Cynthia Keppel, PhD

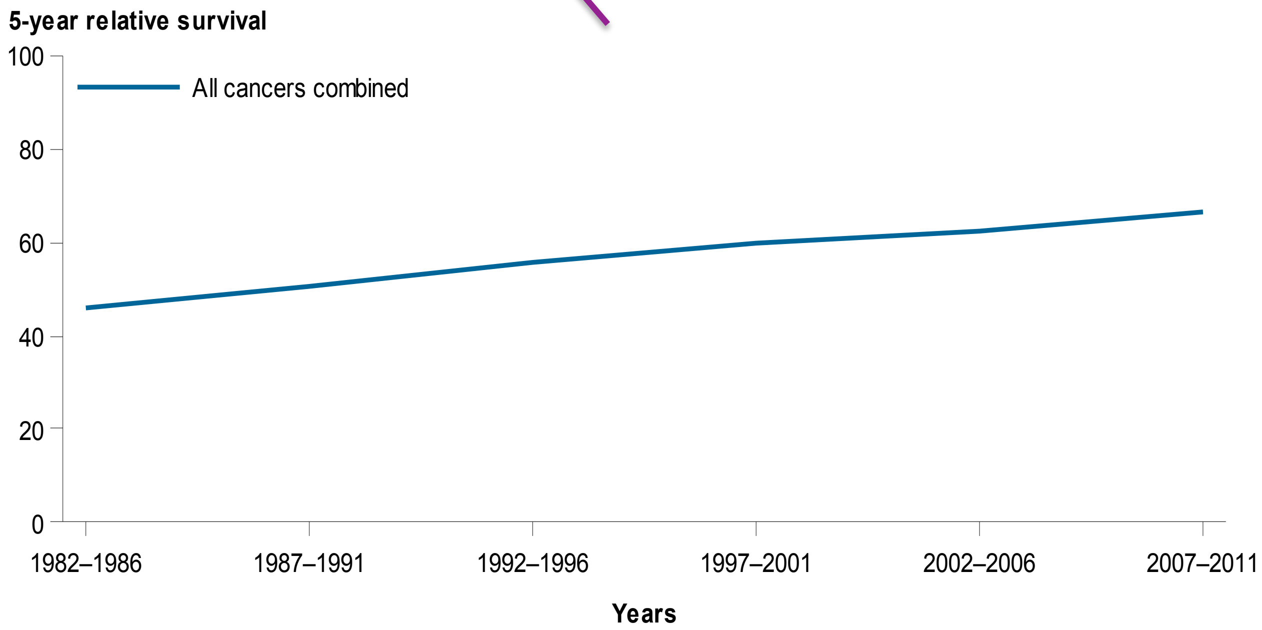
Thomas Jefferson National Accelerator Facility

(Hampton University Proton Therapy institute)

Australian Government
Australian Institute of Health and Welfare

Survival: trend

Five-year relative survival for people diagnosed with cancer increased over time from 46% in 1982–1986 to 67% in 2007–2011.



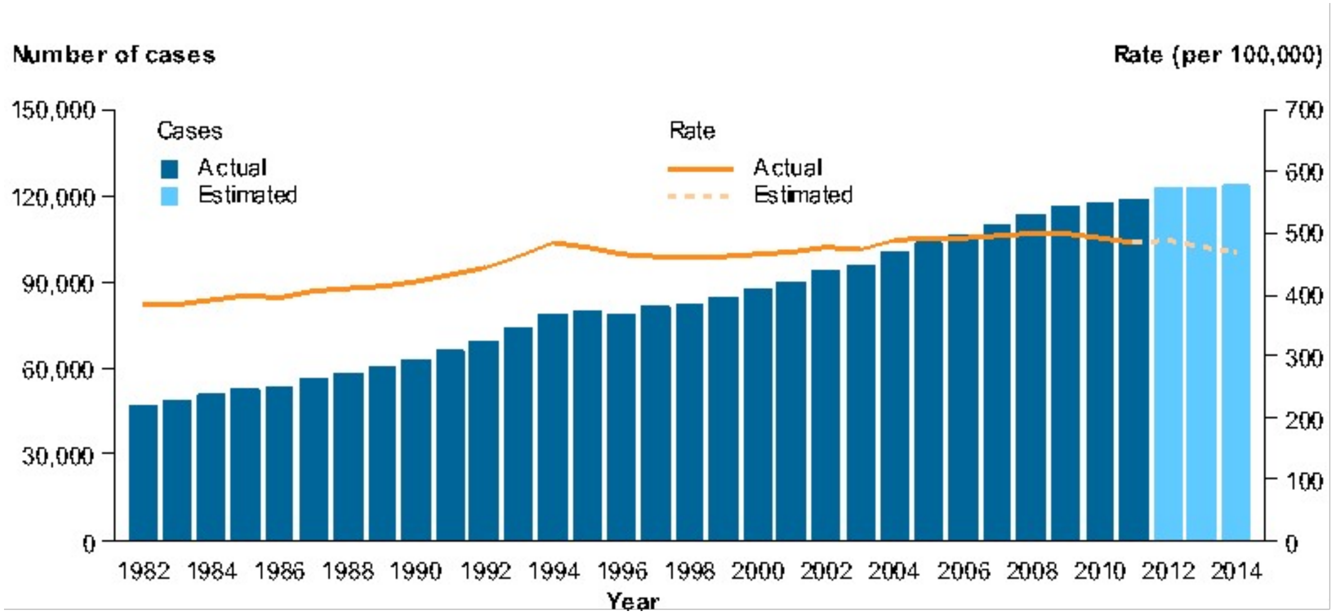
Cancer in Australia: an overview 2014. AIHW 2014

Australian Government
Australian Institute of Health and Welfare

New cancer cases: trend

In 2014, it is estimated that the number of new cancer cases diagnosed will be 2.6 times as high as that in 1982.

Living longer, improved cardiovascular outcomes



Cancer in Australia: an overview 2014. AIHW 2014

CANCER IN AUSTRALIA *in brief* 2014

How cancer is treated

- 5 year survival 67% achieved for all cancer patients.

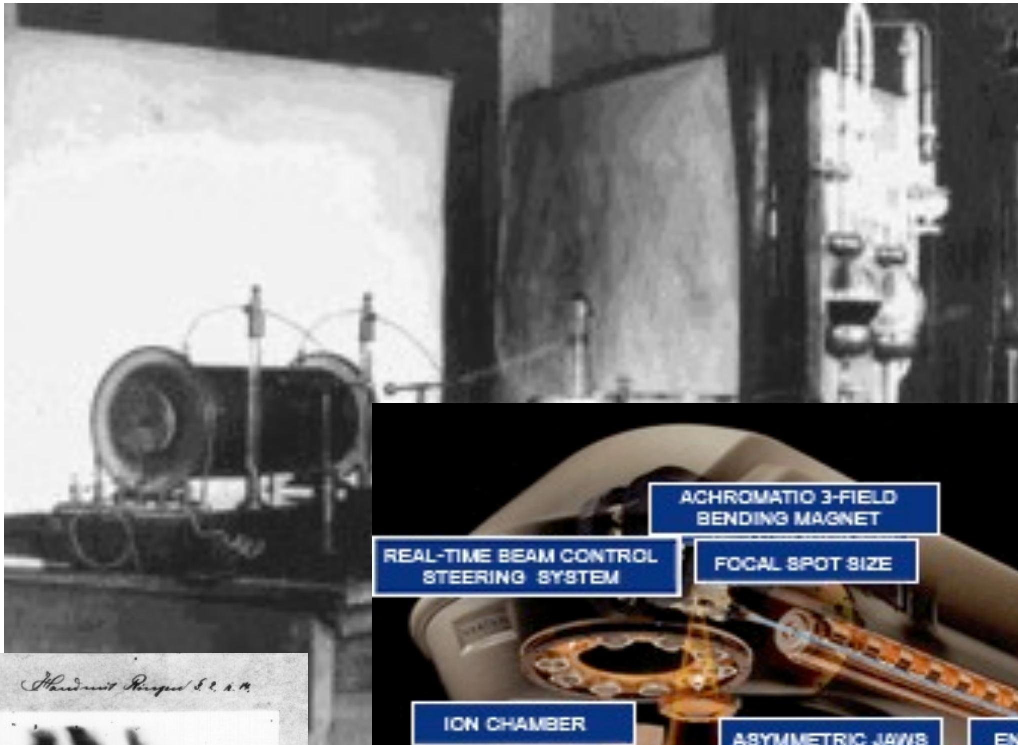
- This is achieved using available therapeutic strategies: radiotherapy, chemotherapy, surgery, immunotherapy, hormone therapy, bone marrow transplants, other….
  - *Disease type*
  - *Localized or Systemic*

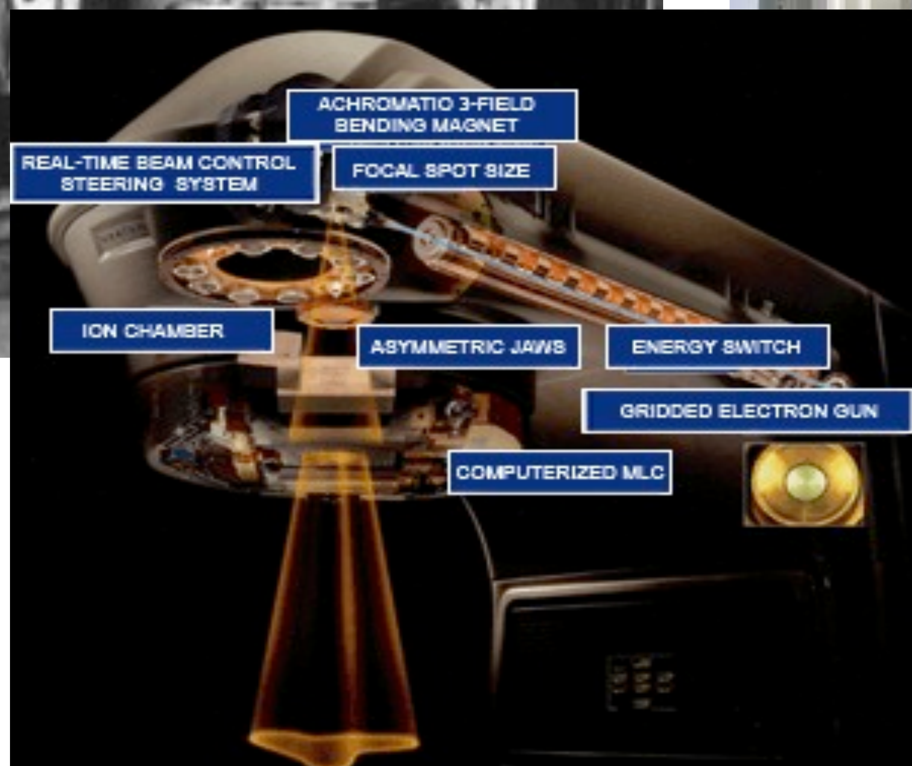
- Disease is well-localized in ~2/3 of patients at time of diagnosis.

- 50% of (USA) cancer patients receive radiation treatment for localized disease sites, most with external beam.

External Beam Radiation Therapy

Predominantly targeted x-rays generated by medical accelerators



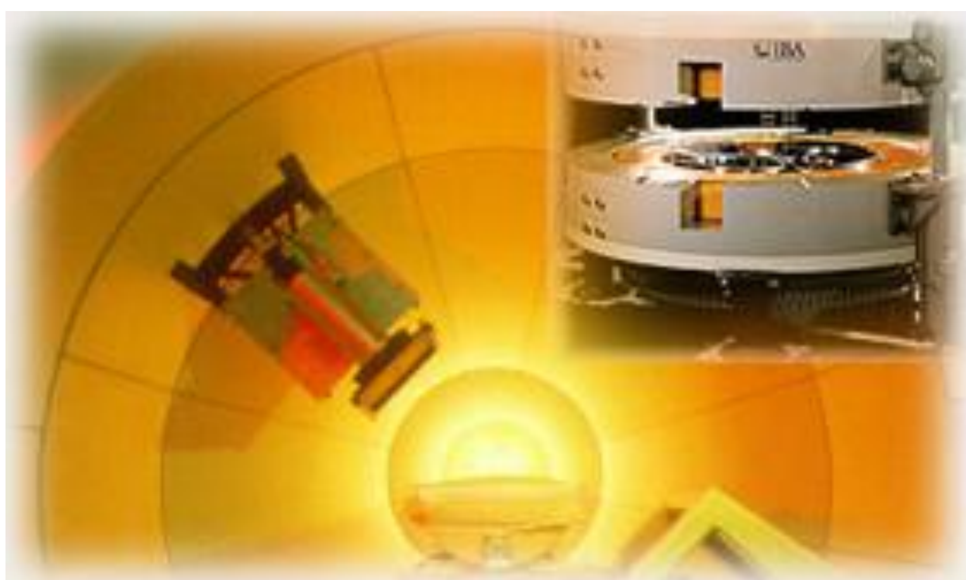


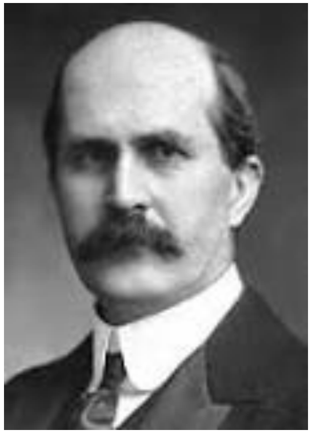
- Proton therapy is also a type of external beam radiation therapy

- Widely recognized as the *most* effective external beam method in the selective destruction of cancer cells.

  Because…….

- The goal in radiation therapy is to deliver lethal doses to the tumor while minimizing or eliminating normal tissue injury.



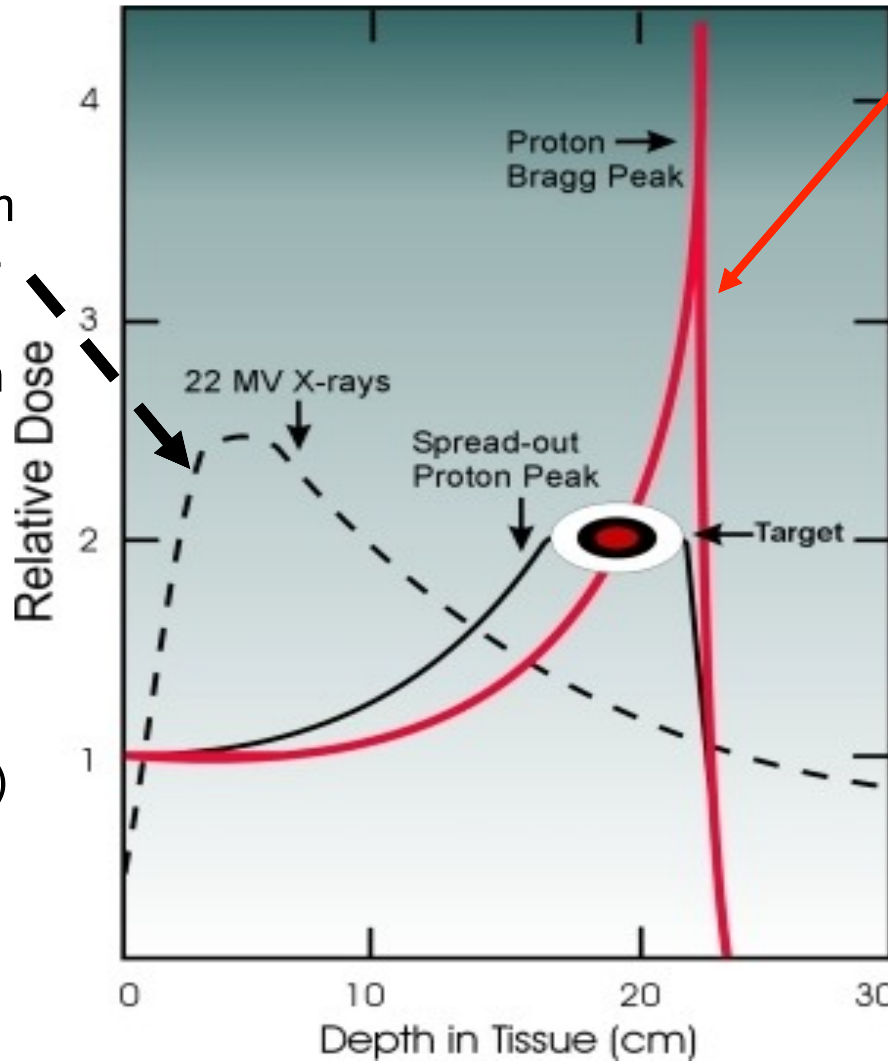


Proton Therapy: *Fundamental Nuclear Physics*

Bragg Peak discovered 1904 in Adelaide!

Conventional beam therapy delivers X-ray radiation along entire path through patient, and maximal dose in front of the tumor

Photons interact with matter (tissue) via photoelecric effect, Compton scattering, pair production



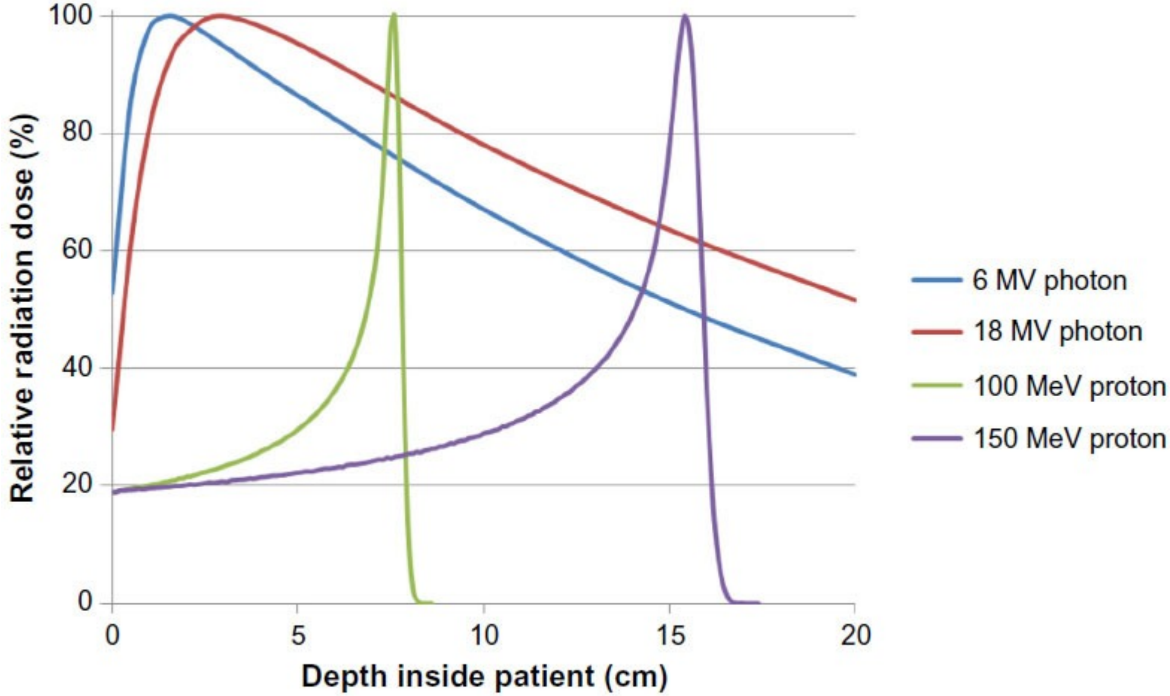
Proton beam treatments deliver minimal dose in front of of the tumor, over 4 times higher dose to the tumor region, and *no dose* behind it

