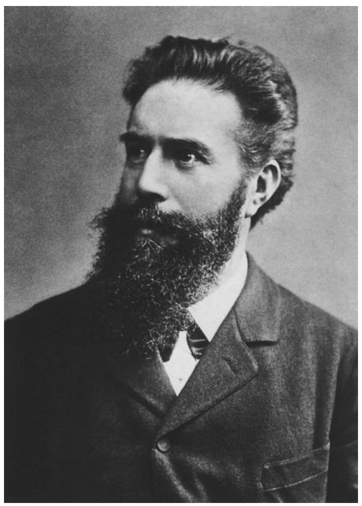
Improving the Outcome of Lung Cancer with Advanced Technology: Photon, Proton and Carbon

Hak Choy, MD

UT Southwestern

Dallas, Texas

1895 – A New Kind of Ray



Wilhelm Röntgen

EINE NEUE ART
VON
STRAHLEN.

VON

DR. W. RÖNTGEN,
Ö. O. PROFESSOR AN DER K. UNIVERSITÄT WÜRZBURG.

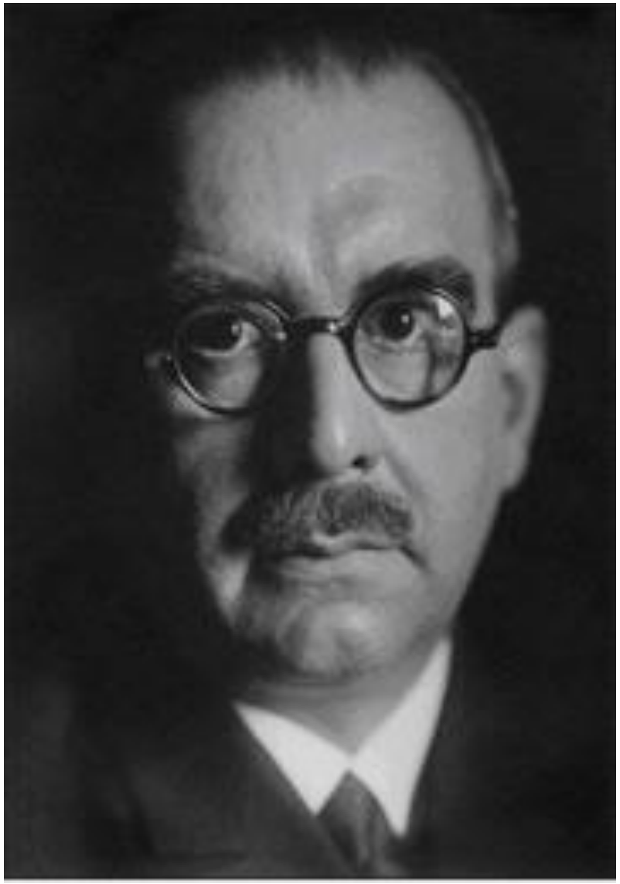
WÜRZBURG.
VERLAG UND DRUCK DER STAHEL'SCHEN K. HOF- UND UNIVERSITÄTS-
BUCH- UND KUNSTHANDLUNG.
Ende 1895.

60 Pf.

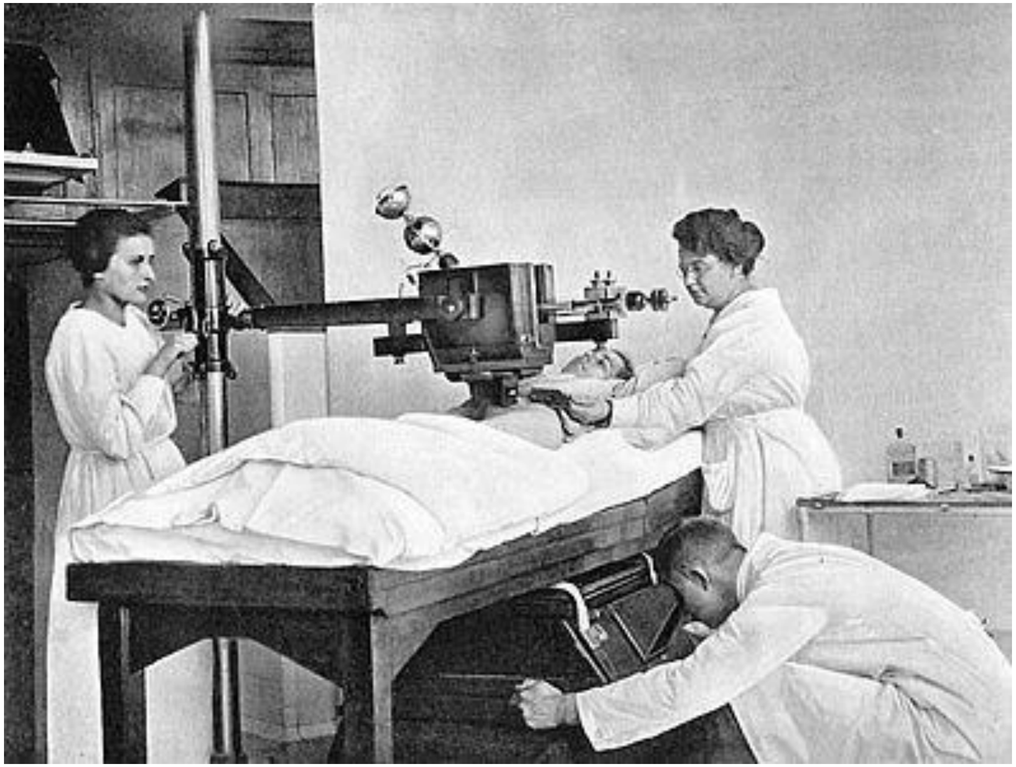
1908 - Stockholm Method of Hypofractionation Using Brachytherapy

Gösta Forsell

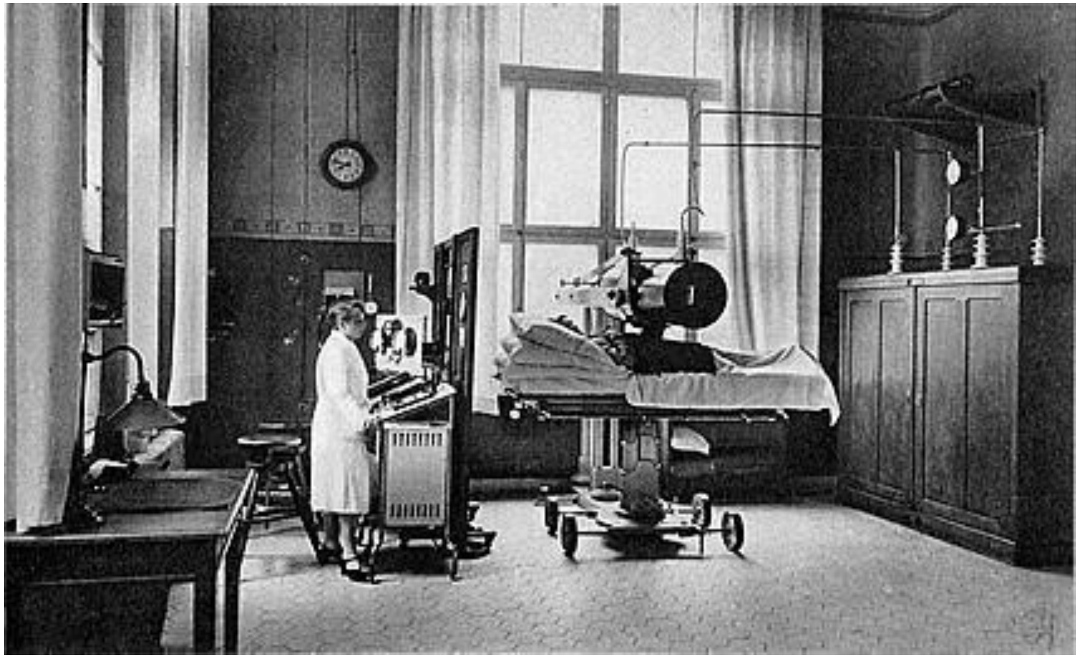
1914 – Erlanger Method of Hypofractionation using Teletherapy



Hermann Wintz



1920 - Cervix Cancer is "Cured" by Hypofractionated Brachy- and Teletherapy



- Gynecological specialist congress - a participant shouted,

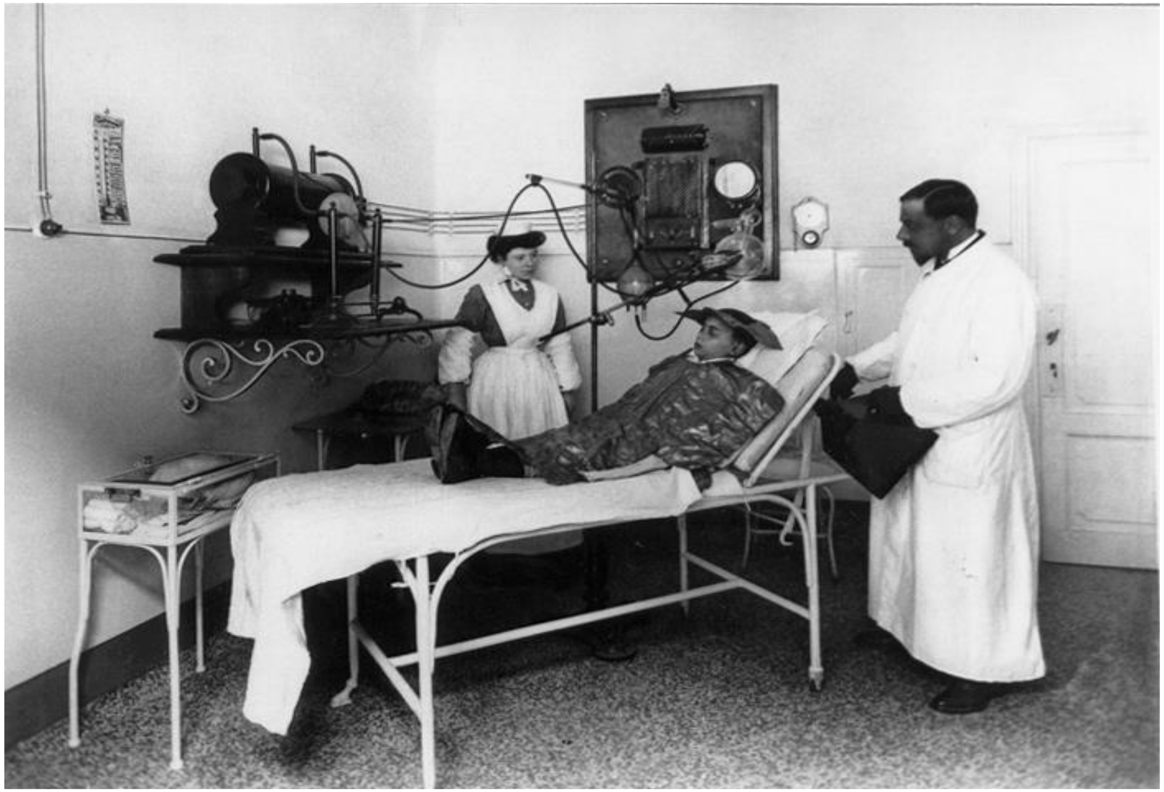
  "Cancer is defeated …"

Late 1920's – The Sky Fell

LATE radiation toxicity: ulceration, denervation, devasculization, stenosis, fibrosis, devitalization

Why did the sky fall?

- Technology problems
  - Very low energy beams (most dose into the skin)
  - Crude guidance
  - Poor understanding of radiation interactions (unable to represent dose



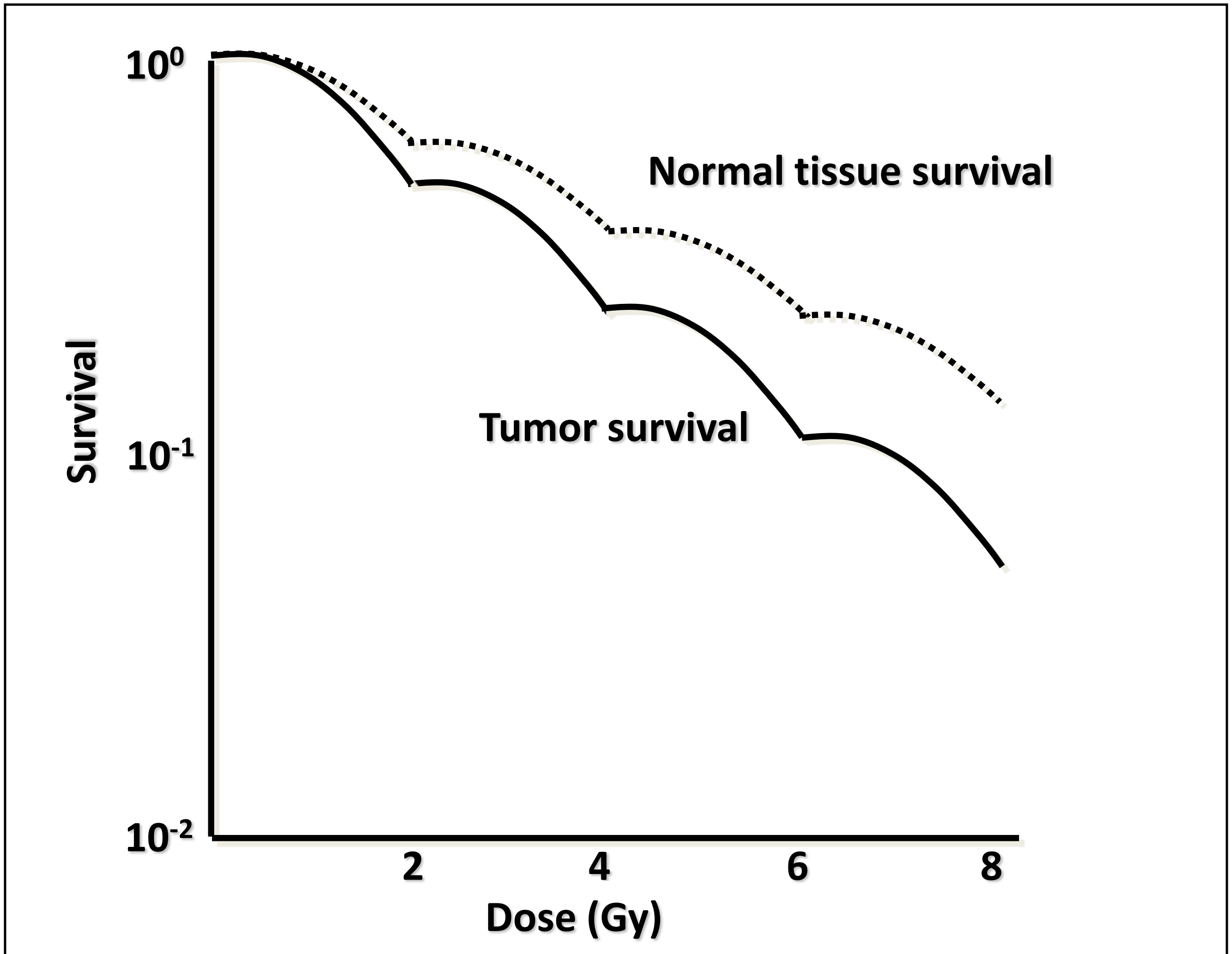
Why did the sky fall?

