Particle Therapy: Past, Present & Future

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Saif Aljabab, MBBS, FRCPC

Assistant Professor

Radiation Oncology

Roswell Park Cancer Center

Disclosures

- Nothing to disclose

Outline

- Why Talk about Particle Therapy? (3)
- The History and Fundamentals of Proton Therapy (15)
- Proton Therapy Past Technology (10)
- Proton Therapy Present Technologies (15)
- Particle Therapy Future Technologies (15)
- Summary (2)

What is your field of practice?

1. Dosimetrist
2. Therapist
3. MD
4. Nurse
5. Physics
6. Administration
7. Other

Do you have any proton experience?

1. I am an expert
2. I have practical experience
3. I understand it well, but no experience
4. I don’t know much about it

Why talk about particle therapy?

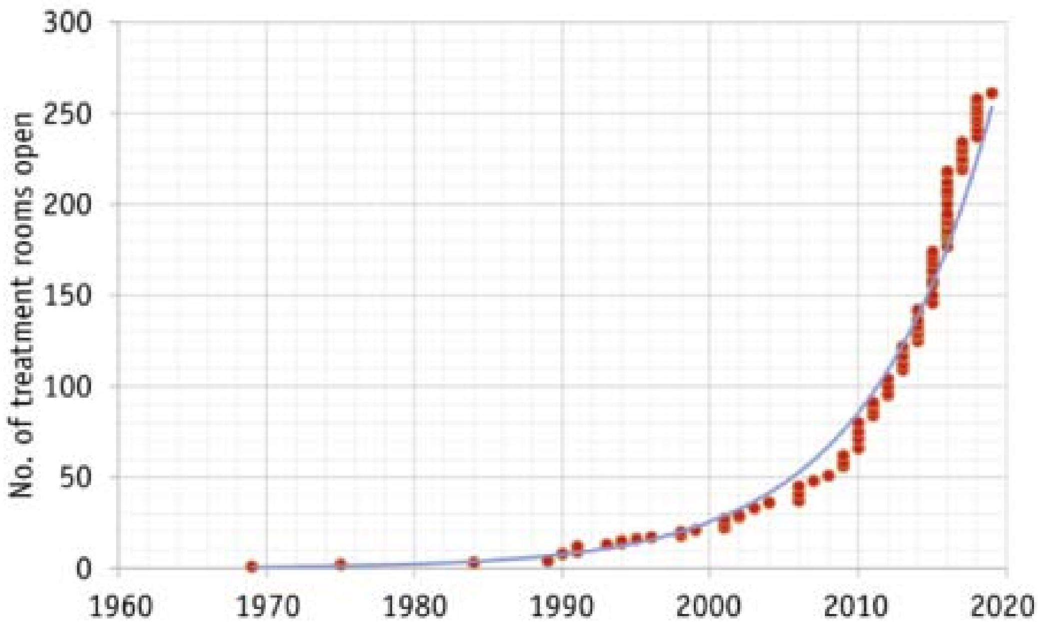


Fig. 5. Number of operating proton beam therapy rooms worldwide, 1970–present.

MD Anderson
Mayo Clinic
Memorial-Sloan Kettering
Massachusetts General Hospital (Harvard)
UCSF
University of Maryland
Cleveland Clinic
University of Washington

**Photo source: Wikipedia*

The History & Fundamentals of Particle Therapy

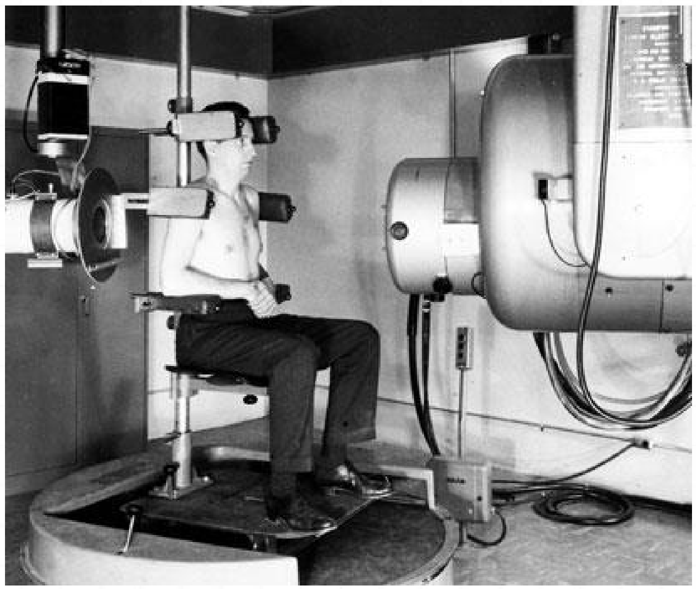
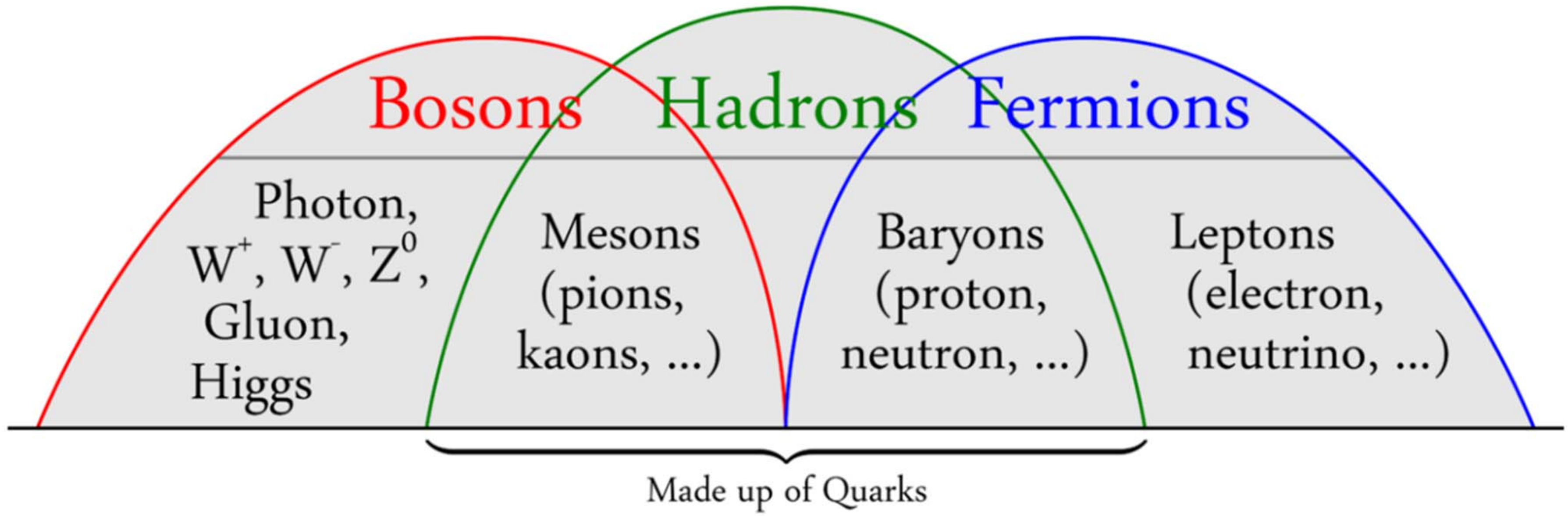


*Photo source: Wikipedia



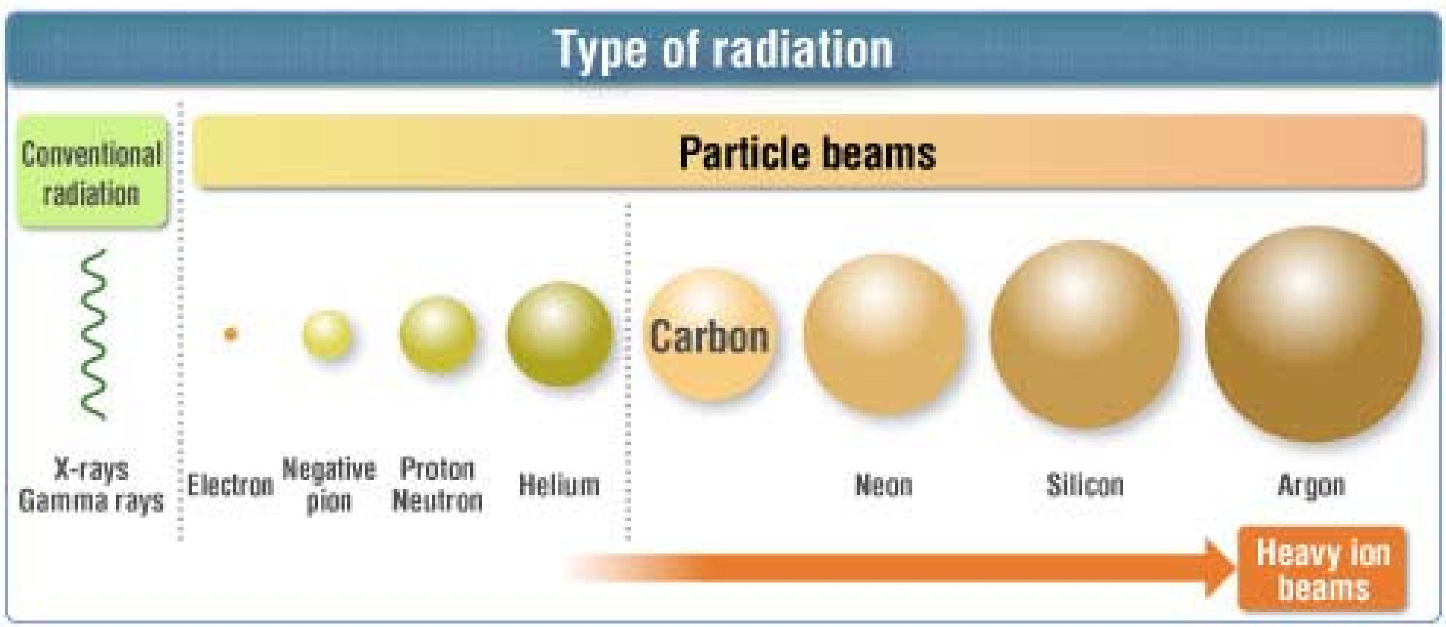
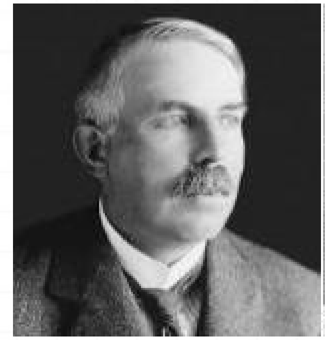
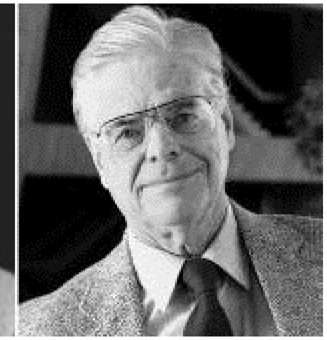


*Photo source= wikipedia and hirt-japan.info

Short History of Proton Beam Therapy

- **Early 1900's:** Discovered by Ernest Rutherford
- **1946:** Described for clinical use by Robert Wilson
- **1954:** First treatment in Lawrence Berkeley National Lab, CA (Pituitary tumors)
- **1958:** 1st use as a neurosurgical tool in Sweden
- **1974:** First large field fractionated proton treatments in Harvard, MA
- **1988:** FDA approved for clinical use
- **1990:** First hospital based proton center opens at Loma Linda University





Wilson RR. Radiological use of fast protons. Radiology. 1946; 47(5):487-491, Photo source= wikipedia

Properties of Proton Therapy

Interaction types:

Electronic

1- Ionization

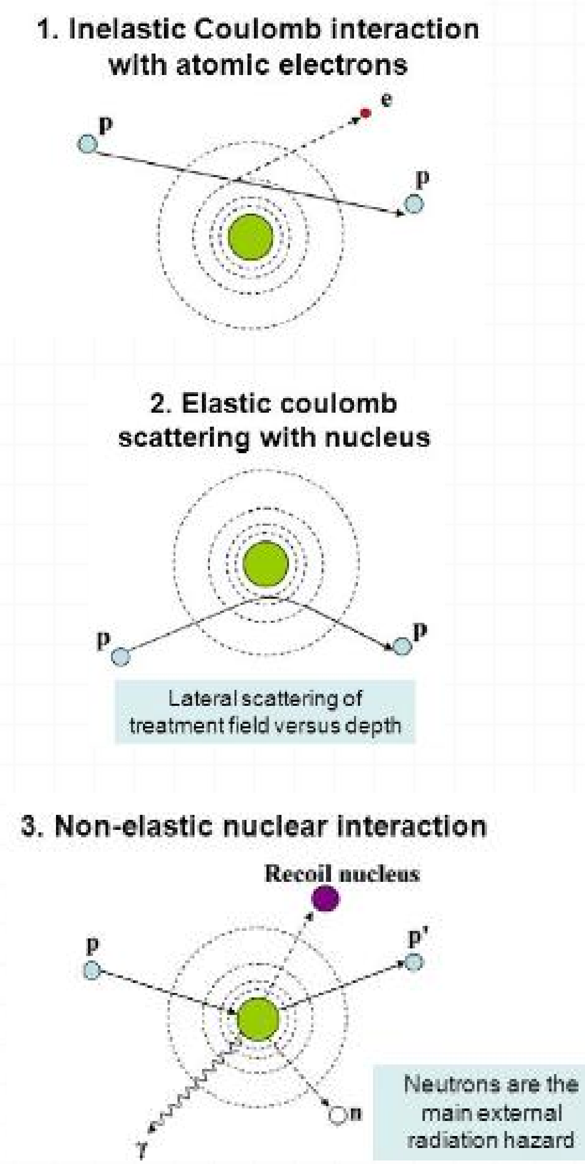
2- excitation

Nuclear

1- Multiple Coulomb Scattering

2- Elastic nuclear collision

3- Nonelastic nuclear interaction



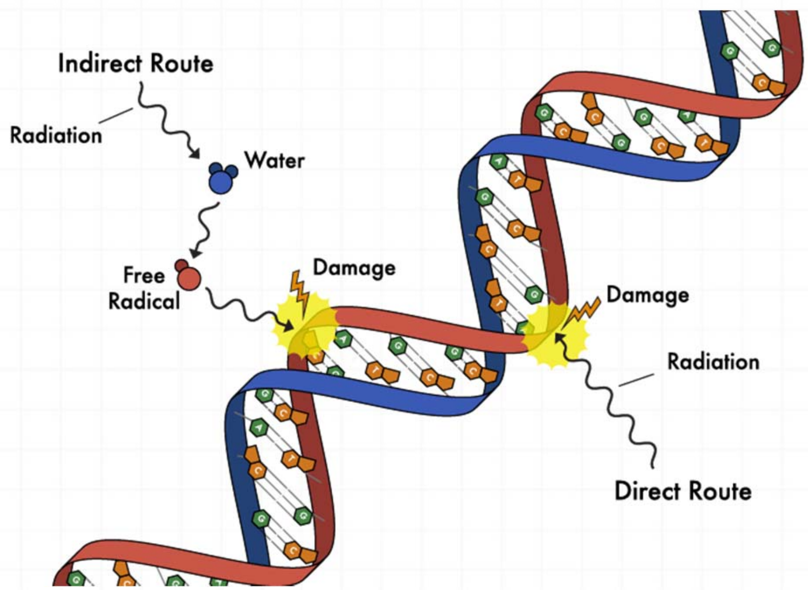
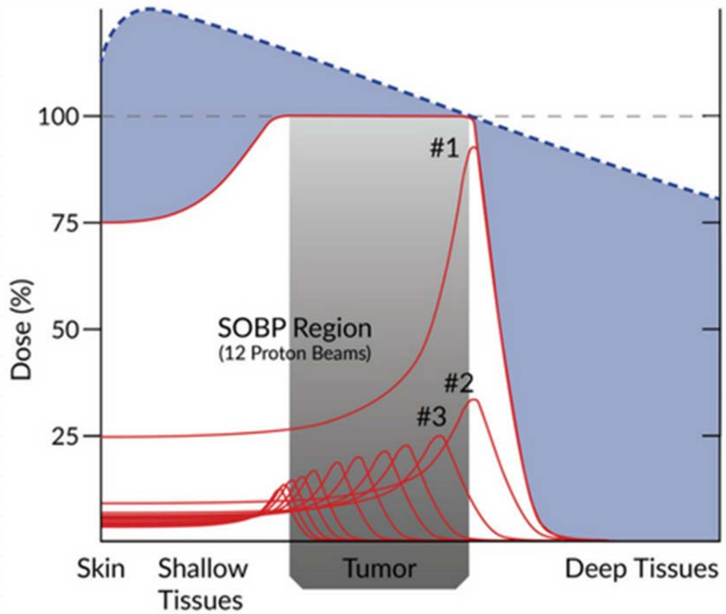
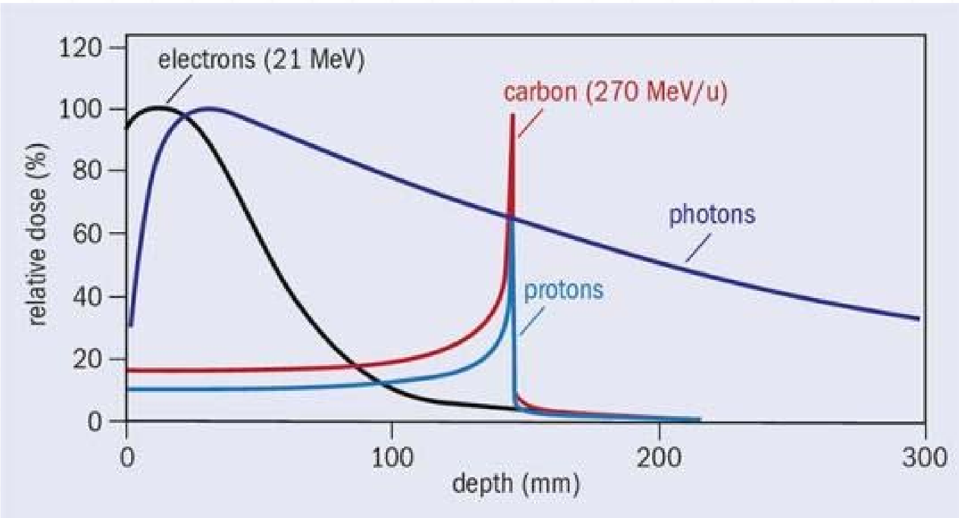


**Photo source: The physics of proton therapy, IOPscience – Institute of Physcis*

Properties of Proton Therapy

- Positively charged particles
- Exhibits the Bragg Peak effect
- Individual beamlets need to be spread to cover depth, thus creating a spread of Bragg peak (SOBP)





Sir William Henry Bragg

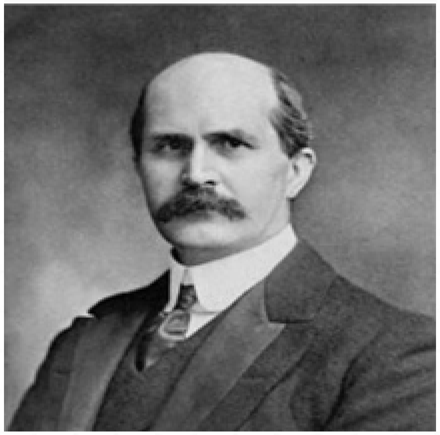


**Photo source: Wikipedia, proton international.com*

Core advantages of Particle Therapy

(1) Reduce Toxicity by minimizing OAR radiation exposure (ALARA)

(2) Widen the Therapeutic Index through safe dose escalation

(1) Reduce Toxicity by ↓Unnecessary Radiation to as Low as Possible (ALARA)

Initiative to Reduce Unnecessary Radiation Exposure from Medical Imaging

FDA CDRH

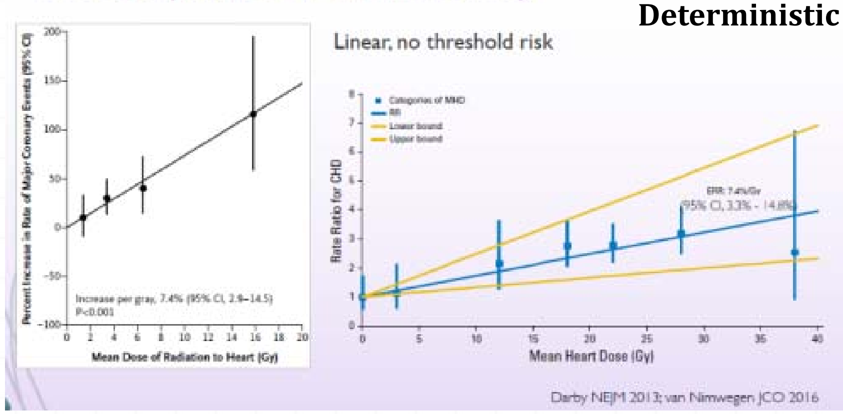
February 2010

There is broad agreement that steps should be taken to reduce unnecessary exposure to radiation. This is safety related.

Type of Procedure	Average Adult Effective Dose (mSv)	Estimated Dose Equivalent (No. of Chest X-rays)
Dental X-ray	0.005-0.01 [6a]	0.25-0.5
Chest X-ray	0.02	1
Mammography	0.4	20
CT	2-16 [6b]	100-800
Nuclear Medicine	0.2-41 [6c]	10-2050
Interventional Fluoroscopy	5-70 [6d]	250-3500

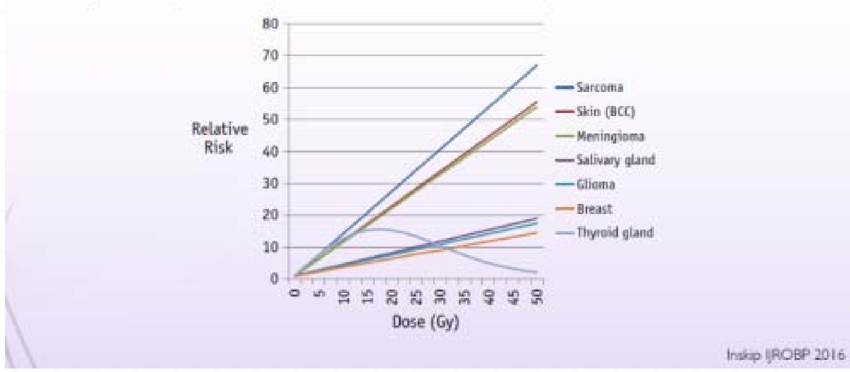
Dose-response for cardiotoxicity

↓Stochastic & Deterministic

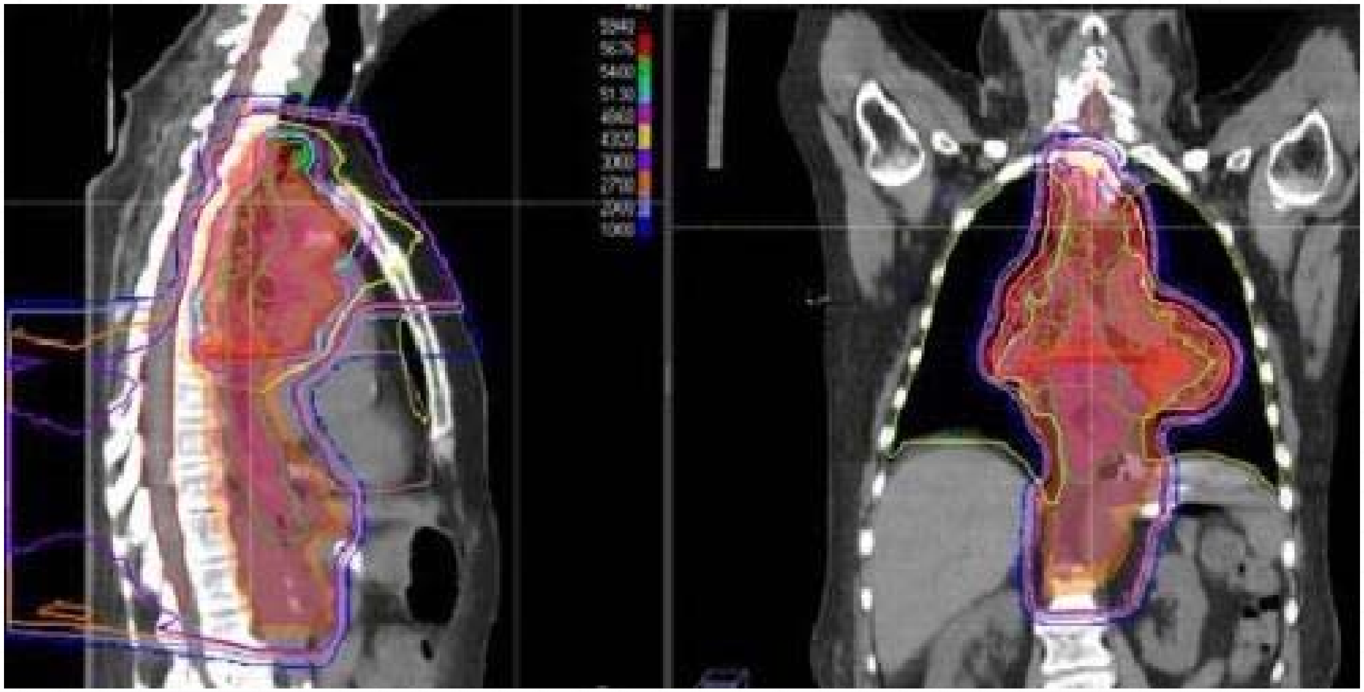


Dose-response for secondary cancers

Summary of analyses from prior CCSS studies: 12,268 5-yr childhood cancer survivors



(1) Reduce Toxicity by ↓Unnecessary Radiation to as Low as Possible (ALARA)

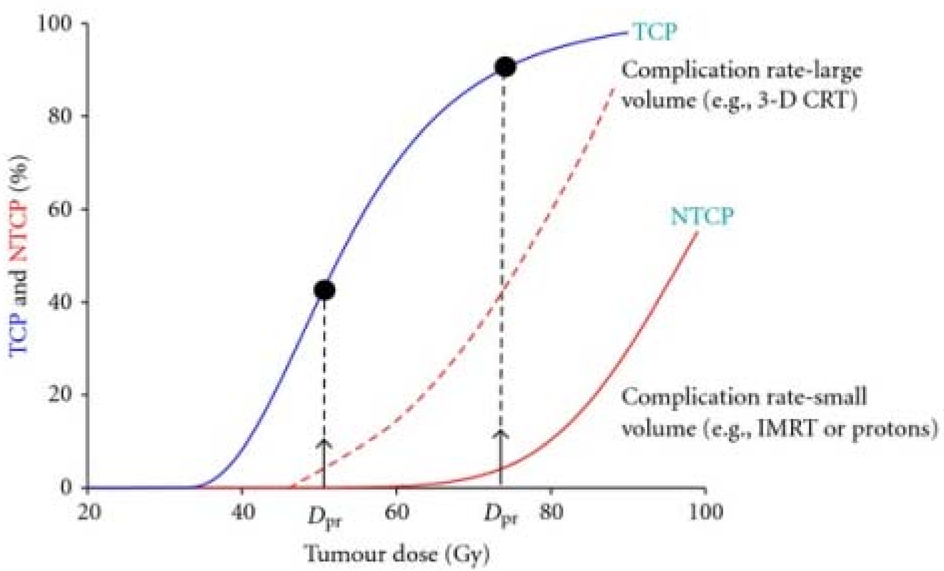


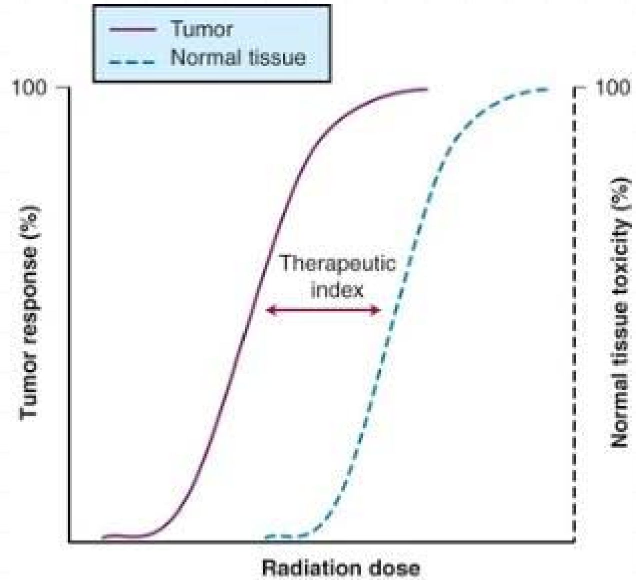
- 74 year old patient with synchronous locally advanced lung and esophageal cancer.
- VMAT technique did not meet constraints.

