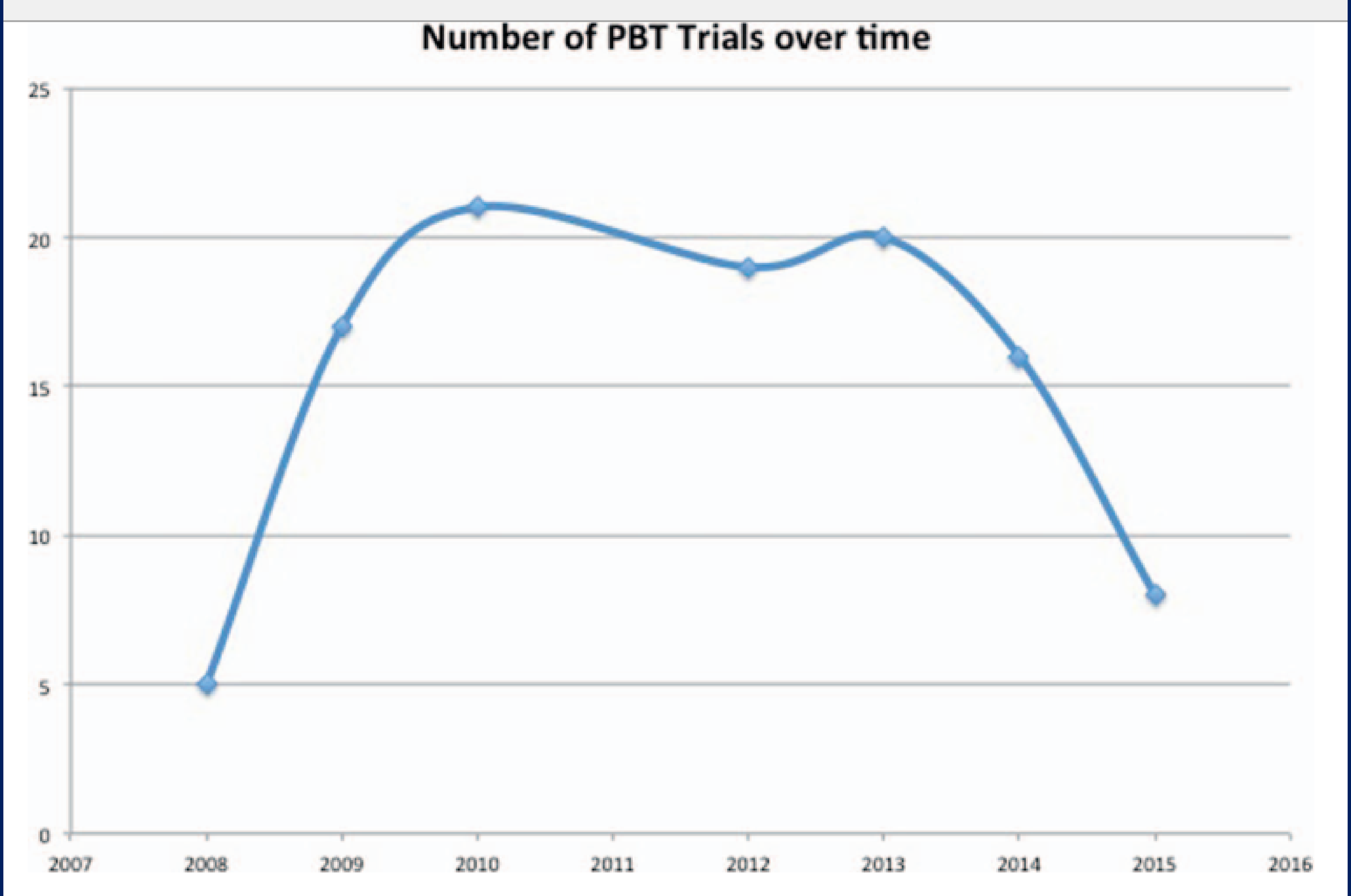
MAX Healthcare

**Source of potential bias and data manipulation**

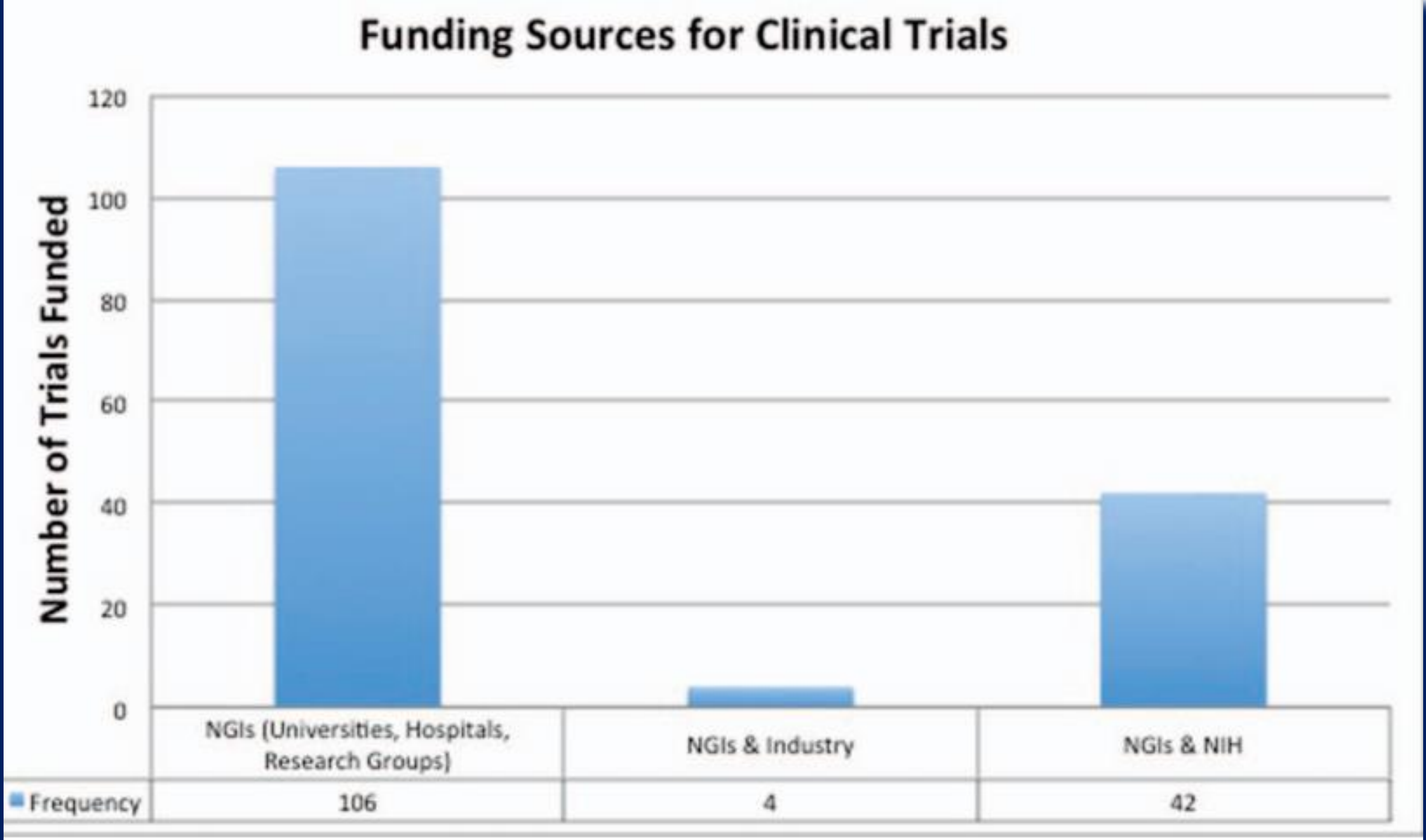
# Phases of clinical trials in proton beam therapy



# Number of proton beam therapy clinical trials over time



# Funding sources for proton beam therapy clinical trials



# Conclusion about PBT trials

- PBT CTs focused on a diverse range of malignancies
- Phase II trials represent the largest type of PBT CTs
- Only a few trials employed a phase III design
- Phase III RCTs may be appropriate for some but not all
- Challenges to PBT trial funding,
- Minimal support from industry
- Modest support from the NIH
- A Principal Barrier to Enrolment: Insurance Coverage

# Conclusion

- Useful in certain clinical scenarios
- Bragg peak
- Uncertainties
- Normal tissue sparing
- Second malignancy less
- Can help dose escalation
- Requires judicious use
- Promising future tool

# Acknowledgement and Courtesy

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My hospital

My patients

My teachers

My family

My students

# THANK YOU