- Technology problems
  - Very low energy beams (most dose into the skin)
  - Crude guidance
  - Poor understanding of radiation interactions (unable to represent dose

- Biology problems
  - As with tumor, normal tissues poorly tolerant of radiation therapy

- Clinical problems
  - Crude understanding of tumor location
  - Normal tissues extensively irradiated

Traditional Radiobiology



US Pioneers Champion Protracted Fractionation

Gilbert Fletcher

Juan Del Regato

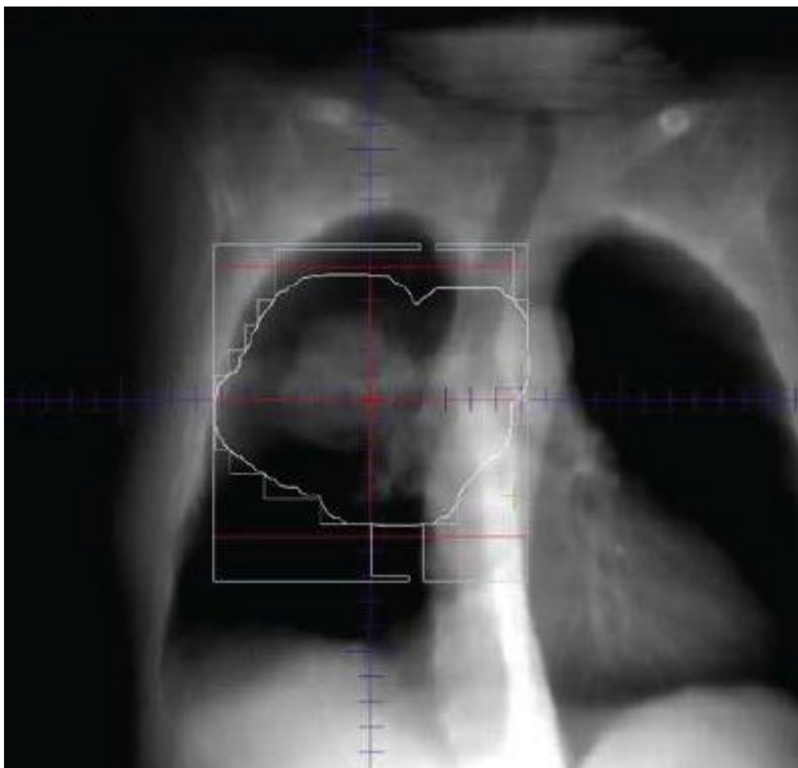
Henry Kaplan

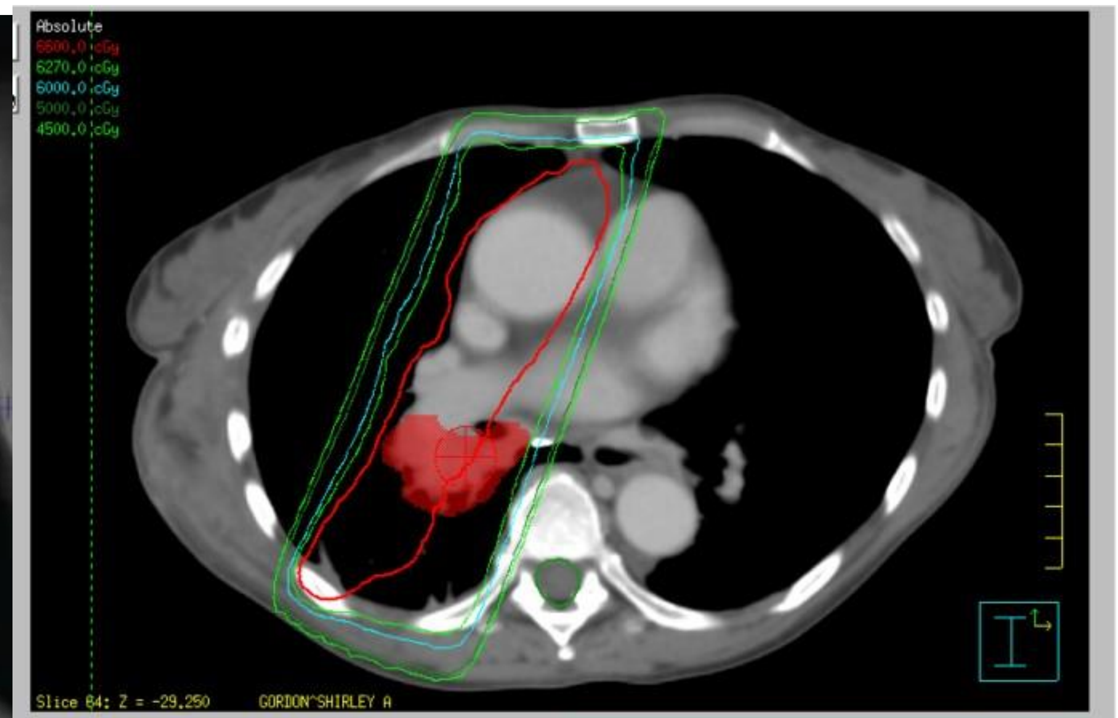
Franz Buschke

Isodore Lampe

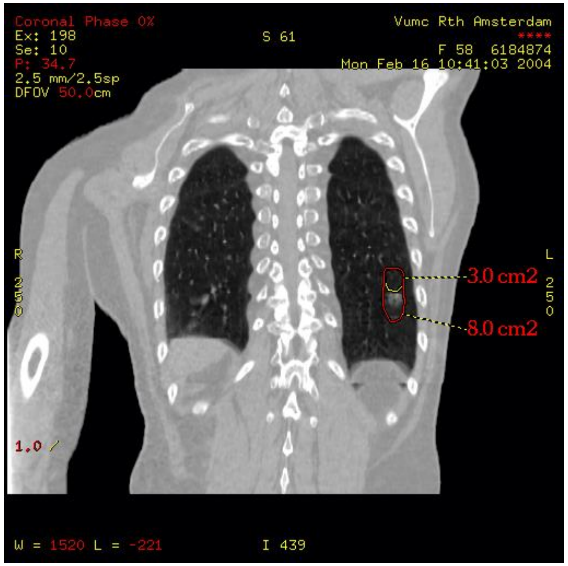
Fletcher, Kaplan, Lampe, Del Regado, and Buschke’s Toolbox

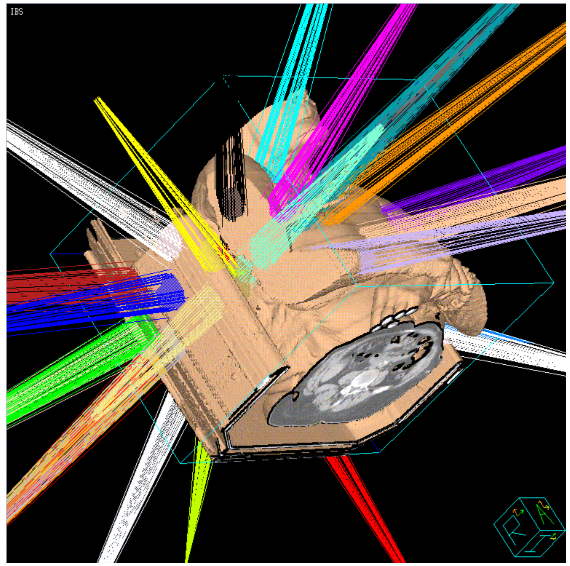
- Mostly 1-D and 2-D teletherapy

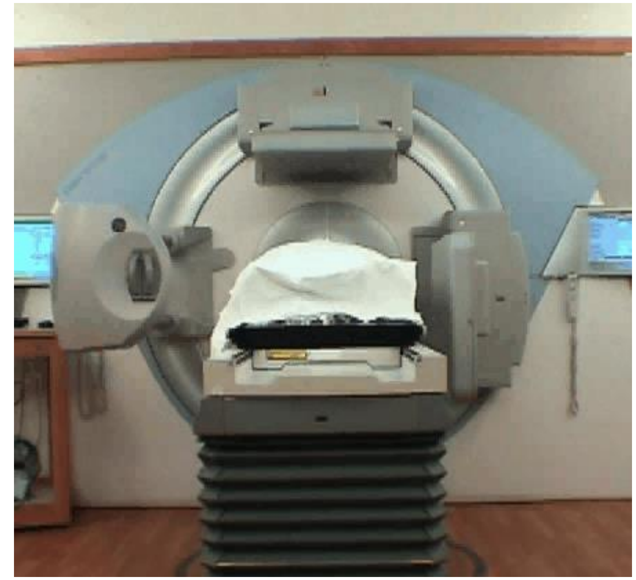




Tools that Fletcher Didn't Have



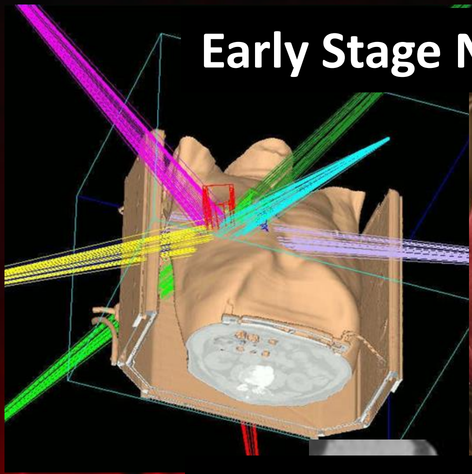


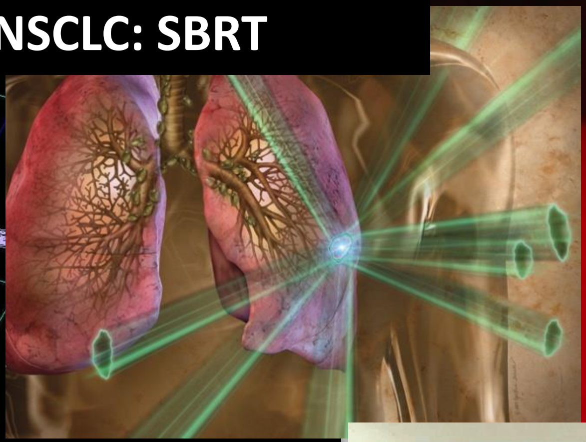


- Stereotactic targeting
- 3-D conformal avoidance
- IMRT
- 4-D motion assessment
- Motion control
- Image guidance
  - –ALL FACILITATING STEREOTACTIC ABLATIVE (SABR) AND IMAGE-GUIDED HYPOFRACTIONATED RADIOTHERAPY

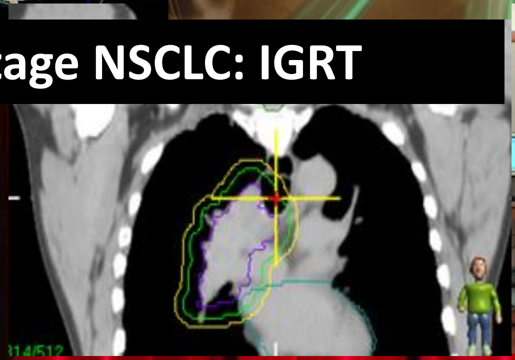
The Advancement of Radiation Therapy Technology