Proton ionization energy deposition

$dE/dx \sim 1/(\beta c)^2$

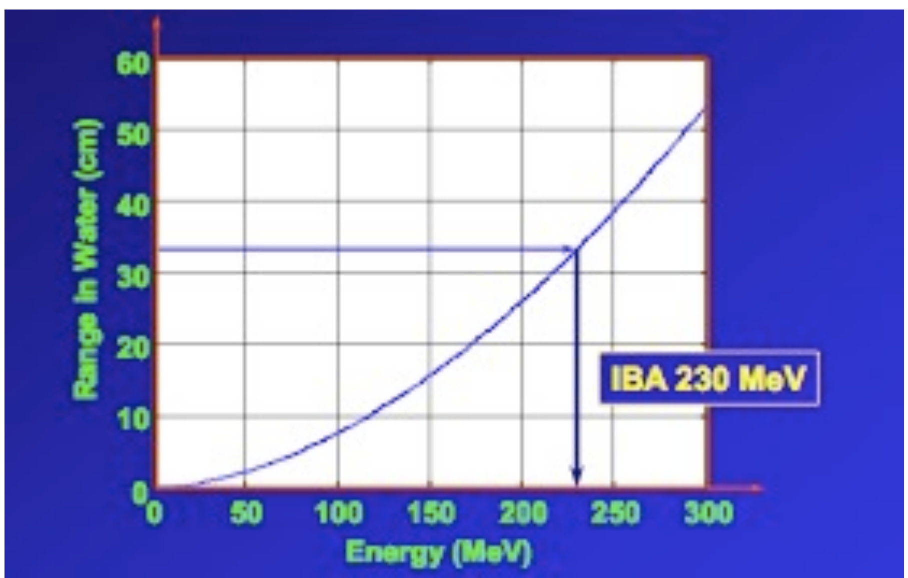
is inversely proportional to the square of the speed of the particle (Bethe-Bloch)

Tumor Site Location



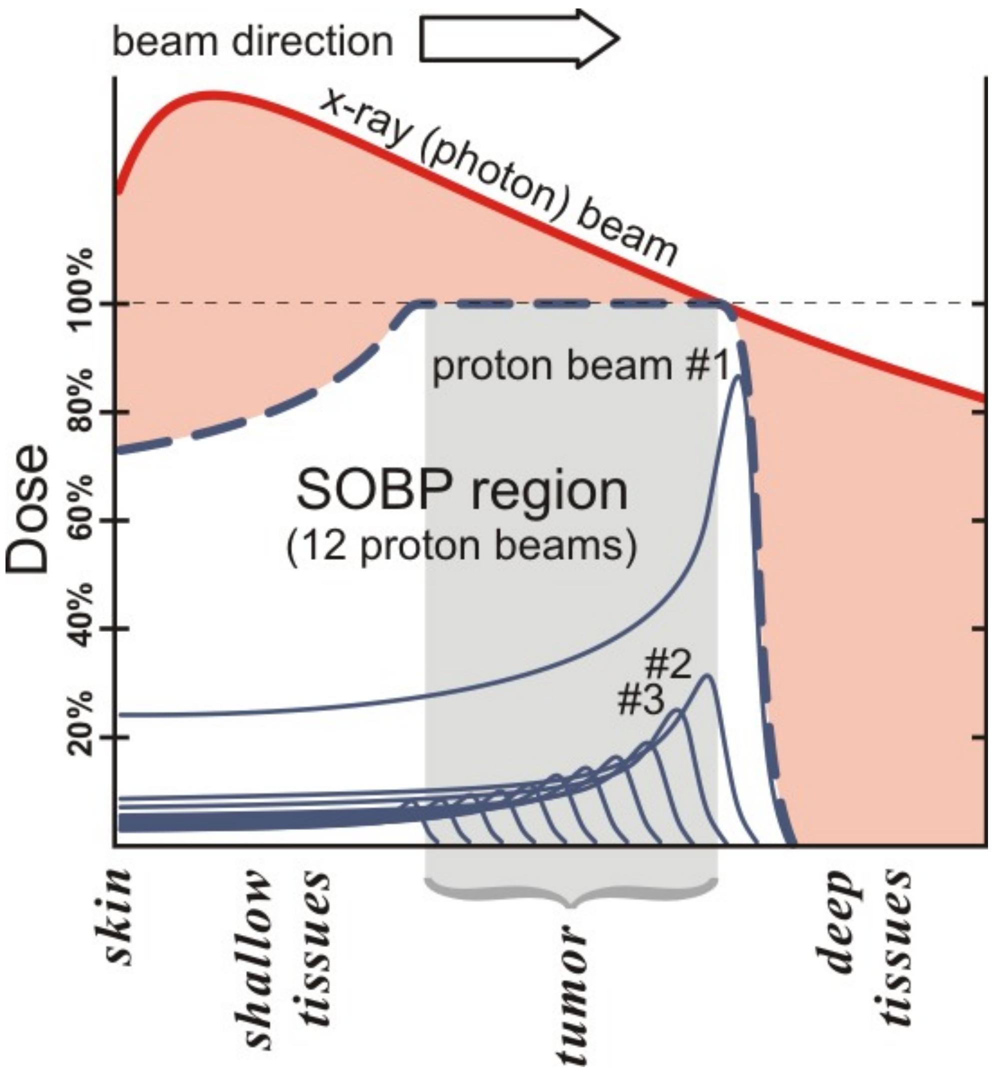
Proton treatment dose depth can be controlled by energy tuning

Higher energy = increased depth in patient



~230 MeV is the needed energy

Tumor Size



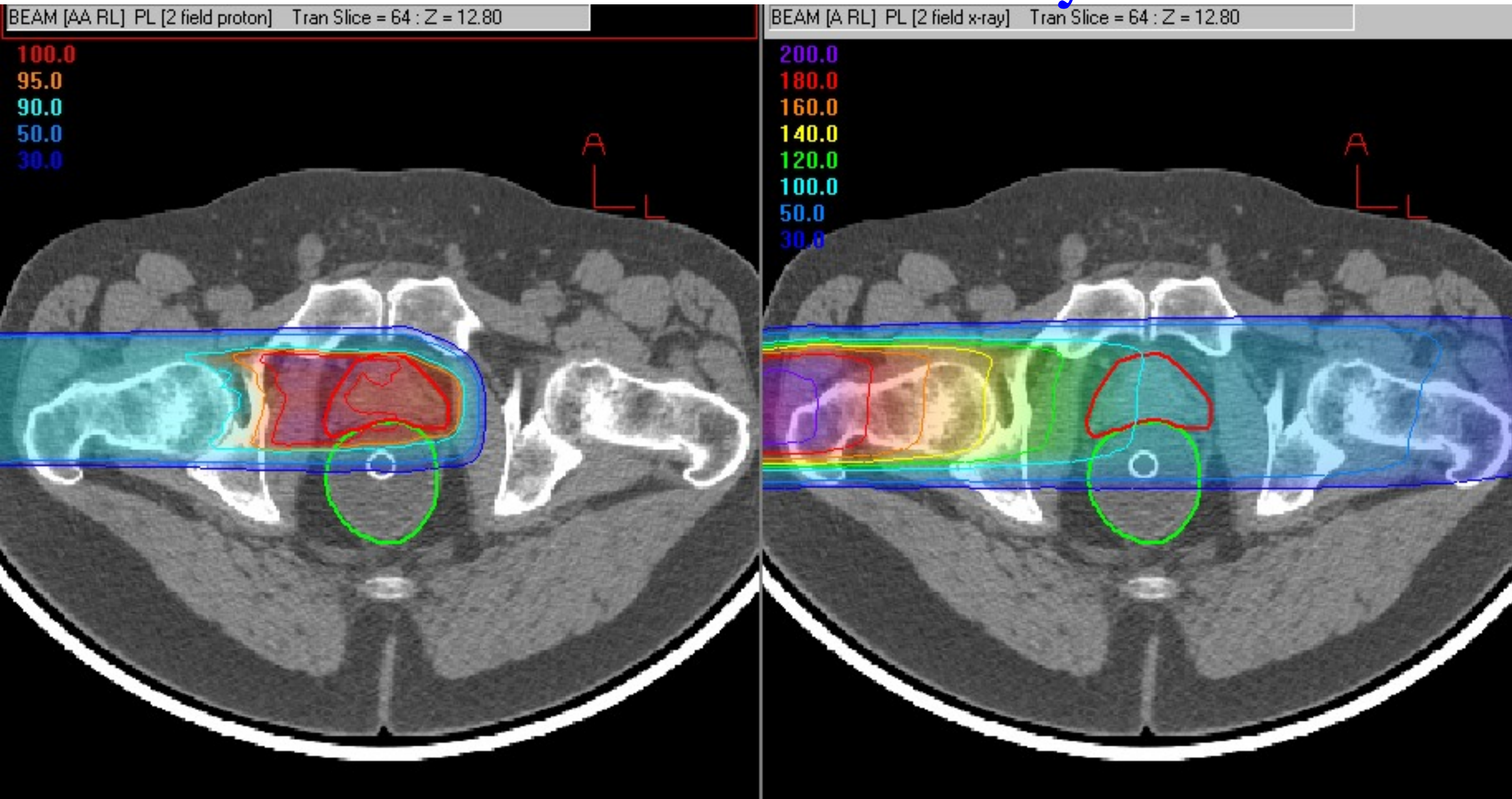
Create "Spread-Out Bragg Peak" (SOBP)

- Multiple energy beams of differing intensity
- Create needed region of constant dose
- Or…"Intensity-Modulated Proton Therapy" – vary dose across treatment volume

Bragg Peak translates to:

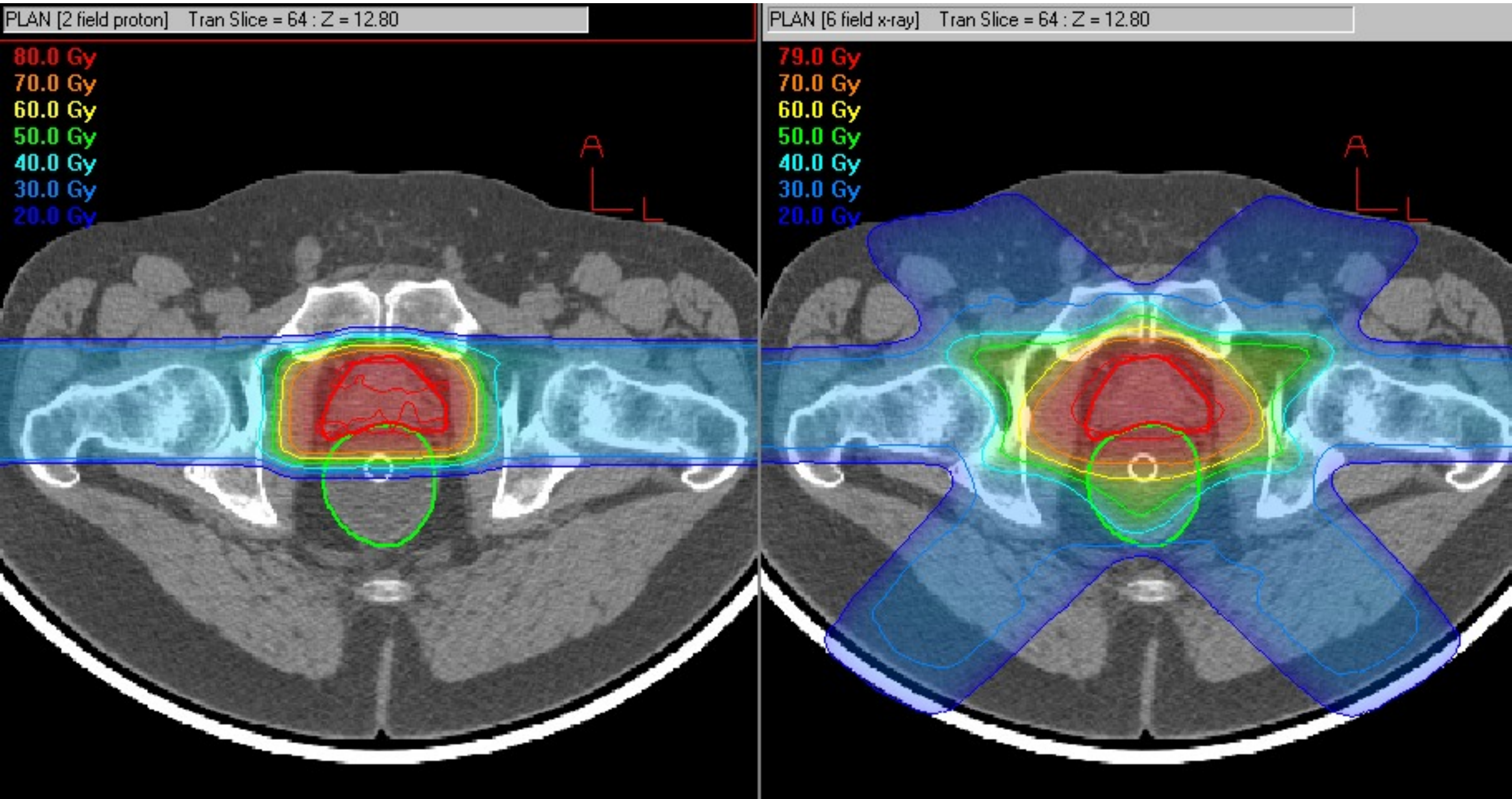
- Minimal proximal dose
- No distal dose
- Optimized dose to tumor

Proton Beam **X-Ray Beam**



Proton Beams **X-Ray Beams**

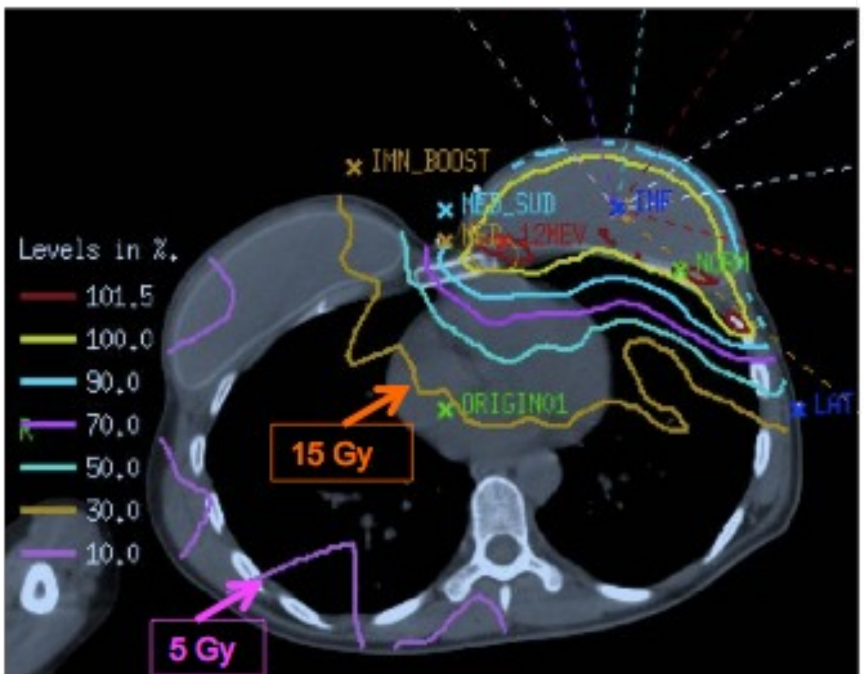
- Lower dose, but to more healthy tissue