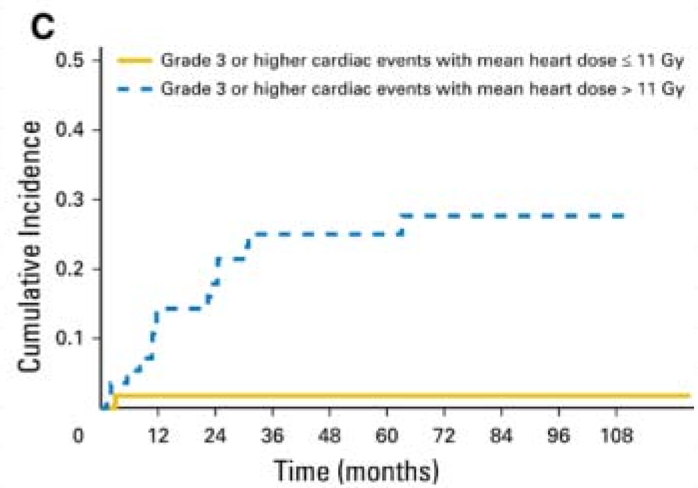
(2) Widen the Therapeutic Index Through Safe Dose Escalation

INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy.

A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617.







Core disadvantages of Particle Therapy

(1) Setup and range uncertainty (Interplay effect)

(2) RBE variability

(3) Limited clinical data

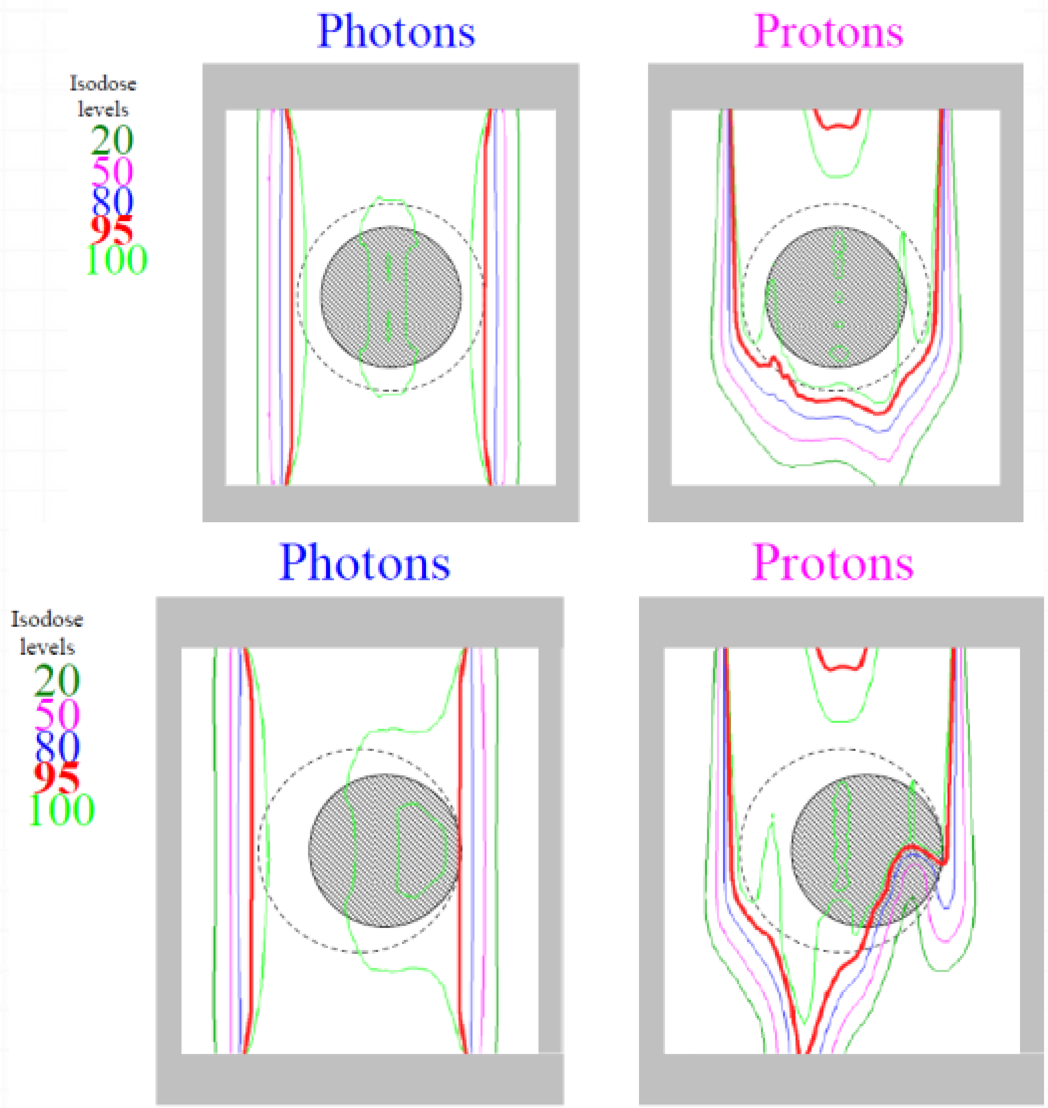
(4) High cost

1- Setup & Range Uncertainty

Source of range uncertainty in the patient	Range uncertainty
Independent of dose calculation:	
Measurement uncertainty in water for commissioning	± 0.3 mm
Compensator design	± 0.2 mm
Beam reproducibility	± 0.2 mm
Patient setup	± 0.7 mm
Dose calculation:	
Biology (always positive)	+ 0.8 %
CT imaging and calibration	± 0.5 %
CT conversion to tissue (excluding I-values)	± 0.5 %
CT grid size	± 0.3 %
Mean excitation energies (I-values) in tissue	± 1.5 %
Range degradation; complex inhomogeneities	- 0.7 %
Range degradation; local lateral inhomogeneities *	± 2.5 %
Total (excluding *)	**2.7% + 1.2 mm**
Total	**4.6% + 1.2 mm**

H. Paganetti: Range uncertainties in proton beam therapy and the impact of Monte Carlo simulations
Phys. Med. Biol. 57: R99-R117 (2012)

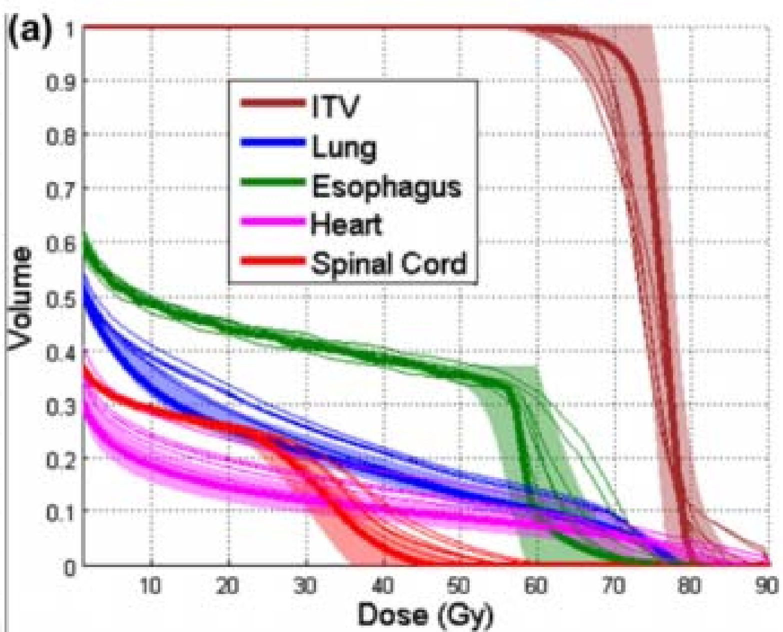
1- Setup & Range Uncertainty



© Engelsman, MGH

Setup & Range Uncertainty

- **Robustness Planning=** Employs extra criteria or constraints in conjunction with the normal objective functions during spot weight optimization. Usually run multiple
- plans for translational shifts & range uncertainty
- Strict IGRT (KV or CBCT) limits (<5mm, <3^0).
- Rigorous QA program.



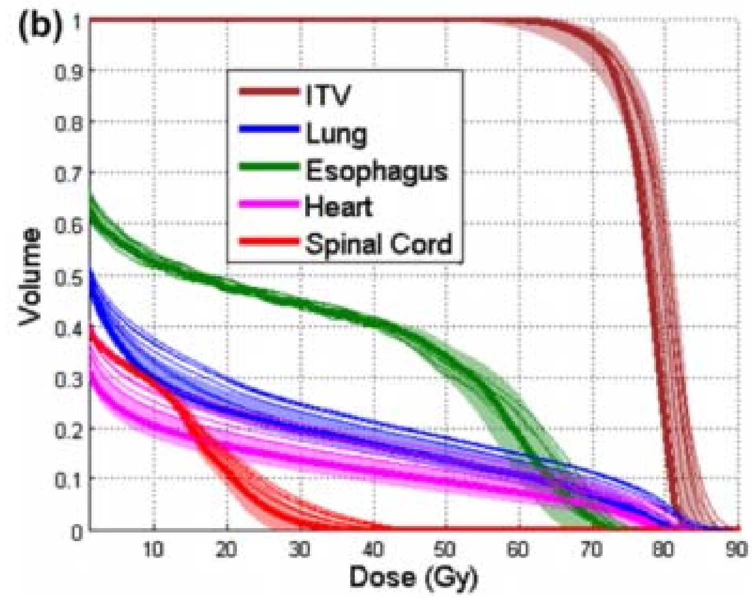
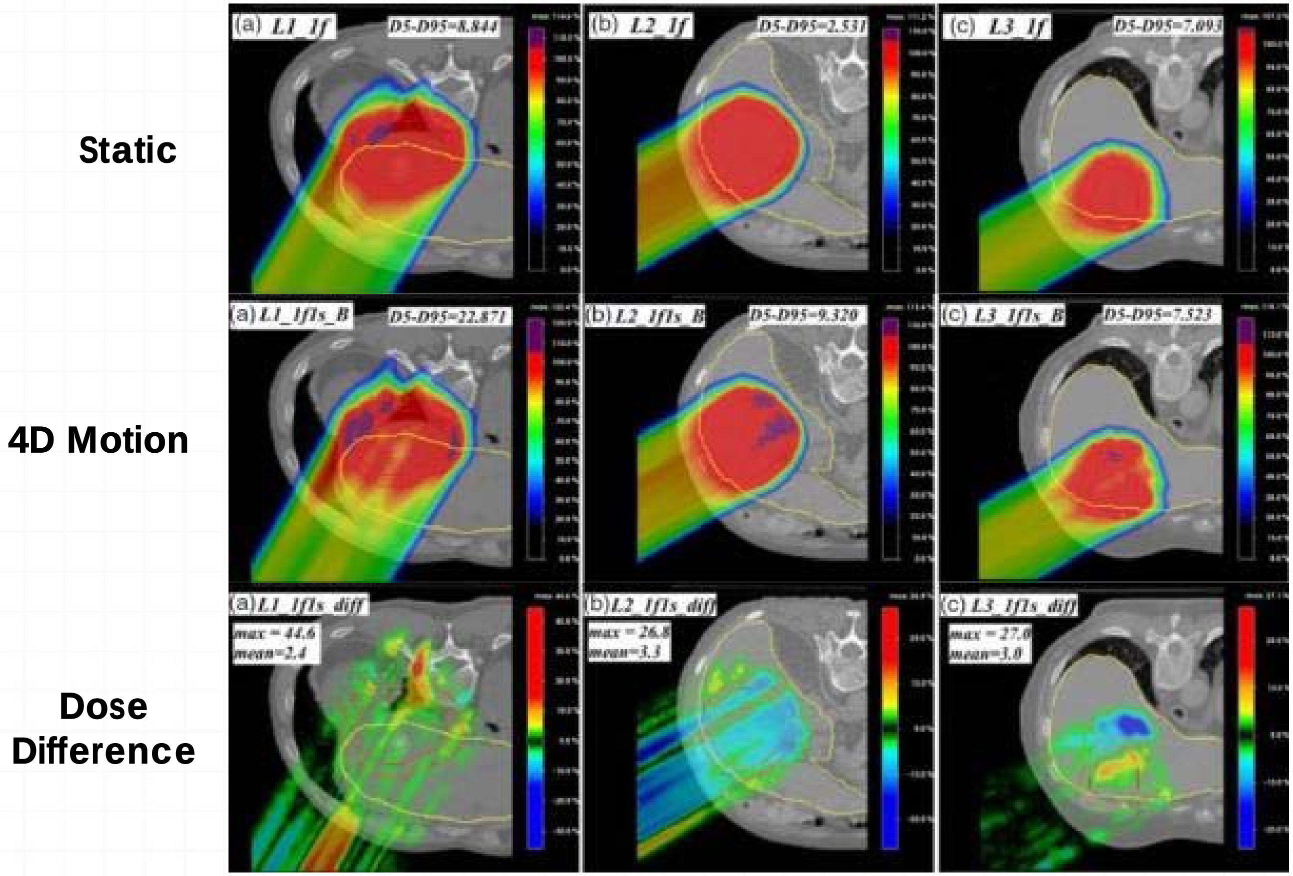


Fig. 2. Nominal dose-volume histograms (DVHs; thick lines), standard deviatior (SD)-DVHs (shaded areas, ±2σ), and weekly DVHs (thin lines) for (a) the multi-fielc optimized plan (MFO-PTV) and (b) the robust-optimized MFO (MFO-RO) plan for a patient. ITV, internal target volume.

Interplay Effect (IMPT)

Interplay Effect= Active scanning + Organ Motion



Zhang et al. Phys Med Biol. 2012; 57(7): 1779-95

2- RBE Variation

Radiobiological issues in proton therapy

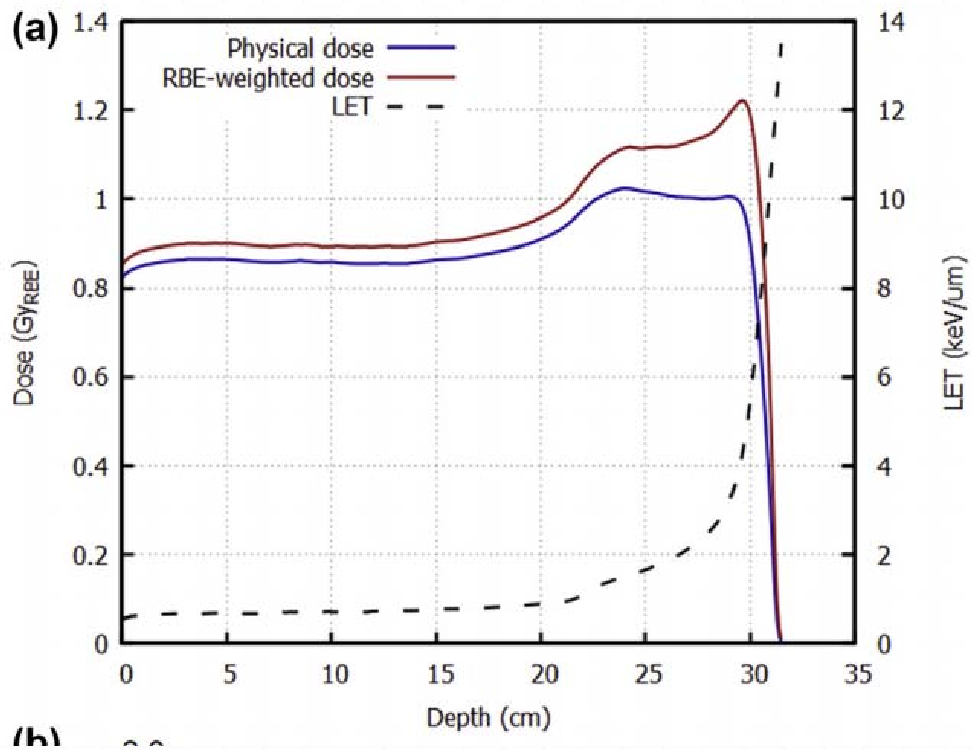
Radhe Mohan, Christopher R. Peeler, Fada Guan, Lawrence Bronk, Wenhua Cao & David R. Grosshans

The Radiobiology of Proton Therapy: Challenges and Opportunities Around Relative Biological Effectiveness

B. Jones *, S.J. McMahon †, K.M. Prise †

- The RBE for particle therapy is a complex function of particle type, radiation dose, linear energy transfer (LET), cell type, endpoint, etc.

- In clinical practice proton therapy **RBE is assumed to have a fixed value of 1.1, in reality can vary from 0.9-1.7**



3- Limited clinical data

- No level I evidence to support the use of proton therapy
- **Randomized phase III accrual is slow**
  i. Patient preference (especially pediatric); refuse to be randomized
  ii. Restrictive insurance policies.
  iii. Small number of proton facilities (until recently)
  iv. Inability to catch up with the rapid improvements in technology
  v. Radiation oncologist practice bias.

NRG Oncology Randomized Trials of Protons versus Photons

T. DeLaney [1]
[1]*F.H. Burr Proton Center- Massachusetts General Hospital, Radiation Oncology, Boston, USA*

Materials and Methods: NRG Oncology is currently conducting four randomized clinical trials of photons versus protons for (1) low grade gliomas, (2) non-small cell lung cancer, (3) esophageal cancer, and (4) hepatocellular tumors. The first is phase II; the others are phase III.

Results: To date (12/31/18)/ target accruals for these studies are: (1) gliomas: 11/120 , (2) non-small cell lung cancer: 137/330 (3) esophageal cancer: activation pending/300 , and (4) hepatocellular tumors: 15/155 . Factors delaying accrual include patient acceptance of randomization as well as insurance coverage denials for proton treatment for some randomized patients, estimated 30-35% for lung. Strategies to improve accrual include 2:1 randomization protons versus photons (gliomas).

Limited clinical data

Should Randomized Clinical Trials Be Required for Proton Radiotherapy?

Michael Goitein, Department of Radiation Oncology, Harvard Medical School, Boston, MA
James D. Cox, Division of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX

Establishing Evidence-Based Indications for Proton Therapy: An Overview of Current Clinical Trials

Mark V. Mishra, MD,* Sameer Aggarwal, MD,† Soren M. Bentzen, PhD, DMSc,‡ Nancy Knight, PhD,* Minesh P. Mehta, MD,§ and William F. Regine, MD, FACR, FACRO*

- New guidelines supporting the use of protons:

i. NCCN Guidelines

ii. ASTRO Guidelines

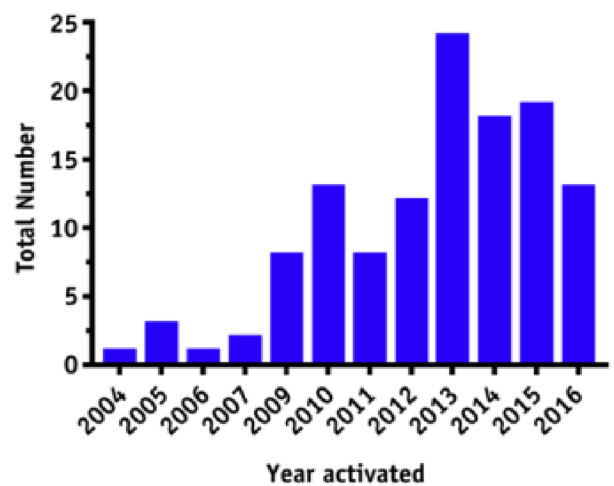


Fig. 2. Activation of clinical trials of proton beam therapy by year.

Study	Institution	Phase	Condition	Radiation arm 1	Radiation arm 2
R03CA188162: IMPT vs IMRT	MDACC	III	Oropharyngeal cancer (head and neck cancer)	Protons*	X-rays*
PARTIQoL (NCT01617161): proton therapy vs IMRT	MGH	III	Low-risk or intermediate-risk prostate cancer	Protons	X-rays
NCT01512589: proton-beam therapy vs IMRT	MDACC	III	Oesophageal cancer	Protons*	X-rays*
RADCOMP (NCT02603341): pragmatic randomized trial of proton vs photon therapy	PTCORI	III	Post-mastectomy stage II or III breast cancer	Protons	X-rays
NRG BN001: dose-escalated IMRT or IMPT vs conventional photon radiation	NRG Oncology	II	Newly diagnosed glioblastoma	Protons*	X-rays*
NRG 1542: proton radiation vs conventional photon radiation‡	NRG Oncology	III	Hepatocellular carcinoma	Protons	X-rays
NCT01182753: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Low-grade and intermediate-grade chondrosarcoma of the skull base	Protons	Carbon ions
NCT01182779: proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	III	Chordoma of the skull base	Protons	Carbon ions
CLEOPATRA (NCT01165671): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Primary gioblastoma	Protons*§	Carbon ions*§
IPI (NCT01641185): proton radiation vs carbon-ion radiotherapy	Heidelberg University, Germany	II	Prostate cancer	Protons	Carbon ions
ISAC (NCT01811394): proton radiation vs carbon-ion radiation therapy	Heidelberg University, Germany	II	Sacrococcygeal chordoma	Protons	Carbon ions
ETOILE (NCT02838602): carbon-ion radiotherapy vs IMRT	Lyon University Hospital, France	III	Radioresistant adenoid cystic carcinoma and sarcomas	Carbon ions	IMRT
BAA-N01CM51007-51: prospective trial of carbon-ion therapy vs IMRT	NCI	I/III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*
CIPHER: prospective multicentre randomized trial of carbon-ion radiotherapy vs conventional radiotherapy	UTSW	III	Locally advanced pancreatic cancer	Carbon ions*	X-rays*

4- High Cost (Large Facility)

Growing pains for US proton therapy

Lancet Oncol 2018
Published Online
July 12, 2018
http://dx.doi.org/10.1016/
S1470-2045(18)30524-2

However, investors badly over-estimated regional demand and referral rates. The $200 million Maryland Proton Treatment Center in Baltimore (MD, USA), which opened in 2016, in affiliation with the University of Maryland Medical Center, is restructuring its debt. The Scripps Proton Treatment Center (San Diego, CA, USA) declared bankruptcy and parted ways with Scripp and is now under new management. In the

Review Article

Cancer, 2016

A Systematic Review of the Cost and Cost-Effectiveness Studies of Proton Radiotherapy

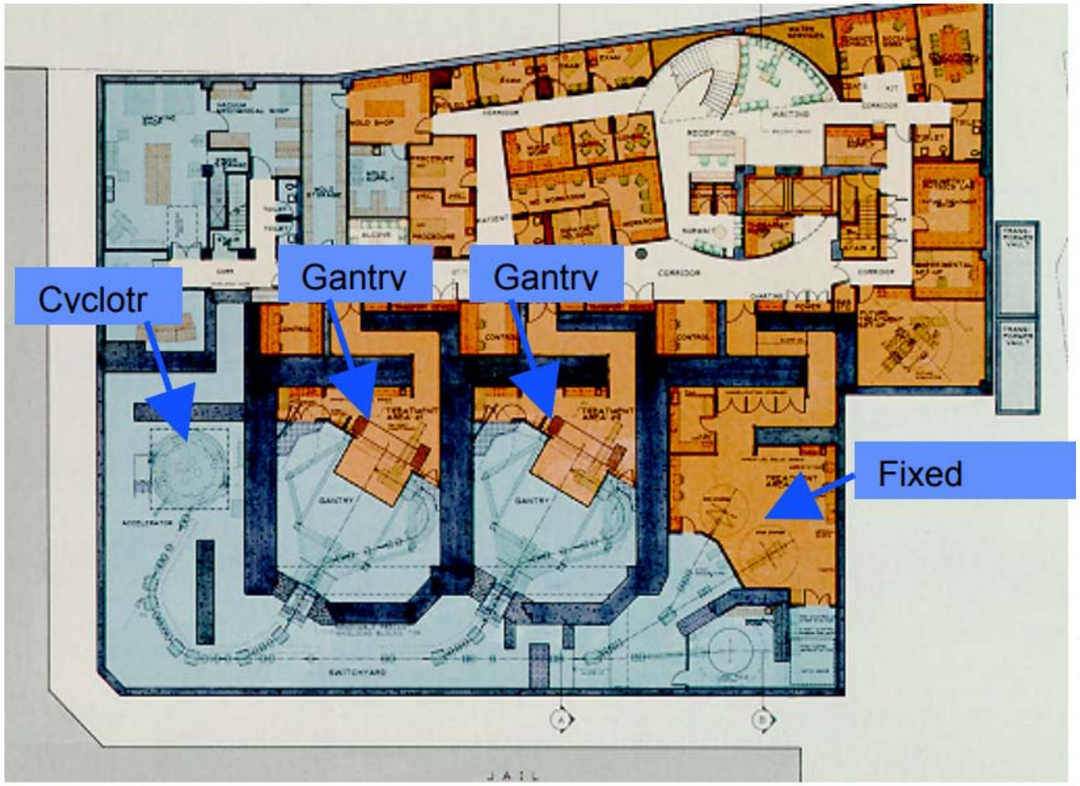
Vivek Verma MD[1]; Mark V. Mishra MD[2]; and Minesh P. Mehta MBChB[2]

Proton therapy of cancer: Potential clinical advantages and cost-effectiveness

JONAS LUNDKVIST[1,2], MATTIAS EKMAN[2], SUZANNE REHN ERICSSON[3], BENGT JÖNSSON[4] & BENGT GLIMELIUS[3,5]

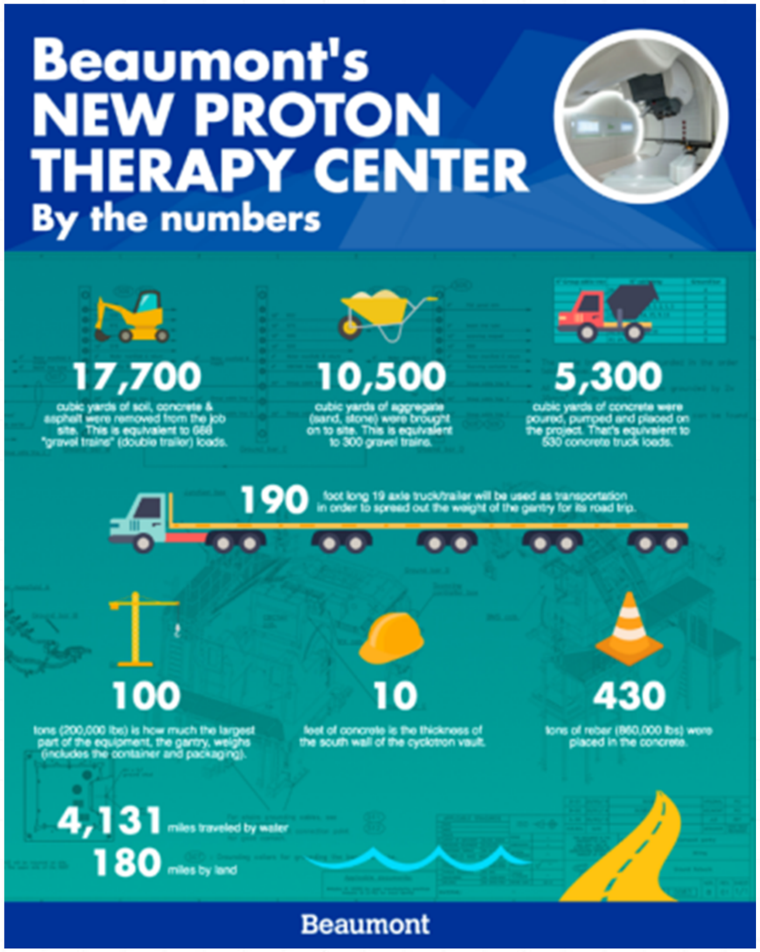
Abstract
Proton therapy may offer potential clinical advantages compared with conventional radiation therapy for many cancer patients. Due to the large investment costs for building a proton therapy facility, however, the treatment cost with proton radiation is higher than with conventional radiation. It is therefore important to evaluate whether the medical benefits of proton therapy are large enough to motivate the higher costs. We assessed the cost-effectiveness of proton therapy in the treatment of four different cancers: left-sided breast cancer, prostate cancer, head and neck cancer, and childhood medulloblastoma. A Markov cohort simulation model was created for each cancer type and used to simulate the life of patients treated with radiation. Cost and quality adjusted life years (QALYs) were used as primary outcome measures. The results indicated that proton therapy was cost-effective if appropriate risk groups were chosen. The average cost per QALY gained for the four types of cancer assessed was about €10 130. If the value of a QALY was set to €55 000, the total yearly net benefit of treating 925 cancer patients with the four types of cancer was about €20.8 million. Investment in a proton facility may thus be cost-effective. The results must be interpreted with caution, since there is a lack of data, and consequently large uncertainties in the assumptions used.

