Clinical Trials In Particle Therapy

Hak Choy, MD

UT Southwestern

Dallas, Texas

"Proton Therapy is *Superior* to the Conventional Radiation Therapy (Photon)."

"Proton Therapy is *Superior* to the Conventional Radiation Therapy (Photon)."

Los Angeles Times | BUSINESS

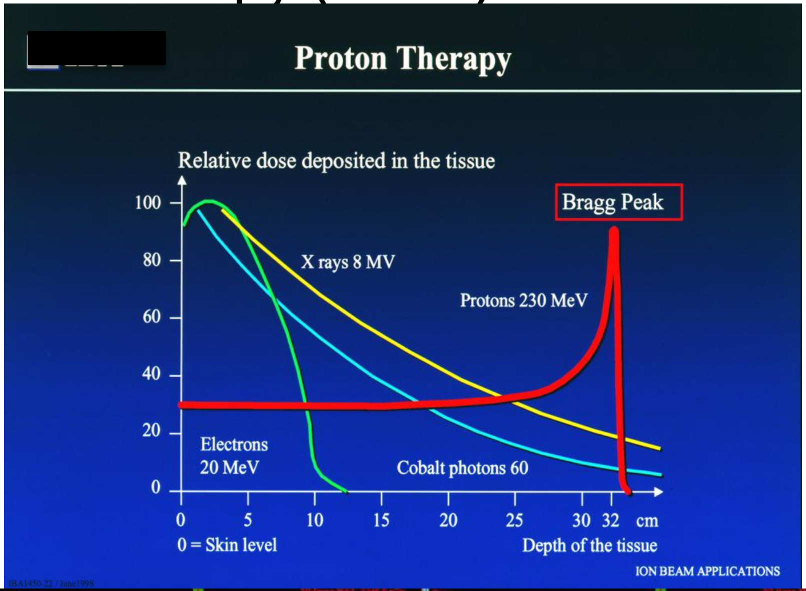
Blue Shield of California to curb coverage of pricey cancer therapy

Blue Shield says the high cost of some proton beam therapies for cancer treatment compared with conventional radiation isn't justified. The decision comes as hospitals build high-tech facilities.

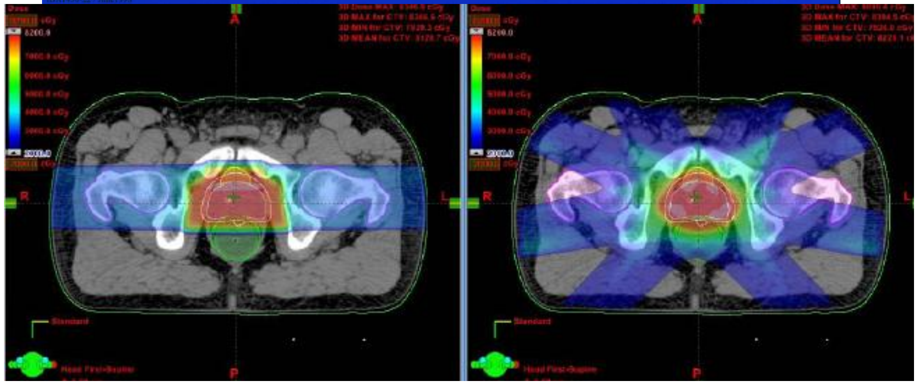
By Chad Terhune

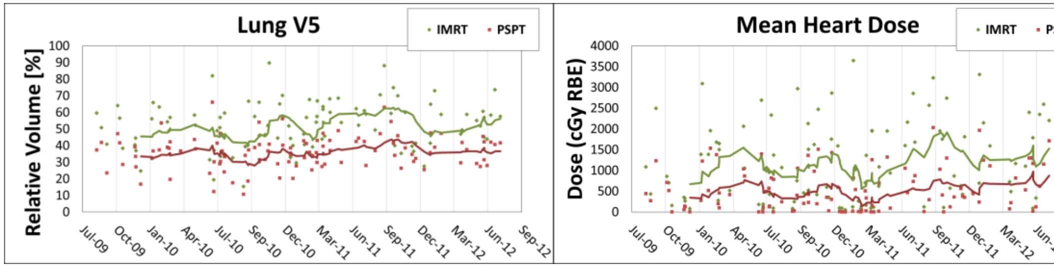
August 28, 2013 | 6:16 p.m.

"Proton/Carbon (Hadron) Radiotherapy is Superior to Intensity Modulated Radiotherapy (IMRT)."



Superior ?





"Proton/Carbon (Hadron) Radiotherapy is Superior to Intensity Modulated Radiotherapy (IMRT)."

Superior ?

Curr Urol Rep (2013) 14:199–208
DOI 10.1007/s11934-013-0320-2

PROSTATE CANCER (D PAREKH, SECTION EDITOR)

Proton Beam Radiation Therapy for Prostate Cancer—Is the Hype (and the Cost) Justified?

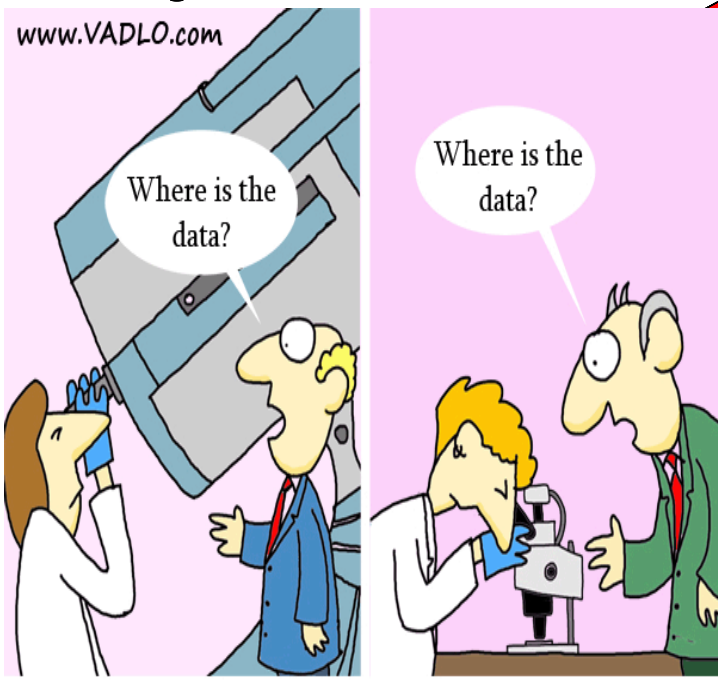
Phillip J. Gray · Jason A. Efstathiou

In Comparing Proton Beam Therapy with Other Modalities
"Is PBT better than IMRT?"

1. "It has **not**, as of yet, sufficiently **answered** the question on the minds of patients, care providers, and policy makers across the country."
2. "Given the clear **limitations in the available data** and the **lack of consensus** regarding the comparative effectiveness of PBT and photon-based radiotherapy, a **more** rigorous and definitive **study in needed**."

2D vs. 3D vs. IMRT vs. Proton

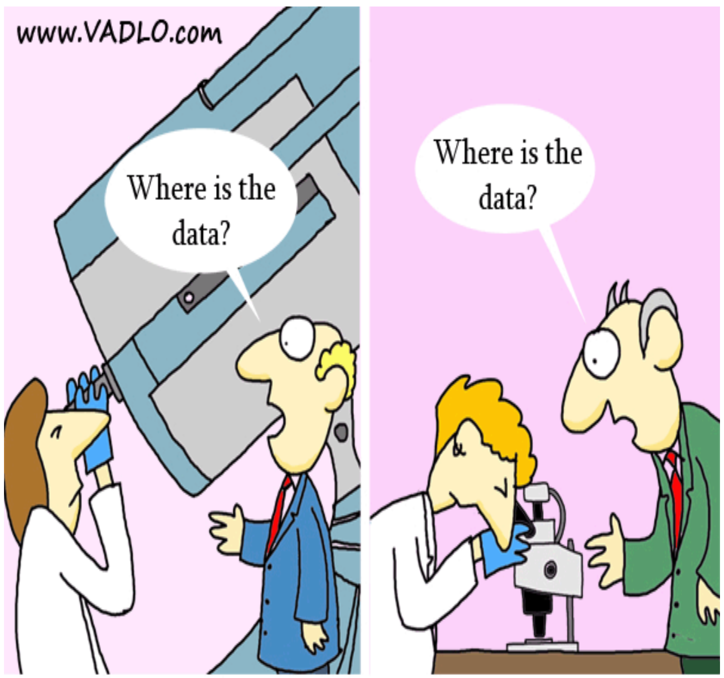
Superior ?



Grand Unification of Sciences

"Proton/Carbon (Hadron) Radiotherapy is Superior to Intensity Modulated Radiotherapy (IMRT)."

Superior ?