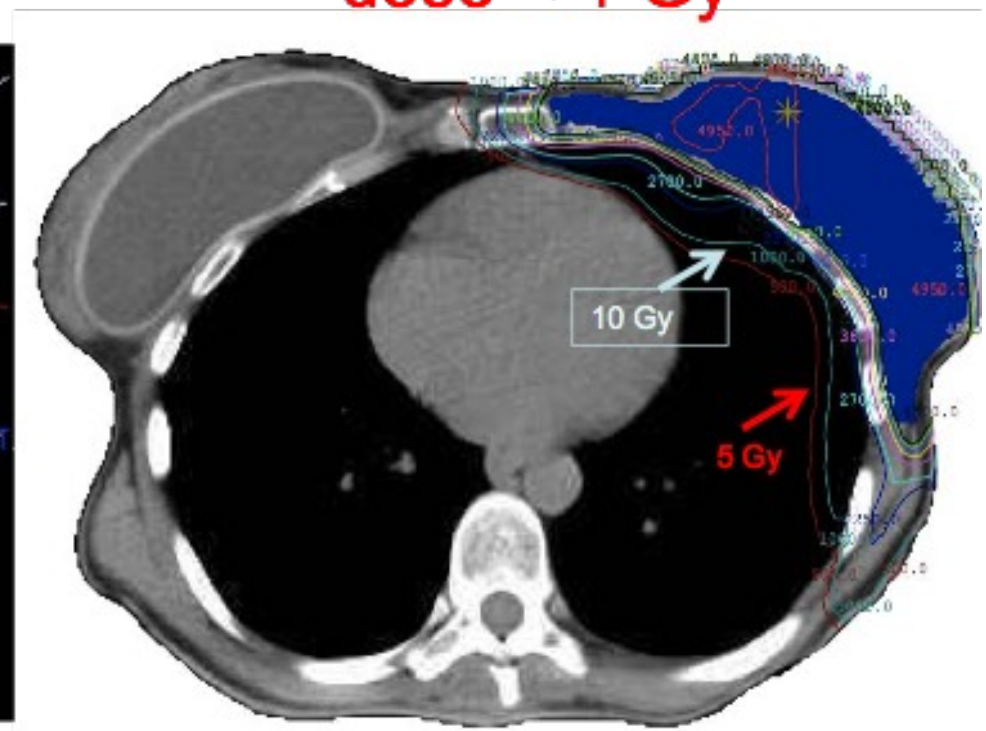


Rationale for Proton Therapy for Breast Cancer
x-rays (IMRT) vs protons

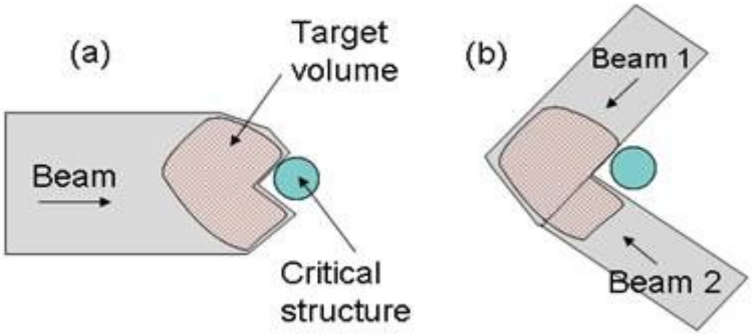
MSK IMRT:
Mean heart dose 6 – 10 Gy

Protons:
Mean heart dose < 1 Gy



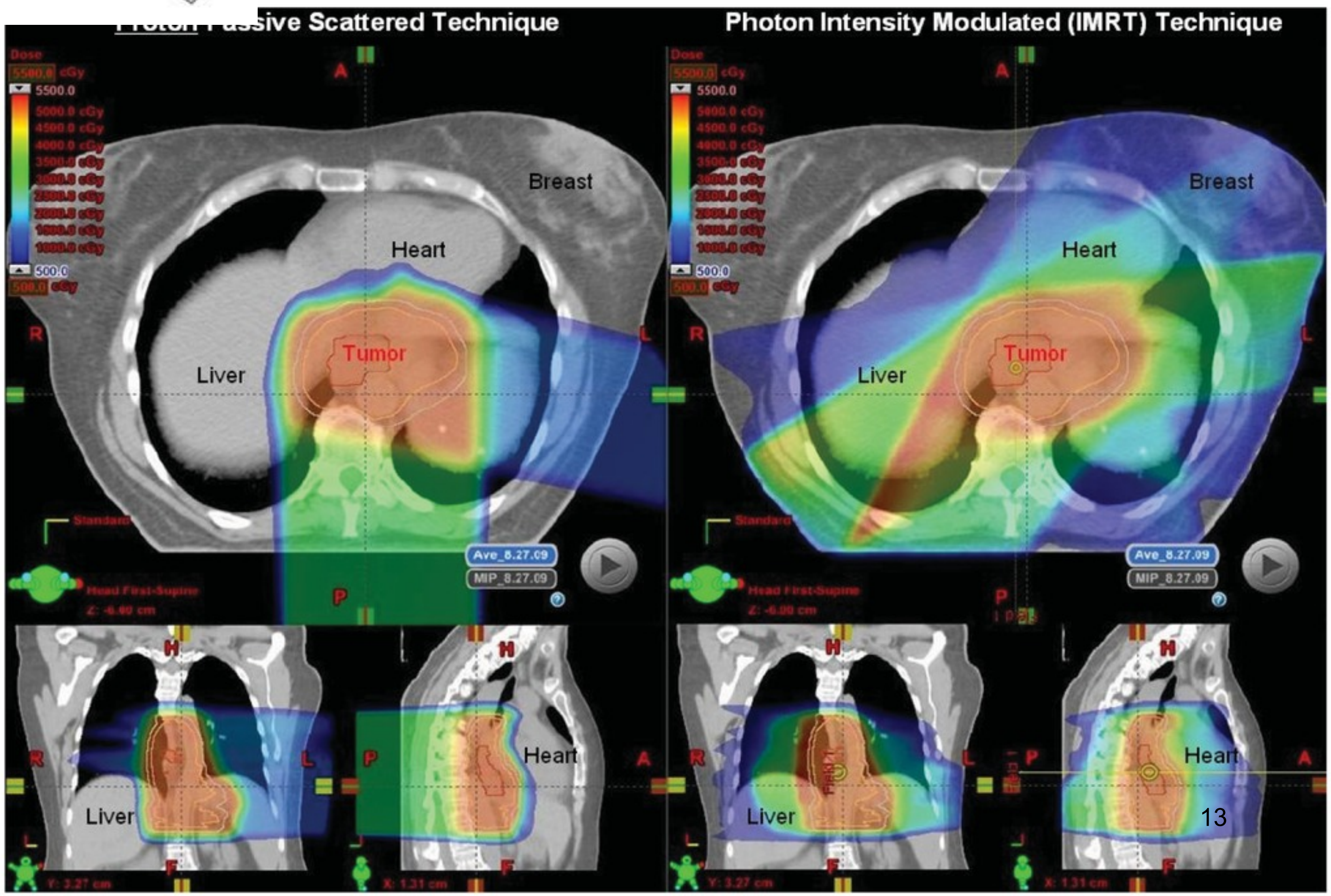


Combinations of Proton Beams

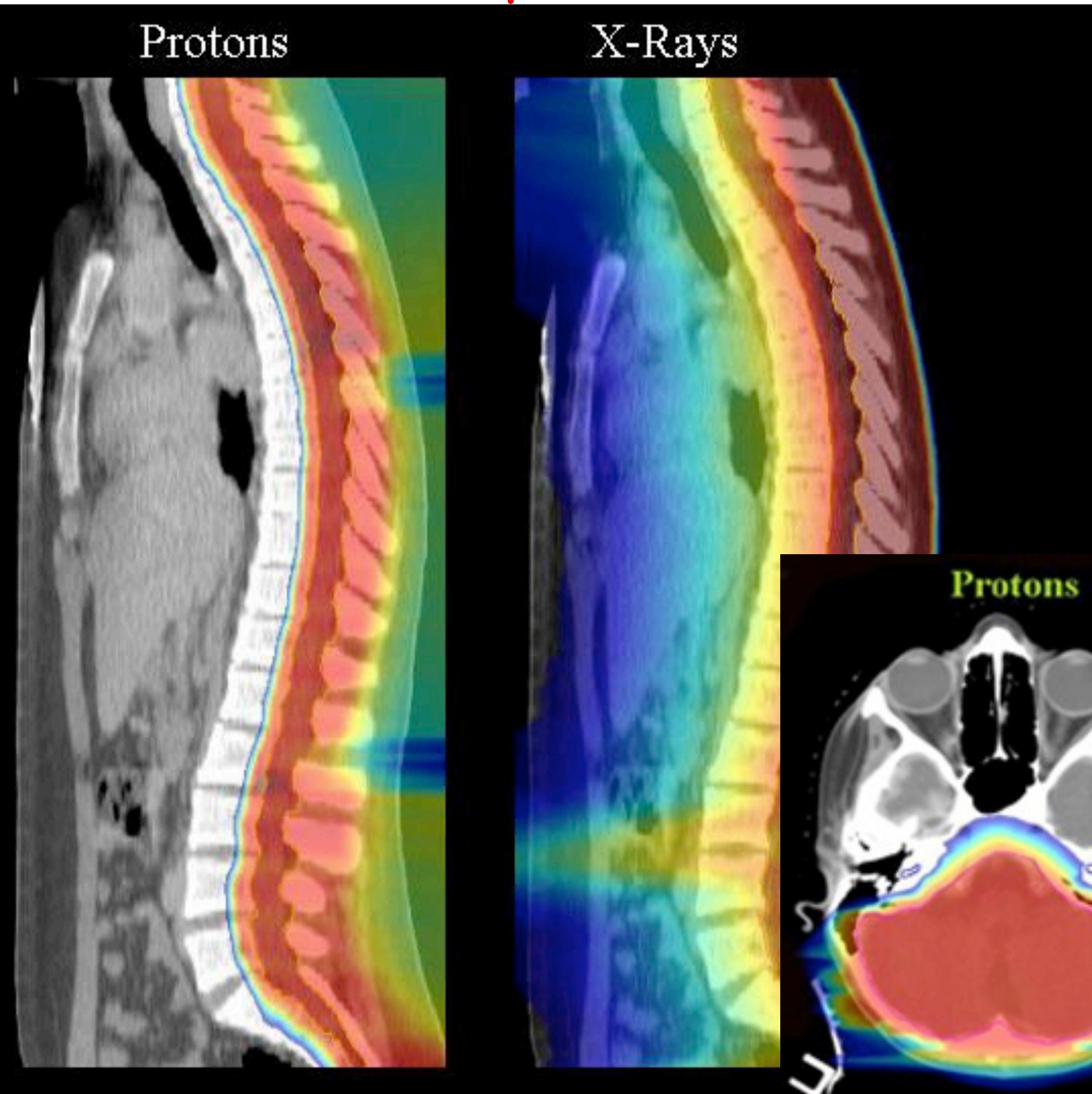


– Can avoid aiming beam at critical structures adjacent to tumors

Example: esophogeal cancer, 5 field x-ray vs. 2 field proton



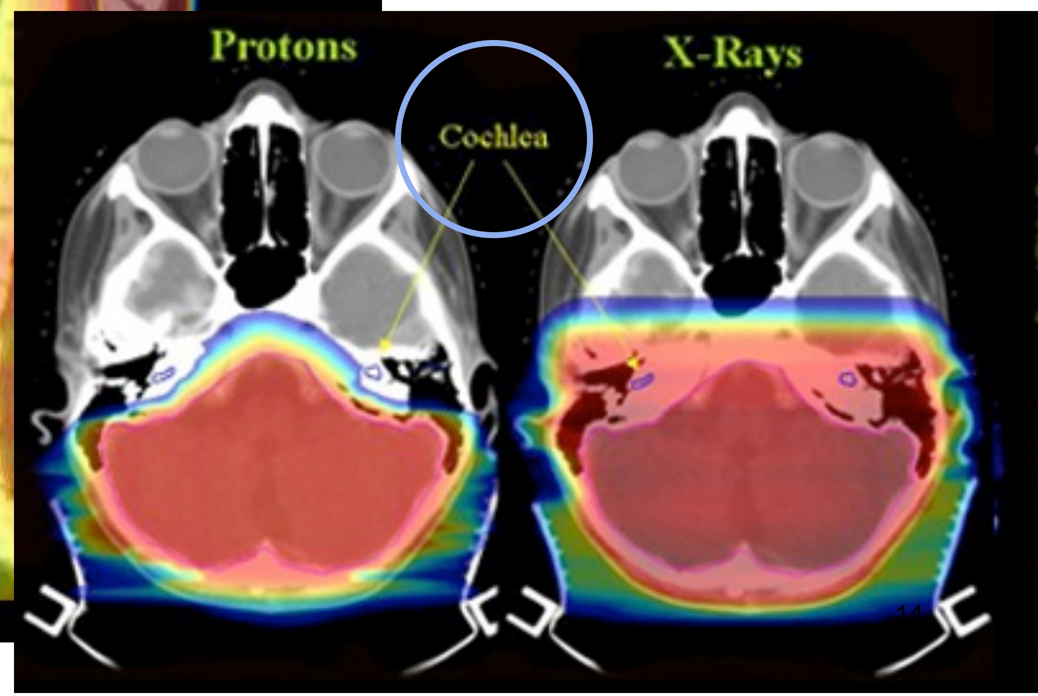
Example…..



Medulloblastoma

Most common malignant brain tumor in children

Spreads to CNS - deliver radiation to the entire neuraxis



Example: Pediatric Brain Tumors

- Low radiation doses can
  - produce decline in memory and intelligence
  - damage the hypothalamus and pituitary gland, effecting production of, for instance, growth hormone
  - play a major role in the development of second, radiation-induced cancers.
- Growing tissues are more likely to experience damage from radiation.

- *Proton radiation spares more normal tissue, and thus may reduce the risk of many complications*

  *- factor of 2-10 in secondary malignancy**

* Paganetti, Athar, Moteabbed, *et al. Phys Med Biol* 2012;57

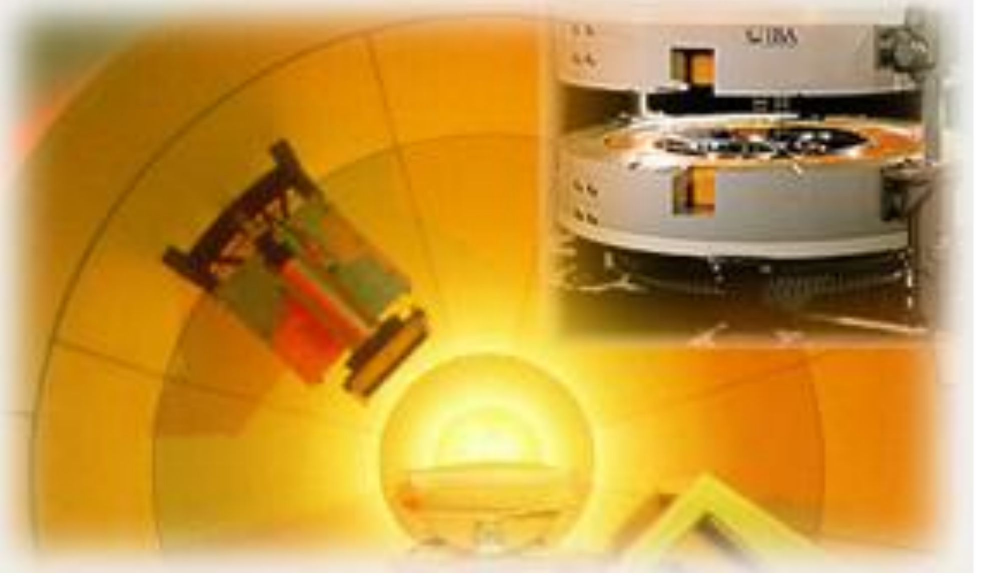
- Proton therapy is a type of external beam radiation therapy

- Widely recognized as the *most* effective external beam method in the selective destruction of cancer cells.

  Because…….

- The goal in radiation therapy is to deliver lethal doses to the tumor while minimizing or eliminating normal tissue injury.

- *Increased dose*
- *Higher relative biological effectiveness*



Dose Escalation Trials Support the Use of Protons for Prostate Cancer

Standard is 65–70

Protons offer better control and lower toxicity than X-Rays

Randomized trial[1-5]	Boost Modality	Planning Technique	High dose arm	5-year control	GI toxicity ≥G2	GI toxicity ≥G3
MD Anderson	X-rays	2-D, 3-D	78.0 Gy	*75%*	*26%*	*7%*
CKVO96-10	X-rays	3-D, IMRT	78.0 Gy	*64%*	*32%*	*5%*
MRC RT01	X-rays	3-D	74.0 Gy	*71%*	*33%*	*10%*
GETUG 06	X-rays	3-D	80.0 Gy	*72%*	*20%*	*6%*
PROG 95-09	Protons	3-D	79.2 Gy	*91%*	*17%*	*1%*

The best outcome for control AND toxicity was achieved using protons

(1) Alan Pollock et al., "Prostate cancer radiation dose response: results of M.D. Anderson Phase III randomized trial," International Journal of Radiation Oncology Biology Physics 53 (2002): 1097-1105. (Note: toxicity updated from Viani et al, ref 6)

(2) ST Peters, WD Heemsbergen, PC Koper et al., "Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy," 24 (2006): 1990-1196.

(3) DP Dearnaley, MR Sydes, JD Graham et al, "Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT101 randomized controlled trial," Lancet Oncology 8 (2007): 475-487.

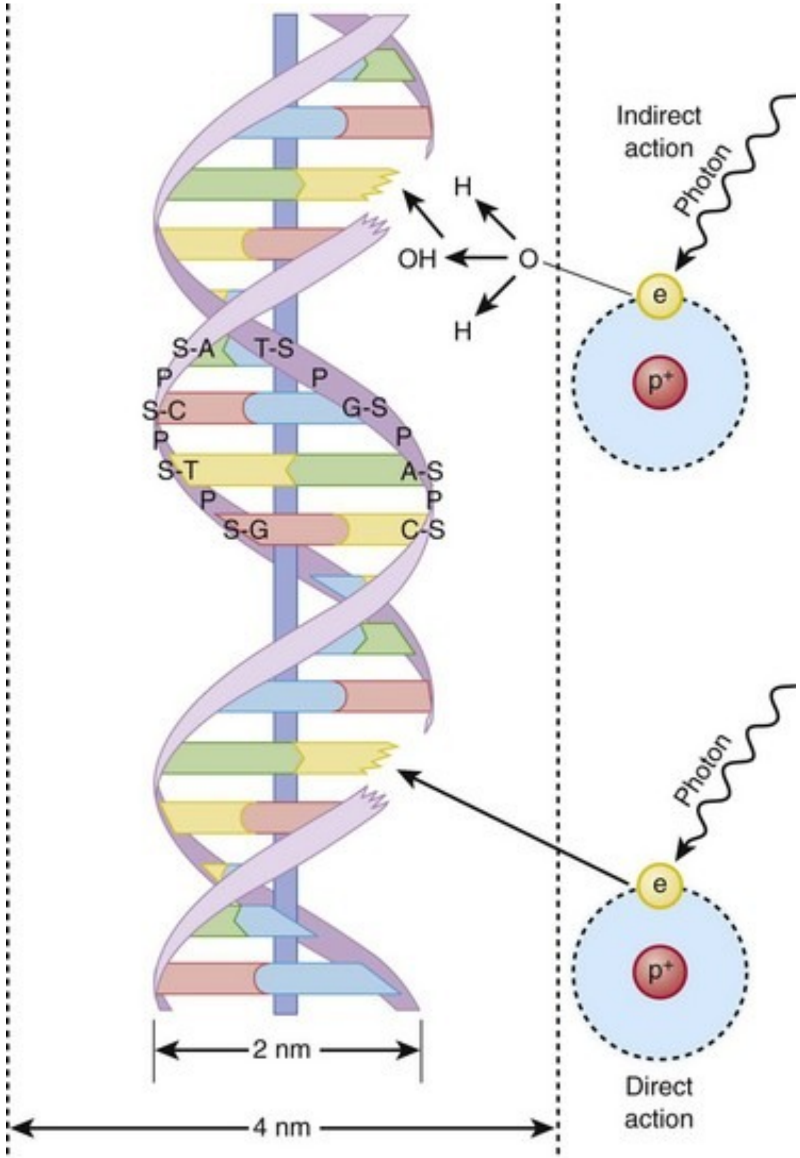
(4) Anthony L. Zietman, "Correction: Inaccurate analysis and results in a Study of Radiation Therapy in Adenocarcinoma of the Prostate," JAMA 299 No. 8 (2008): 898-900. Anthony L. Zietman et al., "Comparison of Conventional-Dose vs. High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate. A Randomized Controlled Trial," JAMA 299 No. 10 (2008): 899-900.

(5) Veronique Beckendorf et al. "70 Gy vs. 80 Gy in localized prostate cancer: 5 year results of GETUG 06 randomized trial," Int J Radiat Oncol Biol Phys (2011) *epublication*

(6) Viani GA et al. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. Int J Radiat Oncol Biol Phys. 2009 Aug 1;74(5):1405-18.

