Proton Radiotherapy 101

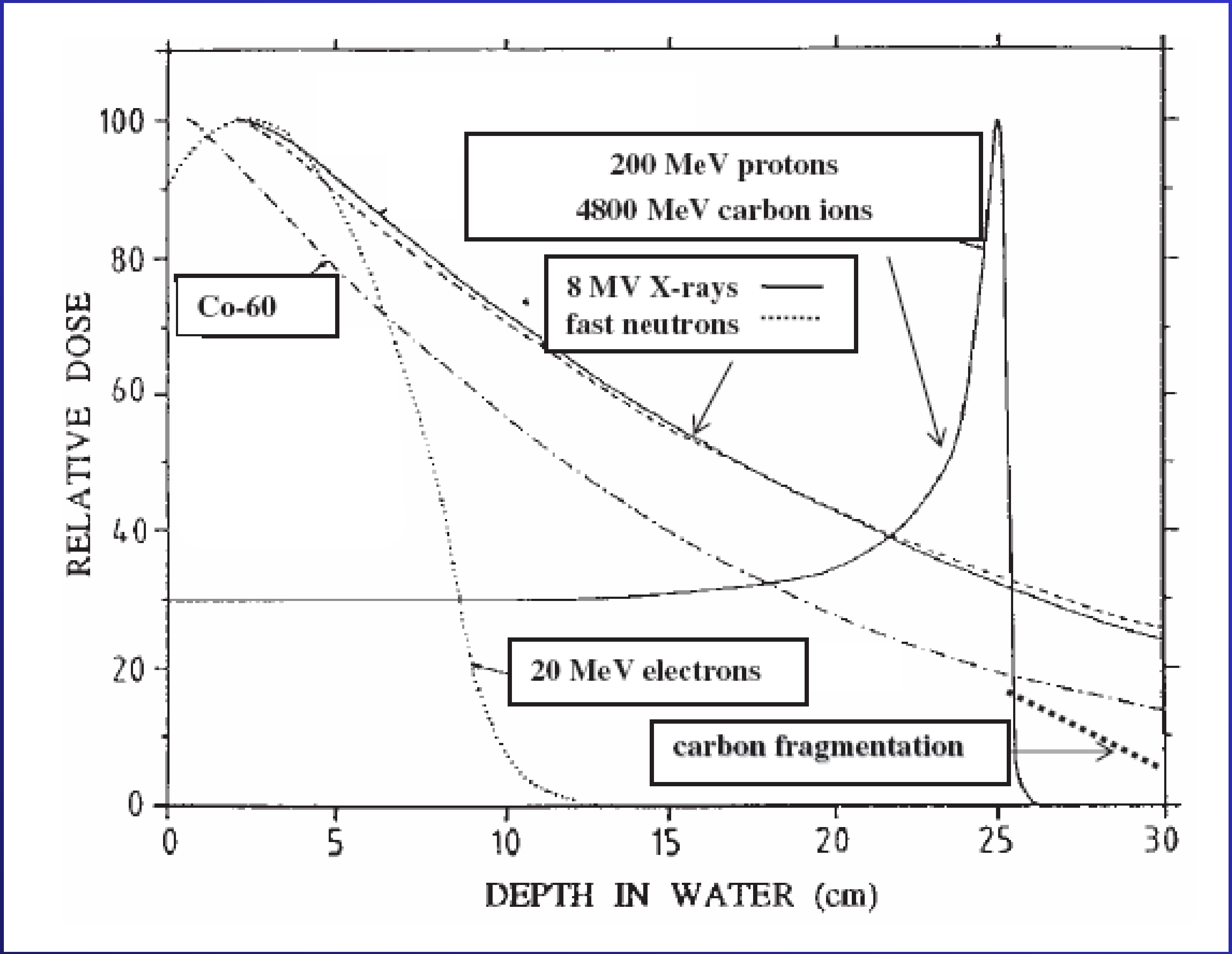
John DeMarco, PhD
UCLA Department of Radiation Oncology

Discussion outline

•A basic review of physics and dosimetry considerations for calculating dose from heavy charged particles.

•Physical versus biological dose.

•Delivery aspects of proton radiotherapy: passive scattering versus spot scanning.



From Amaldi and Kraft, “Radiotherapy with beams of carbon ions, Reports on Progress in Physics, 68, (2005)

Electrons, protons, heavy ions

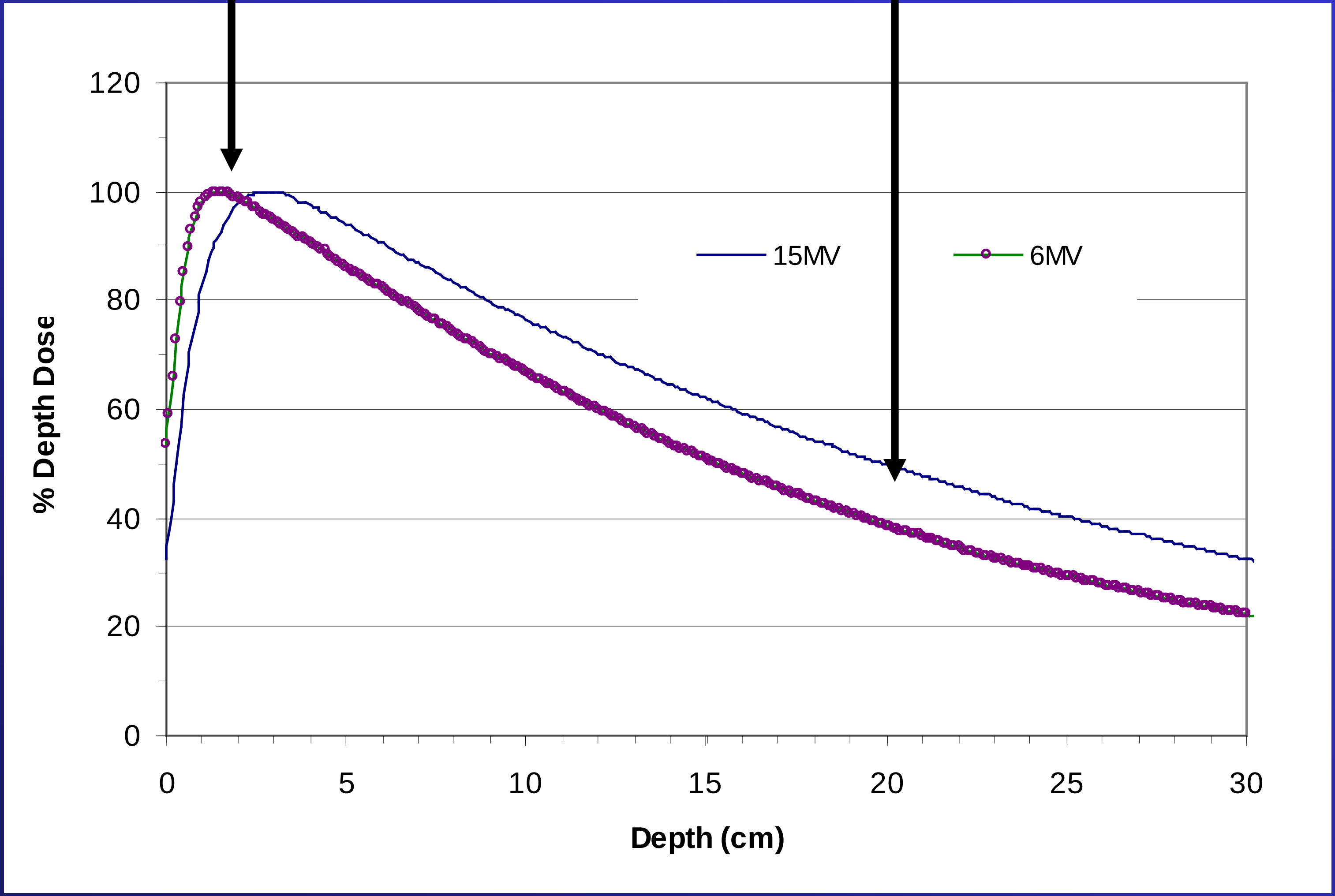
- finite range
- stopping power, linear energy transfer
- primary charged particle will deposit energy while "slowing-down"
- produce secondary charged particles
- protons and heavy ions can undergo nuclear interactions

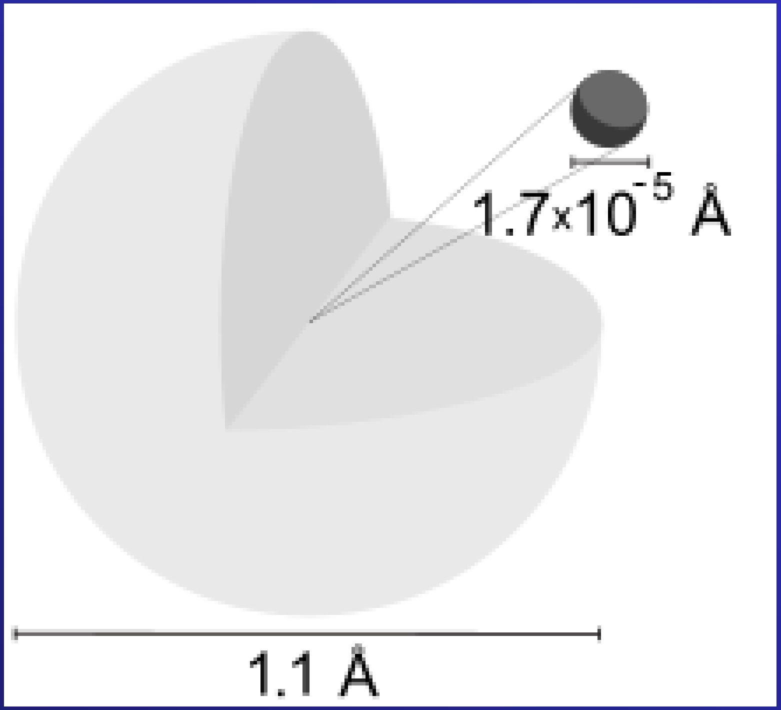
Photons, neutrons

- infinite "range"
- e^{-ux} exponential attenuation
- secondary charged particles responsible for energy deposition
- neutrons and high-energy photons can undergo nuclear interactions.

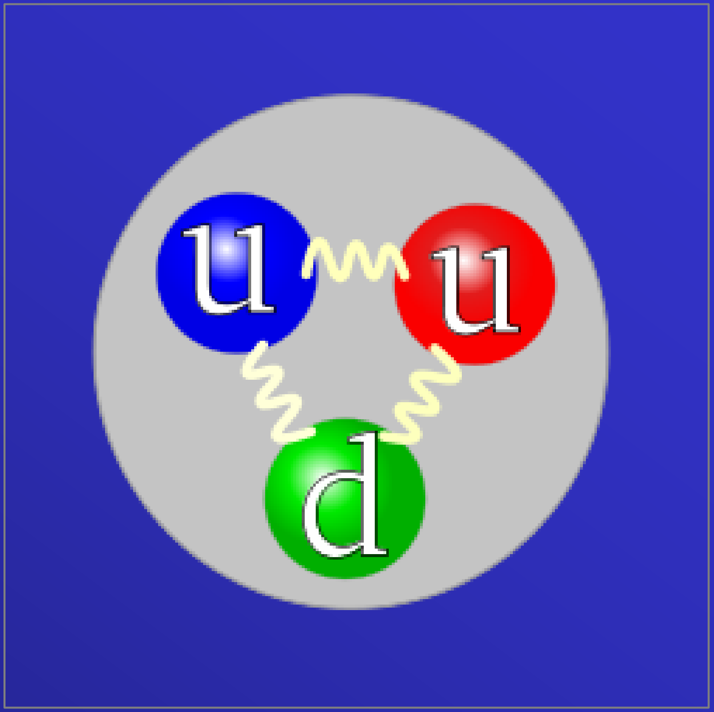
Build-up region (secondary electrons)

Dose fall-off
Photon attenuation, (primary and scatter), secondary electron transport



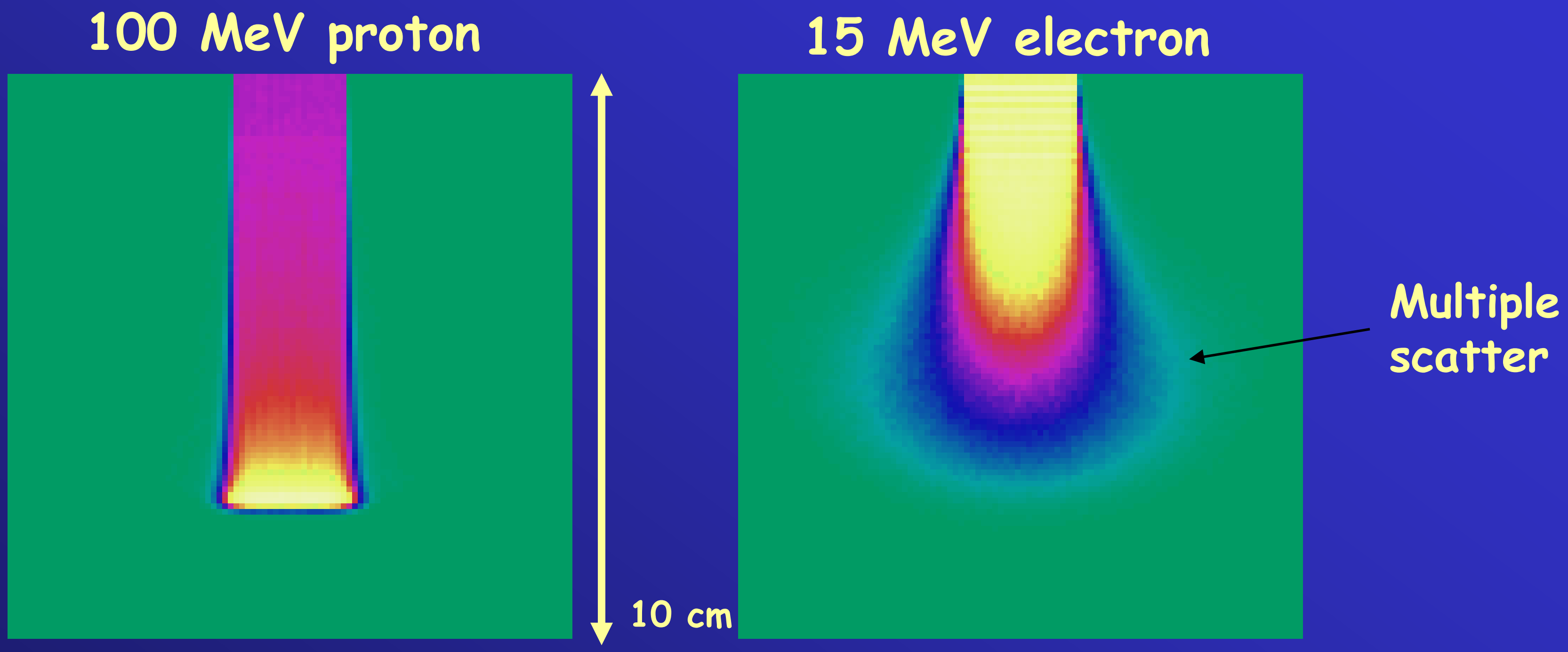


Hydrogen Atom



Proton
Charge = +1
Rest Mass ≈ 938 MeV
Discovered by Ernest Rutherford 1918

Proton vs Electron



Ratio of proton mass to electron mass = <u>1836</u>

How does a proton deposit energy as it moves through a material?

Ionization (Hard Collisions)

Excitation (Soft Collisions)

Interact with surrounding electrons

Electrons interact in the same manner

Elastic Scatter

Non-Elastic collisions

Interact with surrounding nulcei

The charged particle energy loss rate is based upon the collisional and nuclear stopping powers (CSDA)

energy transferred to electrons via ionization and excitation	energy transferred to recoiling atoms via elastic collisions	~~Radiative interactions~~

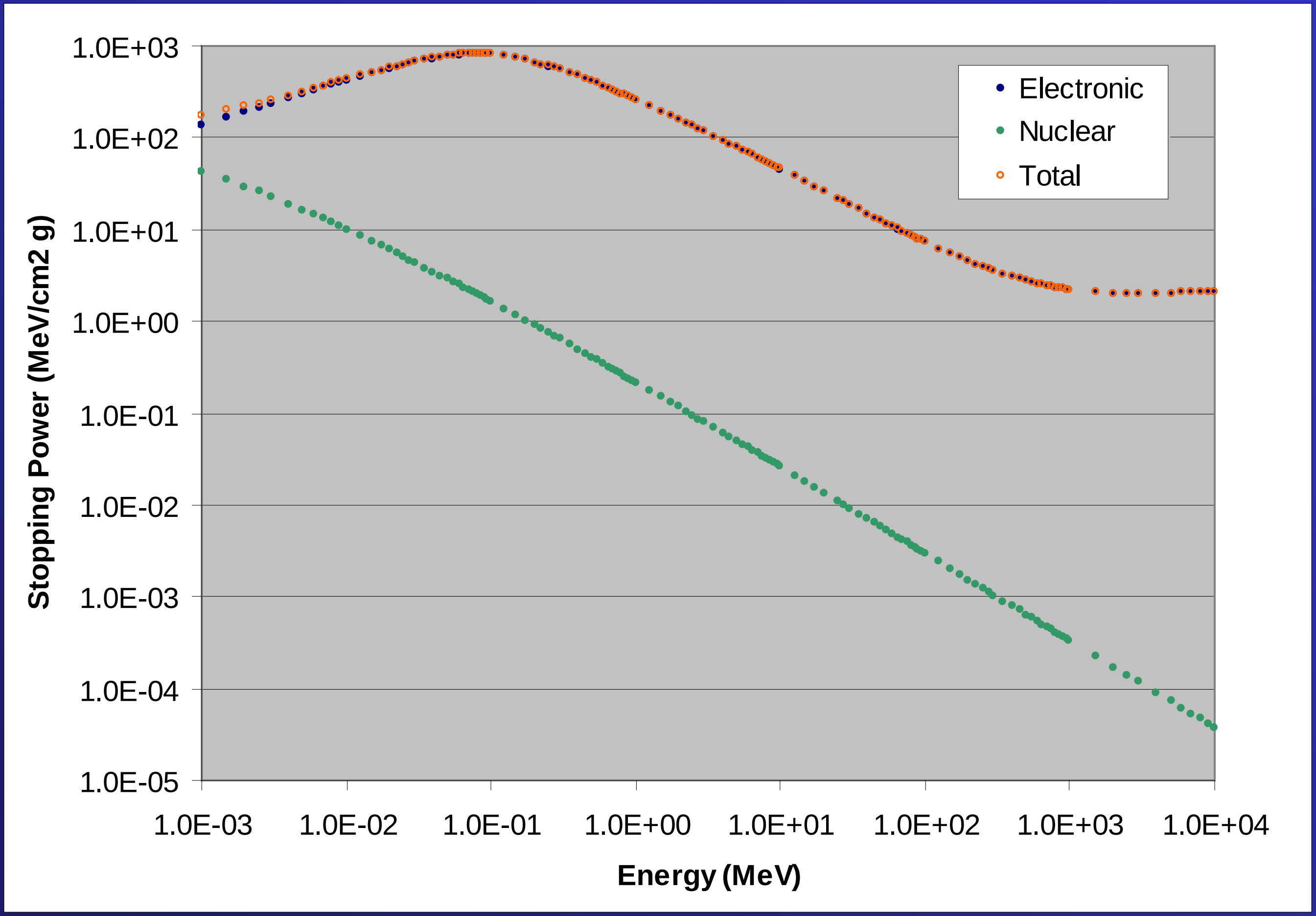
- The stopping power or LET provides a crude characterization of charged particle tracks.