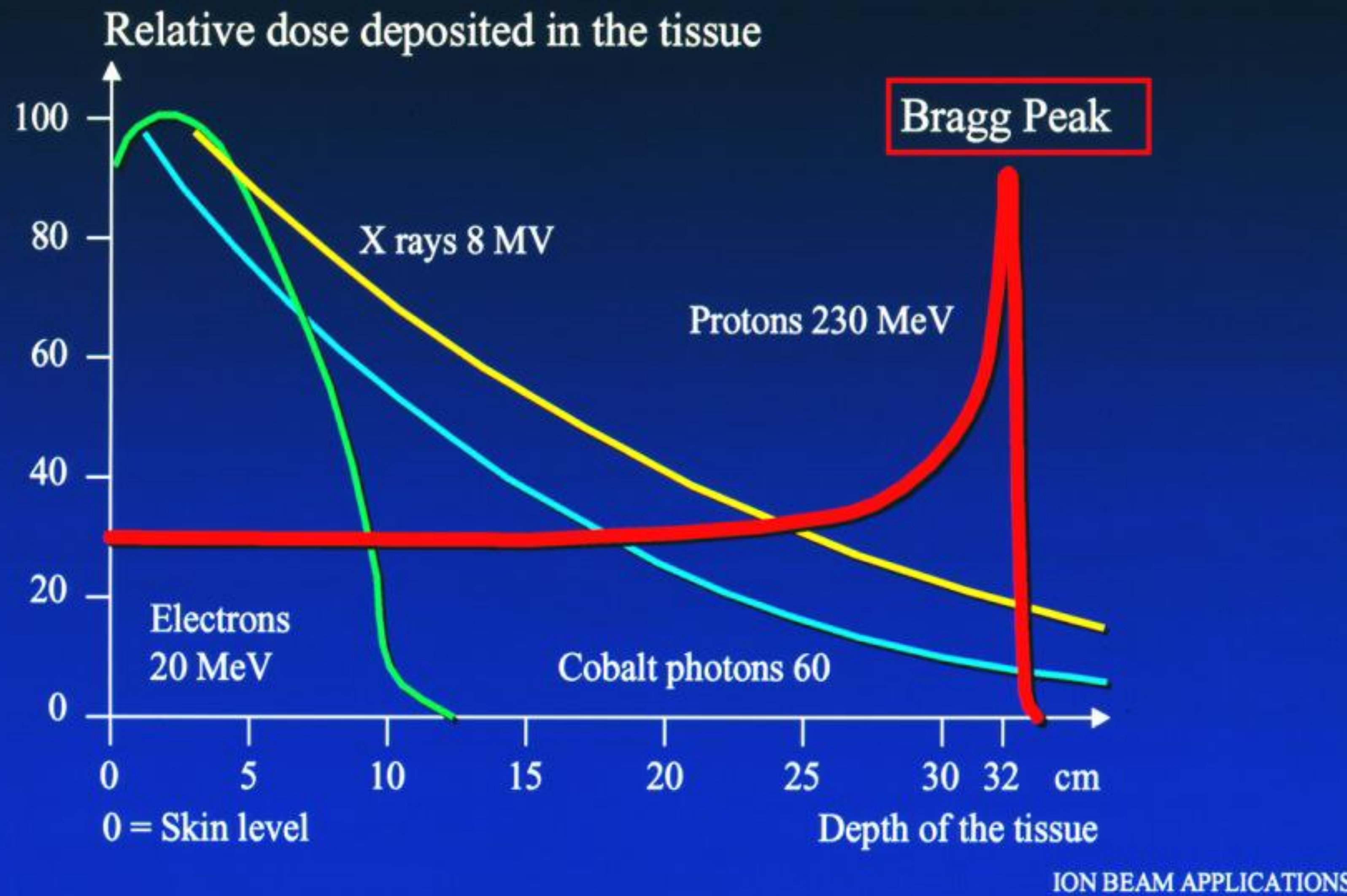


Grand Unification of Sciences

How many phase III Trials Completed Comparing IMRT Vs Proton Therapy ?

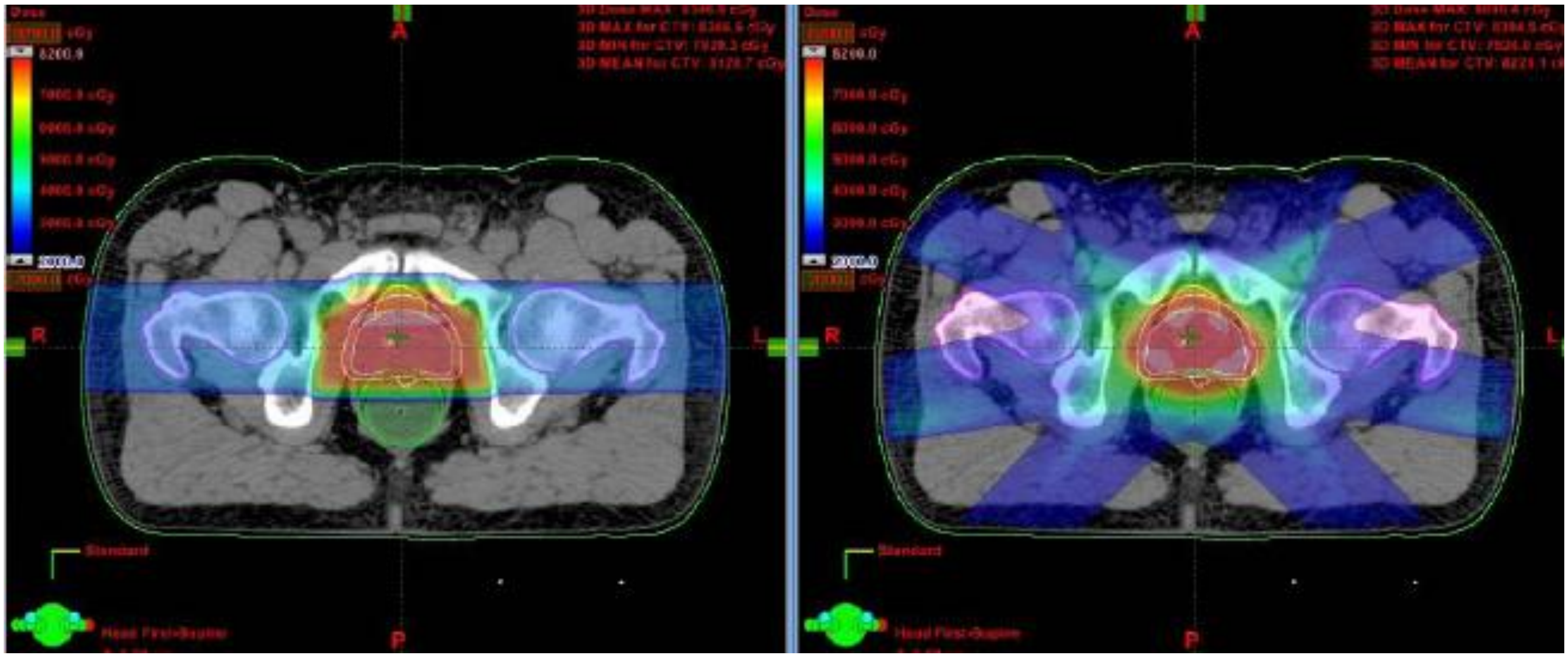
"0"

Dose Distribution Advantage



The Proton plan delivers less scatter radiation dose to the pelvis compared to IMRT plan (axial view) Protons IMRT

RED is high dose, GREEN is intermediate dose, BLUE is lower dose



Protons IMRT

RED : PTV→ related to TUMOR Control→ LC and OS
GREEN; Surrounding critical Normal Tissue → Toxicity, QOL
BLUE : V5 → possible 2nd malignancy

The Proton plan delivers less scatter radiation dose to the pelvis compared to IMRT plan (axial view) Protons IMRT

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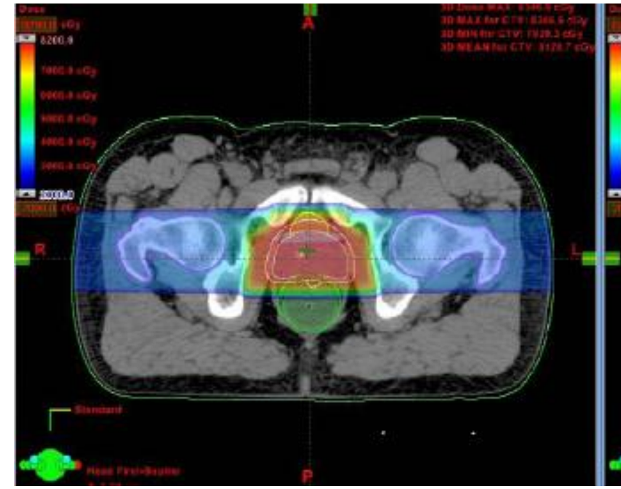


RED : PTV→ related to TUMOR Control→ LC and OS

GREEN; Surrounding critical Normal Tissue → Toxicity, QOL

BLUE : V5 → possible 2nd malignancy

How can **WE** prove the Proton Radiotherapy is Superior to Intensity Modulated Radiotherapy (IMRT) ?