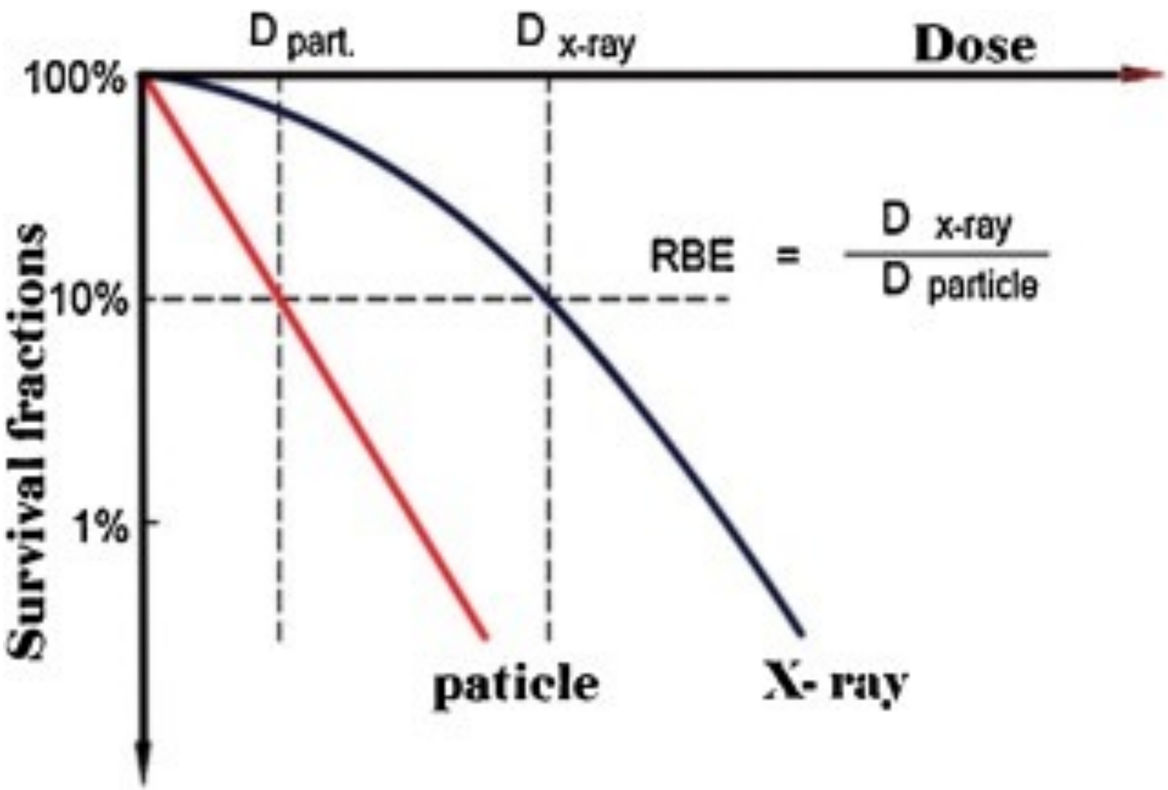
Note: Control rates are measured using the ASTRO definition, except for MRC RT01 which uses the Phoenix definition

Higher "RBE"



- Radiation therapy works by damaging the DNA of cells.
- Double and single strand DNA breaks in sugar-phosphate backbone
- Ionizing radiation ejects an electron from a target molecule - *directly or indirectly*
- Indirect ionization happens as a result of the ionization of water, forming free (hydroxyl) radicals which then damage the DNA - dominant mechanism in x-ray treatments
- Direct (protons) vs. Indirect (photons) injury - different *relative biological effectiveness* (RBE - protons higher)

Particles have enhanced tumor killing power - even for SAME dose



Particles could be protons or other ions

Proton RBE = 1.1: 10% higher than X-rays

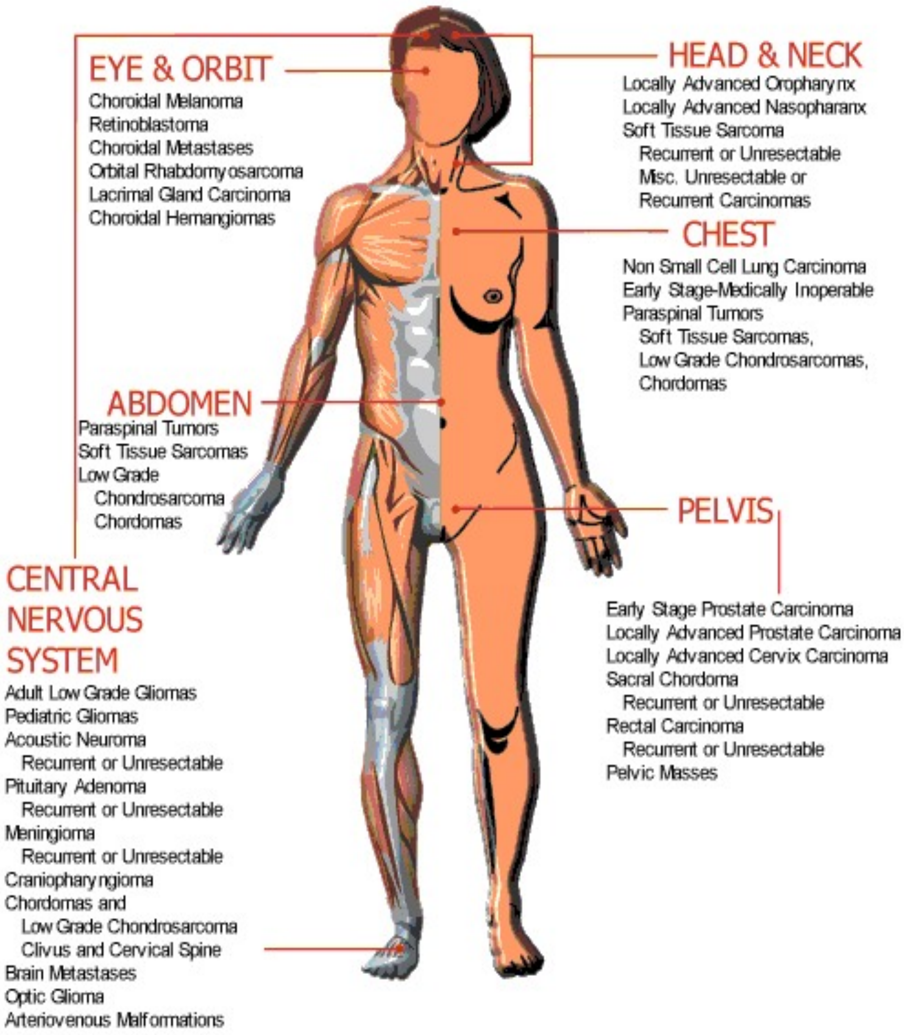
Heavier ions have even higher RBE – factors of 2-4

Advantages of Irradiation with Protons

- Deliver *minimal* dose *in front* of the tumor
- *Deliver* *maximum dose* to the *tumor region*
- *NO DOSE behind* the tumor
- **Protons destroy tumor more effectively** - higher RBE

Many cancers treatable

- More than 137,000 (175,000+) patients were been treated with particle therapy worldwide from 1954 to 2014 (2016).
- 86% were treated with protons and 14% with carbon ions and other particles.
- About 10% of patients are pediatric.



Proton and Particle Therapy in the World

49 particle therapy facilities worldwide

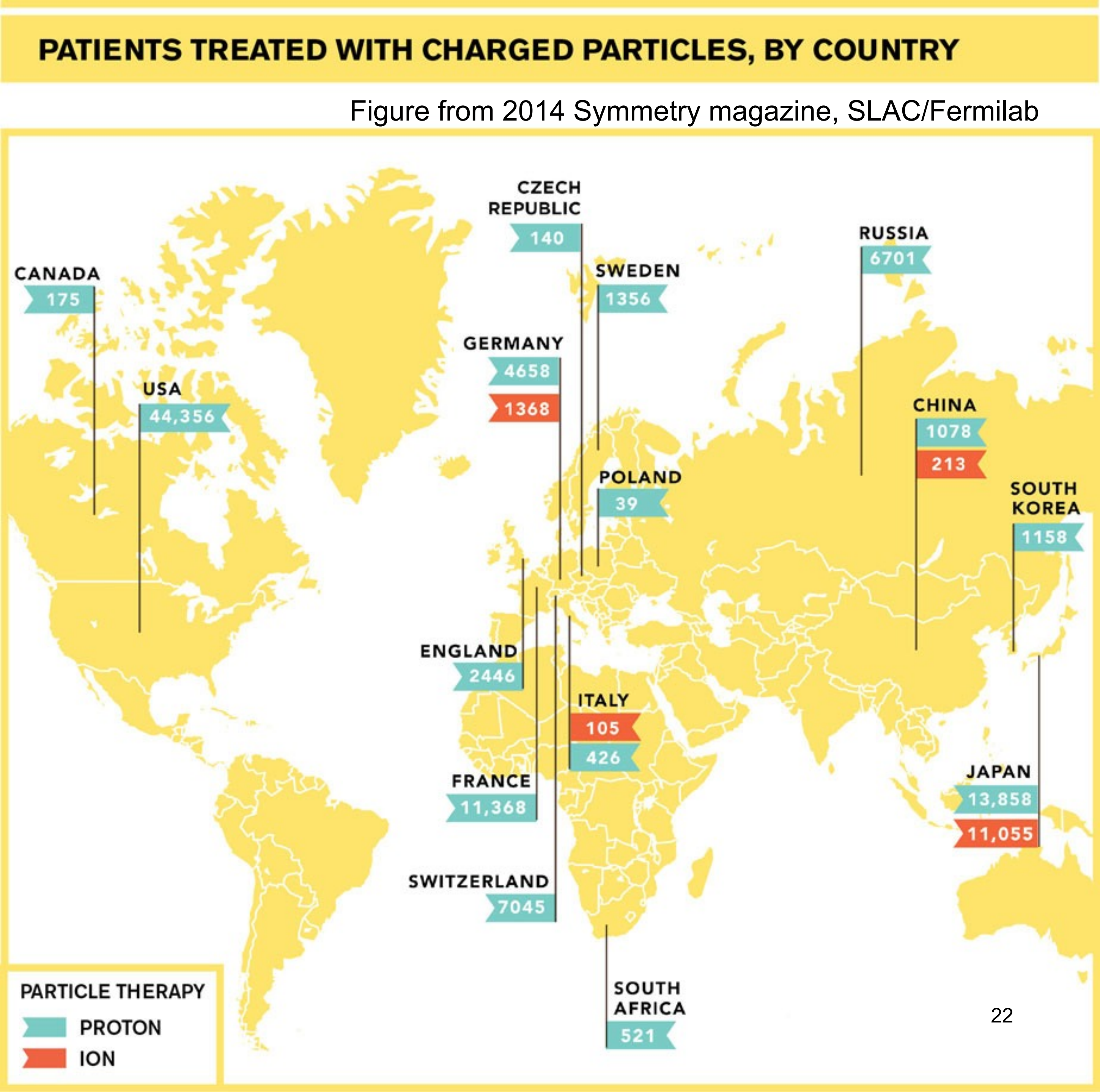
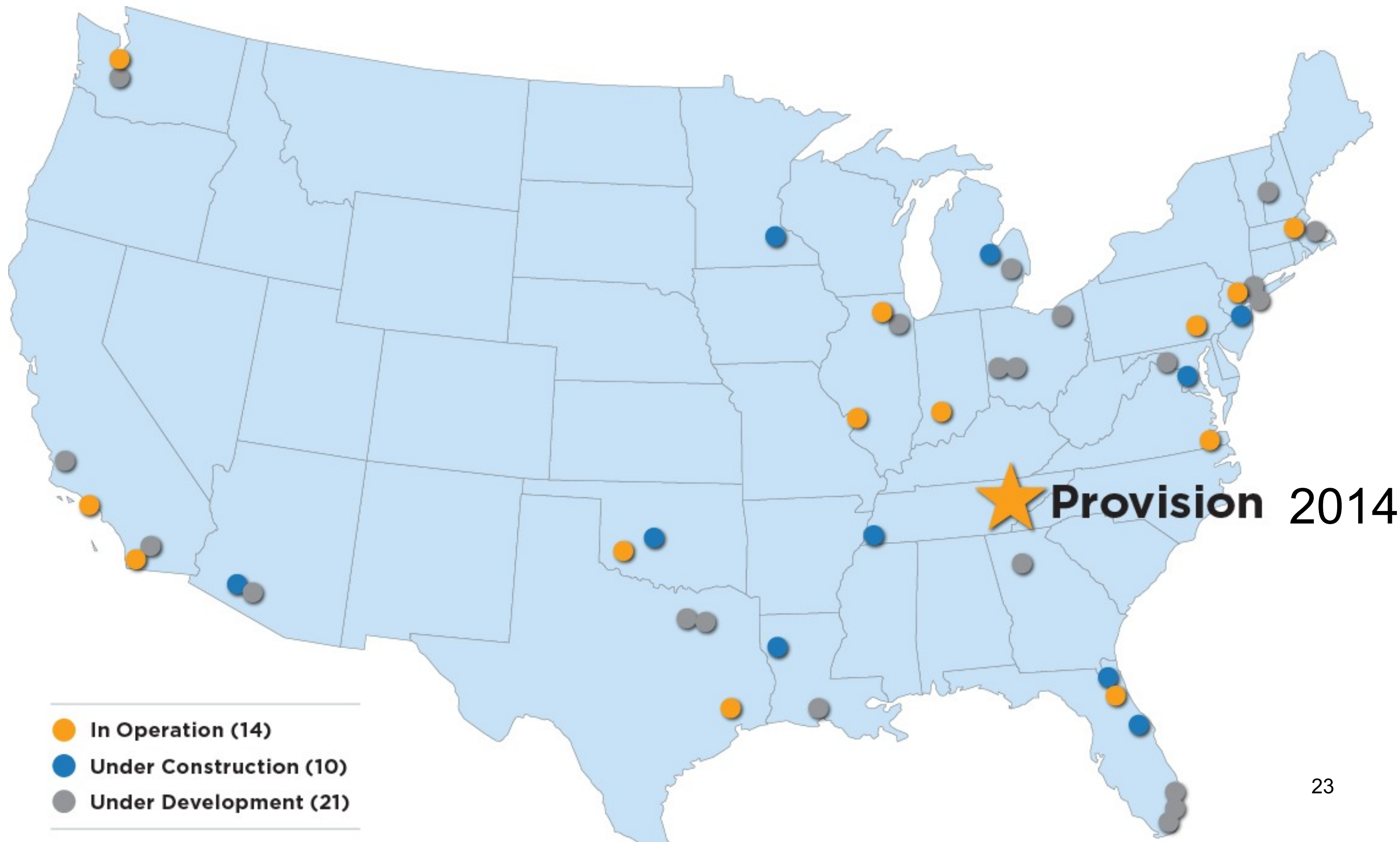


Figure from 2014 Symmetry magazine, SLAC/Fermilab

Proton Therapy in the USA – 19 centers,

- compare to 1 X-ray center for every ~250,000 people, ~1,500 treatment rooms



The global proton therapy market eclipsed the billion-dollar mark for sales orders in 2015

- more than double the 2014 total*

11 new centers started construction in 2016

- eight in the United States
- three in Hong Kong, Belgium and the Netherlands

Introduction of compact proton therapy systems

- can be order of magnitude less expensive

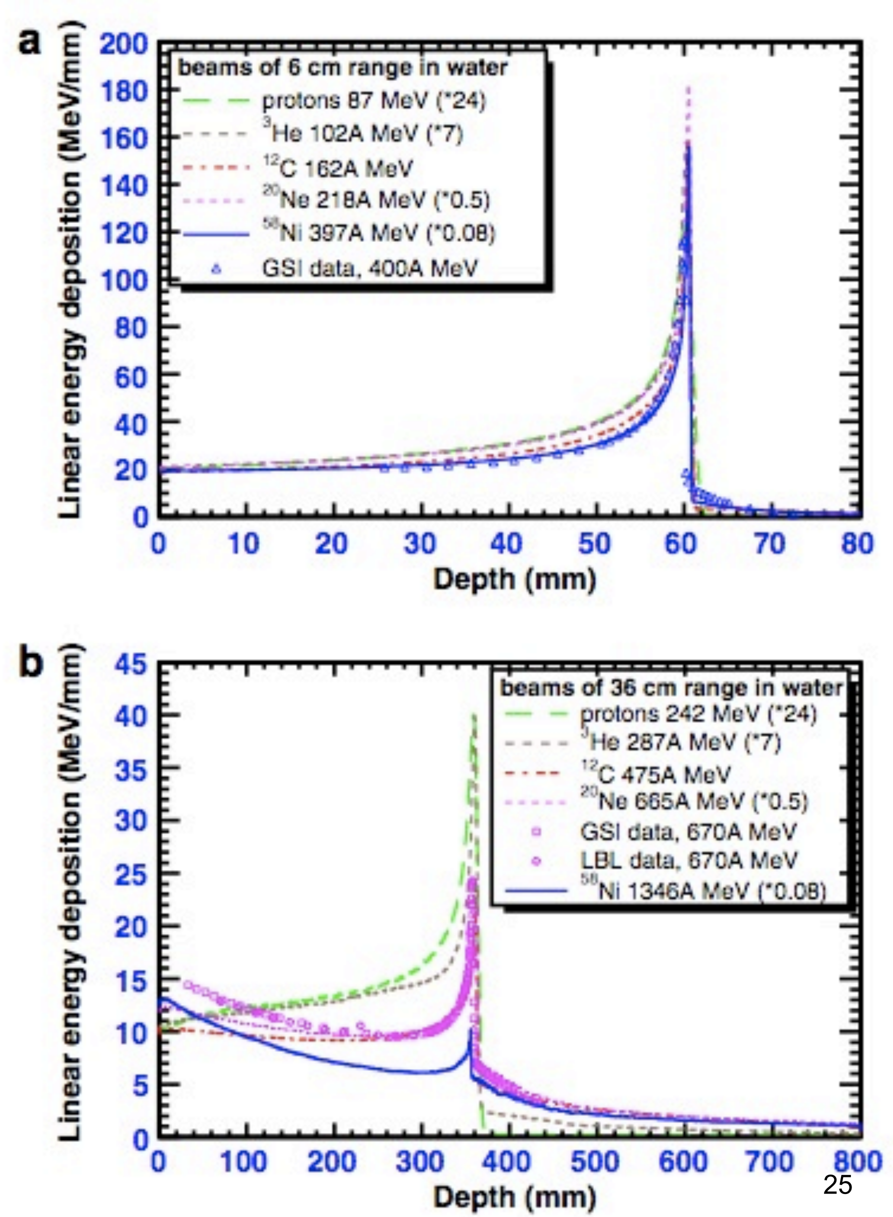
* Data from market intelligence firm Medraysintell

(Carbon) Ion Therapy

- Heavier particles have a higher RBE, making them more effective at treating tumors with an anoxic core
- Example: renal-cell carcinoma - a notoriously radioresistant tumour for which there had been few reports of curative radiotherapy
- Few carbon-beam facilities in the world, 2 in Japan (HIMAC, HIBMC), 3 in Germany (GSI, Marburg, Heidelberg), 1 in China (Shanghai), 1 in Italy (Pavia) - more to come?

But….

- At high energies, nuclear fragmentation plays increasing role with heavier ions - secondary particle tail
- RBE higher for proximal dose as well



I. Pshenichnov et al. / Nucl. Instr. and Meth. in Phys. Res. B 266 (2008) 1094–1098

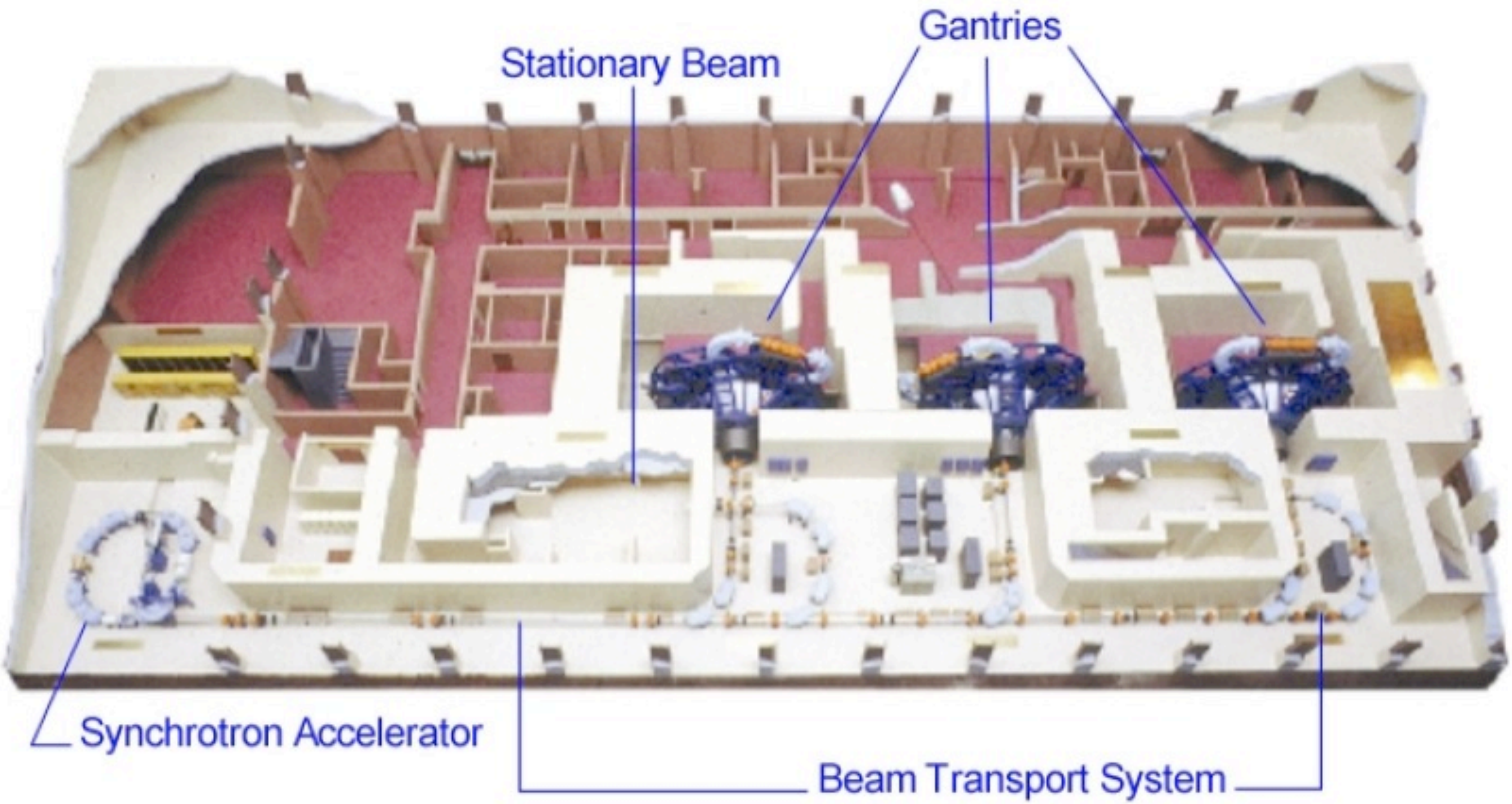
Also even more costly, complicated equipment….

