Proton Radiation Therapy Technology and Clinical Indications

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Provision Health Alliances

provision
Health Alliance

provision center for
PROTON
THERAPY

Proton Therapy Alliances

Provision Health Alliance (PHA)

A comprehensive clinical outpatient healthcare center consisting of multiple physician practice groups, comprehensive diagnostic imaging, advanced chemotherapy and radiation therapy, wellness center, physical therapy, a cyclotron and nuclear pharmacy, and clinical trials and research capabilities.

Provision Center for Proton Therapy (PCPT)

The key cancer radiation therapy component of PHA at Dowell Springs which together with the rest of PHA distinguishes PHA from all other outpatient cancer centers in the world. Currently, there are 11 proton centers in the US.

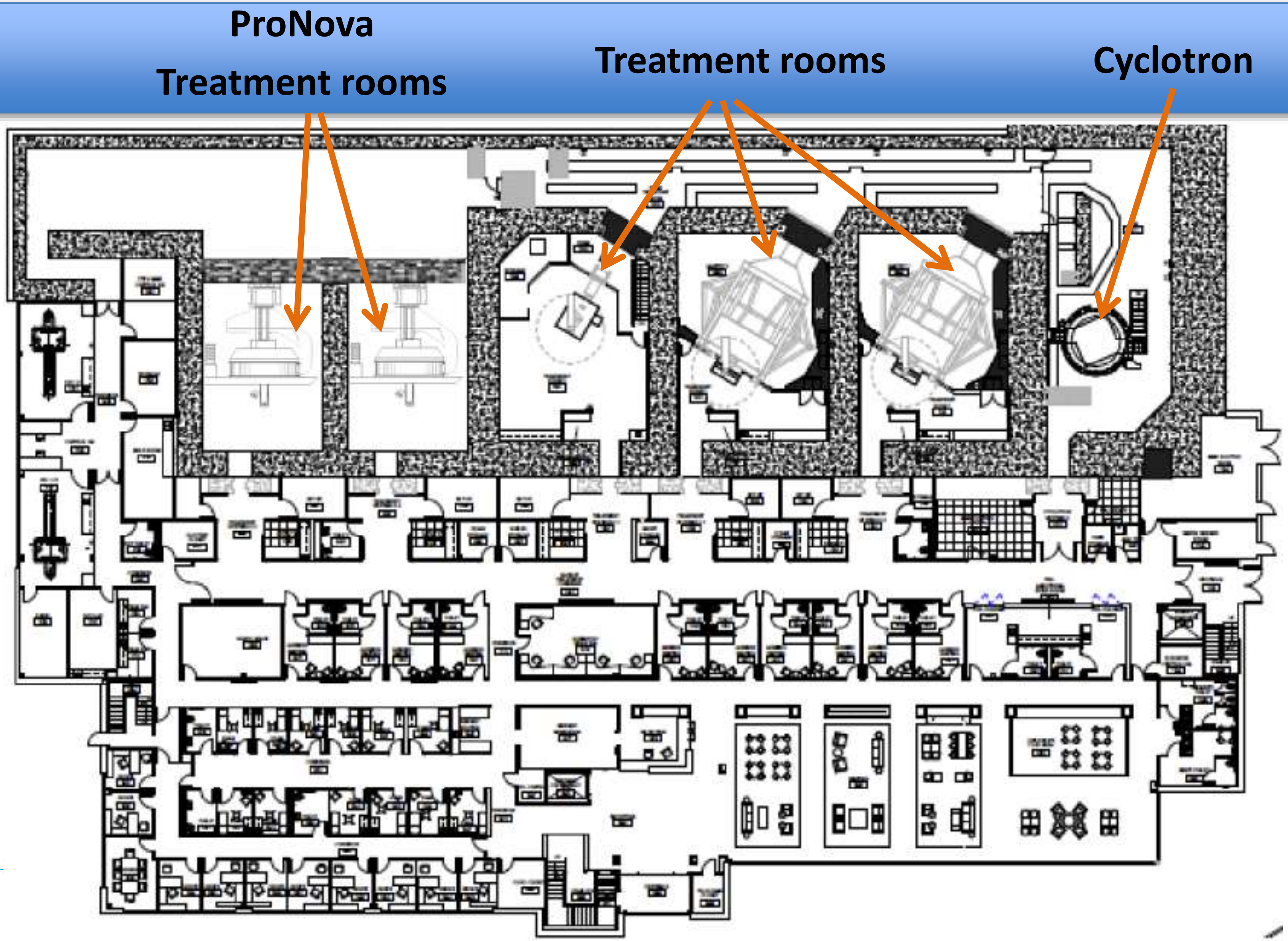
ProNova Solutions, LLC (ProNova)

A US-based developer, manufacturer, and distributor of multi-room proton therapy equipment and solutions which together with PHA and PCPT distinguishes us from all other proton therapy manufacturers and centers in the world.





Provision Center for Proton Therapy
Facility – 1st Floor

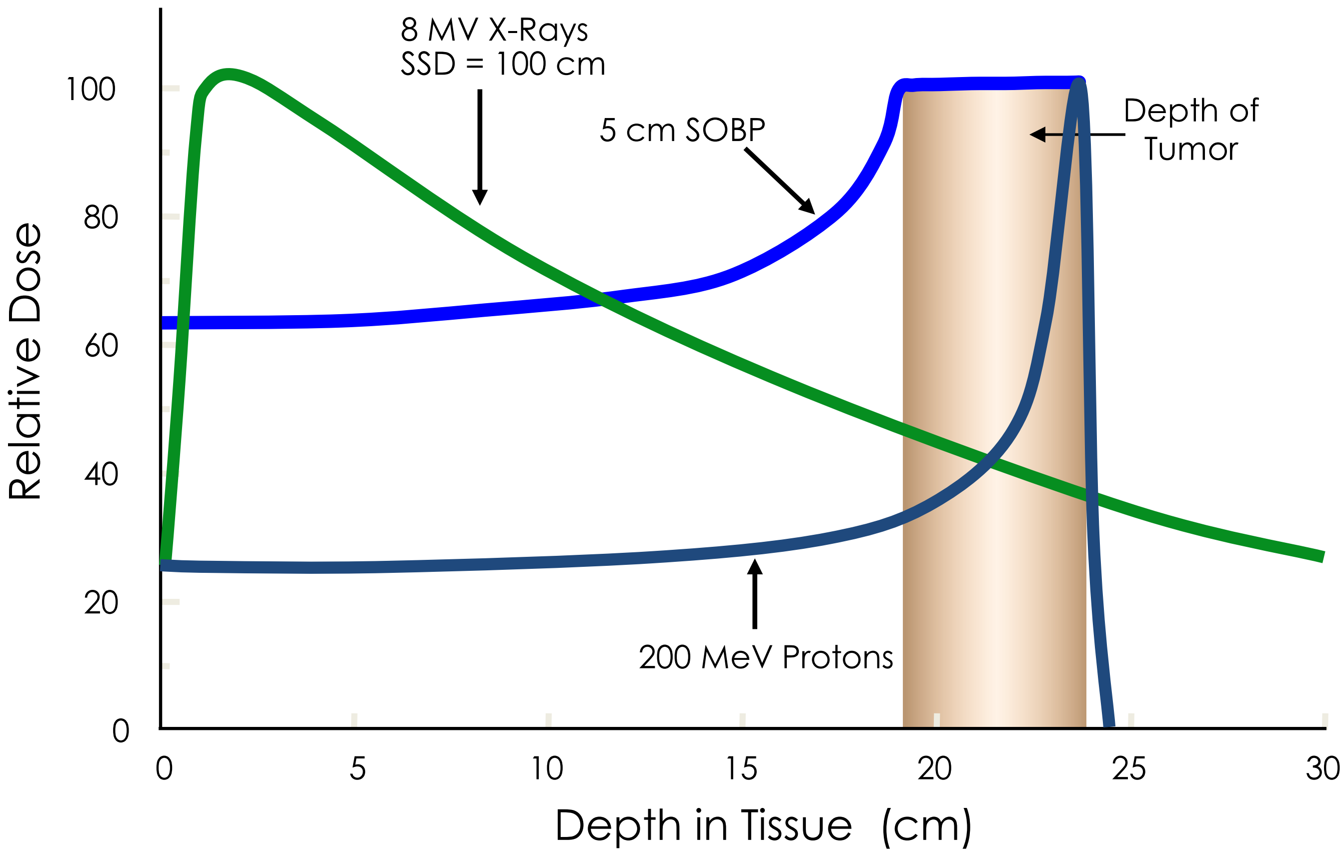


Physics of Protons

- Protons are directly ionizing particles
- Energy Loss is proportional to $1/v^2$
  - Bragg Peak
  - finite range in matter
- Multiple Scattering
  - lateral broadening of beam
- Nuclear interactions

The Physics of Protons

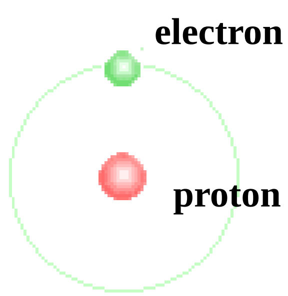
Depth Dose Curves for Different Treatment Modalities



Where do we get the Protons?

Protons are the nucleus of the hydrogen atom.

Protons are created by stripping (ionizing) the electron from the hydrogen atom.



The Hydrogen Atom

Accelerating Protons

In order for protons to be clinically useful for radiotherapy, they must be accelerated to high energy.

Radiotherapy is performed with protons of energy up to 250 MeV (mega-electron volts). mega = 10^6 = 1,000,000

- "room temperature" atoms have energies of ~25 meV (milli-electron volts). milli = 10^{-3} = 1/1000
- so we have to increase their energy by a factor of **~10 billion** for clinical use.

A 200 MeV proton travels at ~1/2 the speed of light.

There are several techniques for accelerating protons:

Synchrotrons, linear accelerators, cyclotrons

“High Energy” can be Misleading

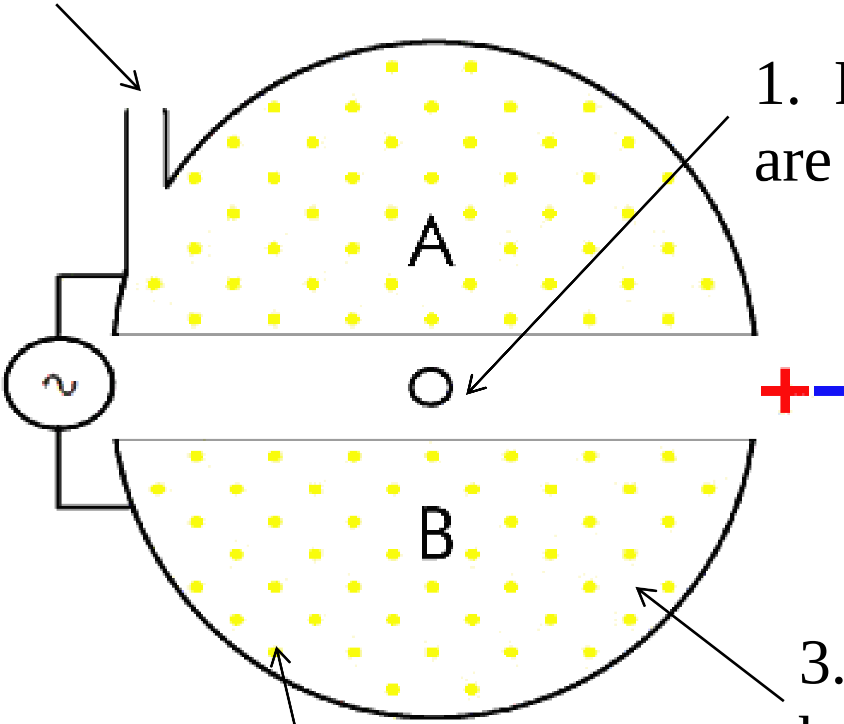
electron volts in perspective

- A light bulb consumes ~10^{20} eV/second.
- Bowl of Wheaties ~10^{24} eV.
- A fly travelling only 1 meter/second has an energy of **~10 billion** MeV.

Protons are tiny – they are ~10^{-15} meters in radius and have a mass of ~10^{-27} kilograms.

How a Cyclotron Works

5. High energy protons are kicked out.



1. Protons (ionized hydrogen) are injected at low energy.

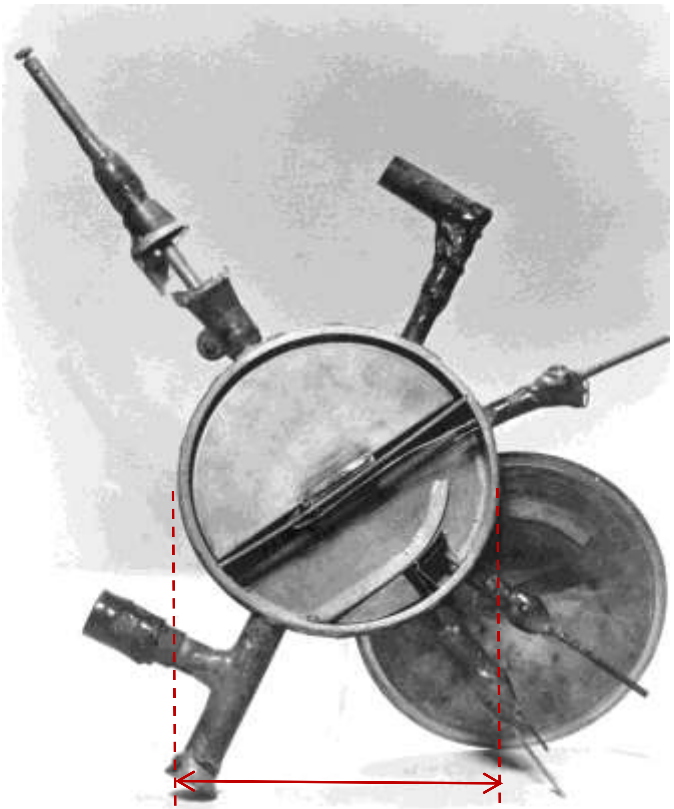
2. Voltage alternates to give the protons a "kick" every time they cross the gap.

3. Magnetic field keeps protons bound in a circular orbit.

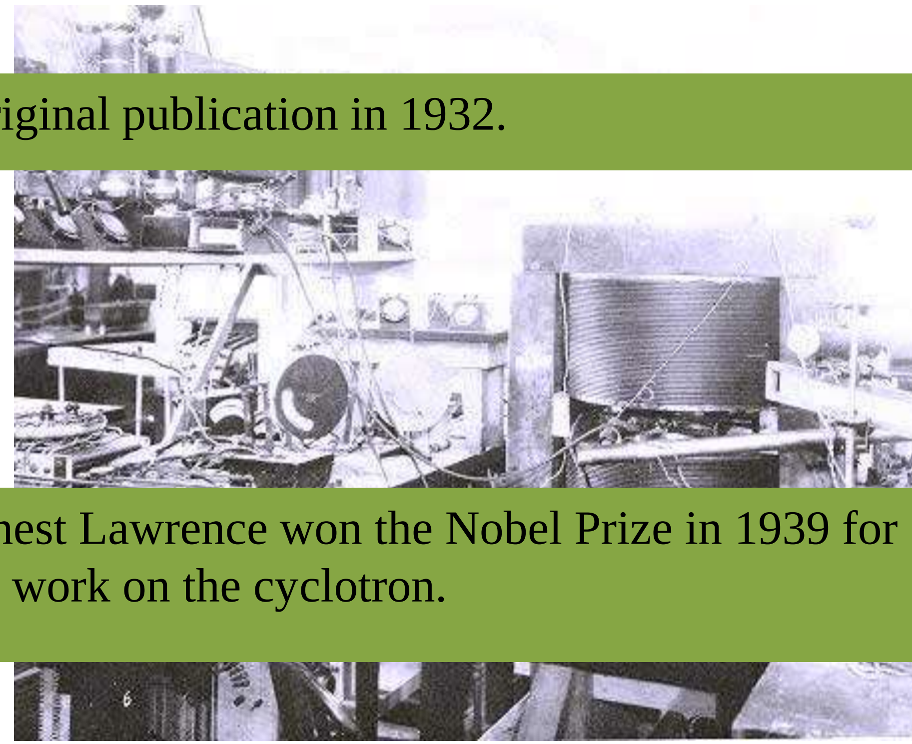
4. As the proton's energy increases, its orbital radius increases.