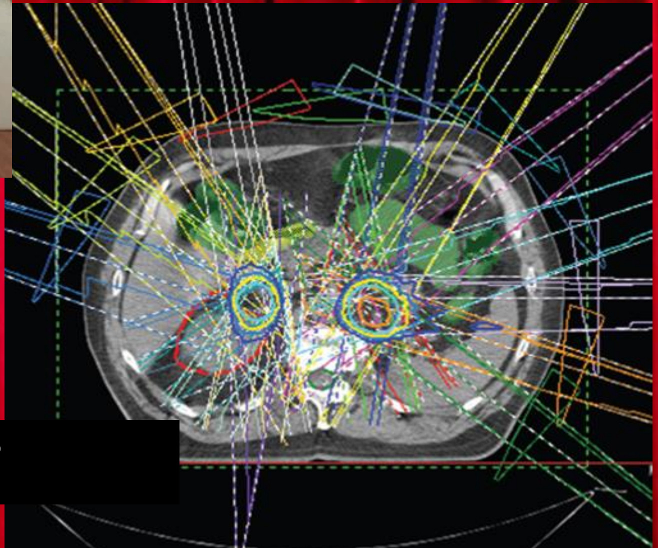
Early Stage NSCLC: SBRT





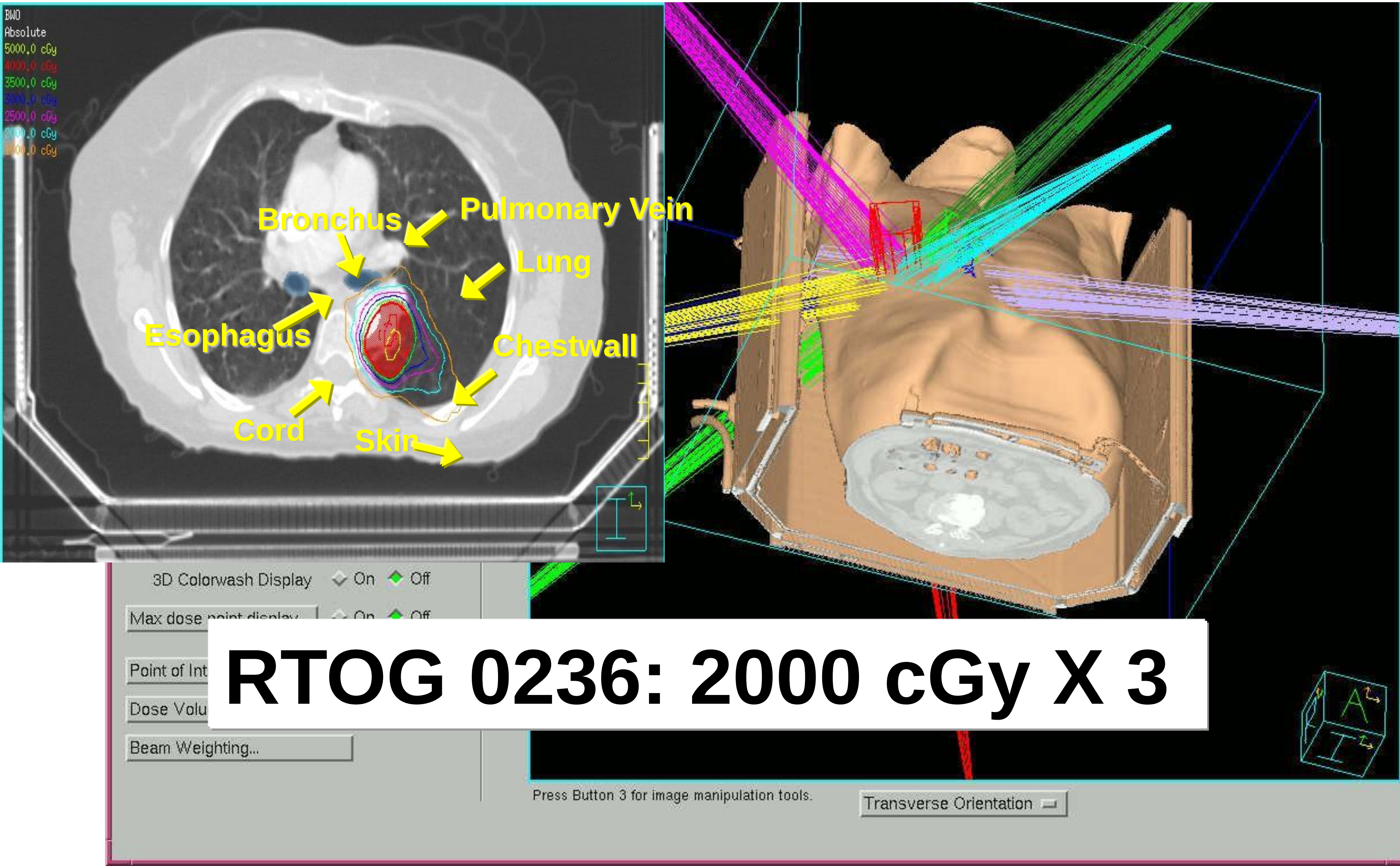
LAStage NSCLC: IGRT





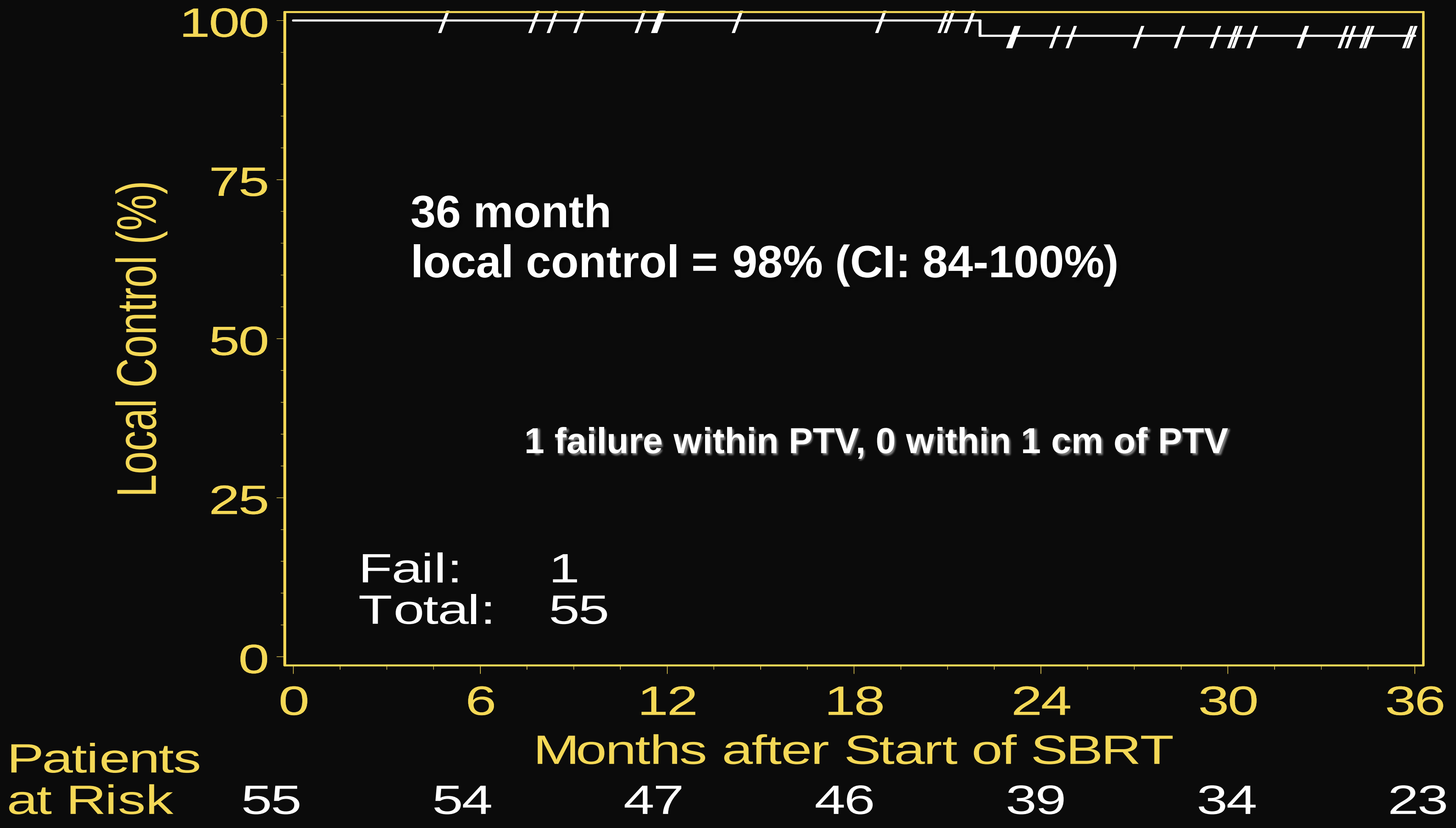
Advanced Stage NSCLC: SBRT

Stereotactic Body Radiation Therapy



RTOG 0236: 2000 cGy X 3

RTOG 0236: Local Control



Timmerman: ASTRO 2009, 11/2/2009 Chicago

JAMA®

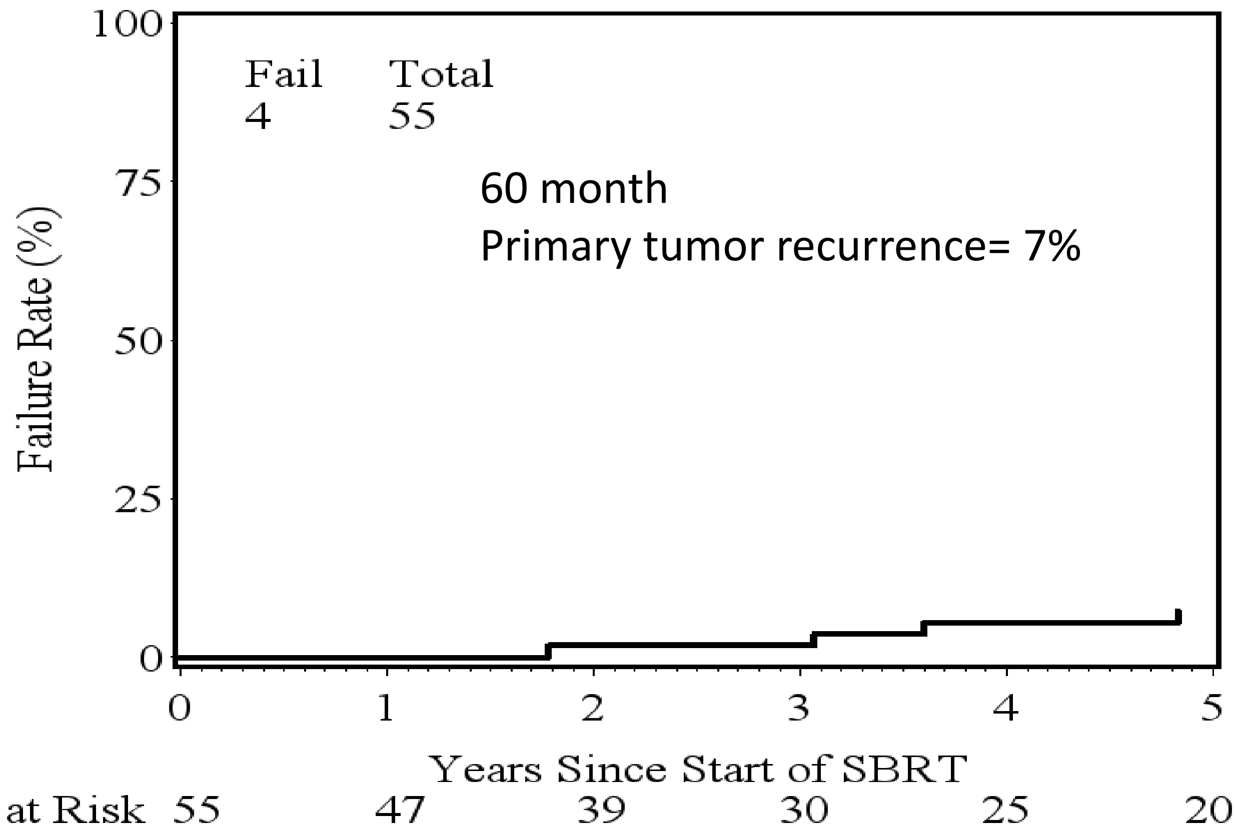
Online article and related content current as of July 15, 2010.

Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer

Robert Timmerman, MD; Rebecca Paulus, BS; James Galvin, PhD; Jeffrey Michalski, MD; William Straube, PhD; Jeffrey Bradley, MD; Achilles Fakiris, MD; Andrea Bezjak, MD; Gregory Videtic, MD;David Johnstone, MD; Jack Fowler, PhD; Elizabeth Gore, MD; Hak Choy, MD

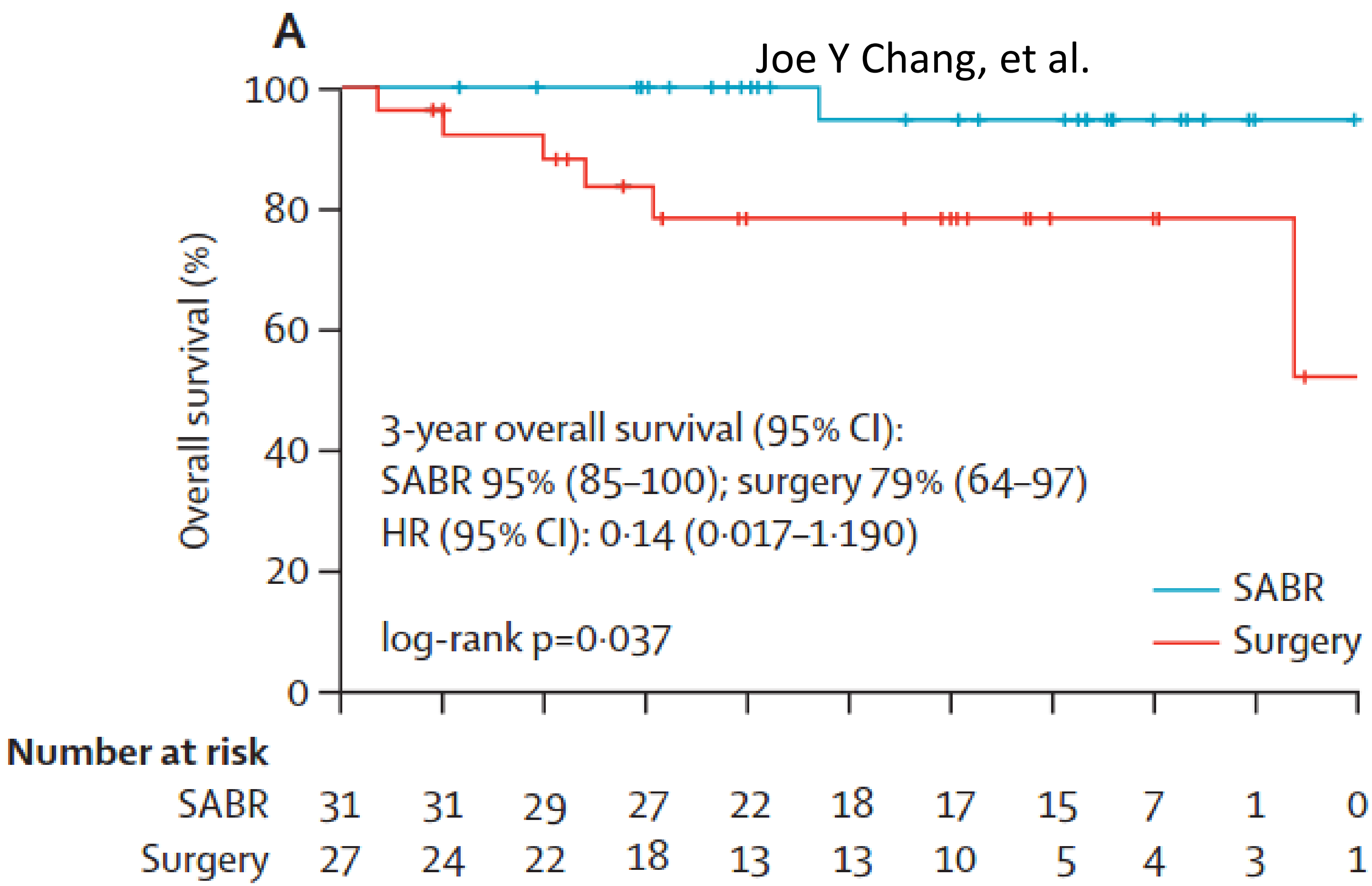
RTOG 0236

Primary (In-field + Marginal) Tumor Recurrence



Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomized trials

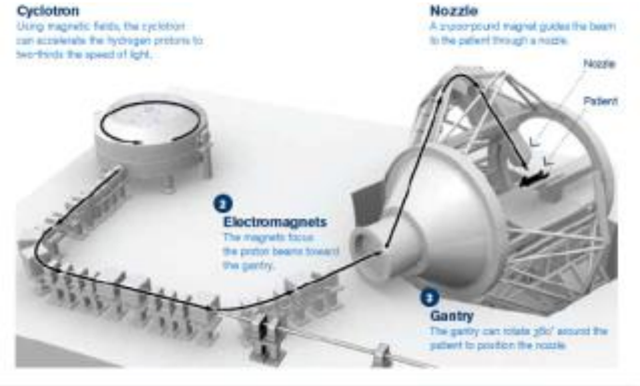
Joe Y Chang, et al.



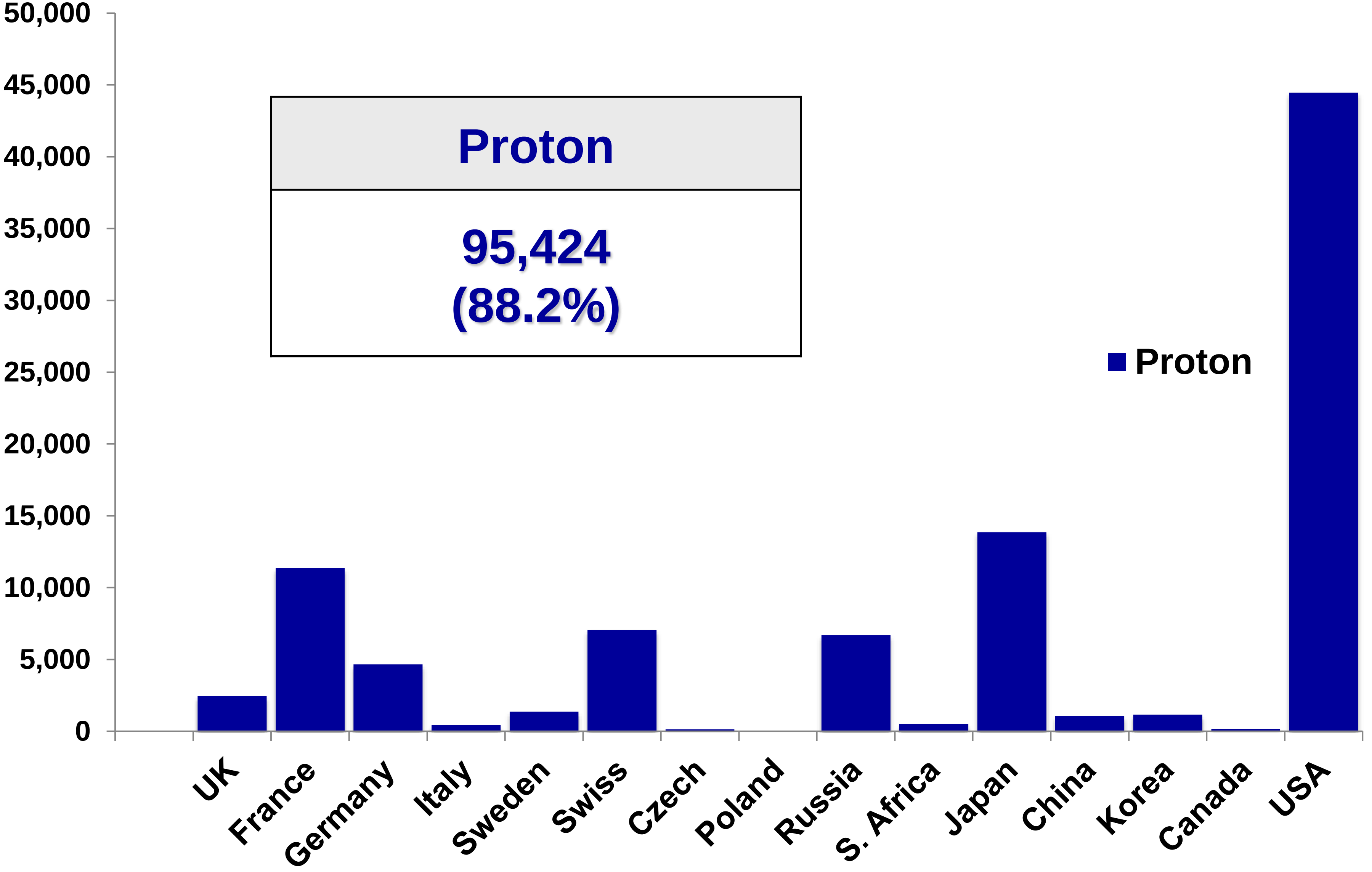
Lancet Oncol 2015; 16: 630–37

Radiation Oncology – Beyond Photon

- **Conventional Therapy**
  - **Standard Care**
- **Proton therapy**
  - **The Recent Technology**