Heidelberg treatment gantry

CNAO accelerator

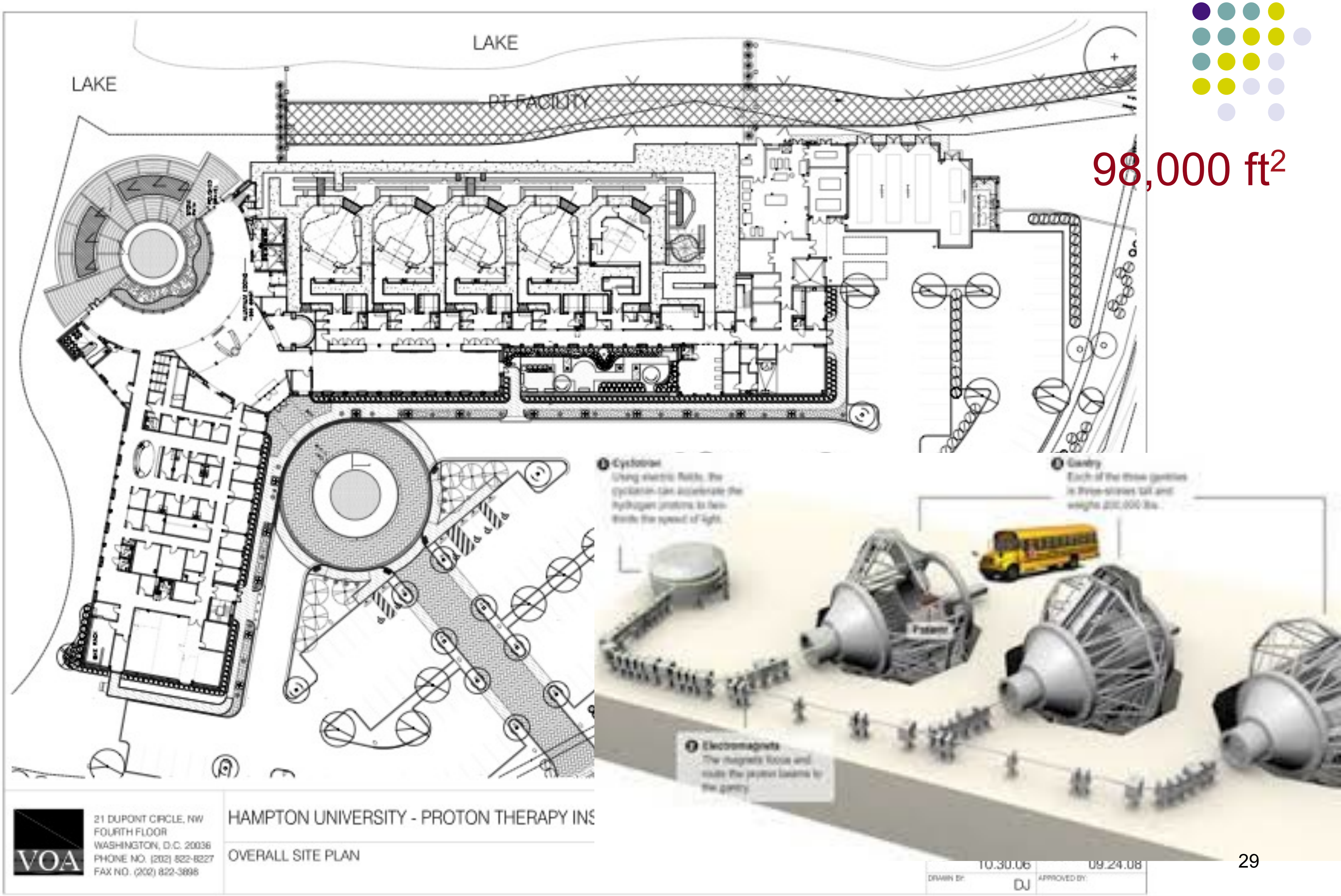
Typical Center Design

LLUMC



LLUM

Hampton University Proton Therapy Institute



98,000 ft^2

Follow the patient experience….

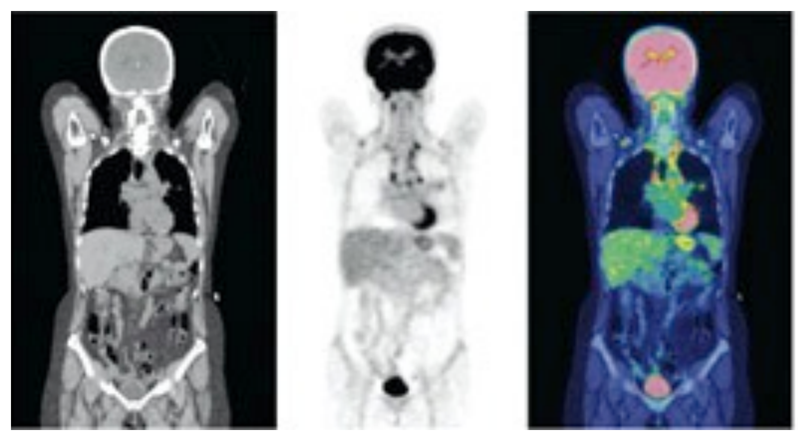
- To assure both treatment and simulation imaging in same position, with no motion, the patient must be immobilized during imaging and treatment.
- The patient lies in a mold lined with plastic and insulating material to have foam placed, in a conformable form, or in an evacuable beanbag.
- Patients who will be treated in the head or neck area are immobilized using lightweight plastic masks which, upon heating, mold to the patient's face, head, and neck.

Patient Experience

- (MRI or PET)/CT scans are performed.
- The patient lies in the custom immobilization device.
- The CT scan creates several high-resolution images to provide accurate information about the patient's anatomy, tumor location and geometry, and tissue density.
- CT images of the tumor and surrounding areas are used to:

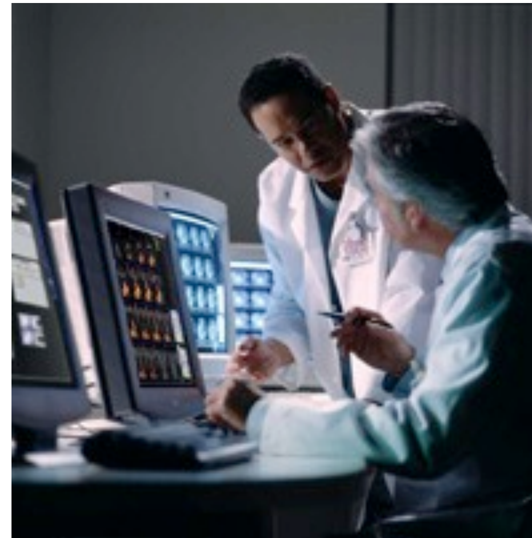
  -design the radiation therapy plan

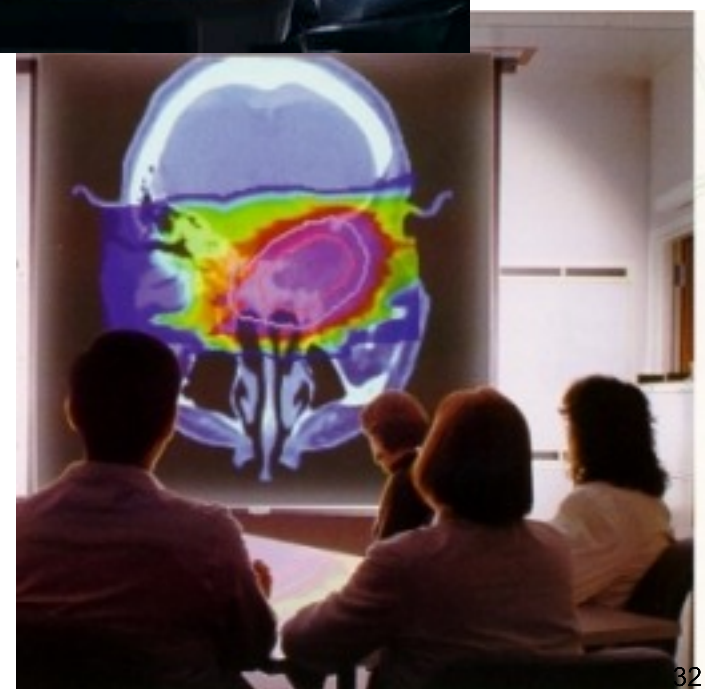
  -align the patient during each treatment



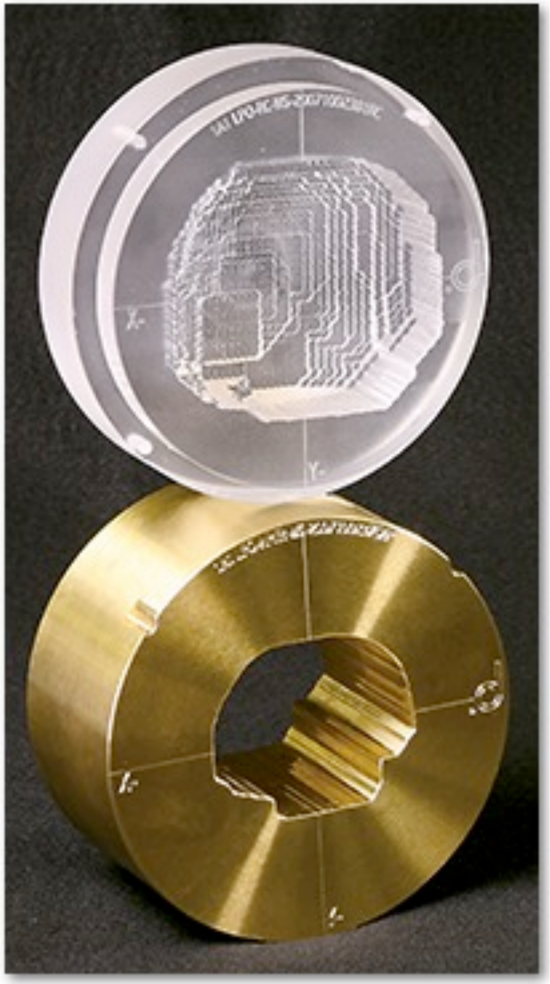
Patient Experience

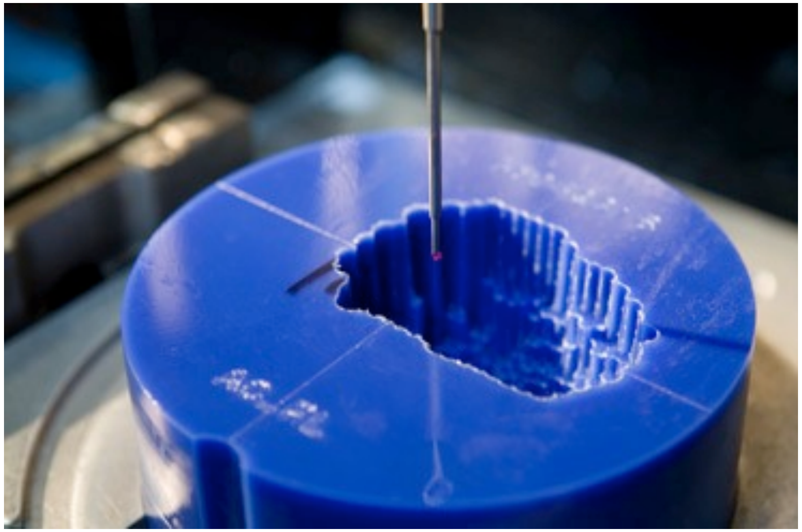
- The CT images are studied by a physician, a medical physicist, and a dosimetrist on a treatment planning computer workstation.
- The tumor and critical structures are outlined using the computer, and the physician selects radiation fields which will minimize the dose to critical structures and normal tissue and maximize the dose to the target.
- The completed and approved plan is used to generate the treatment prescription (target angle, proton beam energy, dose per treatment, etc.)



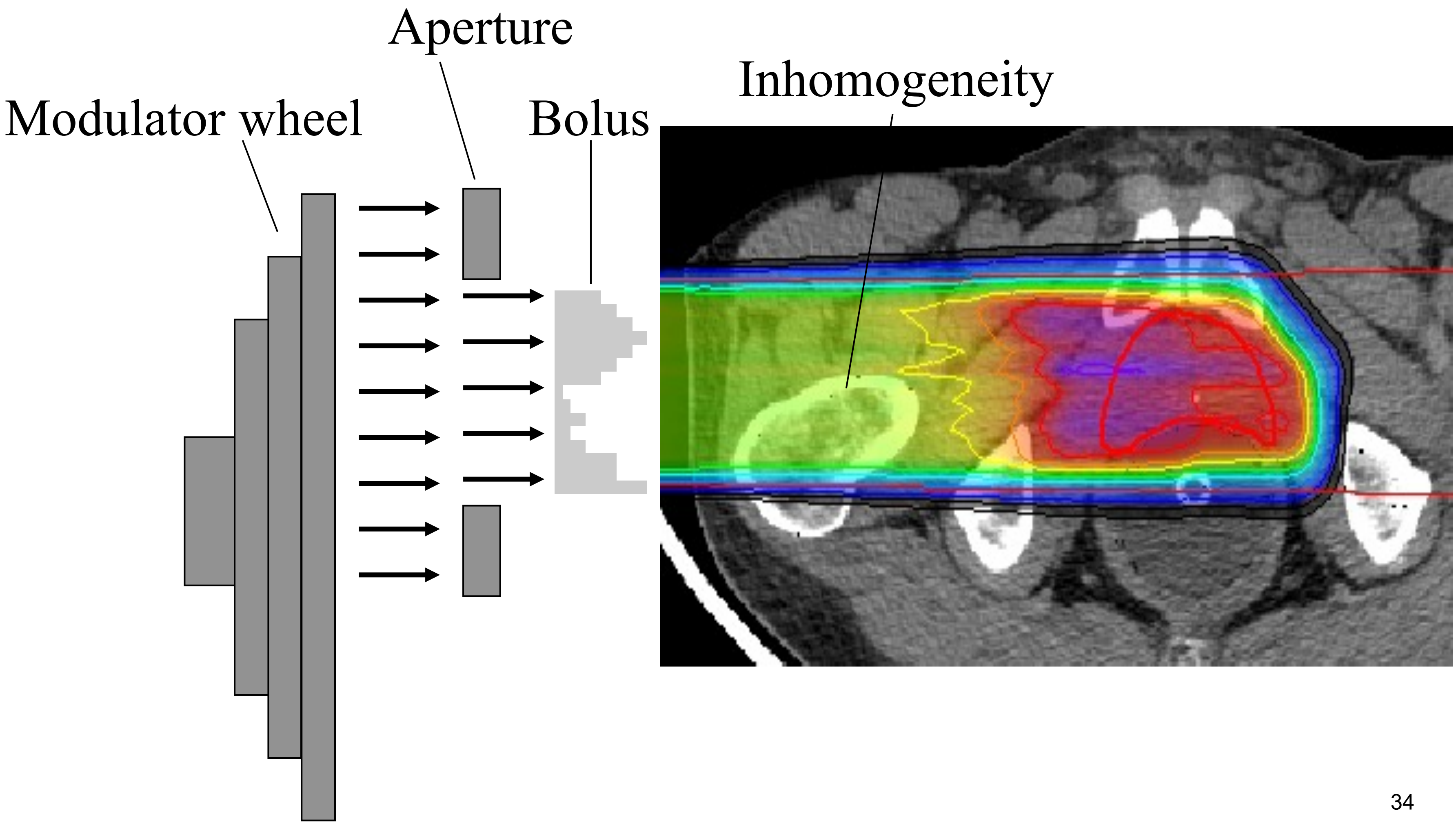


- In the treatment planning process, digital files representing three-dimensional images of the tumor are generated
- The digitized three-dimensional images are sent to specialized machinery to mill customized boluses from high-grade wax or plastic and customized apertures from brass
- The aperture and bolus are placed in the beam line to help conform the proton beam to the shape of the tumor.