Early Cyclotrons 1930’s

First Cyclotron, 1931



4 inch diameter
80,000 eV



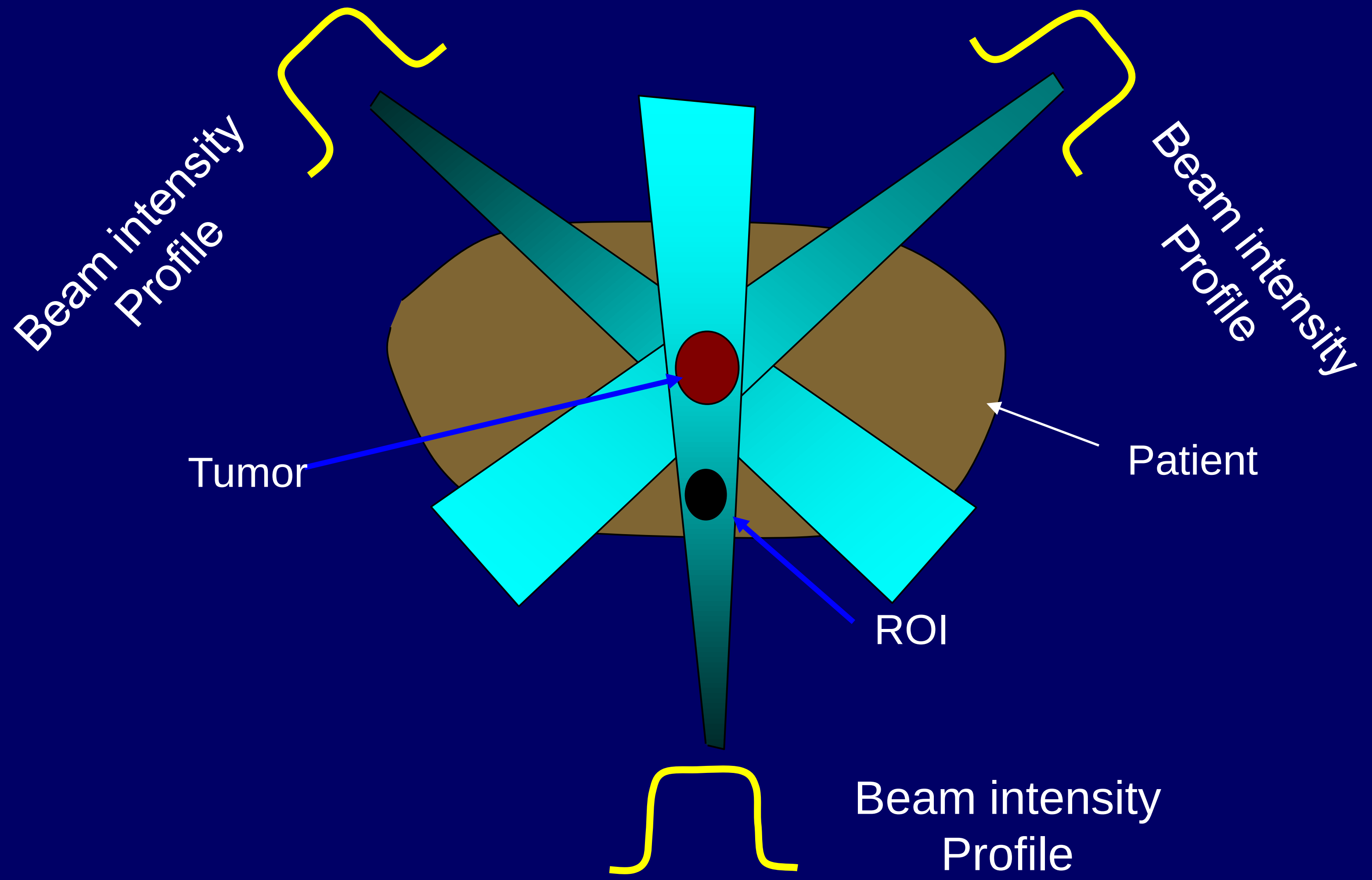
Original publication in 1932.

Ernest Lawrence won the Nobel Prize in 1939 for his work on the cyclotron.

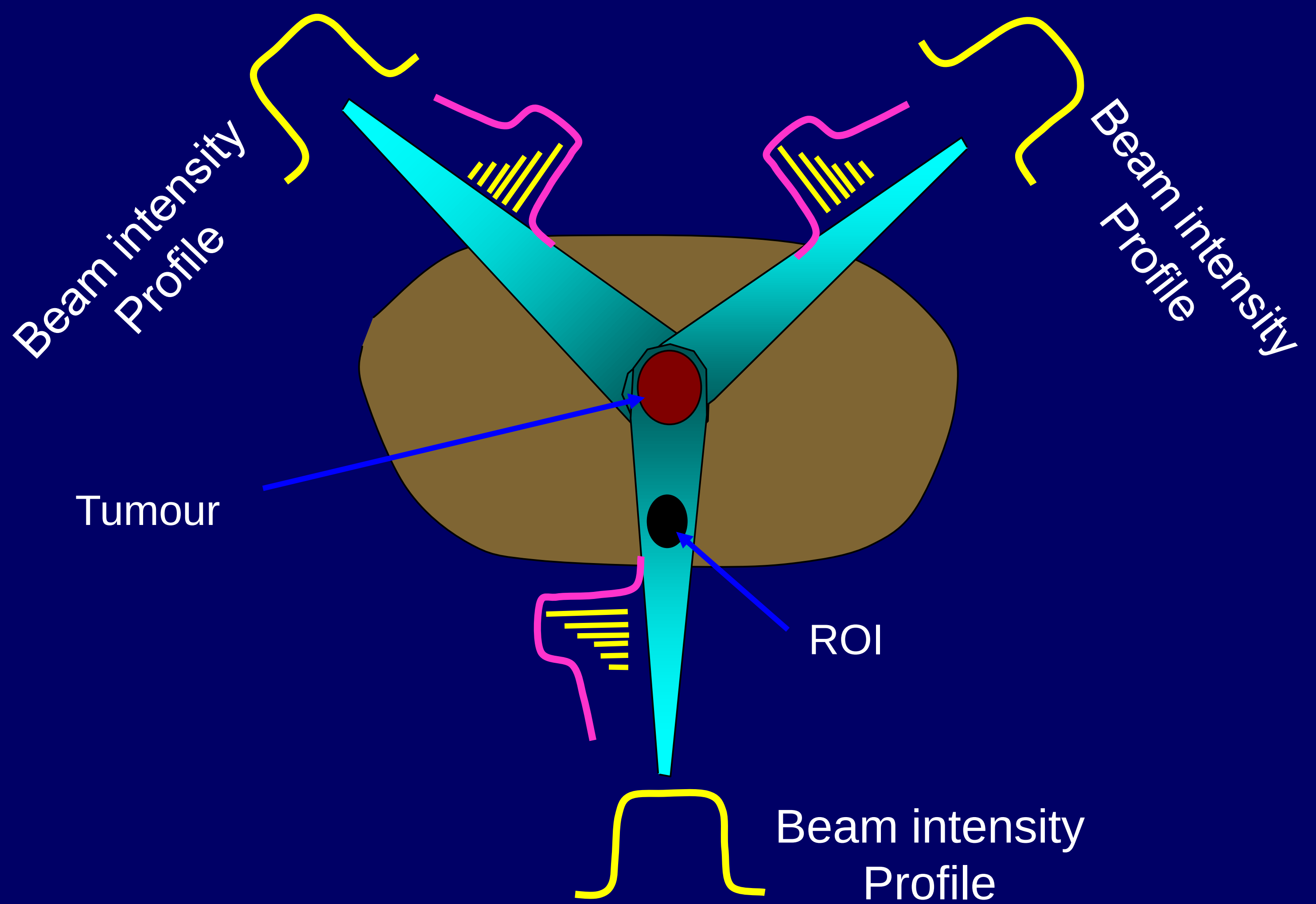
How do we use Protons

- *The same way than x-rays – conventional radiotherapy*

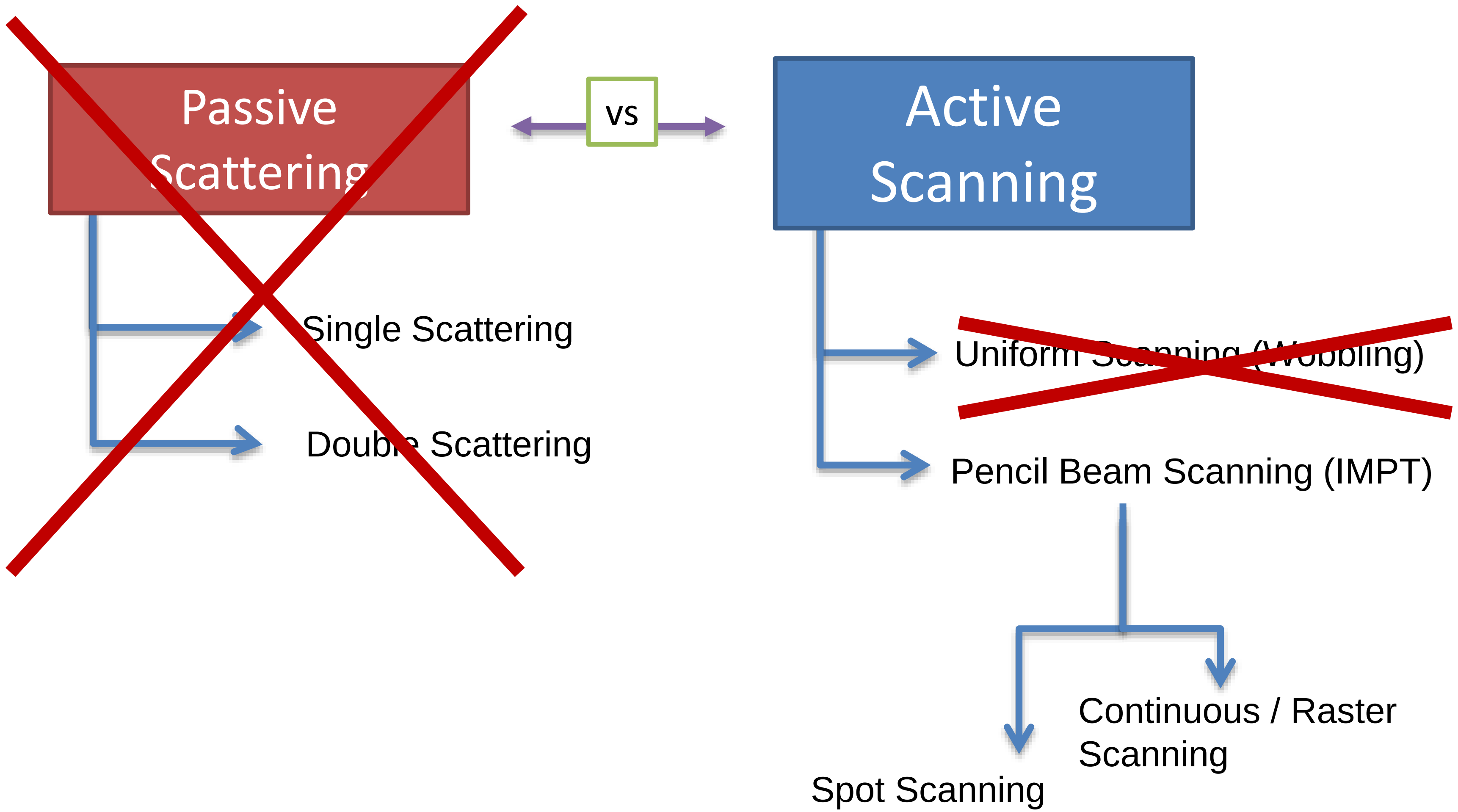
Classical Radiation Therapy



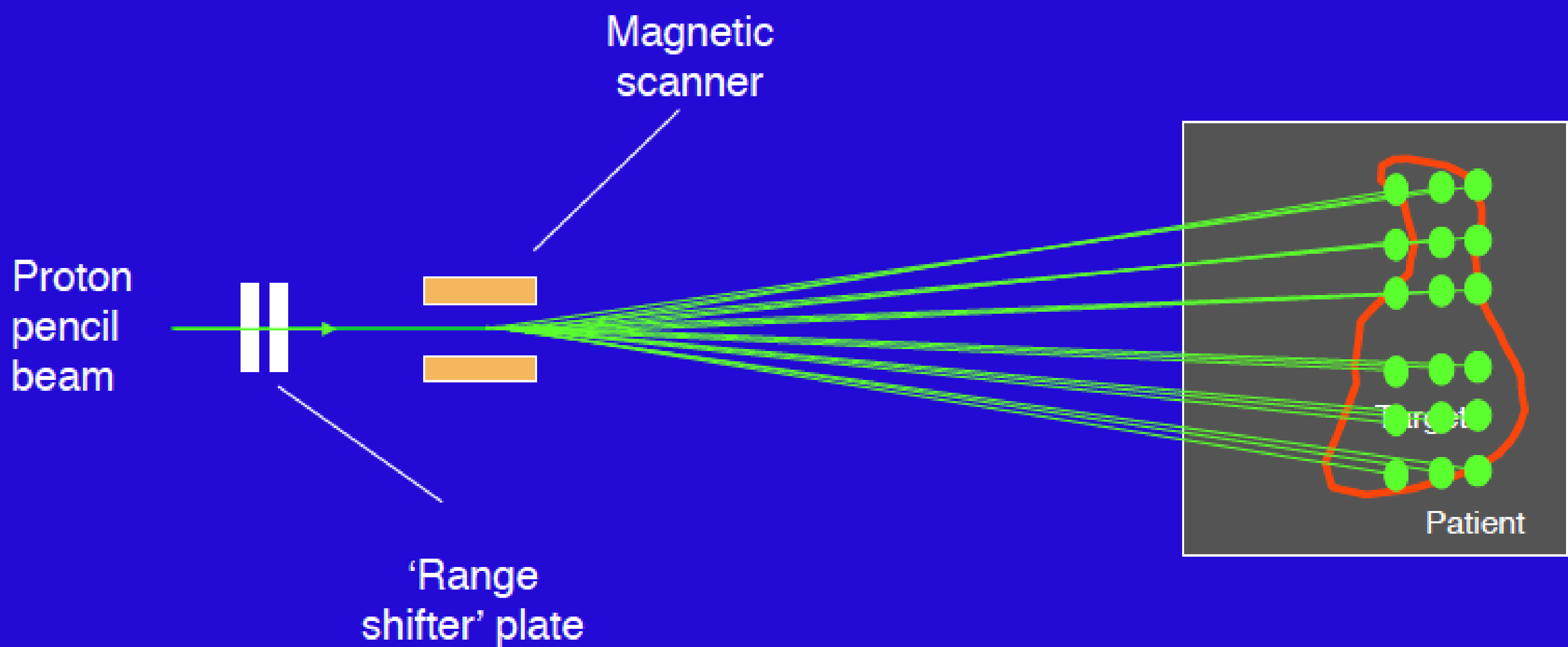
Classical Proton Therapy:
oldest form of IMRT – depth dose modulation