Number of patients treated with Protons in the world



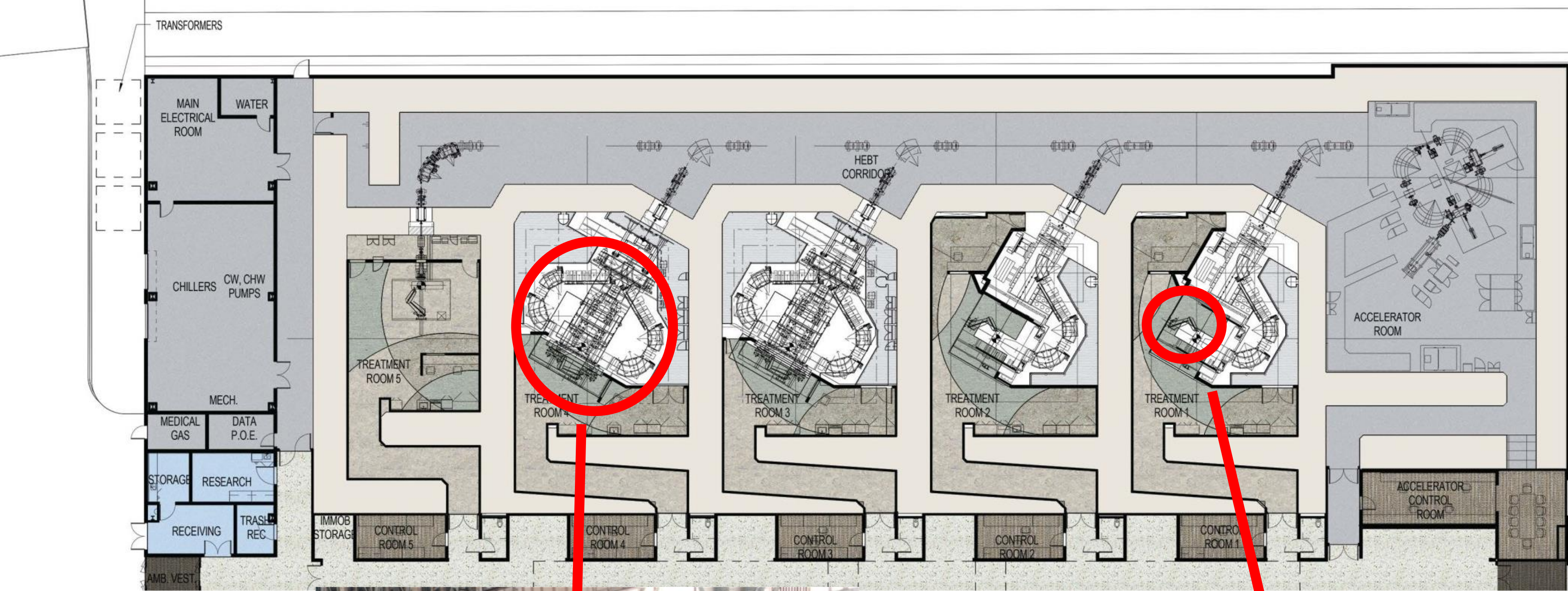
Proton Therapy:
What is it ?
What's the big deal about it ?

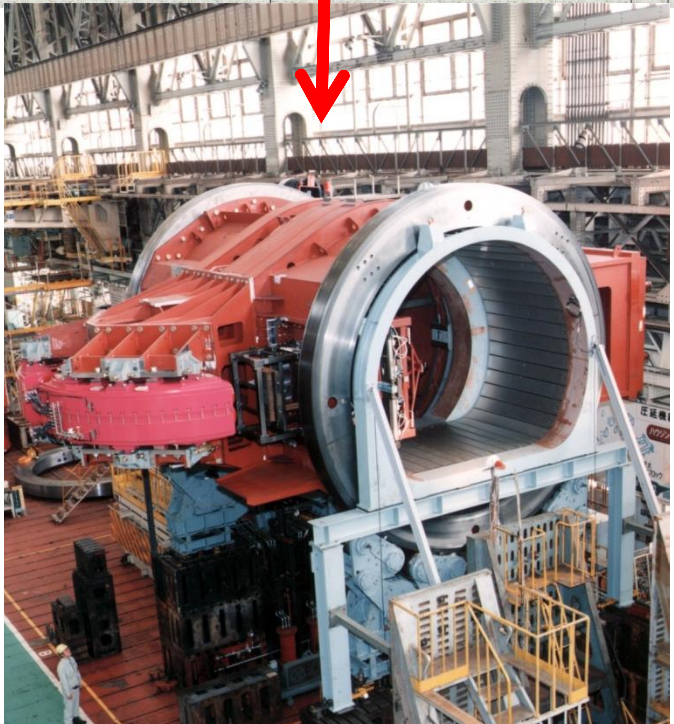
It’s a Big machine !

13 m diameter

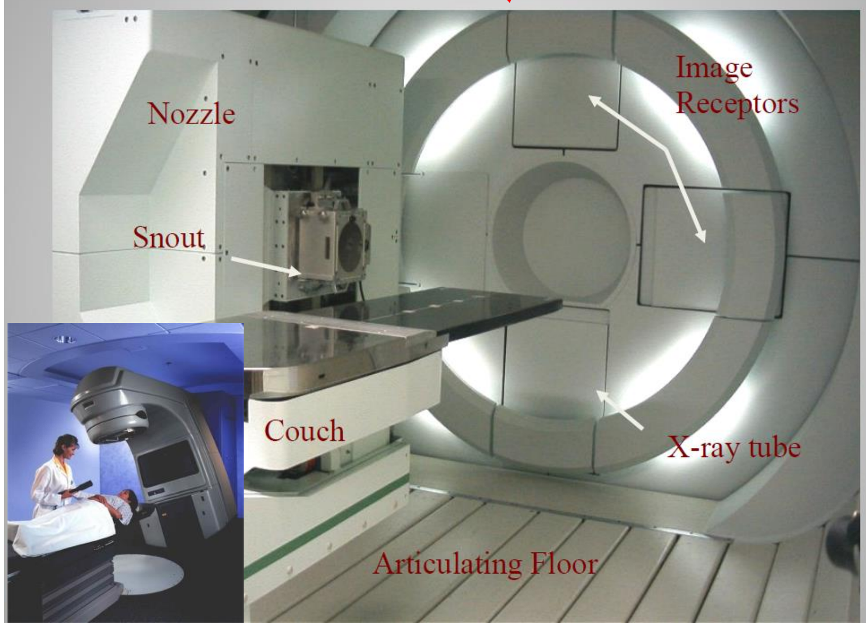
190 tons

SAD ≥ 2.7 m





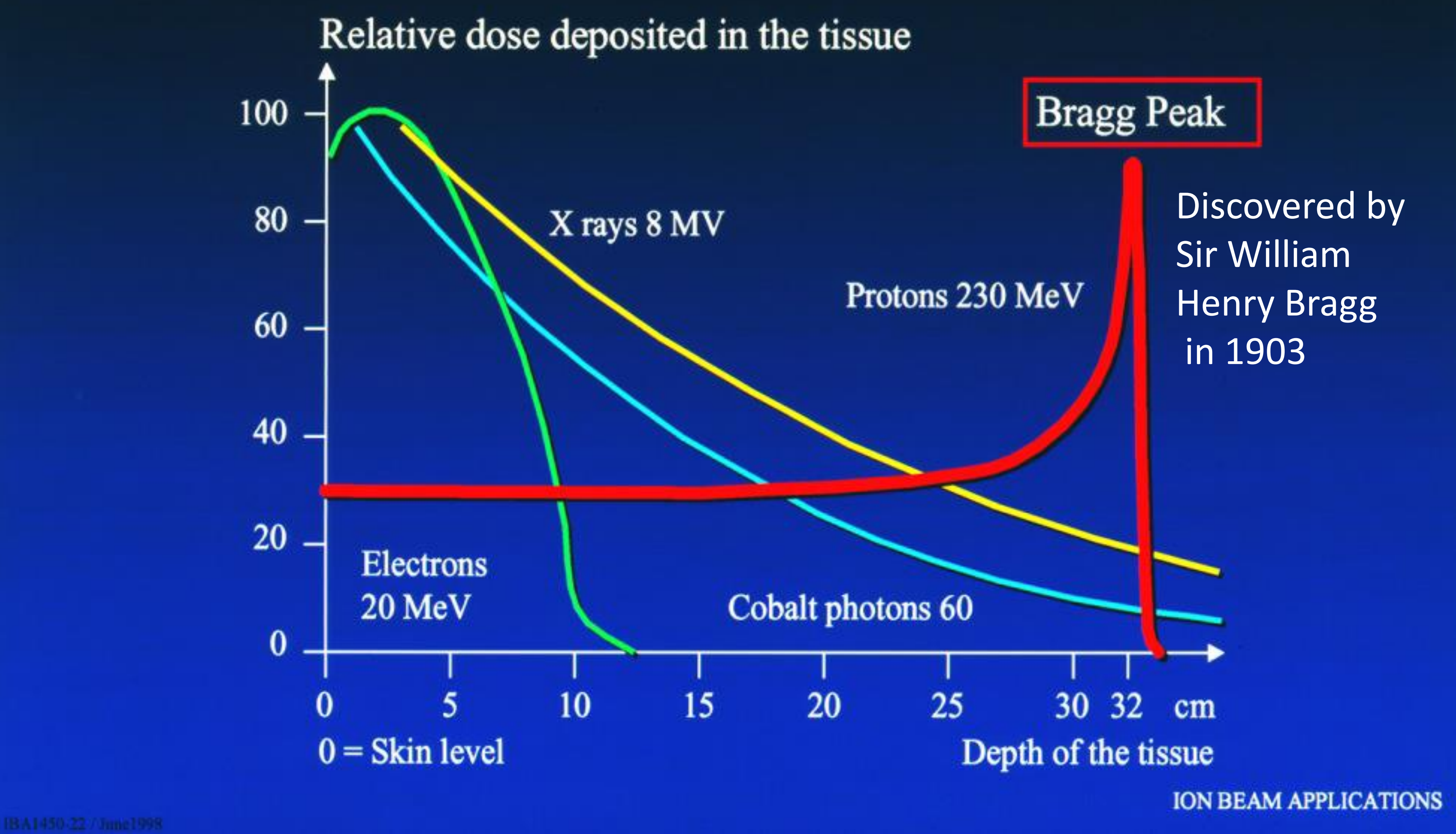
What the patient sees



How Proton is different than X-rays/Photon ?

Mostly in the Physical property
Not much difference in Biology!

Dose Distribution Advantage

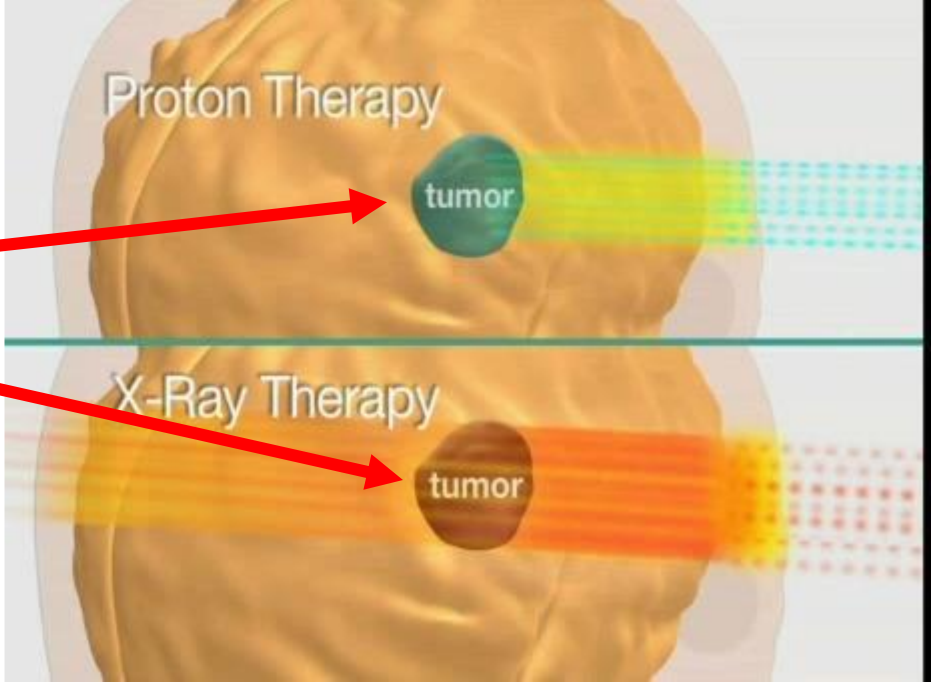


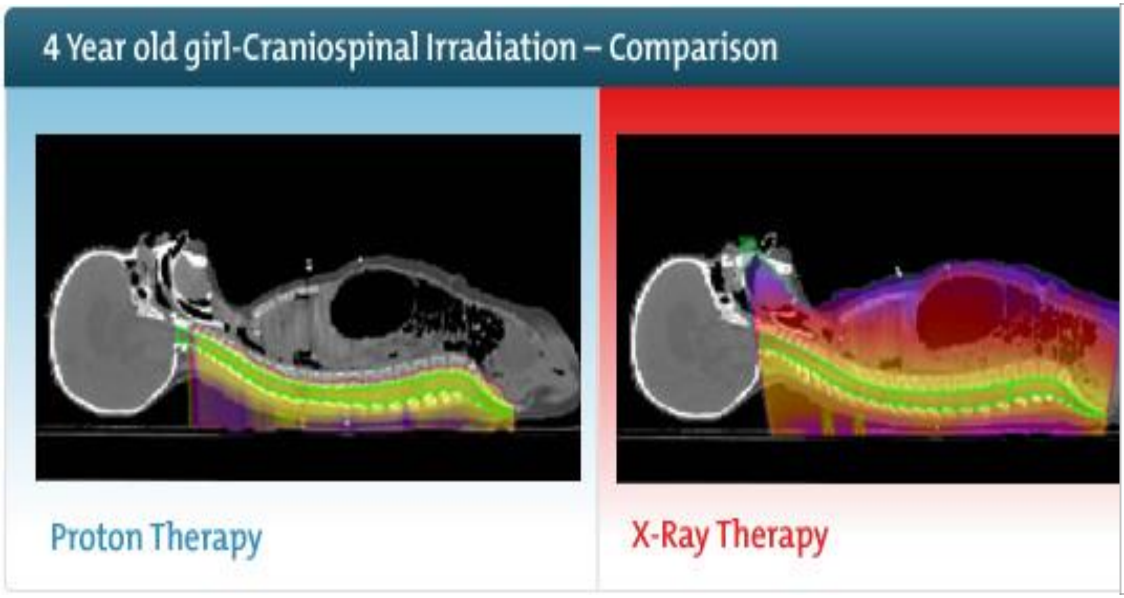
Discovered by Sir William Henry Bragg in 1903