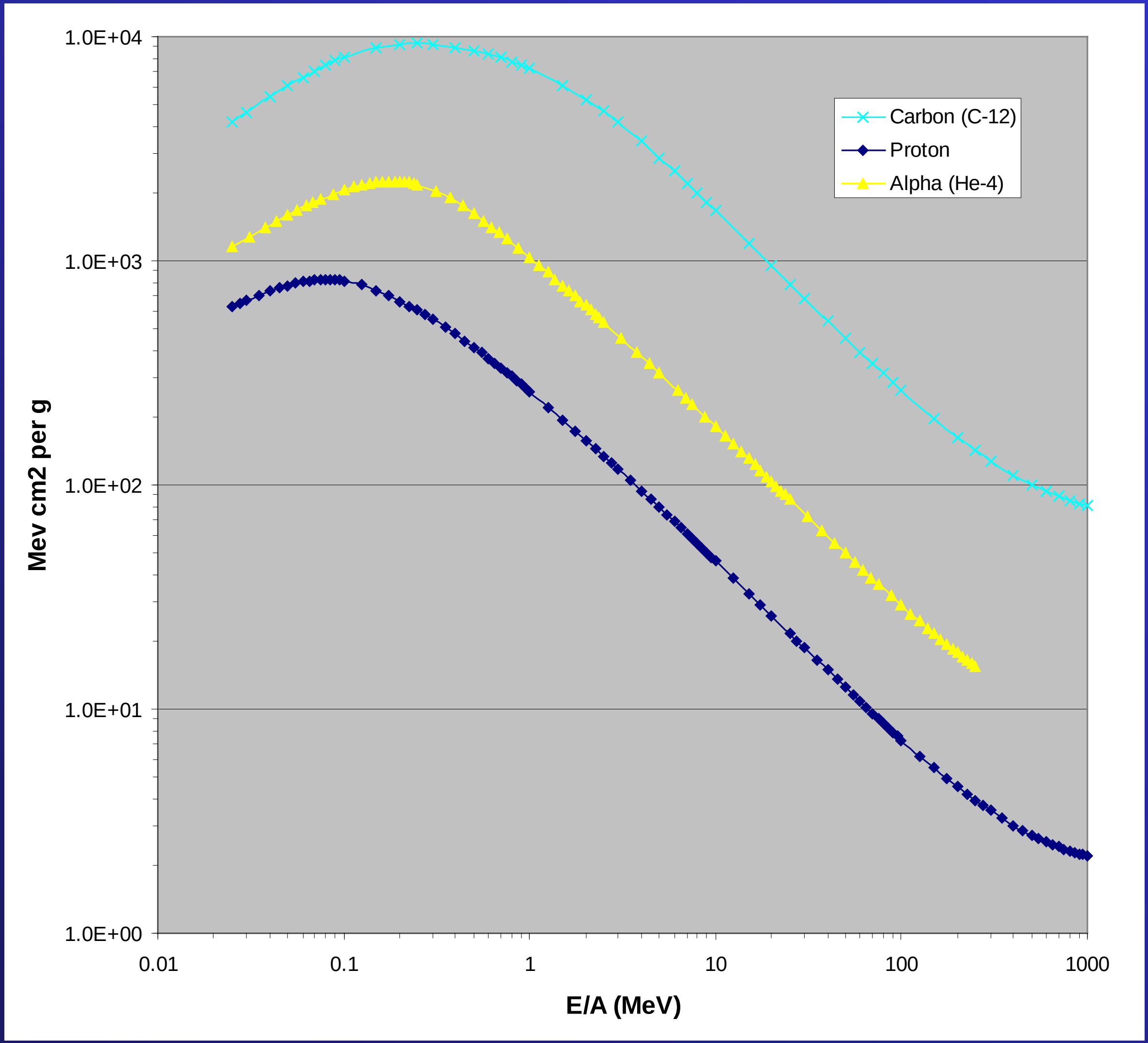
- The radial extension of the particle tracks (and therefore the dose distribution) due to the lateral transport of secondary particles such as δ-rays is not accounted.

- The statistical fluctuation of energy loss along the particle track (energy-loss straggling) is not accounted.

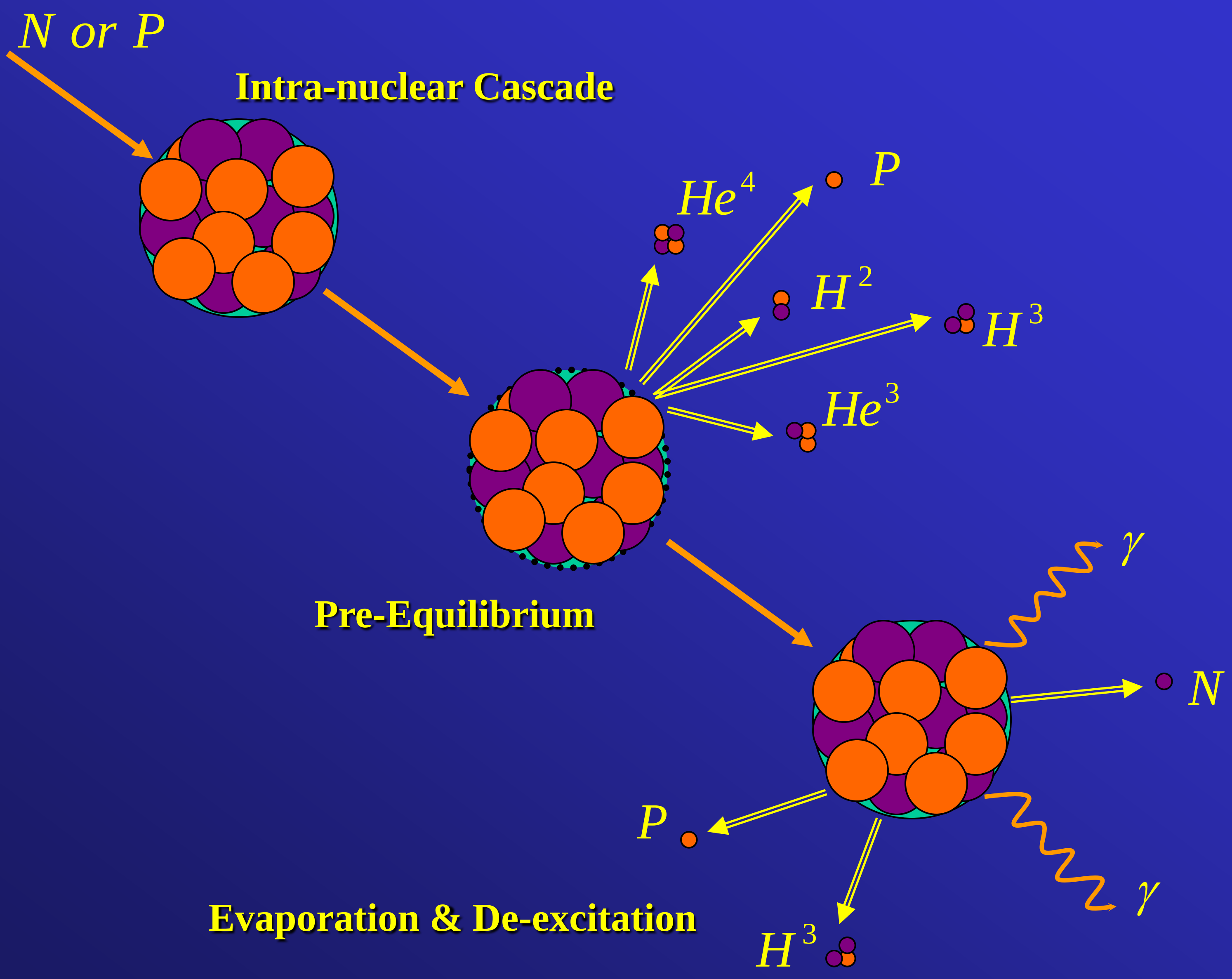
- Particle removal due to inelastic collisions is not accounted.

Comparison of stopping power components for protons incident on water



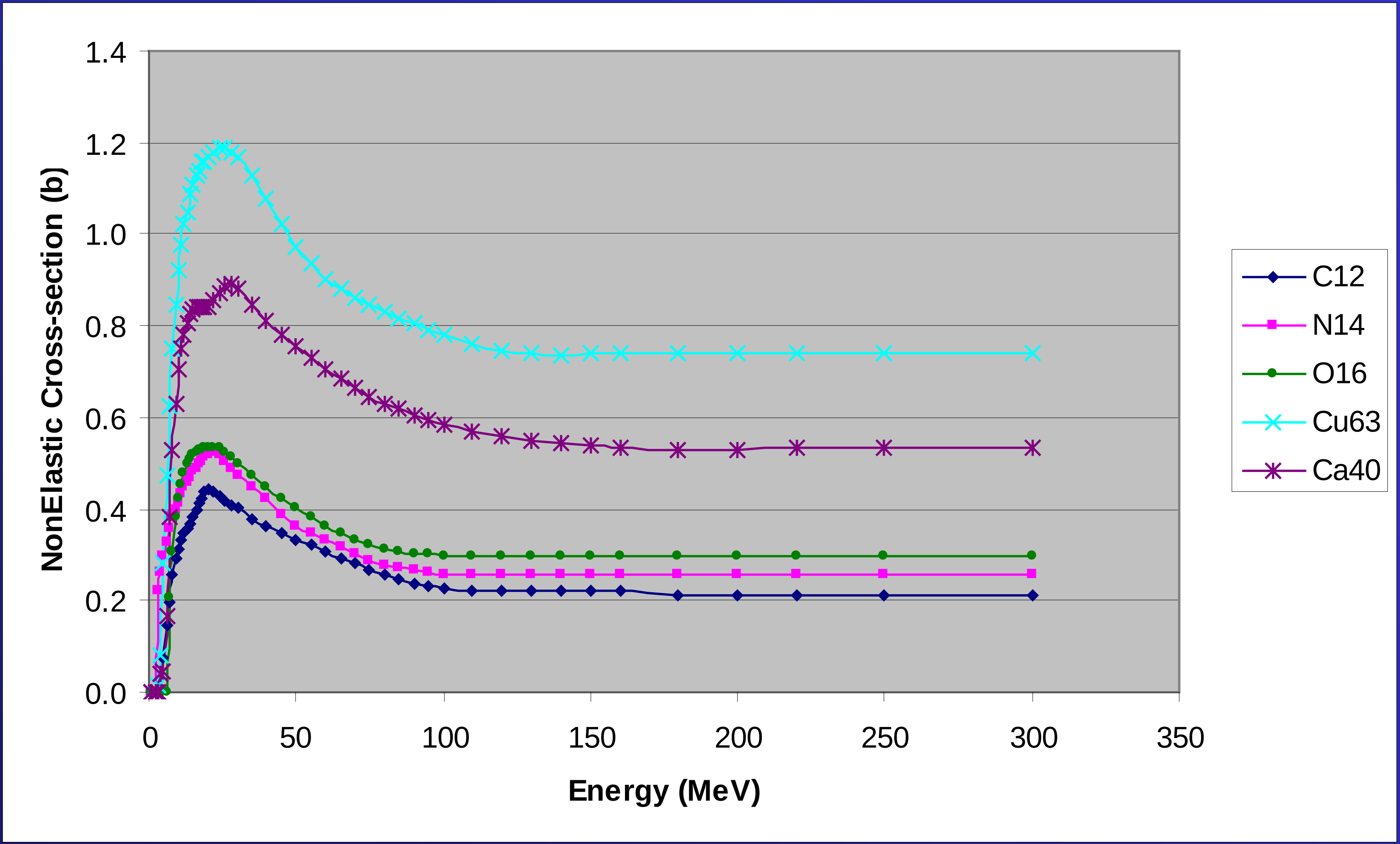


A comparison of stopping power values for different heavy ions



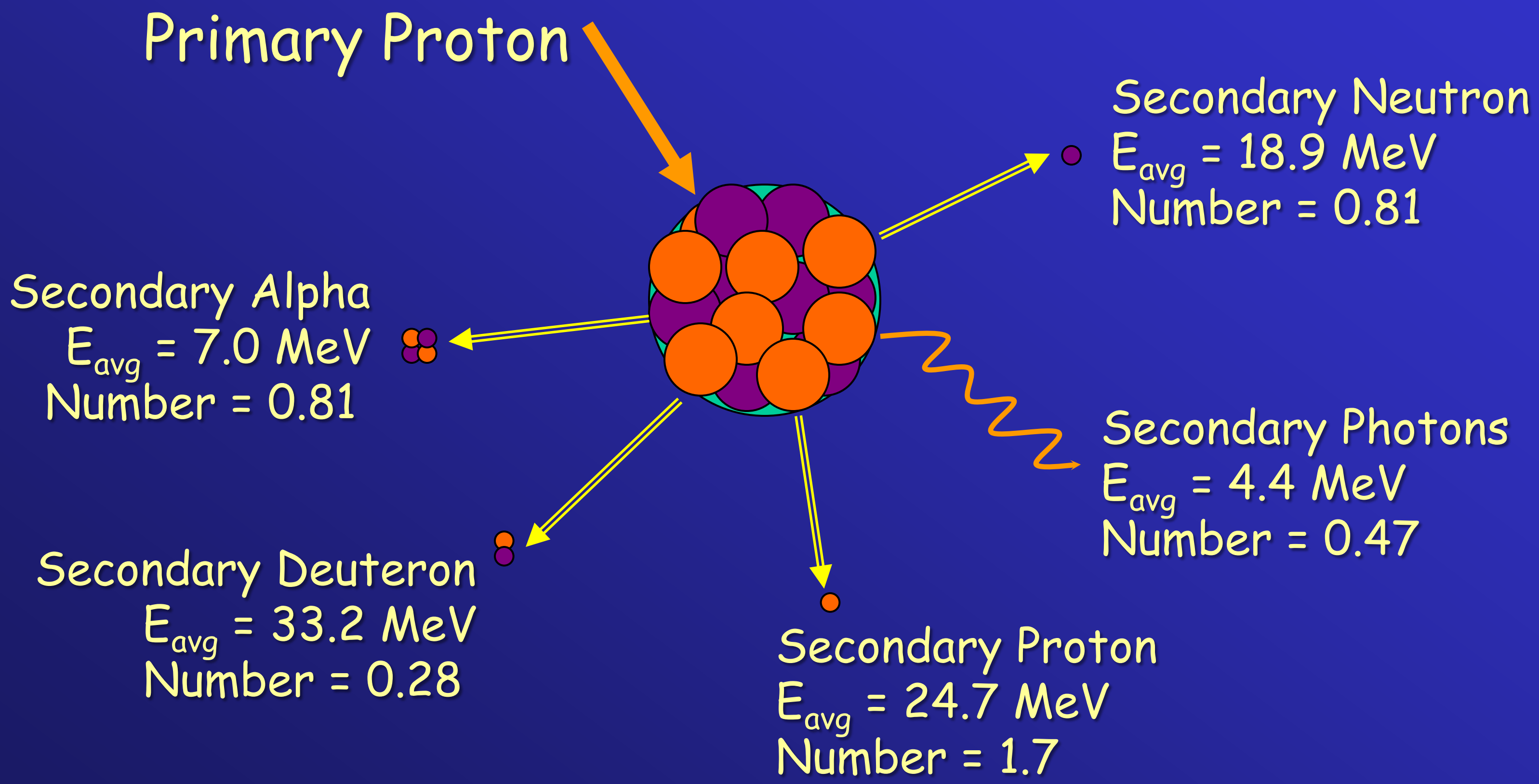
N or P
Intra-nuclear Cascade
He^4
P
H^2
H^3
He^3
Pre-Equilibrium
γ
N
P
γ
H^3
Evaporation & De-excitation

Non-elastic cross-section for protons



ICRU Report 63

Nuclear Data for Neutron and Proton Radiotherapy and for Radiation Protection



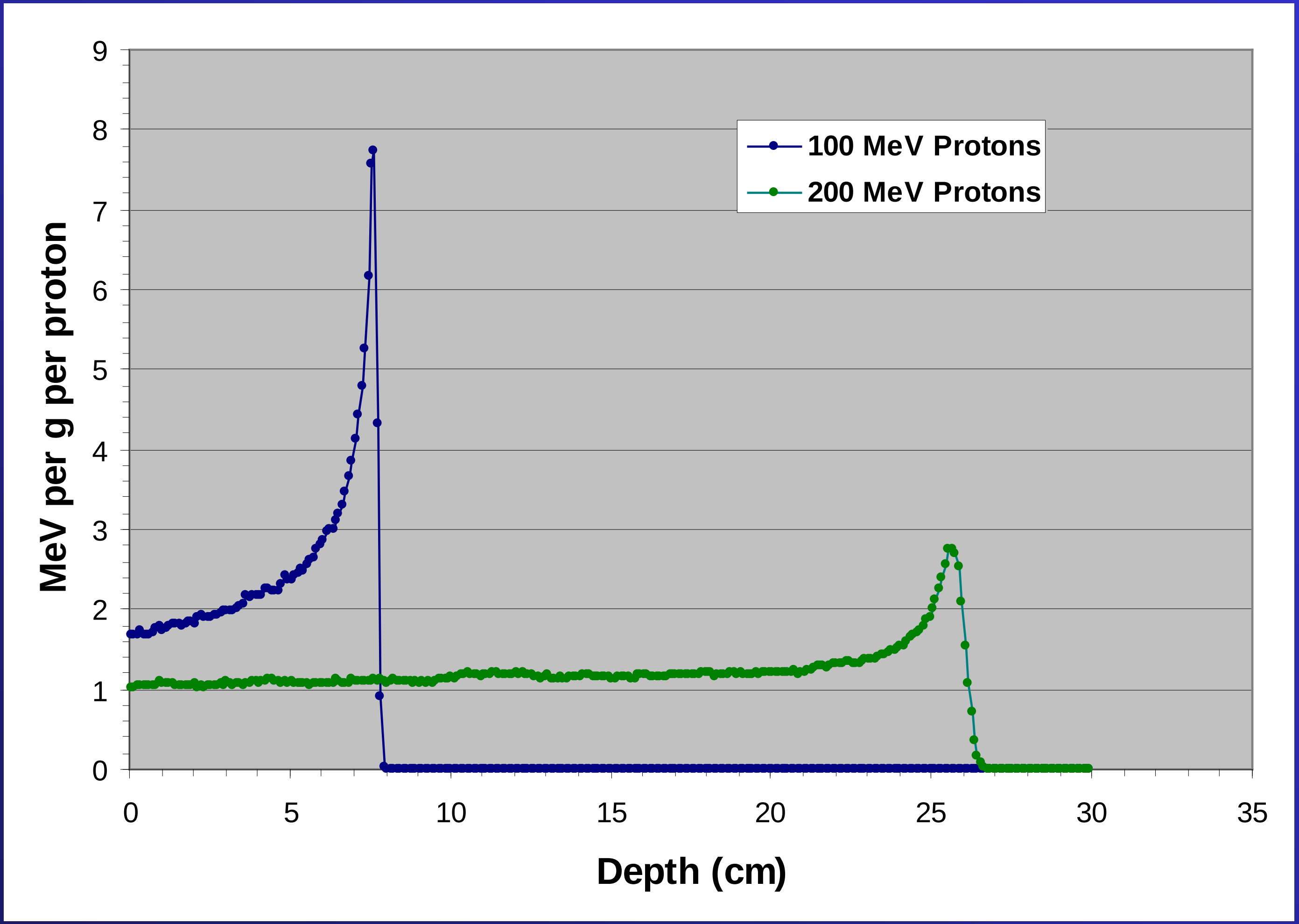
Cross-section and energy transfer summary for 60 MeV p + ^{16}O			
σ_{non} = 362 mb			
Neutrons	$M_n = 0.438$	$E_n = 11.93$ MeV	$f_n = 0.087$
Protons	$M_p = 1.322$	$E_p = 17.45$ MeV	$f_p = 0.385$
Deuterons	$M_d = 0.192$	$E_d = 24.60$ MeV	$f_d = 0.079$
Tritons	$M_t = 0.000$	$E_t = 00.00$ MeV	$f_t = 0.000$
Alphas	$M_\alpha = 0.733$	$E_\alpha = 5.82$ MeV	$f_\alpha = 0.071$
Gammas	$M_\gamma = 0.549$	$E_\gamma = 4.65$ MeV	$f_\gamma = 0.043$
A > 4 recoils	-	-	$f_{A>4} = 0.046$

Cross-section and energy transfer summary for 200 MeV p + ^{16}O			
σ_{non} = 295 mb			
Neutrons	$M_n = 1.265$	$E_n = 36.74$ MeV	$f_n = 0.232$
Protons	$M_p = 2.165$	$E_p = 43.39$ MeV	$f_p = 0.470$
Deuterons	$M_d = 0.428$	$E_d = 45.75$ MeV	$f_d = 0.098$
Tritons	$M_t = 0.000$	$E_t = 00.00$ MeV	$f_t = 0.000$
Alphas	$M_\alpha = 0.853$	$E_\alpha = 9.87$ MeV	$f_\alpha = 0.042$
Gammas	$M_\gamma = 0.373$	$E_\gamma = 4.38$ MeV	$f_\gamma = 0.008$
A > 4 recoils	-	-	$f_{A>4} = 0.021$