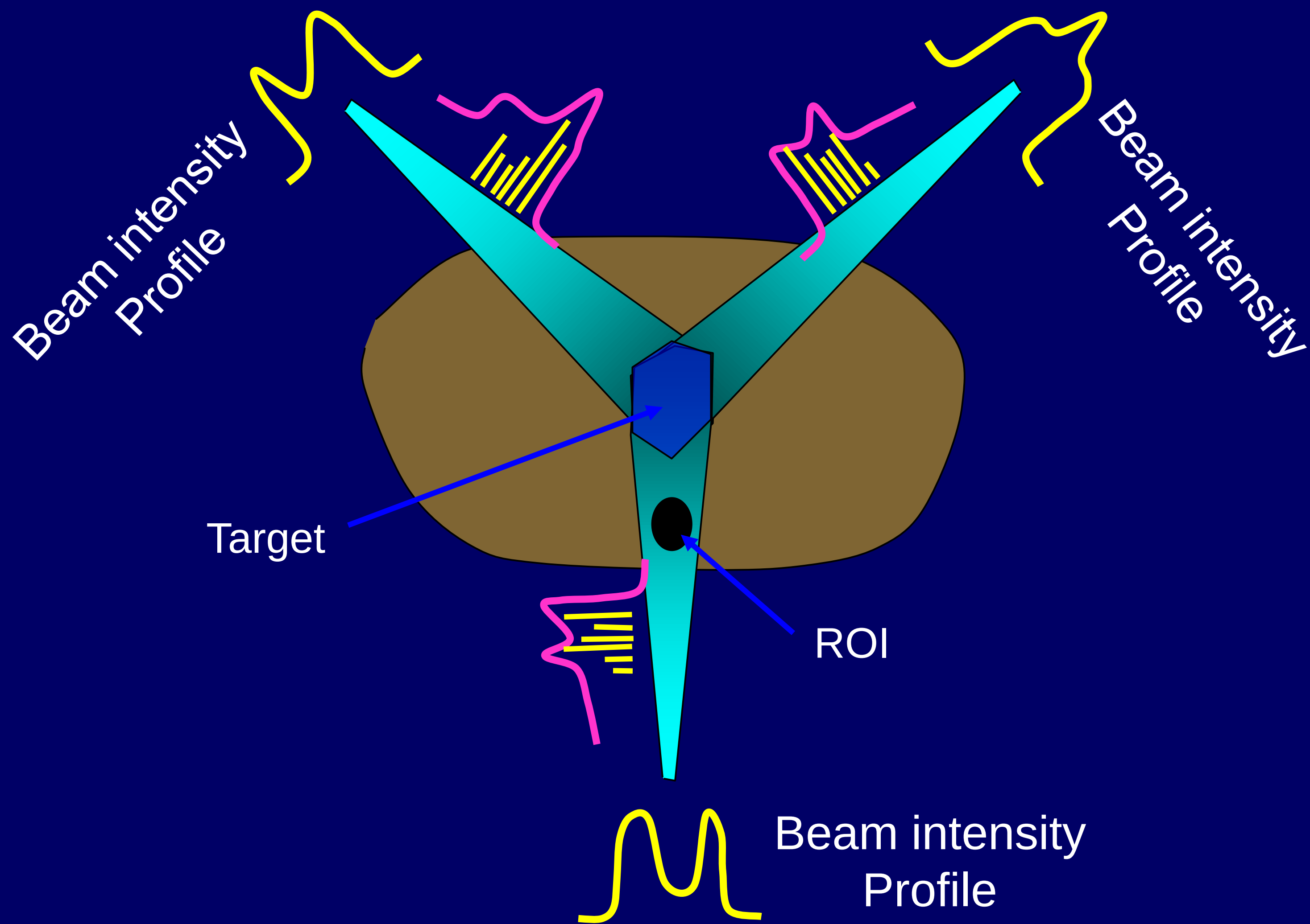
Beam Delivery Systems



Active scanning

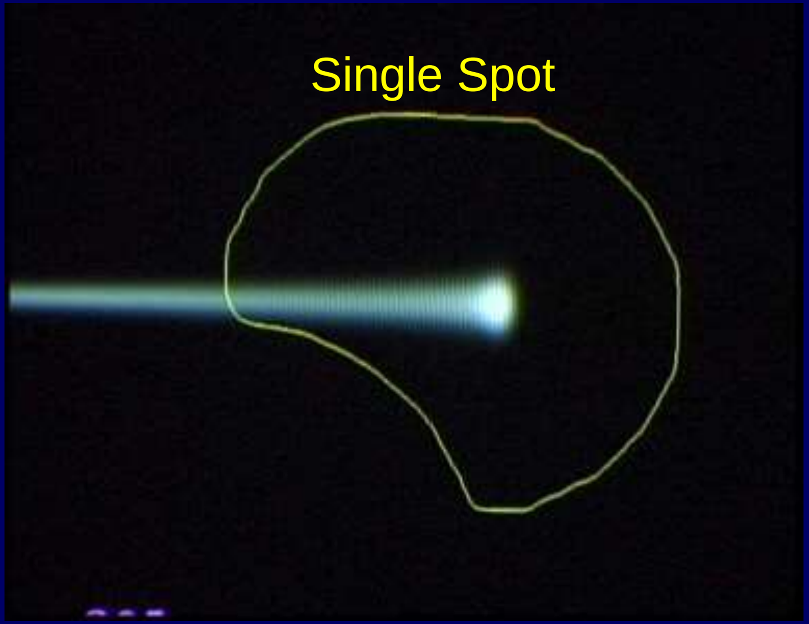


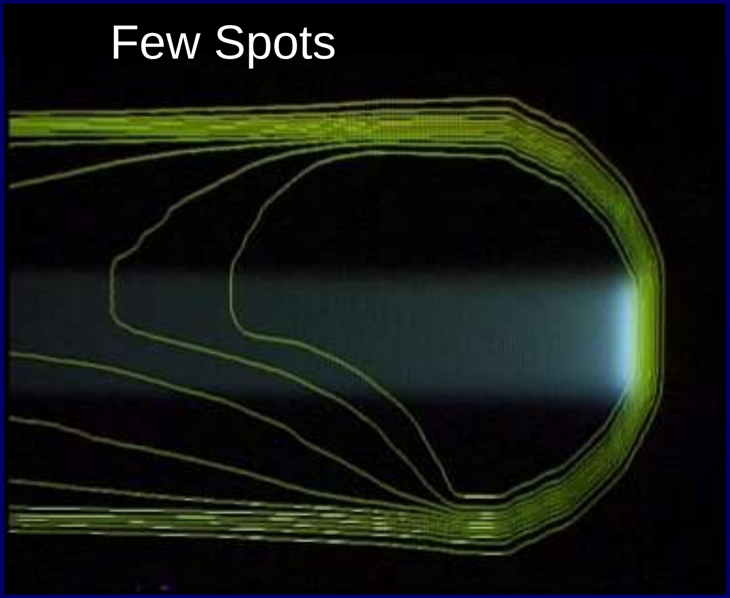
Pencil Beam Scanning Proton Therapy: Best form of IMRT

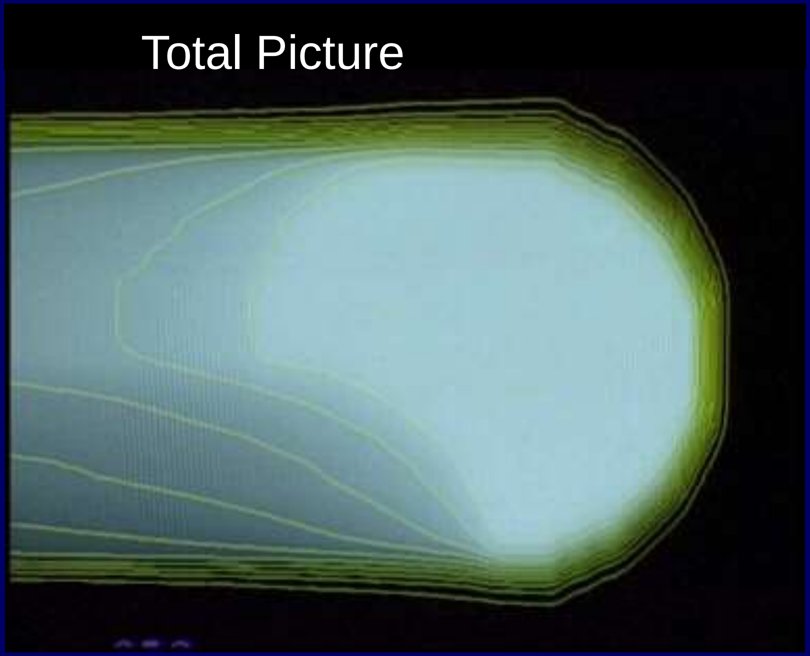


Spot Scanning Principle

Pictures - With compliments from PSI

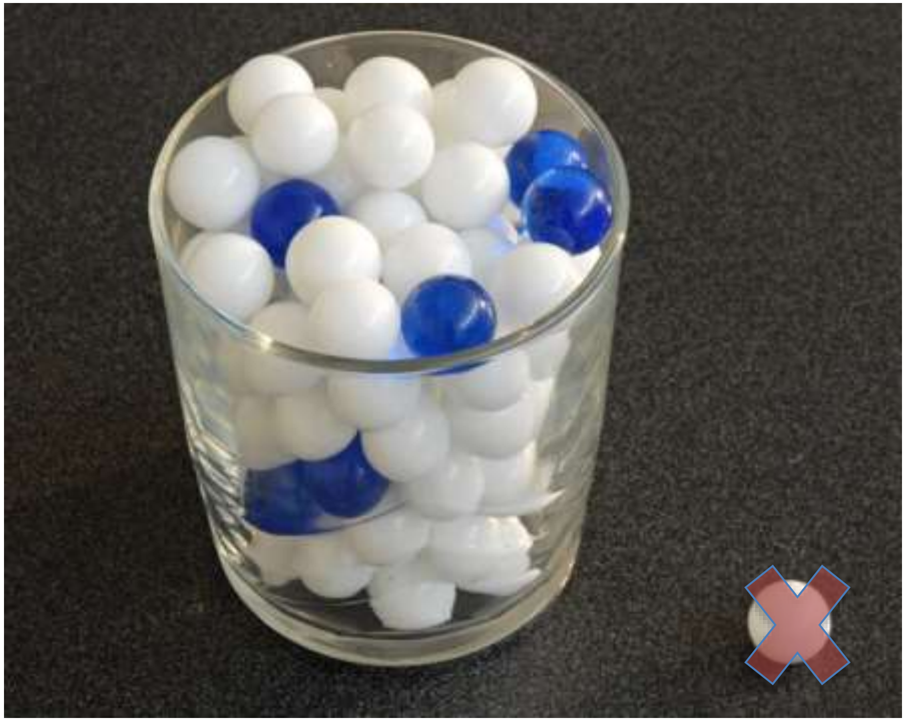






Pencil Beam Scanning (PBS)

– Filling the target with spheres of Radiation dose



“There is no advantage whatsoever to irradiating <u>uninvolved healthy tissue”</u>

Dr. Herman Suit

Harvard / MGH Proton Center (1)

(1) Herman Suit, “The Grey Lecture 2001: Coming Technological Advances in Radiation Oncology,” International Journal of Radiation Oncology Biology Physics 53 No. 4 (2002): 798-809.

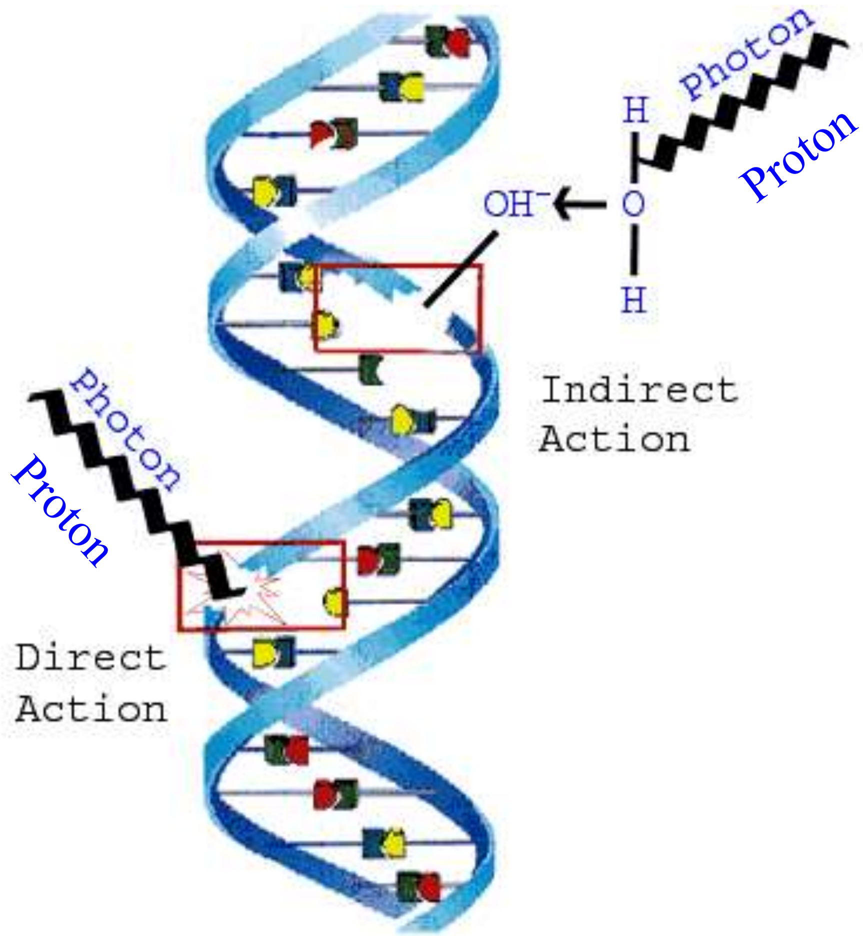
The Goal of Radiation Therapy for 100 years:

↑ Therapeutic Ratio = ↑ Tumor Control / ↓ Normal Tissue Complications

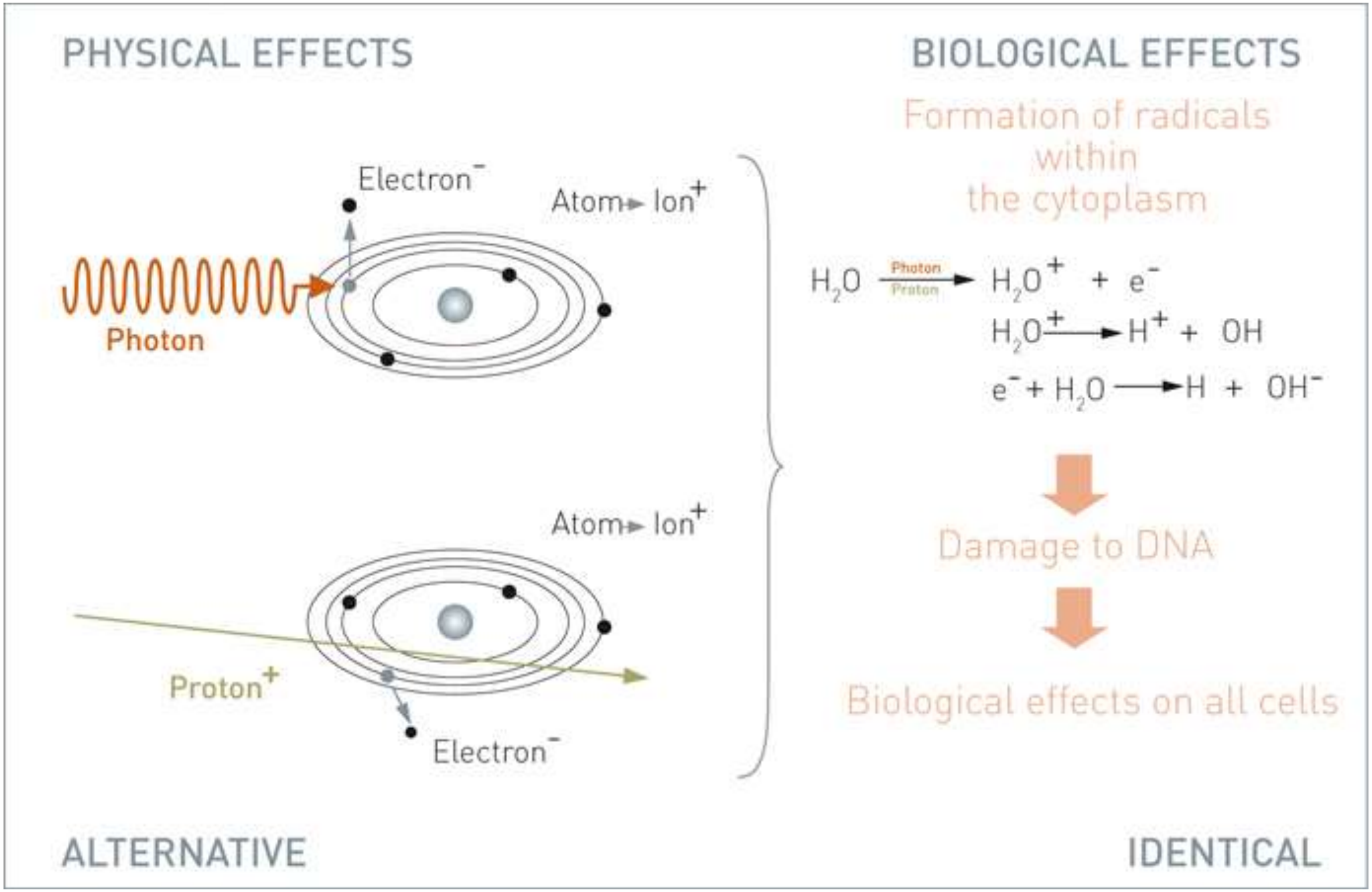
Potential improvement in <u>quality of life</u>

<u>Cost savings</u> by decreasing complications

How does Radiation Kill cells ?

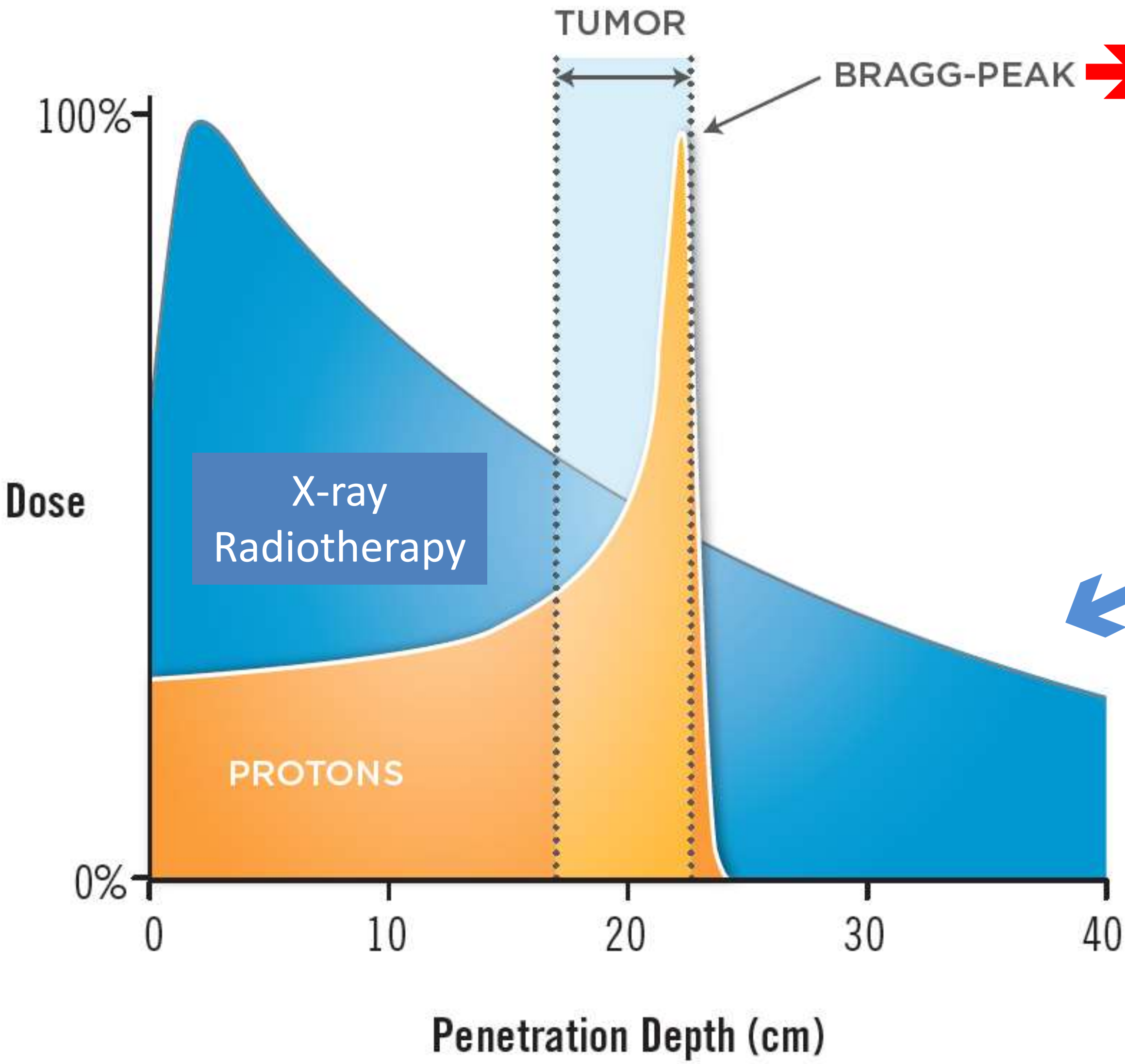


How does Radiation Kill cells ?