1. Understanding the impact on biologically-effective proton dose distributions delivered to the patient
2. linear energy transfer (LET) guided plan optimization with intensity modulated proton therapy (IMPT)
3. Minimize the uncertainties: dose distribution, range uncertainty, intra-fractional motion, inter-fractional anatomic changes
4. Randomized Phase III trials in certain Tumor

RTOG 1308

Phase III Randomized Trial Comparing Overall Survival after Photon versus Proton Radiochemotherapy for Inoperable Stage II-IIIB NSCLC

SCHEMA

S T R A T I F Y

Stage
1. II
2. IIIA
3. IIIB

GTV Volume
1. ≤ 130 cc
2. > 130 cc

Histology
1. Squamous
2. Non-Squamous

Neoadjuvant Chemo
1. No
2. Yes

R A N D O M I Z E

Arm 1: Photon dose—Higher achievable dose between 60-70 Gy, once daily plus platinum-based doublet chemotherapy*

Arm 2: Proton dose—Higher achievable dose between 60-70 Gy (RBE), once daily plus platinum-based doublet chemotherapy*

Both Arms: Consolidation chemotherapy x 2 is allowed*

PCORI:

Patient-Centered Outcomes Research Institute

Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients with Stage II or III Breast Cancer

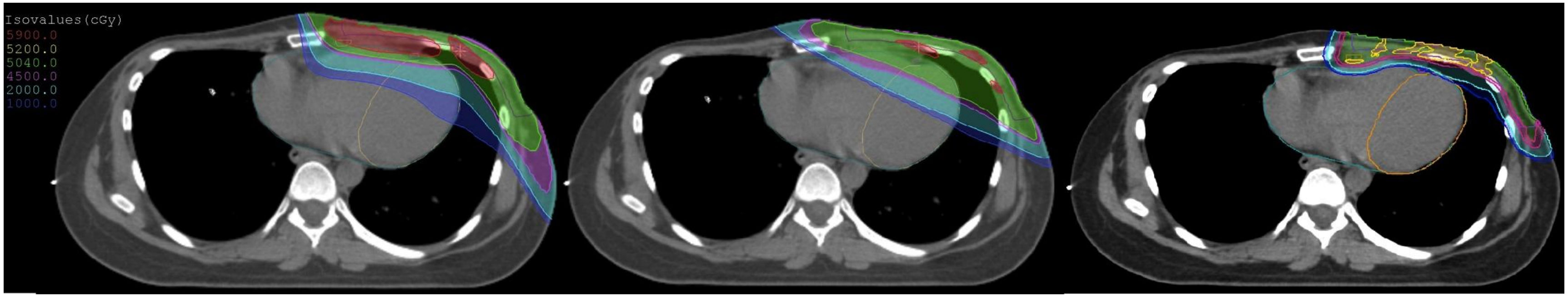
Principal Investigator Justin Bekelman, MD

Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients with Stage II or III Breast Cancer

Surgery

Photon

Proton



Photons/Electrons Photons Protons

The primary outcomes: major cardiovascular events, such as **heart attacks, chest pain, and other heart problems**

Number of pts need to be randomized: **1716**

Project Budget: **$11,830,530**

Phase III: Proton Beam or Intensity-Modulated Radiation Therapy in Treating Patients with Low or Low-Intermediate Risk Prostate Cancer

Jason Alexander Efstathiou, Principal Investigator

PRIMARY OBJECTIVES:

I. Compare the reduction in mean Expanded Prostate Cancer Index Composite (EPIC) **bowel scores** for men with low or intermediate risk prostate cancer (PCa) treated with PBT versus IMRT at 24 months following radiation (where higher scores represent better outcomes).

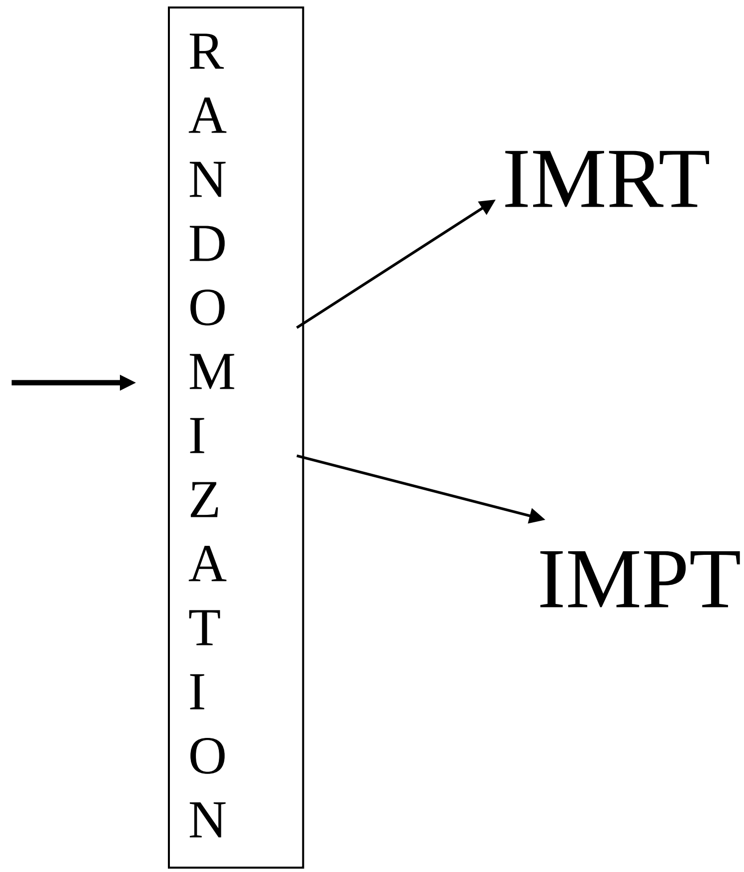
SECONDARY OBJECTIVES:

I. Assess the effectiveness of PBT versus IMRT for men with low or intermediate risk PCa in terms of disease-specific **quality of life** as measured by patient-reported outcomes, perceptions of care and adverse events.

II. II. Assess the **cost-effectiveness** of PBT versus IMRT under current conditions and model future cost-effectiveness for alternative treatment delivery and cost scenarios.

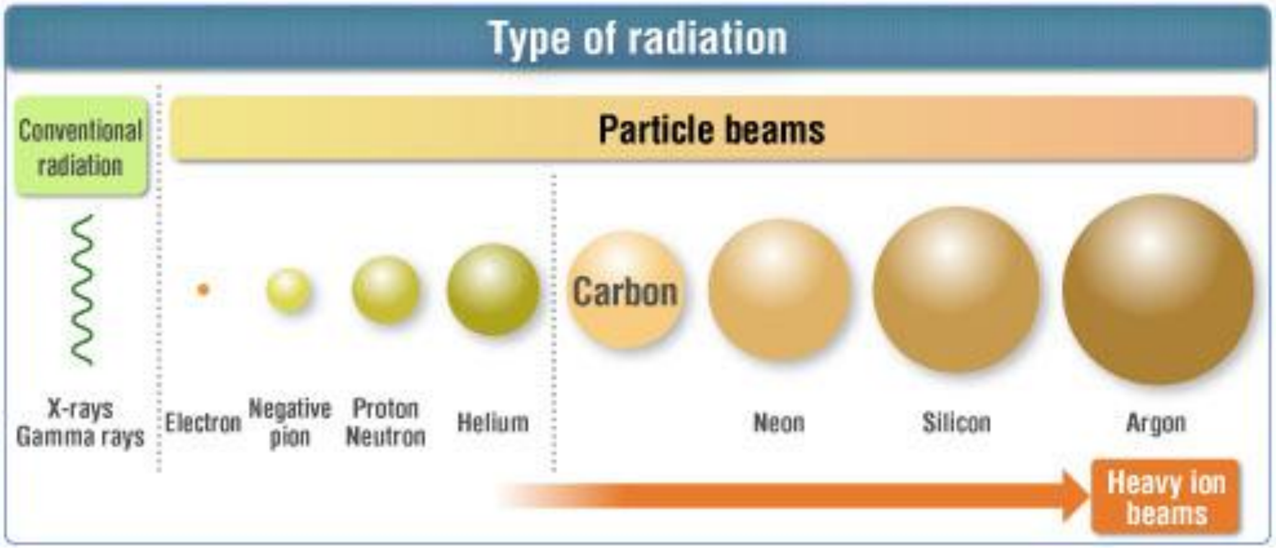
Clinical Trials: IMPT vs. IMRT

1) Brain Tumors
2) H/N Cancer
3) Breast Cancer
4) Lung Cancer
5) HCC
6) Prostate Cancer



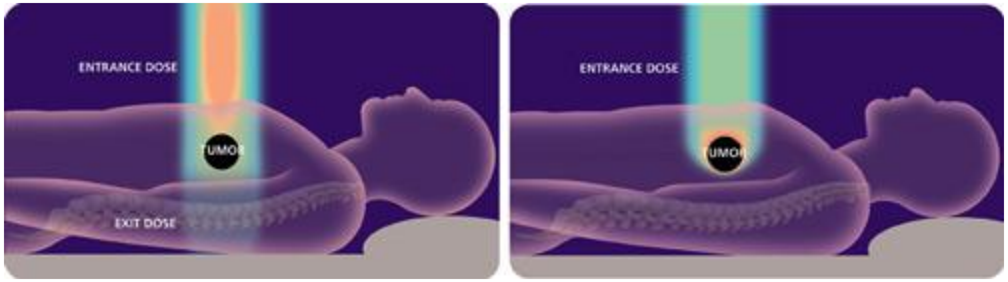
How about the Carbon Therapy ?

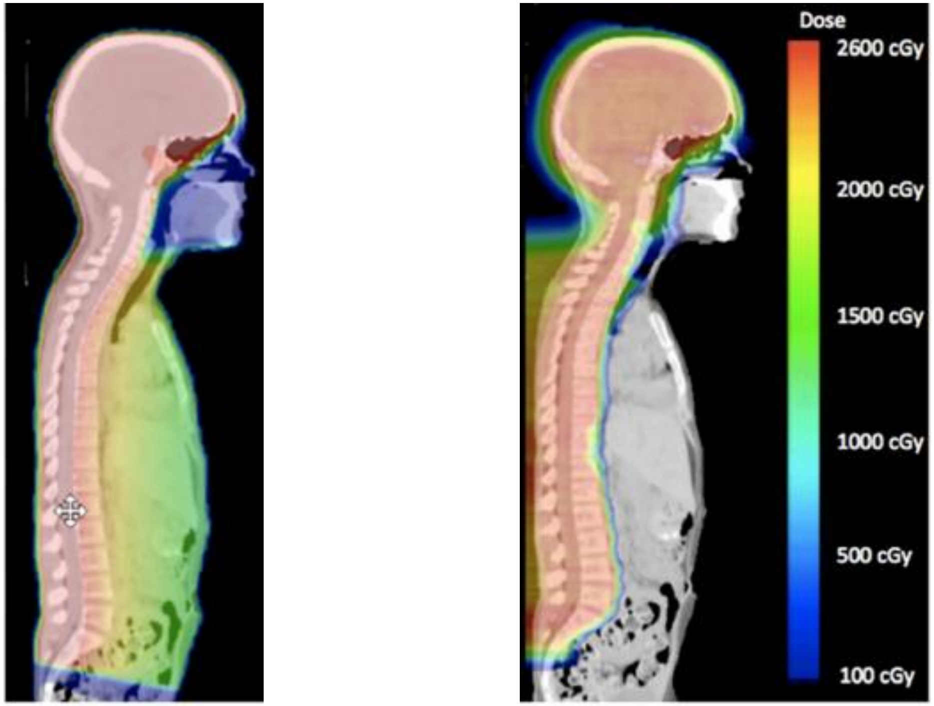
What is Heavy Ion therapy?