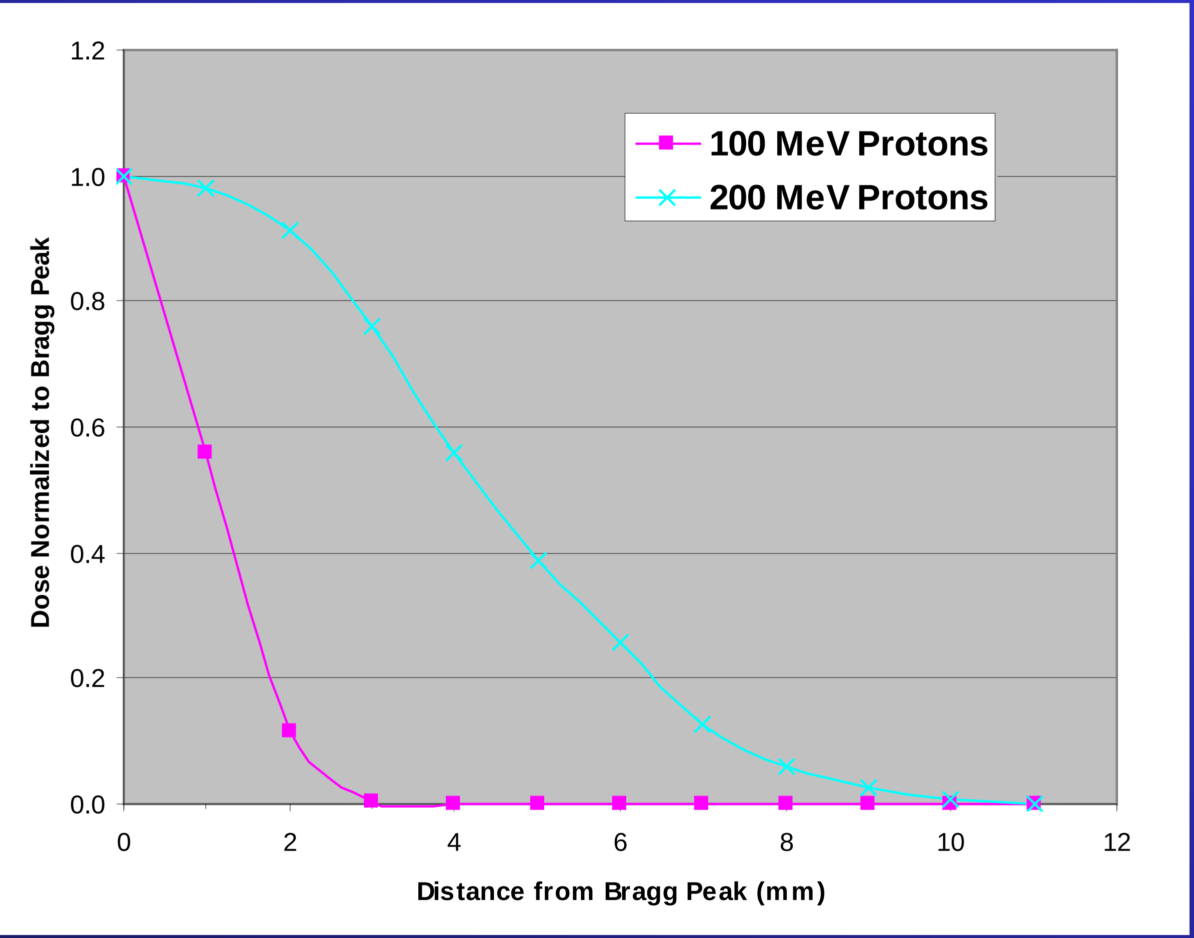
Why do we care about the proton nuclear interactions and the associated by-products?

- Radiation protection & shielding from the secondary neutron and photon contamination
- The LET (linear energy transfer) and RBE (relative biological effectiveness) of secondary charged particles
- Treatment planning considerations for the primary proton: removal and end-of-range straggling

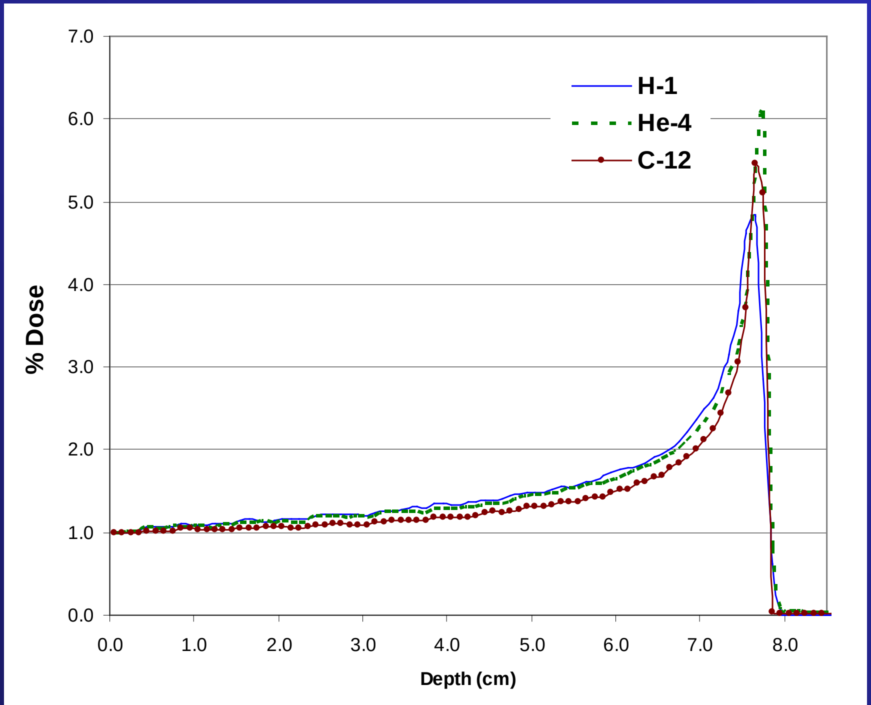
Absorbed dose comparison of 100 vs. 200 MeV protons in water: the influence of nuclear interactions

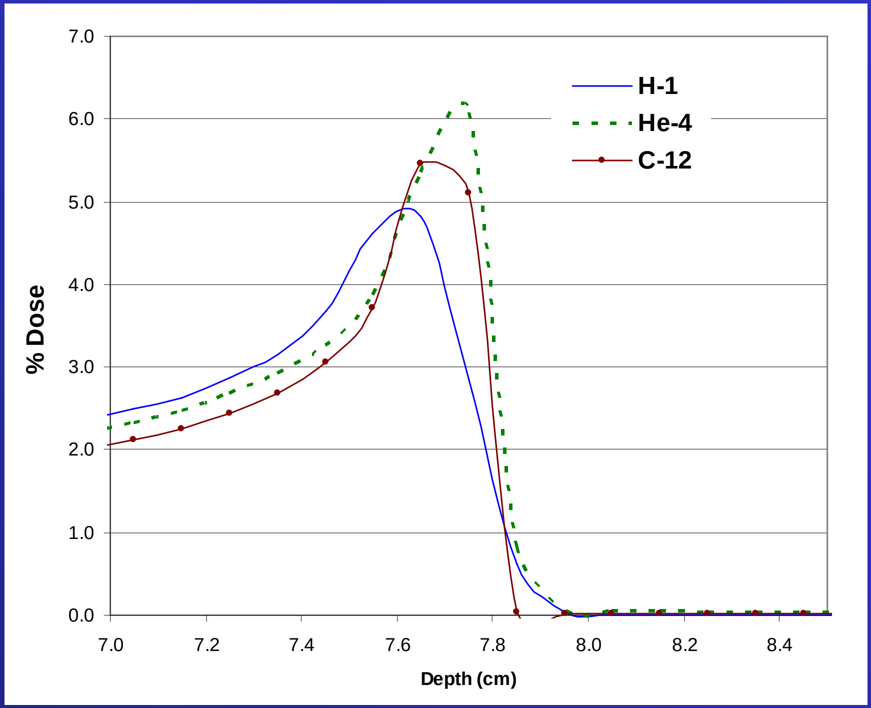


End-of-range characteristics of 100 versus 200 MeV protons in water.

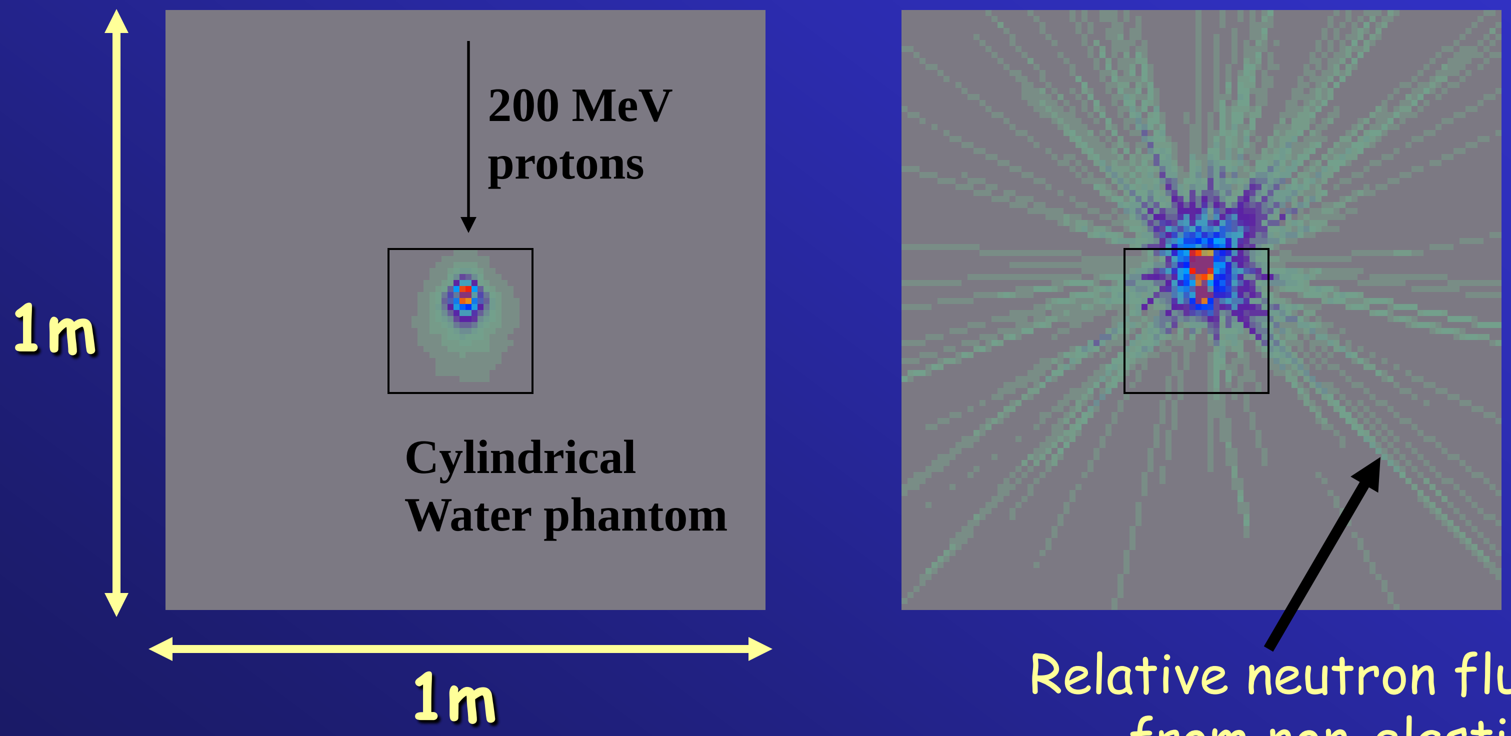


Depth dose and end-of-range characteristics of protons, alpha particles, and carbon ions



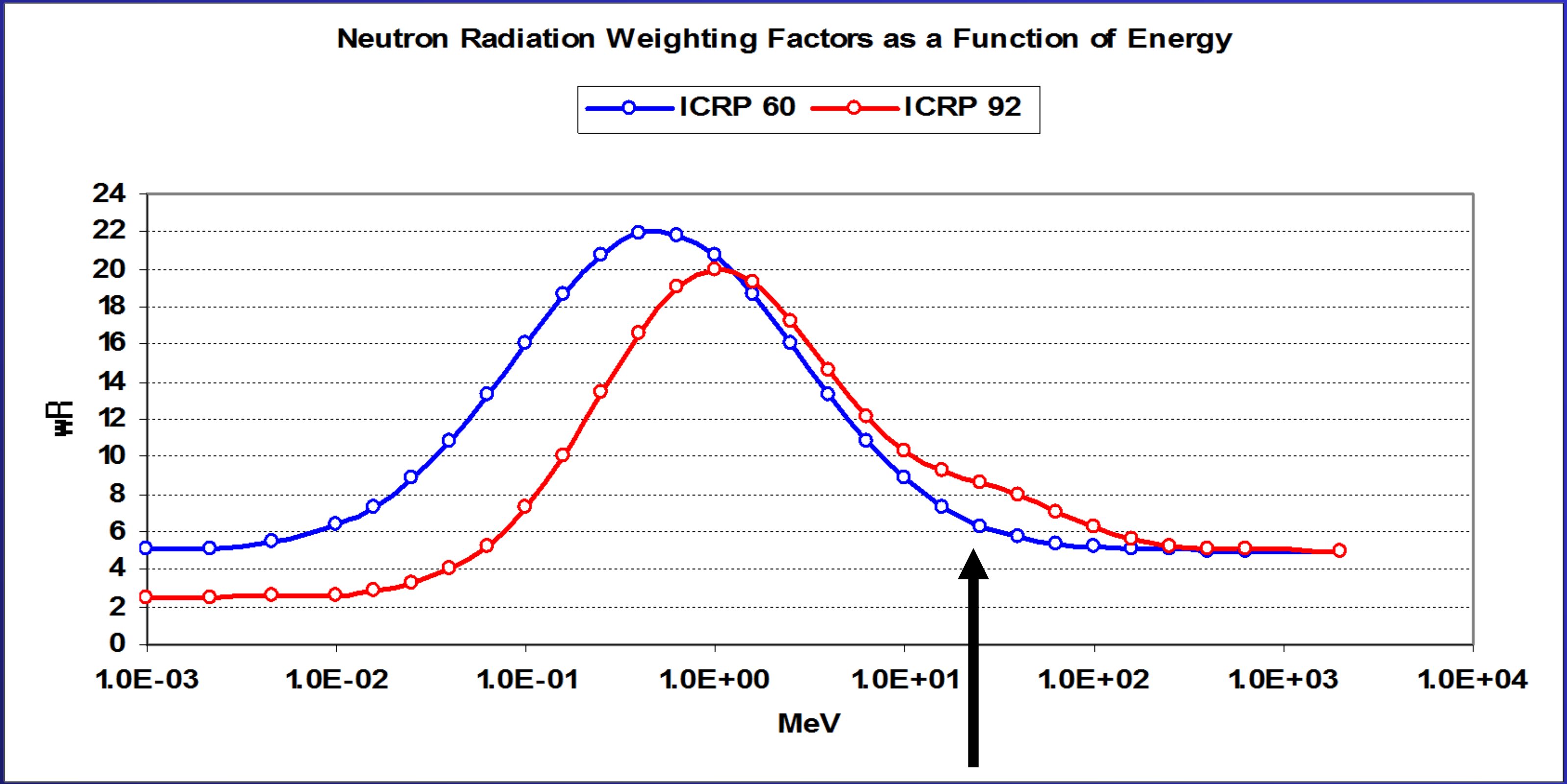


Secondary neutron production associated with passive collimation components



Relative neutron fluence from non-elastic interactions of proton in a simulated brass collimator

"Biological" vs. Physical Dose for Neutrons

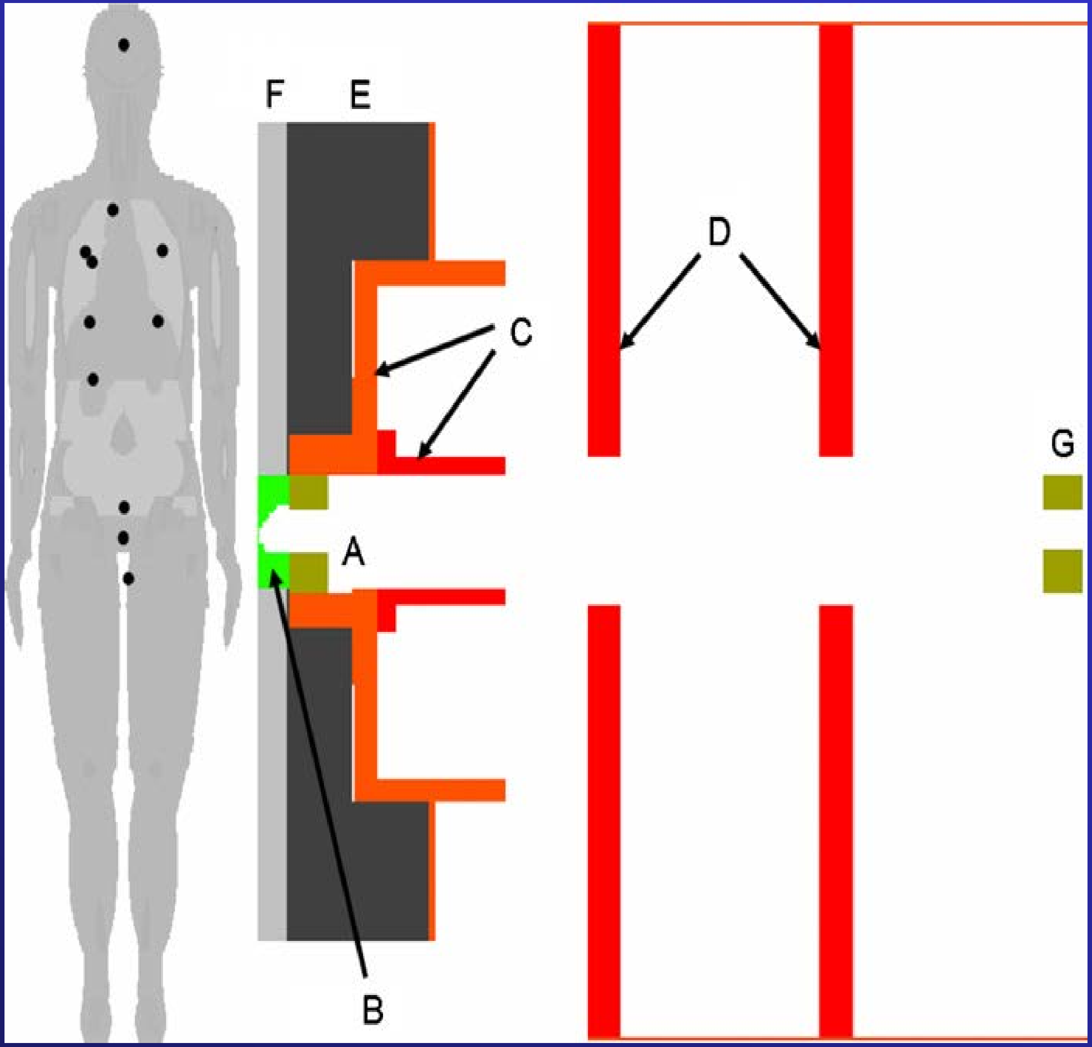


E_{avg} = 20 MeV

Equivalent dose ($H_{T,R}$)

$$H_{T,R} = w_R D_{T,R}$$

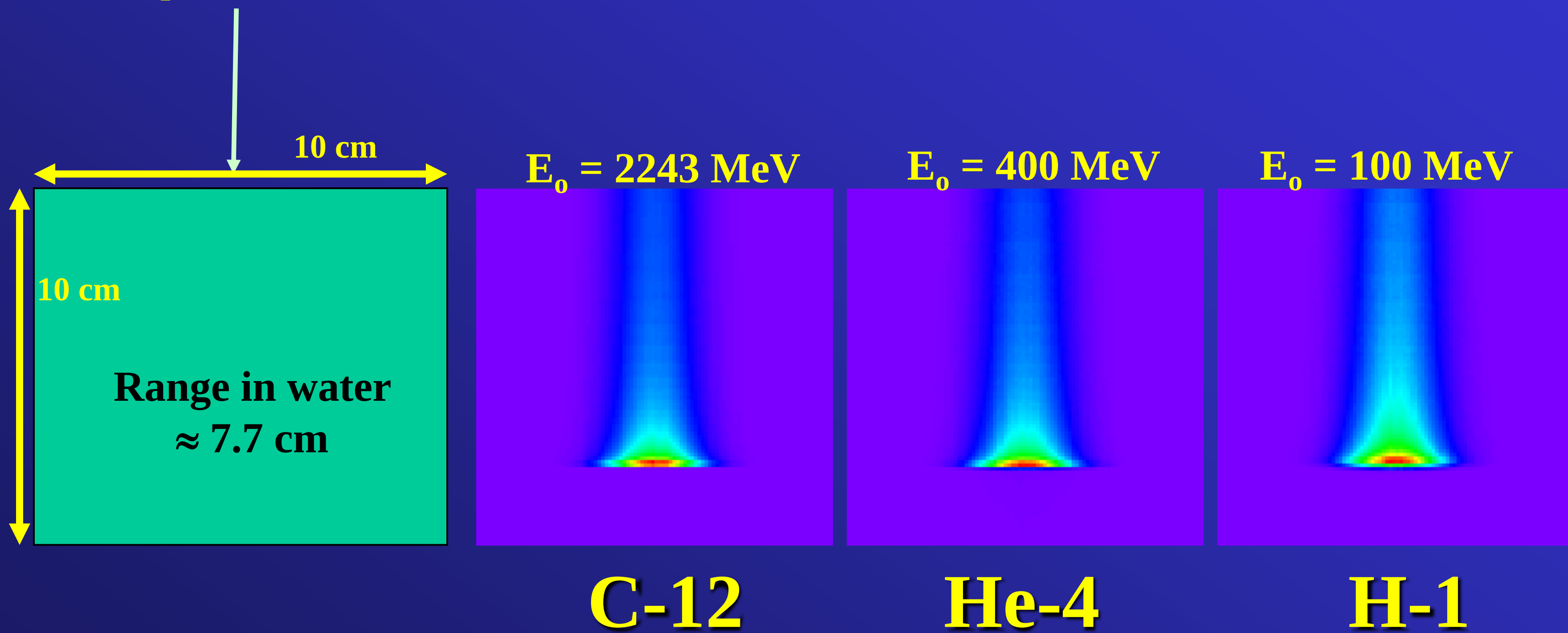
Type and energy range	Radiation weighting factor (w_R)
Photons, all energies	1
Electrons & muons, all energies	1
Neutrons, energy < 10keV	5
10 keV to 100 keV	10
100 keV to 2 MeV	20
2 MeV to 20 MeV	10
> 20 MeV	5
Protons, other than recoil protons, E>2MeV	5
Alpha particles, fission fragments, heavy nuclei	20