The Value of Protons

Protons are **physically superior** to X-rays:



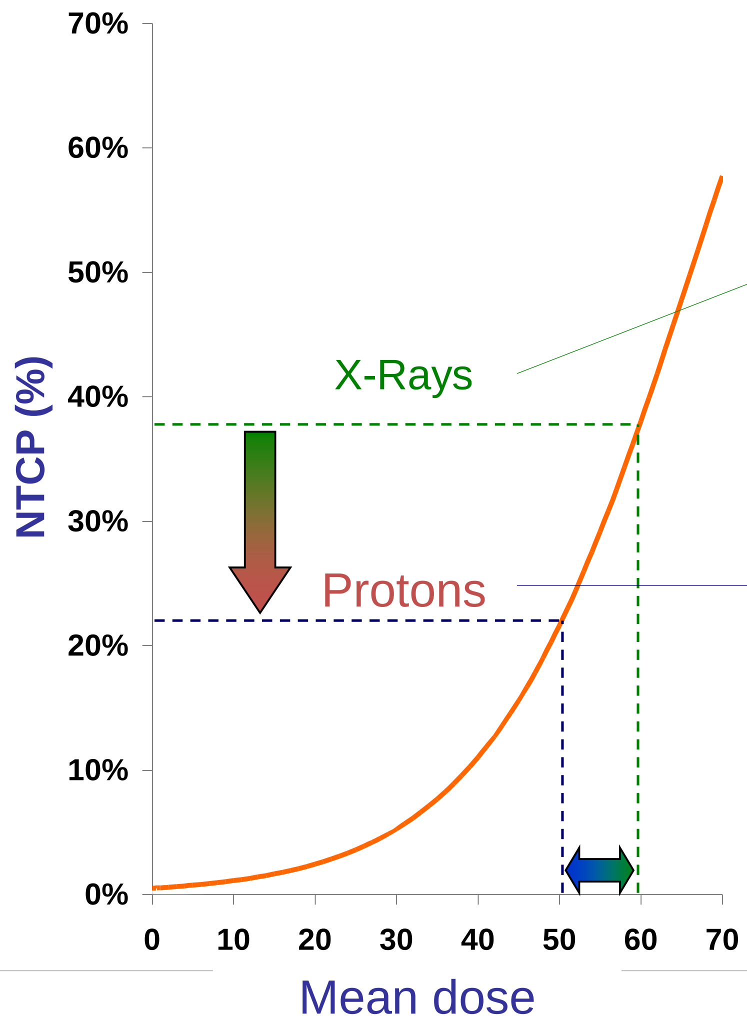
Protons

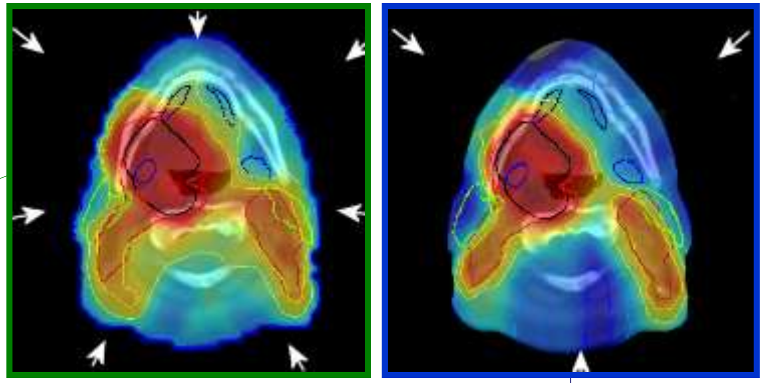
X-Rays do not stop

Continue to travel into normal tissues beyond the target

Individualized treatment - NTCP-models and *in silico* studies

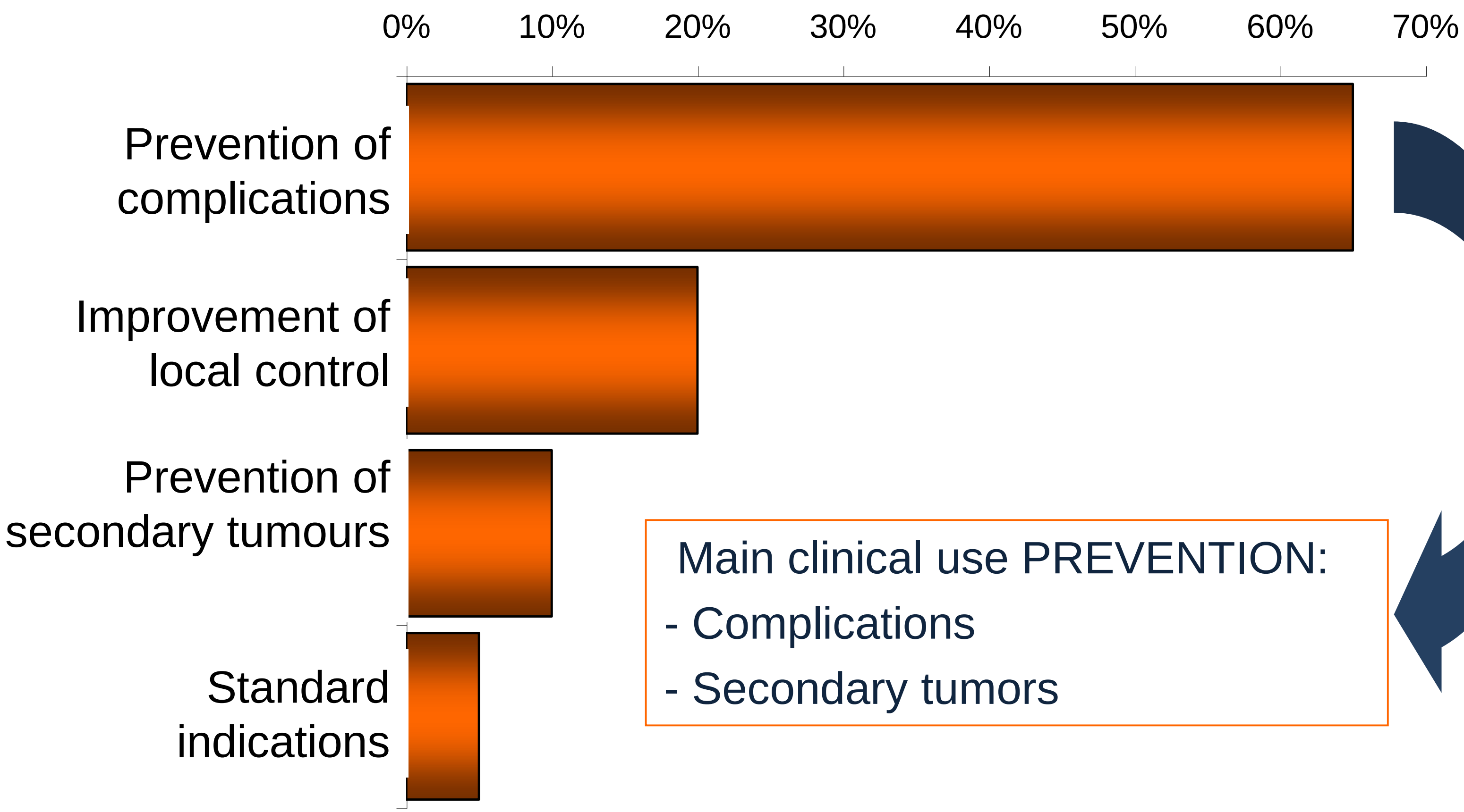
With Compliments – Dr Hans Langendijk - UMCG





Conversion of: *Dose difference*
to:
Clinical benefit (NTCP-value)

Proton therapy → Categories of indications



Main clinical use PREVENTION:

- Complications
- Secondary tumors

Source: Horizon scanning report (Health council of the Netherlands 2009)

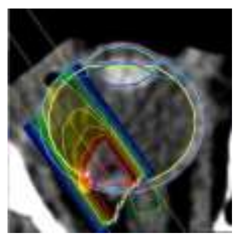
Proton Therapy – Past and Current Environment

- **First patient treatment in the U.S. occurred at Berkeley in 1954**
  - First IMRT treatment didn't occur until the early 1990s
- **Harvard - MGH began treating patients in 1961**
- **The first hospital based proton center in the U.S. was built at the Loma Linda University Medical Center in 1990**
  - Loma Linda initially treated prostate, brain, and some head and neck tumors
- **Currently: 15 operating centers in the U.S. and over 30 worldwide**
  - There are another 30+ proton centers in development in the U.S.
- **Medicare has paid for proton therapy since 1997**
- **Every major national insurance carrier has paid for proton therapy**

What Cancers Can Protons Treat?

Classic indications:

Base of skull tumors
Eye (uveal) melanomas
Brain tumors
Pediatric tumors
Spinal / Paraspinal tumors
Prostate cancers



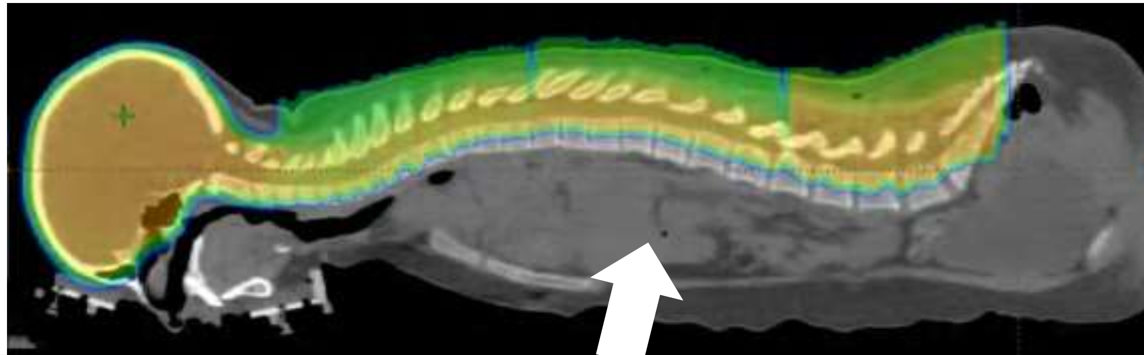
Lung
Liver
Breast
Esophagus
Pelvic tumors
Large sarcomas
Mediastinal tumors
Reirradiation of recurrent tumors

Pediatric Treatments

The Value of Protons

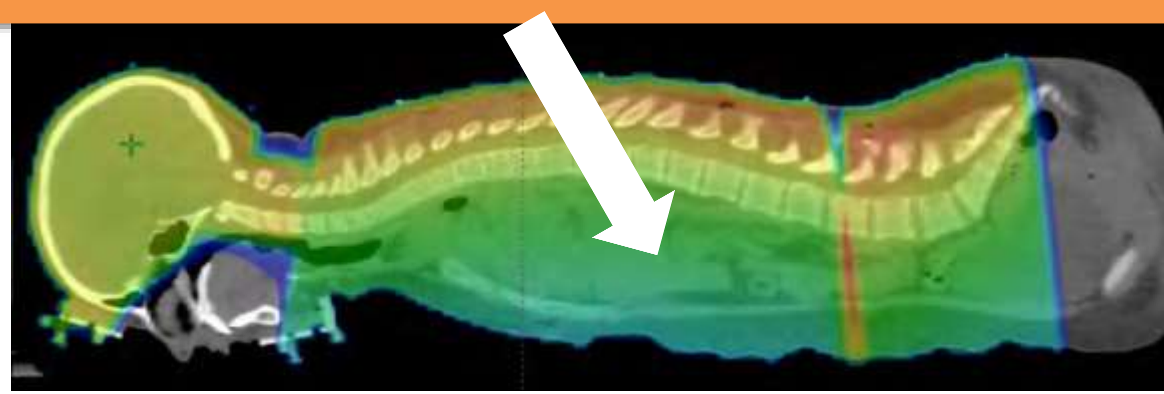
Protons are **physically superior** to X-rays:

Protons



Protons avoid unnecessary radiation

to heart, lungs, intestines delivered by X-rays

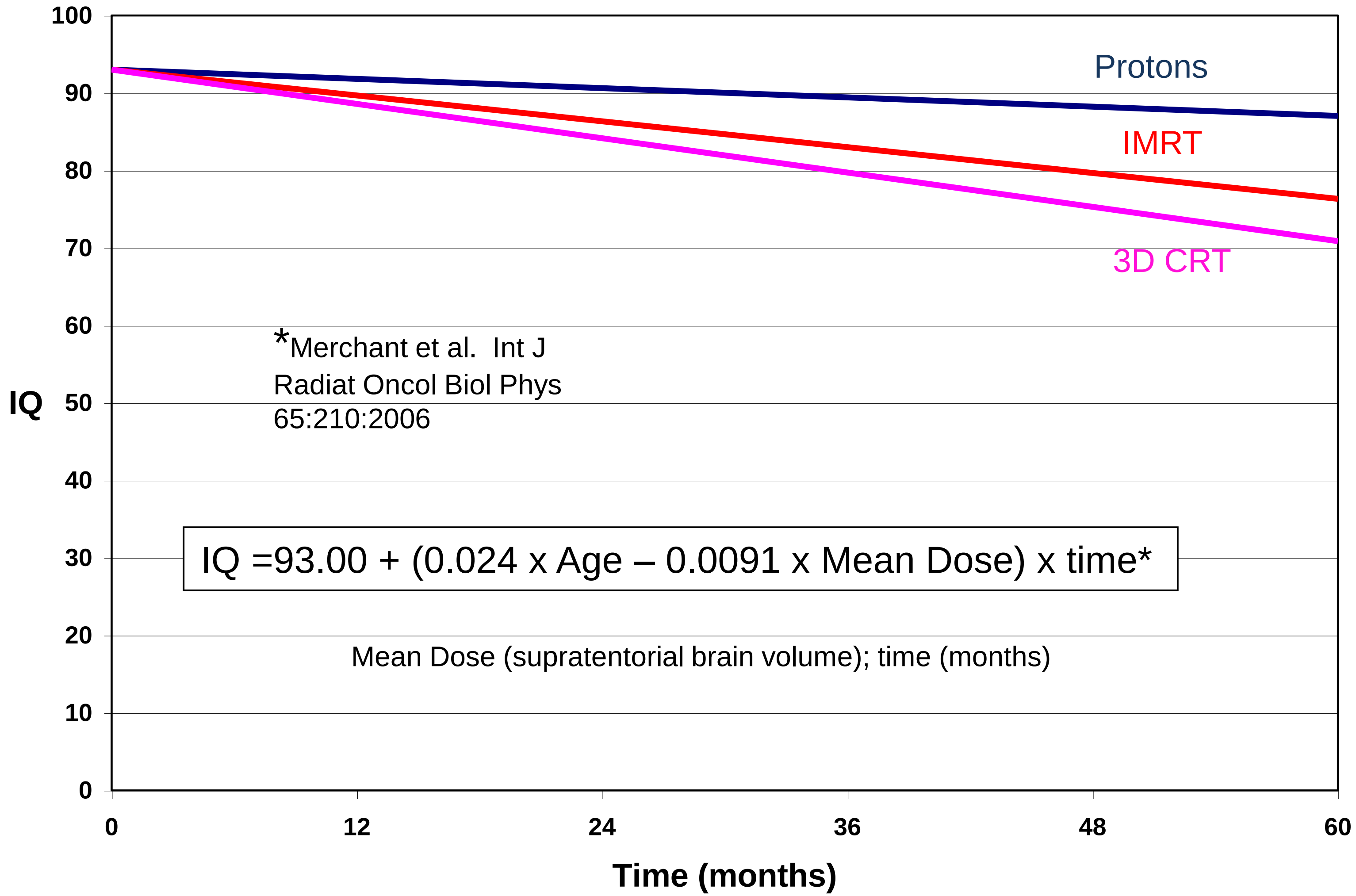


X-Rays do not stop

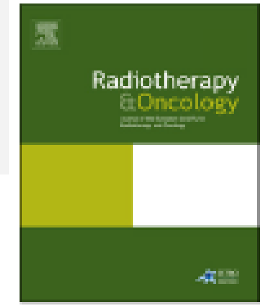
- Continue to travel
- into normal tissues
- beyond the target