Particle Therapy Past Technology



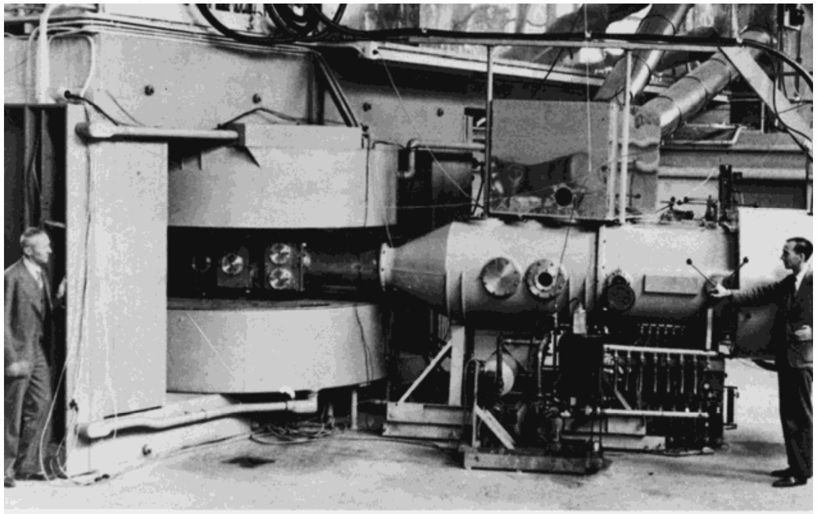
2005_Proton Beam Radiotherapy – The State of the Art_ Paganetti et al. MGH, MA, USA

High Cost Large Facility



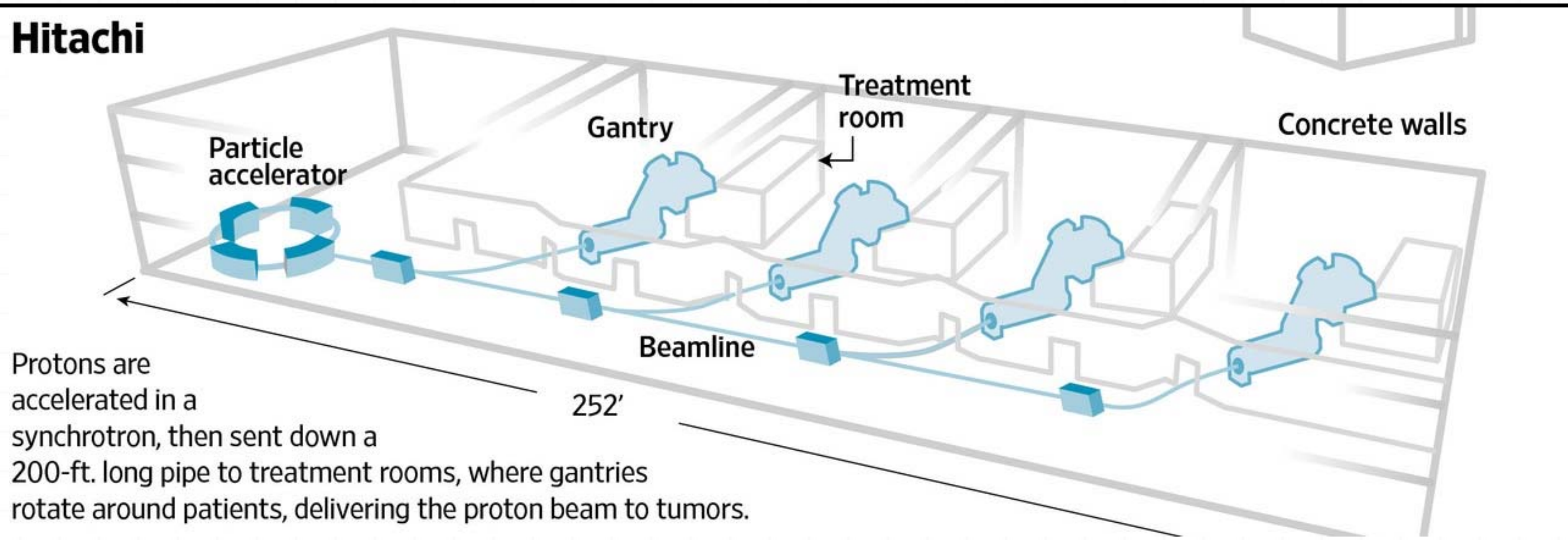
- $200,000,000 – 350,000,000
- Usually far away from main campus
- Large facility with a large cyclotron/synchrotron
- High maintenance demands with on-site engineers

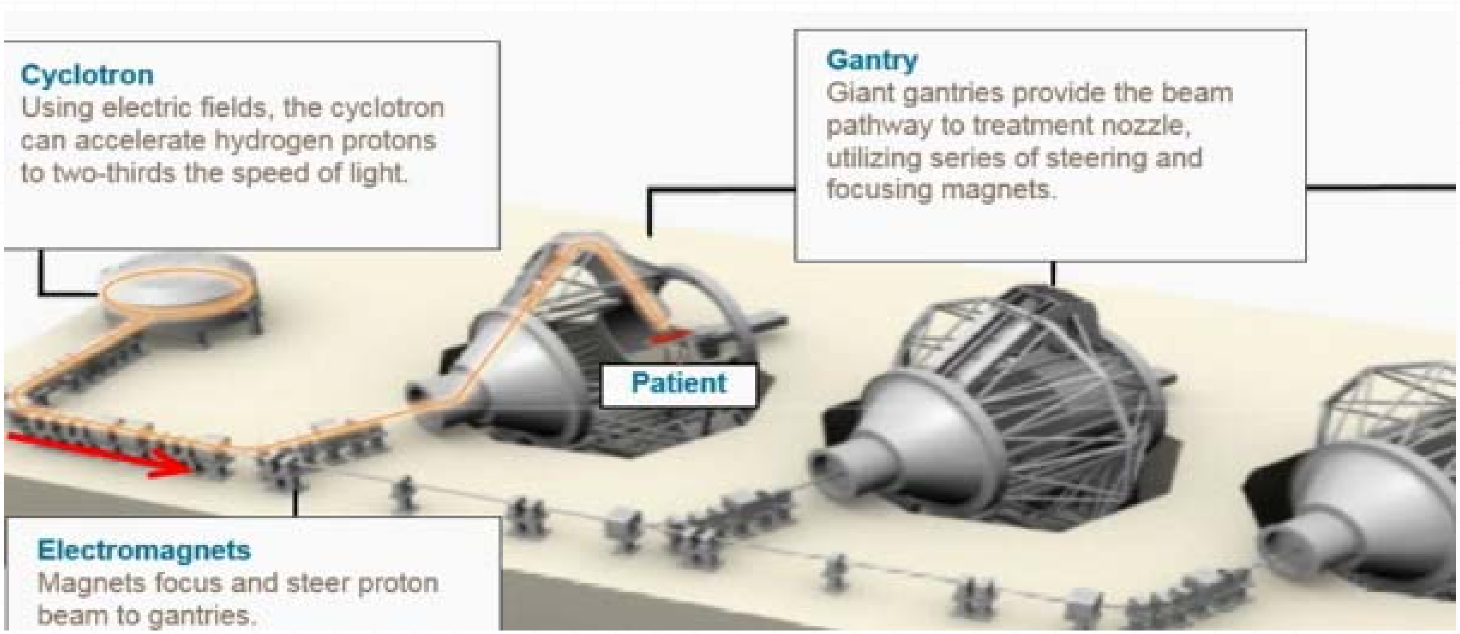
Large Particle Accelerators



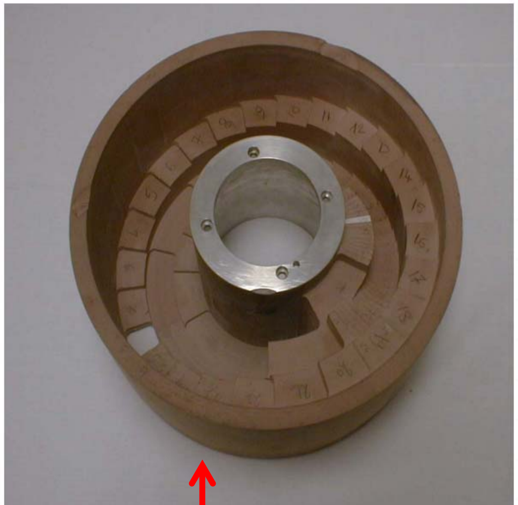
- First cyclotron developed by Ernest Lawrence in 1932.
- Cyclotrons can accelerate particles to 2/3 light speed
- Proton clinical range used for treatment is usually between 70 – 250 MeV to a depth of 7-31cm.

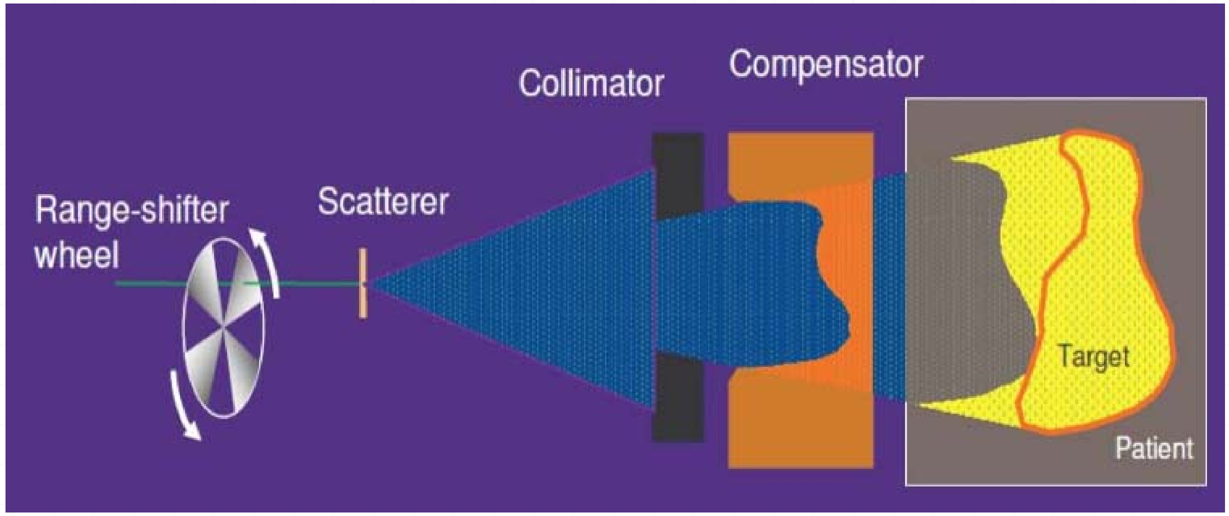
Shared Beam Line





Passive Scatter System





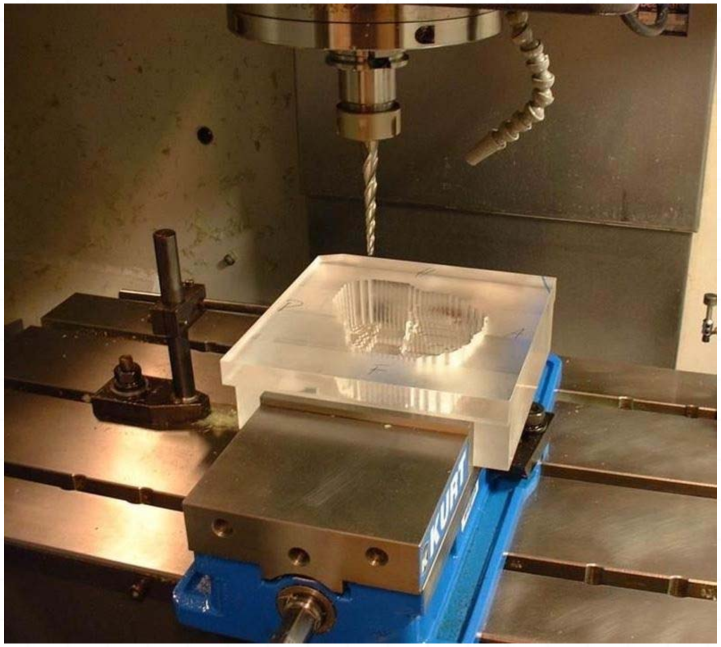
Range Modulator

Range Compensator

Brass Aperture

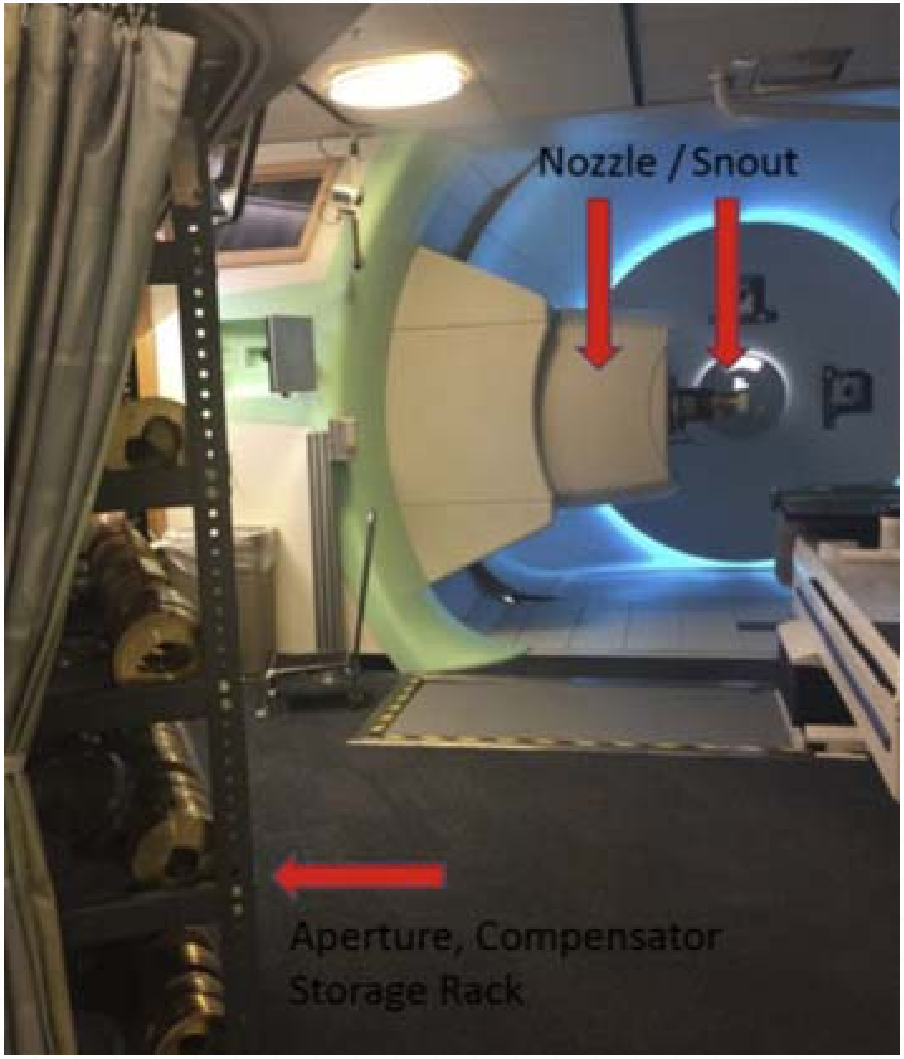
2005_Proton Beam Radiotherapy – The State of the Art_ Paganetti et al. MGH, MA, USA

Milling Machine for Production



*Photos from= Machining's Role in Making Cancer History, Derek Korn, Modern Machine Shop, 5/3/2006

Treatment Head



*Maquilan, Genevieve, et al. "Radiation Safety for Pregnant Workers at a Proton Facility." *International Journal of Radiation Oncology* Biology* Physics* 100.3 (2018): 560-564.

Fixed Beam Angle

- Most Proton facilities build <2010 had multiple fixed beam angle rooms.
- This was due to the "anticipation" that prostate patients would be the main bulk of treated patients.
- Rely on couch kicks to acquire different angles.

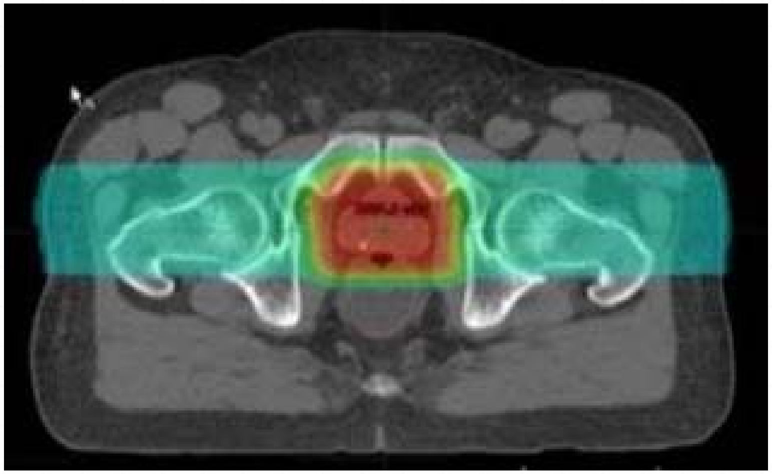
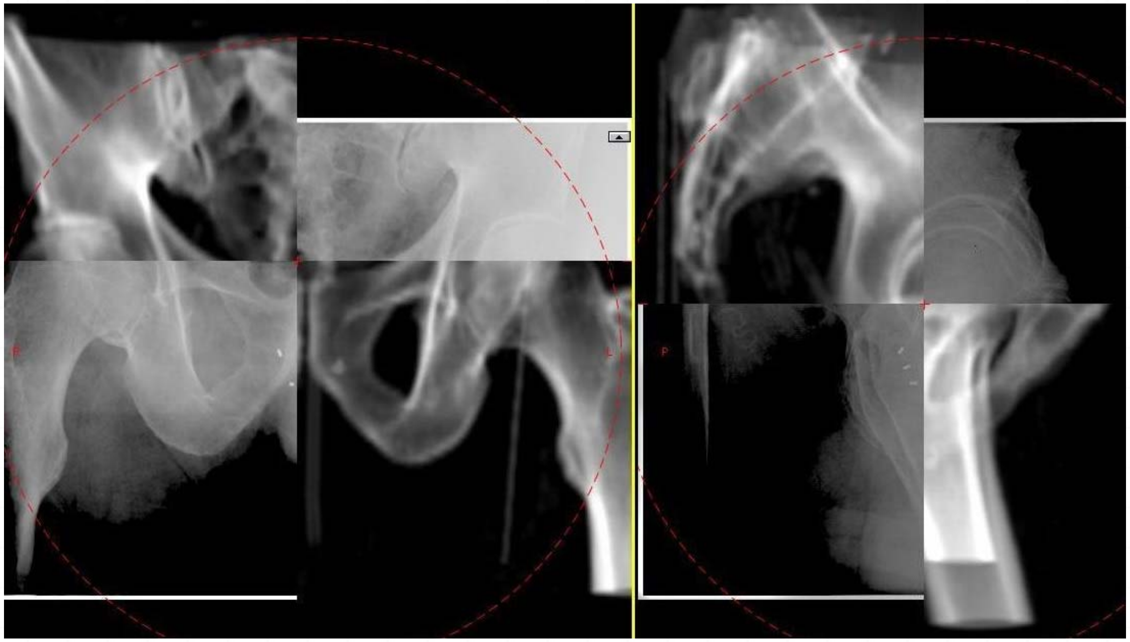


**Photo source: SCCA UW Proton Center*

IGRT Capabilities

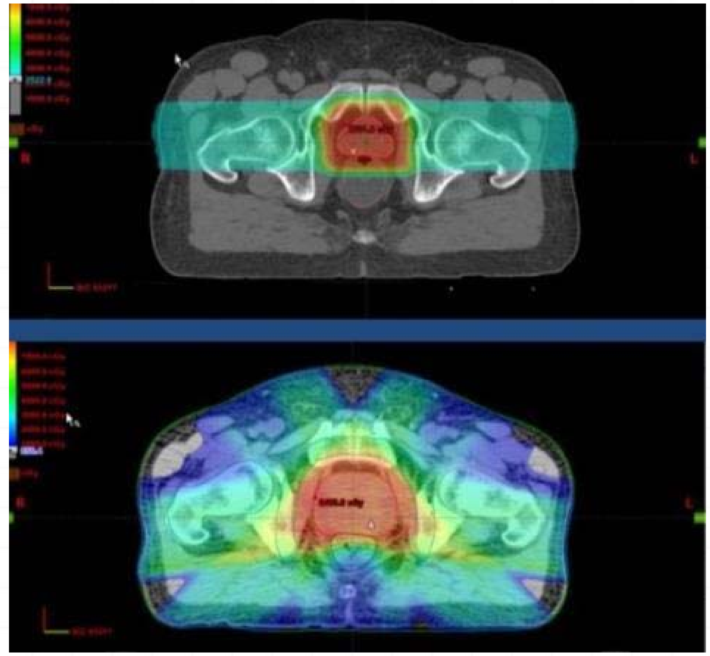


- Most Proton facilities operate with 3 Kv imaging panels with no CBCT option.
- Not ideal for certain disease sites (H&N, Lung, Liver…etc)

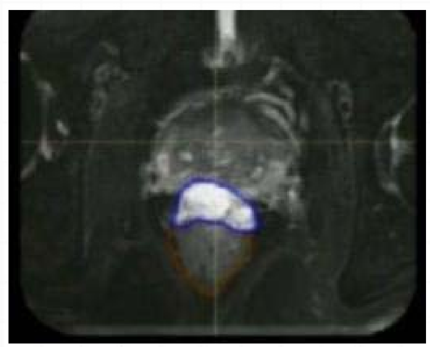
Clinical Application: Prostate

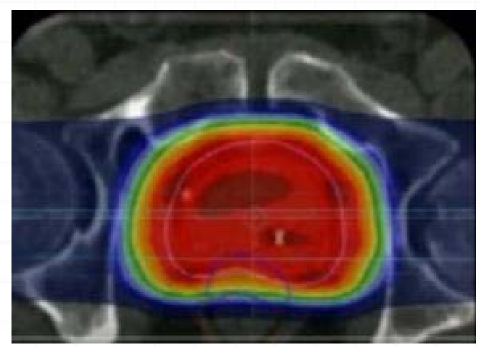
Comparative Toxicities and Cost of Intensity-Modulated Radiotherapy, Proton Radiation, and Stereotactic Body Radiotherapy Among Younger Men With Prostate Cancer

Hubert Y. Pan, Jing Jiang, Karen E. Hoffman, Chad Tang, Seungtaek L. Choi, Quynh-Nhu Nguyen,



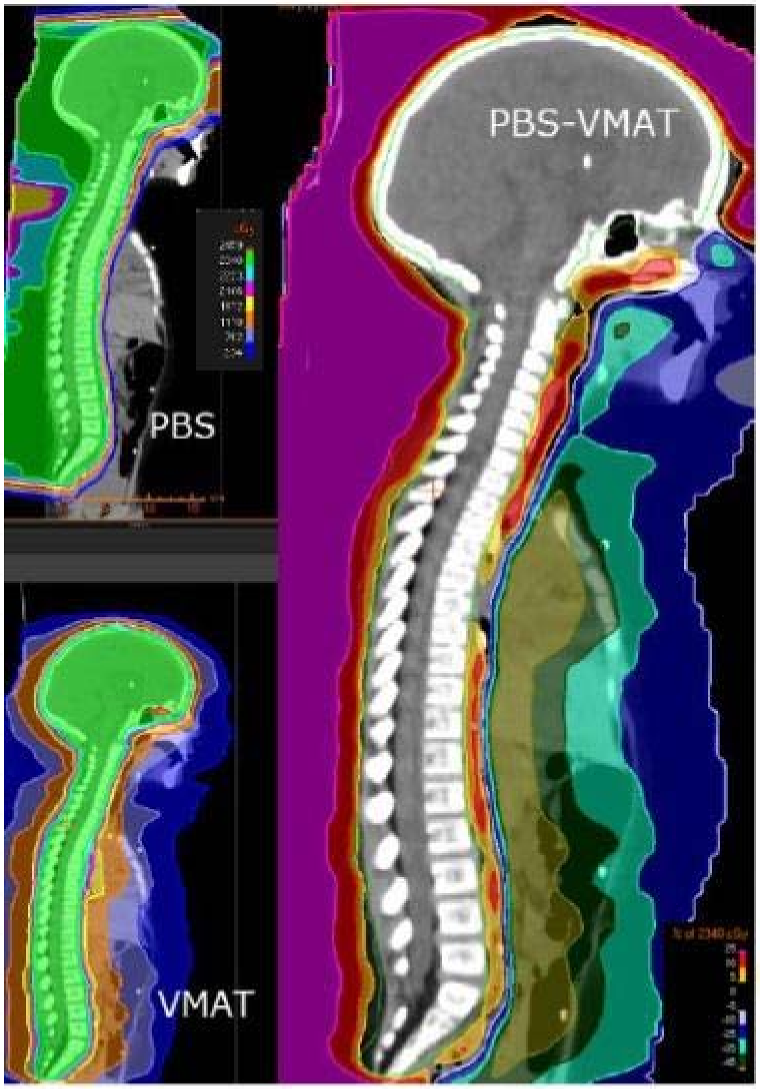
- Historically better than 4 field box.
- Typically 2 lateral beams.
- Proton therapy associated with significant reduction in urinary toxicity but increased bowel toxicity (twice the cost of IMRT)
- Cofounding factor: Rectal Balloon
- New entry: SpaceOAR