Passive collimation system for treating prostate cancer at the MD Anderson Proton Therapy Center

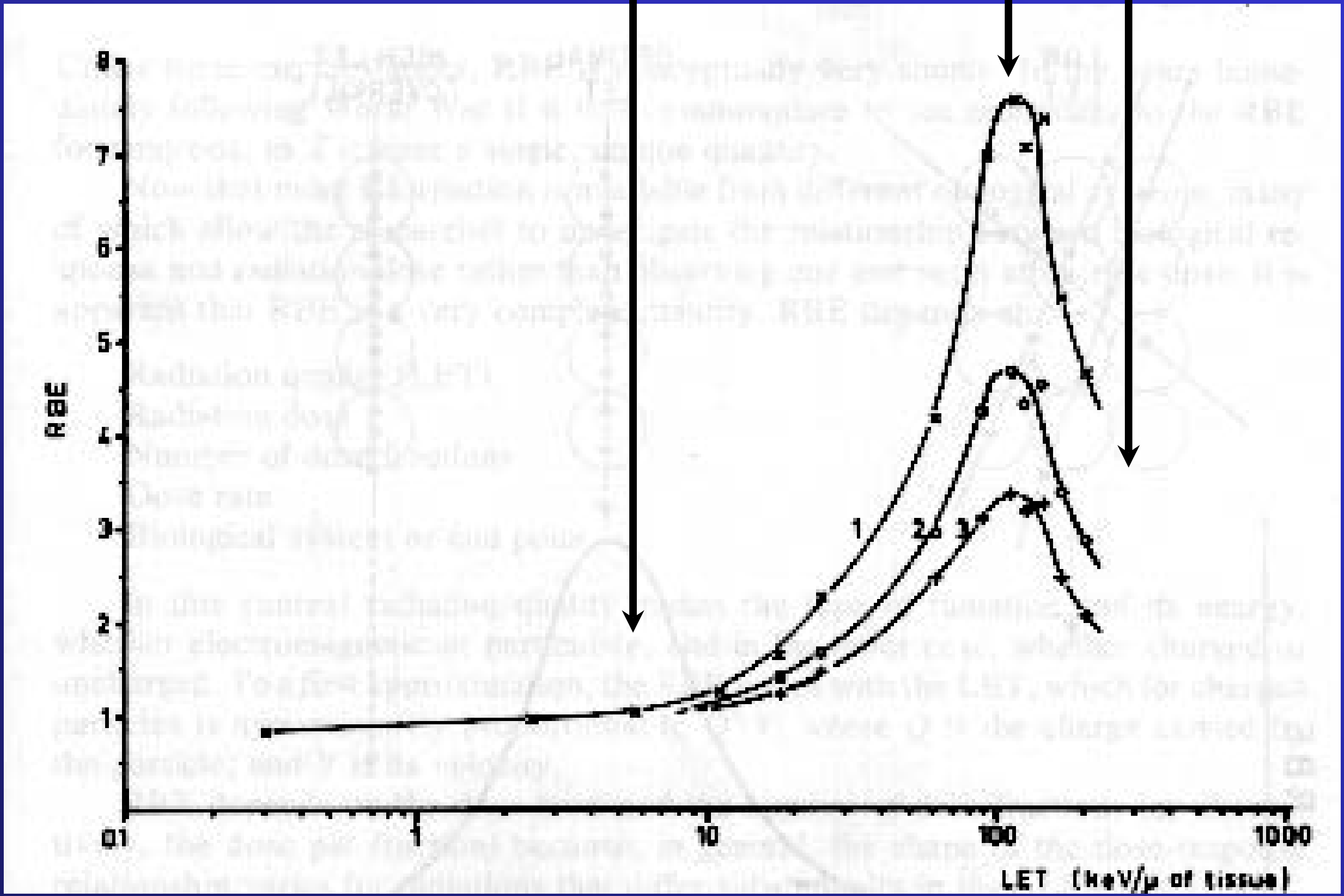
Tue et al., **Reducing stray radiation dose to patients receiving passively scattered proton radiotherapy for prostate Cancer", Med. Phys. 53, (2008).**

Gaussian pencil beam of monoenergetic ions incident on a water phantom



Optimal

Low LET ≈100 keV/μm Overkill



From Hall

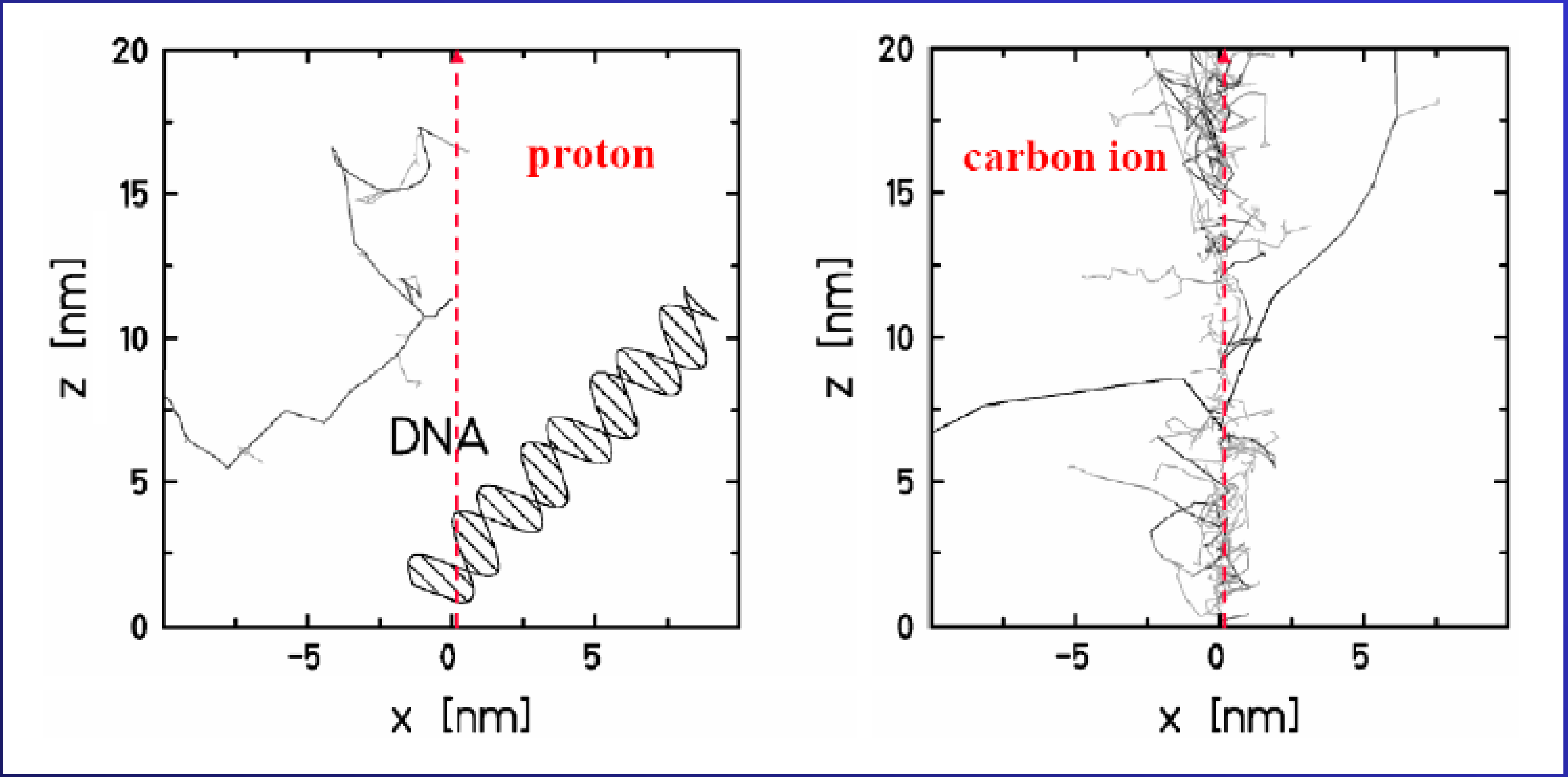
A comparison of LET values for different heavy ions

Charged particle $^{M}N^{Z}$	E (MeV u^{-1}) Range = 262 mm	LET (keV μm^{-1}) at various residual ranges in water (mm)				
		262	150	70	30	1
$^{1}H^{+1}$	200.0	0.5	0.6	0.8	1.1	4.8
$^{4}He^{+2}$	202.0	1.8	2.2	3.1	4.4	20.0
$^{7}Li^{+3}$	234.3	3.7	4.6	6.2	8.9	40.0
$^{11}B^{+5}$	329.5	8.5	10.0	13.5	19.0	87.5
$^{12}C^{+6}$	390.7	11.0	13.5	17.5	24.5	112.0
$^{14}N^{+7}$	430.5	14.5	17.5	22.5	31.5	142.0
$^{12}O^{+8}$	468.0	18.0	21.5	28.0	39.0	175.0

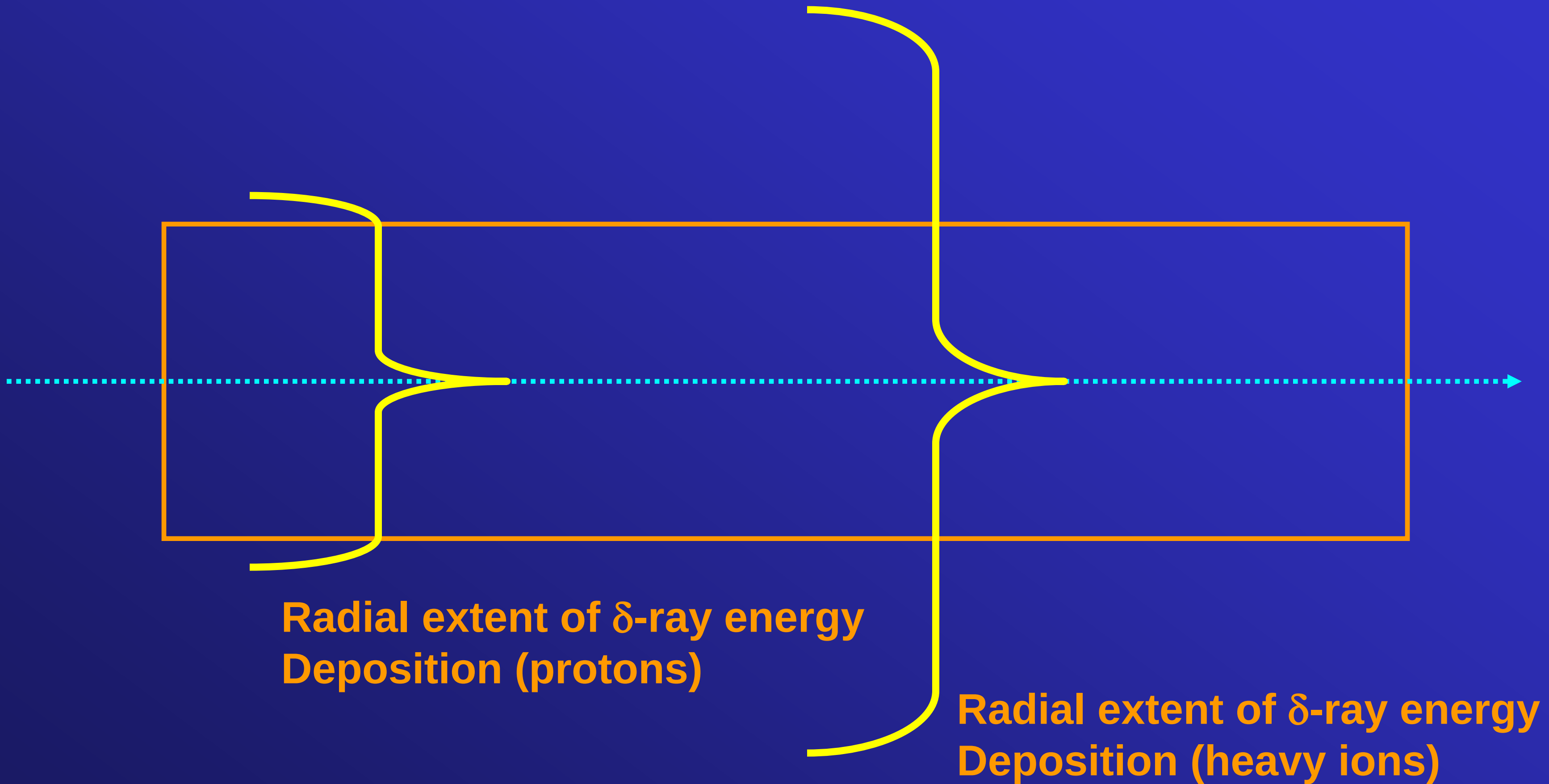
Plateau

Peak

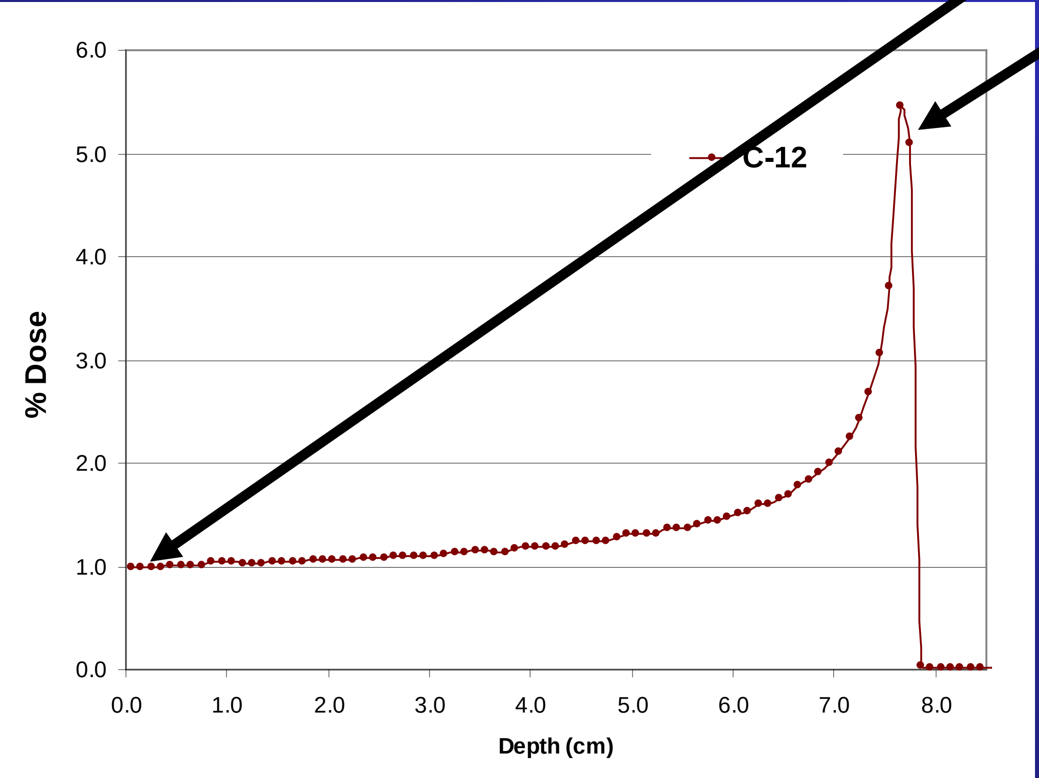
GEANT4 Monte Carlo simulations of proton and carbon energy deposition tracks in water



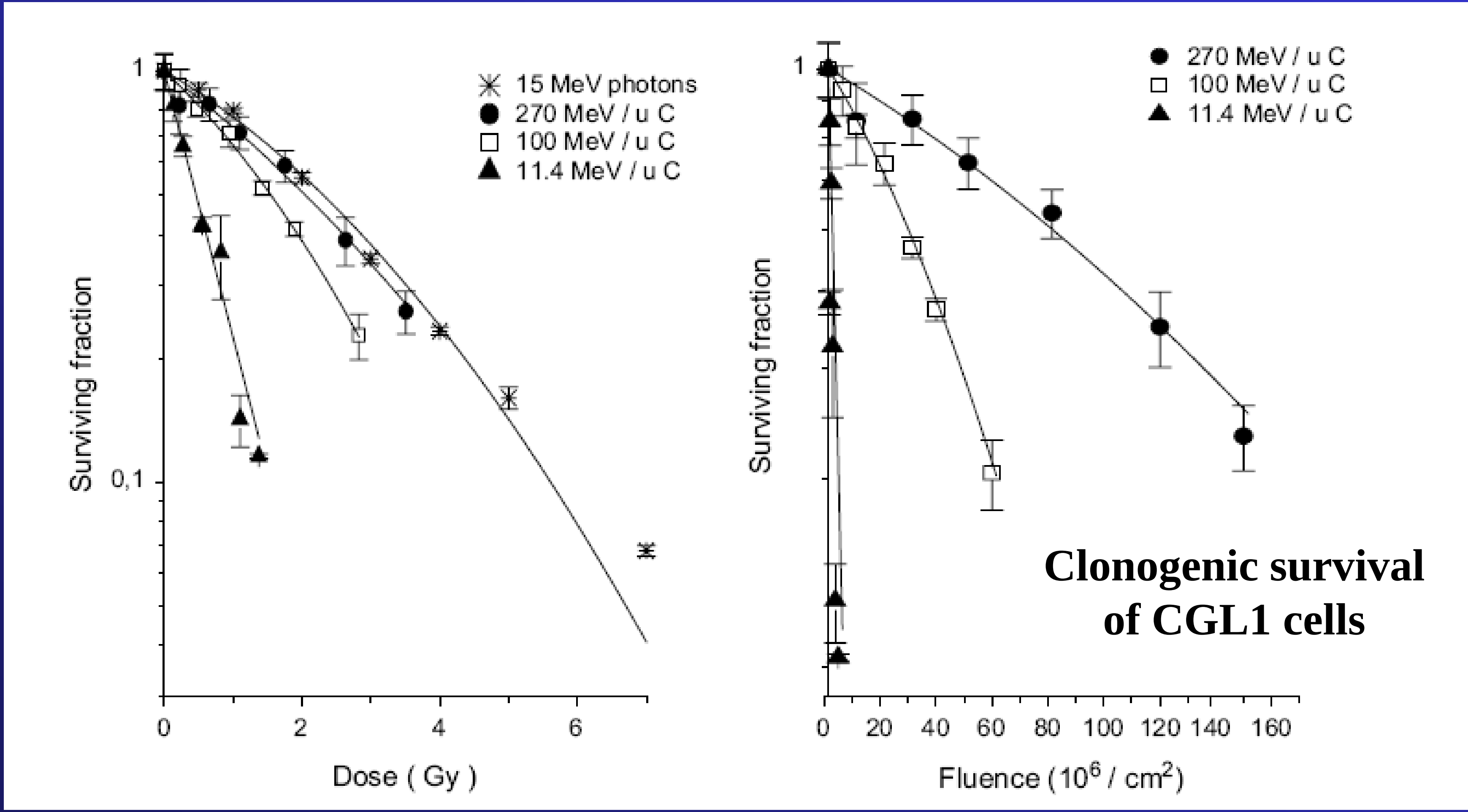
Discrete ion-electron collisions producing knock-on electrons (δ-ray)