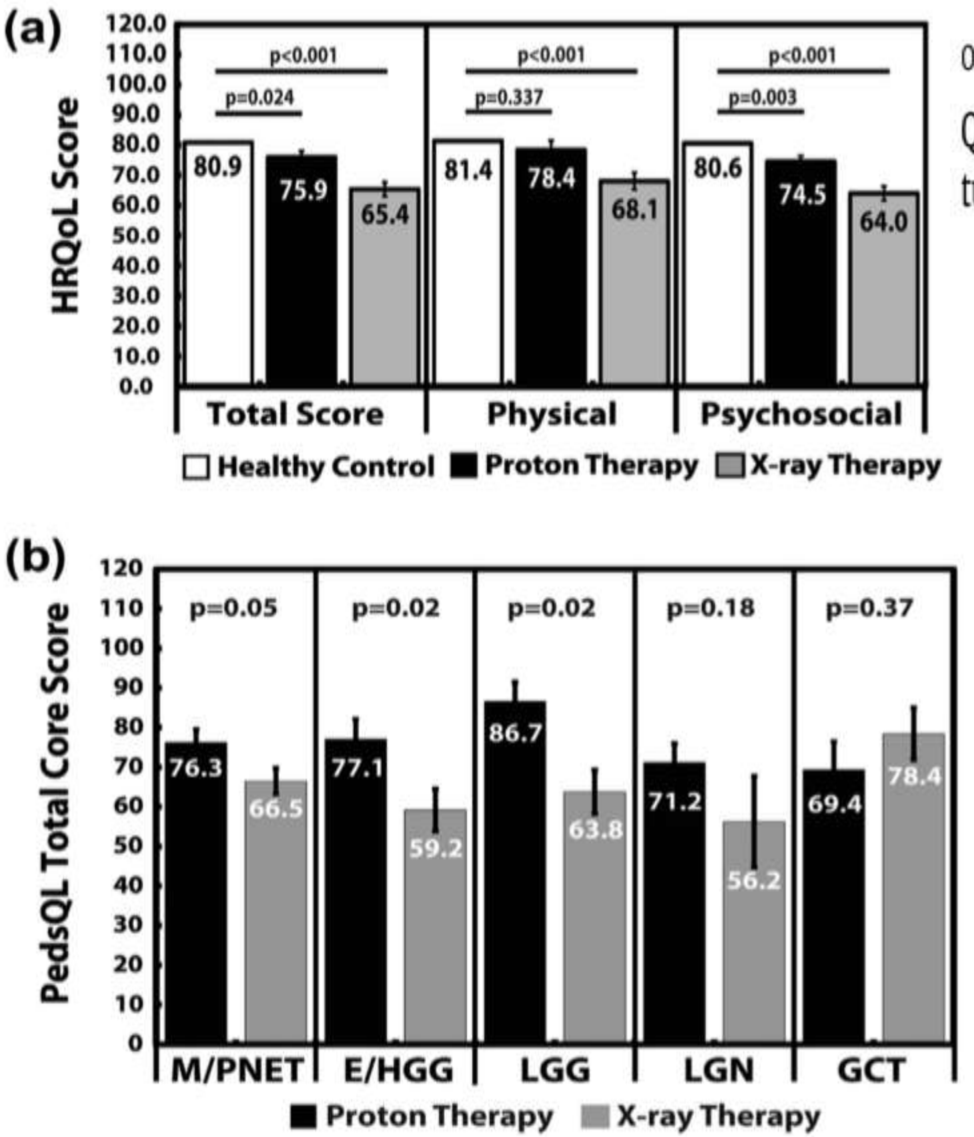
provision Health Alliance

Medulloblastoma Longitudinal IQ
IMRT vs. IMPT



Quality of Life





Original article

Quality of life outcomes in proton and photon treated pediatric brain tumor survivors

QOL for children 2-18 yrs treated at MGH (n=57) or Stanford (n=60)

Protons scored 10 pts higher in Psychosocial and Physical domains vs photons

Significant differences seen in Total QoL scores for Medulloblastoma, Ependymoma/High Grade Glioma, and Low Grade Glioma

International Journal of
Radiation Oncology
biology • physics
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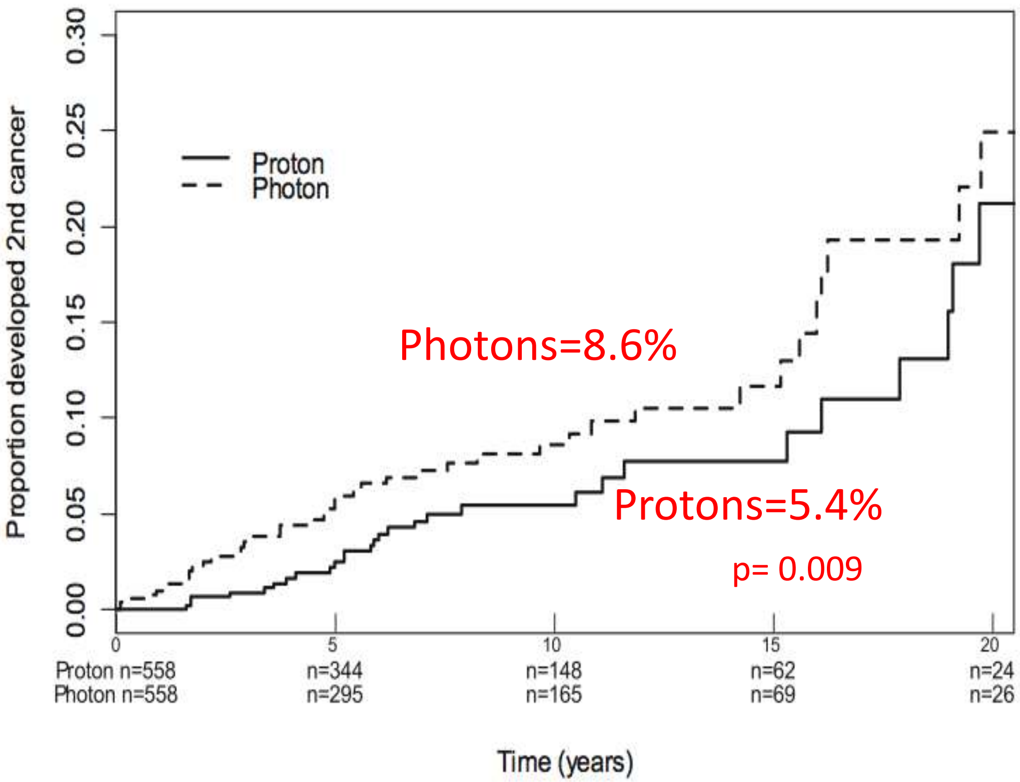
Second Malignancy

Late Effect

Incidence of Second Malignancies Among Patients Treated With Proton Versus Photon Radiation

Christine S. Chung, MD, MPH,* Torunn I. Yock, MD, MCh,† Kerrie Nelson, PhD,‡ Yang Xu, MS,§ Nancy L. Keating, MD, MPH,§,¶ and Nancy J. Tarbell, MD†,||



558 proton pts treated from MGH (1973 to 2001) compared with 558 matched photon pts (SEER)

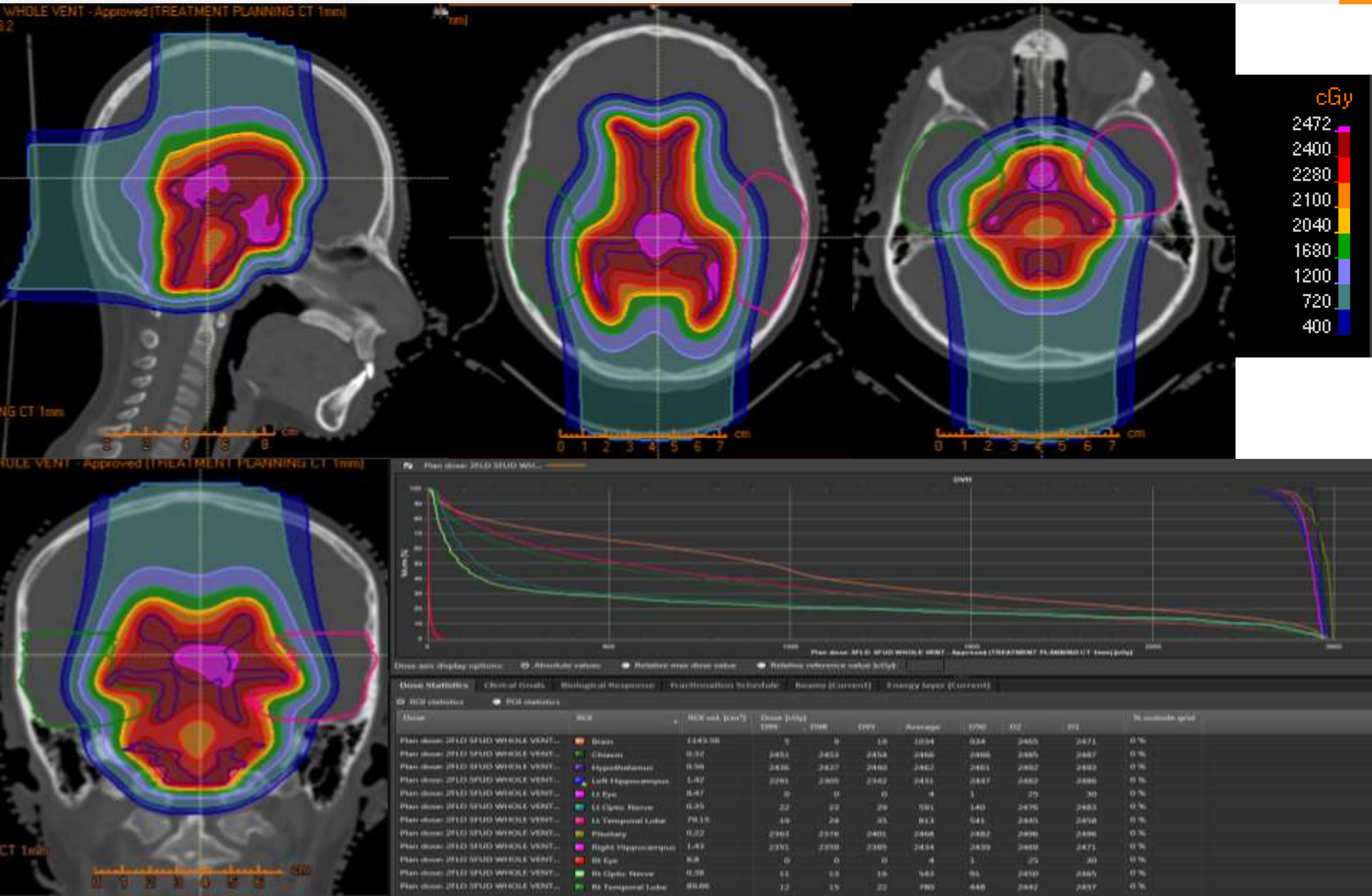
Hazard ratio

=0.52

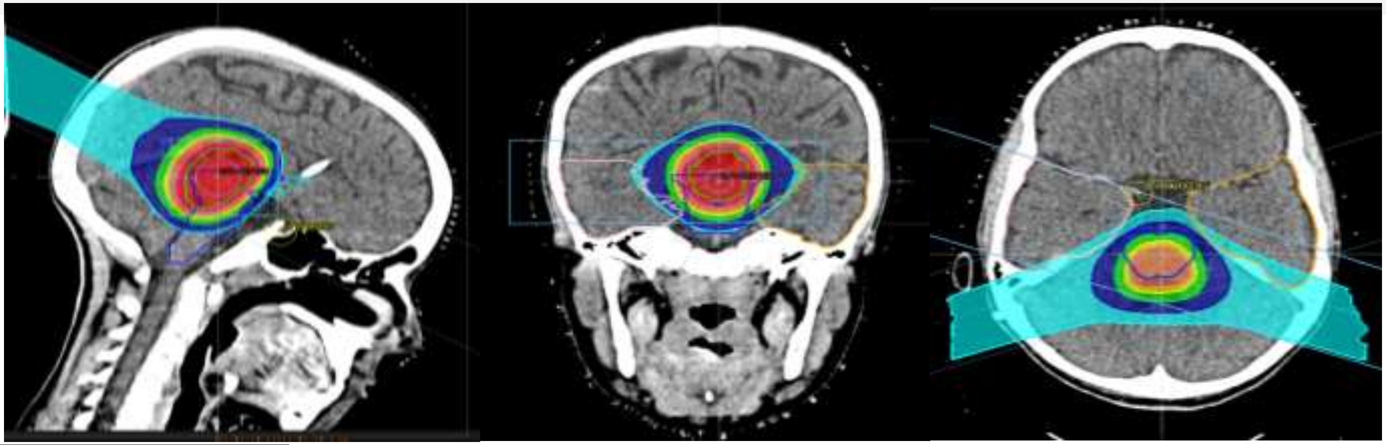
(CI 0.32-0.85, p=0.009)

Recent Cases At Provision

Bifocal Germinoma



Tectal Glioma 50.4 CGE



Dose	ROI	ROI vol. [cm³]	Dose [cGy] D99	D98	D95	Average	D50	D2	D1	%
Plan dose: Brain 50.4C...	Brainstem	30.07	27	47	151	3273	3746	5166	5172	0 %
Plan dose: vmat (TREA...	Brainstem	30.07	669	741	976	4204	4883	5231	5241	0 %
Plan dose: Brain 50.4C...	CTV 50.4	18.02	5054	5067	5079	5127	5130	5178	5181	0 %
Plan dose: vmat (TREA...	CTV 50.4	18.02	5040	5048	5063	5146	5144	5242	5247	0 %
Plan dose: Brain 50.4C...	Hypothalamus	0.64	34	42	62	585	517	1488	1583	0 %
Plan dose: vmat (TREA...	Hypothalamus	0.64	828	866	953	2243	2053	3984	4062	0 %
Plan dose: Brain 50.4C...	Left Temporal Lobe	85.95	0	0	0	504	193	1470	1866	0 %
Plan dose: vmat (TREA...	Left Temporal Lobe	85.95	134	143	169	956	957	2697	3301	0 %
Plan dose: Brain 50.4C...	Right Temporal Lobe	91.45	0	0	0	485	137	1645	1904	0 %
Plan dose: vmat (TREA...	Right Temporal Lobe	91.45	159	179	277	1137	1045	3093	3652	0 %

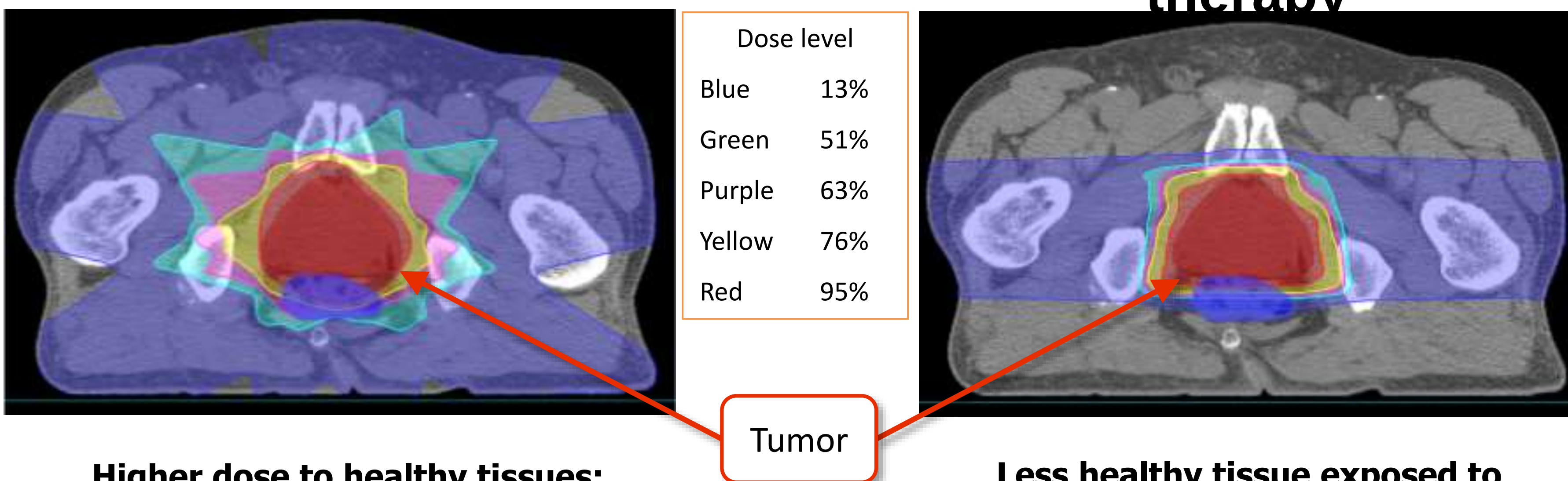
Prostate Cancer

Radiotherapy for Prostate Cancer

Conventional radiotherapy X-rays (IMRT) exposes more healthy tissue to radiation

Conventional radiotherapy X-rays (IMRT)