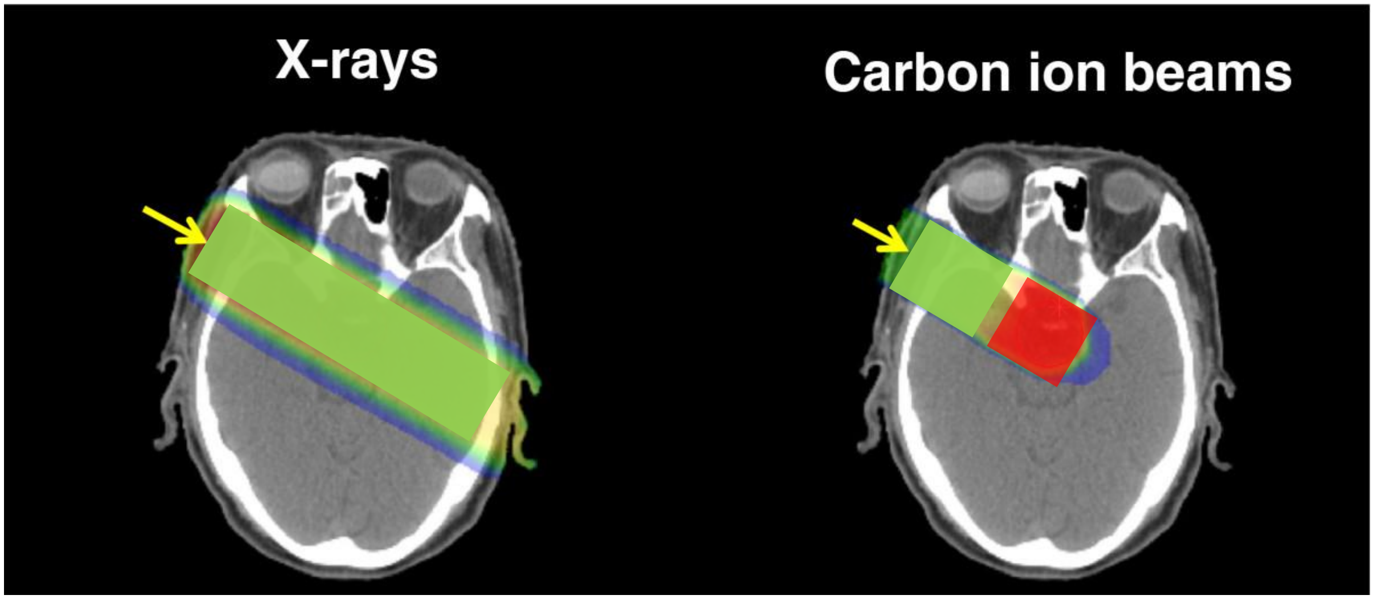
It is a radiation therapy with accelerated nuclei of He-4, Li-6, Be-8, B-10, C-12 …