Energy (MeV/u)	Energy on target (MeV/u)	LET (keV/μm)	Range in water (mm)
270.0	266.4	13.8	137
100.0	86.5	29.5	19.8
11.4	9.65	172	0.41



The biological considerations of heavy particle radiotherapy and accounting for RBE

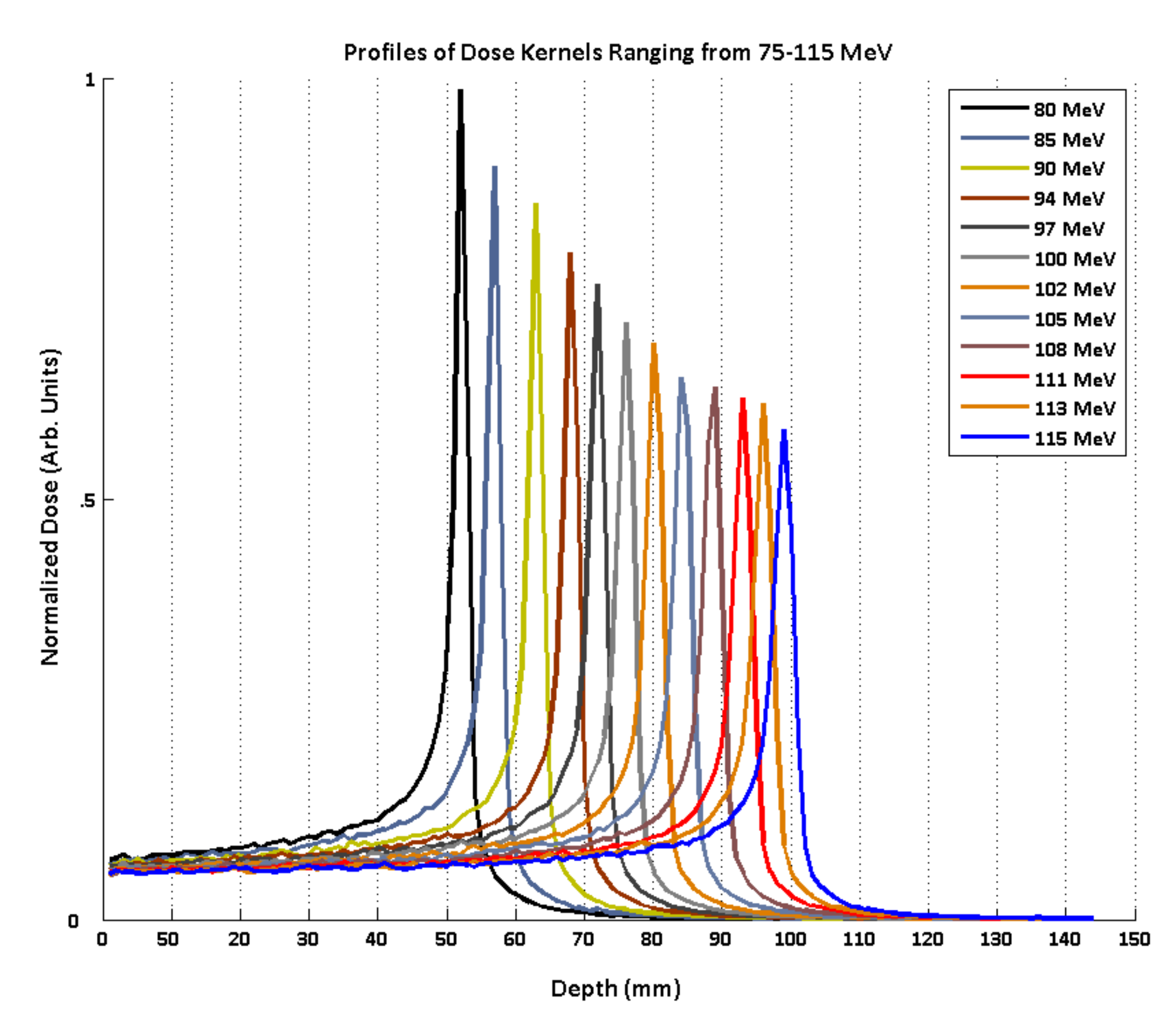


Clonogenic survival of CGL1 cells

Bettega et al., "Neoplastic transformation induced by carbon ions", IJROBP, 73, (2009)

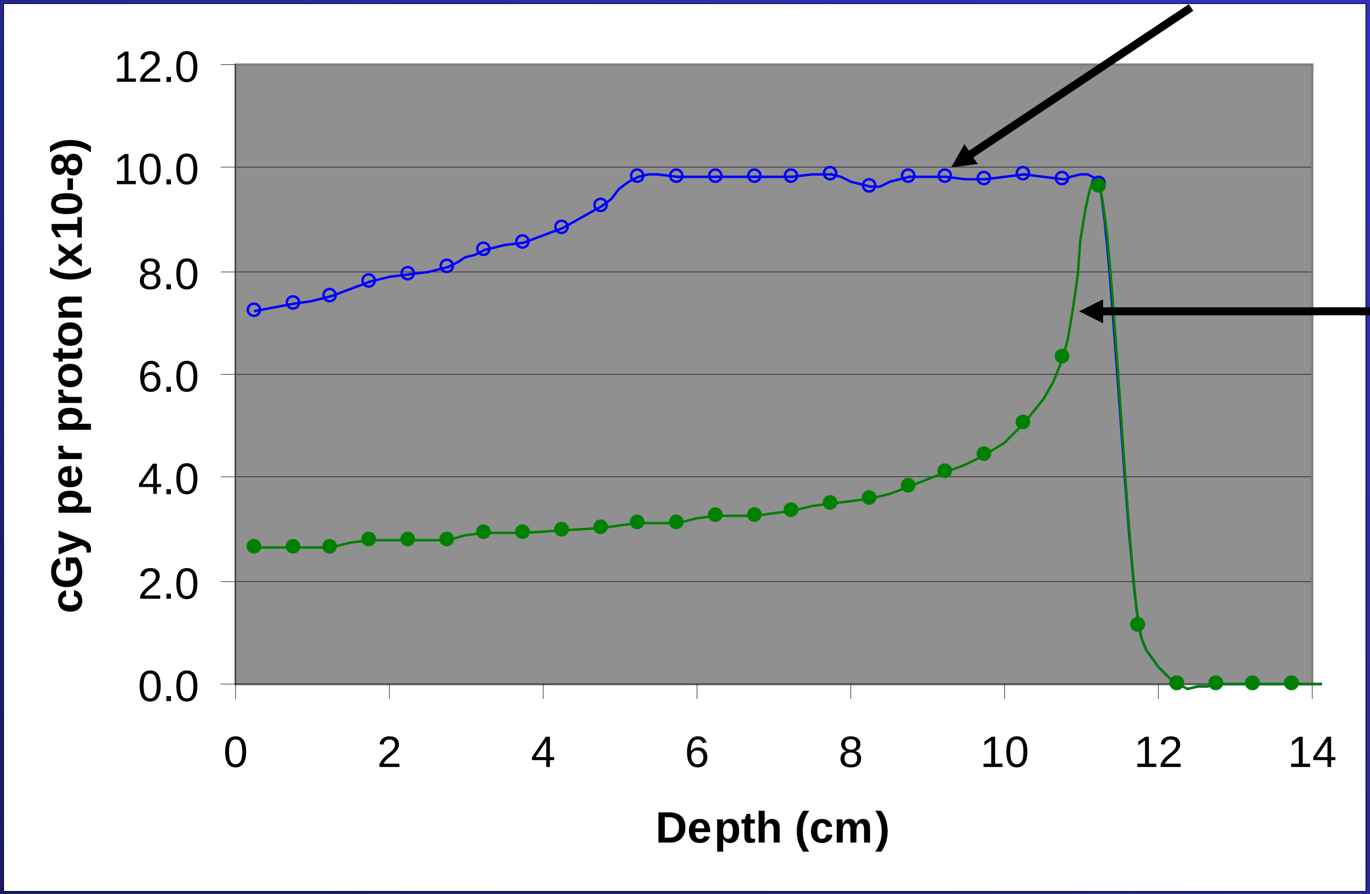
Monoenergetic Bragg Peaks

Each energy has a maximum range based upon the material stopping powers.



Spread-Out Bragg Peak and physical dose

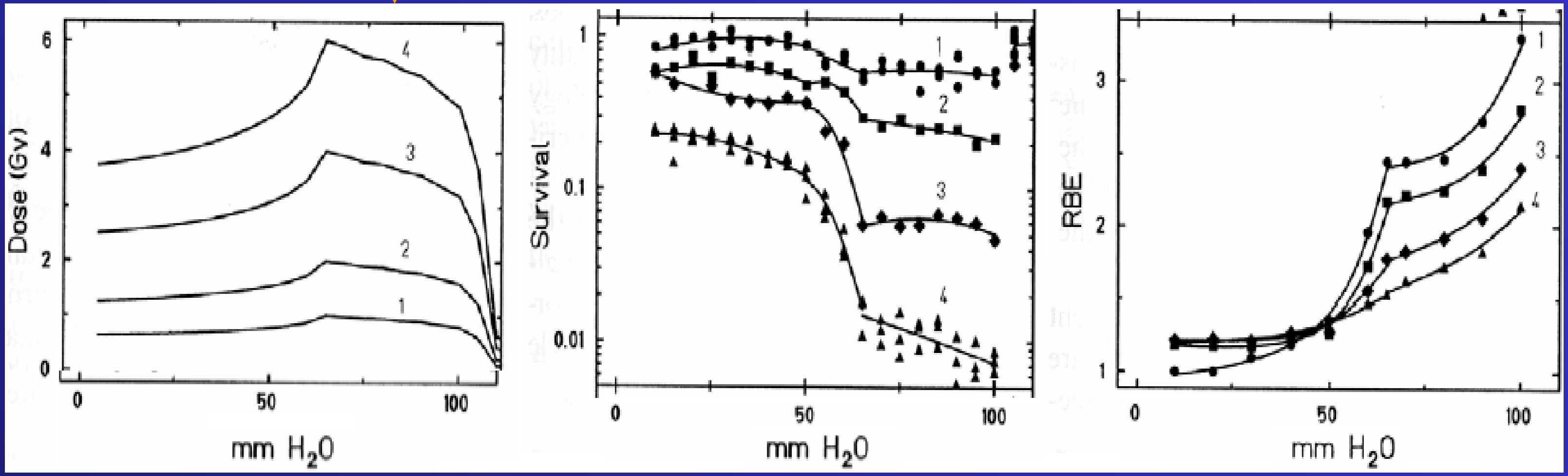
Modulated depth dose curve over a depth of approximately 6.5 cm.



Un-modulated depth dose curve

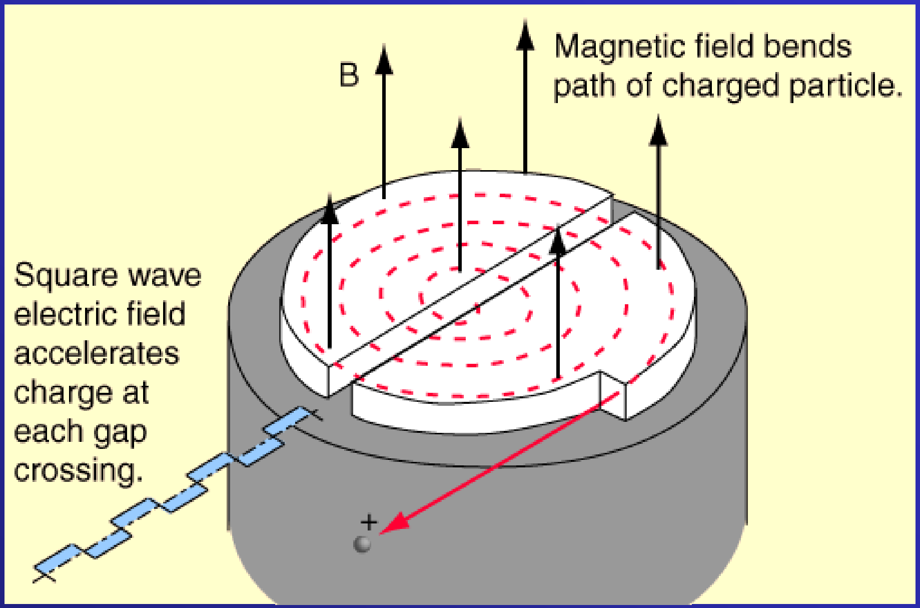
Broad, parallel beam of 125 MeV monoenergetic protons

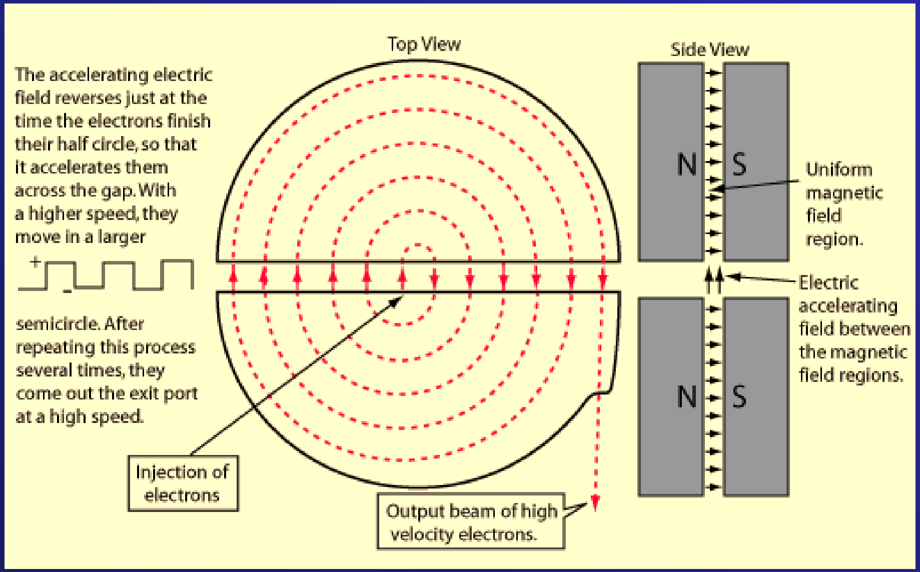
Spread-out bragg peak?



Comparison of the physical absorbed dose (left panel) and measured cell survival of CHO cells (central panel) in an SOBP for various doses. RBE values **calculated** from the measured cell survival are shown in the right panel. The dose has to decrease at the distal part in order to achieve a homogeneous biological effect over the simulated tumour.

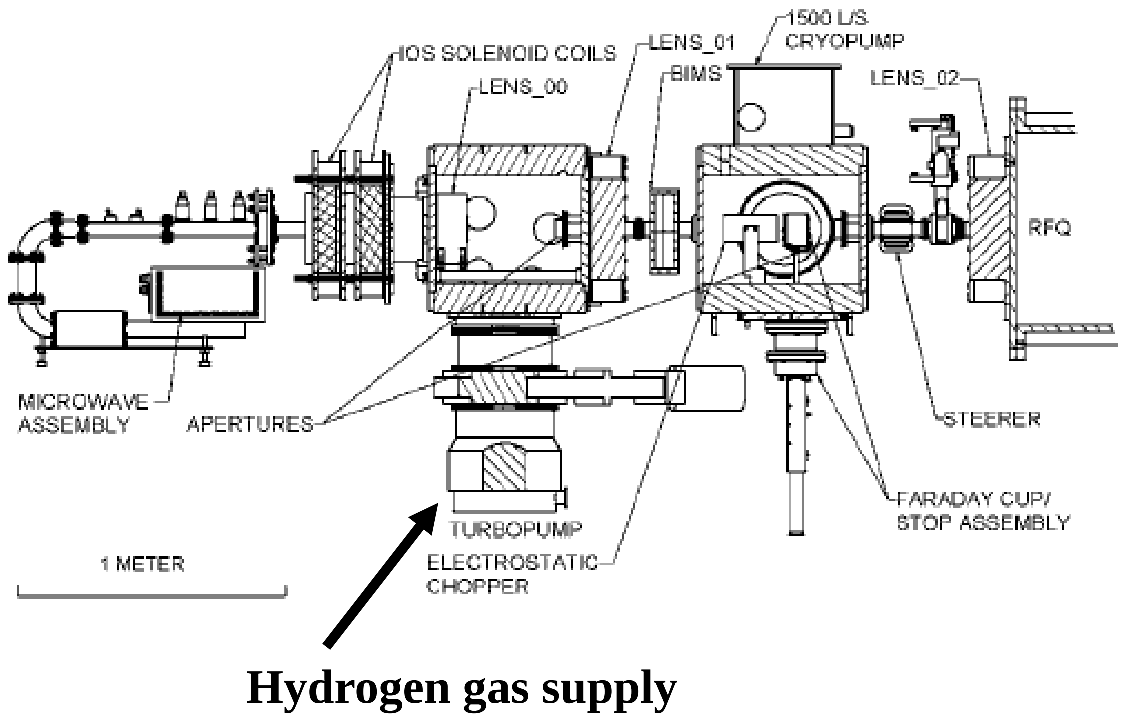
From Amaldi and Kraft, "Radiotherapy with beams of carbon ions, Reports on Progress in Physics, 68, (2005)