Proton therapy

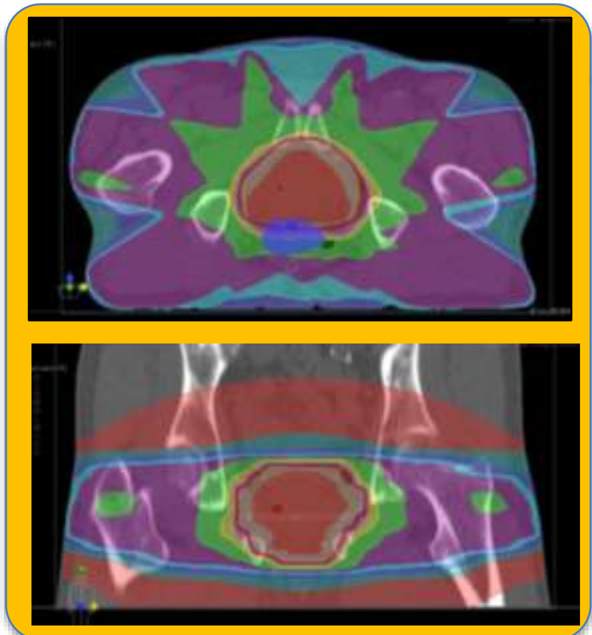


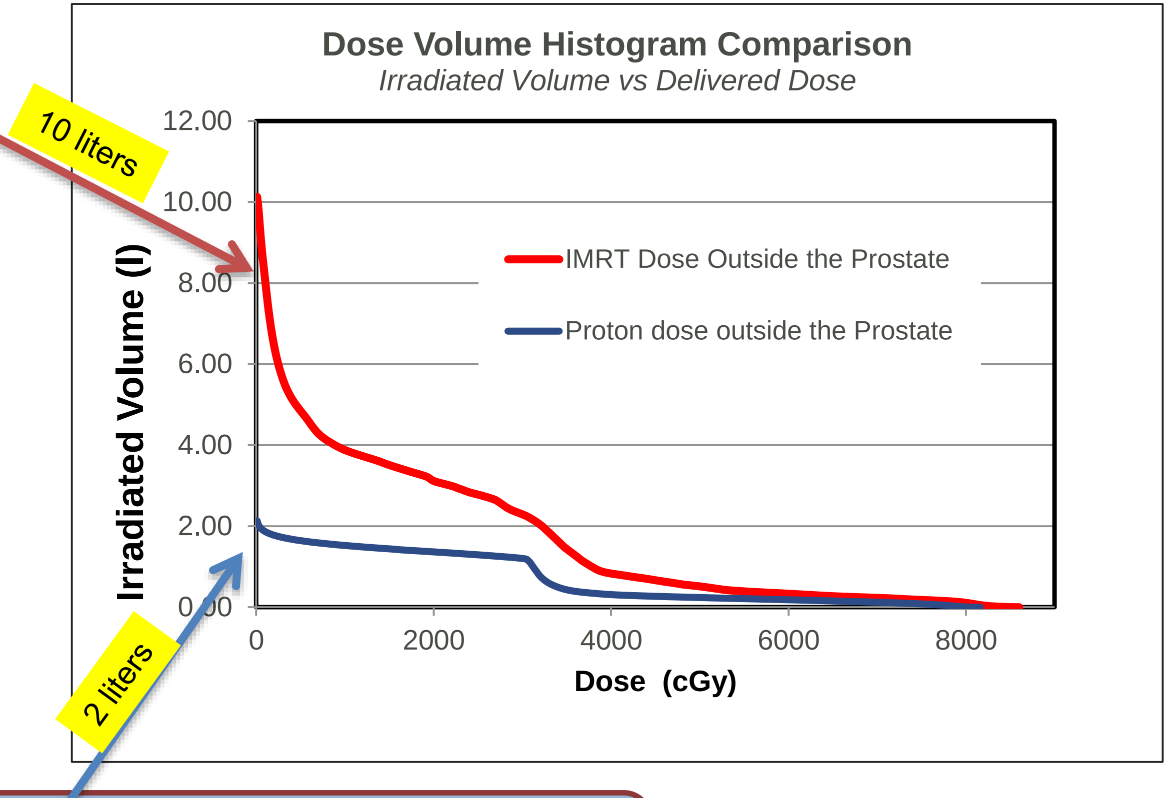
Higher dose to healthy tissues: Pelvis, rectum and bladder

Less healthy tissue exposed to radiation with protons

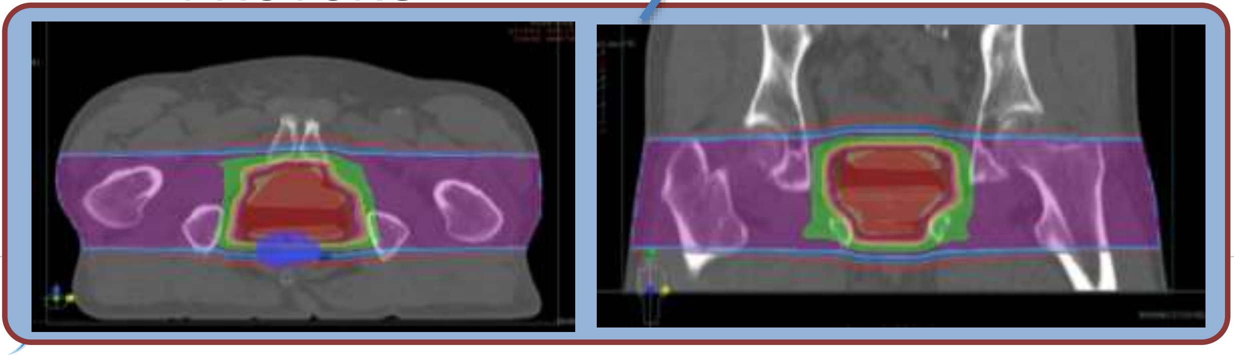
Proton and IMRT – Prostate Plan

IMRT (10 liters)





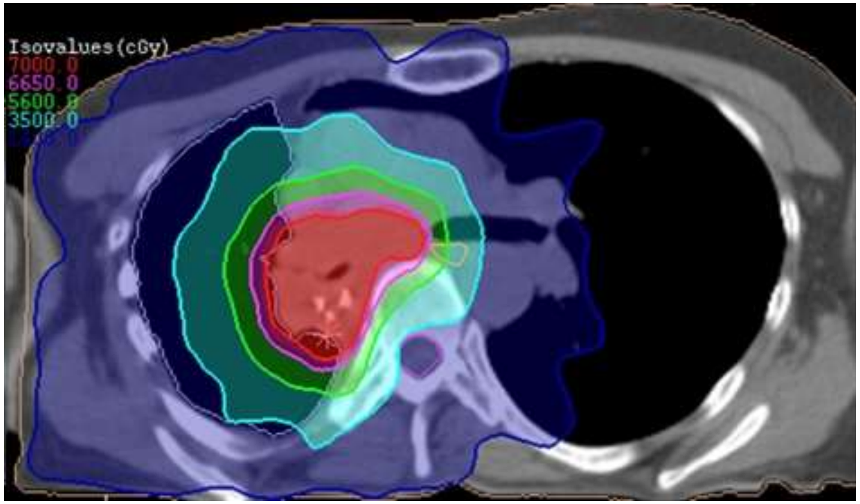
PROTONS



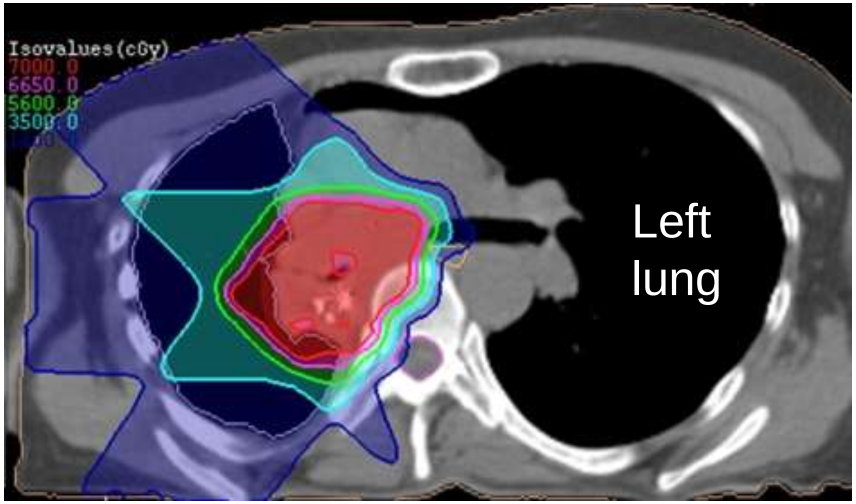
Lung Cancer

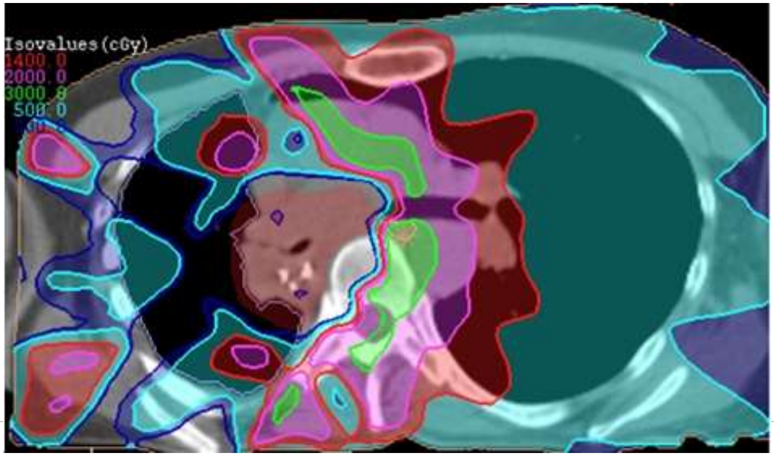
Why Protons for Lung Cancer ?

Conventional radiotherapy X-rays (IMRT)



Protons



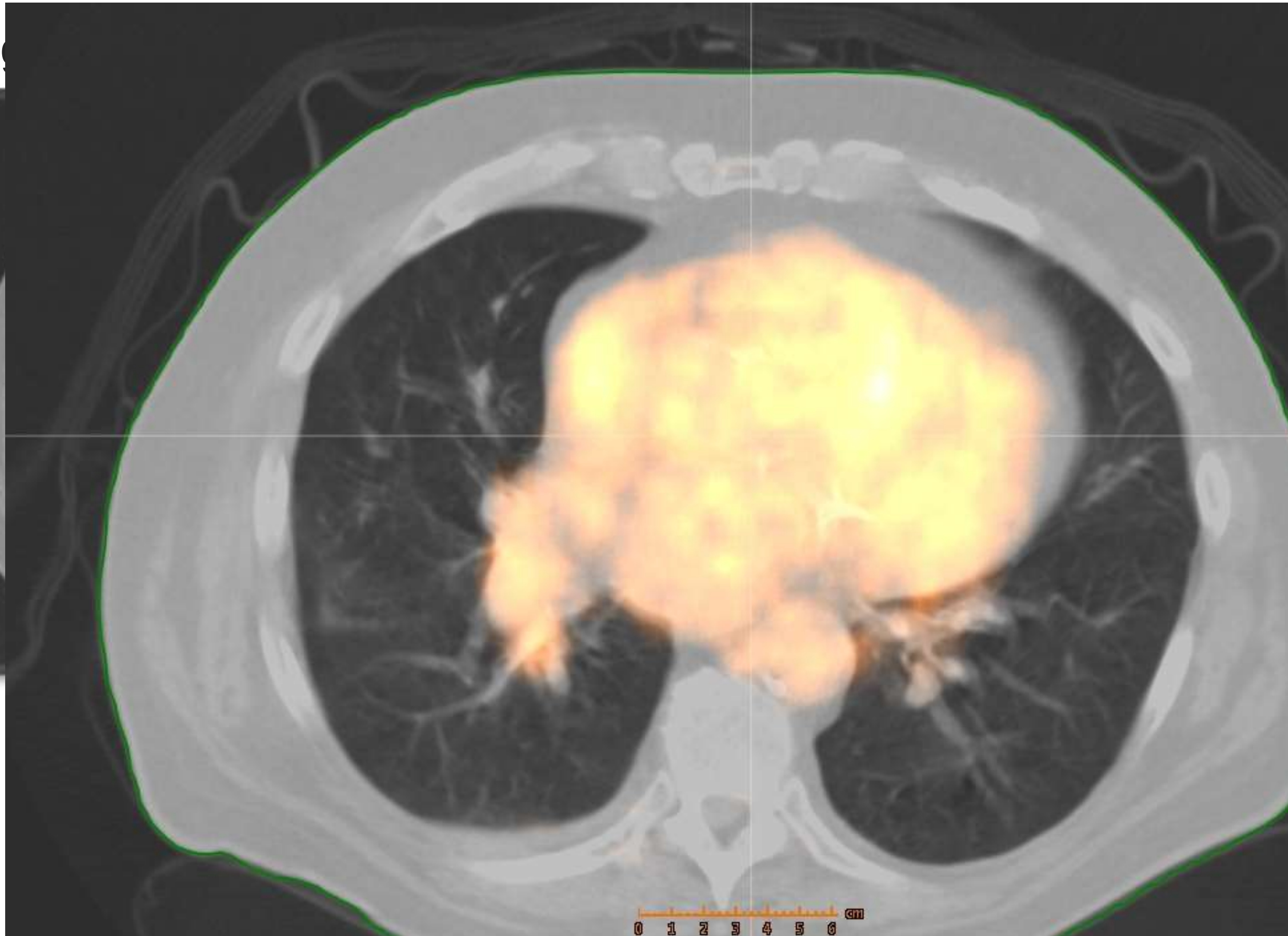


Difference

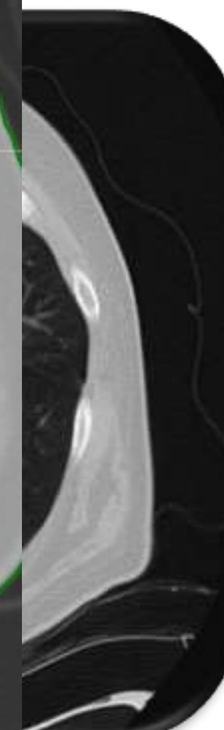
Protons decrease unnecessary dose to:
Left lung
Esophagus
Heart
Spinal cord

Clinical Case 1

Ri



nth



M.D. Anderson treatment related toxicity data for inoperable locally advanced lung cancer:

NSCLC treated with radiation therapy + chemotherapy[1]

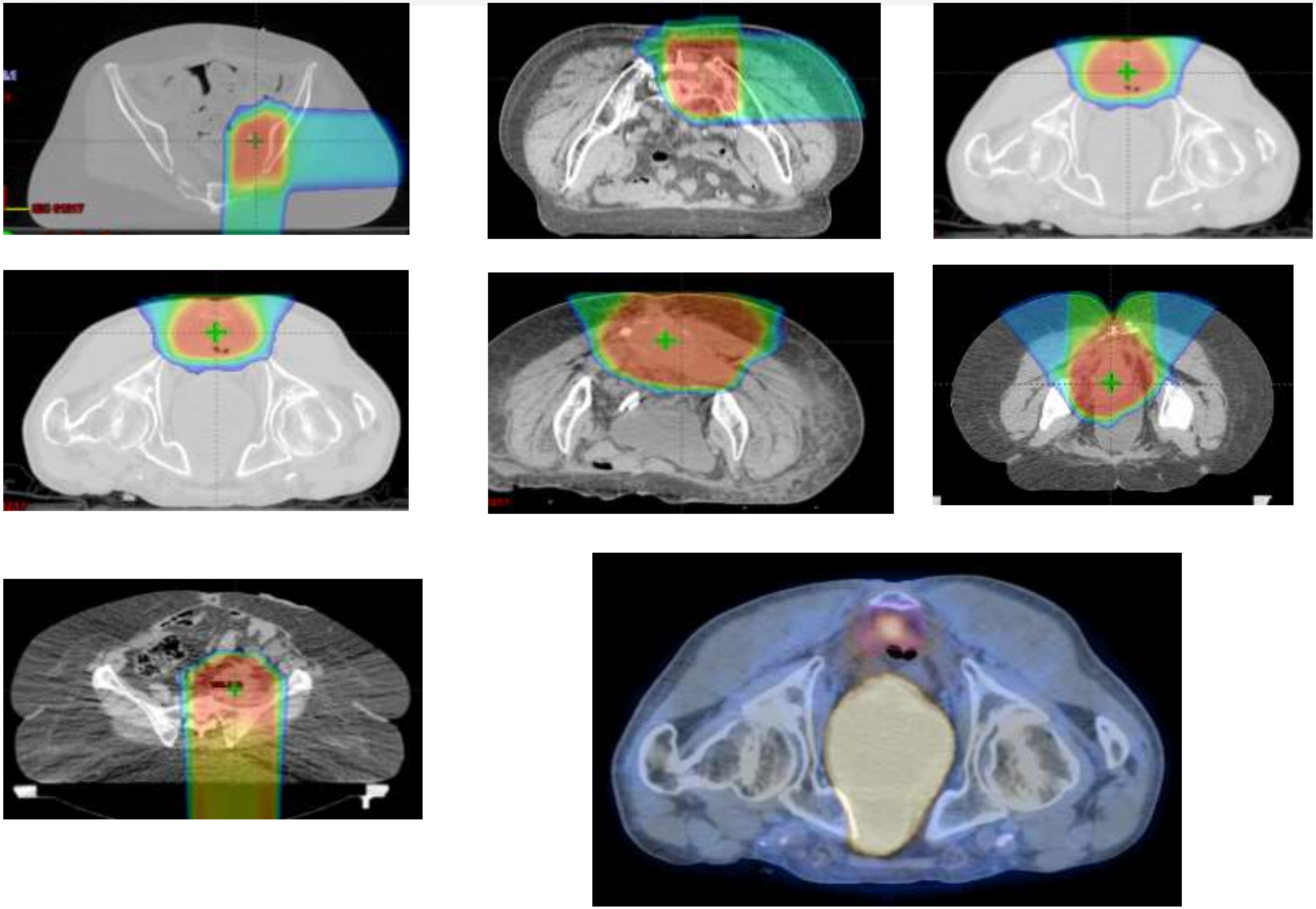
	3D CRT	IMRT	Protons
Dose	63 Gy	63 Gy	74 CGE
% patients stage IIIA-B2	*87%*	*91%*	*87%*
Toxicity			
Esophagitis – G3+	*18%*	*44%*	*5%* ↓
Pneumonitis – G3+	*30%*	*9%*	*2%* ↓