1) Heavy Ions Stop In Tumor





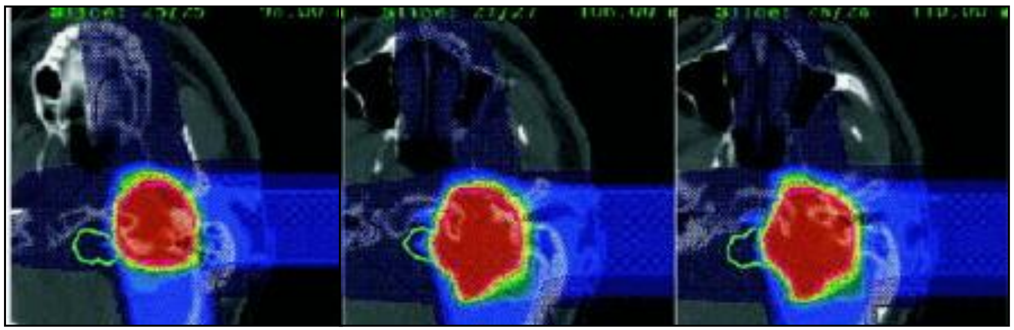
2) Heavy Ions exhibit low entrance dose



3) Heavy Ions – have very sharp edges

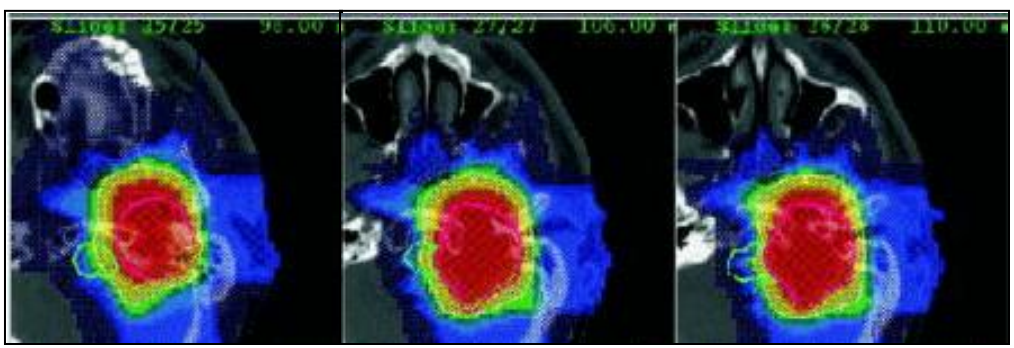
Sharp

Carbon

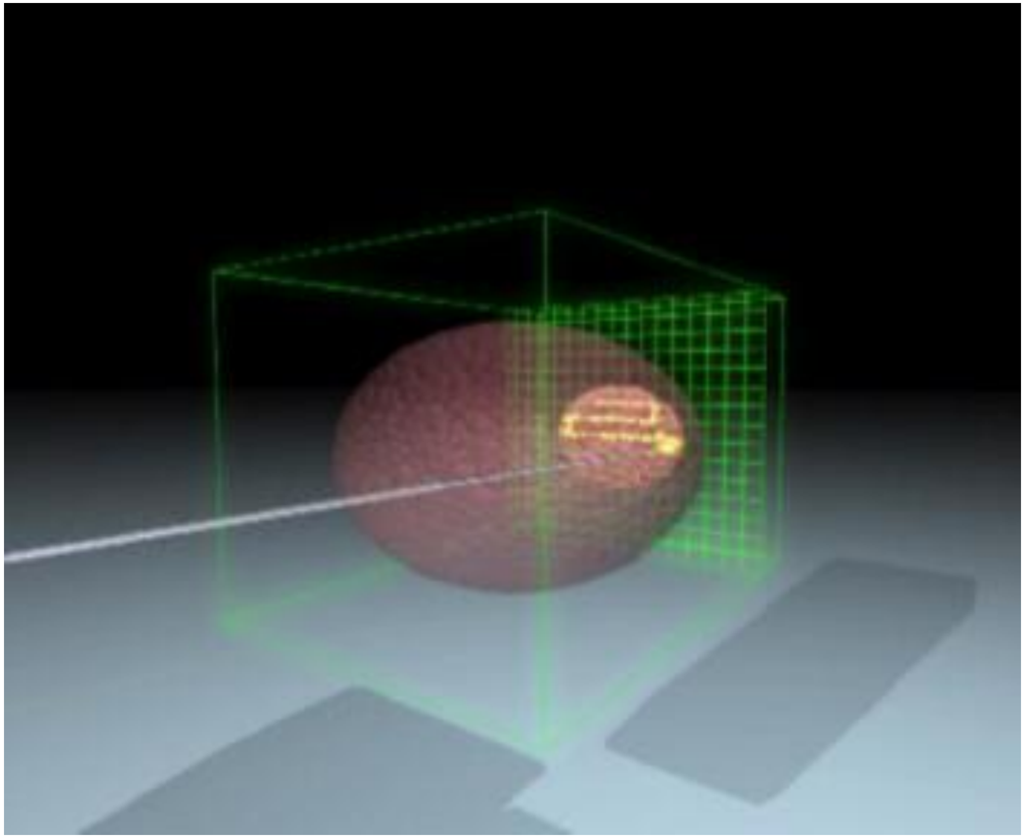


Proton or

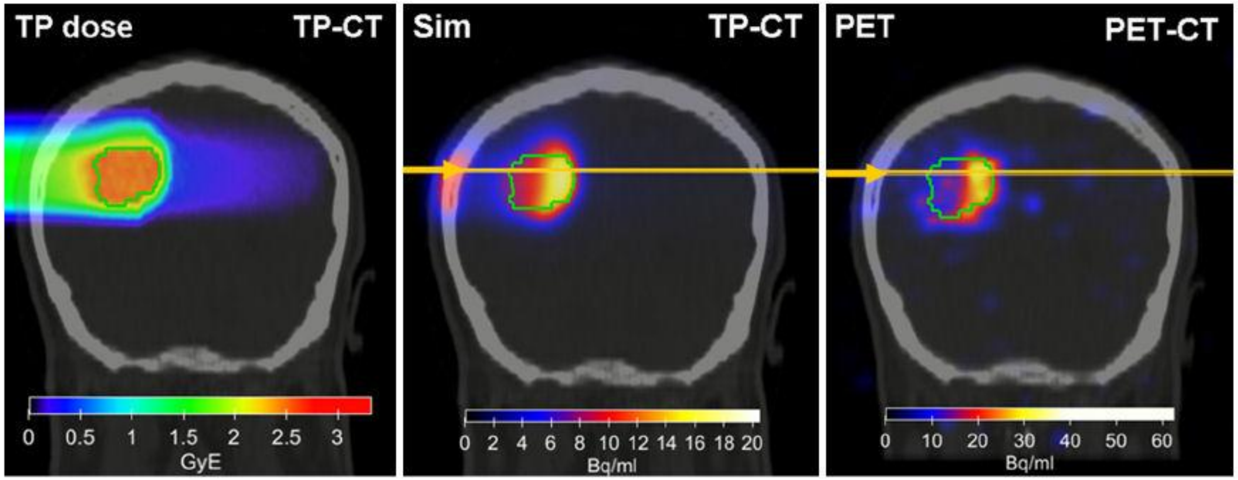
X-ray



4) Heavy Ions – Are Magnetically Controlled to Very High Precision



5) Heavy Ions – Offer Unique Verification of Energy Deposition



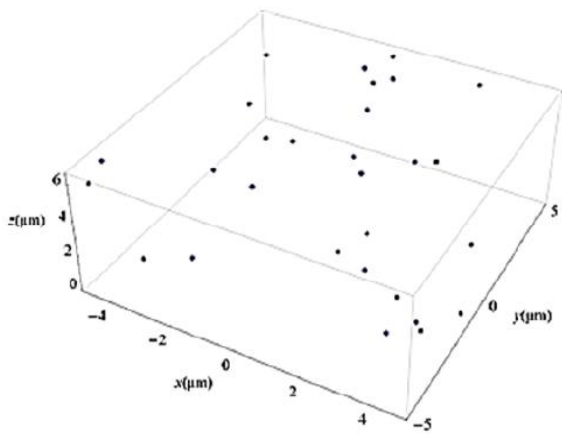
The biological responses seen after heavy charged particle exposure is mostly driven by the unique **pattern of energy deposition**

- Energy deposition patterns become more discrete

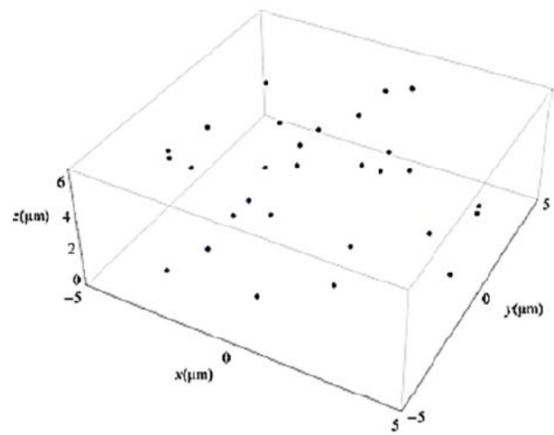
Random Energy Deposition

Discrete Energy Deposition

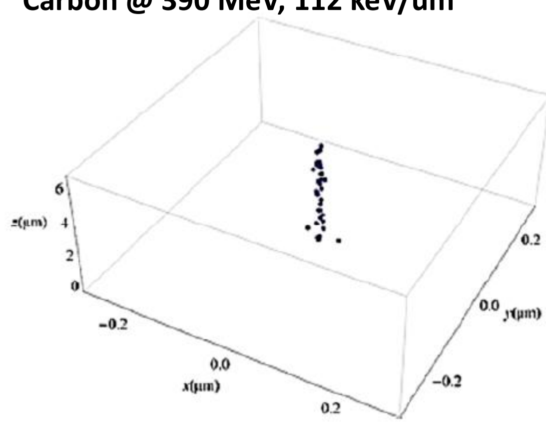
X-rays << 1 keV/um



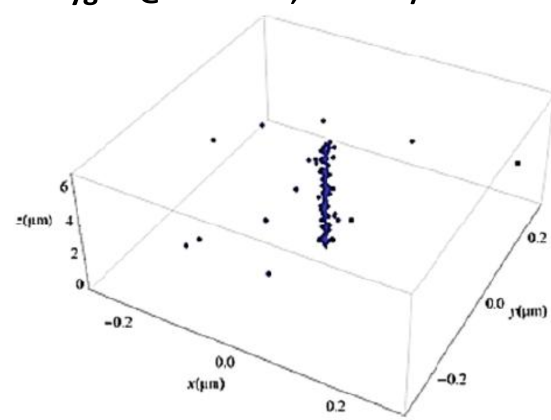
Protons @ 200 MeV, 20 keV/um



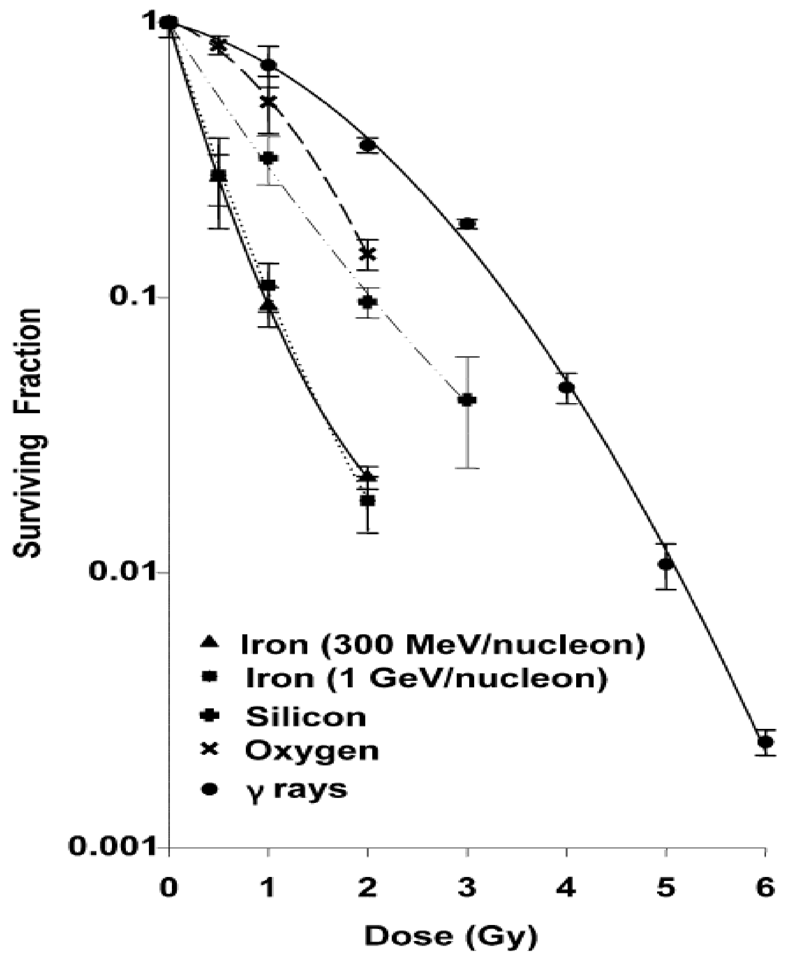
Carbon @ 390 MeV, 112 keV/um



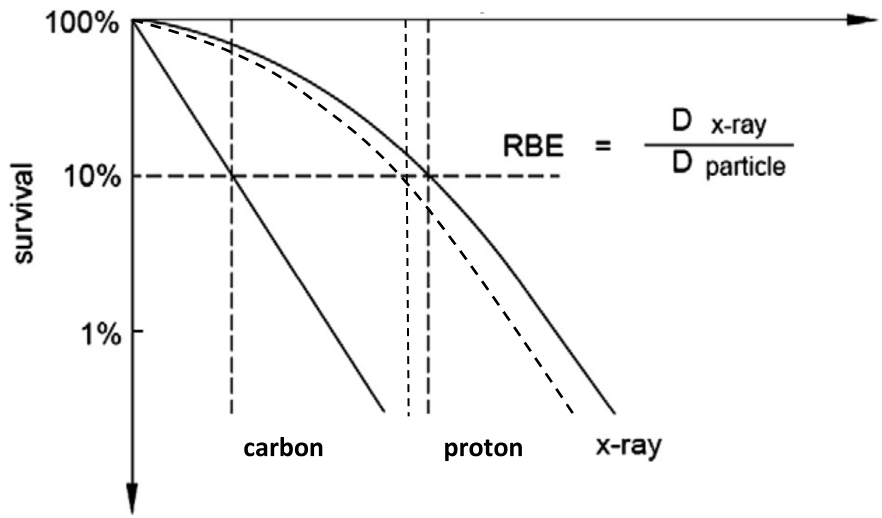
Oxygen @ 468 MeV, 175 keV/um



Discrete patterns of energy deposition result in clustered DNA damage and greater cell killing