Reproduced from HyperPhysics, C.R. Nave 2012

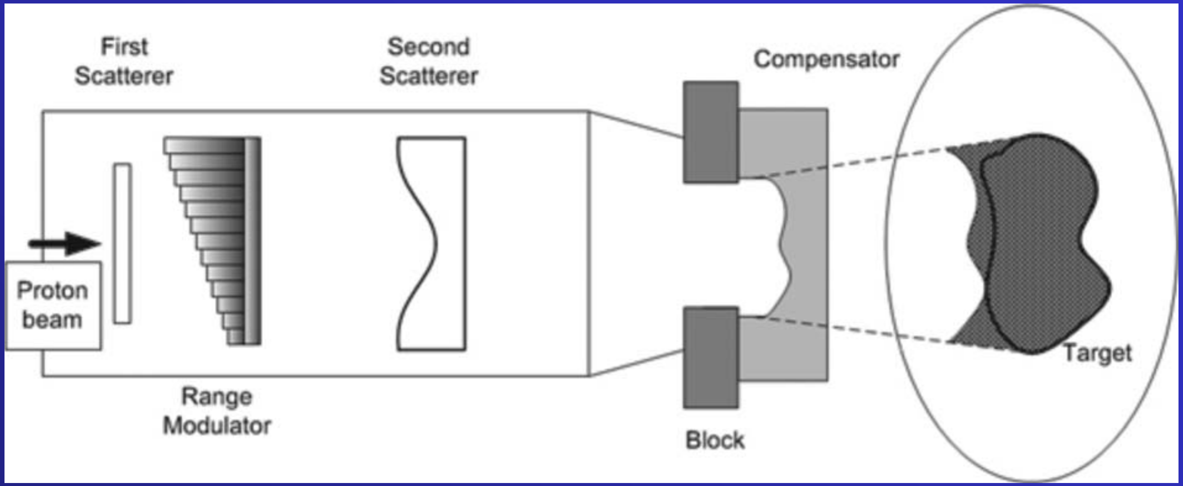
Midwest Proton Radiotherapy Institute

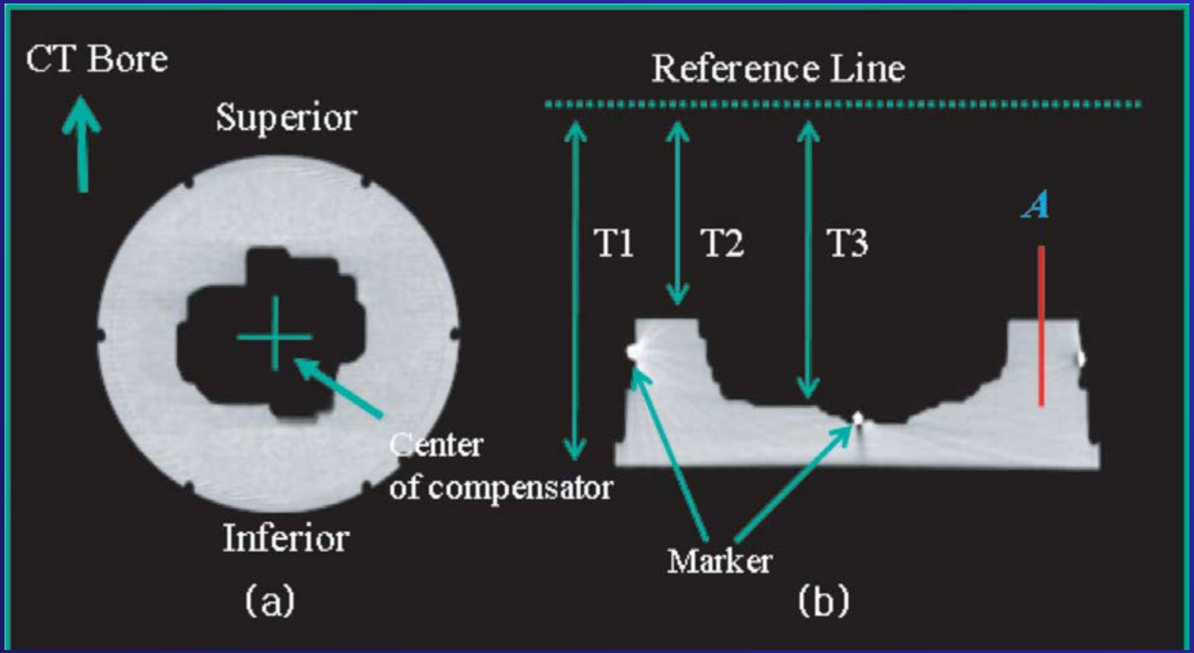


Microwave source based proton injector
20 keV injection energy

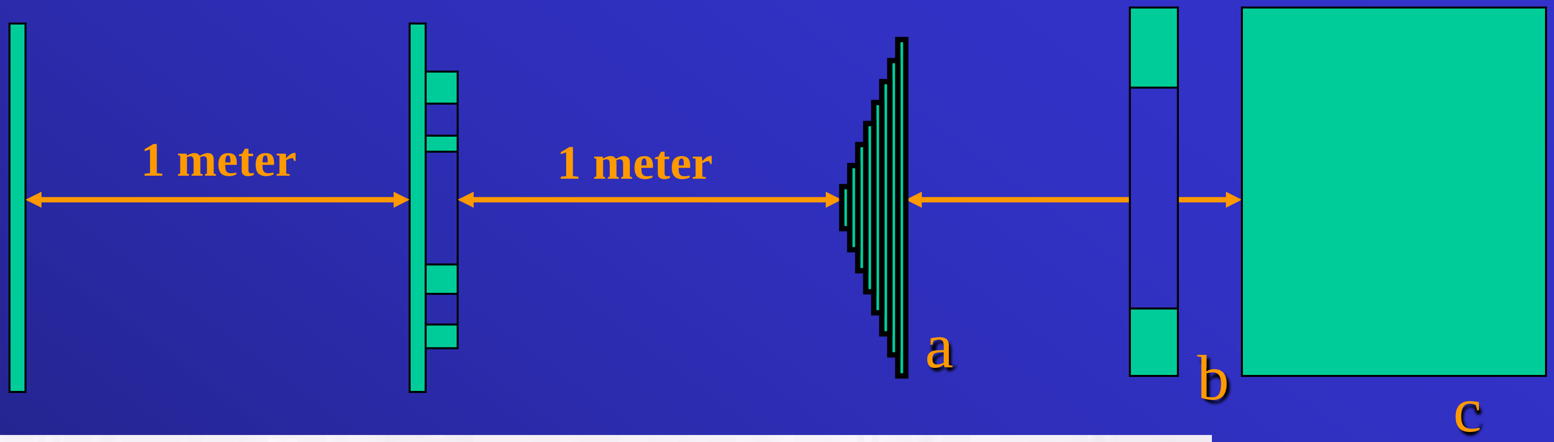
208 MeV maximum accelerated proton energy

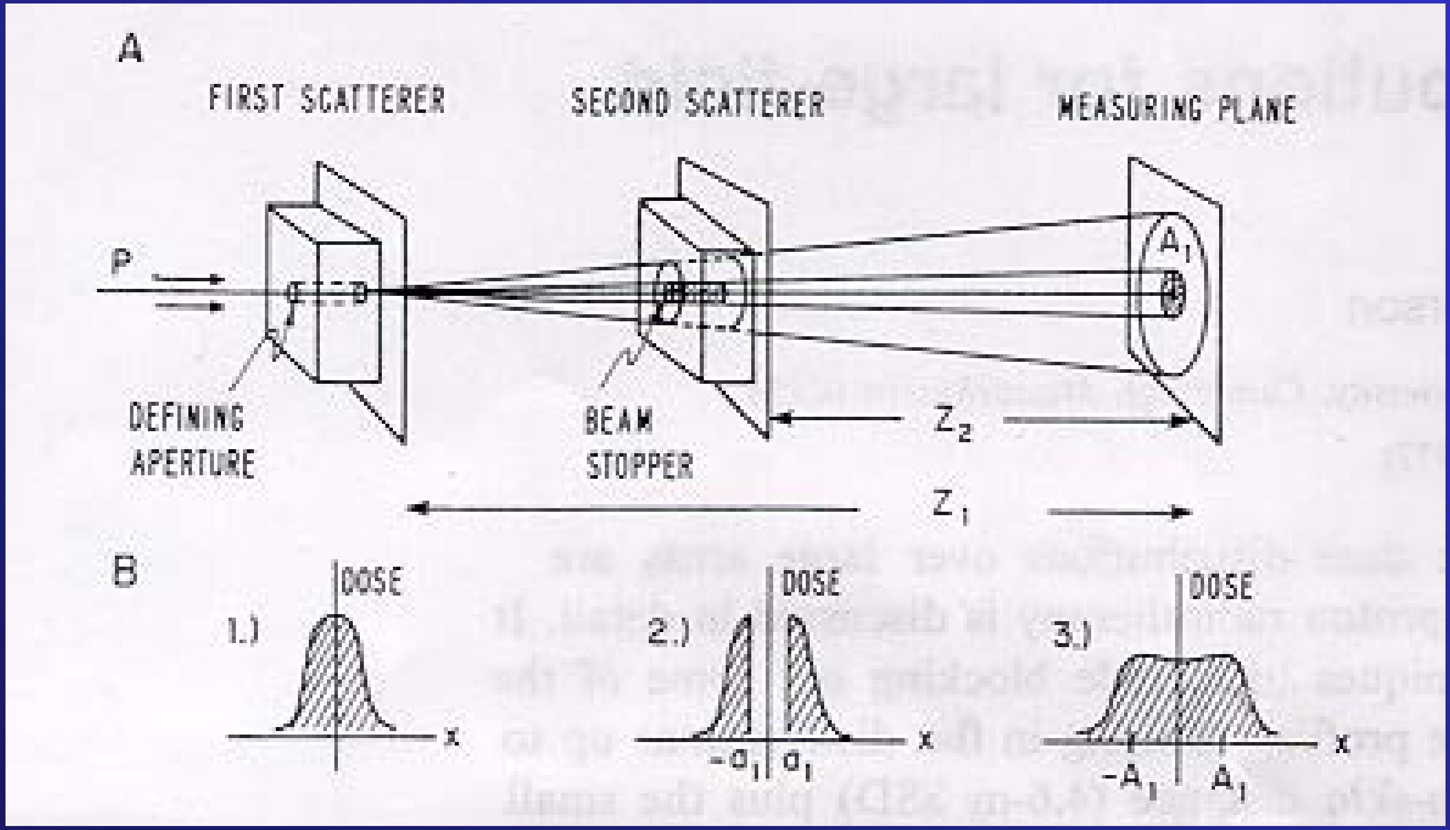
Passive Scattering System





Yoon et al. "**Computerized tomography-based quality assurance tool for proton range Compensators", Med. Phys., 35, (2008).**



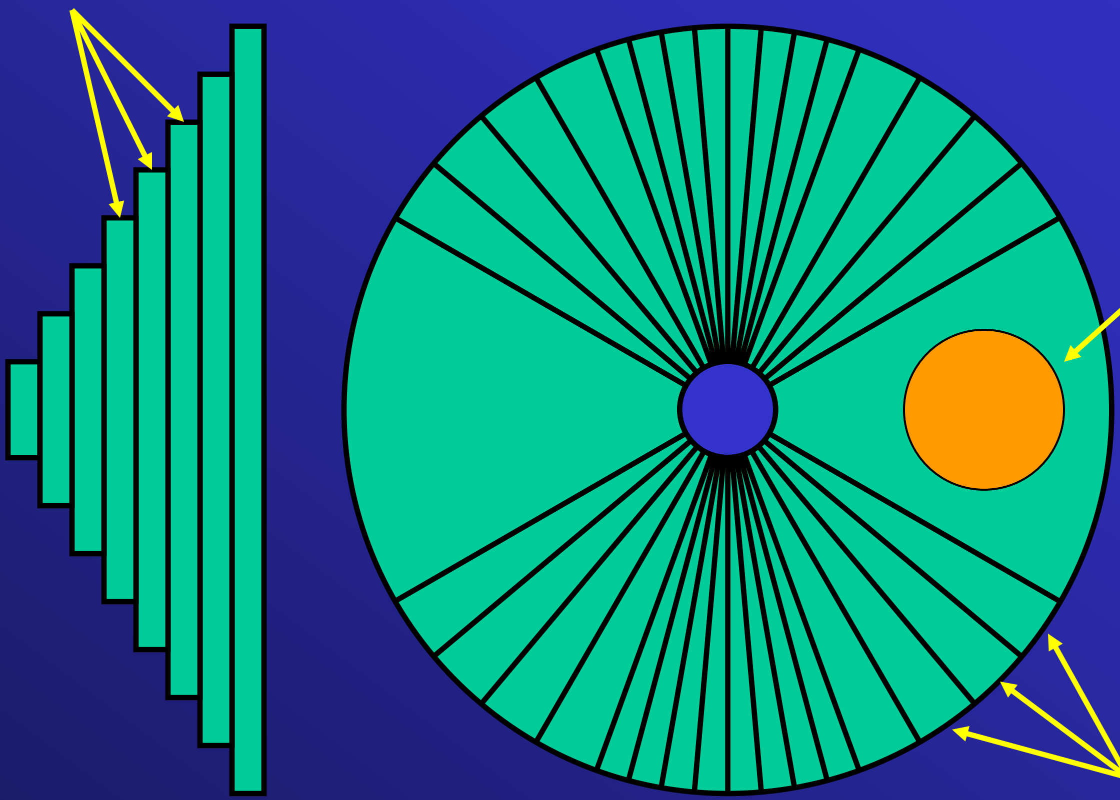


a. Range wheel
b. collimator
c. H_2O phantom

Range Modulation Wheel

The thickness of each plate determines the energy of the shifted bragg peak

Beam Port

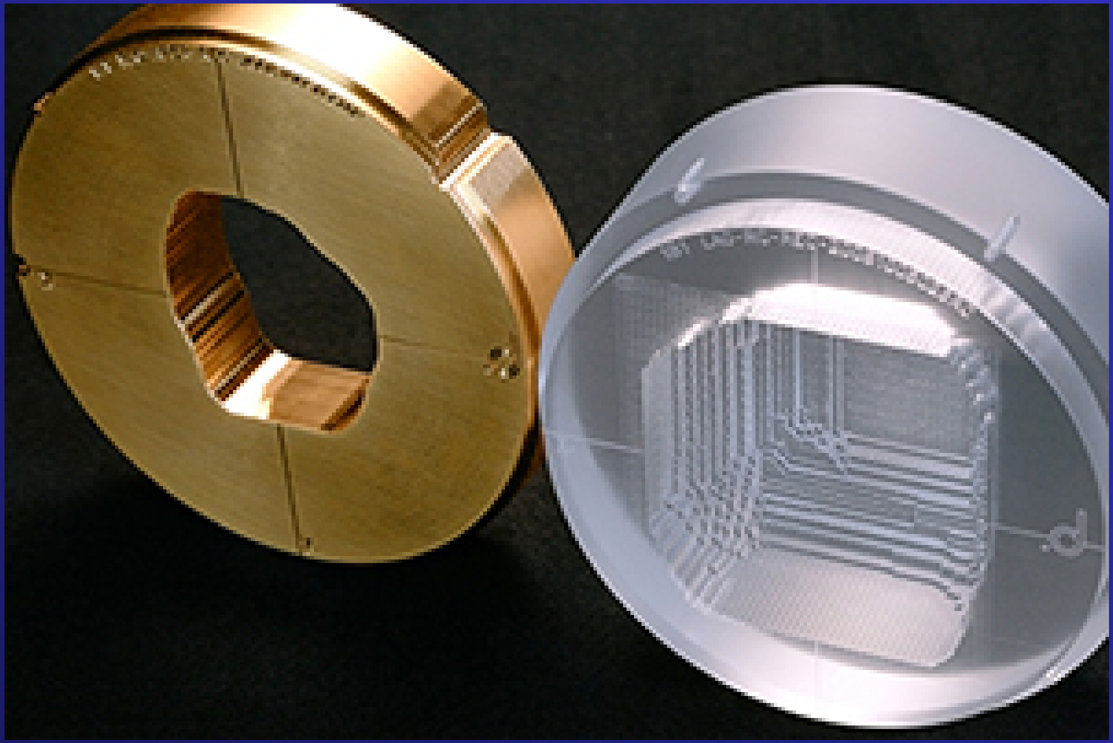


Side View

Beams-Eye View

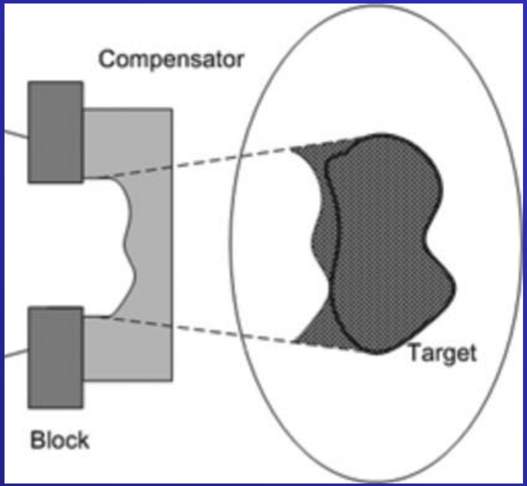
The opening angle of each pie section determines the relative weight of each bragg peak.

Range Modulation versus Fluence Modulation



Brass collimator serves to collimate the incident beam in-plane and cross-plane

Plastic compensator modulates the energy as a function of PTV depth.



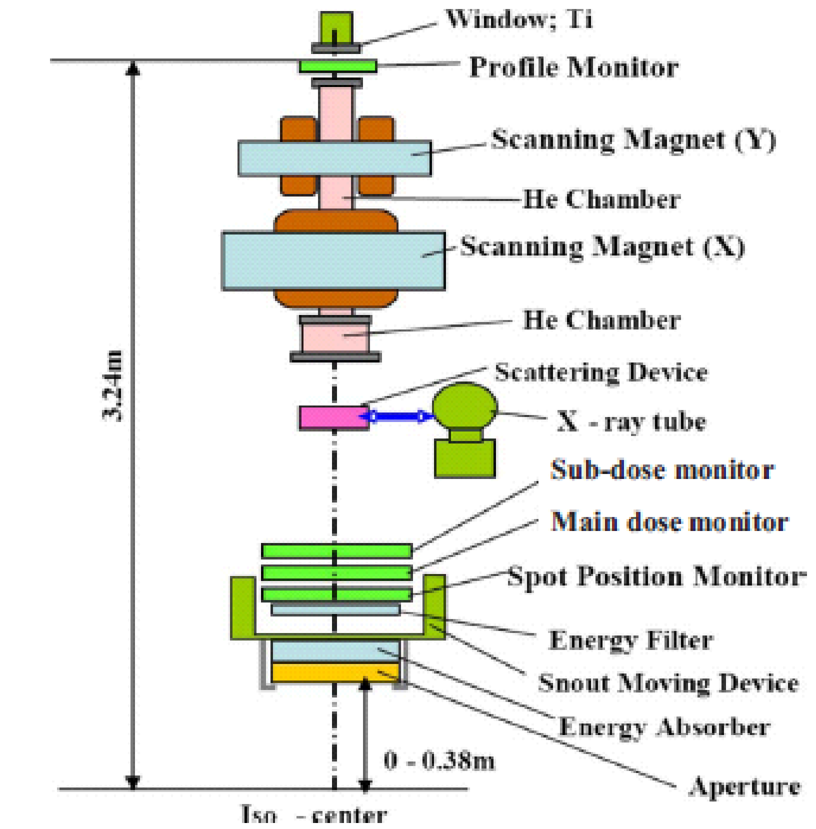
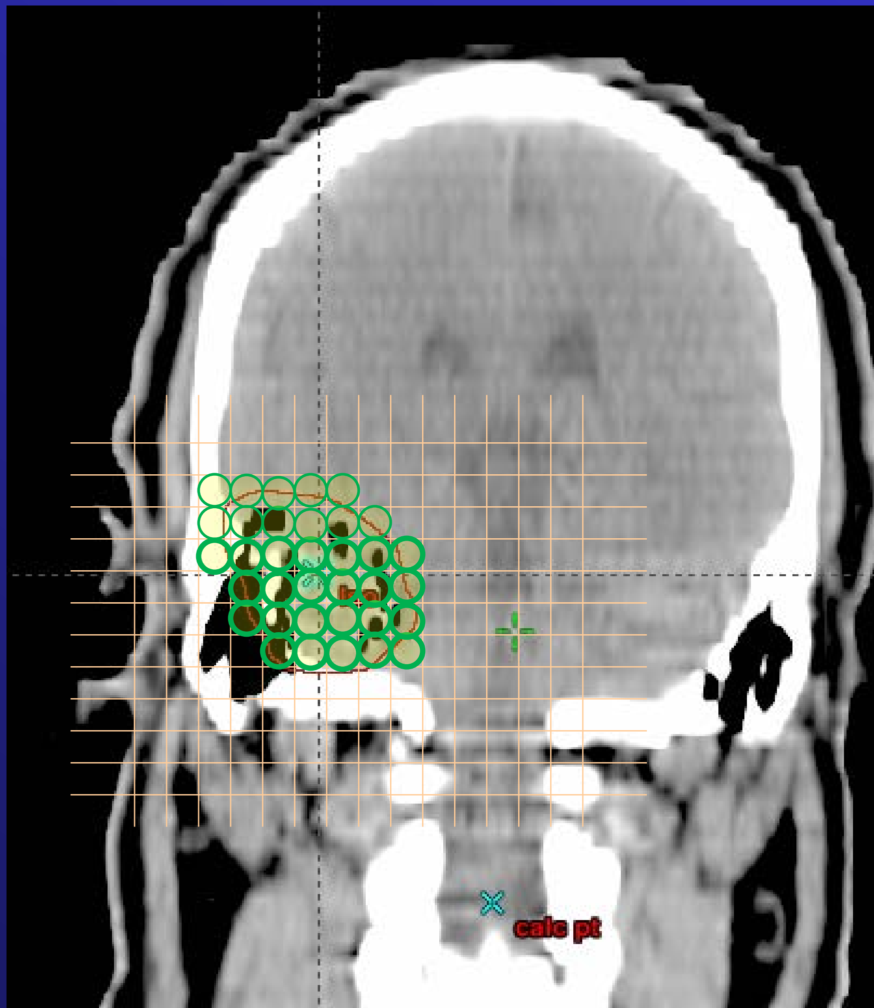


FIG. 3. Schematic of the scanning proton beam nozzle of the Hitachi Pro-Beat machine at PTC-H.