[1] Samir Sejpal et al., “Early findings on toxicity of proton beam therapy with concurrent chemotherapy for nonsmall cell lung cancer,”
Cancer. 2011 Jul 1;117(13):3004-13

Lung Cancer Proton Therapy Trials

Study name	Trial type	Modalities	Description	Selection criteria (inoperable)
Proton with chemo				
M.D. Anderson	Phase II	Protons and chemo	-Primary goal is to improve survival -Chemo and 74 CGE of proton therapy	Stage IIIA and IIIB
Loma Linda	Phase I/II	Protons and chemo	-Chemo with accelerated proton therapy -5 week RT (first two weeks – daily; final three weeks – twice daily)	Stage II,IIIA or IIIB
University of Florida	Phase II	Protons and chemo	-Chemo with higher 74 CGE dose delivered by protons	Stage IIIA or IIIB
UPENN	Phase I/II	Protons and chemo	- Chemo with 5.5 – 7.5 weeks of proton radiation (total dose not disclosed)	Stage IIIA that are eligible for surgery
UPENN	Phase I	Protons and Nelfinavir	-Goal is to test the highest safest dose of proton therapy that can be given concurrently with drug	Stage IIIA or IIIB
Randomized				
M.D. Anderson	Phase II	Protons and x-rays	-Randomize between x-rays and protons	Stage II-IIIB
PCG	Phase III	Protons and x-rays	-Randomize between x-rays and protons	Stage IIIA - IIIB
Hypofractionation				
M.D. Anderson	Phase I	Protons	-Hypofractionating starting at 45 Gy in 15 Fx to 60 Gy in 15 Gy	-NSLC, small cell lung cancer, thymic or carcinoid tumors
University of Florida	Phase II	Protons	Hypofractionating: -48 CGE in 4 fx (peripherally located) -60 CGE in 10 fx (centrally located)	Stage I
Dose escalation				
M.D. Anderson	Phase II	Protons	-Dose escalation to 87.5 CGE in 35 Fx	Stage IA, IB, and selected stage II

Rectal Re-irradiation



A. Berman and J. Plastaras – U PENN (PTCOG – Essen 2013)

Breast Cancer

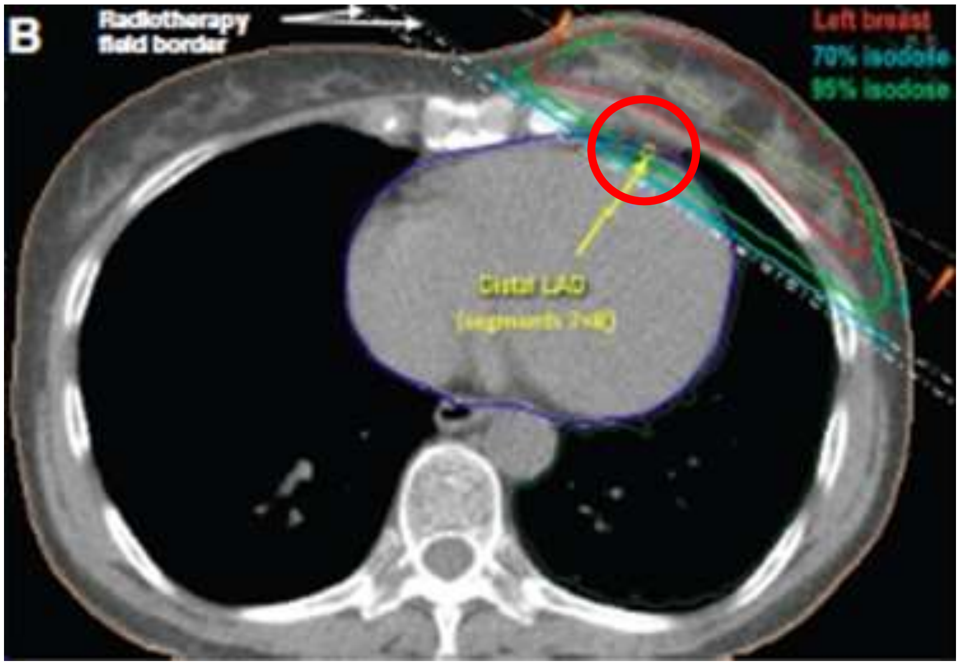
Breast Cancer Treatment

- **Many breast cancer patients will receive radiation therapy as part of their course of treatment**

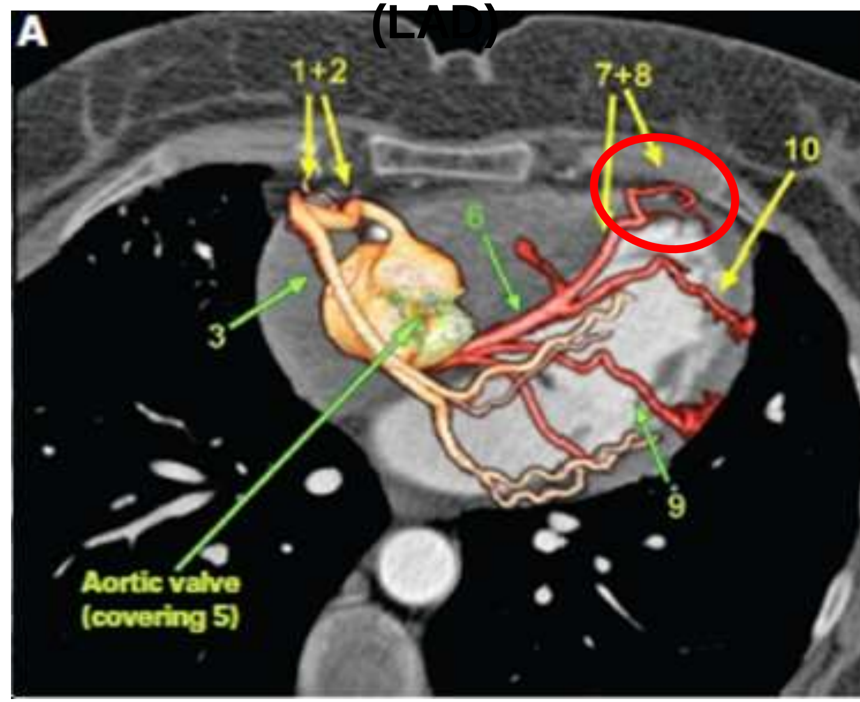
- **Patients are at risk for post treatment complications resulting from radiation to the heart, lungs and contralateral breast**
  - These risks may increase if patients:
    - a) Receive cardio-toxic chemotherapy drugs
    - b) Have smoking history
    - c) Left sided breast cancer

- **Protons can spare critical structures and can deliver approximately 10 times less radiation to the heart than conventional X-Ray radiation**

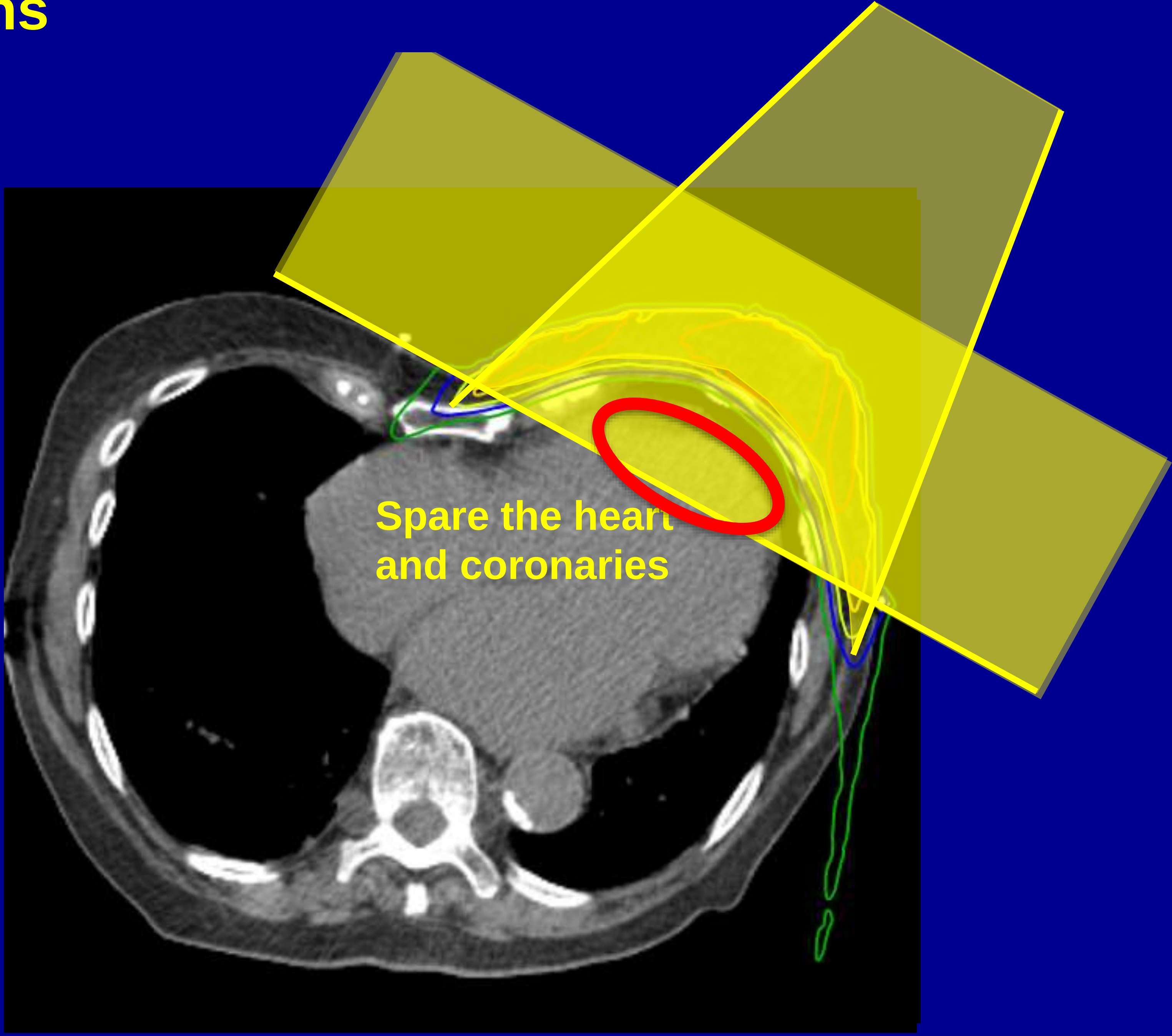
Coronary Exposure to Radiation in Conventional Radiotherapy for Breast Cancer



Stenosis of the main coronary artery left anterior descending (LAD)



Use Protons



The NEW ENGLAND JOURNAL of MEDICINE

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Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

Sweden and Denmark: **Population-based study of 2168 pts post-radiotherapy for Breast Cancer**

Risk of major coronary events: Myocardial infarction
Coronary revascularization
Death from ischemic heart disease

…were correlated with mean radiation dose delivered to the heart.

The Risk of major coronary event increases by 7.4% per gray of exposure to the heart[1]

Heart toxicity (cont)

ASTRO states that *"in patients with breast cancer, it is recommended that the irradiated heart volume be minimized to the greatest possible degree without compromising the target dose"*[1]

	3DCRT	IMRT	Tomo	Protons
LAD mean dose	23.7	19.9	10.6	**5.8 Gy**
Heart mean dose	7.3	8.2	10.5	**0.9 Gy**
Total Lung V5 Gy	33.6%	54.6%	46.3%	**20.6%**
Contral. Breast mean	1.5	3.9	[illegible]	**0.2 Gy**
Unspecified normal tissue volume ≥ 10 Gy (cc)	2817	[illegible]	[illegible]	**353**

57.5% reduction in the Risk of major coronary event

[1] Gagliardi et al., "Radiation dose-volume effects in the heart," Inte [illegible] cs Supplement 2010: S77-S85

2 Fagundes, M. et al. "Cardiac Sparing Adjuvant Proton Radiother [illegible] 2013.

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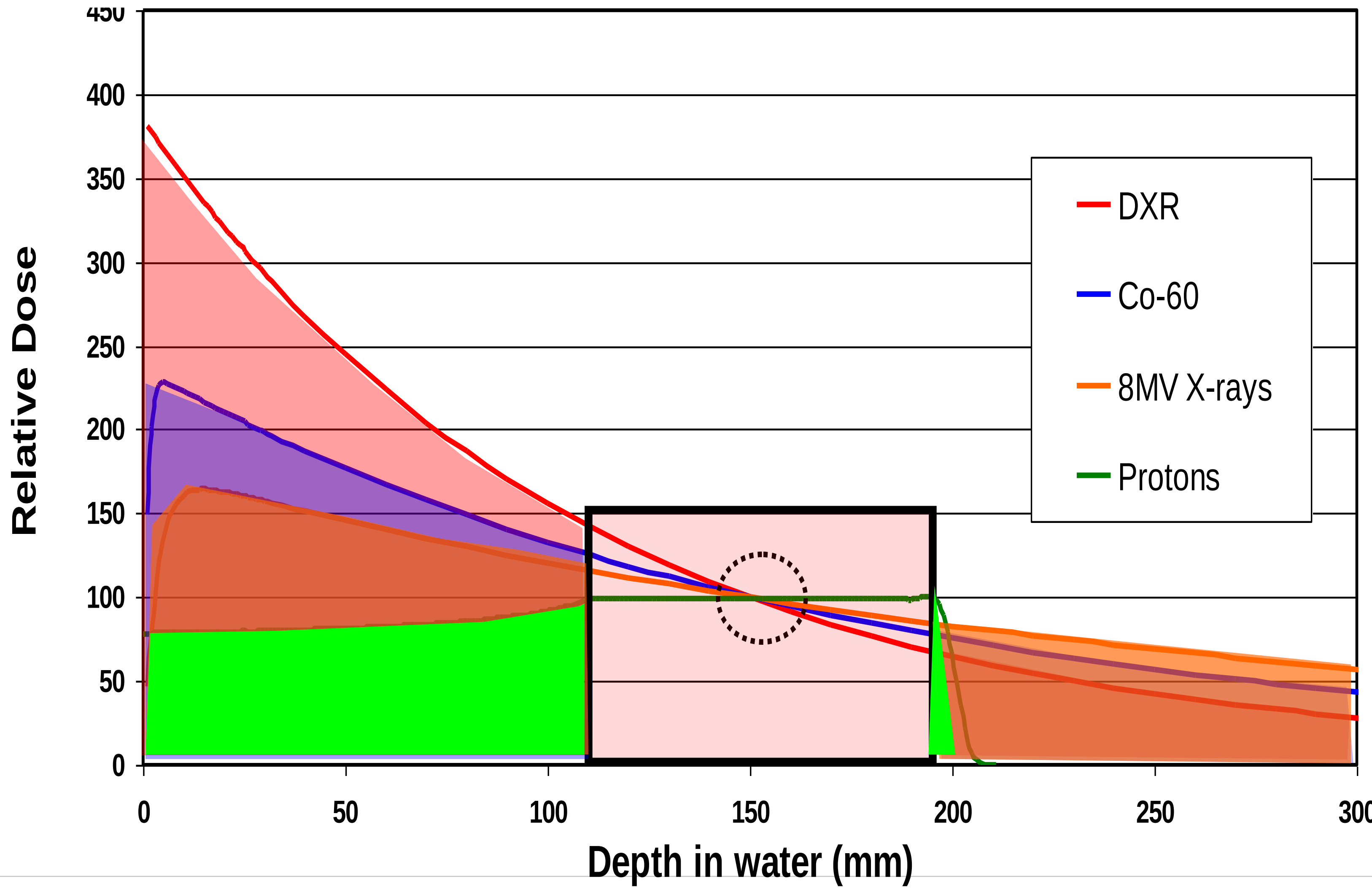
“Direct Radiation Complications Never Occur In Unirradiated Tissues”

Dr. Herman Suit
Harvard / MGH Proton Center [1]

(1) Herman Suit, “The Grey Lecture 2001: Coming Technological Advances in Radiation Oncology,” International Journal of Radiation Oncology Biology Physics 53 No. 4 (2002): 798-809.