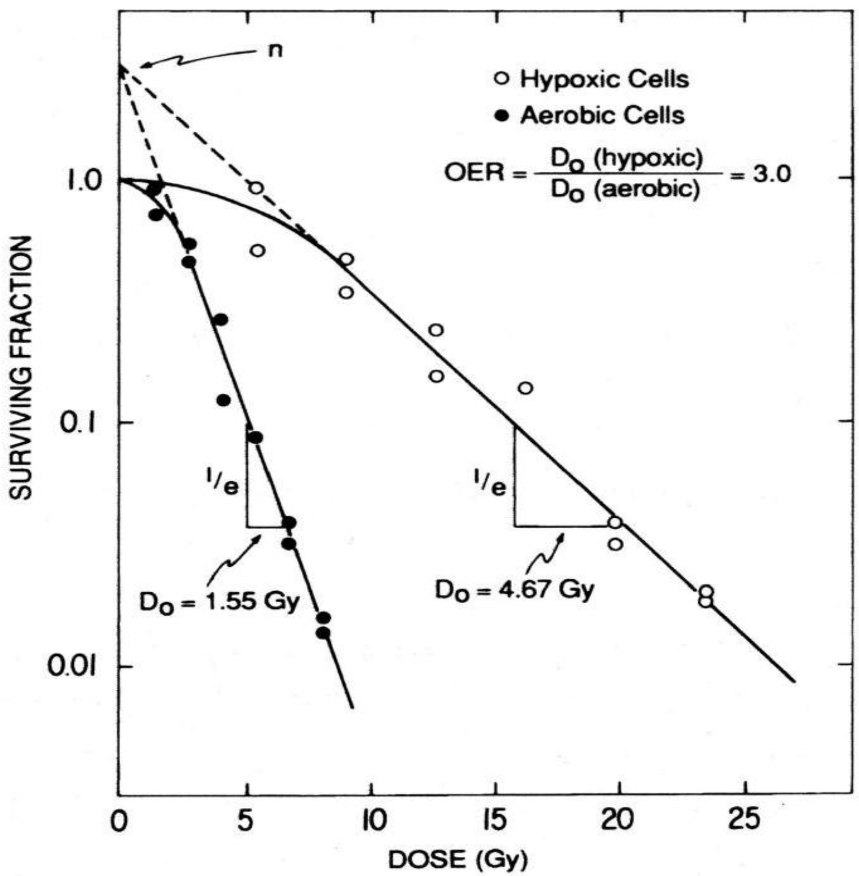
Enhanced cell killing described by Relative Biological Effectiveness



- Common RBE values:
  - X-ray (reference) 1.0
  - Protons 1.0 - 1.2
  - Carbon 2 - 4

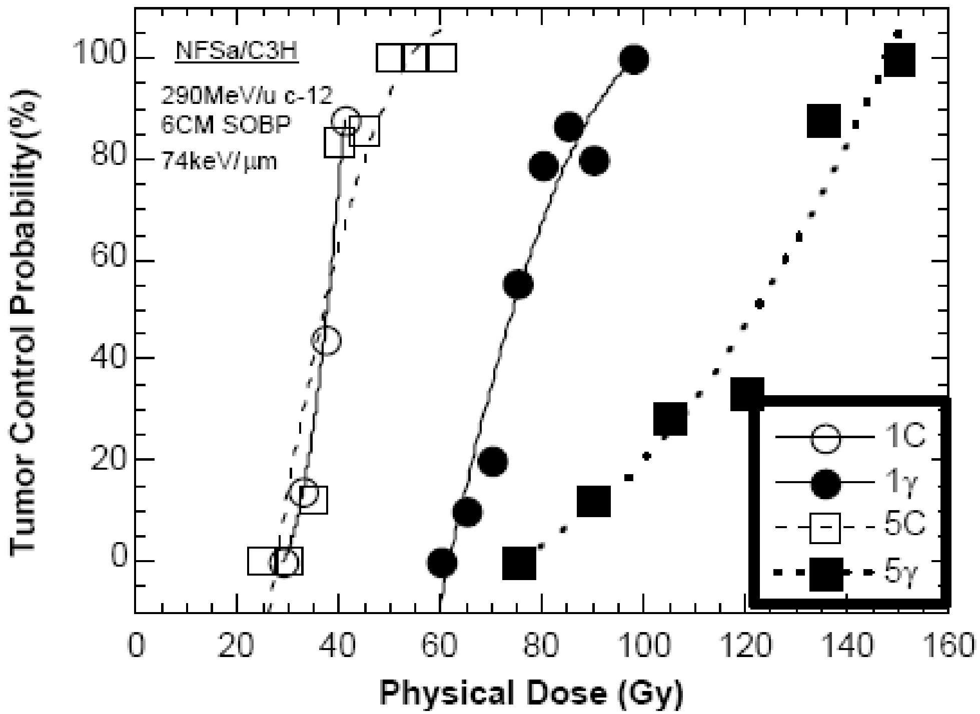
Heavy charged particles can overcome radioresistance due to hypoxia

- Hypoxia limits the efficacy of radiotherapy



Decreased repair between dose fractions with heavy charged particles

- Conventional radiotherapy delivers dose in daily fractions
  - Daily schedule based on potential for
  - Tumor reoxygenation
  - Normal tissue sparing (1920s)



Advantages with heavy charged particles: Physics and **BIOLOGY !**

- Enhanced cell killing for the same amount of dose
  - Opportunities to treat radioresistant tumors
- Potential to enhance tumor response in hypoxic settings
- Limited tumor sparing with dose fractionation
  - Precise placement of dose limits normal tissue exposure
- Novel tissue effects
  - Dose thresholds achieved at lower dose
  - Enhanced immunologic response
  - Reduction in metastatic potential

Chemoradiotherapy for Locally Advanced Pancreatic Cancer

Study	N	Treatment	Radiation Dose (Gy)	Local Control (%)	Survival Rate (%) 1-yr	Survival Rate (%) 1.5-yr
ECOG (1985)	47	5FU + RT	40	68	32	11
	44	5FU alone	-	68	26	21
Crane (2002)	61	5FU + RT	30	46	28	7
	34	GEM + RT	30	45	42	12
Okusaka (2004)	42	GEM + RT	50.4	94	28	25
Murphy (2007)	74	GEM + RT	20-42	74	46	24
NIRS (2012)	46	Carbon ion	45.6-52.8	87	47	26
NIRS (2013)	47	GEM + Carbon	45.6-55.2	-	74	**54 (2yr)**

GEM: Gemcitabine

More than Doubled Survival Rate !

Slide Courtesy of Dr. Shigeru Yamada (NIRS

Local Control and Survival Rates with Different Modalities for Mucosal Malignant Melanoma

Authors	N	Modality	5-yr OS (%)
Gilligan (1991)	28	Radiotherapy (+/- Surgery)	18
Shibuya (1992)	28	Radiotherapy (+/- Surgery)	25
Chang (1998)	163	Surgery (+/- RT, +/- Chemotherapy)	32
Patel (2002)	59	Surgery (+/- RT, +/- Chemotherapy)	35
Lund (1999)	58	Surgery (+/- RT, +/- Chemotherapy)	28
NIRS (2011)	102	Carbon ion alone	35
NIRS (2011)	100	Carbon ion + Chemotherapy	60

Slide Courtesy of Dr. Azusa Hasegawa (NIRS

Local Control and Survival Rates with Different Modalities for Mucosal Malignant Melanoma

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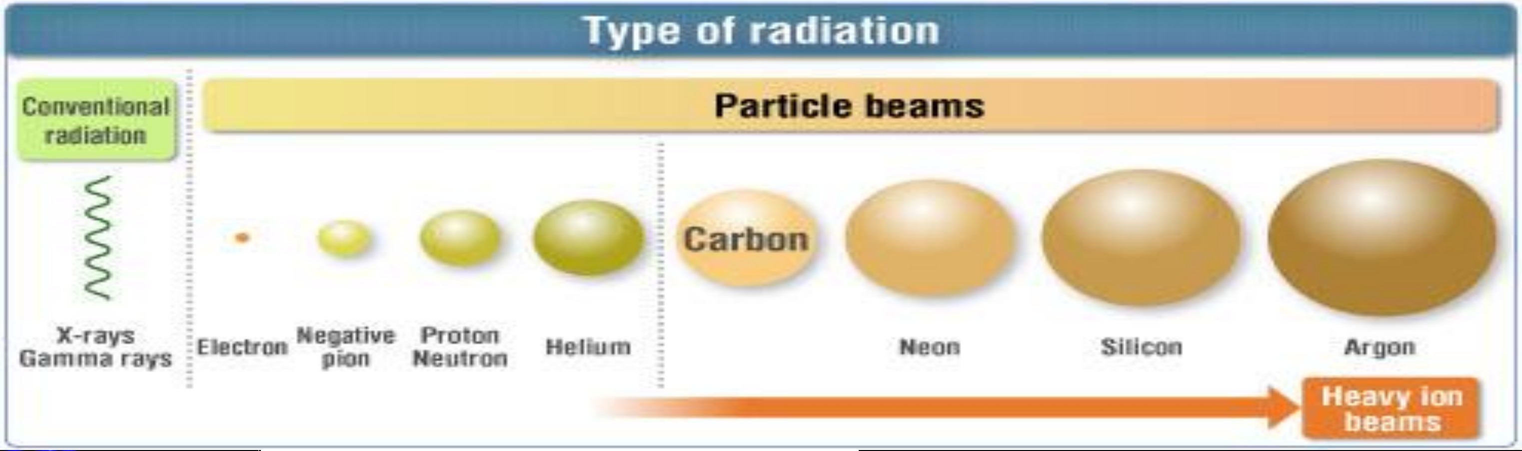
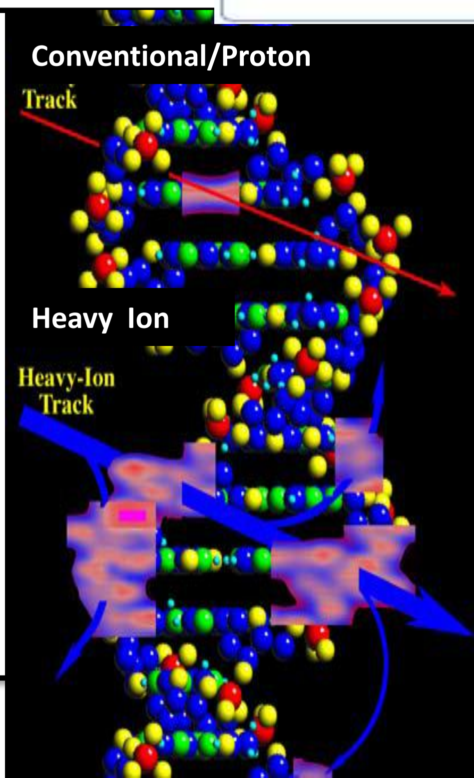
Slide Courtesy of Dr. Azusa Hasegawa (NIR

Why Heavy Ion Therapy over conventional photon or proton Therapy ?