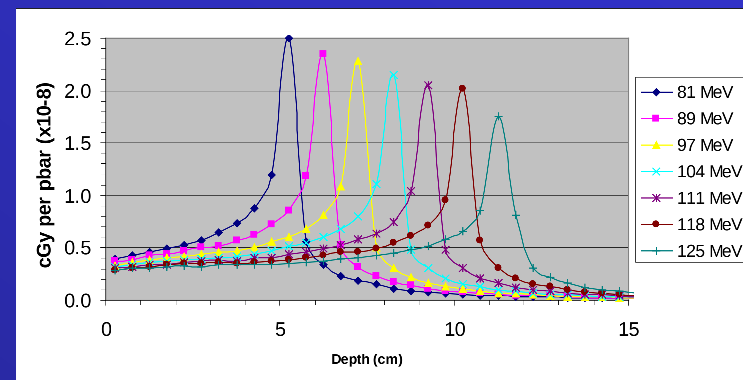
Commissioning of the discrete spot scanning proton beam delivery system at the University of Texas M.D. Anderson Cancer Center, Proton Therapy Center, Houston

Michael T. Gillin,a Narayan Sahoo, Martin Bues, George Ciangaru, Gabriel Sawakuchi, Falk Poenisch, Bijan Arjomandy, Craig Martin, Uwe Titt, Kazumichi Suzuki, Alfred R. Smith, and X. Ronald Zhu

Department of Radiation Physics, U.T. MD Anderson Cancer Center, Med. Phys. 37, (2010).

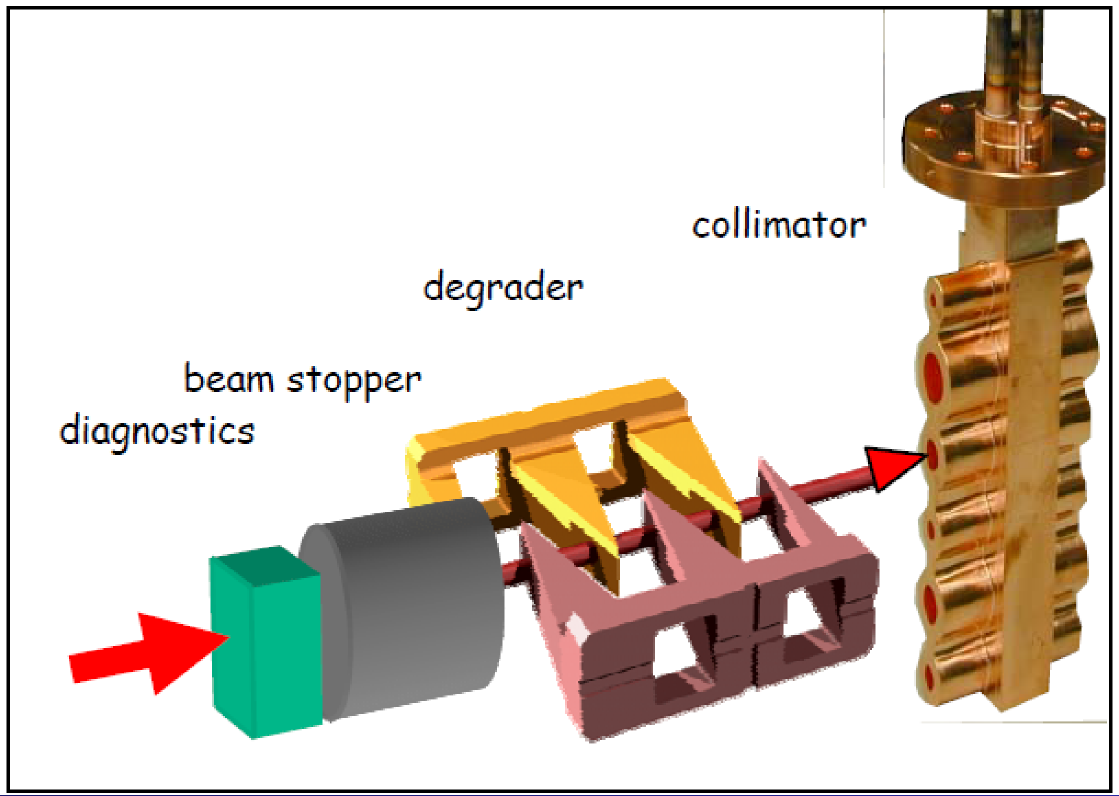


Spot Scanning & IMPT (Intensity Modulated Proton Therapy)



Modulate energy as a function of PTV depth

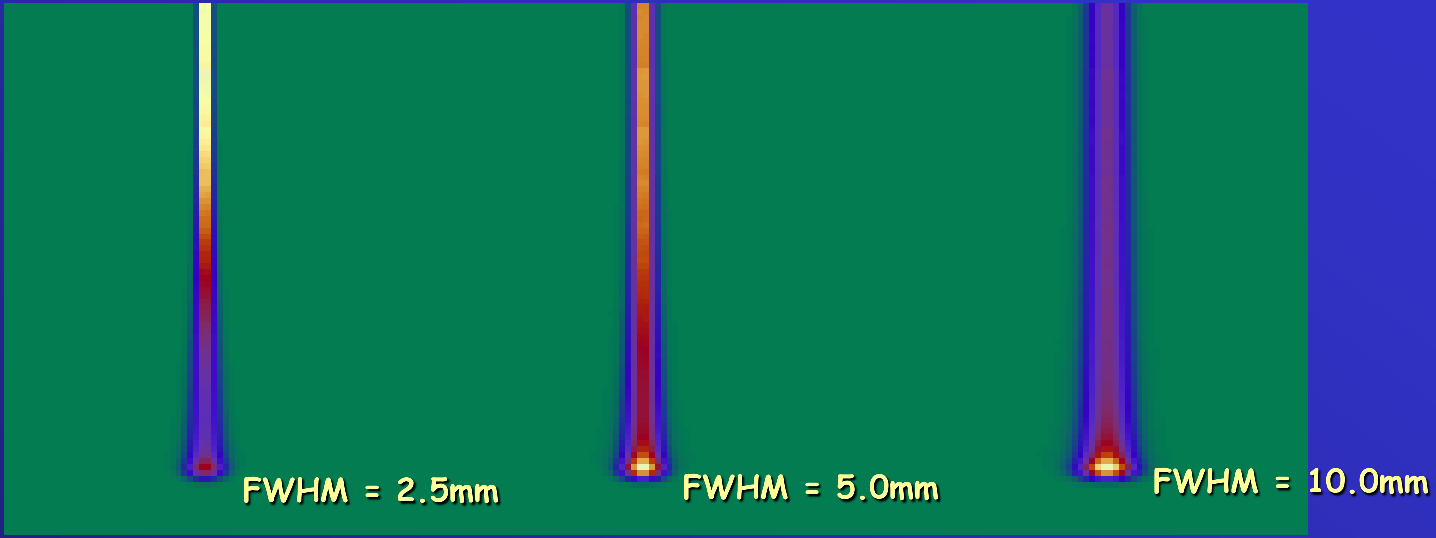
Proton "spot"

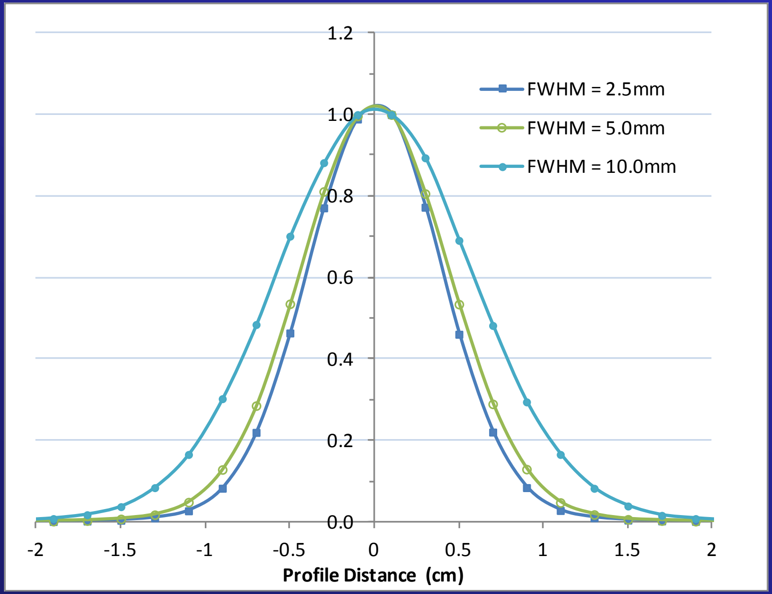


Energy modulation can be accomplished using a pair of opposed wedge degraders that operate on a 50ms time scale

THE SUPERCONDUCTING CYCLOTRON AND BEAM LINES OF PSI'S NEW PROTON THERAPY FACILITY "PROSCAN"
J.M. Schippers, J. Cherix, R. Dölling, P.A. Duperrex, J. Duppich, M. Jermann, A. Mezger, H.W. Reist, and the *PROSCAN* team, PSI, Villigen, Switzerland

Monte Carlo generated spot kernels





Virtual spot scanning with 100 MeV protons, Bragg peak depth ≈ 7.0cm

5mm FWHM

2.5mm FWHM

1.5mm FWHM

Virtual spot scanning with 100 MeV protons
Bragg peak depth ≈ 7.0cm

Spot size FWHM = 1mm

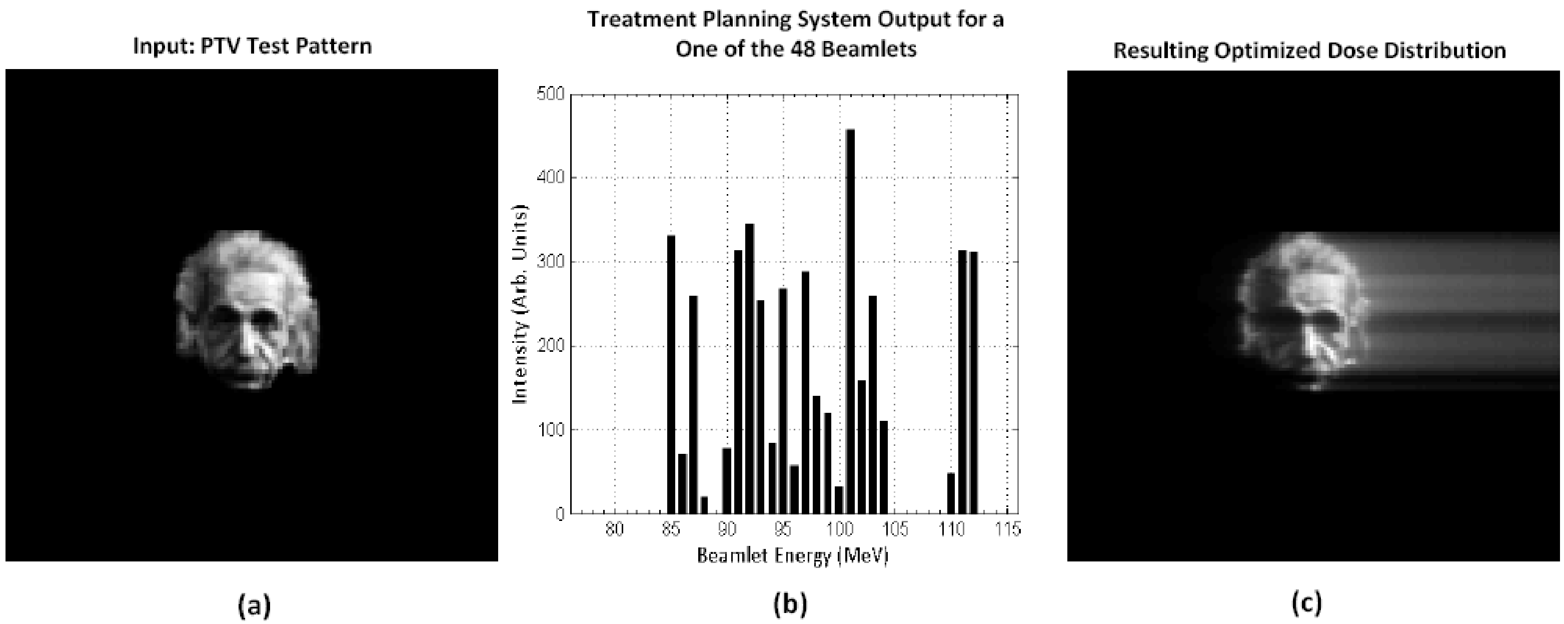
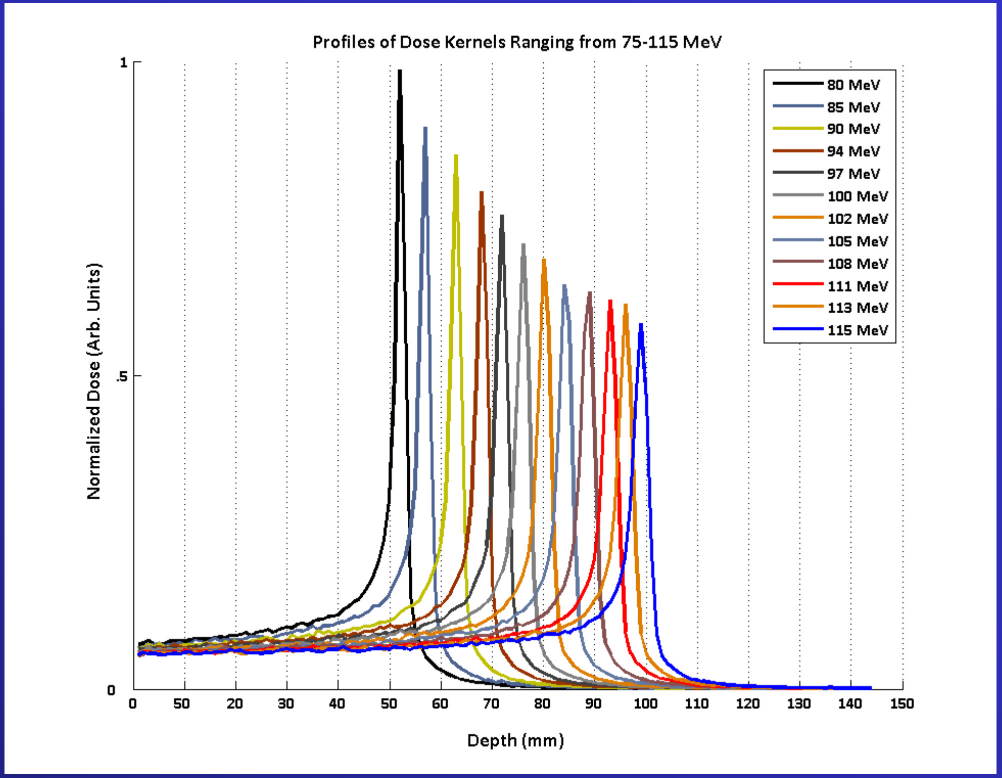


Fig. 2 (a) Test PTV: 4.8 cm x 4.8 cm low resolution image of A. Einstein in water phantom (voxel size= .1 cm x .1 cm x 1cm) (b) Treatment planning system output for optimal energy and intensity modulation of one of the 48 antiproton beamlets (20^{th} from top) originating from the right. (c) The resulting dose distribution calculated from the optimized energy and intensity modulation produced by the treatment planning system.

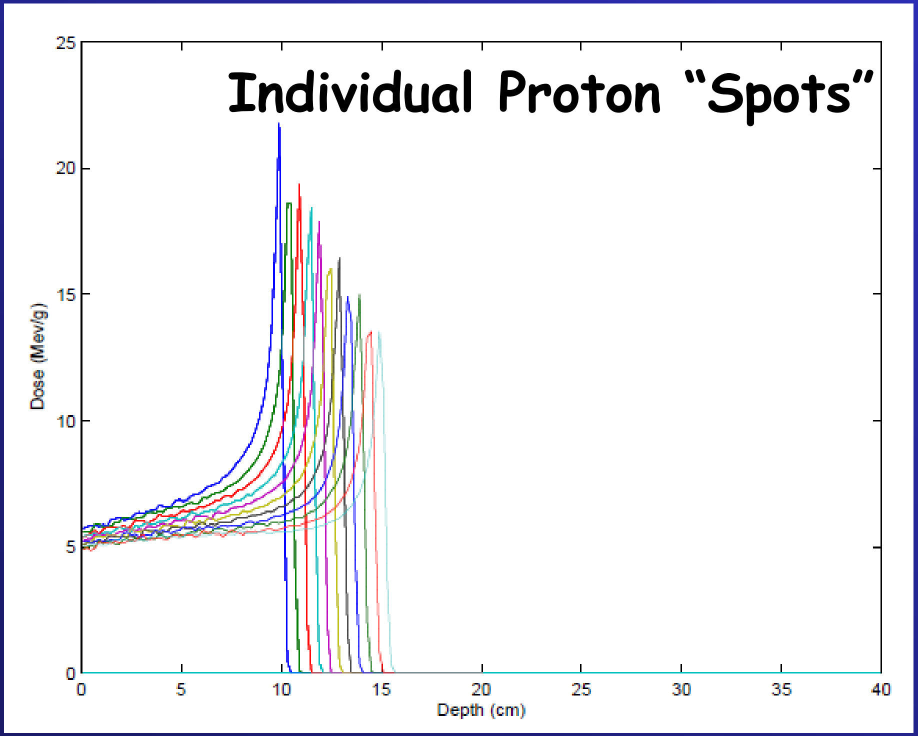
Antiproton Radiotherapy: Development of Physically and Biologically Optimized Monte Carlo Treatment Planning Systems for Intensity and Energy Modulated Delivery

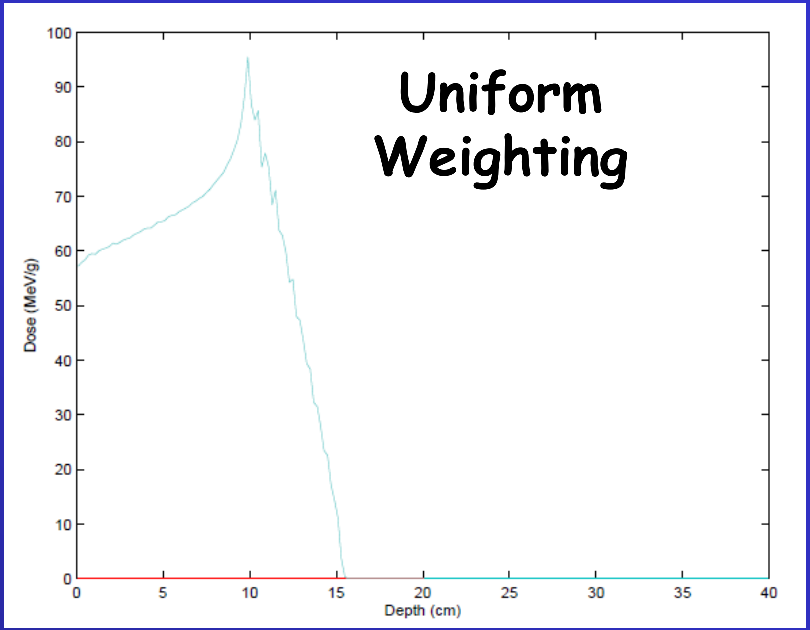
Courtesy of Benjamin Fahimian, Submitted to Young Investigator Symposium AAPM 2009.