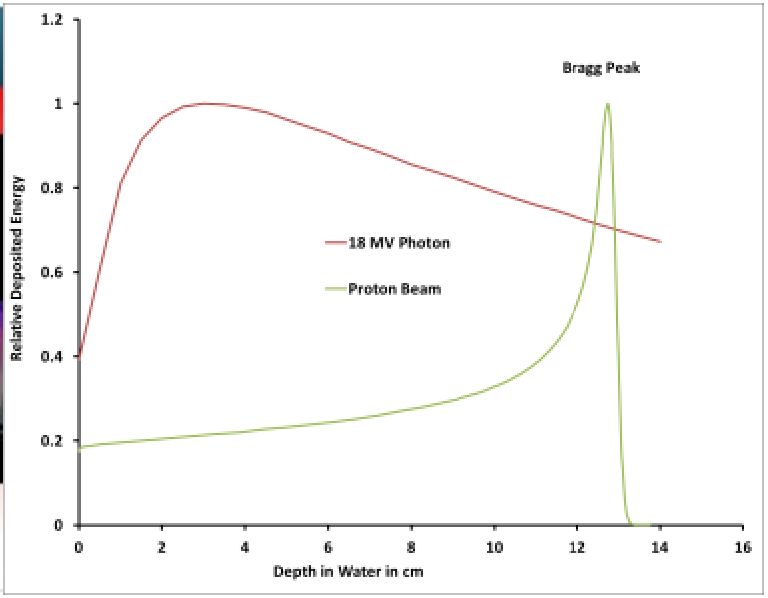
Effectiveness of Particle Therapy

Provide a lethal dose to the tumor…

…while sparing the surrounding healthy tissue







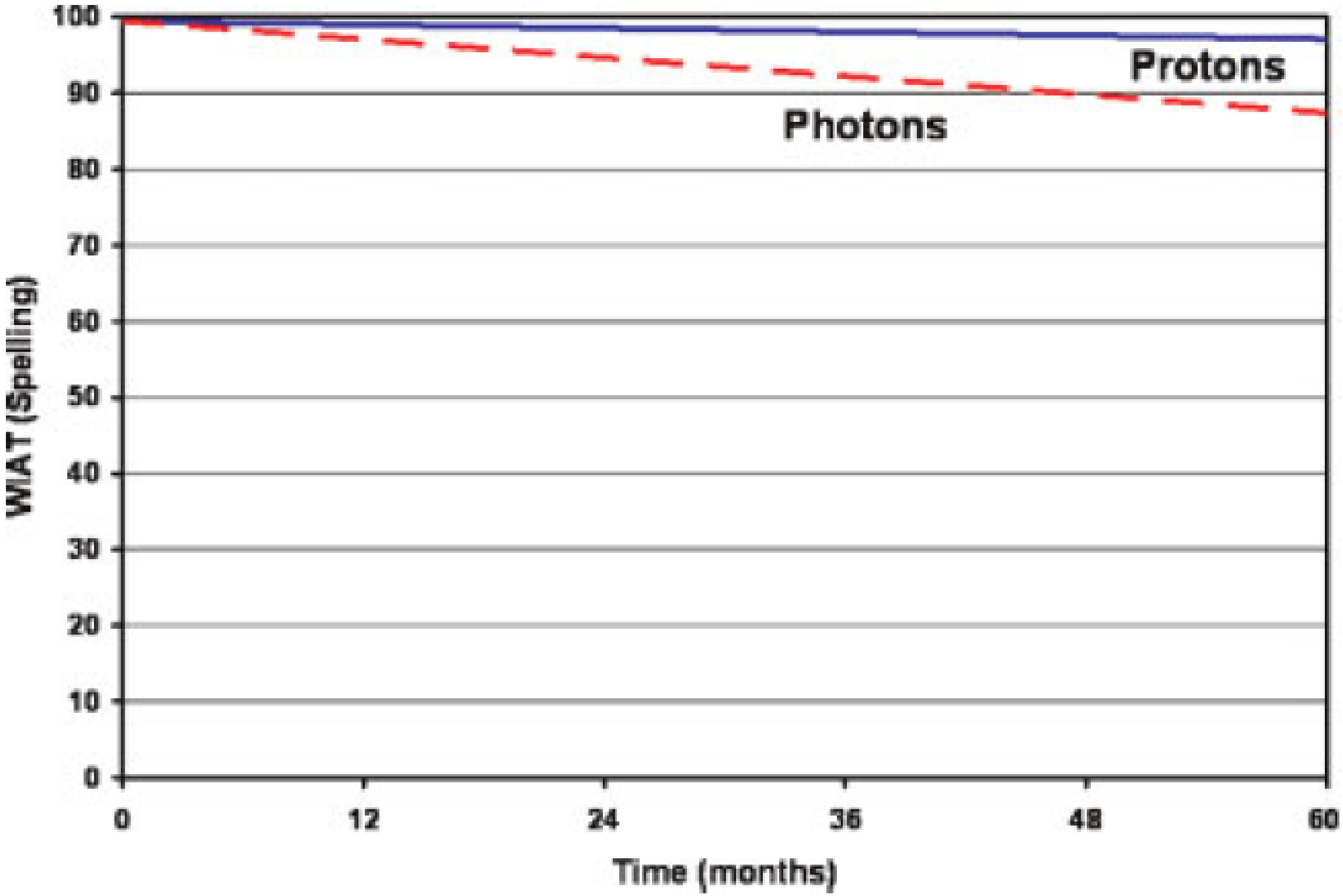


Fig. 3. Estimated WIAT spelling score for patients with optic pathway glioma planned for treatment with scanning proton beam (blue line) and conformal photon radiation therapy (red/dashed line). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Pediatr Blood Cancer 2008;51:110–117

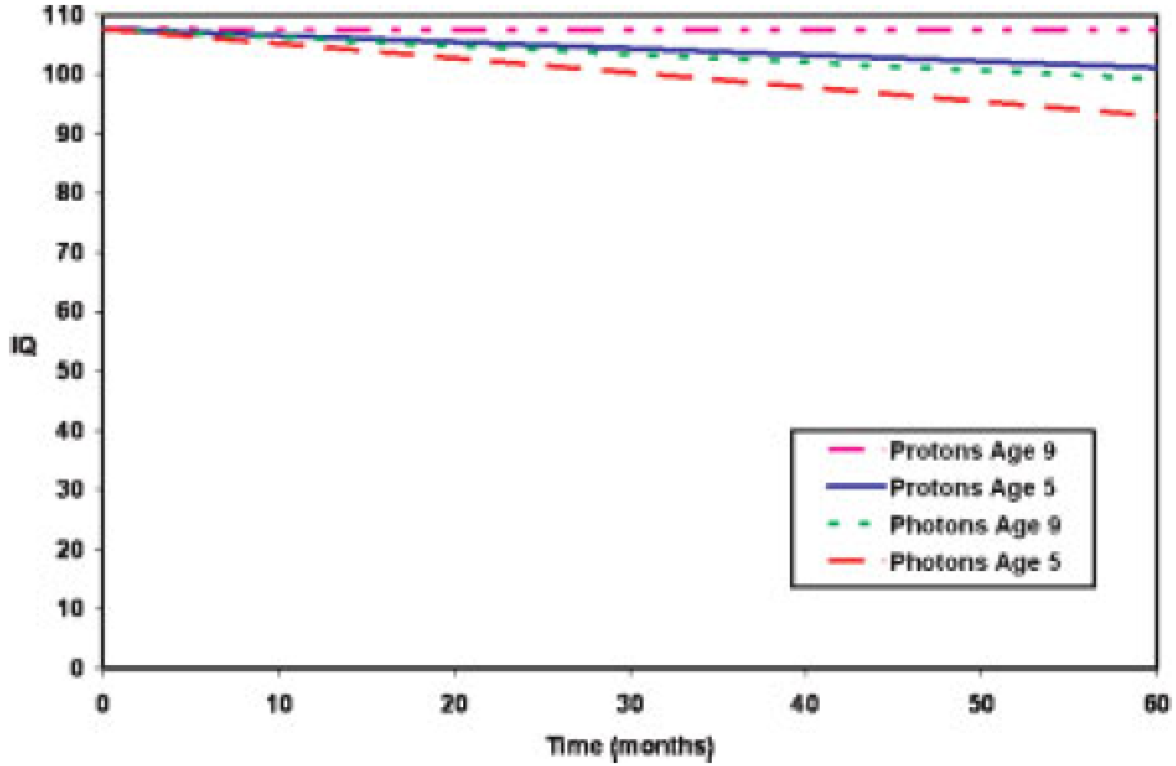
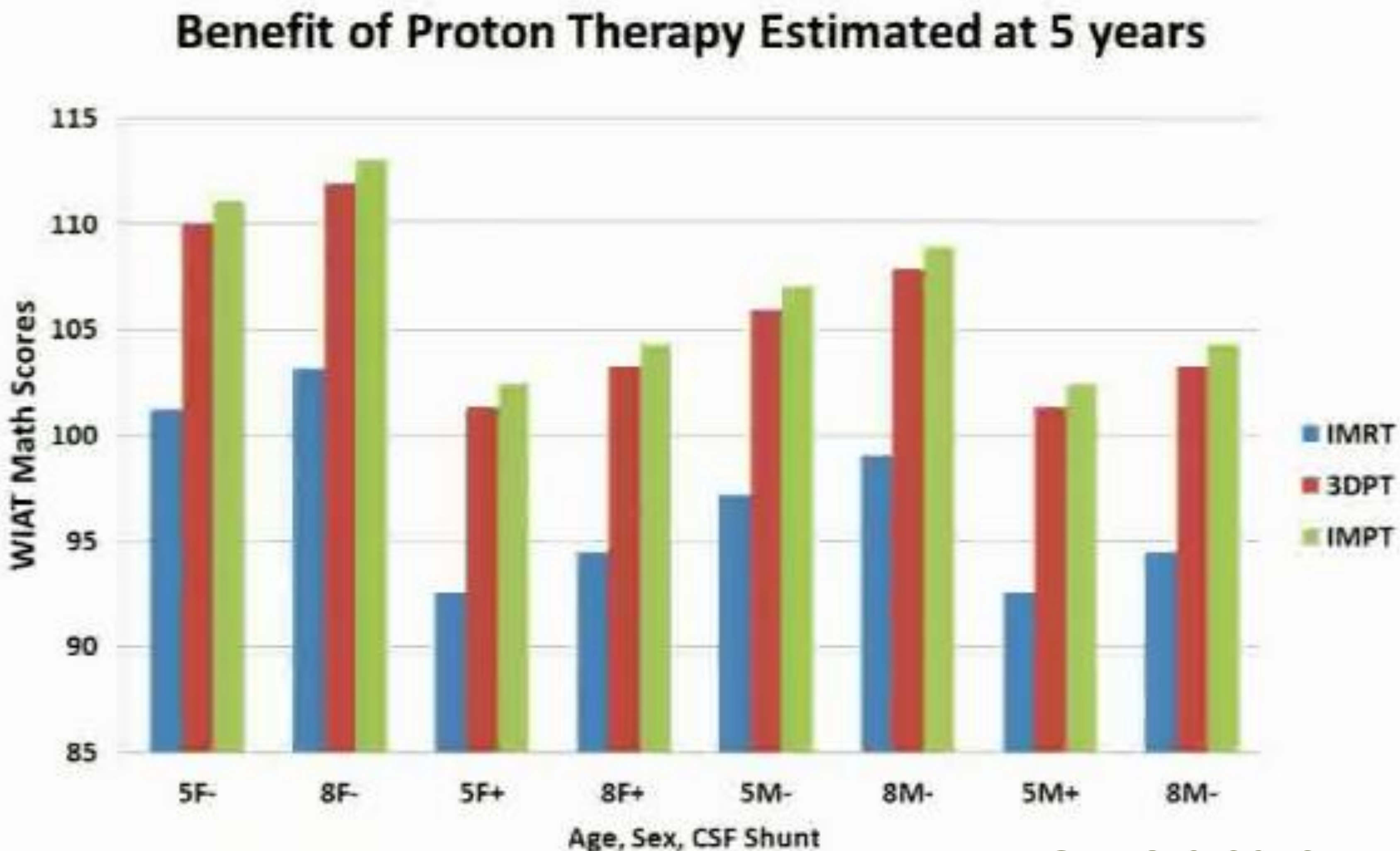


Fig. 5. Estimated IQ for patients ages 5 and 9 with craniopharyngioma planned for treatment with scanning proton beam therapy and conformal photon radiation therapy. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Pediatr Blood Cancer 2008;51:110–117

Model Application



ASTRO 9-2013

General Hypothesis of using Proton Beam for Lung Cancer

1. Proton therapy can significantly reduced the volume of lung/heart exposed to radiation and sparing of normal tissues compared to photon therapy: Potential reduced Toxicities and perhaps better survival.

2. Higher dose conformity of dose distributions can be exploited to escalate tumor dose:

   Possible better tumor control.

Long-term outcomes after proton therapy, with concurrent chemotherapy, for stage II–III inoperable non-small cell lung cancer

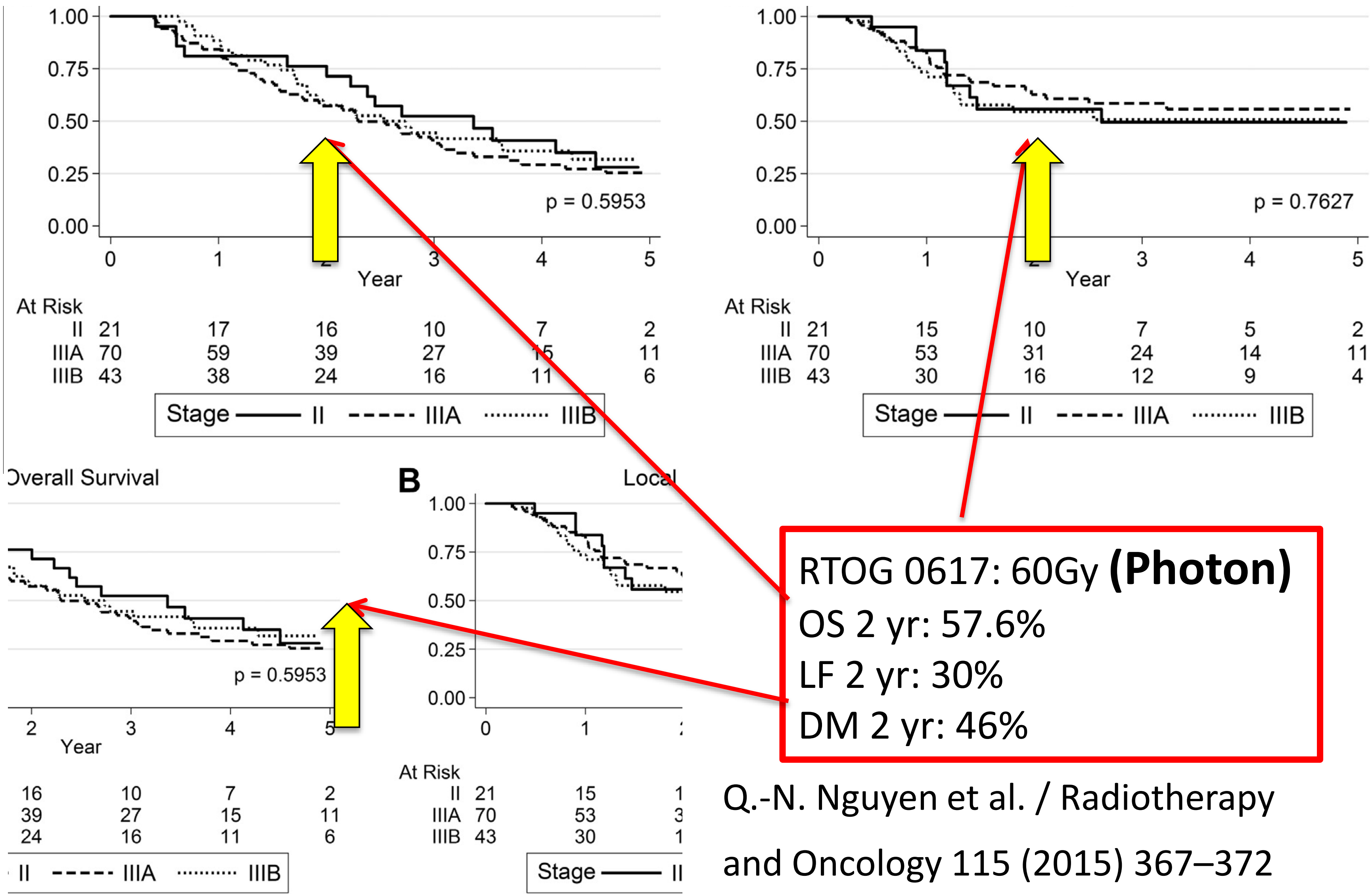
Q.-N. Nguyen et al. / Radiotherapy and Oncology 115 (2015) 367–372