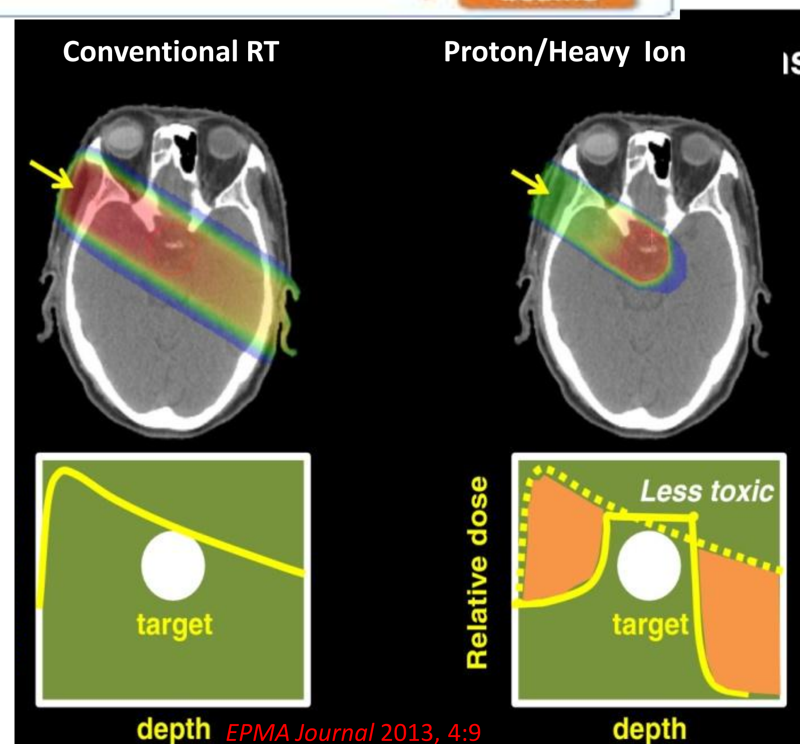


CANCER DNA



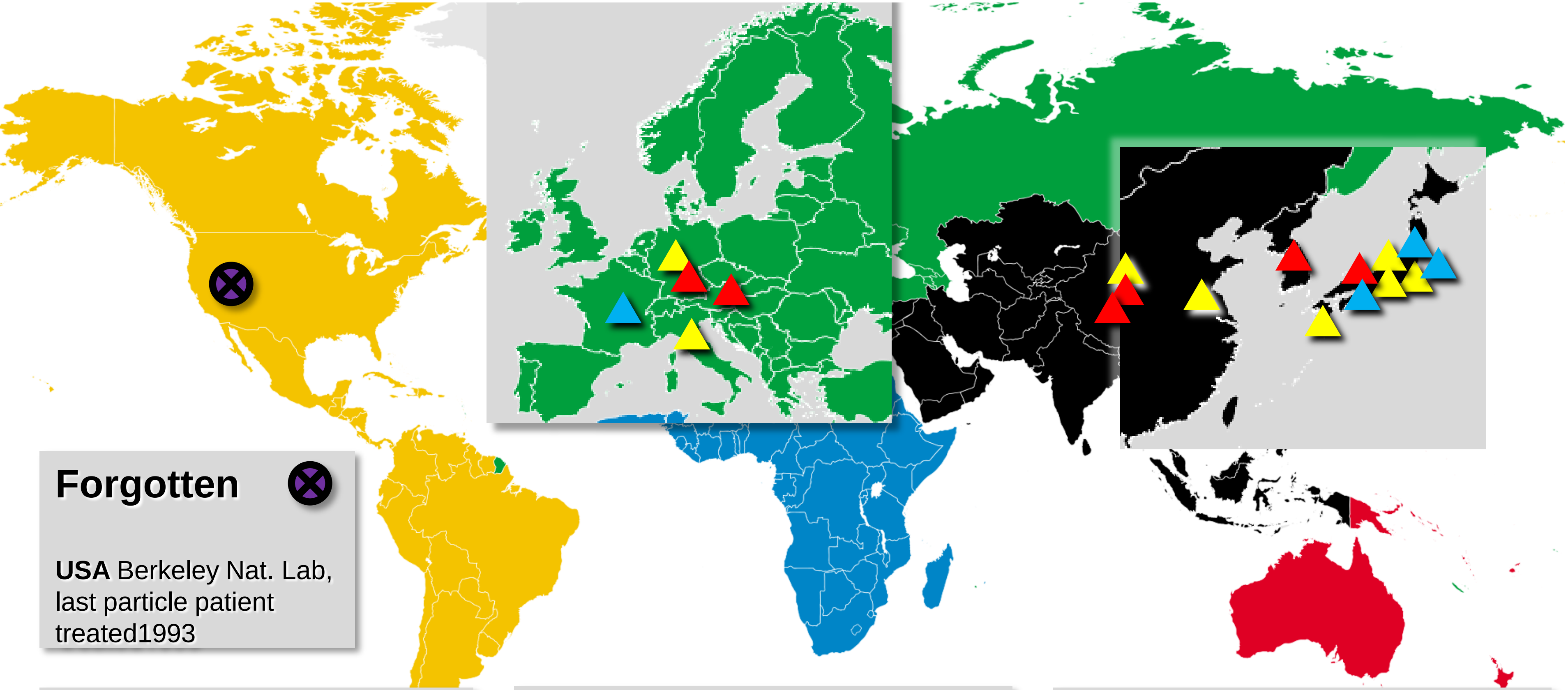
What Is the Best Radiotherapy?

- Photons (x-rays)
  - Neither precise nor potent
- Protons
  - Precise, but not potent
- Heavy Ions
  - The MOST precise and MOST potent



EPMA Journal 2013, 4:9

World Wide Heavy Ion Therapy Centers



Forgotten

USA Berkeley Nat. Lab, last particle patient treated1993

Operational (8)

China Fudan Univ CC, Shanghai
China IMP-CAS, Lanzhou
Germany HIT, Heidelberg
Italy CNAO, Pavia
Japan HIMAC, Chiba
Japan HIBMC,Hyogo
Japan GHMC, Gunma
Japan SAGA-HIMAT, Tosu

Under Construction(6)

China HITFiL, Lanzhou
China Another Center, Lanzhou
Germany MIT, Marburg
Austria MedAustron, Wiener Neustadt
Japan i-ROCK, Kanagawa
South Korea KHIMA, Busan

Advanced Planning(4)

France ETOILE, Lyon
Japan Okinawa
Japan Yamagata
Japan Osaka

Total : 18

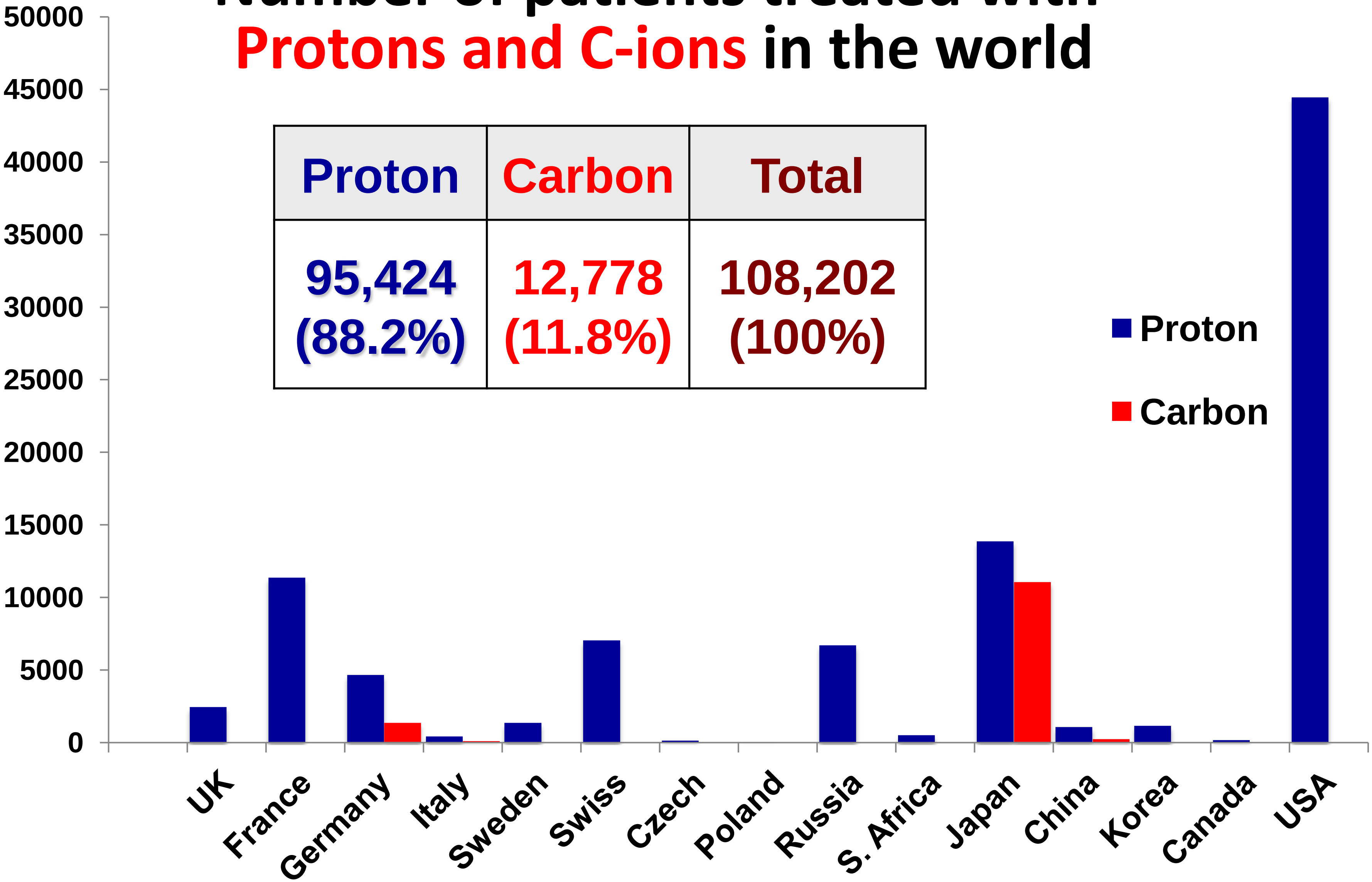
ALL CARBON CENTERS BUILT WITH GOVERNMENTAL SUPPORT