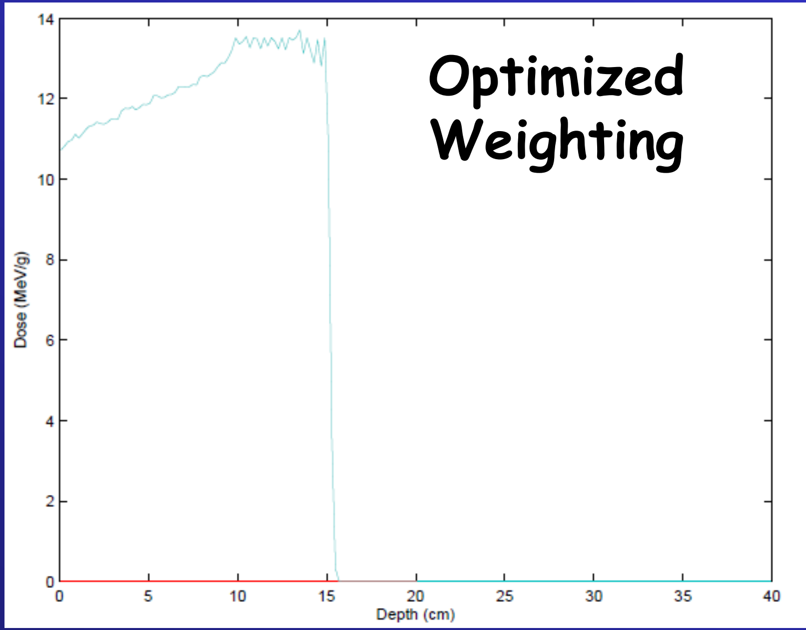
Monte Carlo calculated monoenergetic dose kernels



Fahimian 2009


Individual Proton "Spots"
Dose (Mev/g)
Depth (cm)
0
5
10
15
20
25
30
35
40


Uniform Weighting
Dose (MeV/g)
Depth (cm)
0
10
20
30
40
50
60
70
80
90
100


Optimized Weighting
Dose (MeV/g)
Depth (cm)
0
2
4
6
8
10
12
14

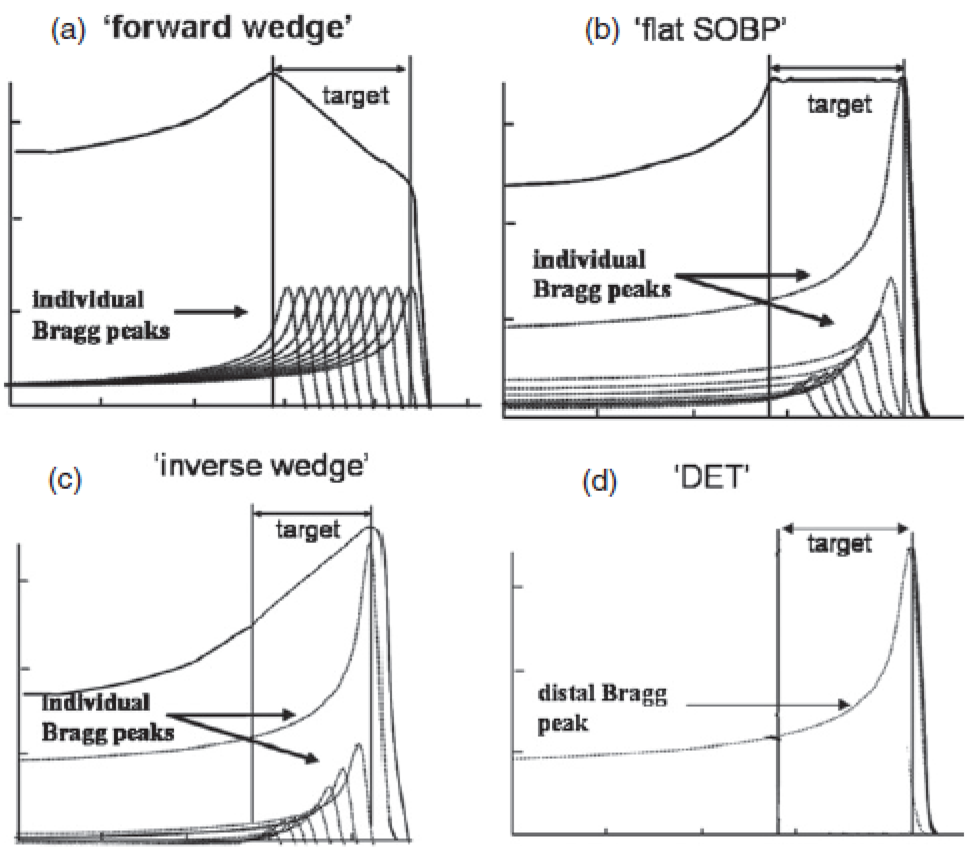


Figure 2. Schematic representation of the initial beamlet weights for a single field approaching the target from left to right: (a) individual Bragg peaks with identical weighting resulting in an initial 'forward wedge' dose distribution; (b) individual Bragg peaks with reduced weighting from distally to proximally resulting in an 'flat SOBP' dose distribution; (c) individual Bragg peaks with reduced weighting from distally to proximally such to deliver an initial 'inverse wedge' dose distribution; (d) selection of the most distal Bragg peak only, for a given lateral position (DET approach).

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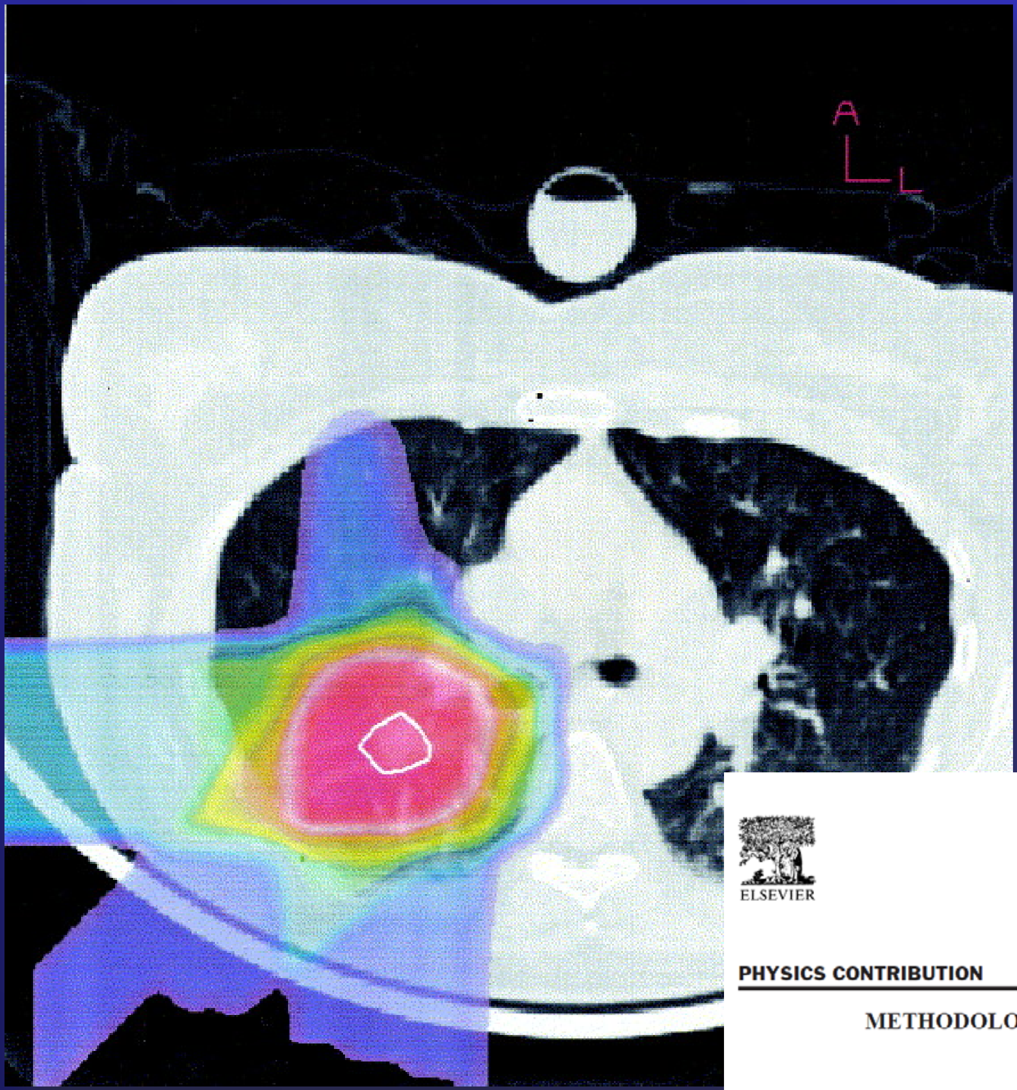
The influence of the optimization starting conditions on the robustness of intensity-modulated proton therapy plans

F Albertini[1], E B Hug[1,2] and A J Lomax[1,3]

[1] Center for Proton Therapy, Paul Scherrer Institut, 5232 Villigen PSI, Switzerland
[2] University of Zurich, Zurich, Switzerland
[3] Department of Physics, Swiss Institute of Technology (ETH), Zurich, Switzerland

Proton Range Uncertainty: Motion & Heterogeneities



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0360-3016/01/$–see front matter

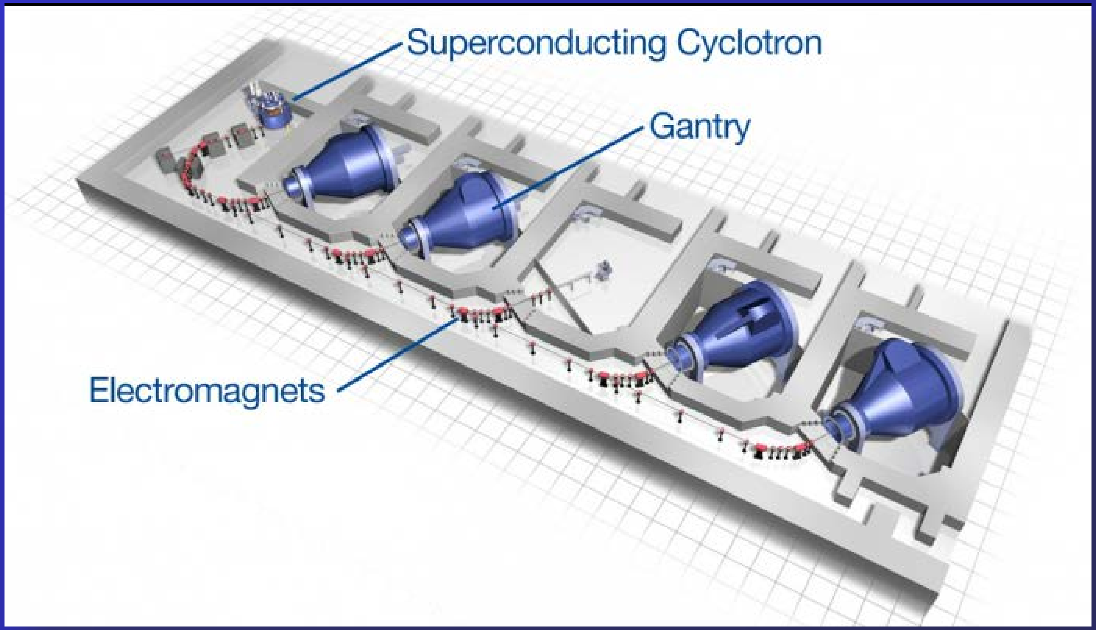
PII S0360-3016(00)01555-8

PHYSICS CONTRIBUTION

METHODOLOGIES AND TOOLS FOR PROTON BEAM DESIGN FOR LUNG TUMORS

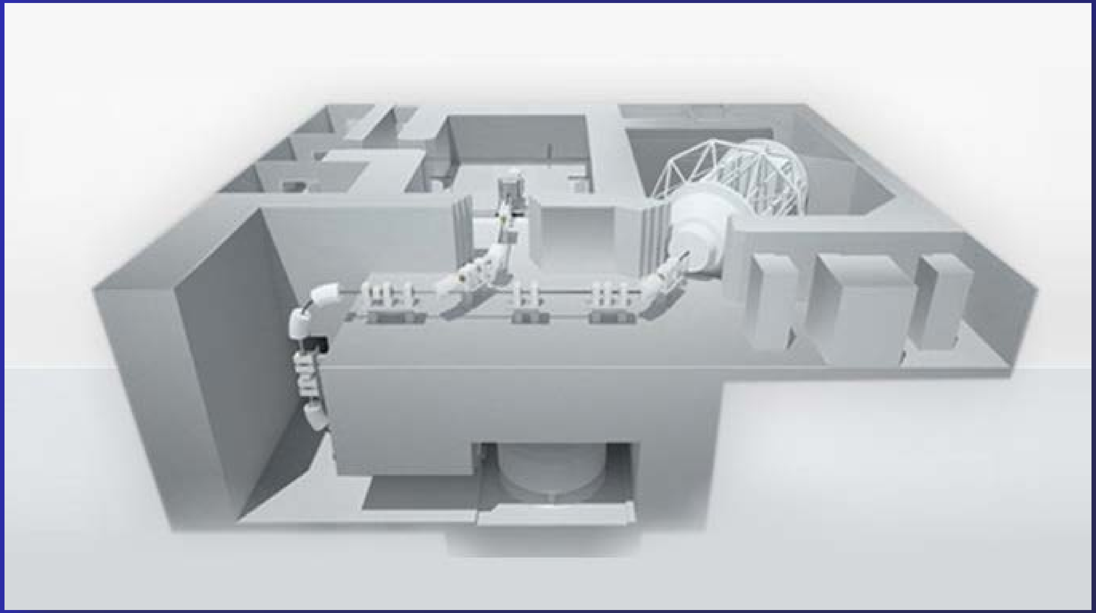
Michael F. Moyers, Ph.D., Daniel W. Miller, Ph.D., David A. Bush, M.D., and Jerry D. Slater, M.D.

Department of Radiation Medicine, Loma Linda University Medical Center, Loma Linda, CA



5-room Proton Therapy Facility

(courtesy of Advanced Particle Therapy (APT) and Varian Medical



2-room Proton Therapy Facility

(Proteus Nano, courtesy of iba Proton Therapy

Cyclotron

Proton Beam-Line

courtesy of iba Proton Therapy

Heidelberg Ion Treatment Facility

Gantry Tx area

Ceiling-mounted x-ray unit for image guidance

Stationary beam port

Robotic table

Fixed Beam Room

Gantry Room

courtesy of iba Proton Therapy

Intensity-Modulated Radiation Therapy, Proton Therapy, or Conformal Radiation Therapy and Morbidity and Disease Control in Localized Prostate Cancer

Nathan C. Sheets, MD
Gregg H. Goldin, MD
Anne-Marie Meyer, PhD
Yang Wu, PhD
YunKyung Chang, PhD
Til Stürmer, MD, PhD
Jordan A. Holmes, BS
Bryce B. Reeve, PhD
Paul A. Godley, MD, PhD
William R. Carpenter, PhD
Ronald C. Chen, MD, MPH

Context There has been rapid adoption of newer radiation treatments such as intensity-modulated radiation therapy (IMRT) and proton therapy despite greater cost and limited demonstrated benefit compared with previous technologies.

Objective To determine the comparative morbidity and disease control of IMRT, proton therapy, and conformal radiation therapy for primary prostate cancer treatment.

Design, Setting, and Patients Population-based study using Surveillance, Epidemiology, and End Results–Medicare-linked data from 2000 through 2009 for patients with nonmetastatic prostate cancer.

Main Outcome Measures Rates of gastrointestinal and urinary morbidity, erectile dysfunction, hip fractures, and additional cancer therapy.

Results Use of IMRT vs conformal radiation therapy increased from 0.15% in 2000 to 95.9% in 2008. In propensity score–adjusted analyses (N=12 976), men who received IMRT vs conformal radiation therapy were less likely to receive a diagnosis of gastrointestinal morbidities (absolute risk, 13.4 vs 14.7 per 100 person-years; relative risk [RR], 0.91; 95% CI, 0.86-0.96) and hip fractures (absolute risk, 0.8 vs 1.0 per 100 person-years; RR, 0.78; 95% CI, 0.65-0.93) but more likely to receive a diagnosis of erectile dysfunction (absolute risk, 5.9 vs 5.3 per 100 person-years; RR, 1.12; 95% CI, 1.03-1.20). Intensity-modulated radiation therapy patients were less likely to receive additional cancer therapy (absolute risk, 2.5 vs 3.1 per 100 person-years; RR, 0.81; 95% CI, 0.73-0.89). In a propensity score–matched comparison between IMRT and proton therapy (n=1368), IMRT patients had a lower rate of gastrointestinal morbidity (absolute risk, 12.2 vs 17.8 per 100 person-years; RR, 0.66; 95% CI, 0.55-0.79). There were no significant differences in rates of other morbidities or additional therapies between IMRT and proton therapy.

Conclusions Among patients with nonmetastatic prostate cancer, the use of IMRT compared with conformal radiation therapy was associated with less gastrointestinal morbidity and fewer hip fractures but more erectile dysfunction; IMRT compared with proton therapy was associated with less gastrointestinal morbidity.

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PROSTATE CANCER IS THE MOST common malignancy in men, with more than 200 000 diagnoses and 30 000 deaths per year.[1] Recent advances in technology have led to costlier treatments such as minimally invasive radical prostatectomy, intensity-modulated radiation therapy (IMRT), and proton therapy. The adoption of these technologies resulted in a $350 million increase in health care expenditures in 2005 alone.[2] The Institute of Medicine, Agency for Healthcare Research and Quality, Secretary of the Department of Health and Human Services, and others have called for comparative effectiveness research of localized prostate cancer treatments,[3-5] which is especially relevant for radiation therapy, for which IMRT has gradually replaced the older technique of conformal radiation therapy during the past 10 years. More recently, there has been a substantial increase in the number of proton facilities built, and direct-to-consumer advertising is likely to lead to an increase in its use.[6-8] The clinical benefit from these newer treatments is unproven, and comparative effectiveness research examining different radiation techniques is lacking. Given these trends in use, multiple recent reports have specifically called for research on proton therapy.[9]

Author Affiliations: Department of Radiation Oncology (Drs Sheets, Goldin, and Chen and Mr Holmes), Cecil G. Sheps Center for Health Services Research (Drs Meyer, Godley, Carpenter, and Chen), School of Medicine (Mr Holmes), Lineberger Comprehensive Cancer Center (Drs Meyer, Wu, Reeve, Godley, Carpenter, and Chen), School of Nursing (Dr Chang), Department of Epidemiology (Dr Stürmer), Department of Health Policy and Management, School of Public Health (Drs Reeve and Carpenter), University of North Carolina at Chapel Hill.
Corresponding Author: Ronald C. Chen, MD, MPH, Department of Radiation Oncology, University of North Carolina Hospitals, CB #7512, Chapel Hill, NC 27599 (ronald_chen@med.unc.edu).

POINT/COUNTERPOINT

Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to Colin G. Orton, Professor Emeritus, Wayne State University, Detroit: ortonc@comcast.net. Persons participating in Point/Counterpoint discussions are selected for their knowledge and communicative skill. Their positions for or against a proposition may or may not reflect their personal opinions or the positions of their employers.

Within the next 10–15 years protons will likely replace photons as the most common type of radiation for curative radiotherapy

Richard L. Maughan, Ph.D.
Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania 19104
(Tel: 215-662-7887, E-mail: maughan@xrt.upenn.edu)

Frank Van den Heuvel, Ph.D.
Department of Experimental Radiotherapy, UZ-Gasthuisberg - University of Leuven, Leuven B-3000, Belgium
(Tel: 32 16 34 76 40, E-mail: frank.vandenheuvel@uz.kuleuven.ac.be)

Colin G. Orton, Ph.D., Moderator

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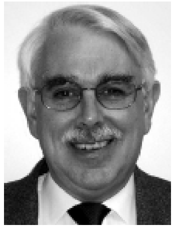
OVERVIEW

Interest in proton therapy has increased dramatically in the past couple of years, especially in the United States. The obvious physical benefits of protons are offset by the high costs. The promise of innovative new technologies to reduce the cost of proton therapy machines, however, combined with impressive results being accumulated, might make proton therapy not only a feasible alternative to conventional techniques for curative patients, but possibly the treatment of choice at some time in the not-too-distant future. This is the premise debated in this month's Point/Counterpoint.



Arguing for the Proposition is Richard L. Maughan, Ph.D. Dr. Maughan received his Ph.D. in physics from the University of Birmingham in England. He started his career at the Gray Laboratory, London in 1974, and moved to Wayne State University in 1983 where he was responsible for the medical physics aspects of a neutron therapy program. He is now Professor, Vice Chair and Director of Medical Physics in the Department of Radiation Oncology at the University of Pennsylvania. His research interests are particle therapy (neutrons, protons, heavy ions), with a particular emphasis on proton therapy.

Arguing against the Proposition is Frank Van den Heuvel, Ph.D. Dr. Van den Heuvel is Professor at the Katholieke Universiteit, Leuven, Belgium and the Director of Medical Physics in the Department of Experimental Radiotherapy at the University Hospitals Gasthuisberg in Leuven, having previously spent almost 10 years at Wayne State University, Detroit. He obtained his Ph.D. in physics from the Free University in Brussels. His main interests lie in patient and organ positioning, incorporating radiobiological models into clinical planning, use of exotic particles for treatment, and using computers to make his life easier.

FOR THE PROPOSITION: Richard L. Maughan, Ph.D.

Opening Statement

Over the past sixty years technical advances in radiotherapy have led to new radiation delivery techniques which have allowed for tumor dose escalation and improved normal tissue sparing. We have progressed from orthovoltage x rays, through ^{60}Co units, high energy linacs, conformal therapy, to intensity modulated radiation therapy (IMRT) and tomotherapy. The clinical efficacy of these advances has been readily accepted by physicians and physicists and the new technologies have been rapidly applied to the benefit of many patients. In no case have controlled clinical trials of