Type of Toxicity	No. of patients experiencing toxicity (%)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Dermatitis	74 (55)	33 (25)	19 (14)	8 (6)	0
60–66 Gy(RBE)	14 (61)	5 (22)	2 (9)	2 (9)	0
70–72 Gy(RBE)	19 (56)	9 (26)	4 (12)	2 (6)	0
74 Gy(RBE)	41 (52)	19 (25)	13 (17)	4 (5)	0
Esophagitis	69 (51)	25 (19)	33 (25)	6 (4)	1 (1)†
60–66 Gy(RBE)	10 (43)	3 (13)	8 (35)	2 (9)	0
70–72 Gy(RBE)	24 (71)	6 (18)	3 (9)	1 (3)	0
74 Gy(RBE)	35 (45)	16 (21)	22 (29)	3 (4)	1 (1)
Radiation pneumonitis	68 (51)	35 (26)	29 (22)	2 (1.5)	0
60–66 Gy(RBE)	14 (61)	5 (22)	4 (17)	0	0
70–72 Gy(RBE)	20 (6)	9 (26)	5 (15)	0	0
74 Gy(RBE)	34 (44)	21 (27)	20 (26)	2 (3)	0

† Two-sided Fisher's exact test

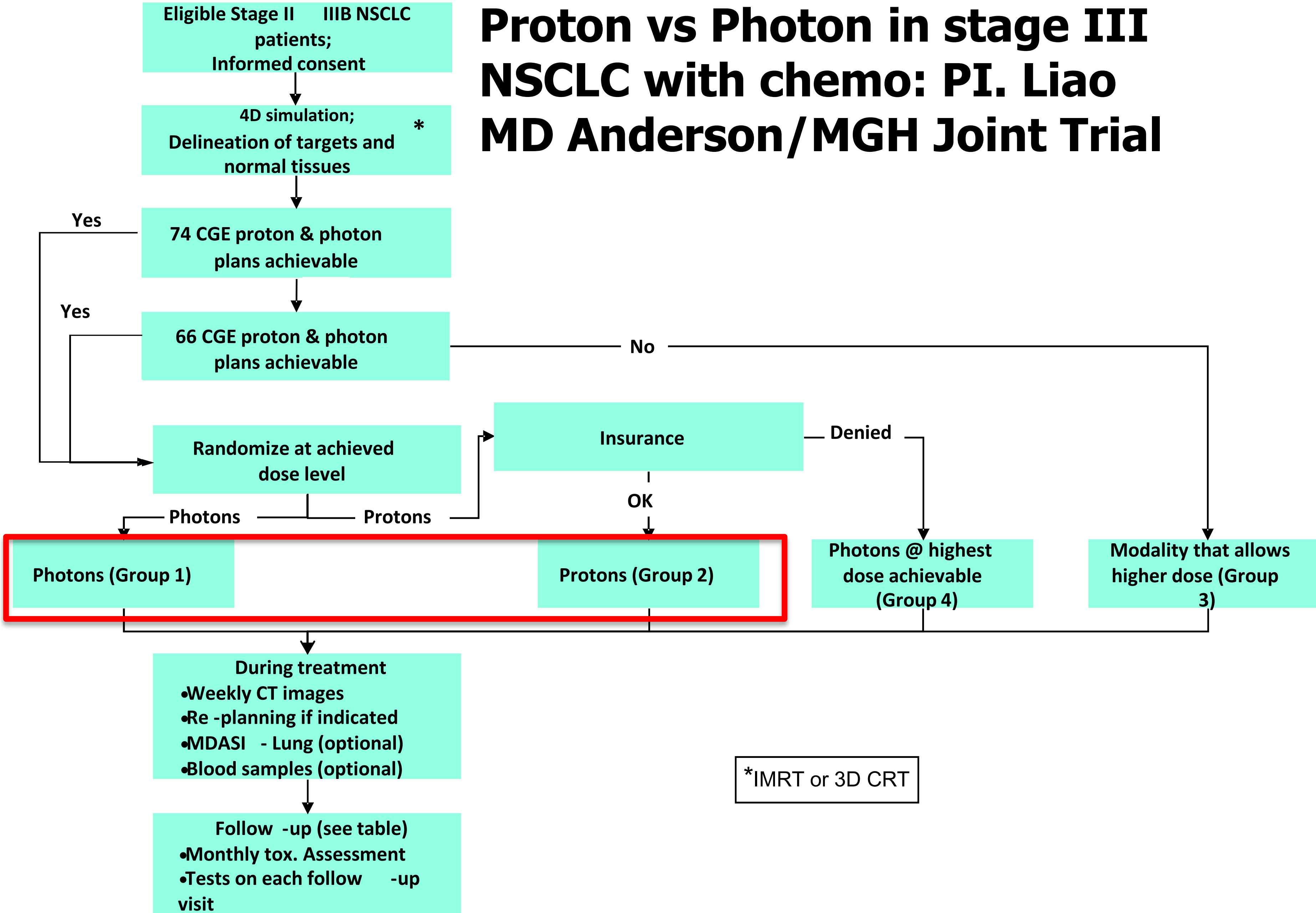
1. Proton therapy can significantly reduced the volume of lung/heart exposed to radiation and sparing of normal tissues compared to photon therapy: Potential reduced Toxicities→ improve survival ?”

Long-term outcomes after proton therapy, with concurrent chemotherapy, for stage II–III inoperable non-small cell lung cancer

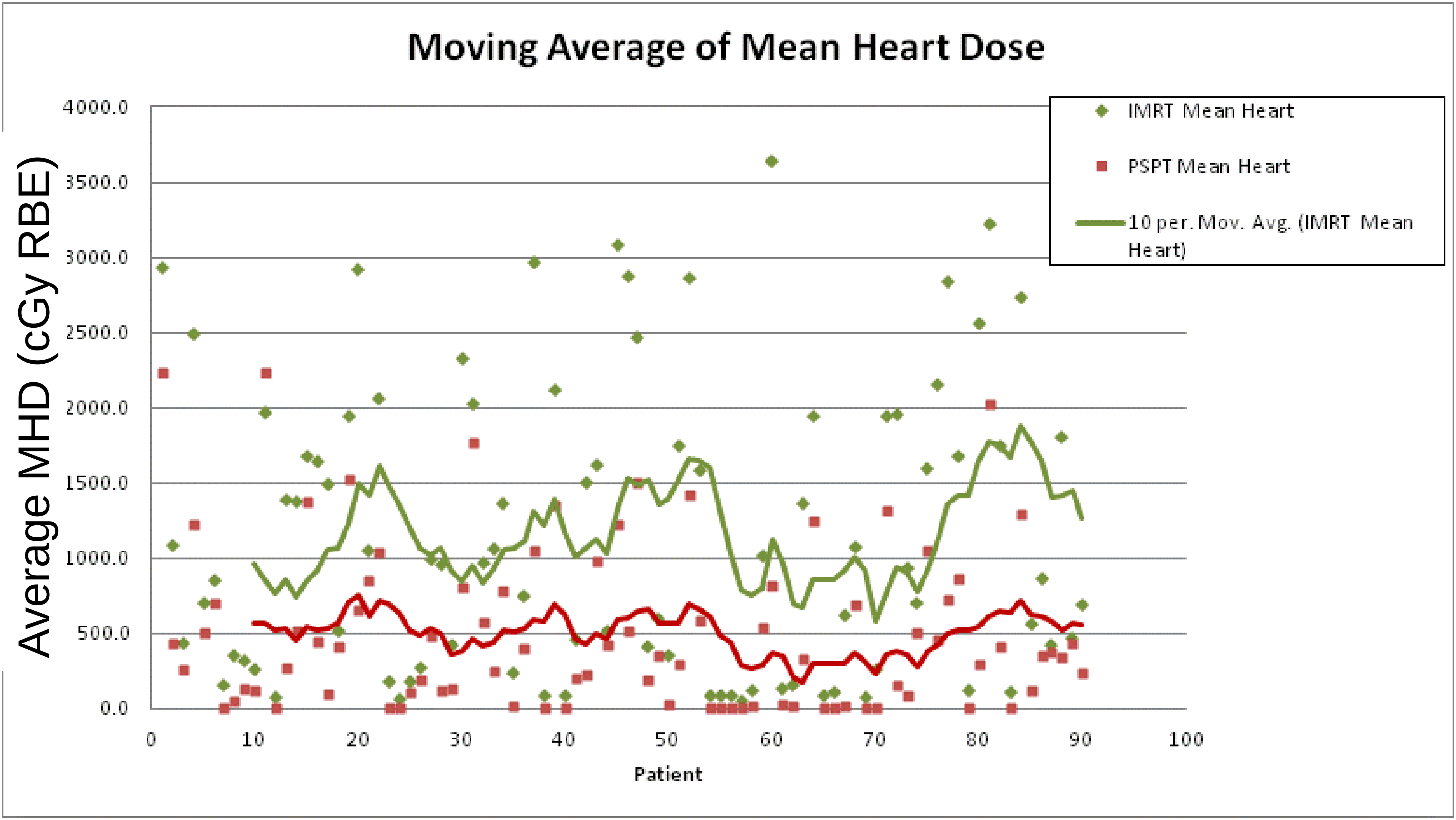


Q.-N. Nguyen et al. / Radiotherapy and Oncology 115 (2015) 367–372

Random Phase II trial comparing Proton vs Photon in stage III NSCLC with chemo: PI. Liao MD Anderson/MGH Joint Trial



IMRT vs. PSPT - Latest Results



Personal Communication From Dr Liao 2015

How can we demonstrate 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: 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

STRATIFY

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

RANDOMIZE

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

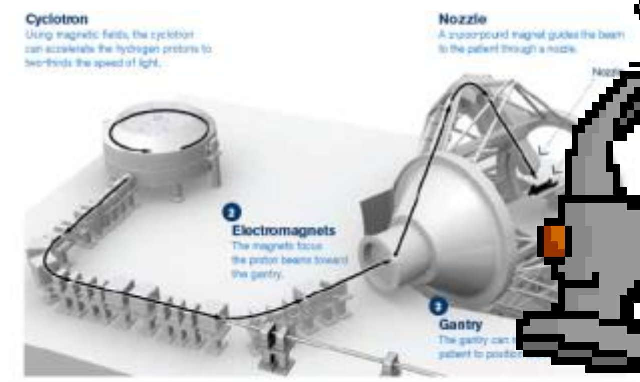
Arm 2: Proton dose—Higher achievable dose between 60-70 Gy (RBE), once daily plus platinum-based doublet chemotherapy*

Both Arms: Consolidation chemotherapy x 2 is allowed*

Target Accrual: 560, Accrual as of 1/15: 48

Radiation Oncology – Beyound Photon and Proton

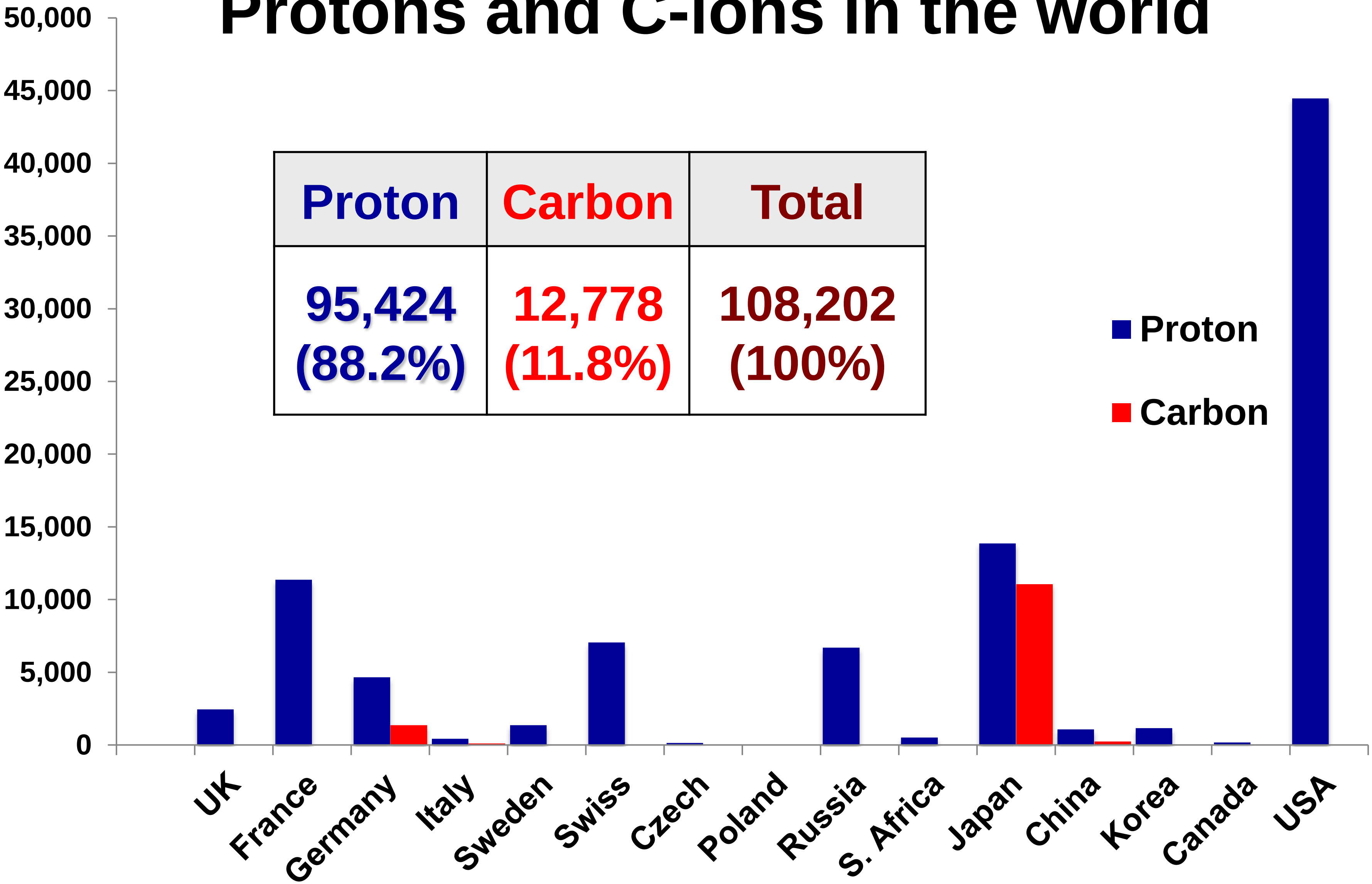
- ❑ **Conventional Therapy**
    - ○ **Standard Care**
- ❑ **Proton therapy**
    - ○ **The Recent Technology**



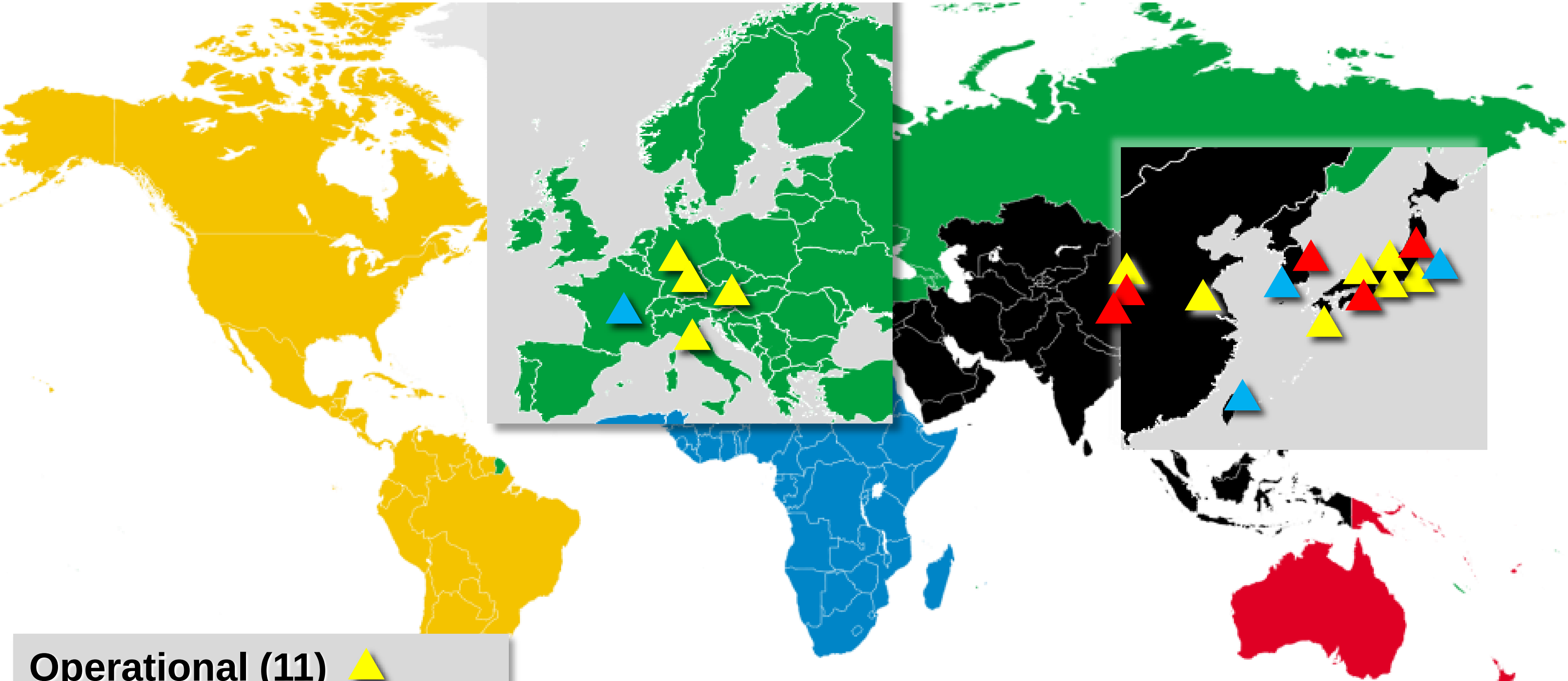
- ❑ **Heavy Ion Therapy**
    - ○ **The Most Advanced Technology**