Rectum V70 Gy (RBE)		
Balloon	Empty Rectum	SpaceOAR
8.7%	10 %	0.0 %

Clinical Application: Pediatrics



Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy

Daniel J. Indelicato, Stella Flampouri, Ronny L. Rotondo, Julie A. Bradley, Christopher G. Morris, Philipp R. Aldana, Eric Sandler & Nancy P. Mendenhall

Proton Therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers

Roos Leroy, PhD,* Nadia Benahmed, MSc,* Frank Hulstaert, MD,* Nancy Van Damme, PhD,† and Dirk De Ruysscher, PhD‡

- Common indication for protons
- 23 primary studies , 650 patients total, 15 pediatric cancer sites.
- Very low level evidence, no RCT

- **Conclusion:** Although PT reduces the radiation dose to normal tissues, to date the critical clinical data on the long-term effectiveness and harm with PT are lacking. High quality trials are needed.
- Retrospective/prospective studies reveal: ↓ cognitive decline, endocrine dysfunction, hearing loss, 2nd cancer, cardiac mortality, ovarian failure and vascular risk.
- No survival difference

Clinical Application: CNS

Proton beam therapy with concurrent chemotherapy for glioblastoma multiforme: comparison of nimustine hydrochloride and temozolomide

Authors Authors and affiliations

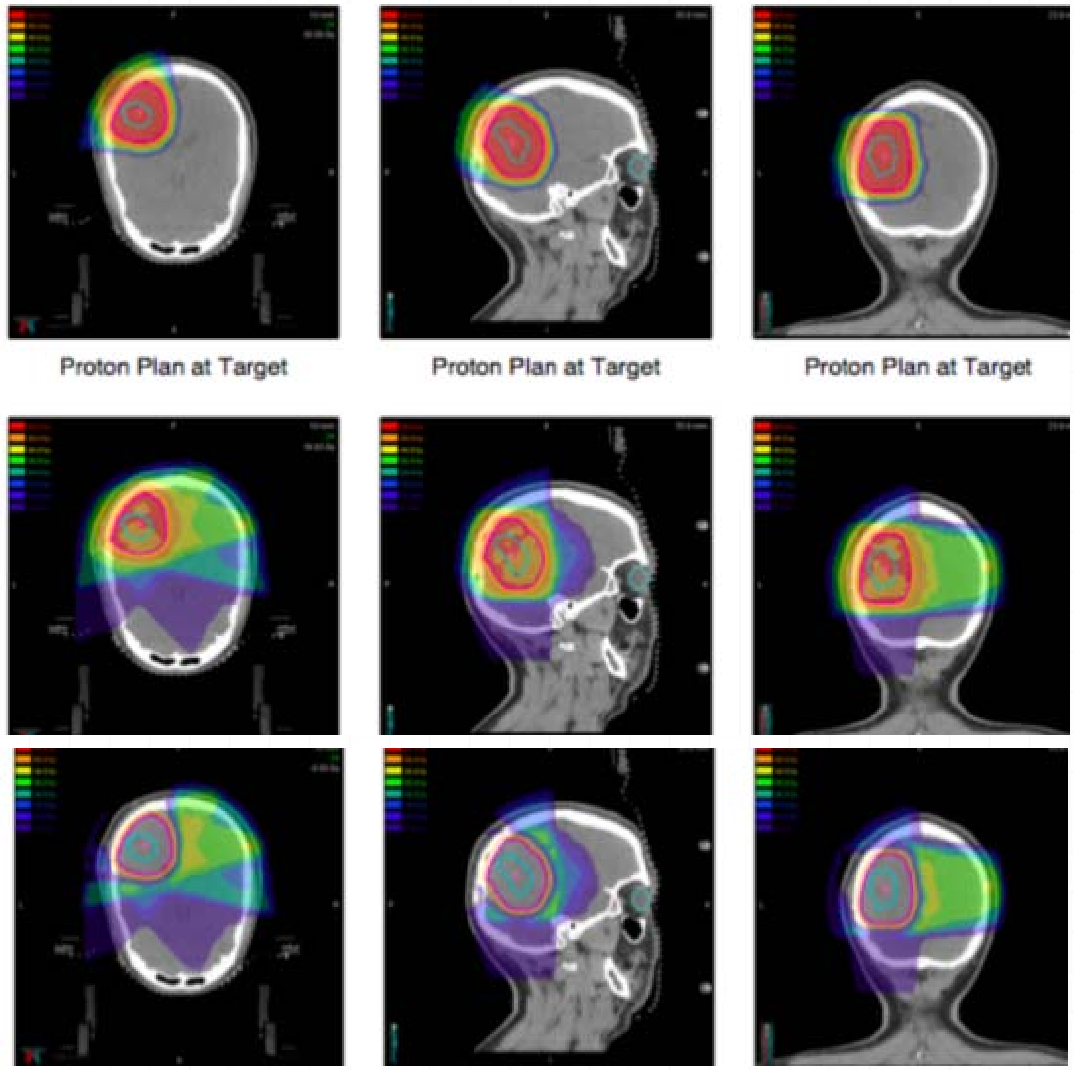
Masashi Mizumoto, Tetsuya Yamamoto, Eiichi Ishikawa, Masahide Matsuda, Shingo Takano, Hitoshi Ishikawa,

Long-Term Clinical Outcomes of Pencil Beam Scanning Proton Therapy for Benign and Non-benign Intracranial Meningiomas

Fritz R. Murray MD, James W. Snider MD, Alessandra Bolsi MSc,

- Lower dose to normal brain structures (such as hippocampi, pituitary, optics, normal brain)
- Decreased long term neurocognitive, neuroendocrine function and 2^{nd} ca.

Current CNS Indications	
Craniospinal Irradiation	Low Grade Glioma
Meningioma	Chordoma/Chondrosarcoma
Vestibular Schwannoma	Pituitary tumors
Re-irradiation	Peds



Clinical Application: Ocular Melanoma

The COMS Randomized Trial of Iodine 125 Brachytherapy for Choroidal Melanoma

V. Twelve-Year Mortality Rates and Prognostic Factors: COMS Report No. 28

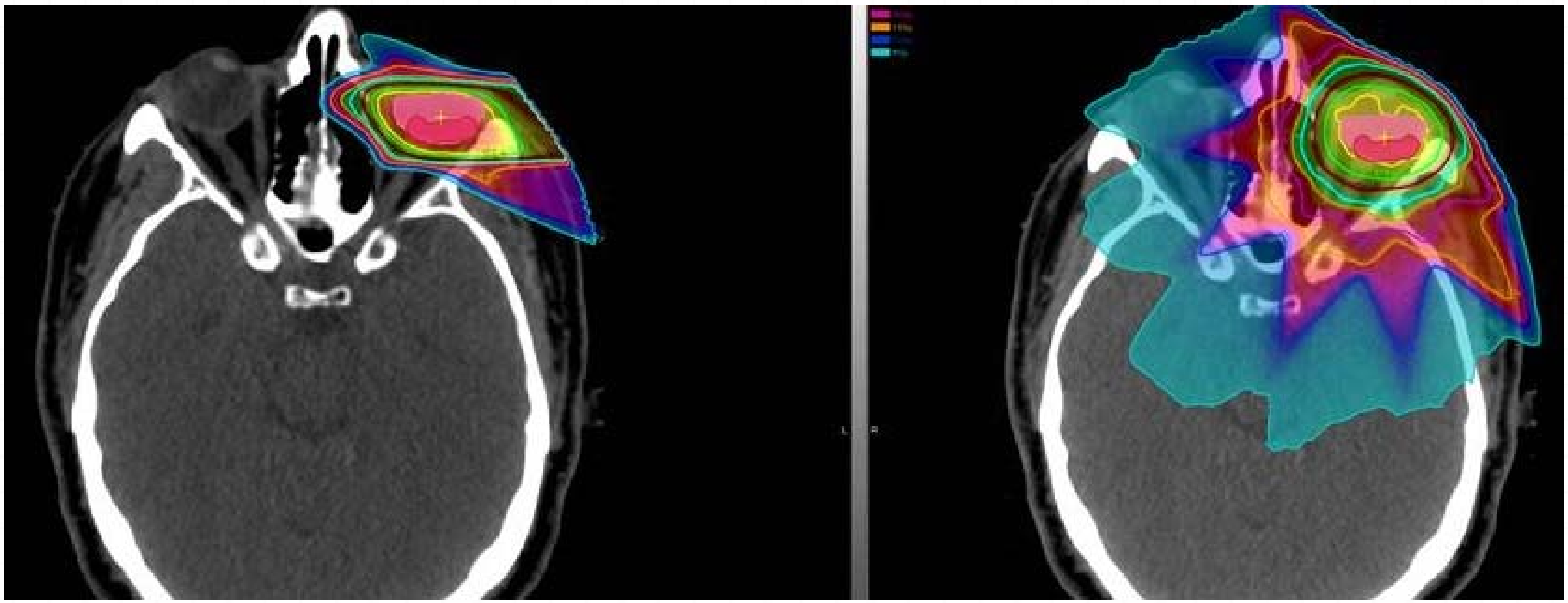
Collaborative Ocular Melanoma Study (COMS) Group[*]

Long-term Results of the UCSF-LBNL Randomized Trial: Charged Particle With Helium Ion Versus Iodine-125 Plaque Therapy for Choroidal and Ciliary Body Melanoma

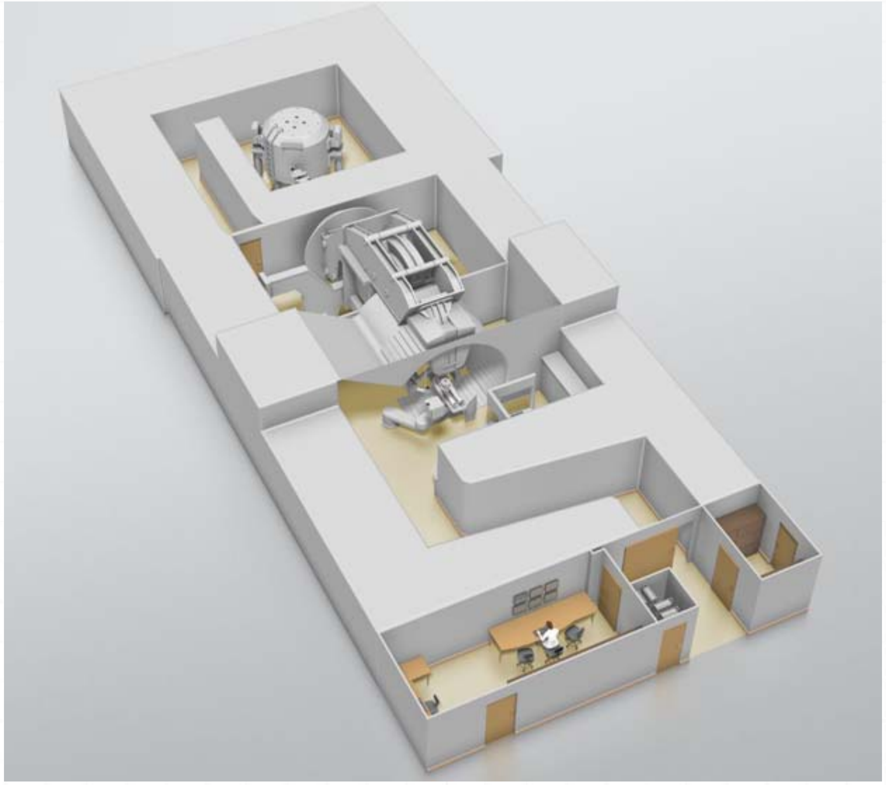
Kavita K. Mishra, MD, MPH,[*] Jeanne M. Quivey, MD,[*,†]

A Randomized Controlled Trial of Varying Radiation Doses in the Treatment of Choroidal Melanoma

Evangelos S. Gragoudas, MD; Anne Marie Lane, MPH; Susan Regan, PhD; Wenjun Li, MS; Heidi E. Judge, BA; John E. Munzenrider, MD; Johanna M. Seddon, MD; Kathleen M. Egan, ScD



Particle Therapy Present Technologies



The Rise of Proton Therapy

- Since 1990, the number of operating proton facilities in the US has increased from 2 to 28 with 15 more under construction.
- Internationally, up to 27 countries will have a proton center by 2021.

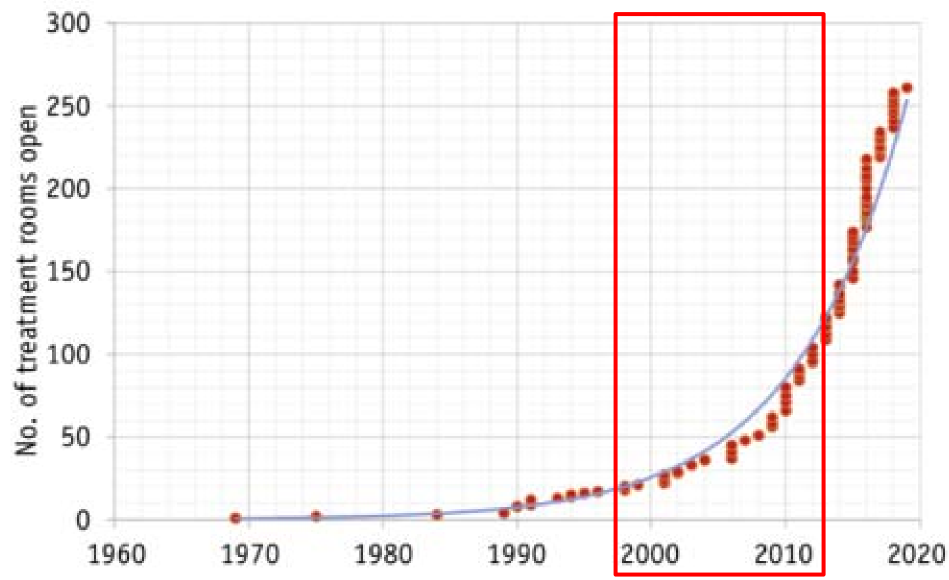
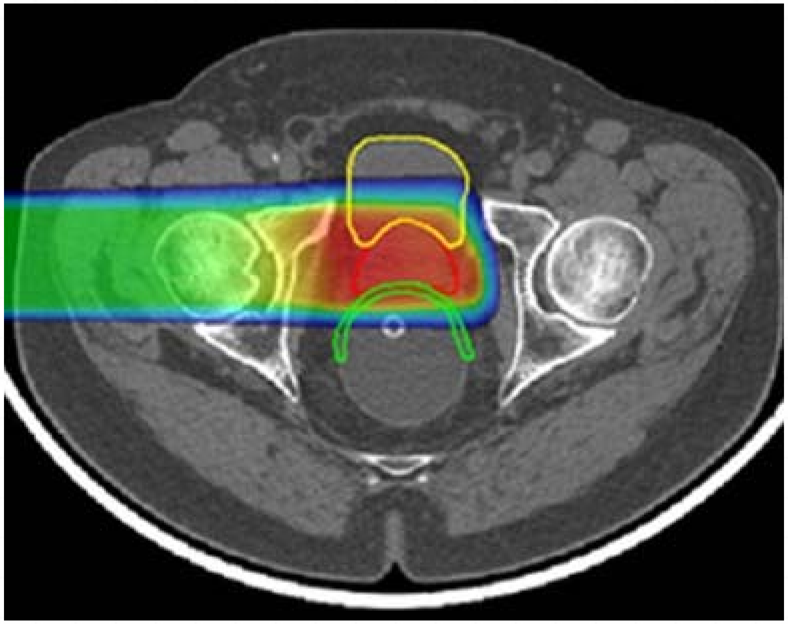
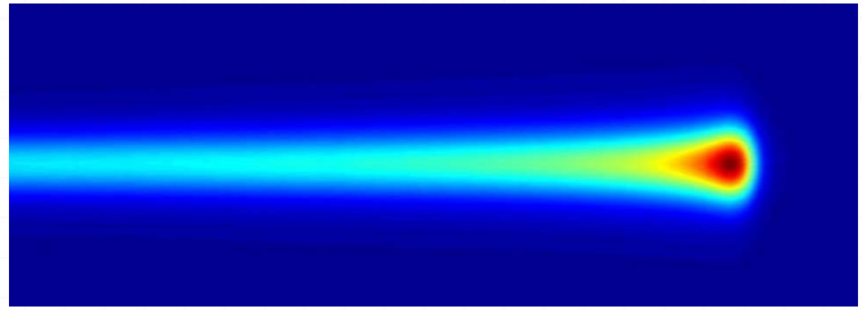
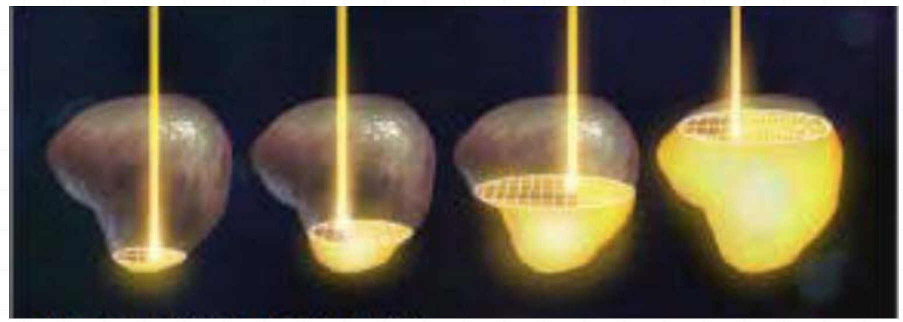


Fig. 5. Number of operating proton beam therapy rooms worldwide, 1970–present.

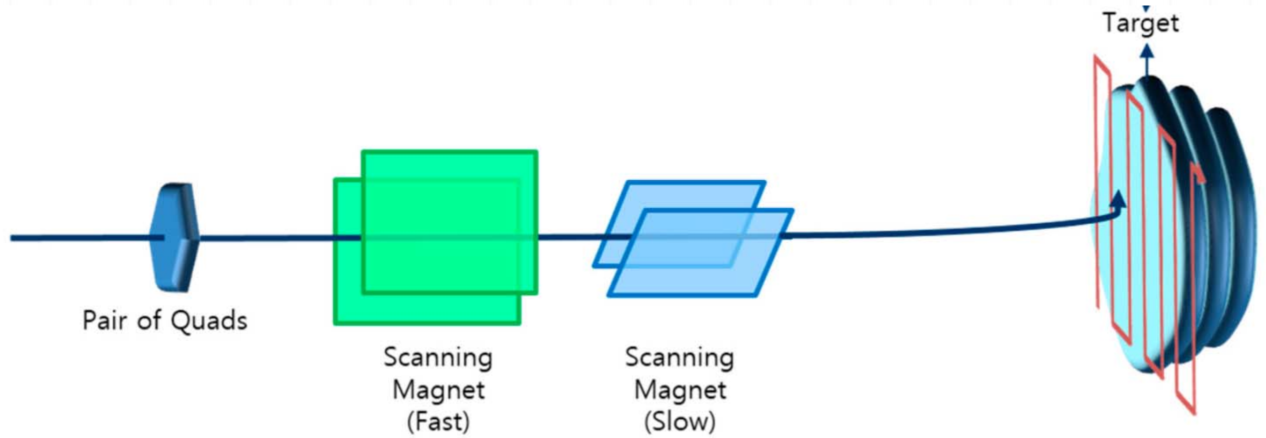
1-Pencil Beam Scanning







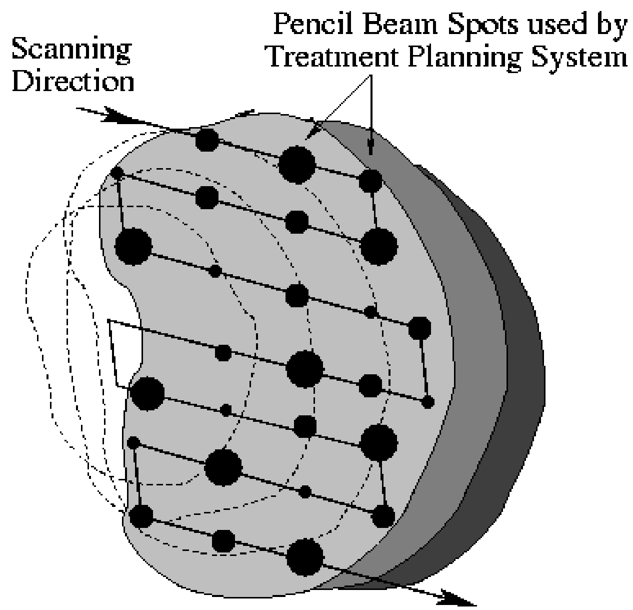
Pencil Beam Scanning

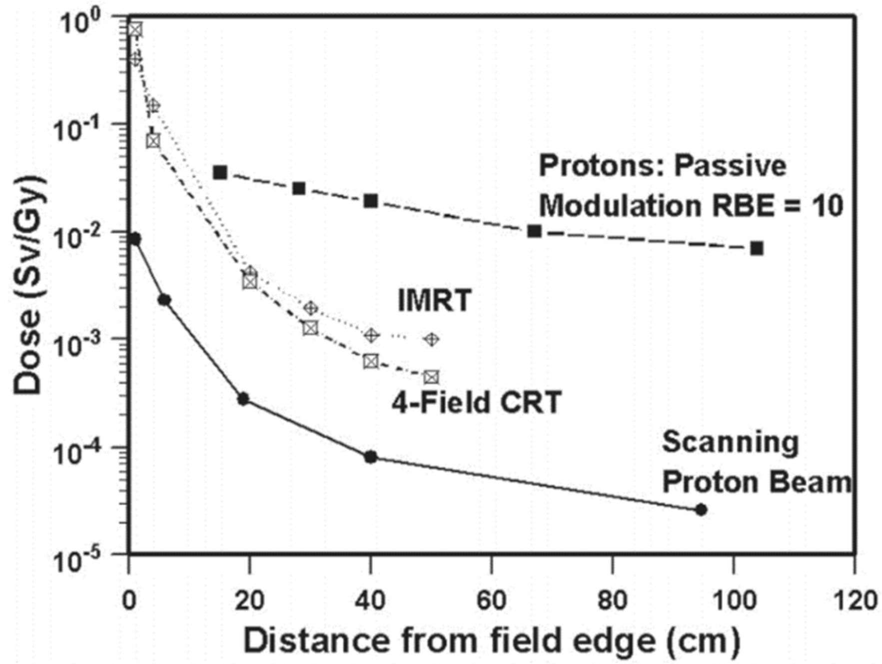


*Photos from= Machining's Role in Making Cancer History, Derek Korn, Modern Machine Shop, 5/3/2006
*Maquilan, Genevieve, et al. "Radiation Safety for Pregnant Workers at a Proton Facility." *International Journal of Radiation Oncology* Biology* Physics* 100.3 (2018): 560-564.

Improved Conformality & Reduced Neutron Contamination

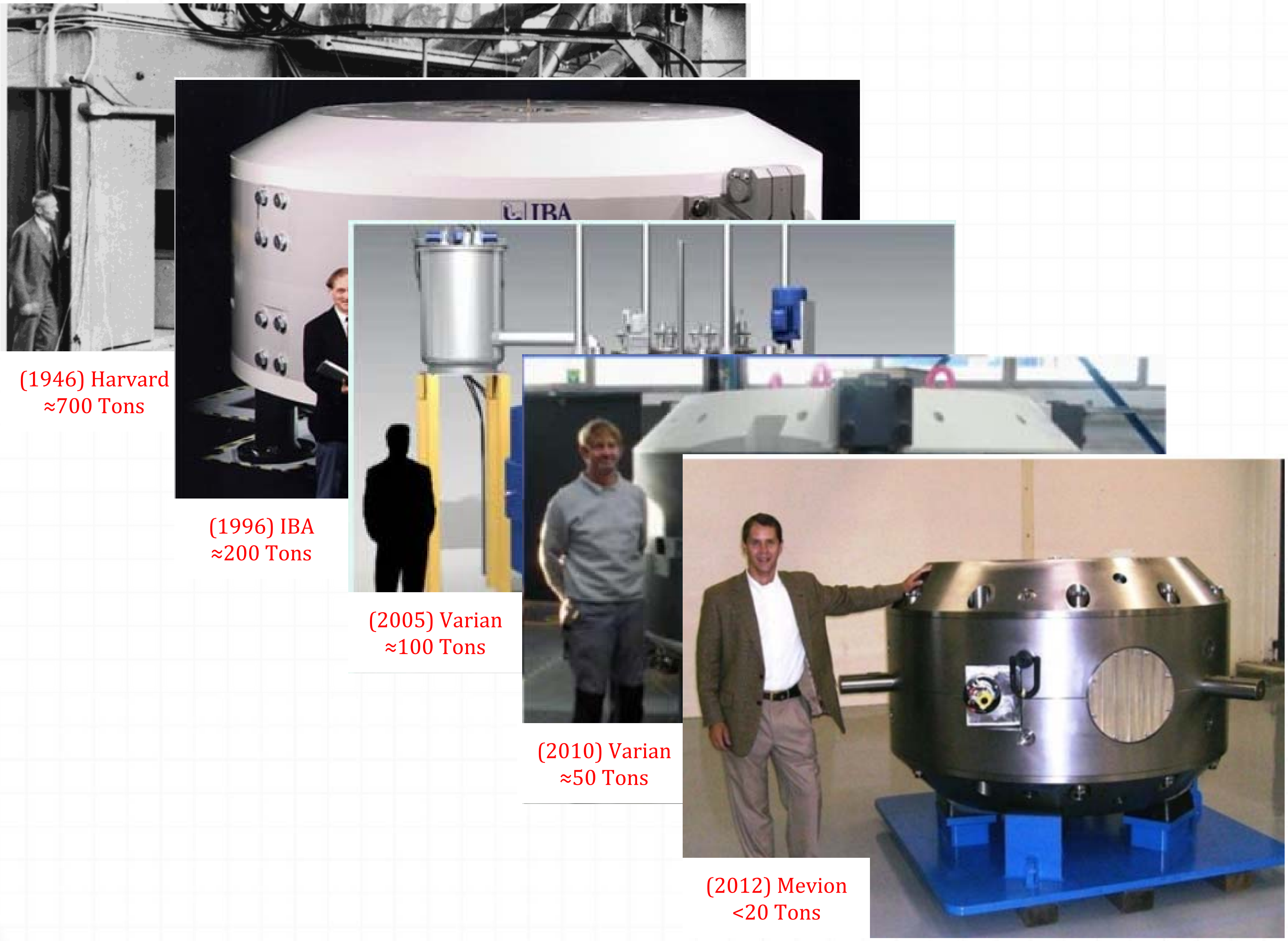
The Impact of Protons on the Incidence of Second Malignancies in Radiotherapy **Eric J. Hall, D.Phil., D.Sc.**





*Photos from=Proton Beam Therapy – The state of the Art1, Paganetti, Medical Physcis, Jan, 2005