- USA pioneered the heavy ion therapy
  - Clinical trials ran at Lawrence Berkeley National Lab
    - First proton patient in the world 1954 at LBL
    - First heavier ion patient in the world 1975 at LBL
  - A huge therapy experience was gained with governmental support
  - Lack of funding closed the program in 1993

- Japan and Germany obtained the USA experience and data
  - their governments supported every single installation
  - they dominate the clinical and research landscape
  - Carbon therapy is approve by the Govt/Private Ins.

Number of patients treated with Protons and C-ions in the world

Proton	Carbon	Total
95,424 (88.2%)	12,778 (11.8%)	108,202 (100%)



ALL CARBON CENTERS BUILT WITH GOVERNMENTAL SUPPORT

1. Office of Science and Technology Policy(OSTP) at the White House
2. National Cancer Institute (NCI)
3. Dep't of Energy (DOE)

"They all understand the need of Heavy Ion Therapy Center for patient Care and Research" in US

- Italians, Austrians, Chinese built Heavy Ion Therapy Facility

- ***Almost 40 years after the first heavy ion patient, there is still no heavy ion therapy center in the USA***

Planning for a National Center for Particle Beam Radiation Therapy Research (P20)

Key Dates

Posted Date	January 28, 2013
Letter of Intent Due Date(s)	April 21, 2013; December 21, 2013
Application Due Date(s)	May 21, 2013; January 21, 2014
AIDS Application Due Date(s)	Not Applicable
Scientific Merit Review	October 2013; June, 2014
Advisory Council Review	January 2014; October 2014
Earliest Start Date	April 2014; December 2014
Expiration Date	January 22, 2014
Due Dates for E.O. 12372	Not Applicable

Targeting Tumors with Particle Beams

Today, the National Cancer Institute (NCI), part of the National Institutes of Health, and the Department of Energy (DOE) are each announcing the selection of several new research awards to advance particle beam therapies for the treatment of cancer. Particle beam approaches use directed protons — or heavier ions, such as carbon ions — to target and kill cancerous tissue. Because the delivered particles interact strongly with tissue at a certain distance within the body that depends on the energy of the beam, the damage to surrounding healthy tissue can be minimized, offering an important possible alternative or supplement to more conventional radiotherapy (using x-rays or gamma rays), chemotherapy, and surgery. At present, there are 14 proton therapy centers in the United States; there are only a few carbon ion therapy facilities worldwide, but none are in the United States. The NCI awards announced today support planning for the establishment of a Center for Particle Beam Radiation Therapy as a national research resource, and the DOE awards address development of improved hardware that could shrink the size, increase the maneuverability, and considerably reduce the steep costs of particle beam therapy equipment.

The Planning Grant awards for the national research center are being made by NCI. The planned center would serve as a research adjunct to an independently created and funded, sustainable clinical facility for particle beam radiation therapy. Ultimately, the proposed center is expected to perform clinically relevant research using ion beams. The planning grants include pilot projects that will enable a research agenda in particle beam delivery systems, dosimetry, radiation biology, and/or translational pre-clinical studies. NCI encourages other researchers to collaborate with the awardees in advancing the capabilities for particle beam therapies.

The DOE awards are being made under the Accelerator Stewardship Program. The machinery needed to produce and control particle beams, such as synchrotrons, cyclotrons, and related beam delivery systems, is expensive and complex. This machinery, however, can be used in a variety of fields, ranging from high-energy physics to materials science to medical treatment. The DOE program has the responsibility for long-term, fundamental research and development of such instrumentation. The new efforts will support improvements in the generation of the accelerated particles and in the powerful magnets that direct the charged particle beams, aiming to make these key components smaller, lighter, more versatile, and potentially less expensive.

http://m.whitehouse.gov/blog/2015/02/10/targeting-tumors-particle-beams

Posted by Tof Carim on February 10, 2015 at 11:15 AM EST

A Prospective Randomized Phase 3 Trial of Carbon Ion versus Conventional Radiation Therapy for Locally Advanced, Unresectable Pancreatic Cancer

Solicitation Number: HHS-NIH-NCI-ETSB-51007-51
Agency: Department of Health and Human Services
Office: National Institutes of Health
Location: National Cancer Institute, Office of Acquisitions

Notice Details | Packages | Interested Vendors List | Print | Link

Original Synopsis
Dec 10, 2014
2:52 pm

Return To Opportunities List | Watch This Opportunity | Add Me To Interested Vendors

Solicitation Number:
HHS-NIH-NCI-ETSB-51007-51

Notice Type:
Sources Sought

ALL FILES

Sources Sought Notice
Dec 10, 2014
Sources Sought Notic...
Attachment 1-Backgro...

CIPHER: CIPHER PC

Carbon Ion versus PHoton thERapy for Pancreatic Cancer

Lead Institution – **University of Texas Southwestern Medical Center** Dallas, Texas

Jeffrey Meyer, M.D.

Hak Choy, M.D, Robert Timmerman, M.D.

Jeffrey Meyer, M.D., Steve Jiang, Ph.D.

Arnold Pompos, Ph.D., Michael Story, Ph.D.

National Institute of Radiological Science (NIRS)

Chiba, Japan

Hirohiko Tsujii, MD, PhD.

Tadashi Kamada , MD, PhD.

Shigeru Yamada MD., Ph.D.

Koji Noda, Ph.D.

Yoshiya Furusawa , Ph.D

Heidelberg Ion Therapy(HIT)

Heidelberg, Germany

Jürgen Debus, MD. Ph.D.

Oliver Jäkel, Ph.D.

Peter Peschke, Ph.D.

Kristian Karger, Ph.D.

Amir Abdollahi, Ph.D.

National Centre of Oncological Hadrontherapy (CNAO)

Pavia, Italy

Roberto Orrechia, MD., Ph.D.

Piero Fossati, MD., PhD.

Silvia Molinelli MS.

Marco Durante, Ph.D.

Gunma University Heavy-ion Radiotherapy Maebashi, Japan

Takashi Nakano, MD.Ph,D,

Tatsuaki Kanai, Ph.D.

Akihisa Takahashi, Ph.D.

Tatsuya Ohno MD, PhD

CIPHER PC

Randomization

<u>Carbon Ion Arm</u>

Induction chemotherapy

↓

55.2 GyE in 12 fractions (3 weeks)

Weekly concurrent gemcitabine ($1000 mg/m^2$)

↓

Continued chemotherapy

<u>Photon Arm</u>

Induction chemotherapy

↓

50.4 Gy in 28 fractions + concurrent capecitabine

↓

Continued chemotherapy

<u>Eligibility Criteria:</u>

1)Adenocarcinoma histology

2)Age $\geq$18 yo

3)Locally advanced tumor presentation

4)Tumors not in direct contact with the duodenum or stomach (NIRS experience, 5mm gap)

The 2nd ISIT: International Symposium on Ion Therapy schedule: Oct 22-23
Dallas, Texas

http://www.isit-sw.org

Conclusion

1. It appears that proton beam is more precise than photon

Conclusion

1. It appears that proton beam is more precise than photon
2. It appears that caron beam is more precise and potent than photon

Conclusion

1. It appears that proton beam is more precise than photon
2. It appears that caron beam is more precise and potent than photon
3. The physics of proton/Carbon may indeed be precise and predictable, however the actual delivery of proton/Carbon therapy comes with many uncertainties: dose distribution, range uncertainty, intra-fractional motion, inter-fractional anatomic changes

Conclusion

1. It appears that proton beam is more precise than photon
2. It appears that caron beam is more precise and potent than photon
3. The physics of proton/Carbon may indeed be precise and predictable, however the actual delivery of proton/Carbon therapy comes with many uncertainties: dose distribution, range uncertainty, intra-fractional motion, inter-fractional anatomic changes
4. The higher biological dose of carbon therapy can potentially cause higher normal tissue toxicity when the distal margin of the tumor is uncertain.

Conclusion

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7. Our treatment decision must be based on **evidence-based** medicine

Thank you !

Which answer indicates correctly the advantages for each type of radiation the

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1. Photons – precise, not potent
2. Photons – not precise, potent
3. Carbon ions – precise, potent
4. Protons – not precise, potent
5. Protons – not precise, not potent

Answer: 3– Carbon ions – precise, potent

U. Linz. Physical and Biological Rationale for Using Ions in Therapy. In: U. Linz (Ed) Ion Beam Therapy: Fundamentals, Technology, Clinical Applications, pp 45-59, Springer, 2012.