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%)



World Wide Heavy Ion Therapy Centers



Operational (11)

Austria MedAustron, Wiener Neustadt
China Fudan Univ CC, Shanghai
China IMP-CAS, Lanzhou
Germany HIT, Heidelberg
Germany MIT, Marburg
Italy CNAO, Pavia
Japan HIMAC, Chiba
Japan HIBMC,Hyogo
Japan GHMC, Gunma
Japan SAGA-HIMAT, Tosu
Japan i-ROCK, Kanagawa

Under Construction(5)

China HITFiL, Lanzhou
China Another Center, Lanzhou
Japan, Osaka
Japan, Yamagata
South Korea KHIMA, Busan

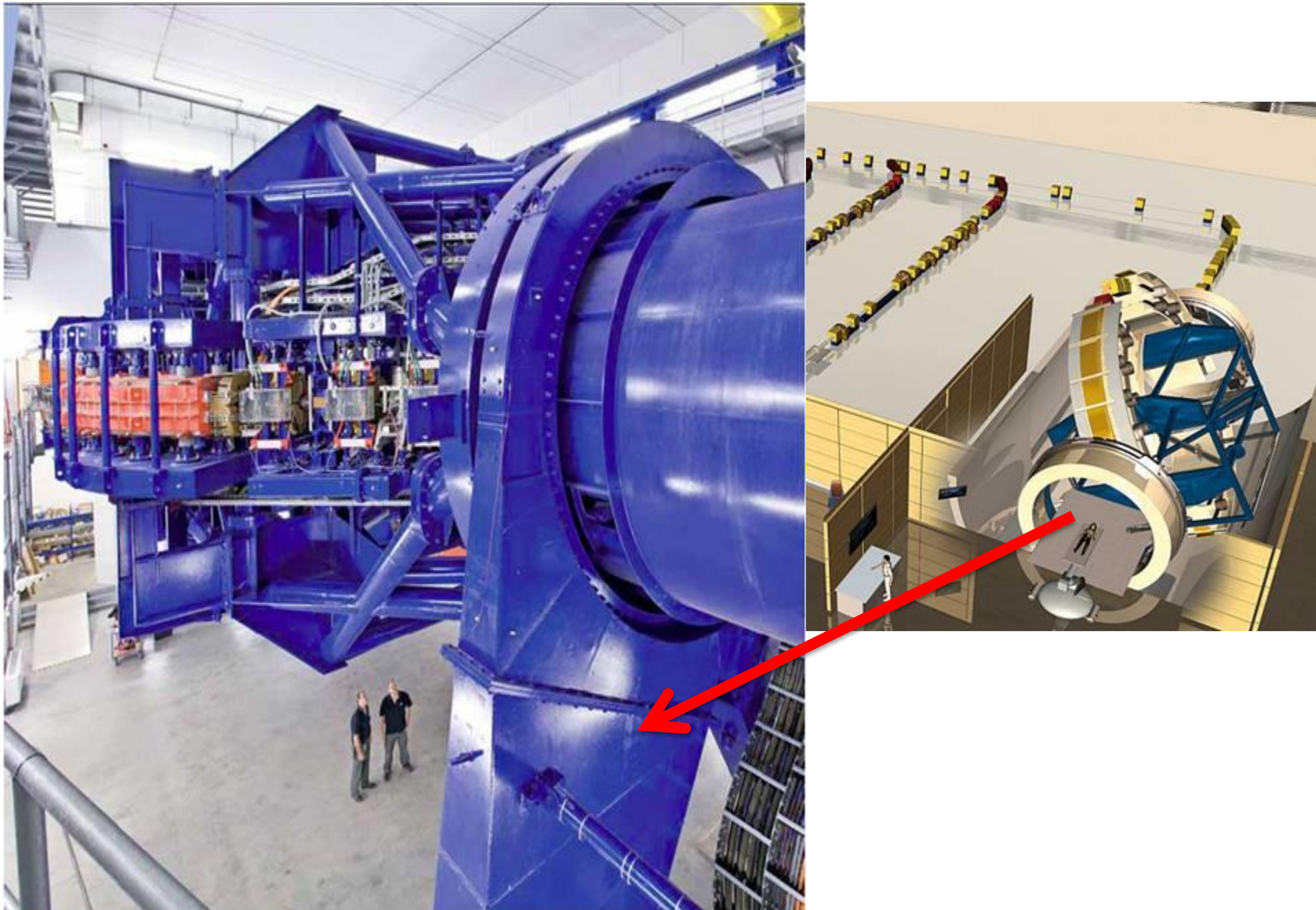
Advanced Planning(4)

Japan Okinawa
Taiwan, CMU
Taiwan, Taichung Univ
South Korea, Yonsei University

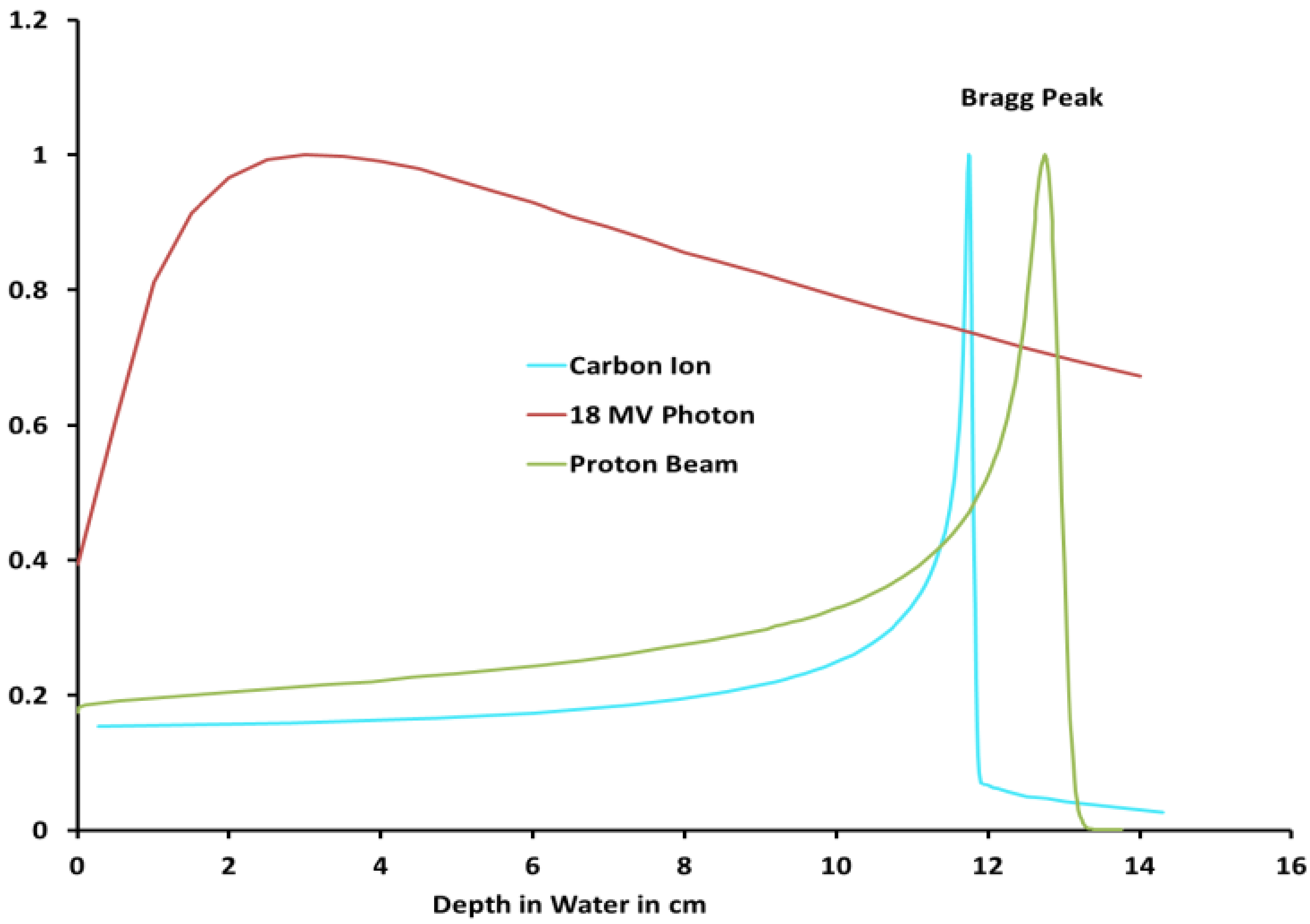
Total : 20

AP End of 2015

It’s the Biggest Radiation Therapy Machine



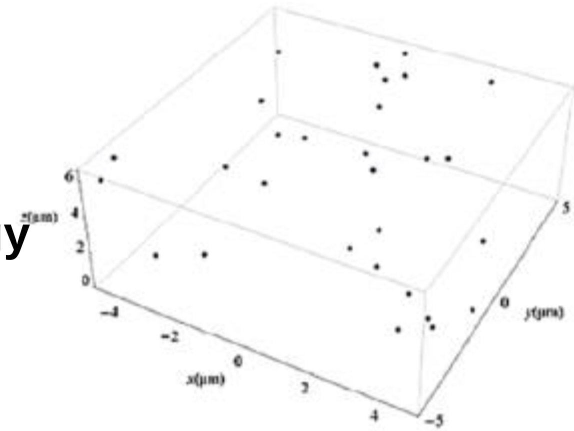
Perhaps, we can do better with Heavy Ion Therapy (Carbon) !



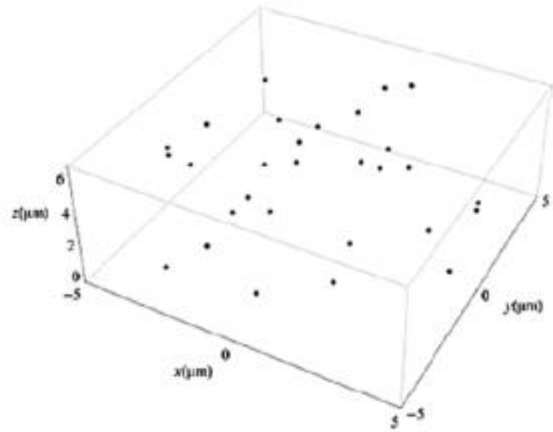
- Energy deposition patterns become more discrete