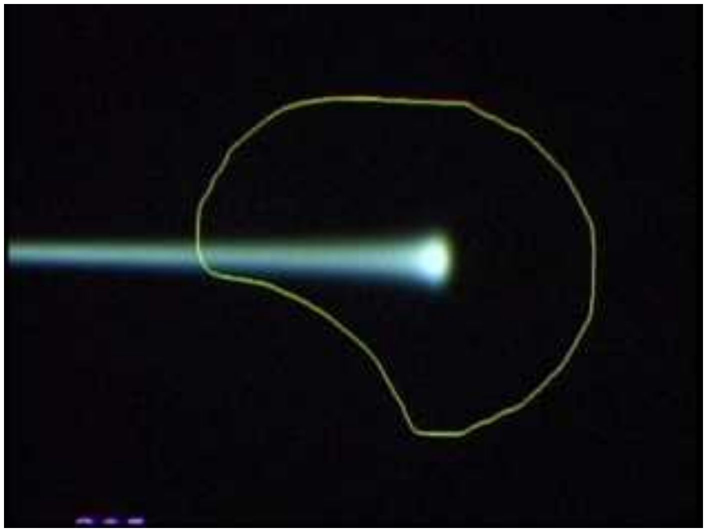




Proton Beam Design

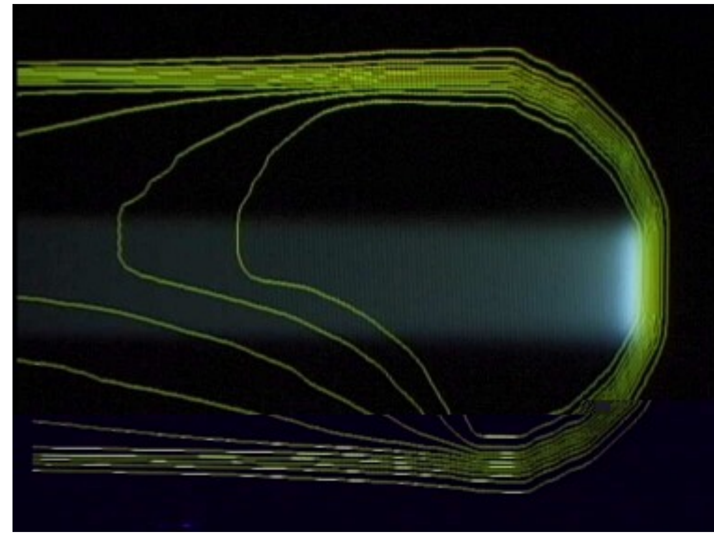


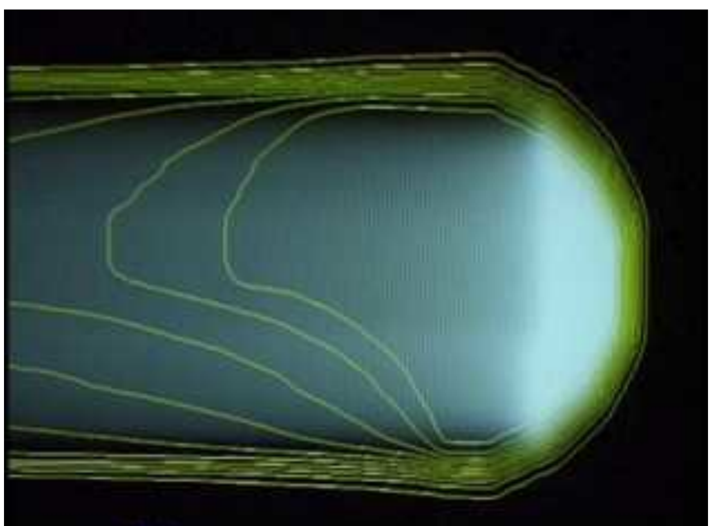
Alternatively.... Spot/Pencil Beam (raster) Scanning



One spot

... a few spots

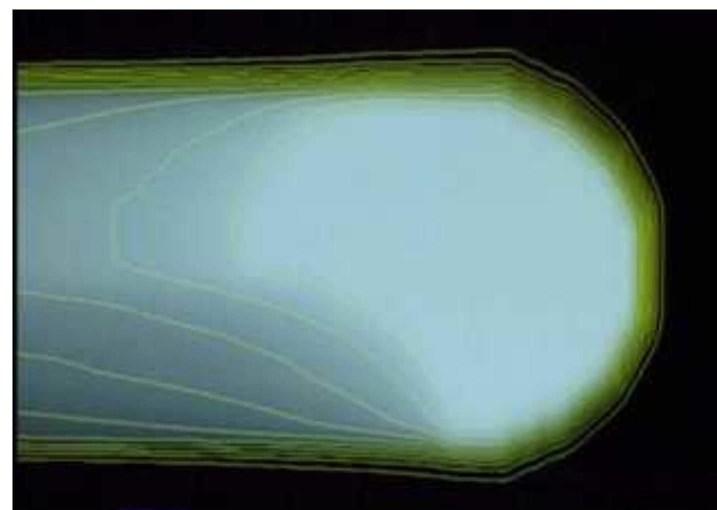




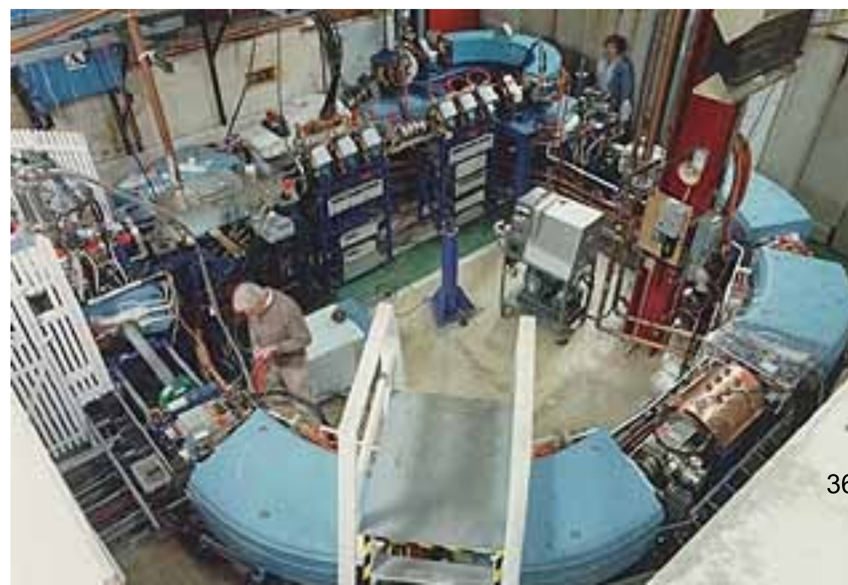
... more

... until it is

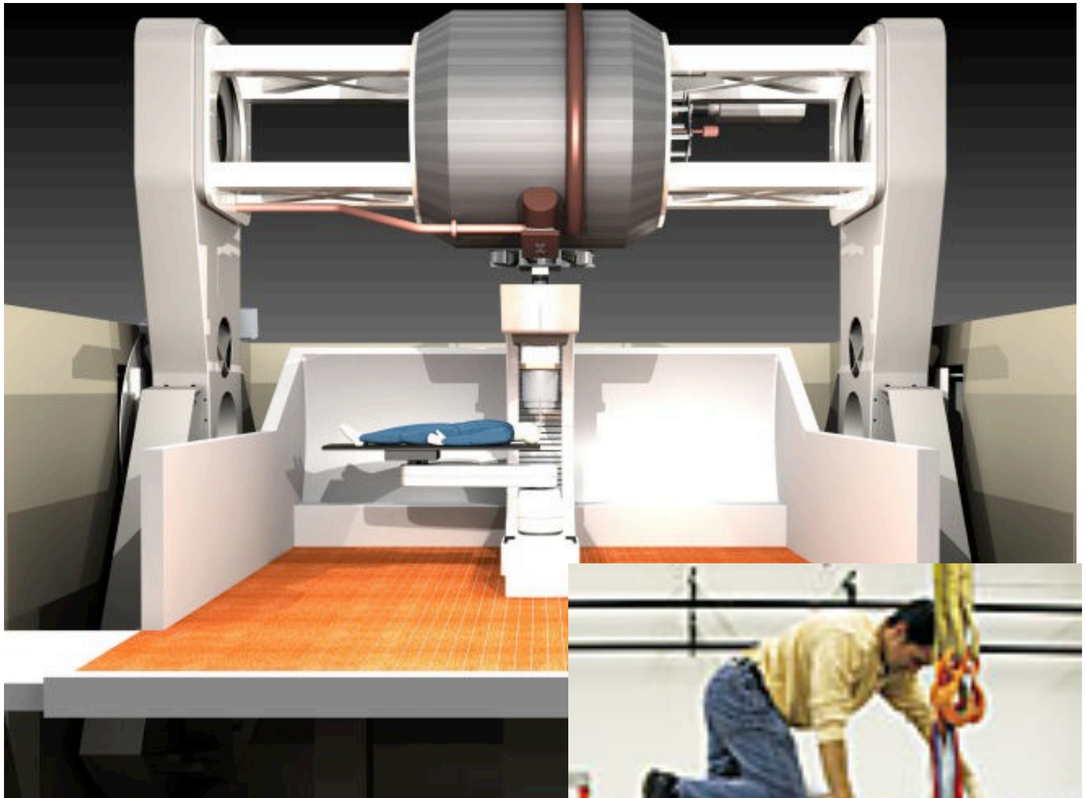
complete



The Accelerator



New Ideas - Single Gantry Unit



MEVION medical systems

- Mevion S250

  MIT Plasma Science and Fusion Center

- The world's highest magnetic field cyclotron, operating at 10 T
- A synchrocyclotron - a cyclotron in which the frequency of the driving RF electric field is varied to compensate for the mass gain of the accelerated particles.
- St. Louis Washington University first delivery
- 4 clinical sites

New Ideas - ProTom

PROTOM INTERNATIONAL, INC.

Proton Therapy and Tomography Technology

Protom International

MIT Bates Linear Accelerator Center

Lebedev Physics Institute

- Proton Synchrotron
- Relatively compact size - external ring diameter less than 16 feet, with total weight approximately 15 tons

- Flint, Michigan clinical center commissioning

- Higher energy to facilitate proton tomorgraphy

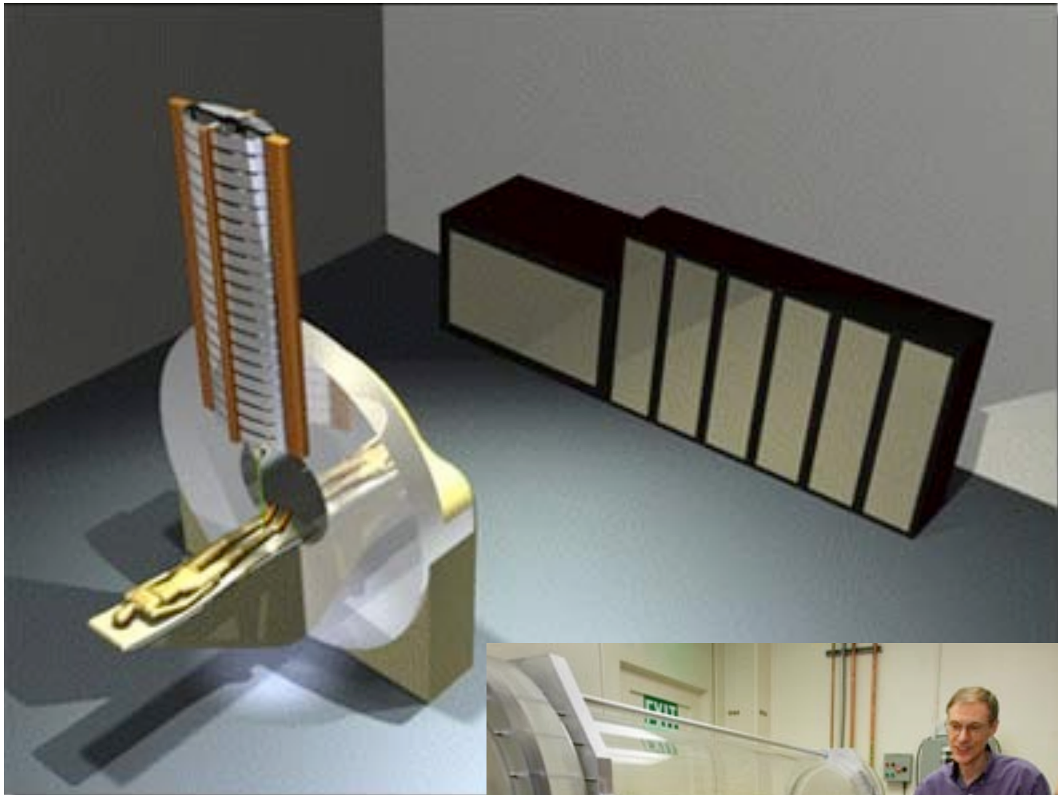
New Ideas on the Horizon - Dielectric Wall Accelerator

Lawrence Livermore National Laboratory

UC Davis Cancer Center

TomoTherapy, Incorporated

Compact Particle Acceleration Corporation (CPAC)



TomoTherapy

- Prototype can accelerate protons up to 100 MeV in a meter
- An evacuated hollow tube with dielectric walls - can withstand the high electric-field gradations necessary for accelerating protons in a short distance.

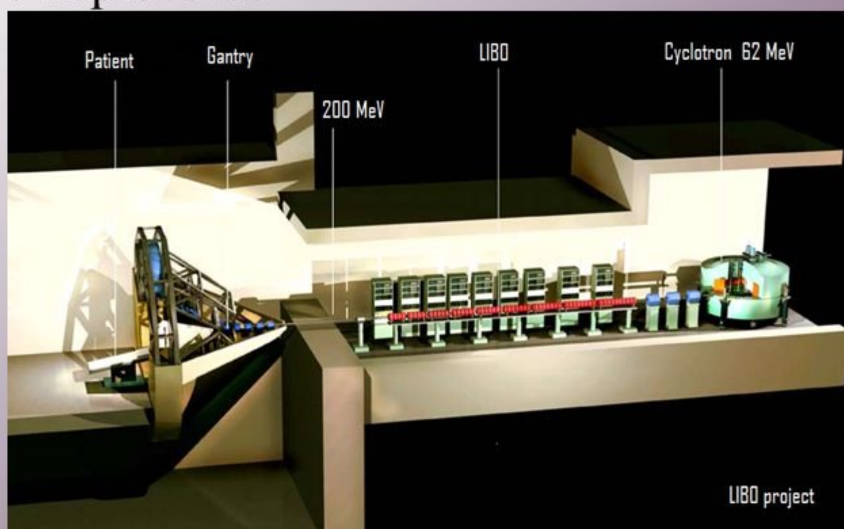
New Ideas on the Horizon - Linacs for Proton Therapy?

The University of Manchester

The Cockcroft Institute of Accelerator Science and Technology

Overview

- Compact linac in proton therapy
- At the moment using degraders to vary the energy delivered to the patient
- Can we improve it?



Also…

- Advanced Oncotherapy
  - CERN
- INFN

Back, again, to the patient experience…

- Treatment rooms use gantries to deliver the proton beam. The gantries can be rotated 360 degrees to deliver the beam at the angles prescribed by the physician, *within a few mm isocenter.*

Heidelberg

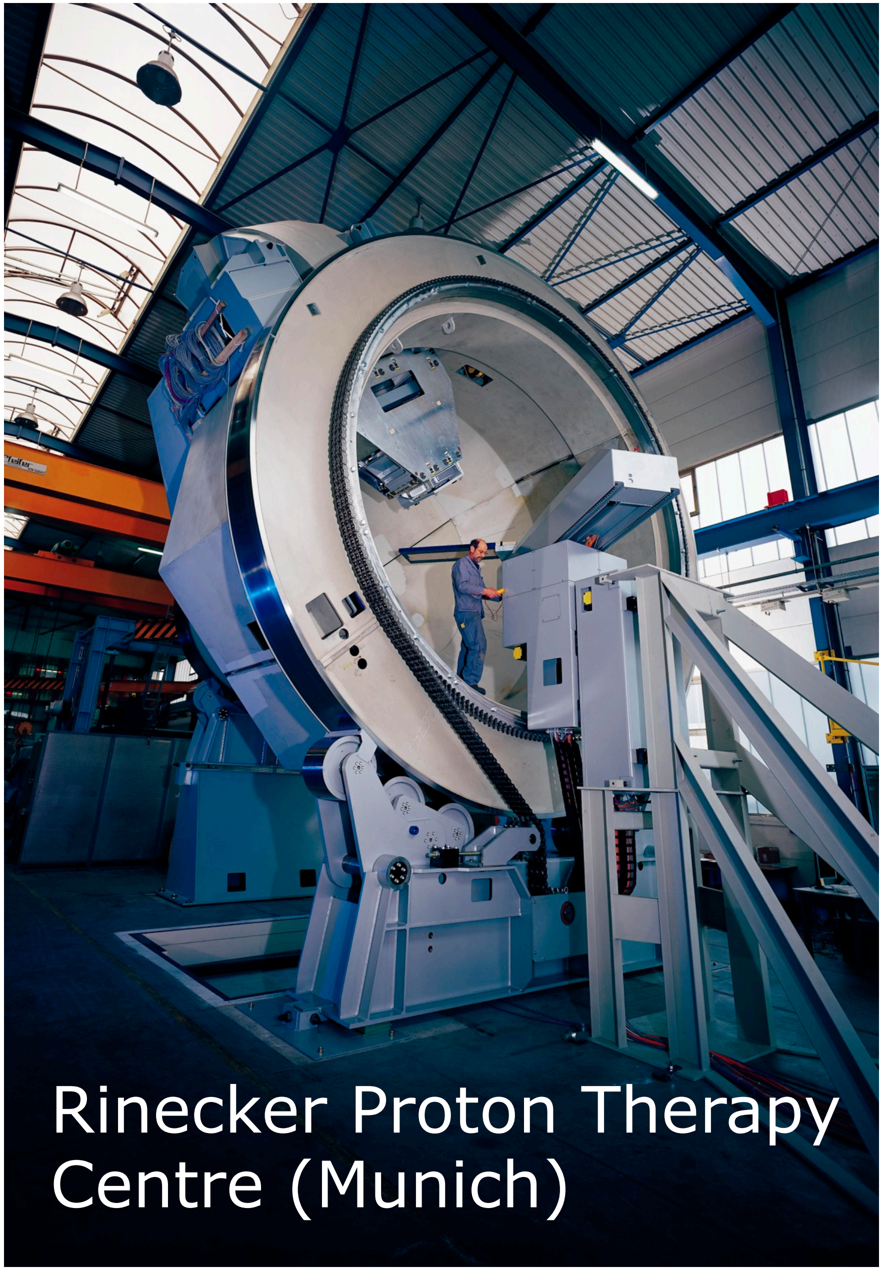
HUPTI

PSI

Gantries

- Most of the ~40 ft. tall, 90 ton, gantry is concealed by the walls and floor of the treatment room--the patient only sees the front of the proton nozzle rotating prior to treatment

- The gantry supports the bending and focusing magnets, vacuum system, and all equipment necessary for controlling and monitoring patient treatment.

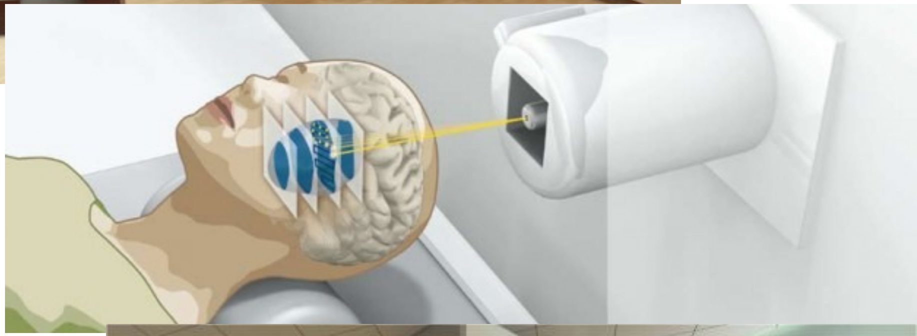


Rinecker Proton Therapy Centre (Munich)

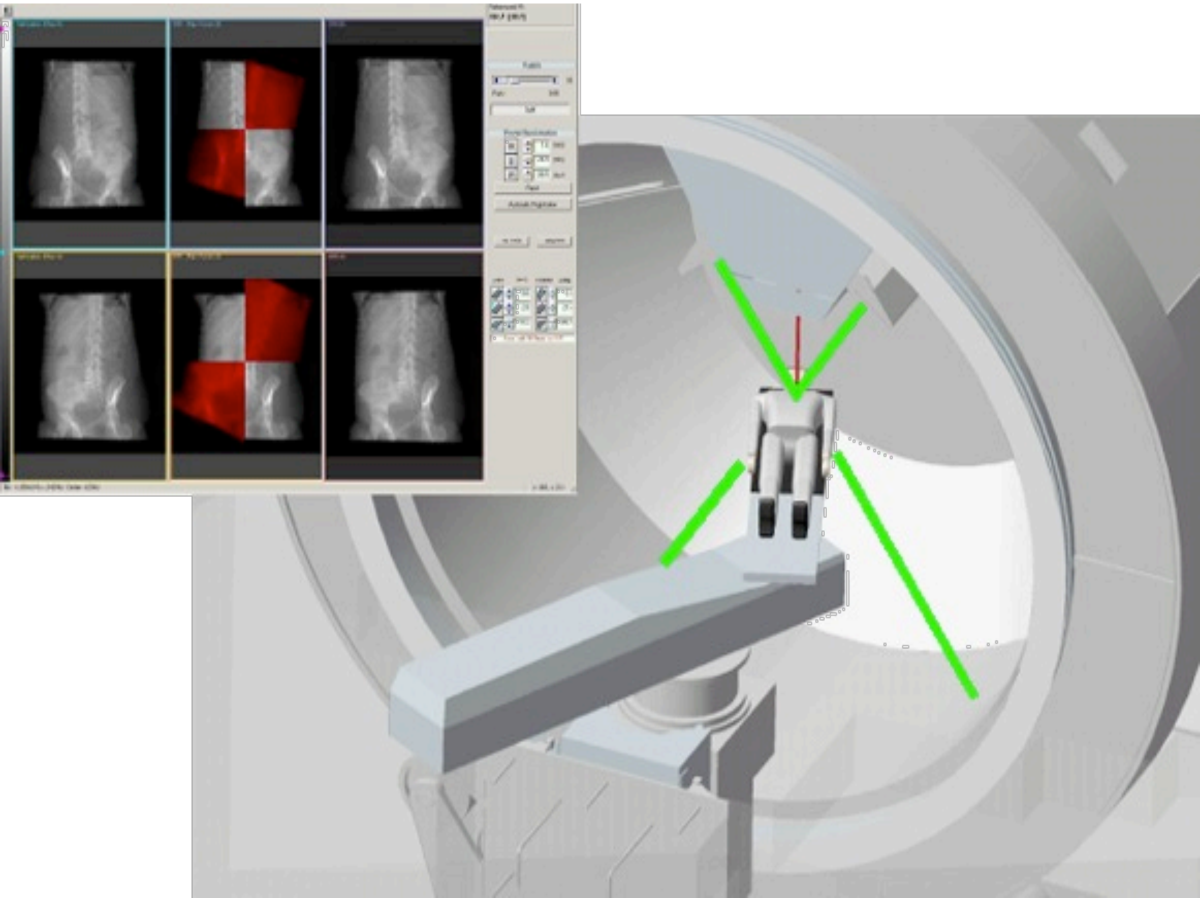
- *Or,* a horizontal beam line (HBL) may be used.