2- Cyclotron Size



(1946) Harvard
≈700 Tons

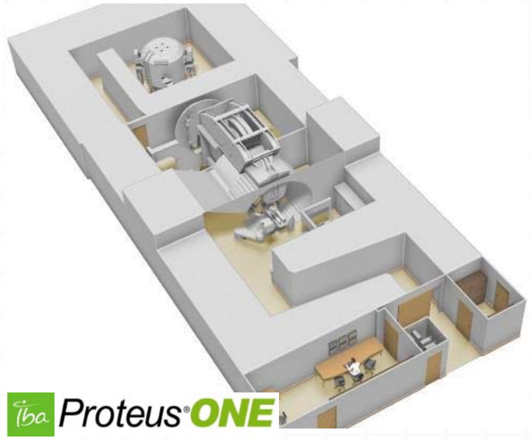
(1996) IBA
≈200 Tons

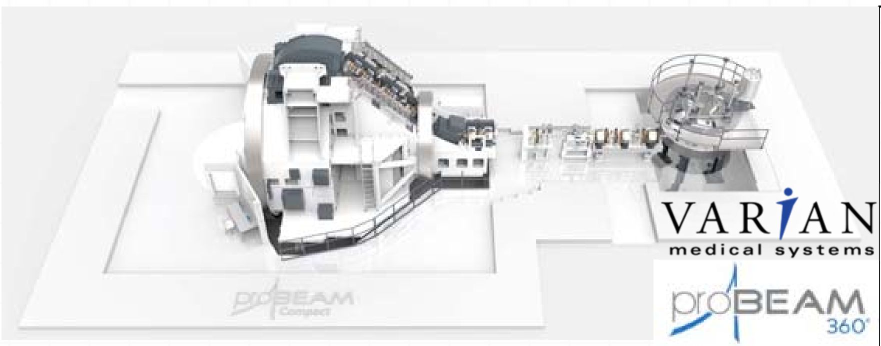
(2005) Varian
≈100 Tons

(2010) Varian
≈50 Tons

(2012) Mevion
<20 Tons

Single Room Proton Facility





- **2012:** FDA approved world's first compact proton therapy system.
- Up to **↓80%** reduction in ***footprint***
- Up to **↓ 90%** LESS ***energy usage***
- Up to **↓ 80%** lower ***capital cost $$***
- Up to **↓ 70%** less ***operational and clinical staff***

3- Half & Full Gantry

Critical Review

Empowering Intensity Modulated Proton Therapy Through Physics and Technology: An Overview

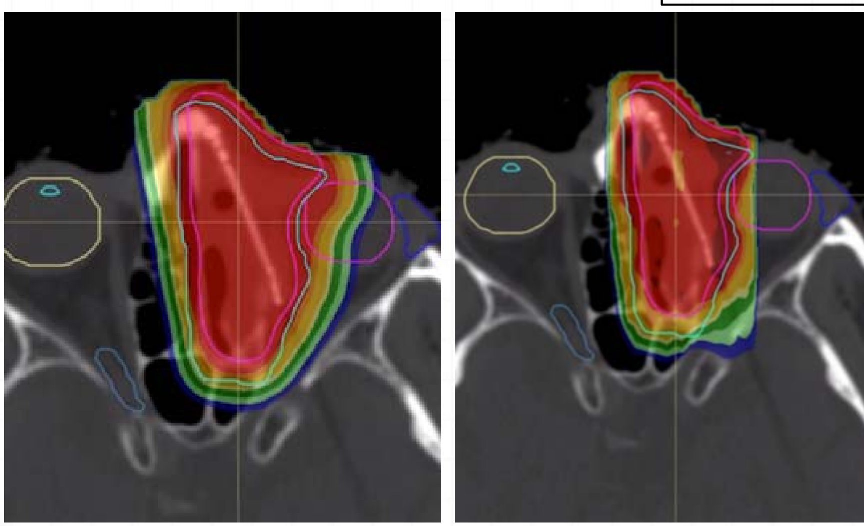
Radhe Mohan, PhD, FAAPM, FASTRO,* Indra J. Das, PhD, FACR, FASTRO,† and Clifton C. Ling, PhD, FAAPM, FASTRO‡

- Diameter= ***30 feet***
- Weight= ***120 tons***

(Equivalent to Boeing 757 with passenger & cargo)

4- Adaptive Apertures

- Some modern proton systems have dynamic MLC capabilities.
- *This approach combines the advantages of both pencil beam scanning (**improved conformality**) and passive scatter system (**reduced lateral penumbra**)*



Photos= Mevion system

5- Improved IGRT Capabilities

Original article

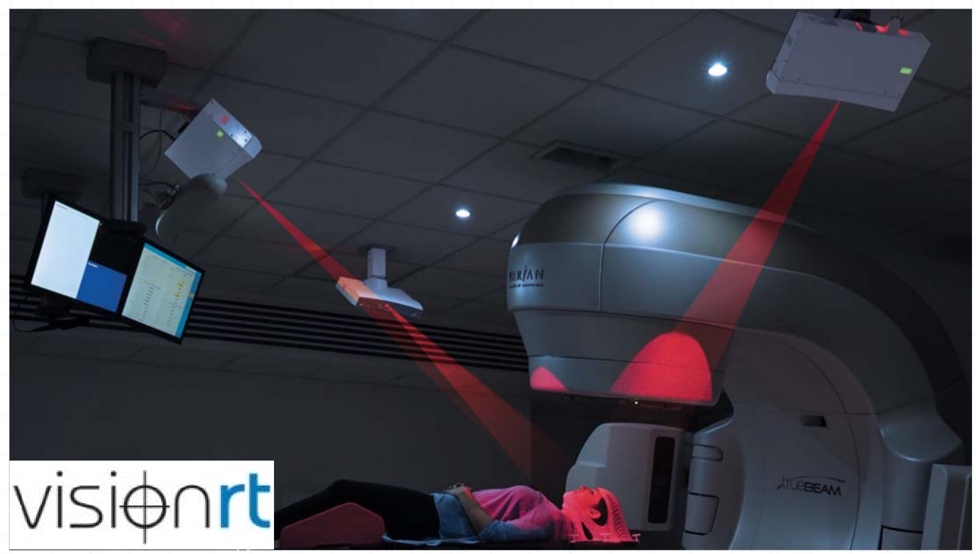
Toward adaptive proton therapy guided with a mobile helical CT scanner

Baozhou Sun*, Deshan Yang, Dao Lam, Tiezhi Zhang, Thomas Dvergsten, Jeffrey Bradley, Sasa Mutic, Tianyu Zhao

Department of Radiation Oncology, Washington University School of Medicine, St. Louis, United States

New proton facilities have a variety of IGRT options:

- CBCT
- CT on rails
- Mobile helical CT
- Surface guided RT



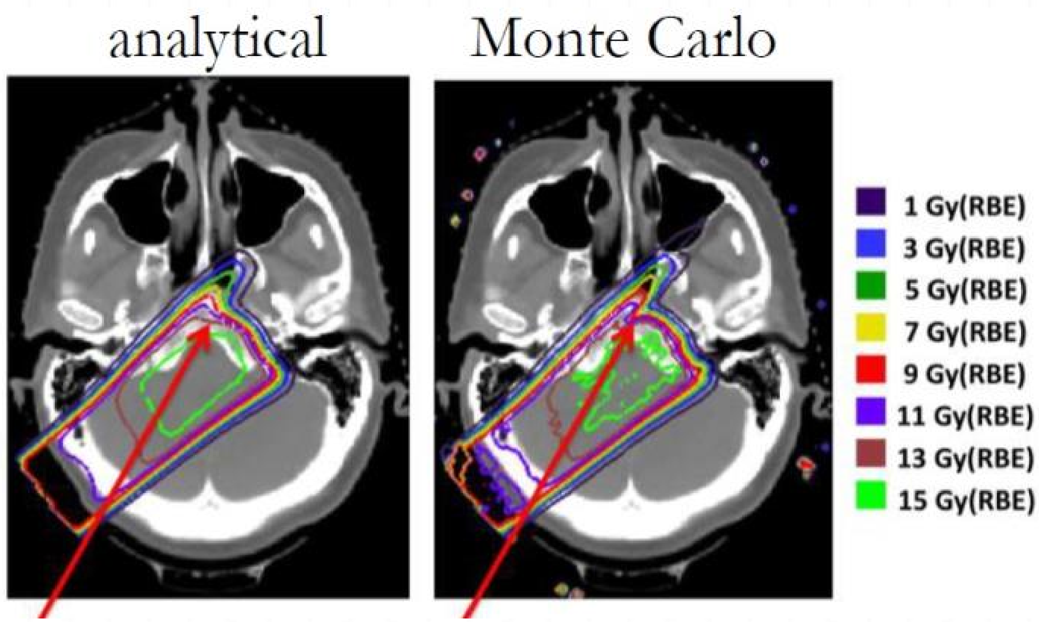
5- Monte Carlo Dose Calculation

Clinical implementation of full Monte Carlo dose calculation in proton beam therapy

Harald Paganetti, Hongyu Jiang [1], Katia Parodi[2], Roelf Slopsema[3] and Martijn Engelsman

Clinical Monte Carlo versus Pencil Beam Treatment Planning in Nasopharyngeal Patients Receiving IMPT

Balu Krishna Sasidharan, MBBS, MD[1]; Saif Aljabab, MD[2]; Jatinder Saini, PhD[3]; Tony Wong, PhD[3]; George Laramore, PhD, MD[2]; Jay Liao, MD[2]; Upendra Parvathaneni, MD[2]; Stephen R. Bowen, PhD[4]



(Paganetti *et al.*, 2008)

MC calculations are now widely accepted especially in certain disease sites:

- Lung
- H&N
- Breast

Monte Carlo Dose Calculation

Setup & Range Uncertainty

Source of range uncertainty in the patient	Range uncertainty	Monte Carlo dose calculation
Independent of dose calculation:		
Measurement uncertainty in water for commissioning	± 0.3 mm	
Compensator design	± 0.2 mm	
Beam reproducibility	± 0.2 mm	
Patient setup	± 0.7 mm	
Dose calculation:		
Biology (always positive)	+ 0.8 %	
CT imaging and calibration	± 0.5 %	
CT conversion to tissue (excluding I-values)	± 0.5 %	→ ± 0.2 %
CT grid size	± 0.3 %	
Mean excitation energies (I-values) in tissue	± 1.5 %	
Range degradation; complex inhomogeneities	- 0.7 %	→ ± 0.1 %
Range degradation; local lateral inhomogeneities *	± 2.5 %	→ ± 0.1 %
Total (excluding *)	**2.7% + 1.2 mm**	**2.4 % + 1.2 mm**
Total	**4.6% + 1.2 mm**	

H. Paganetti: Range uncertainties in proton beam therapy and the impact of Monte Carlo simulations
Phys. Med. Biol. 57: R99-R117 (2012)

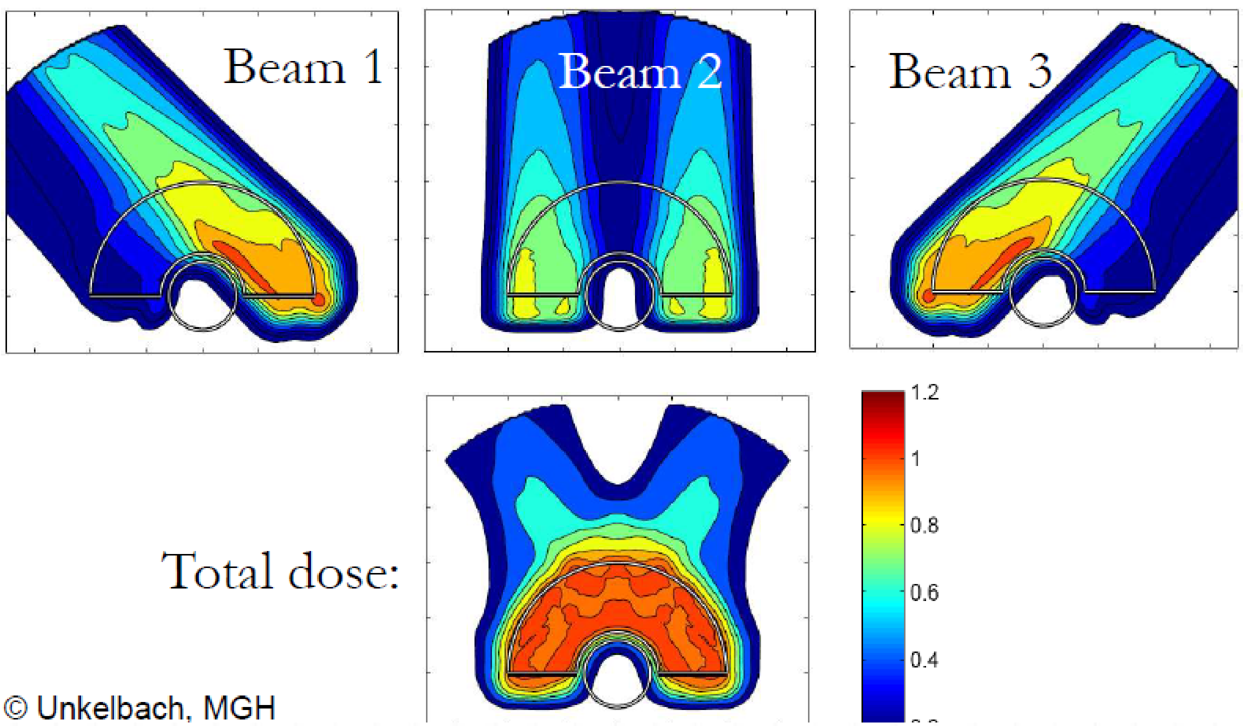
6- Multi-field Optimization (MFO)

Monte Carlo-based multi-field optimization in proton therapy: a new hybrid approach

F. Tommasino[1,2], L. Widesott[3], F. Fracchiolla[3], S. Lorentini[3], R. Righetto[3], C. Algranati[3], E. Scifoni[2], F. Dionisi[3], D. Scartoni[3], D. Amelio[3], M. Cianchetti[3], M. Schwarz[2,3], M. Amichetti[3], P. Farace[3]
[1] Department of Physics, University of Trento; [2] Trento Institute for Fundamental Physics and Applications (TIFPA), INFN;
[3] Proton Therapy Department, Azienda Provinciale per I Servizi Sanitari (APSS), Trento;

Addressing range uncertainties

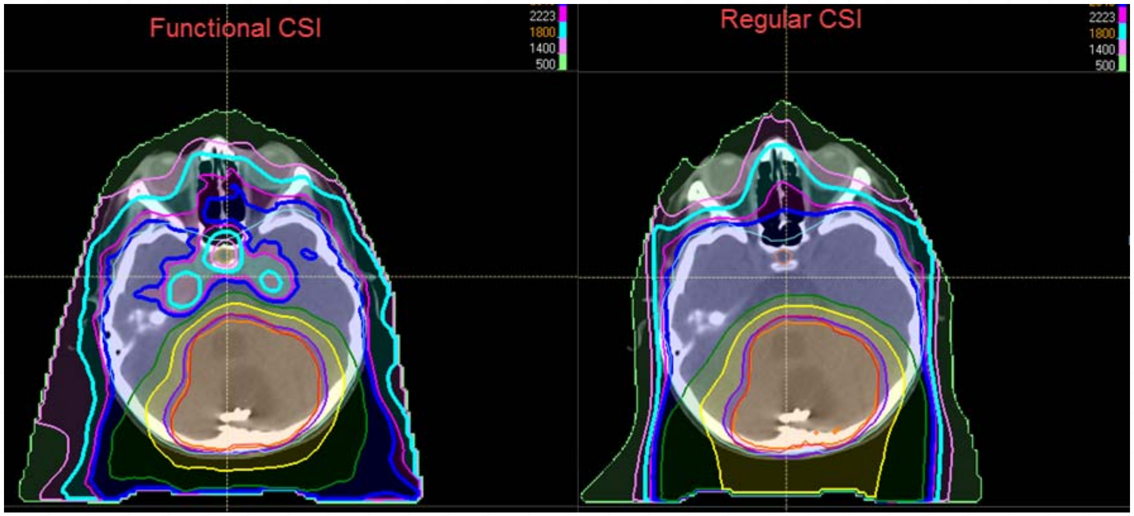
Mitigating range uncertainties using robust planning in IMPT

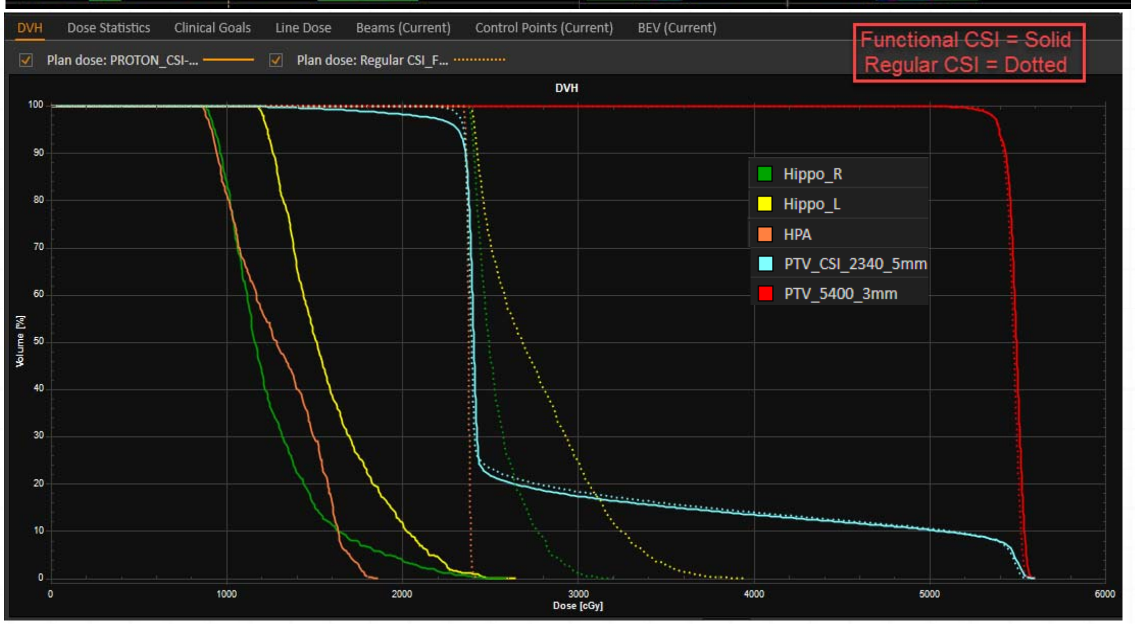


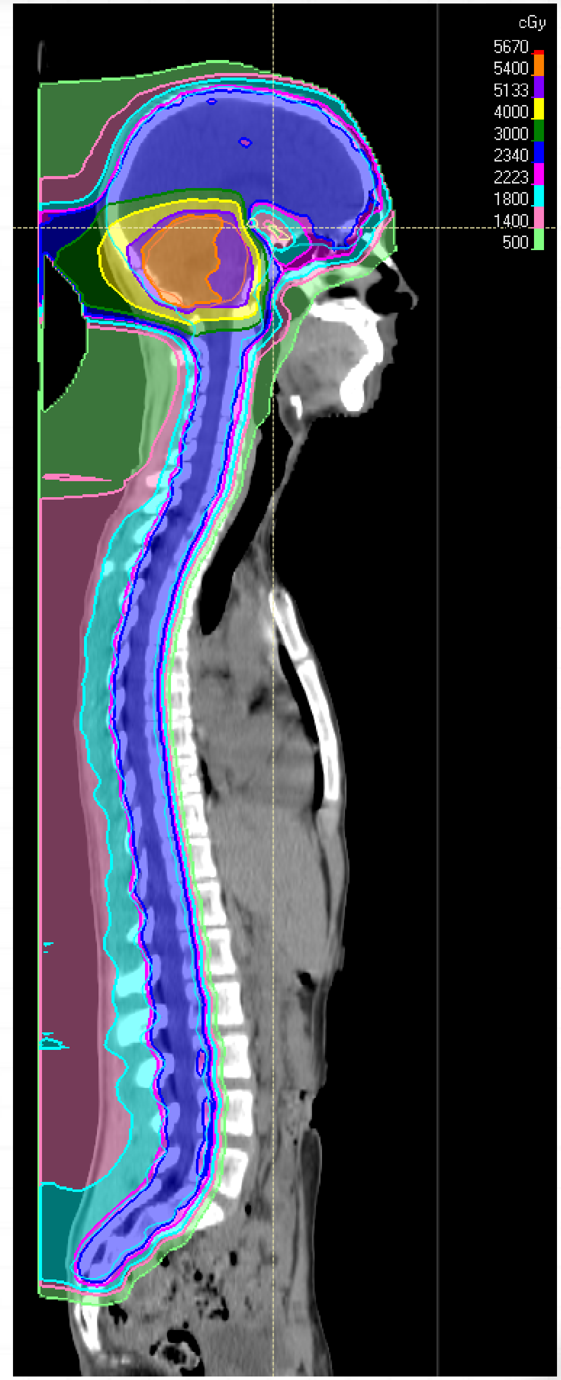
© Unkelbach, MGH

Hypothalamic-Pituitary Axis and Hippocampus Sparing with Cranio-Spinal Intensity Modulated Proton Therapy: A Dosimetric and Comparative Analysis

Saif Aljabab, MBBS, Jack Zheng, MD, Shadonna Maes, CMD, Avril O'Ryan-Blair, CMD, Jackie Castro, CMD, Laval Grimard, MD, Ralph Ermoian, MD, Phillip Taddei, PHD







Neutron Radiotherapy followed by a Proton Boost for Locally Advanced Salivary Gland Tumors: Early Clinical Experience

Saif Aljabab, MBBS, FRCPC, Andrew Liu, Tony Wong, Ph.D. , Jay J. Liao, MD, George E. Laramore, MD, Ph.D. , Upendra Parvathaneni, MBBS, FRANZCR

Neutron Radiotherapy and Gamma Knife Radiosurgery Boost for Locally Advanced Adenoid Cystic Carcinoma with Skull base Invasion

Andrew Lui [1], George Laramore, Ph.D., M.D. [2], Upendra Parvathaneni, MBBS, FRANZCR [2], Lia Halasz, M.D. [2], Jason K. Rockhill, M.D., Ph.D. [2], Saif Aljabab, MBBS [2], Jay J Liao, M.D. [2]

Figure 4. NRT Plan, Prescription= 18.4 nGy

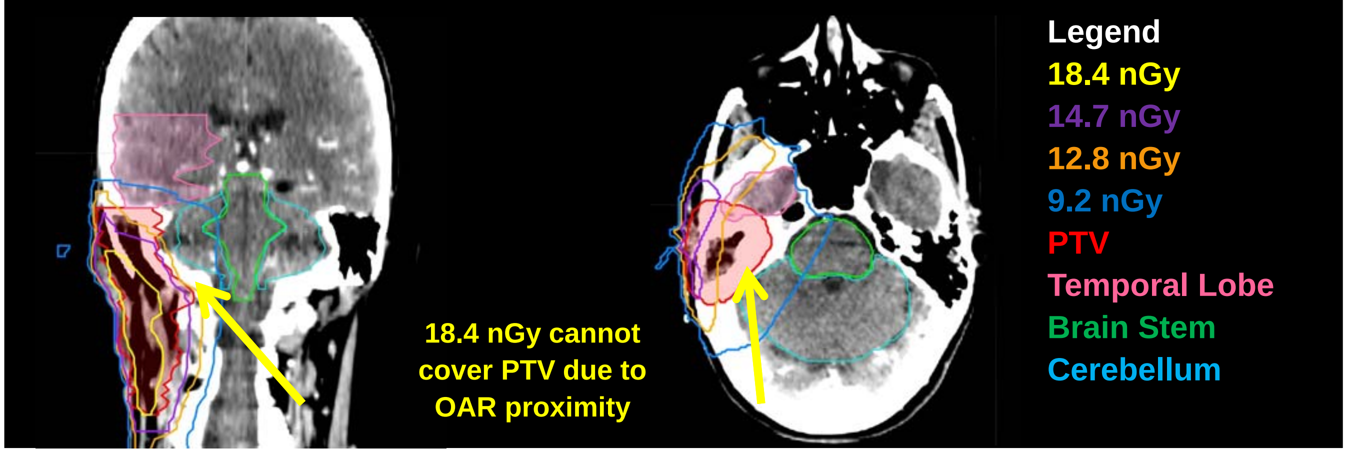
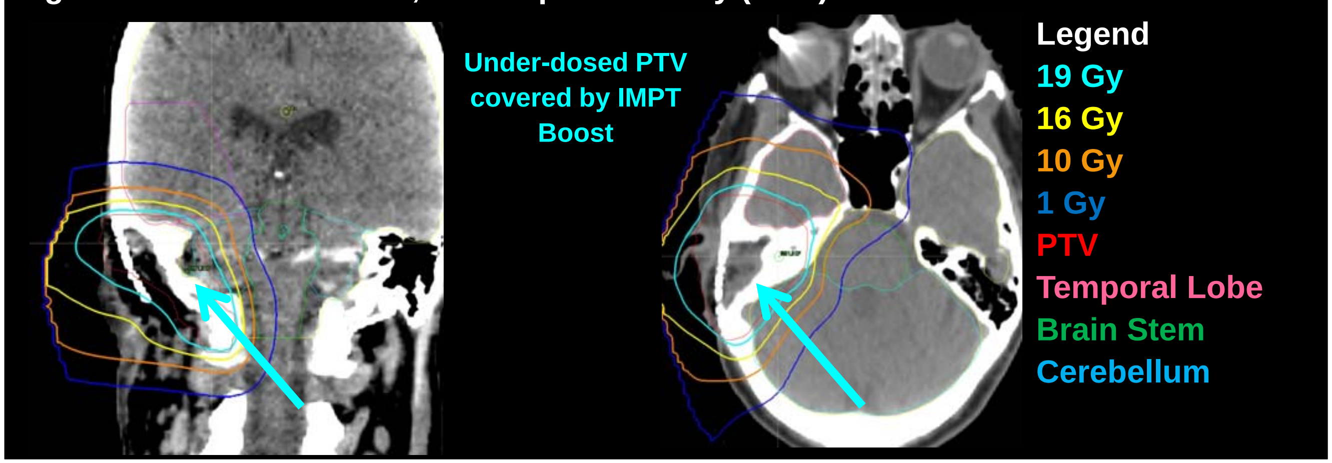
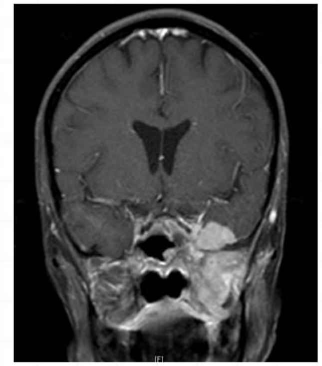
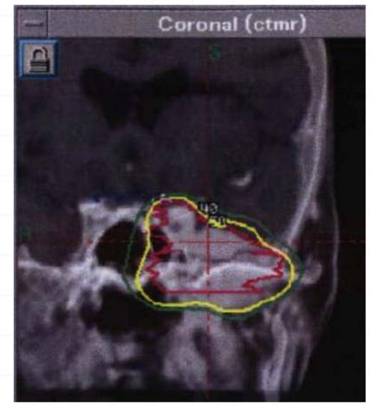
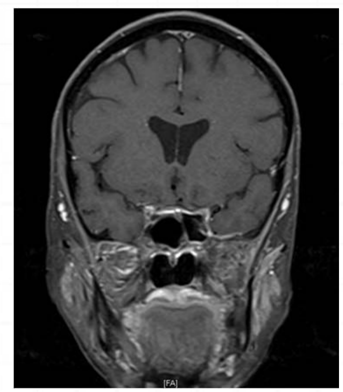


Figure 5. IMPT Boost Plan, Prescription= 20 Gy (RBE)