Treatment Modality Evolution



Cost of Complications

- **The average lifetime cost of a severe heart attack has been estimated to be about $1 million[1]**
- **~75% of health care costs in the U.S. goes to the treatment of chronic diseases[2]**
- **In 2010 the cost of cardiovascular disease / stroke in the U.S. was about $432 billion (1 in every 6 dollars spent on healthcare)[3]**

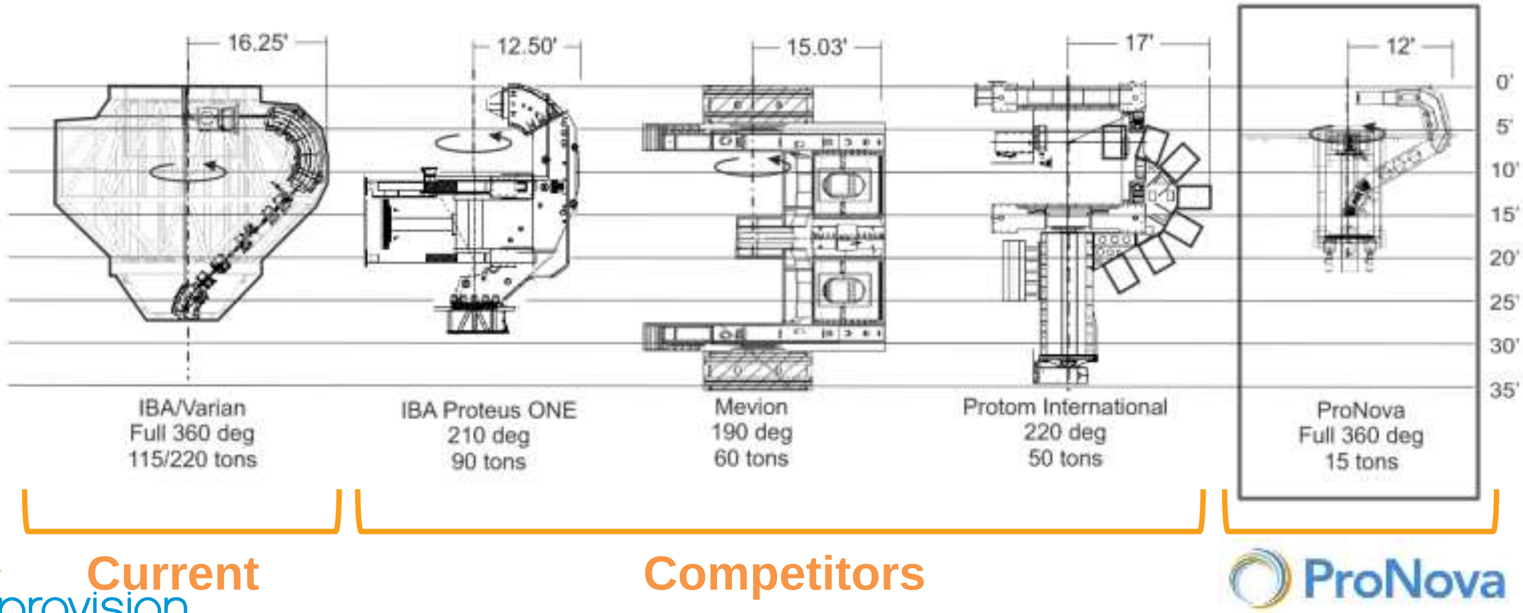
The best way to reduce the overall cost of cancer care is to eliminate the chronic side effects of treatment

1 *National Business Group On Health.*
2 "Chronic Disease Prevention and Health Promotion". *Centers for Disease Control and Prevention.* August 5, 2013. http://www.cdc.gov/chronicdisease/index.htm
3 Mensah G, Brown D. An overview of cardiovascular disease burden in the United States. *Health Aff* 2007; 26:38-48.

The Future of Proton therapy

Leveraging Technology

- **Superconducting magnets have multiple benefits**
  - Dramatically smaller size, weight, and power
  - 2X higher magnetic field, 0.5X bend radius
- **ProNova leverages superconducting magnet technology**
  - Maintains 360° rotation similar to radiation therapy
  - Ample room for full ring imaging at isocenter
  - Simplified shipping and installation reducing cost and time to market



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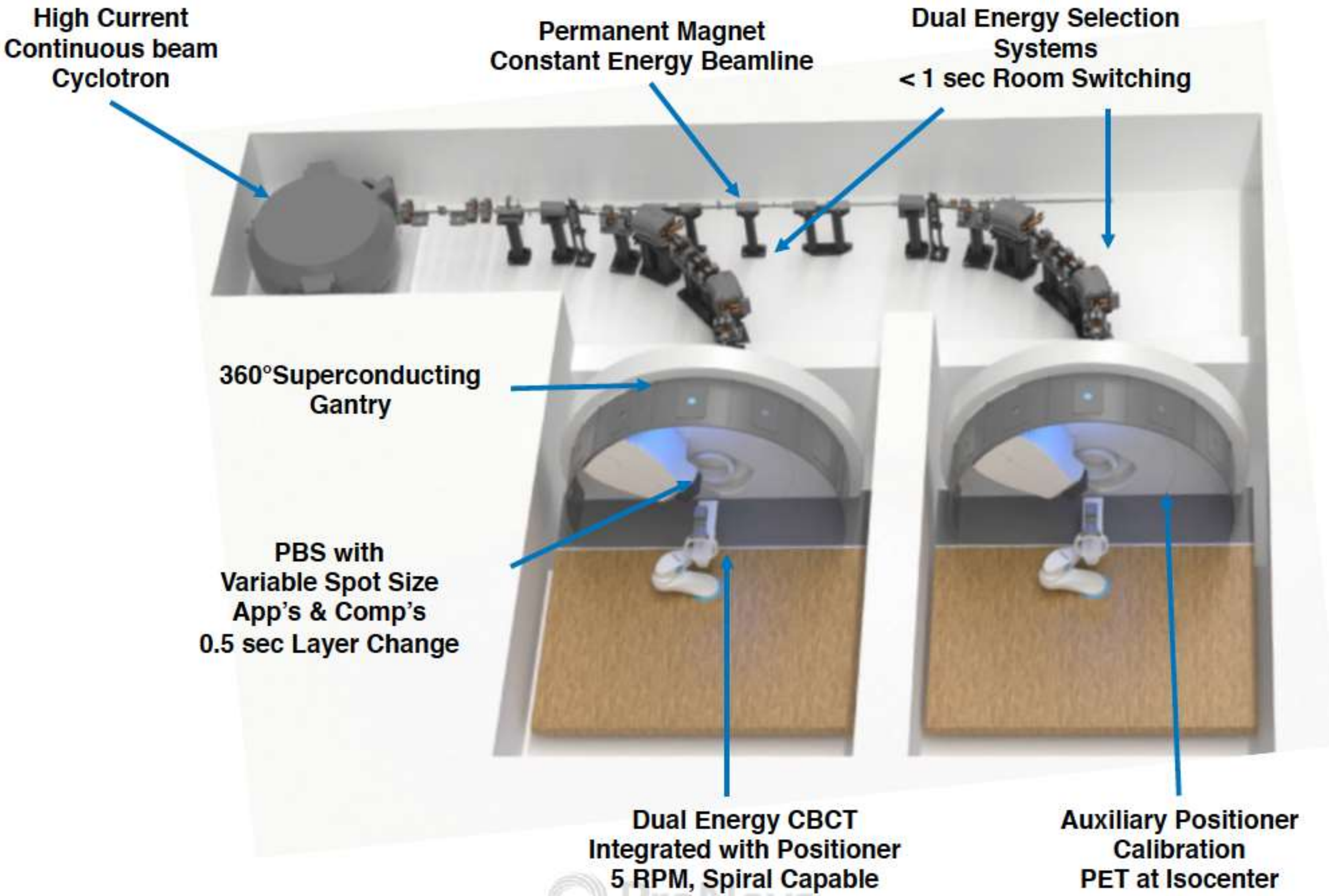
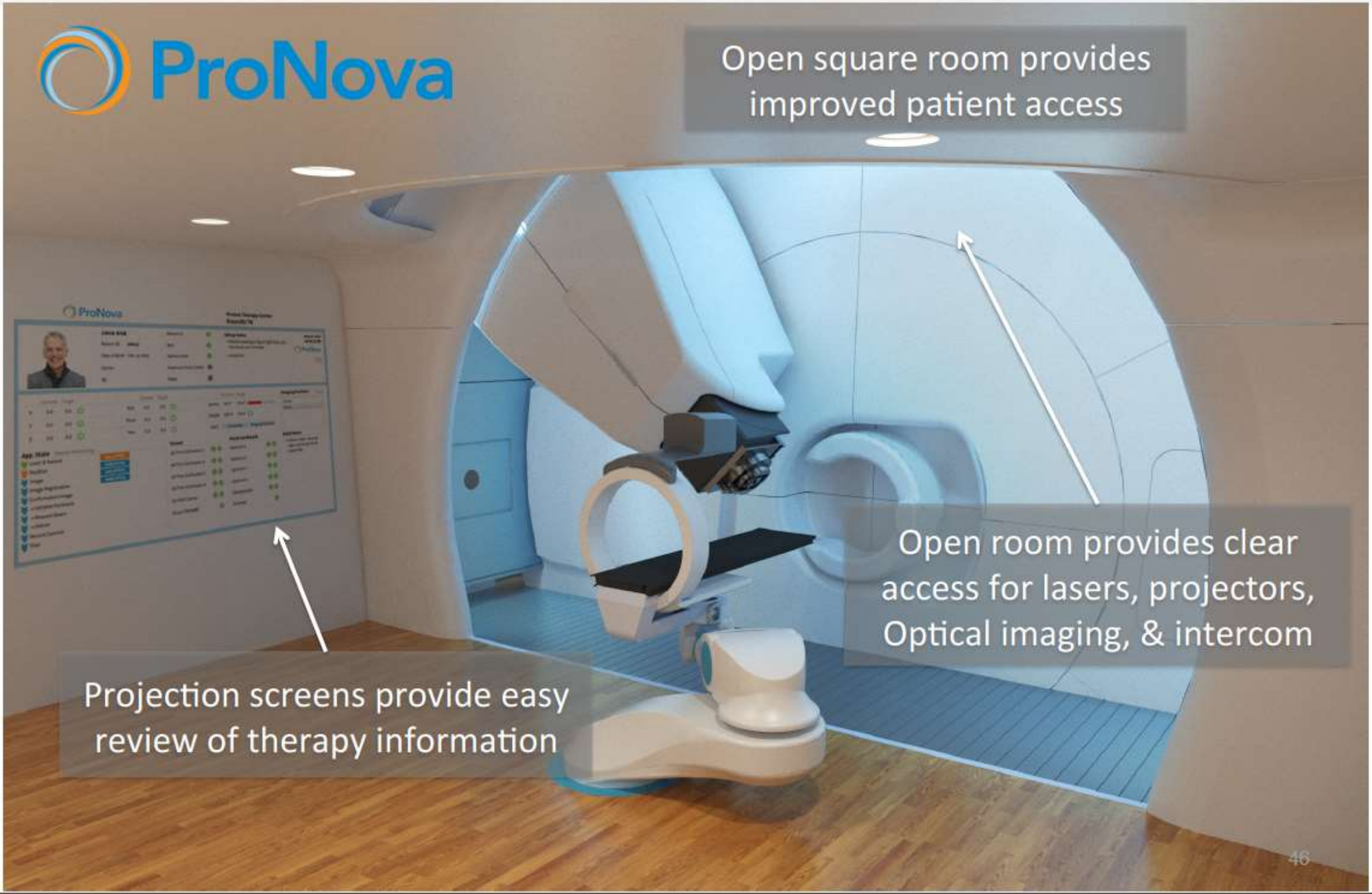
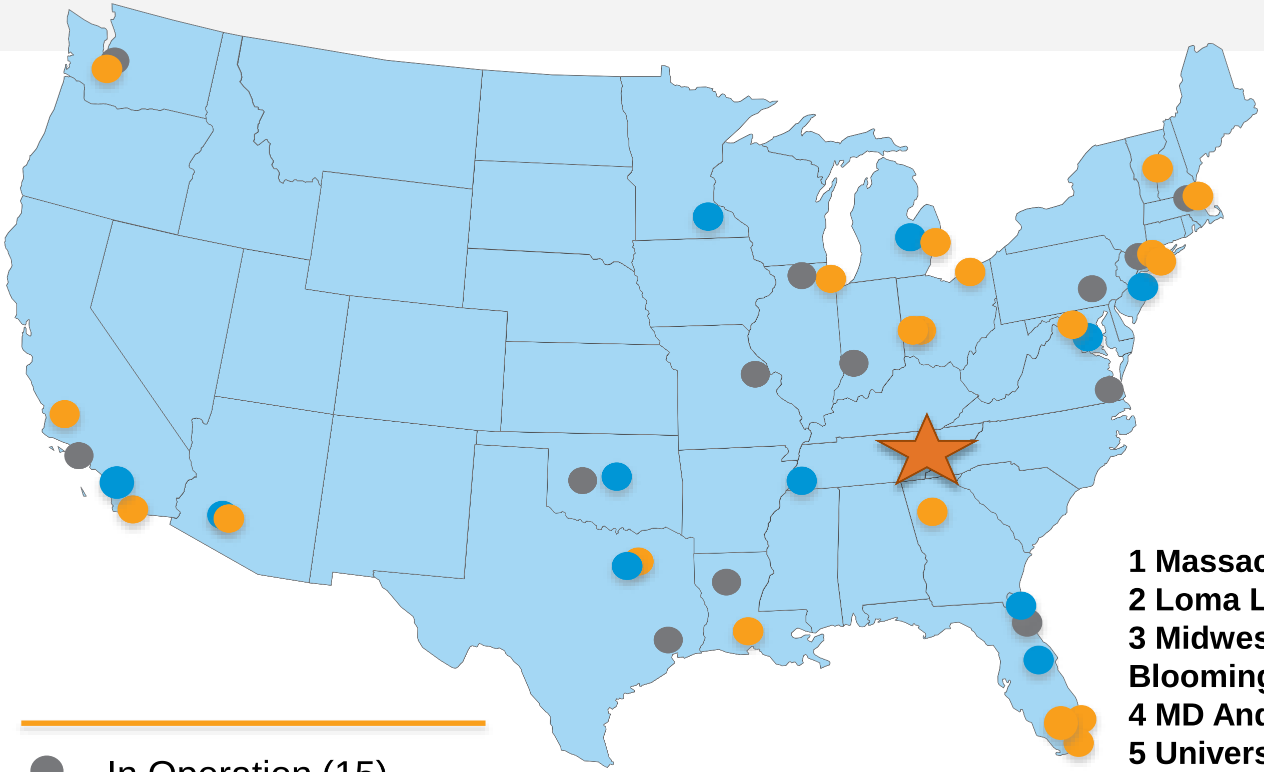
SC360 Efficient 1, 2, 3+ Room Solution




ProNova
Open square room provides improved patient access
Open room provides clear access for lasers, projectors, Optical imaging, & intercom
Projection screens provide easy review of therapy information

ProNova R&D and Manufacturing Facility

U.S. Proton Therapy Centers



In Operation (15)

Under Construction (13)

Under Development (21)

1 Massachusetts General Hospital, Boston
2 Loma Linda University Medical Center, Calif.
3 Midwest Proton Radiotherapy Institute, Bloomington
4 MD Anderson Cancer Center, Houston (PTCH)
5 University of Florida Proton Therapy Institute, FL
6 ProCure Proton Therapy Center Oklahoma City, O
7 University of Pennsylvania Health System, Philadelphia
8 Hampton University Proton Therapy Institute, Hampton
9 ProCure Proton Center, Chicago
10 ProCure Proton Center, New Jersey
11 ProCure Proton Therapy Center, Seattle
12 Washington University, St. Louis
13 Provision Center for Proton Therapy, Knoxville
14 Scripps Proton Therapy, San Diego
15 Willis Knight Shreveport LA

The future of Proton Therapy

- **All truth passes through three stages.**
  - *First, it is ridiculed.*
  - *Second, it is violently opposed.*
  - *Third, it is accepted as being self-evident –*
    - ***Arthur Schopenhauer (1788 1860)***

The Truth of Proton Therapy is now almost through the second Phase

Provision Center for Proton Therapy

Thank You

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