- In the HBL room the patient is adjusted relative to the fixed beam to achieve proper delivery angle.

- *Or,* ProCure, Mevion make an "inclined beam"….



Position Verification – 90% of treatment time



- 30 × 40 cm² amorphous silicon panels
- Semi-automated image matching and position correction procedure
- Only 2 X-ray axes needed
- Position correction possible for any treatment position
- **Total accuracy: ± 0.5 mm**

Lasers also standard, 4D gating technologies being implemented, plus on-board CT,….

Adaptive Therapy – enabled by on-board imaging

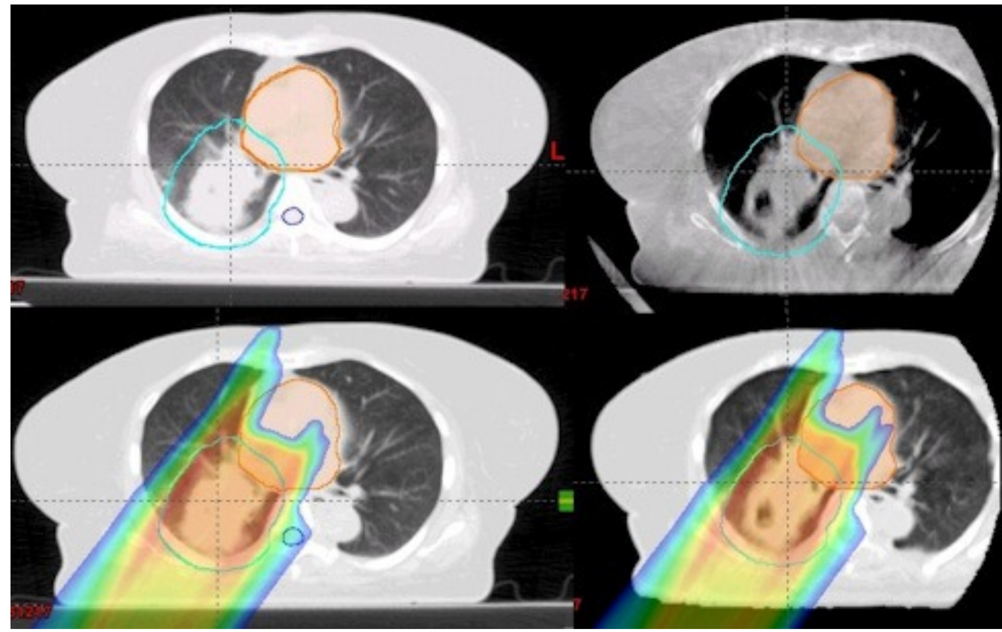
- Regular CT scans taken *<u>during the course of treatment</u>* to identify anatomical changes and adjust the therapy accordingly

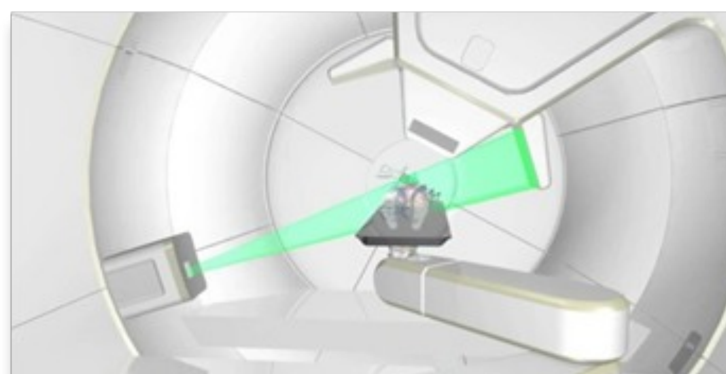
- Tumor enlargement or lung collapse can result in shortened beam penetration

- Tumor shrinkage can result in the radiation penetrating further than intended

Example: Cone beam CT for lung treatments

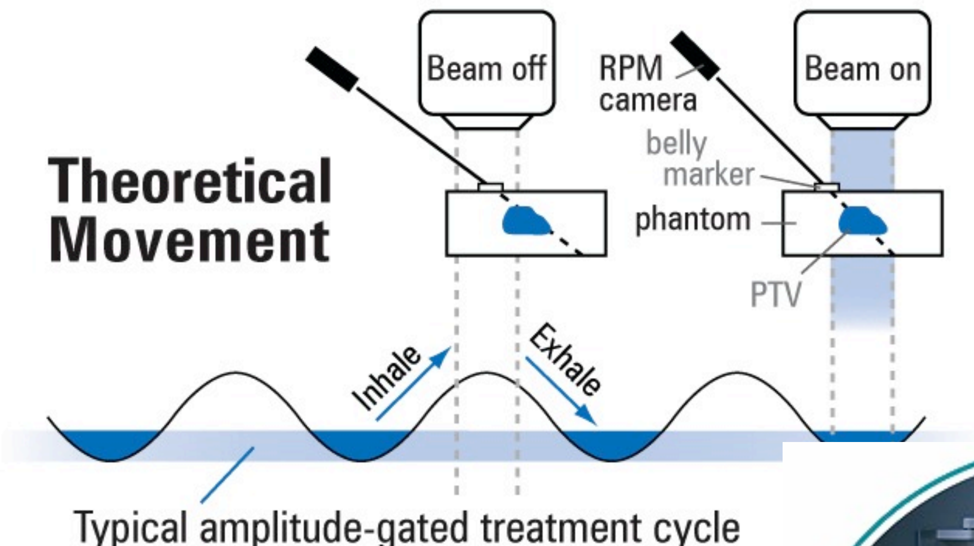
Planning CT On-Board CBCT

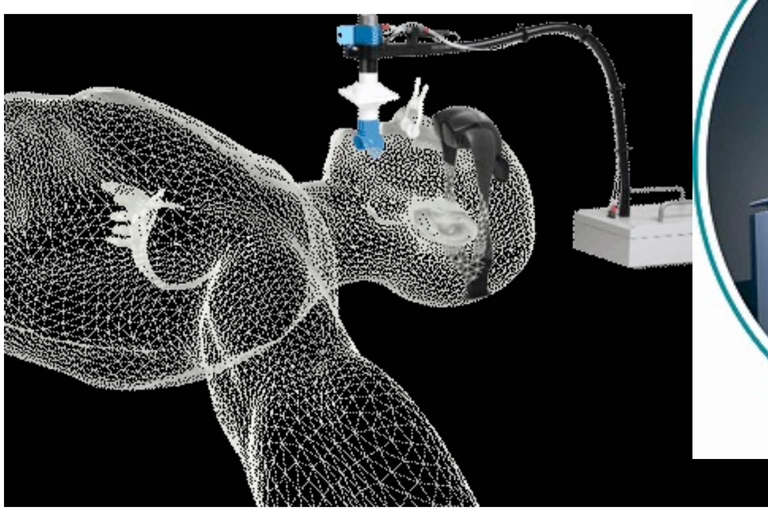




Respiration Gating

Many options in development to account for tumor and organ motion - lung, breast, liver,…





Breath hold

Video capture

Spirometry

Laser interferometry

Other sites / technologies!

PET Image Beam Path Through Patient

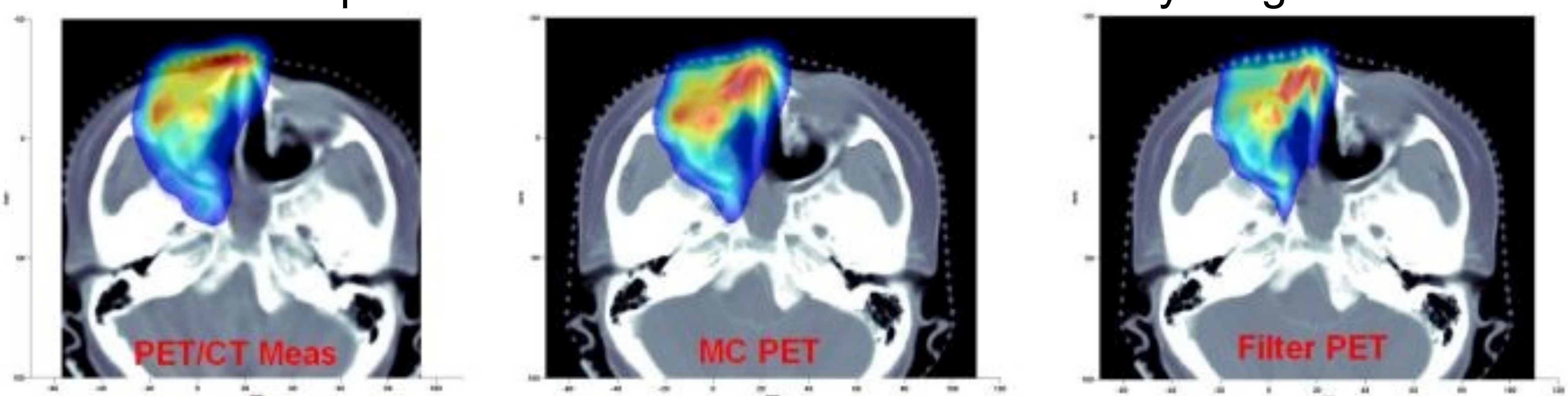
No Injection! Detect annihilation gamma-rays following the decay of positron emitting nuclei (^{11}C and ^{15}O), produced via nuclear reactions between tissue and the impinging ions

Dose verification - difficult:

- No unique correlation between dose and activity distribution
- Patient and tissue specific activity
- Wash-out

Range verification - promising:

- Unique correlation between dose and activity range



Parodi K, et al; Int J Radiat Oncol Biol Phys. 2007 Jul 1;68(3):920-34, Medical Physics 2007: 34, 419-435, Phys Med Biol. 2006 Apr 21;51(8):1991-2009

Passive PET

Measuring proton dose immediately after treatment

Figure 1- Dose Distribution for treatment of prostate tumor

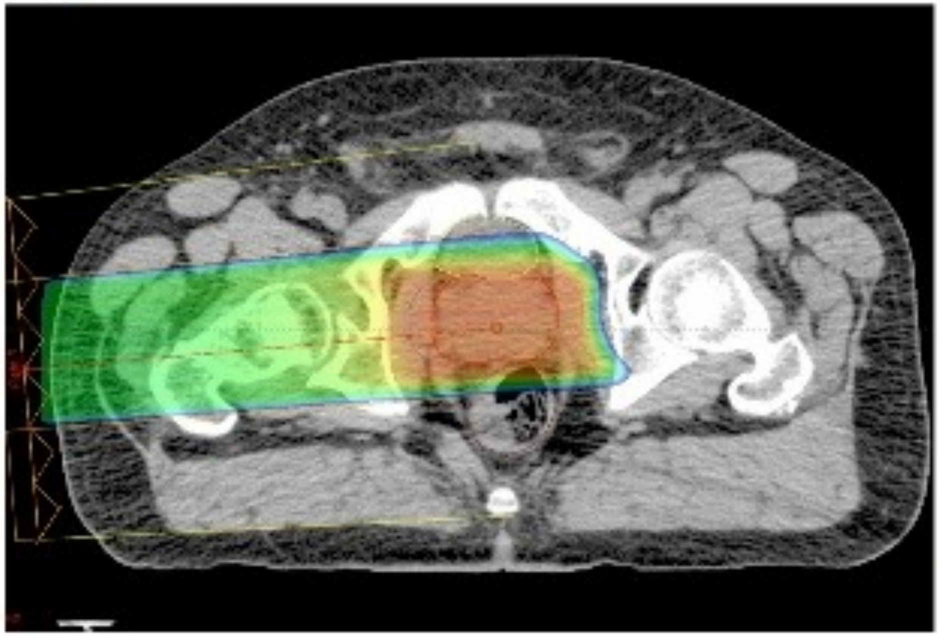
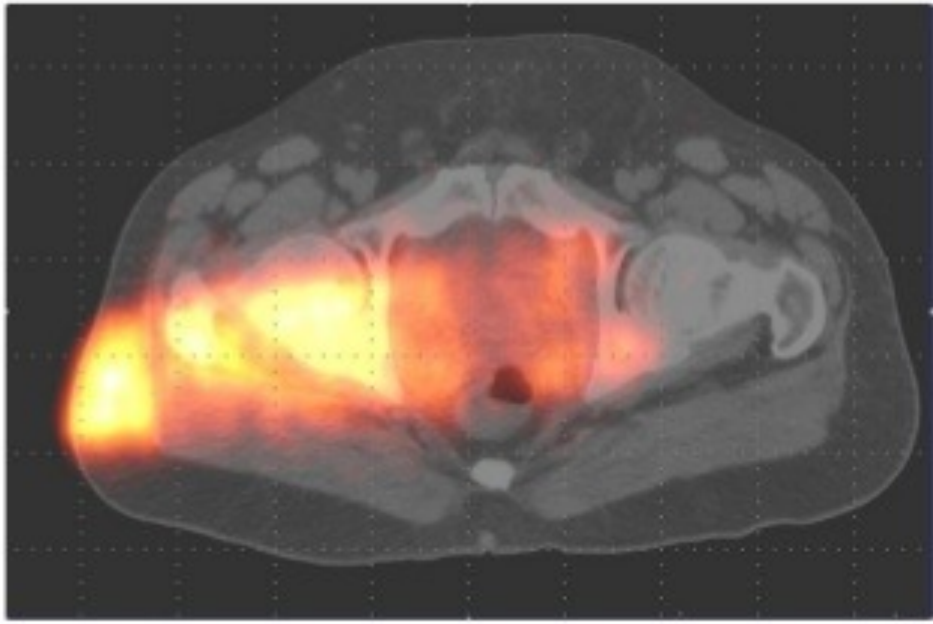


Figure 1 shows the planned dose distribution for the treatment of prostate cancer. The target is outlined in red near the center of the patient.

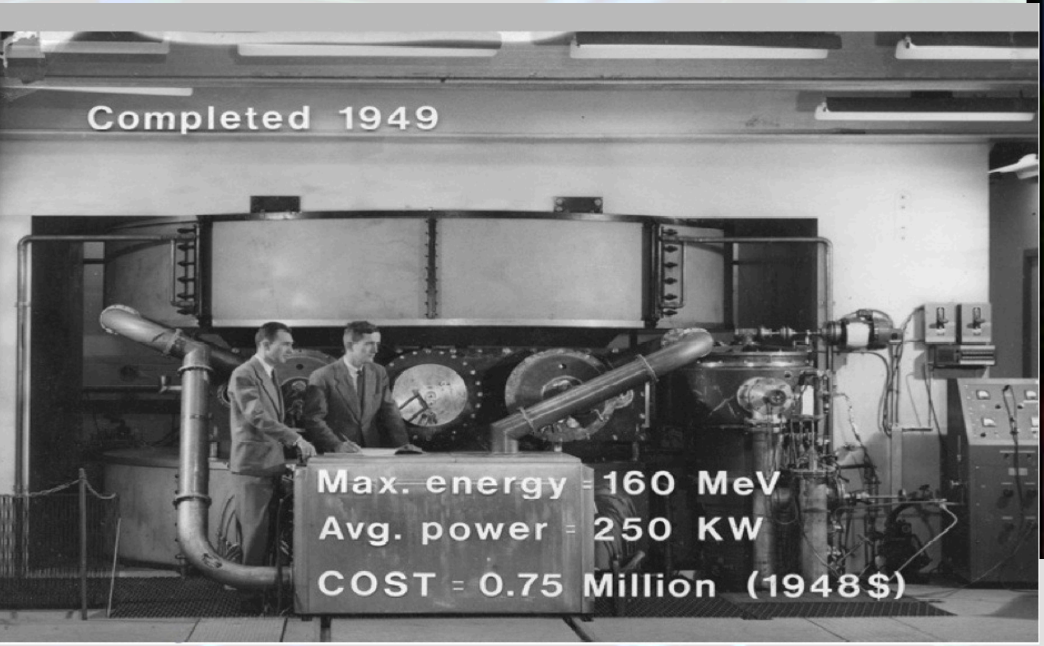
Figure 2-PET/CT image with 1cm x 1cm grid



A PET/CT image illustrating radioactivity 20 minutes after treating the patient in figure 1 was divided into a grid such that the divisions on the patient were approximately 1cm x 1cm. In this image, there are too few decays at the target. An earlier scan showing oxygen decays could more clearly show decays at the region of interest.

Penn Medicine S. Hahn

We’ve come a long way!



Patient Treatments 1974-2002

Patient Treatments 2016

But, we can go further…

- Continue trend toward less expensive, compact equipment
- *Monte Carlo based* treatment planning, full and fast dose simulation
  - *Implement variable RBEs into planning*
- Prompt gamma detection for range verification
- On-board PET or prompt gamma imaging
- Proton tomography – on gantry
- Integrated gating techniques
- More cost-effective building construction, radiation shielding

Thank You!

Hampton University Proton Therapy Institute

~$200M project

Construction started 7/2007, First patient 8/2010

One of two largest in the nation / world

At maximum capacity, can treat >150 patients / day

4 gantries, fixed beam room, *dedicated research line*

Hampton University Proton Therapy center treats its first pediatric patient January 05, 2011

"Reagyn was admitted to the hospital…..the tumor was inoperable because of its location — in the part of the brain that controls balance, heart rate, swallowing and breathing…."