Modern Clinical Uses: H&N

INTERNATIONAL JOURNAL of PARTICLE THERAPY

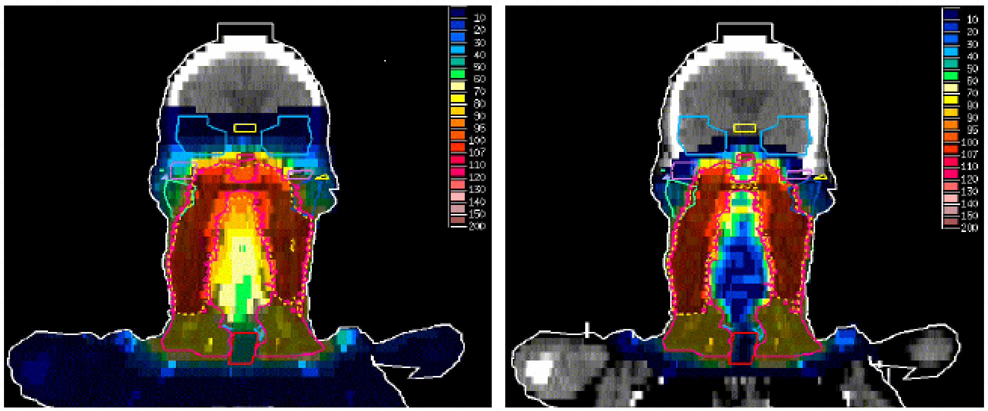
Quality of Life of Postoperative Photon versus Proton Radiation Therapy for Oropharynx Cancer

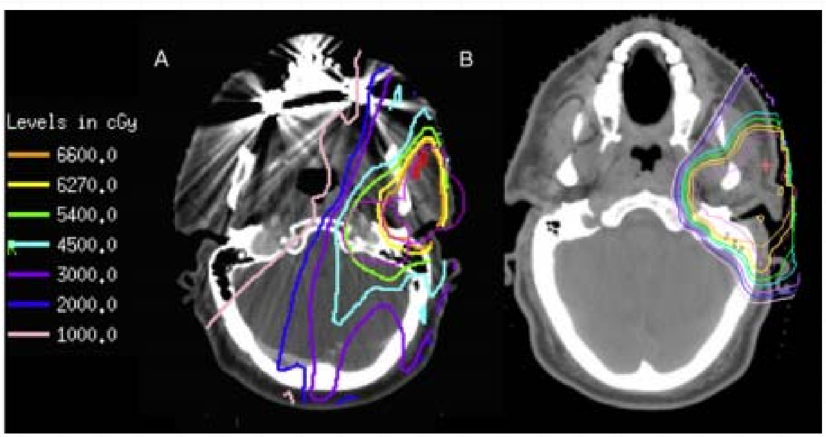
Sonam Sharma, MD[1]; Olivia Zhou[2]; Reid Thompson, MD, PhD[1]; Peter Gabriel,

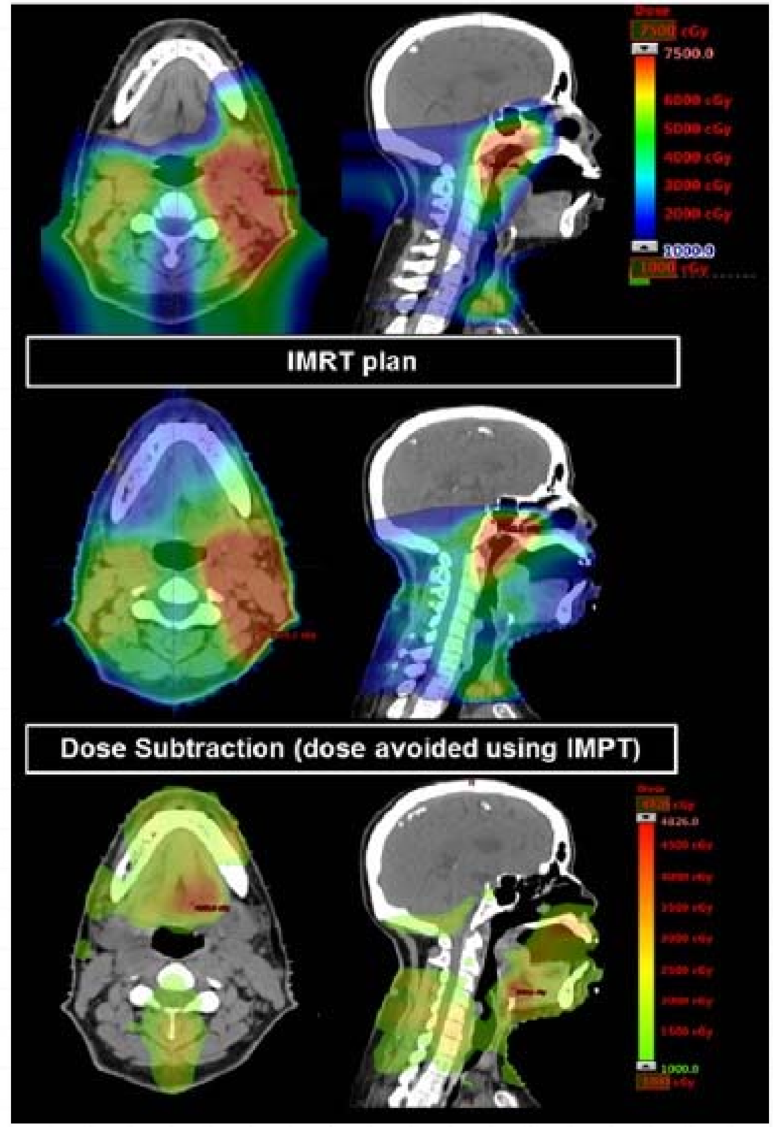
Proton beam radiation therapy results in significantly reduced toxicity compared with intensity-modulated radiation therapy for head and neck tumors that require ipsilateral radiation[☆]

CrossMark

Paul B. Romesser[a], Oren Cahlon[a,b], Eli Scher[a,c], Ying Zhou[d], Sean L. Berry[a], Alisa Rybkin[a], Kevin M. Sine[b], Shikui Tang[b], Eric J. Sherman[e], Richard Wong[f], Nancy Y. Lee[a,*]







Modern Clinical Uses: Breast

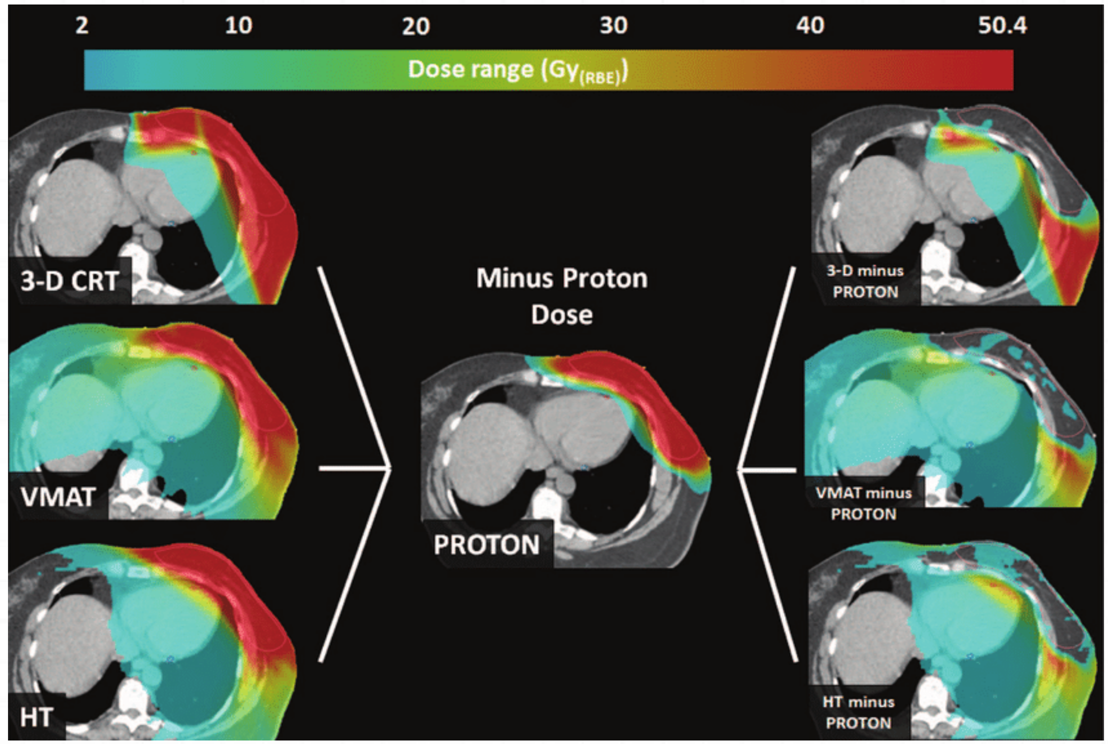
RadComp
PATIENT POWERED

Joint Estimation of Cardiac Toxicity and Recurrence Risks After Comprehensive Nodal Photon Versus Proton Therapy for Breast Cancer

Line B. Stick MSc *, †, Jen Yu PhD ‡, Maja V. Maraldo MD, PhD *, Marianne

Proton beam versus photon beam dose to the heart and left anterior descending artery for left-sided breast cancer

Lilie L. Lin, Sabina Vennarini, Andreea Dimofte, Daniele Ravanelli, Katie Shillington, Sonny Batra, Zelig Tochner, Stefan Both & Gary Freedman



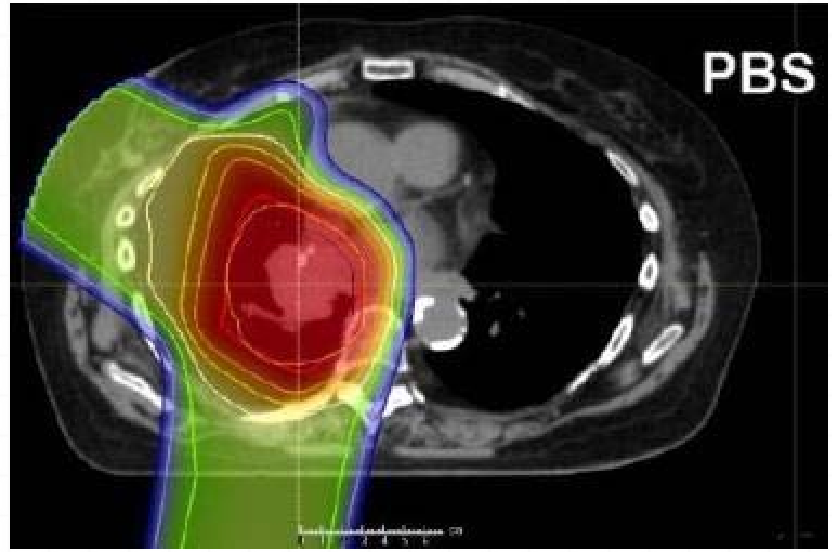
- Clinical data is still evolving for breast.
- Studies show reduction in 2nd ca, heart, LAD and lung doses (even vs DIBH). This is especially evident in bilateral breast irradiation cases.
- However, there is increased skin toxicity.
- Current indications include: reirradiation, bilateral fields with RNI

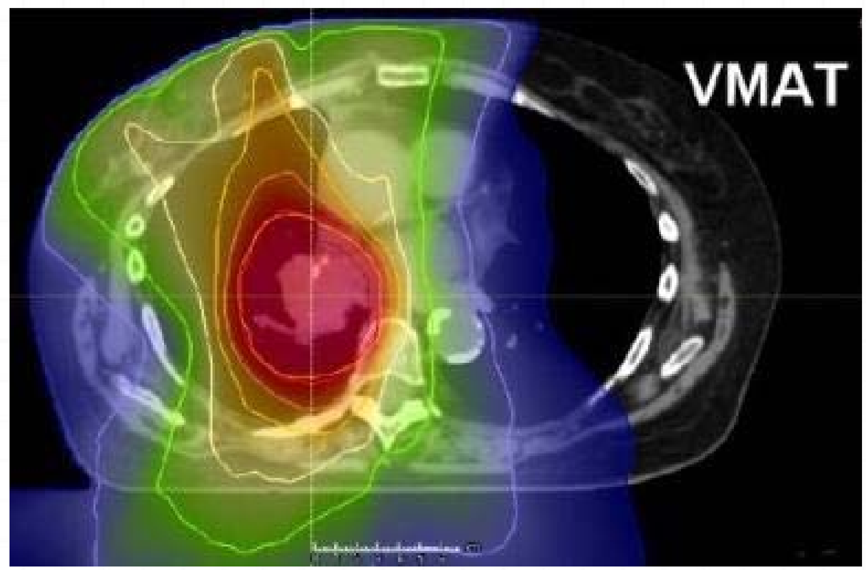
Modern Clinical Uses: Chest

Pencil Beam Algorithms Are Unsuitable for Proton Dose Calculations in Lung
Paige A. Taylor, MS, Stephen F. Kry, PhD, and David S. Followill, PhD

JAMA Oncology | Original Investigation
Proton Beam Radiotherapy and Concurrent Chemotherapy for Unresectable Stage III Non-Small Cell Lung Cancer
Final Results of a Phase 2 Study

- Clinical data still evolving
- Monte-Carlo calculations are necessary
- Protons allowed for safe dose escalation (Stages I-III) at the same time ↓dose to heart, lungs, spinal cord, esophagus and integral dose.
- Not all cases benefit from protons.
- PII study reveals promising survival and toxicity outcomes.
- Major limitations in prior proton clinical studies: No PET, used passive scatter, no Monte carlo calc and no daily CBCT





Modern Clinical Uses: Lymphoma

Proton therapy for adults with mediastinal lymphomas: the International Lymphoma Radiation Oncology Group guidelines

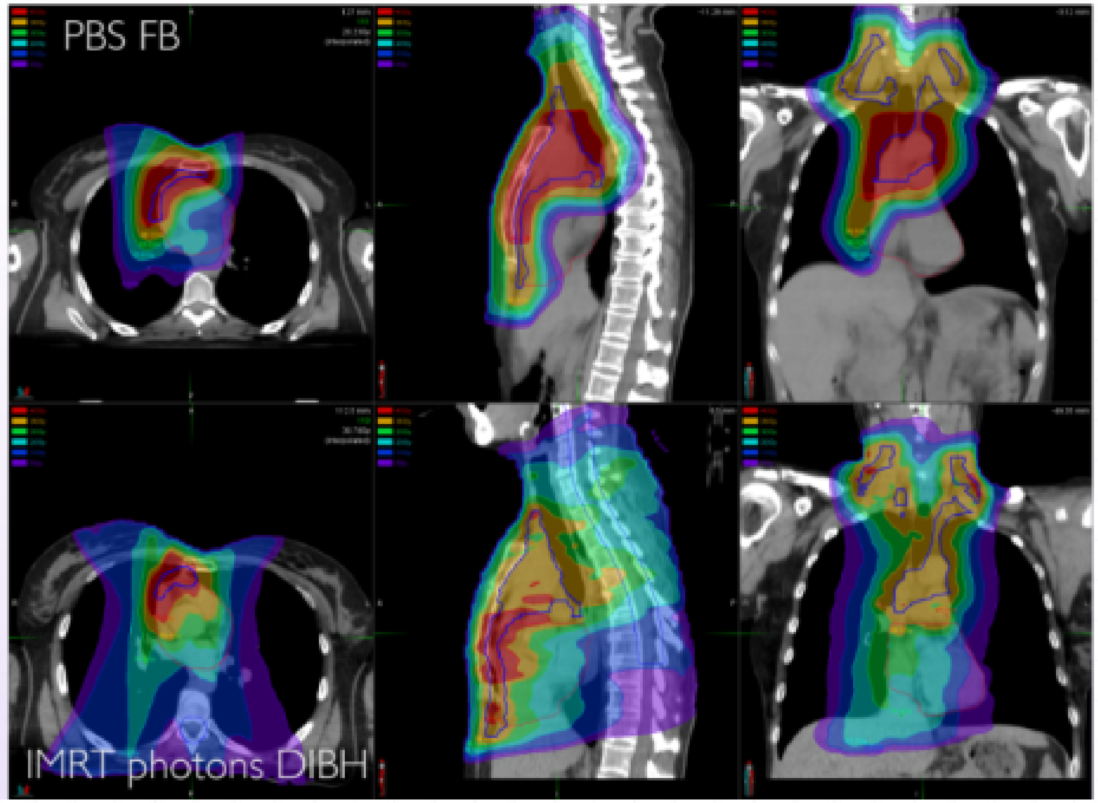
Bouthaina Shbib Dabaja,[1] Bradford S. Hoppe,[2] John P. Plastaras,[3] Wayne Newhauser,[4] Katerina Rosolova,[5,6] Stella Flampouri,[2]

Evidence-based Review on the Use of Proton Therapy in Lymphoma From the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee

Yolanda D. Tseng, MD,* David J. Cutter, MD, DPhil, FRCR,†

- Total of 14 photons vs protons comparative studies
- Majority are mediastinal
- Not one size fit all, benefit is case dependent: ↓ heart, lung, breast dose
- Despite high dose conformity no ↓ RFS

36F PMBCL with PR after DA-REPOCH, 40 Gy

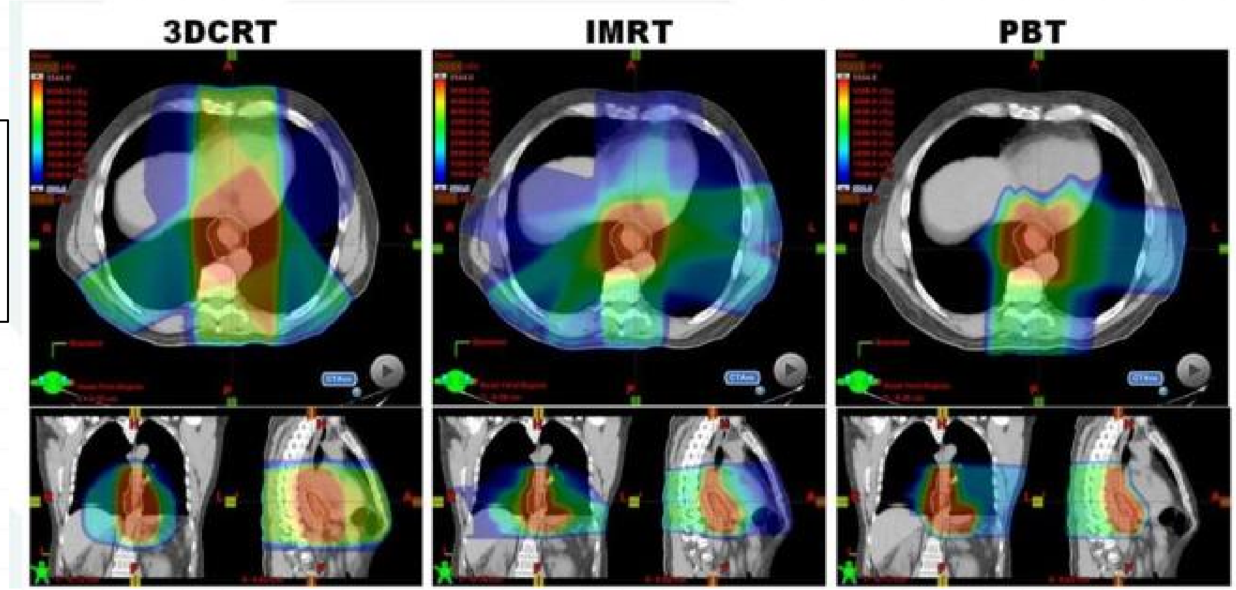


*Courtesy of: Dr. Yolanda Tseng, MD

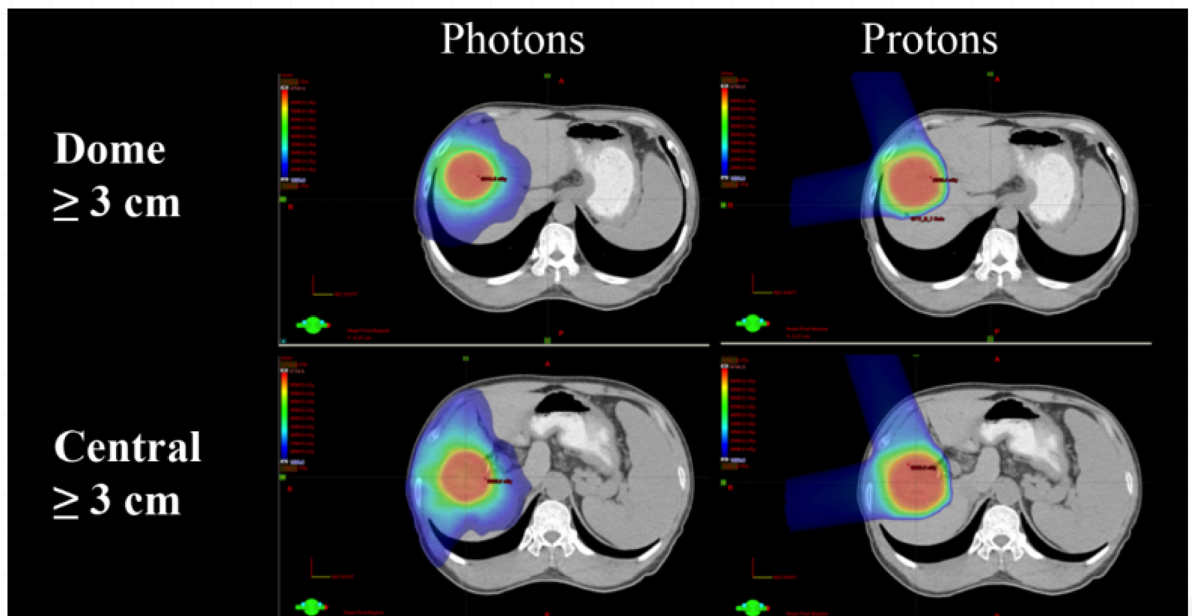
Modern Clinical Uses: GI

Comparative Outcomes After Definitive Chemoradiotherapy Using Proton Beam Therapy Versus Intensity Modulated Radiation Therapy for Esophageal Cancer: A Retrospective, Single-Institutional Analysis

Mian Xi, MD,*,† Cai Xu, MD,*,‡ Zhongxing Liao, MD,*



- Proton decreased pulmonary and cardiac complications
- Compared to IMRT, PBT improved OS and PFS.
- Need confirmation with prospective studies.



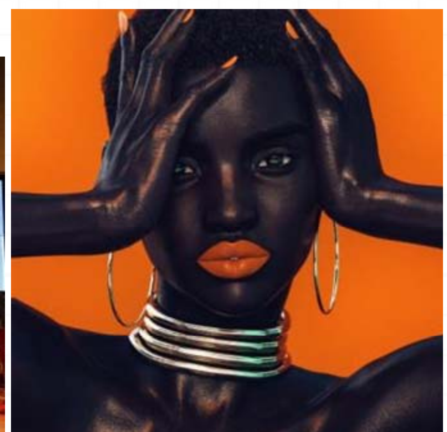
*Courtesy of: Dr. Smith Apisarnthanarax, MD

Particle Therapy Future Technologies

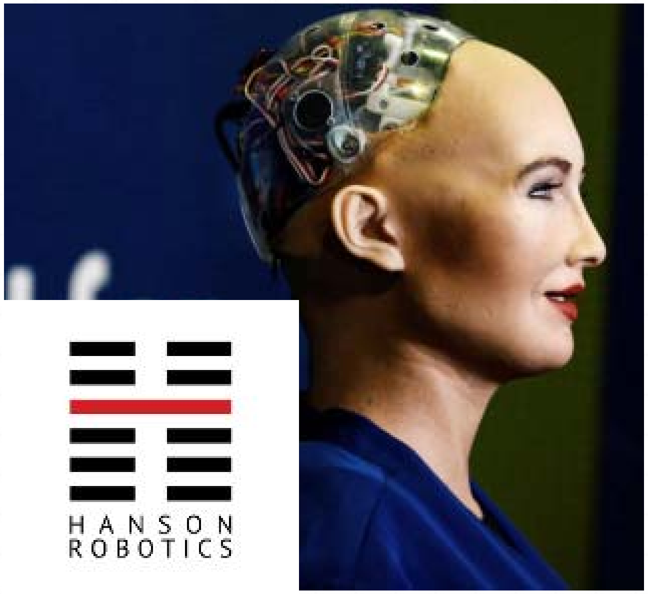
1- Automation

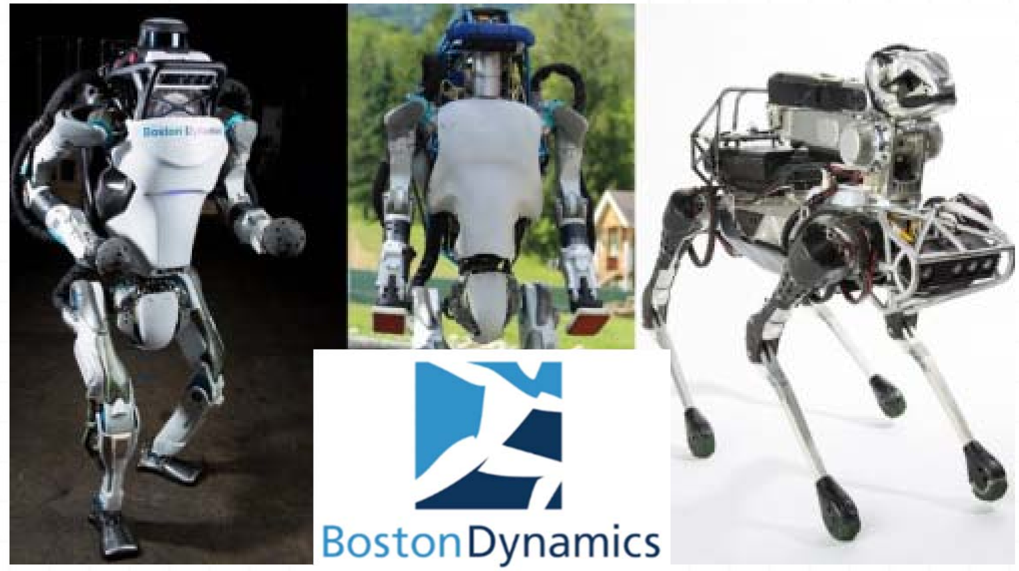
- Automation is the technology by which a process or procedure is performed with minimal human assistance.