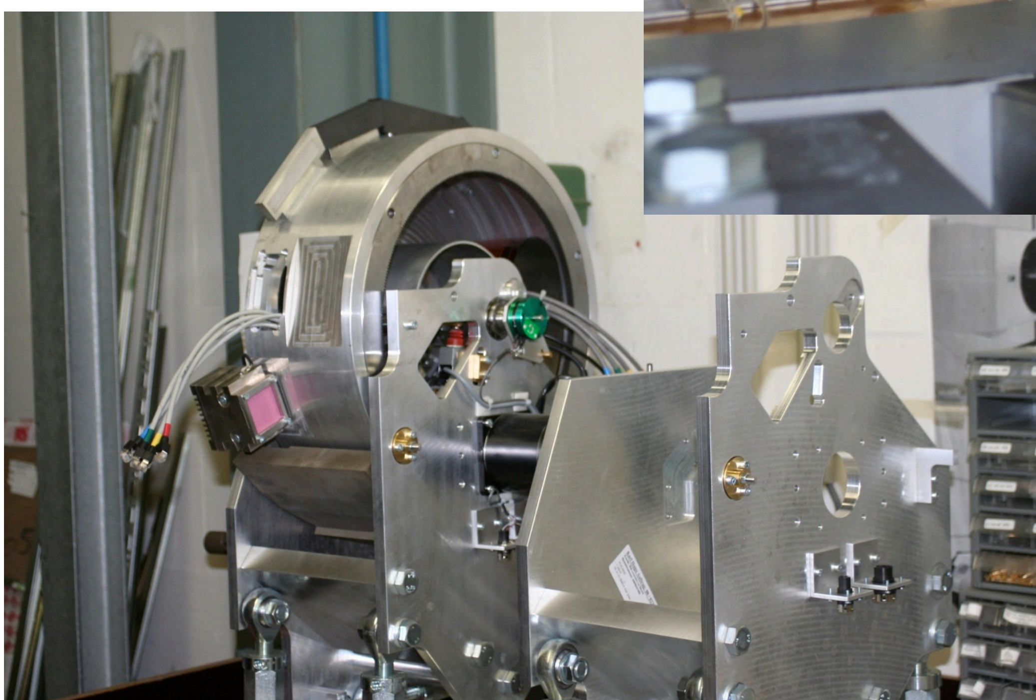
Hampton University Proton Therapy Institute

95% equipment on site for all 5 treatment rooms

Beam line installation complete

Gantry superstructures complete

Beam delivered of cyclotron March 2009

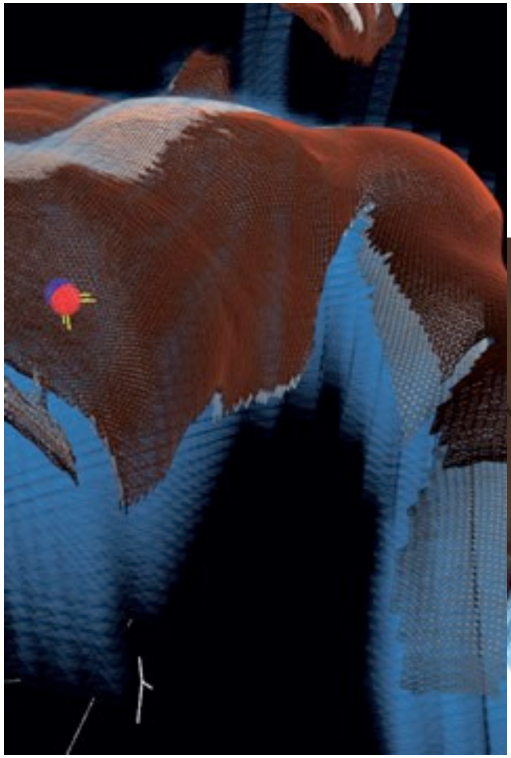


Medulloblastoma

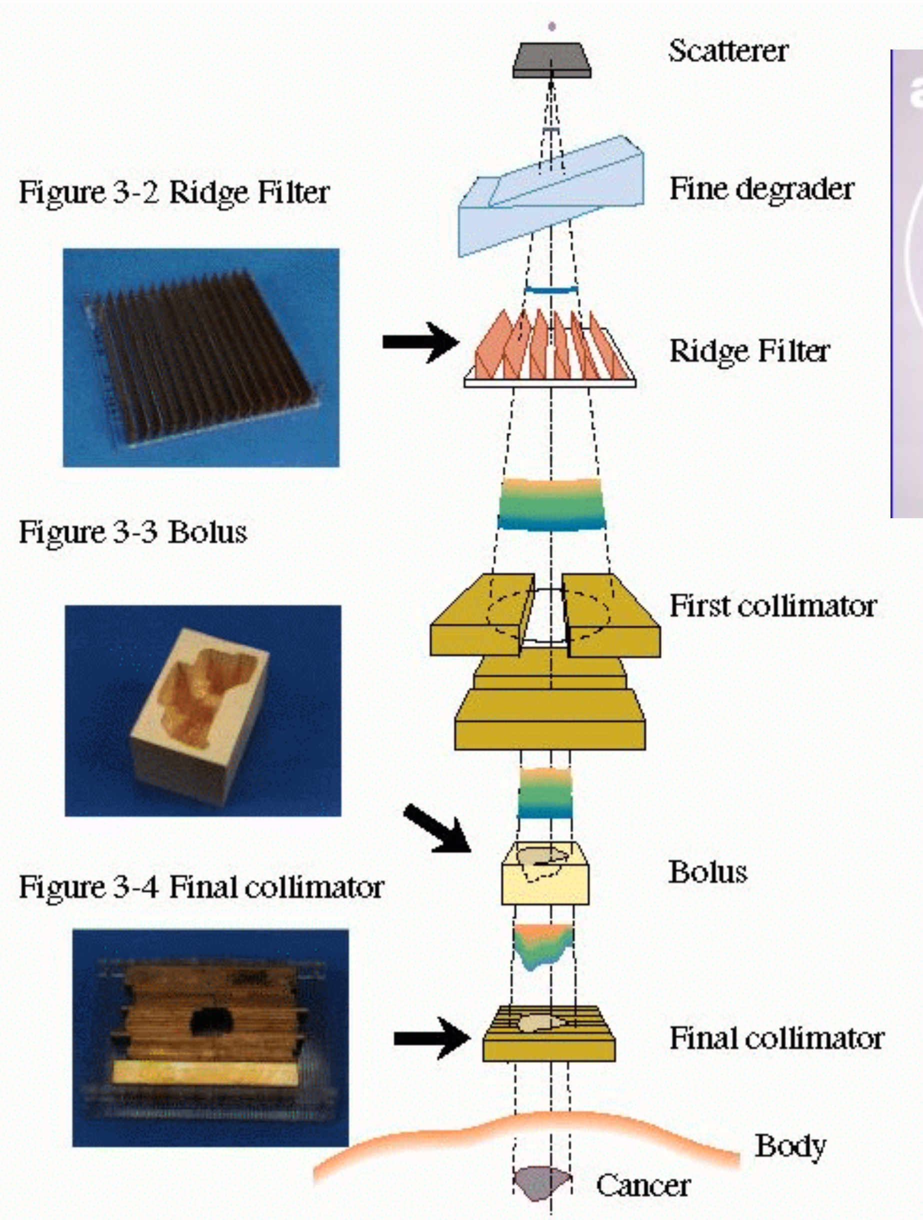
Most common malignant brain tumor in children under 20
•3350 new cases in the United States each year
•IDevelops in the part of the brain that controls balance and coordination
•IA fast-growing cancer that often spreads to the central nervous system
•44% of medulloblastoma patients are diagnosed before the age of 5
•TConventional treatment begins with maximal resection of the tumor and the addition of radiation to the entire neuraxis. Chemotherapy may increase the disease-free survival.
•5 5 year survival in more than 80% of cases

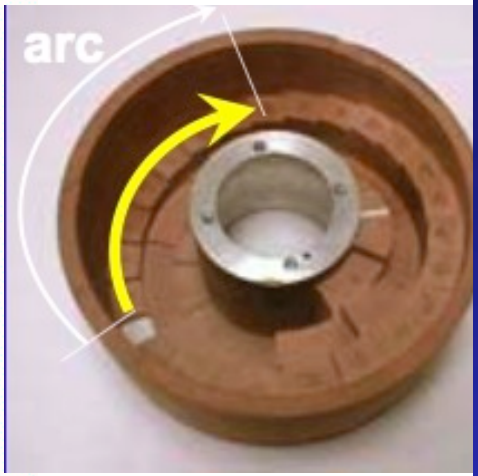
Treatment Planning

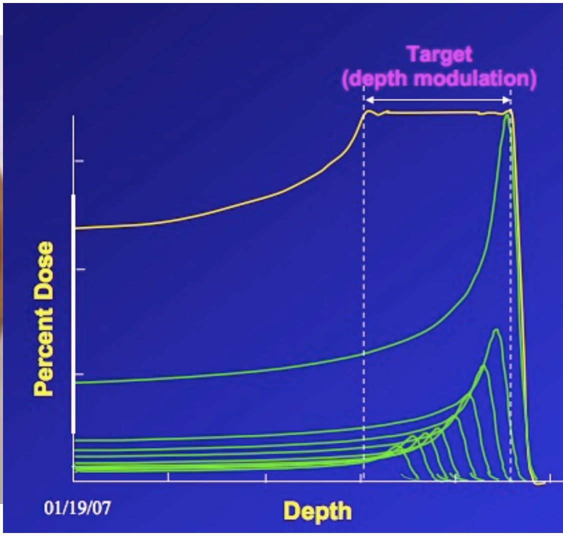
- Proton rounds (weekly)
  - Physician discussion, decision, and prescription
  - Patient position
  - Immobilization
  - Testing or technical hurdles
  - “Interesting” issues (AVM glue, pacemaker / defibrillator in field, prostheses,…!…)
  - Patient-specific concerns



Beam Delivery - Many Options



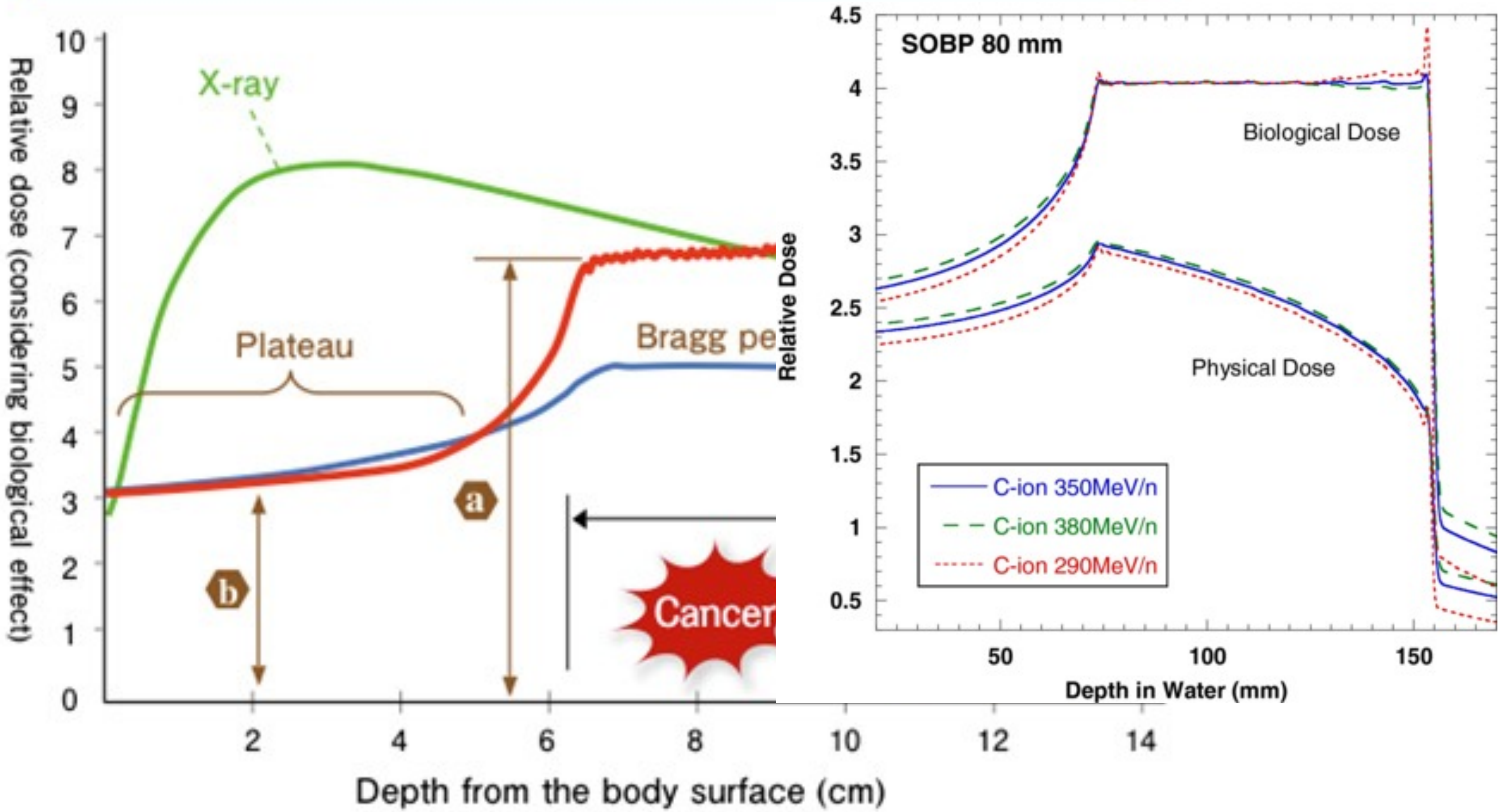




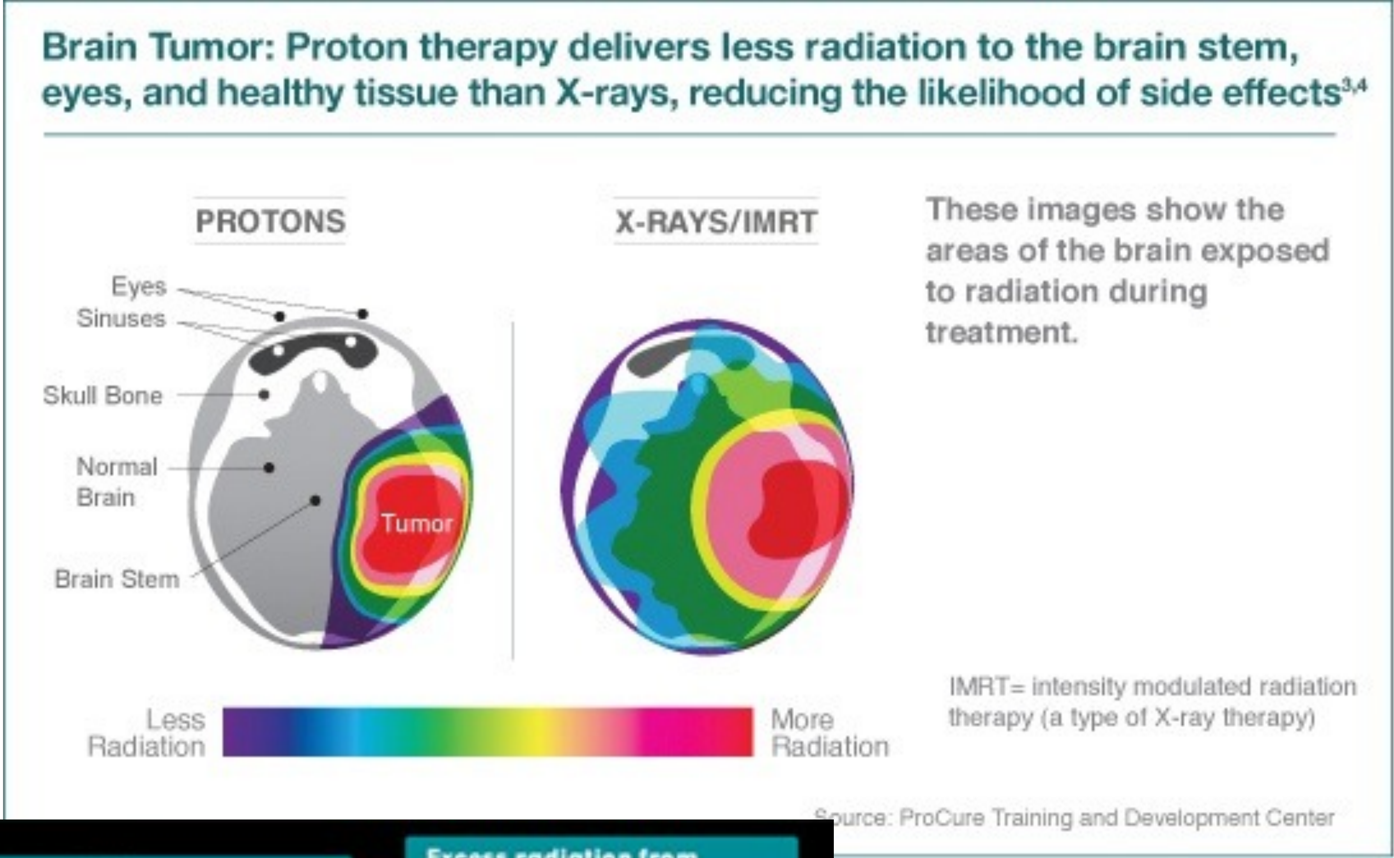
Range modulator, provides spread out Bragg peak (uniform 3D dose)

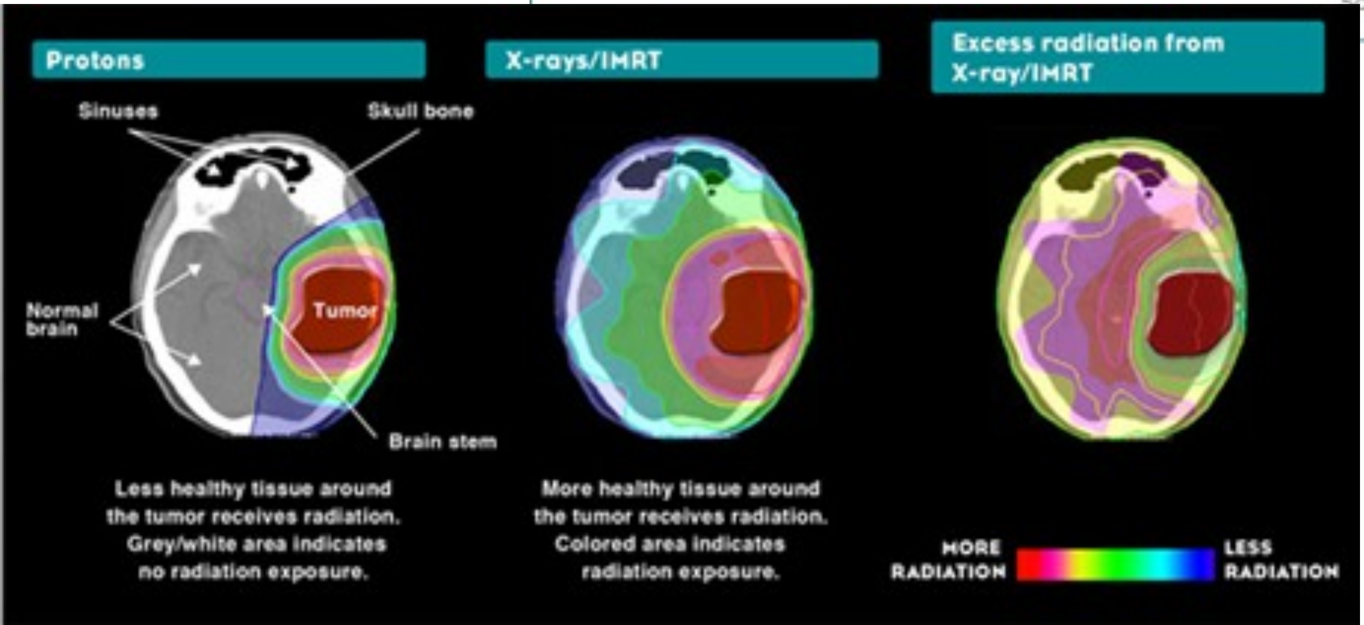
<u>*Alternative:*</u> "Pencil Beam Scanning (PBS)" - rastering, removes degraders, minimizes neutron dose….

When the ratios of peak to plateau (a/b) are compared while considering biological effect, the carbon beam has the largest value.



Proton therapy minimizes damage to healthy tissues that surround the tumor.





- Vernimmen, Harris, Wilson, Melvill, Smit, Slabbert. Int J *Radiat Oncol Biol Phys.* 2001;49(1)
- Bolsi, Fogliata, Cozzi *Radiother Oncol.* 2003;68:1-14.