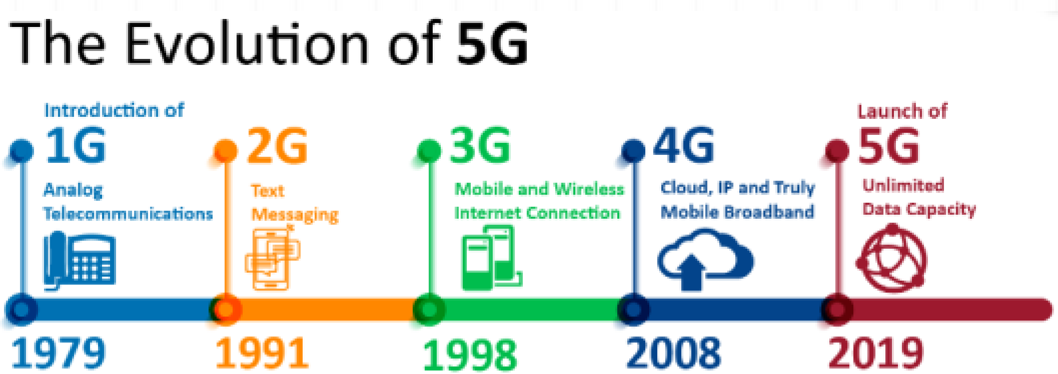


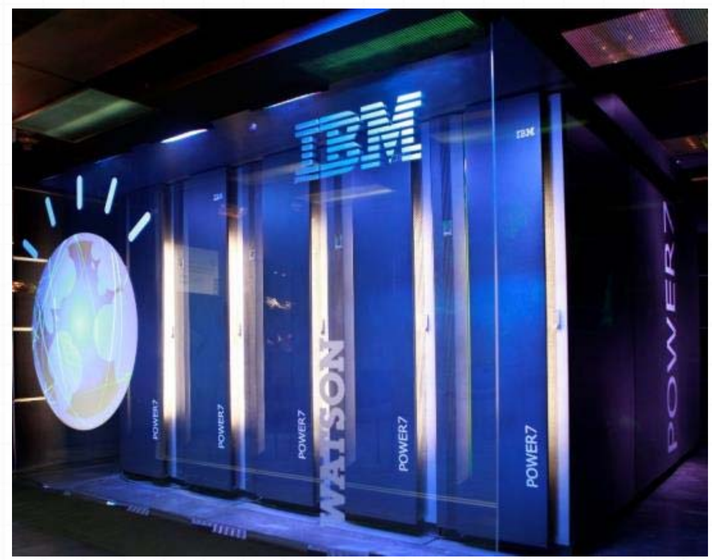



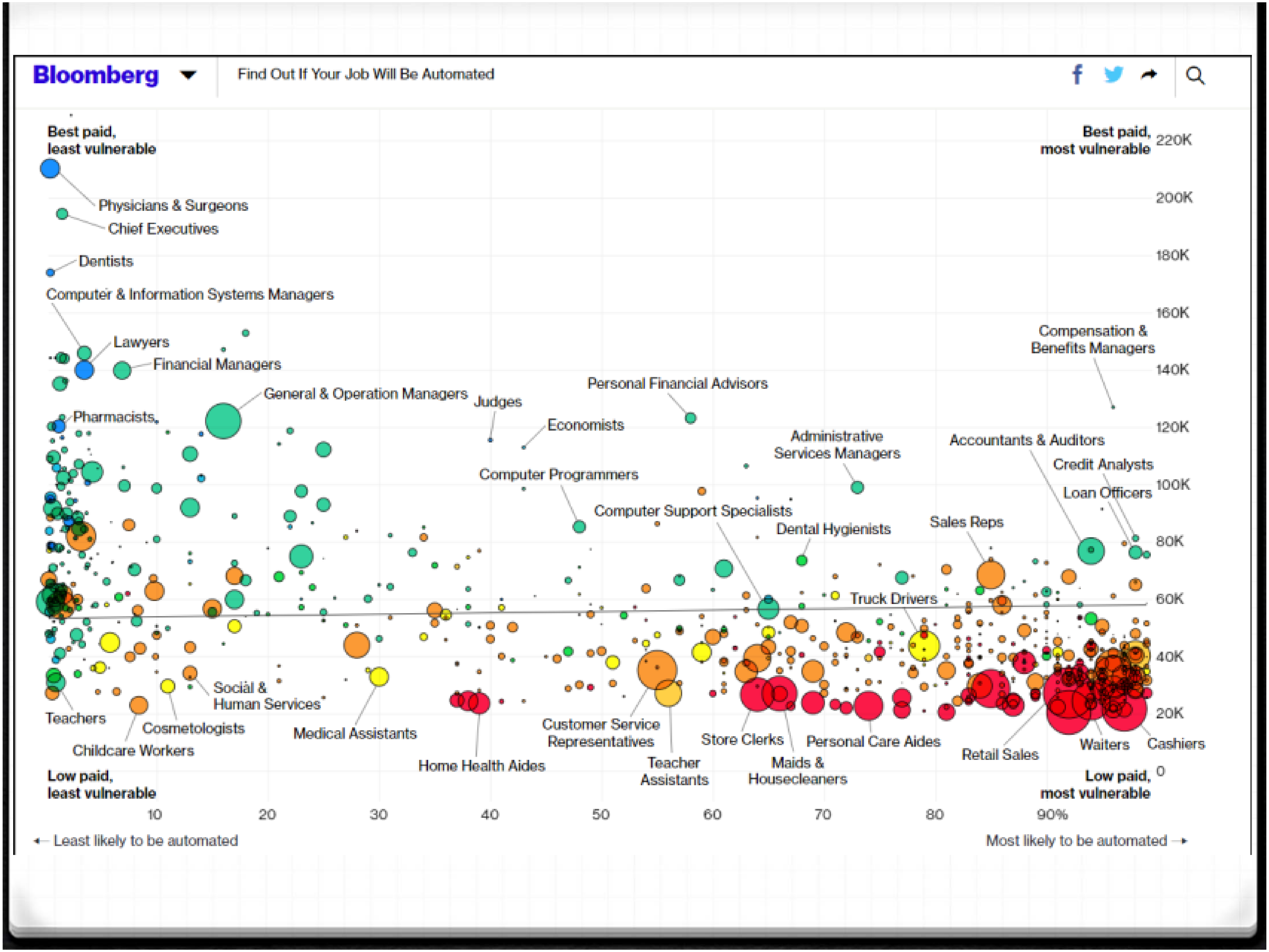

Automation – Robots & AI










Bloomberg
Find Out If Your Job Will Be Automated
Best paid, least vulnerable
Best paid, most vulnerable
Physicians & Surgeons
Chief Executives
Dentists
Computer & Information Systems Managers
Lawyers
Financial Managers
General & Operation Managers
Judges
Pharmacists
Personal Financial Advisors
Economists
Computer Programmers
Computer Support Specialists
Administrative Services Managers
Dental Hygienists
Compensation & Benefits Managers
Accountants & Auditors
Credit Analysts
Loan Officers
Sales Reps
Truck Drivers
Teachers
Childcare Workers
Cosmetologists
Social & Human Services
Medical Assistants
Home Health Aides
Customer Service Representatives
Teacher Assistants
Store Clerks
Maids & Housecleaners
Personal Care Aides
Retail Sales
Waiters
Cashiers
Low paid, least vulnerable
Low paid, most vulnerable
220K
200K
180K
160K
140K
120K
100K
80K
60K
40K
20K
0
10
20
30
40
50
60
70
80
90%
Least likely to be automated
Most likely to be automated

Automation in Medicine?

- Biometric verification
- Medical Scribe AI

An automated medical scribe for documenting clinical encounters

Gregory Finley, Erik Edwards, Amanda Robinson, Michael Brenndoerfer, Najmeh Sadoughi, James Fone, Nico Axtmann, Mark Miller, David Suendermann-Oeft

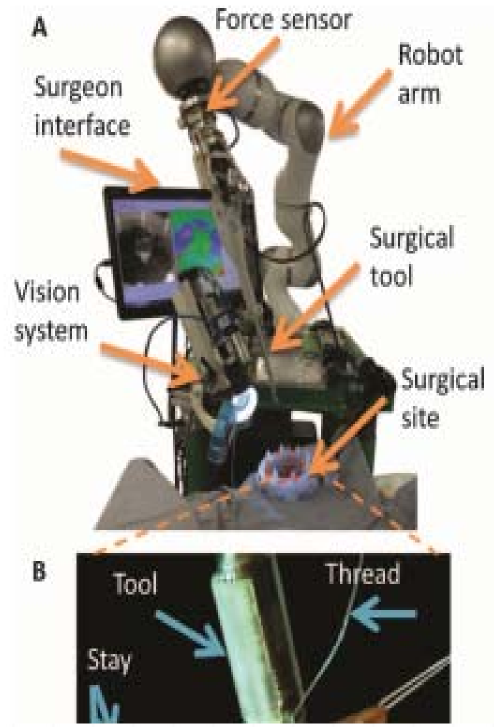
REMINDER: Fellow input requested - Defining directions for the RC regarding AI & Emerging Digital Technologies orientations du Collège royal à l'égard de l'IA et des technologies numériques émergentes Inbox ×

AI Task Force <aitaskforce@royalcollege.ca>
to Undisclosed

French > English Translate message

Le français suivit
This email serves as a reminder for Fellows who have not yet completed the survey.
Dear Royal College Fellow,
I have the honour of chairing a task force on the implications of Artificial Intelligence and Emerging Digital Technologies for specialty medicine in Canada. The task force will be providing Co

- Autonomous robotic surgery (STAR)
- Radiomics



Supervised autonomous robotic soft tissue surgery

Azad Shademan,[1] Ryan S. Decker,[1] Justin D. Opfermann,[1] Simon Leonard,[2] Axel Krieger,[1] Peter C. W. Kim[1]*

The current paradigm of robot-assisted surgeries (RASs) depends entirely on an individual surgeon's manual capability. Autonomous robotic surgery—removing the surgeon's hands—promises enhanced efficacy, safety, and improved access to optimized surgical techniques. Surgeries involving soft tissue have not been performed

Comparison of the accuracy of human readers versus machine-learning algorithms for pigmented skin lesion classification: an open, web-based, international, diagnostic study

Philipp Tschandl, Noel Codella, Bengü Nisa Akay, Giuseppe Argenziano, Ralph P Braun, Horacio Cabo, David Gutman, Allan Halpern, Brian Helba, Rainer Hofmann-Wellenhof, Aimilios Lallas, Jan Lapins, Caterina Longo, Josep Malvehy, Michael A Marchetti, Ashfaq Marghoob, Scott Menzies, Amanda Oakley, John Paoli, Susana Puig, Christoph Rinner, Cliff Rosendahl, Alon Scope, Christoph Sinz, H Peter Soyer, Luc Thomas, Iris Zalaudek, Harald Kittler

Interpretation State-of-the-art machine-learning classifiers outperformed human experts in the diagnosis of pigmented skin lesions and should have a more important role in clinical practice. However, a possible limitation of these algorithms is their decreased performance for out-of-distribution images, which should be addressed in future research.

Automation in Radiation Medicine?

2016 – Washington, DC

- "Contouring and **Auto-**planning"

2017 - Denver, CO

- "**Automated** Planning & image Guidance"
- "How to Select and Evaluate a PET **Auto**-segmentation Tool – Insights from AAPM TG211"
- "**Auto**-segmentation for Thoracic Radiation Treatment Planning: a Grand Challenge"

2018 AAPM Meeting

- "AAPM Medical Physics Student Meeting: The Role of **Automation** in Clinics of the Future"
- "**Automation** & Standardization of Planning, Plan Evaluation and System testing through Advanced Programming in the Treatment Planning System"
- "**Automation** in Radiation Therapy: Past, Present and Future"
- "Intelligent **Automation** for the Treatment Planning Workflows"
- "**Automation** in Radiotherapy – Faster Your Seatbelt!"
- "Hiding the complexity in Treatment Planning/**Automation**"
- "Joint AAPM-ESTRO Symposium: **Automated** Treatment Planning in Clinical Practice"

Recent Automation Abstracts "2019"

MAYO CLINIC

Automated verification plan preparation and 2D-3D gamma analysis for proton patient-specific quality assurance

Danairis Hernandez Morales[1], Jie Shan[1], Wei Liu[1], Kurt E. Augustine[1], Martin Bues[1], Michael J. Davis[1], Mirek Fatyga[1], Jedediah E. Johnson[2], Daniel W. Mundy[2], Jiajian Shen[1], James E. Younkin[1] and Joshua B. Stoker[1]

[1]Mayo Clinic, Phoenix, AZ, [2]Mayo Clinic, Rochester, MN

An automated replanning strategy for near real-time adaptive proton therapy

T. Jagt [1]

[1]*Erasmus Medical Center, Radiation Oncology, Rotterdam, Netherlands*

PO-0820 Full automation of radiation therapy treatment planning

L. Court[1], R. McCarroll[1], K. Kisling[1], L. Zhang[1], J. Yang[1], H. Simonds[2], M. Du Toit[2], M. Mejia[3], A. Jhingran[4], P. Balter[1], B. Beadle[4]

[1]*MD Anderson Cancer Center, Department of Radiation Physics, Houston, USA*

[2]*Stellenbosch University, Radiation Oncology, Stellenbosch, South Africa*

PO-0821 Automatic re-planning of VMAT plans in prostate and HN patients using constrained optimization

L. Künzel[1], O. Dohm[2], M. Alber[3], D. Thorwarth[1]

[1]*University Hospital Tübingen Eberhard Karls University Tübingen, Section for Biomedical Physics, Tübingen, Germany*

[2]*University Hospital Tübingen Eberhard Karls University Tübingen, Radiation Oncology Division of Medical Physics, Tübingen, Germany*

Automated treatment planning of postmastectomy radiotherapy

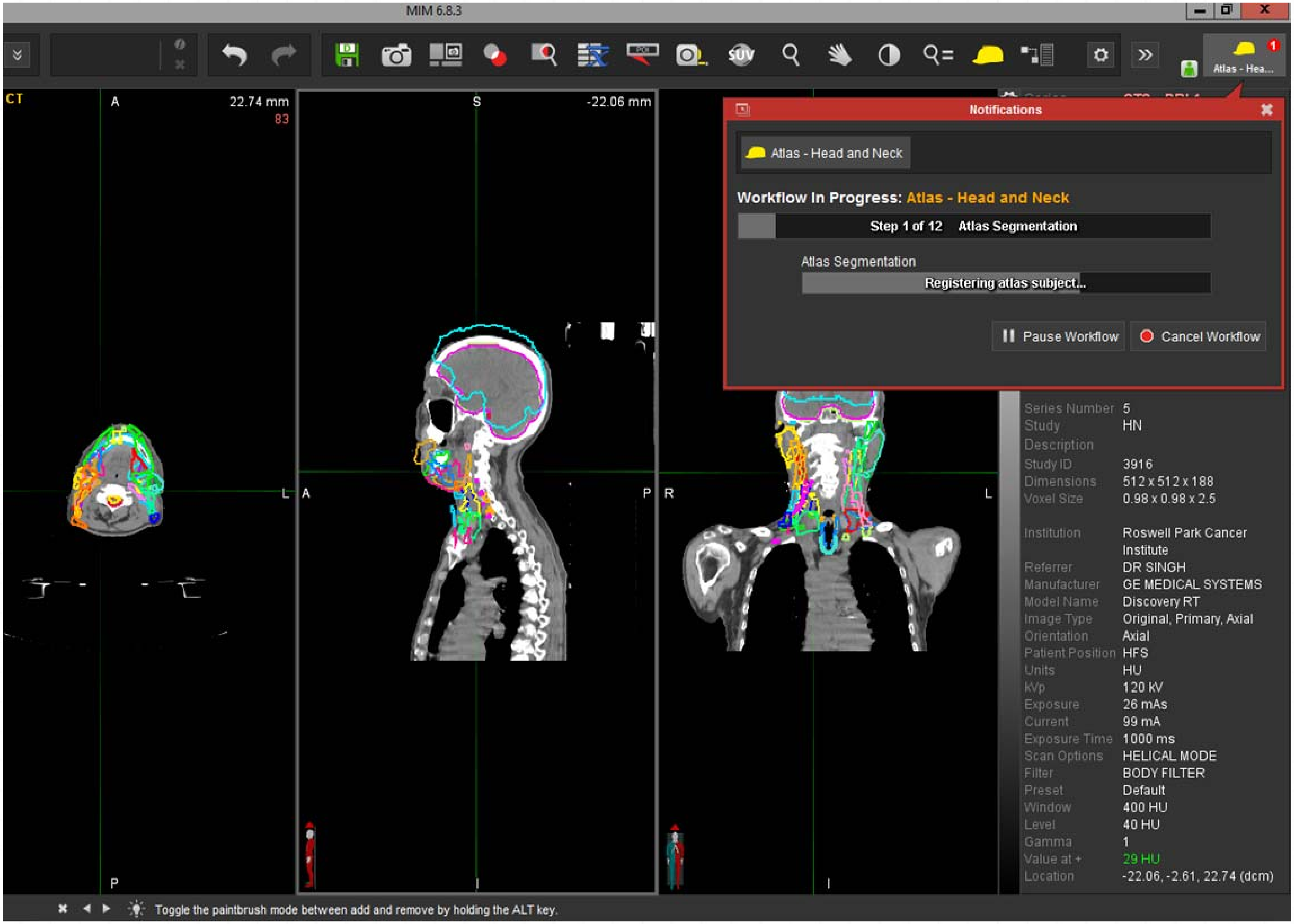
Kelly Kisling, Lifei Zhang, Simona F. Shaitelman, David Anderson, Tselane Thebe, Jinzhong Yang, Peter A. Balter, Rebecca M. Howell, Anuja Jhingran, Kathleen Schmeler, Hannah Simonds ... See all authors

First published: 11 May 2019 | https://doi.org/10.1002/mp.13586

Automation of routine elements for spot-scanning proton patient-specific quality assurance

Danairis Hernandez Morales, Jie Shan, Wei Liu, Kurt E. Augustine, Martin Bues, Michael J. Davis, Mirek Fatyga, Jedediah E. Johnson, Daniel W. Mundy, Jiajian Shen, James E. Younkin, Joshua B. Stoker

First published: 19 October 2018 | https://doi.org/10.1002/mp.13246


MIM 6.8.3
Atlas - Hea...
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Notifications
Atlas - Head and Neck
Workflow In Progress: Atlas - Head and Neck
Step 1 of 12 Atlas Segmentation
Atlas Segmentation
Registering atlas subject...
Pause Workflow
Cancel Workflow
Series Number 5
Study HN
Description
Study ID 3916
Dimensions 512 x 512 x 188
Voxel Size 0.98 x 0.98 x 2.5
Institution Roswell Park Cancer Institute
Referrer DR SINGH
Manufacturer GE MEDICAL SYSTEMS
Model Name Discovery RT
Image Type Original, Primary, Axial
Orientation Axial
Patient Position HFS
Units HU
kVp 120 kV
Exposure 26 mAs
Current 99 mA
Exposure Time 1000 ms
Scan Options HELICAL MODE
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Window 400 HU
Level 40 HU
Gamma 1
Value at + 29 HU
Location -22.06, -2.61, 22.74 (dcm)
Toggle the paintbrush mode between add and remove by holding the ALT key.


MIM 6.8.3
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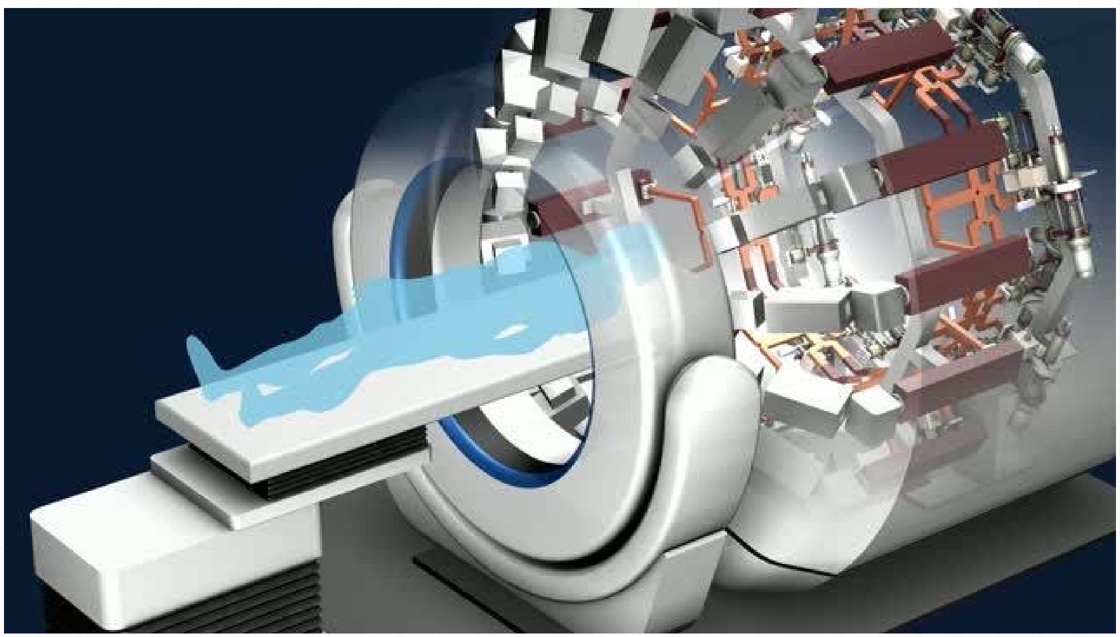
MIM Assistant can save time by automating DICOM transfers, pre-processing data, and more.

2- FLASH Particle Therapy

- Ultra-High dose rate of external beam therapy delivered in less than 1 second (>40,000cGy/sec)
- FLASH investigations re-initiated within the last decade, proton FLASH toxicity studies initiated in 2017, now ongoing first proton Flash tumor control study.



(PHASER)
Pluridirectional
High-energy
Agile Scanning
Electronic
Radiotherapy

Tx Delivery Time= <1sec

Abstract LB-280: FLASH: A novel paradigm changing tumor irradiation platform that enhances therapeutic ratio by reducing normal tissue toxicity and activating immune pathways

Swati Girdhani, Eric Abel, Alexander Katsis, Andrew Rodriquez, Shilpa Senapati, Angel KuVillanueva, Isabel L. Jackson, John Eley, Zeljko Vujaskovic, and Renate Parry

NEWS | PROTON THERAPY | APRIL 09, 2019

Varian Discloses First Preclinical Results of Flash Therapy in Cancer Treatment

First preclinical results with ultra-high-dose proton therapy presented at AACR

Original Article

Treatment of a first patient with FLASH-radiotherapy

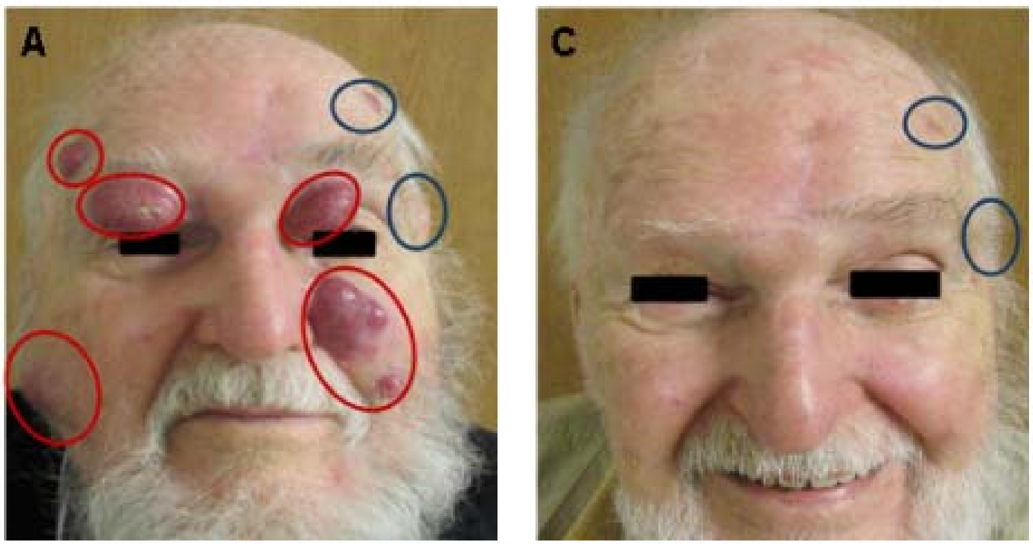
Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

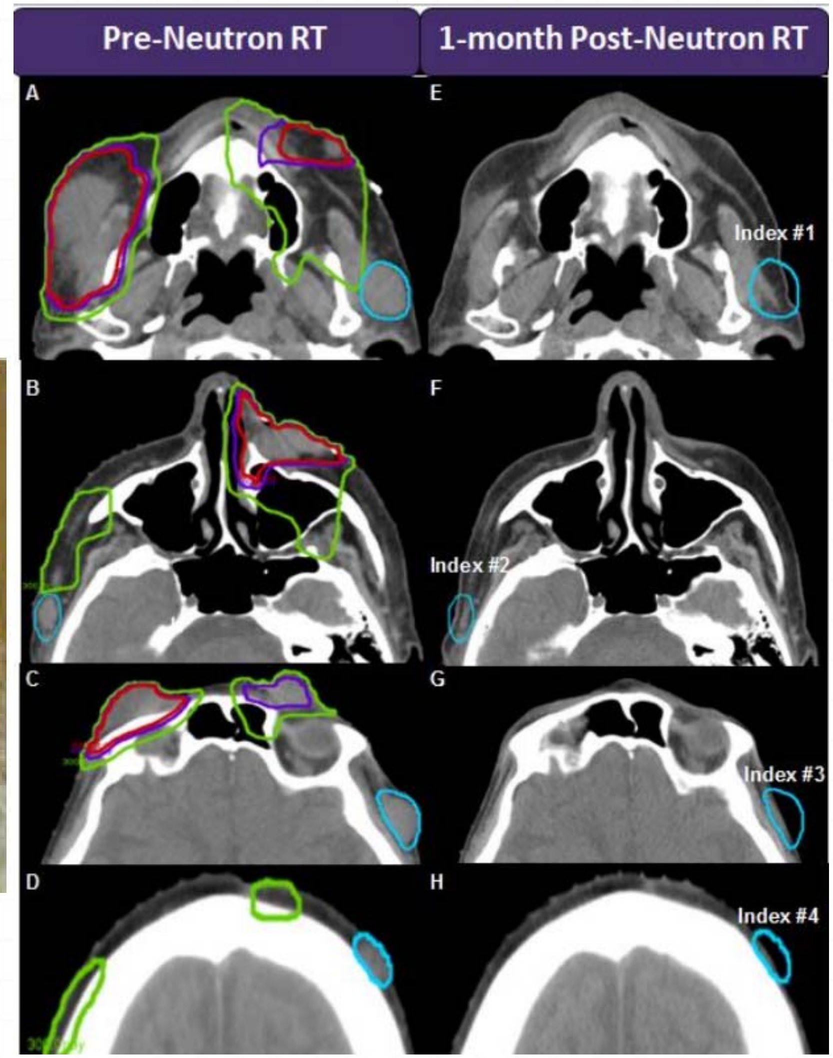
[a] *Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne;* [b] *Radiation Oncology Laboratory, Department of Radiation Oncology. Lausanne University Hospital and University of Lausanne;* [c] *Institute of Radiation Physics, Lausanne University Hospital and University of Lausanne; and* [d] *Department of Dermatology, Lausanne University Hospital and University of Lausanne, Switzerland*

3- Particle Immunotherapy

Case Report: Neutron Radiation Therapy for Refractory Merkel Cell Carcinoma in an Immunotherapy Primed Patient Potentiates the Immune Response

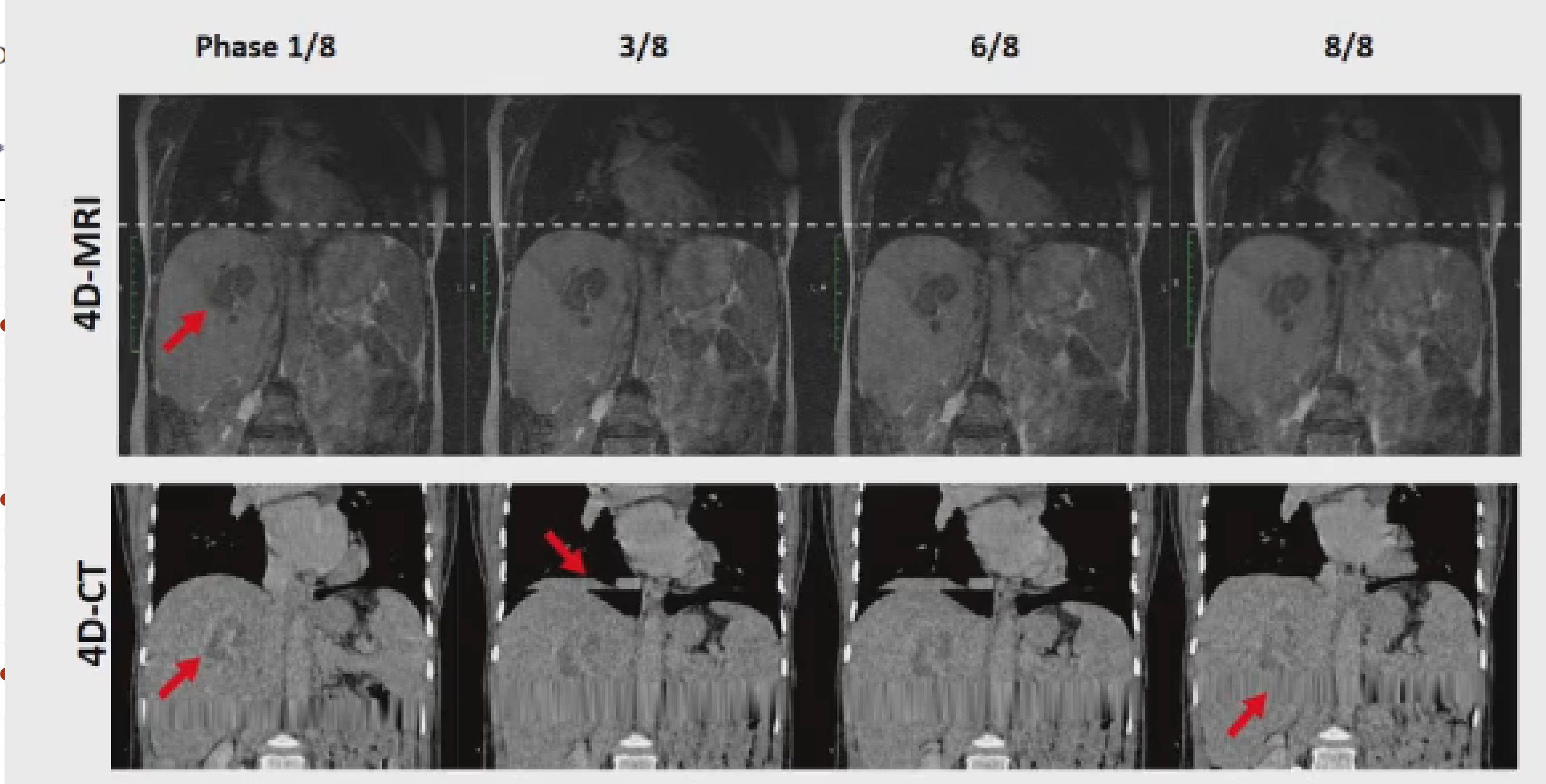
Stephanie K. Schaub, MD[1]*, Jay J. Liao, MD[1], George E. Laramore, PhD, MD[1], Robert D. Stewart, PhD[1],





4- 5DCT

NOVEL BREATHING MOTION MODEL FOR RADIOTHERAPY



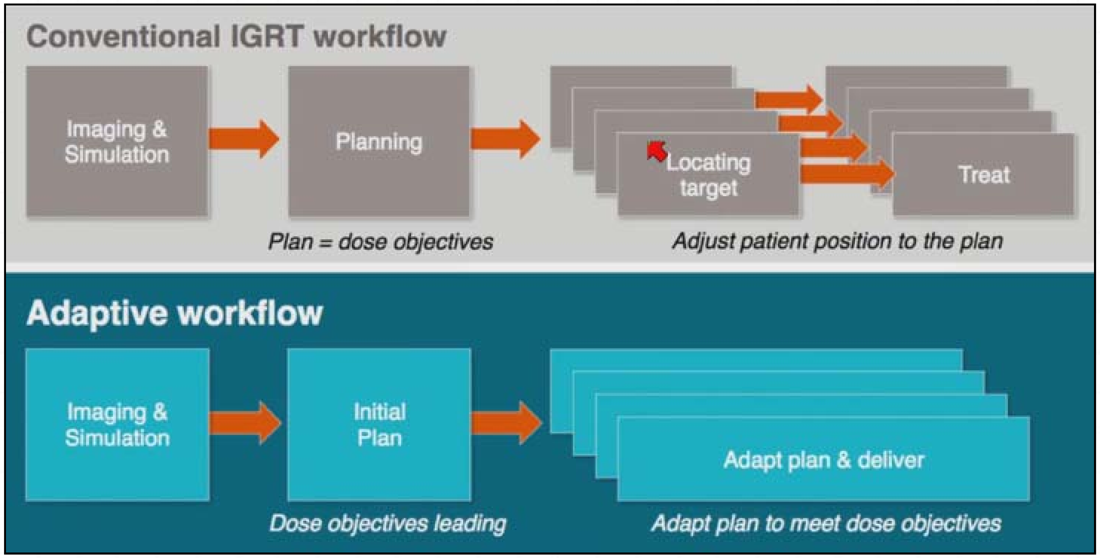
4D-MRI has better tumor contrast and less motion artifacts than 4D-CT

5- Real-time Adaptive Therapy

Precision medicine= Re-planning to account for daily anatomical changes in tumor and OAR spatial relationship.

Benefits=

- Treatment matches anatomy of each day
- Assure normal tissue sparing as intended in initial plan
- Potentially allows for safe dose escalation



To replan or not to replan? That is the question! How frequently is adaptive replanning needed for PBS proton therapy?

S. Schmidt [1]
[1] *Northwestern Medicine, Medical Dosimetry, Warrenville, USA*

An automated replanning strategy for near real-time adaptive proton therapy

T. Jagt [1]
[1] *Erasmus Medical Center, Radiation Oncology, Rotterdam, Netherlands*

'Towards the clinical implementation of Daily Adaptive Proton Therapy (DAPT): implemented key-steps to reach the goal'

F. Albertini [1]
[1] *Paul Scherer Institute, Center for Proton Therapy,*

Deep-learning-based relative stopping power mapping estimation for CBCT-guided adaptive proton radiotherapy

X. Yang [1]
[1] *Emory Univesity, Radiation Oncology, Atlanta, USA*

Evaluation of the clinical benefits of MRI-integrated proton therapy

M. Moteabbed [1]
[1] *Massachusetts General Hospital, Radiation Oncology, Boston, USA*

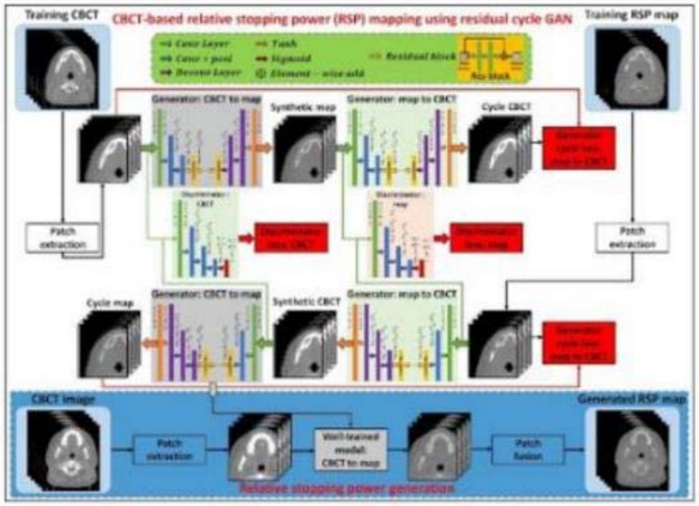


Figure 1. Schematic flow chart of our proposed relative stopping power (RSP) generation.

General Conclusion

Fast adaptation with re-planning is possible with clinically acceptable results (≈3 minutes)

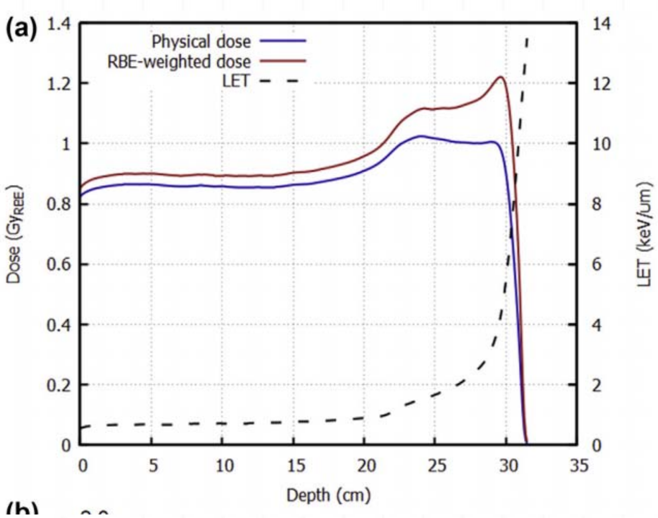
6- LET/RBE Dose Algorithm

Assessment of clinical RBE variability in proton therapy

J. Eulitz [1]

Radiation-Induced Brain Injury in Meningioma Patients Treated with Proton or Photon Therapy

Saif Aljabab, MBBS, Lulu Abduljabar, MBBS, Jiheon Song, MD, Yolanda D. Tseng, MD, Jason Rockhill MD, PHD, James Fink, MD, Lynn Chang, MD, Lia M. Halasz, MD



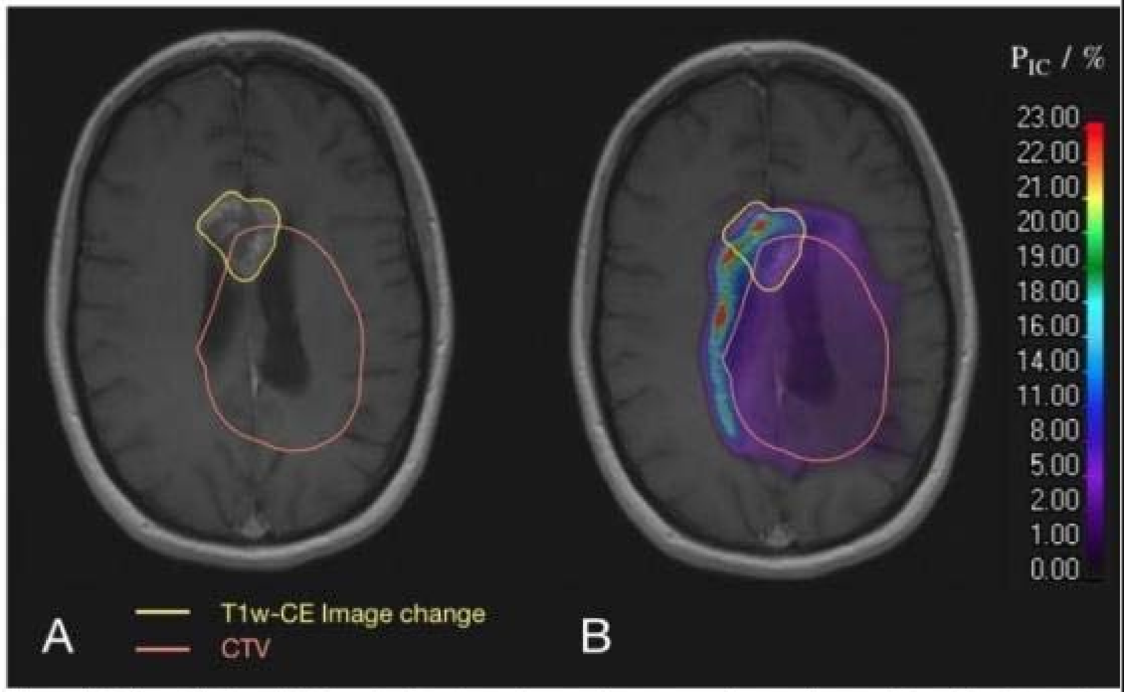


Figure 1: Delineated T1-weighted contrast-enhanced magnetic resonance image changes 12 months after proton therapy and clinical target volume (CTV) for one axial MR image layer of a glioma patient with histological necrosis (A). Cross-validated image change probability P_{IC} distributions for the multivariable logistic regression model (B).

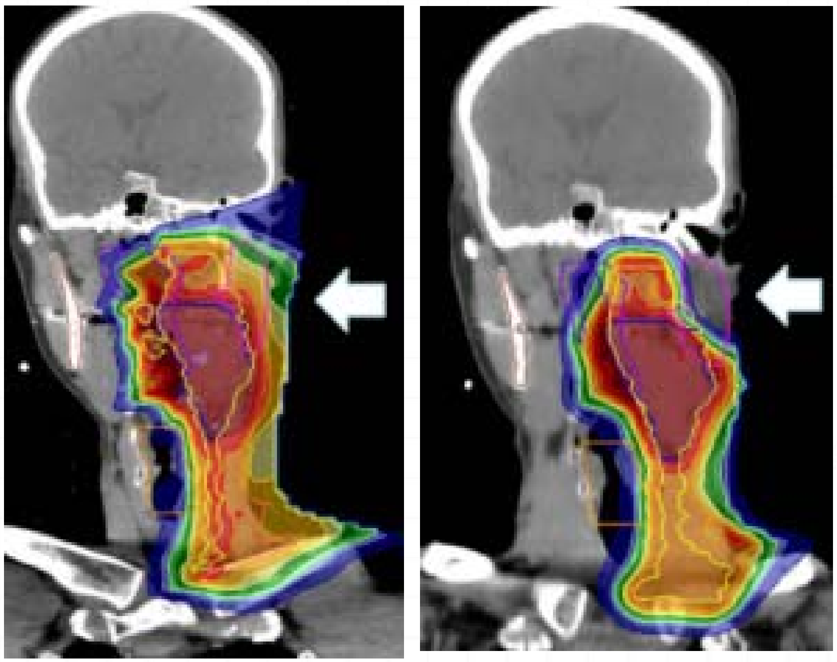
7- ProtoArc Therapy

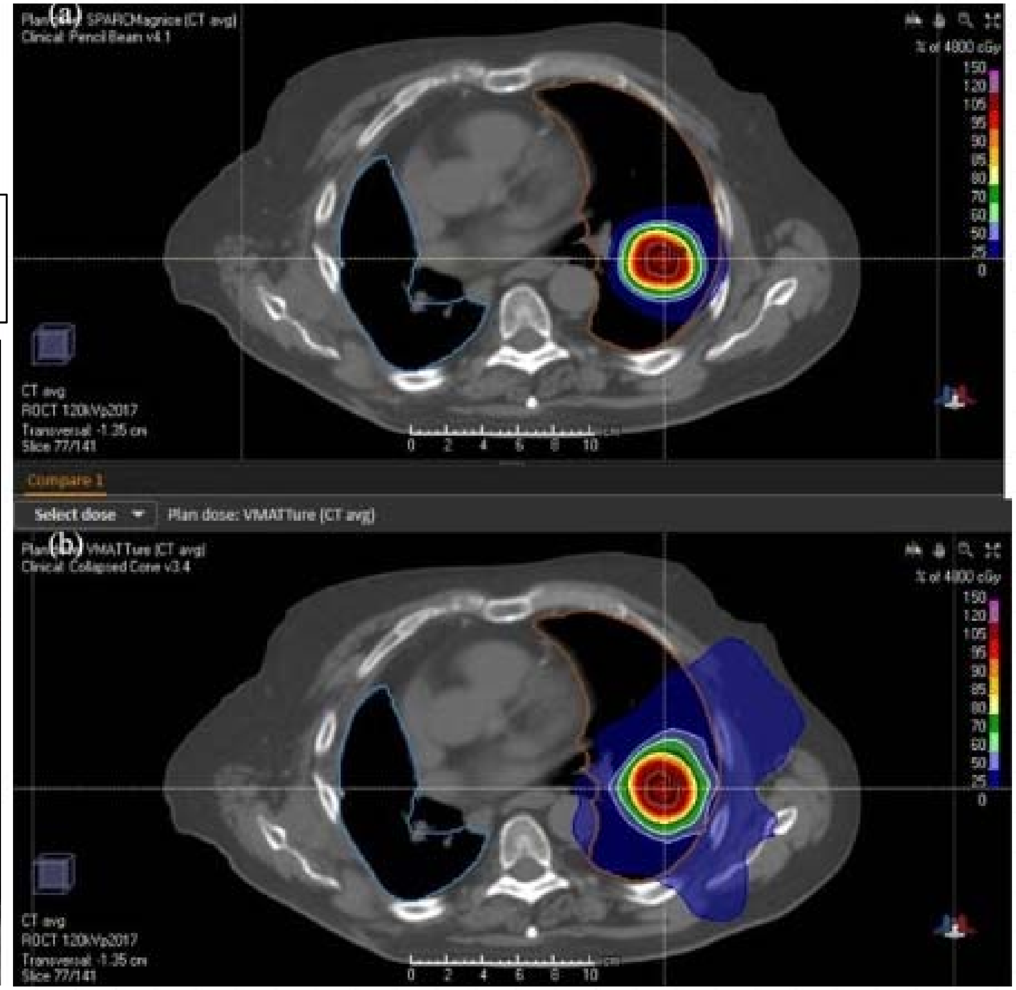
lung stereotactic body radiotherapy(SBRT) using Spot-scanning Proton Arc(SPArc) therapy: A feasibility study

G. Liu [1]

Spot-Scanning Proton Arc Therapy (SPArc) versus Intensity Modulated Proton Therapy (IMPT) for Parotid Sparing in Unilateral Tonsil Cancer

Christian Hyde, Gang Liu, Xiaoqiang Li, Peter Y Chen, Yan Di, Craig Stevens, Peyman





Conclusion:

SPArc has the potential to further reduce ipsilateral lung mean dose over VMAT. It could mitigate the interplay effect and open an option of hypofraction treatment for mobile lung tumor using proton therapy.

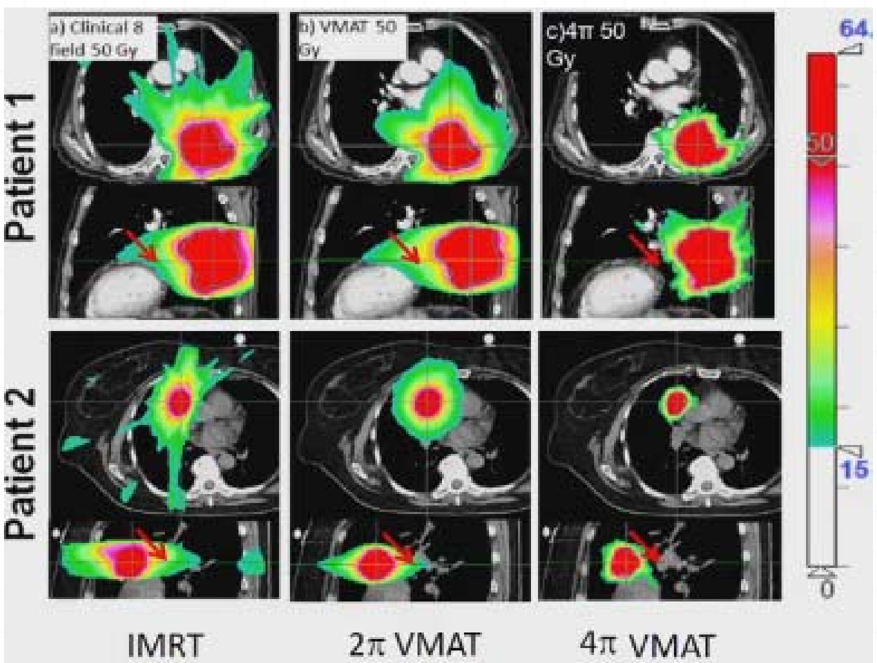
8- 4π Radiotherapy

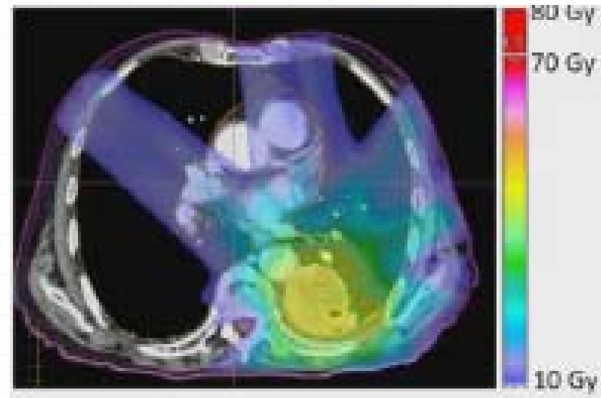
4π Non-Coplanar Liver SBRT: A Novel Delivery Technique

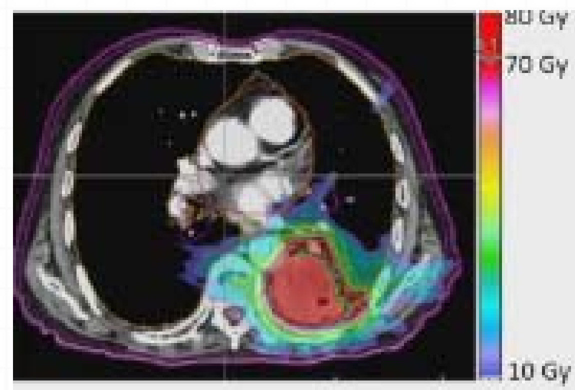
Peng Dong, PhD,* Percy Lee, MD,* Dan Ruan, PhD,* Troy Long, BS,† Edwin Romeijn, PhD,† Yingli Yang, PhD,* Daniel Low, PhD,* Patrick Kupelian, MD,* and Ke Sheng, PhD*

**Department of Radiation Oncology, University of California, Los Angeles, California; and †Department of Industrial and Operations Engineering, University of Michigan, Ann Arbor, Michigan*

- 4π is a method that integrates beam orientation optimization (BOO) and fluence map optimization (FMO) to select **non-coplanar beam angles simultaneously.**







- This allows for ***greater tumor dose escalation (up to 40%)*** without increasing normal tissue doses

Other Technological Advancements in Particle Therapy

Reduction of range uncertainty in particle treatment planning enabled by patient-individual stopping-power prediction using dual-energy CT

N. Peters [1]

Stereotactic Proton Ablative Radiosurgery (SPAR) of the Spine: A report on toxicity and efficacy

S. Park [1]

[1] *Mayo Clinic, Radiation Oncology, Rochester, USA*

The radiosensitization effect of internalized gold nanoparticles in proton therapy

C. Cunningham [1]

[1] *NRF iThemba LABS, Department of Radiobiology, Cape Town, South Africa*

NTCP robustness evaluation in head and neck proton therapy: from treatment plan to delivery

D. Scandurra [1]

[1] *Groningen Proton Therapy Centre - UMCG, Radiation Oncology, Groningen, Netherlands*

Concurrent pencil beam scanning proton therapy and hyperthermia: a new frontier in particle therapy

J. Snider- III [1]

[1] *University of Maryland School of Medicine, Radiation Oncology, Baltimore, USA*

Application of 3D printed compensators for pediatric patients in treatment planning of shallow situated H&N tumours

T. Kajdrowicz(1), A. Wochnik(1), A. Chmiel(2), K. Krzempek(1), D. Krzempek(1), W. Komenda(1), K. Małecki(2), G. Mierzwińska(1), P. Olko(1), M. Owcarz(1), U. Sowa(1), R. Stokłosa(1), J. Swakoń(1) and R. Kopeć(1)

Which of the following will have the most impact on the future of Radiation Medicine?

1. Particle Therapy
2. FLASH Radiotherapy
3. Immunotherapy
4. Adaptive Radiotherapy
5. Automation
6. Other

Will Automation negatively impact our job market?

1. Yes, Very Much
2. Yes
3. Maybe
4. No
5. It will actually improve the job market!

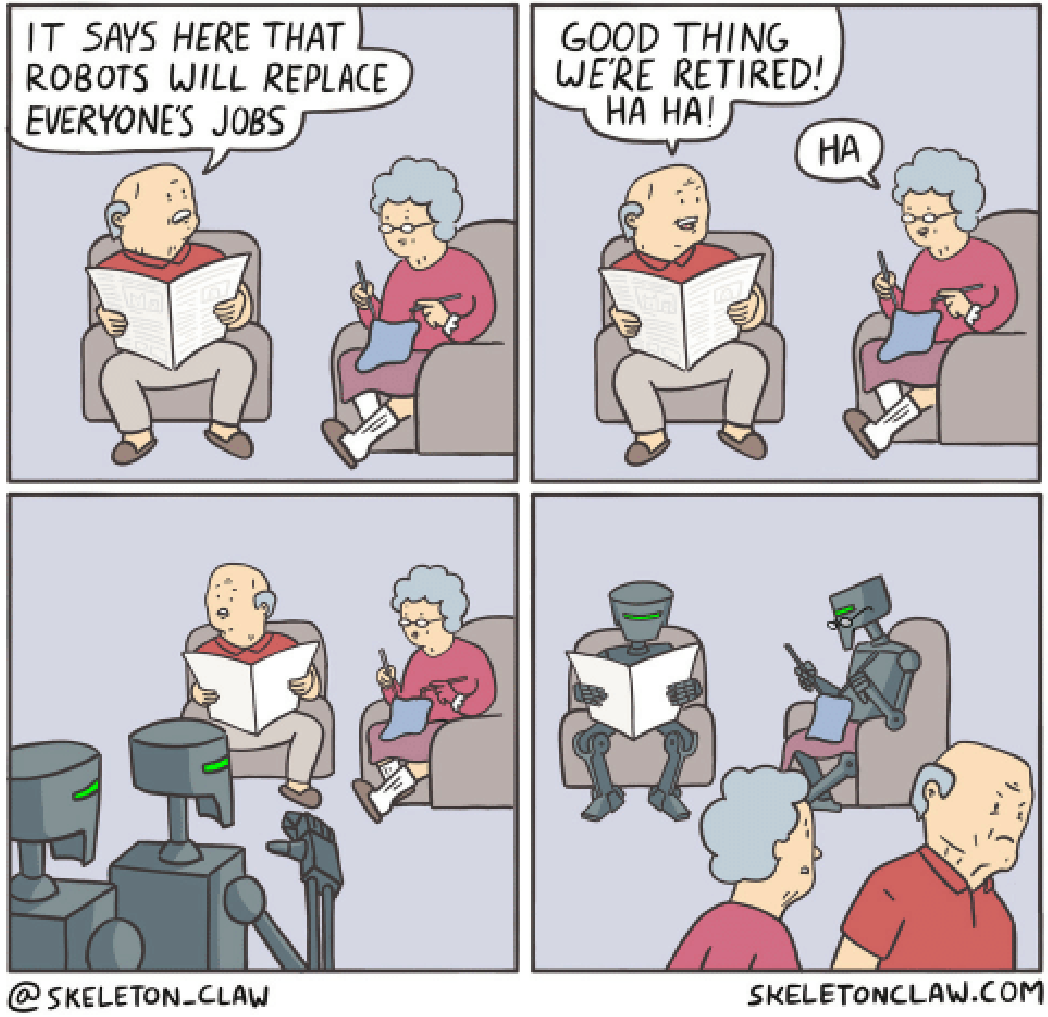
Summary

- Proton therapy is growing worldwide and its technology is evolving rapidly.
- Proton therapy is not for everyone, careful selection of appropriate cases is required
- PIII clinical data are underway. Non-randomized and retrospective clinical data are mostly in favor of proton therapy.
- Single room proton therapy provides state of the art proton technology at 80-90% cost reduction.

Strong Indications to use Protons			Situational Indications to use Protons	
Adult CNS	H&N (T4 NPC, PNS)	Retroperitoneal Sarcoma	H&N (Unilateral, Other)	GU Malignancies
Pediatric	Ocular Melanoma	Spinal or Paraspinal	GI Malignancies	Lymphoma
Re-irradiation	Skull Base Sarcoma		Chest Malignancies	Sarcoma
HCC	XRT sensitivity syndromes		Breast (Bilateral + RNI)	

Thank You

- Questions?



Automation