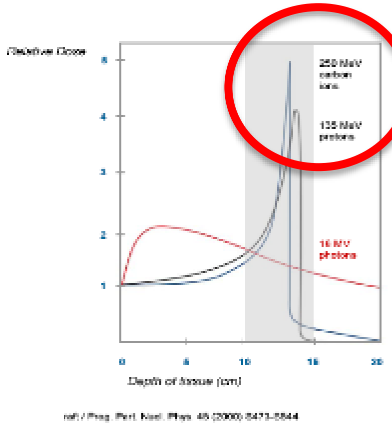
Scatter Energy Deposition

X-rays << 1 keV/um

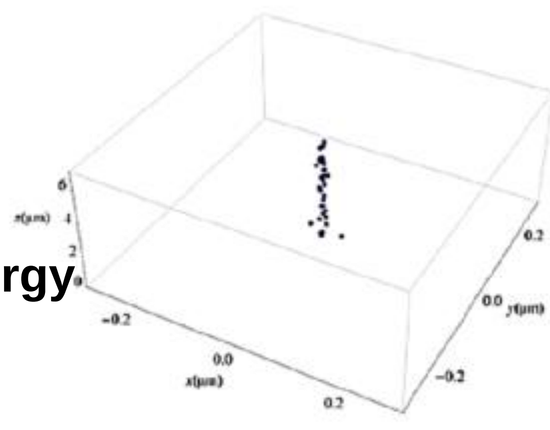


Protons @ 200 MeV, 20 keV/um

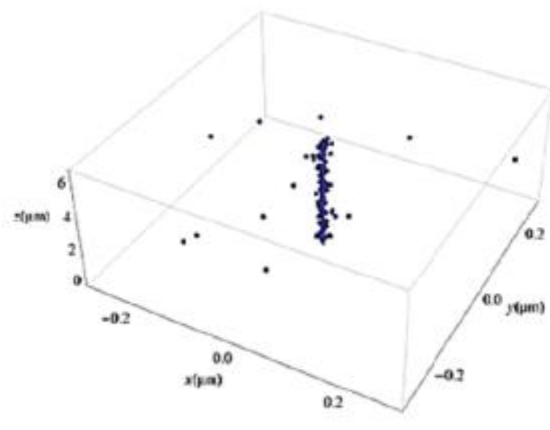


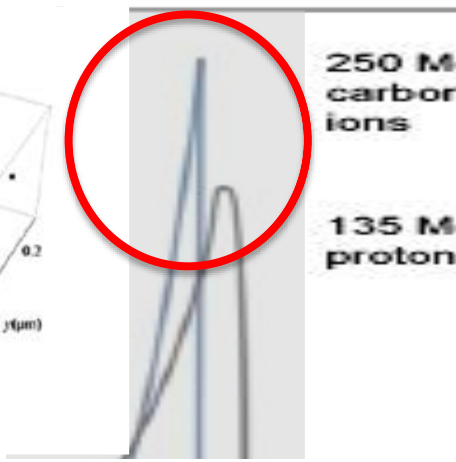


Carbon @ 390 MeV, 112 keV/um



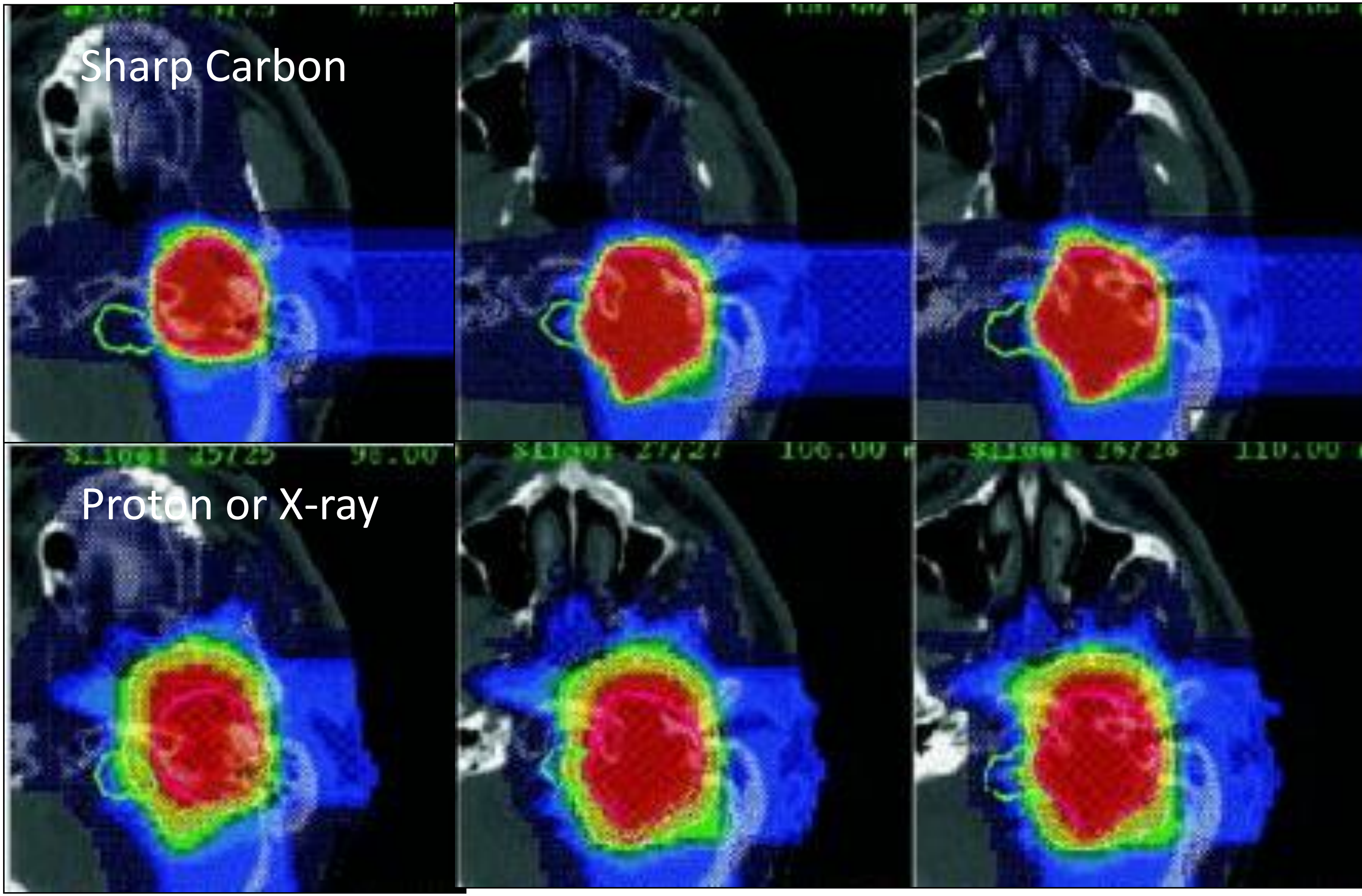
Oxygen @ 468 MeV, 175 keV/um





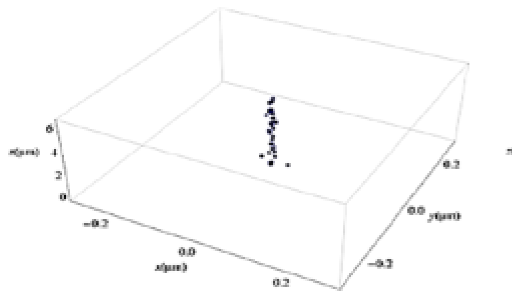
Discrete Energy Deposition

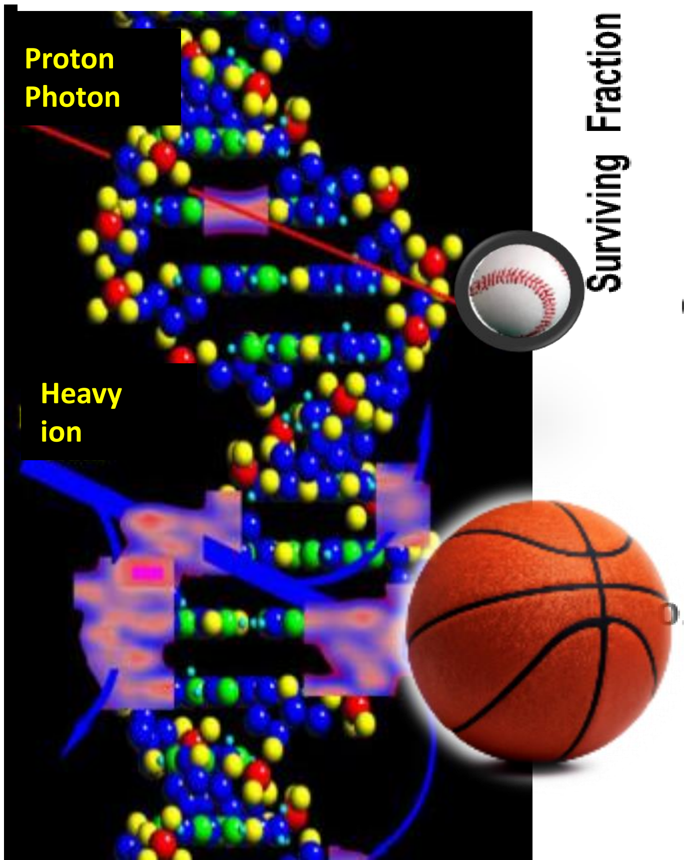
3) Heavy Ions – have very sharp edges

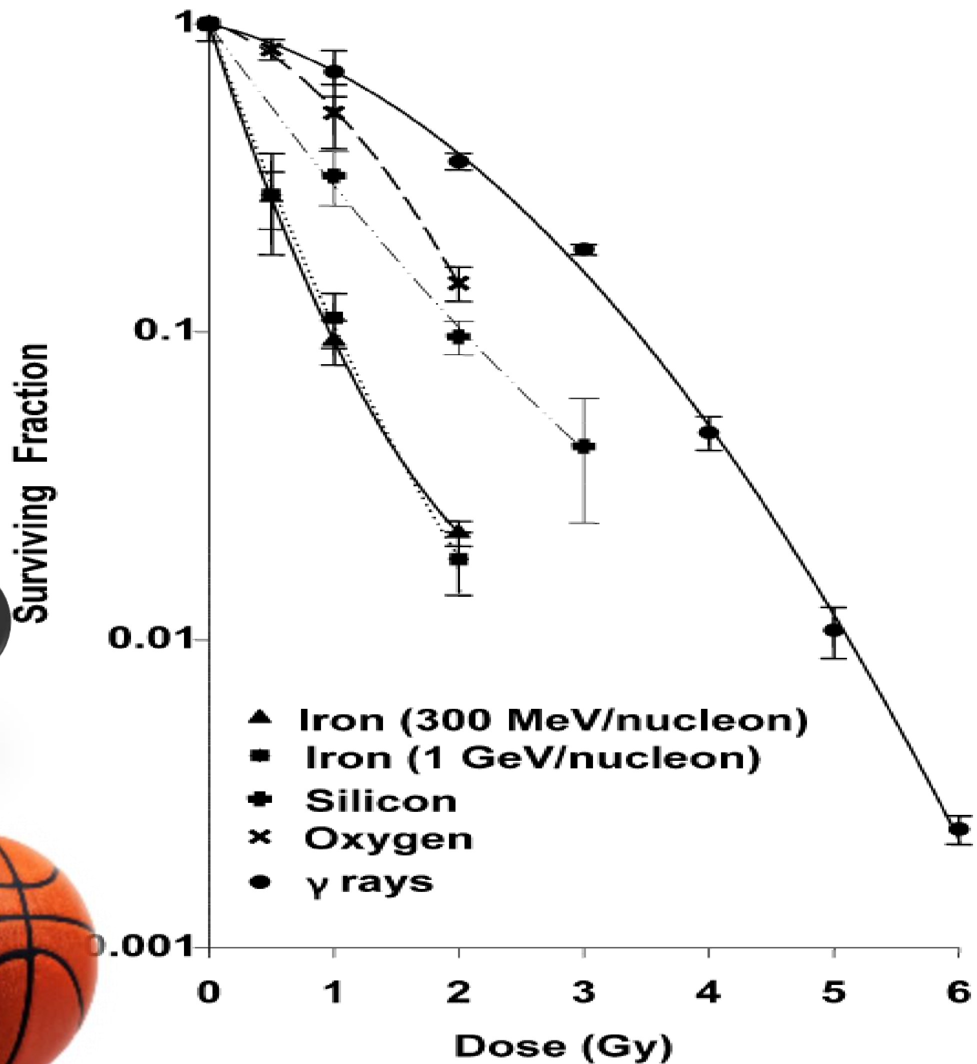


Discrete patterns of energy deposition result in clustered DNA damage and greater cell killing

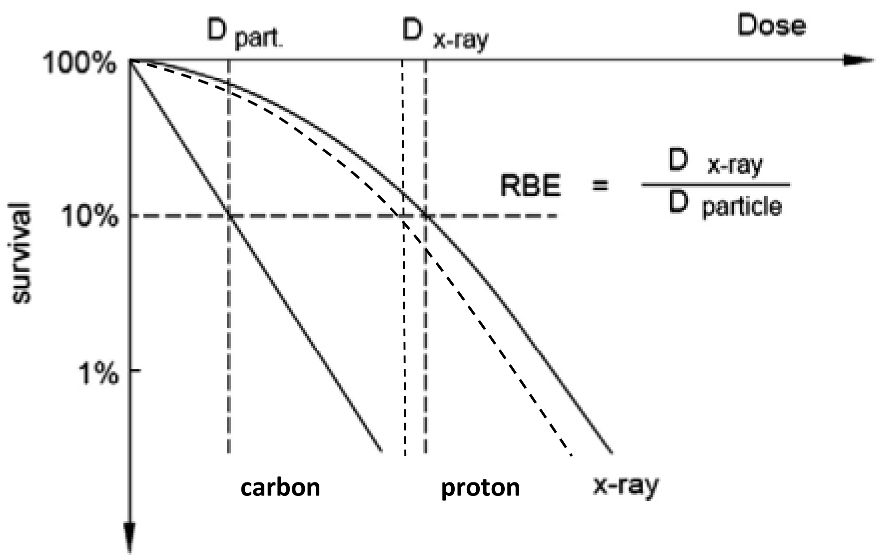
Carbon @ 390 MeV, 112 keV/um

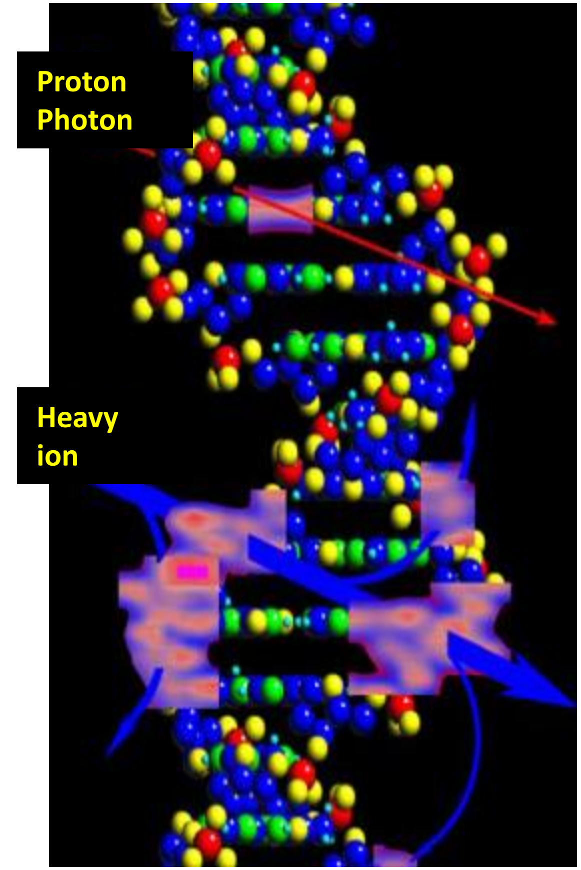




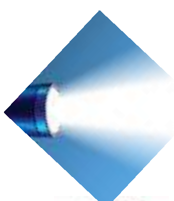


Enhanced cell killing described by Relative Biological Effectiveness





Common RBE values:

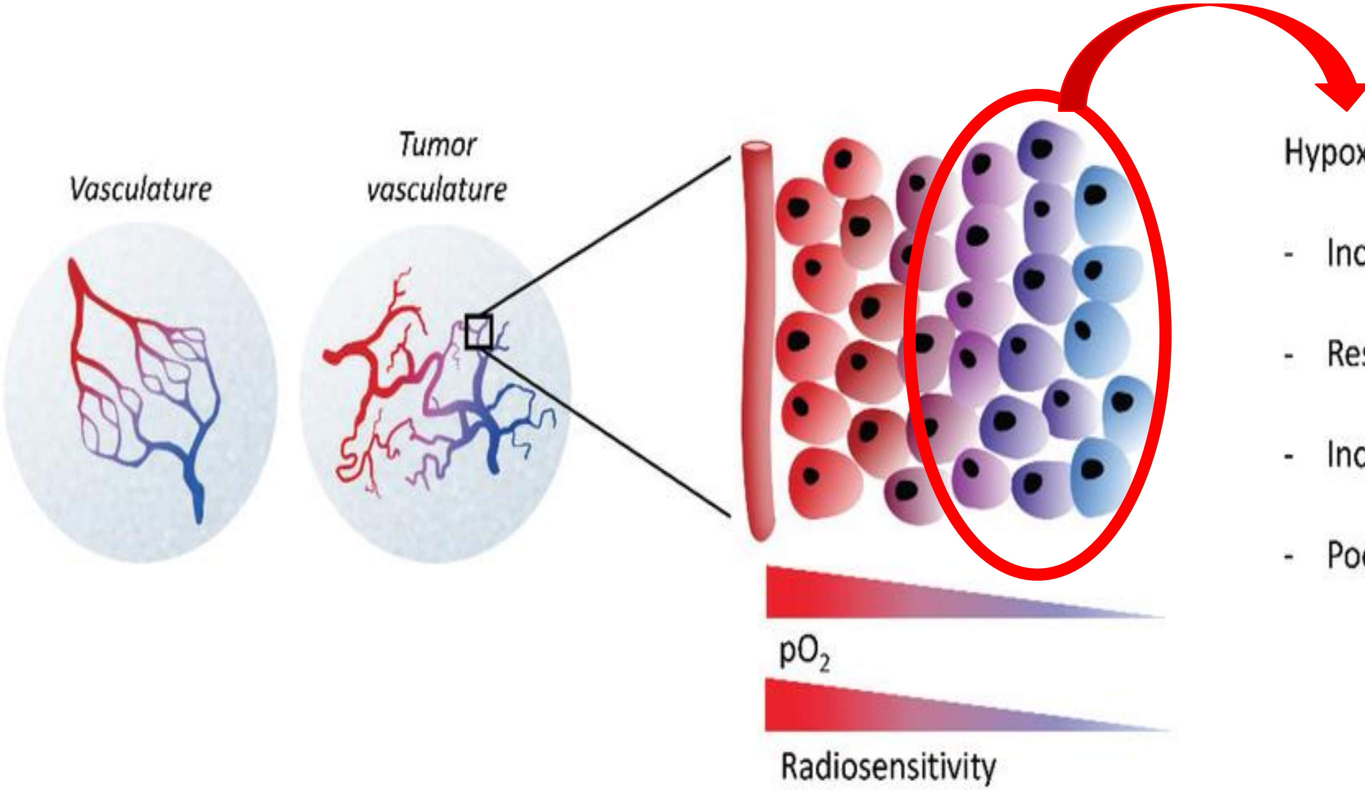


X-ray (reference) 1.0

Protons 1.0 – 1.4

Carbon 3 - 4

Heavy charged particles can overcome radioresistance due to hypoxia

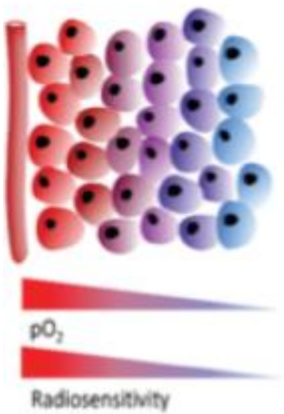


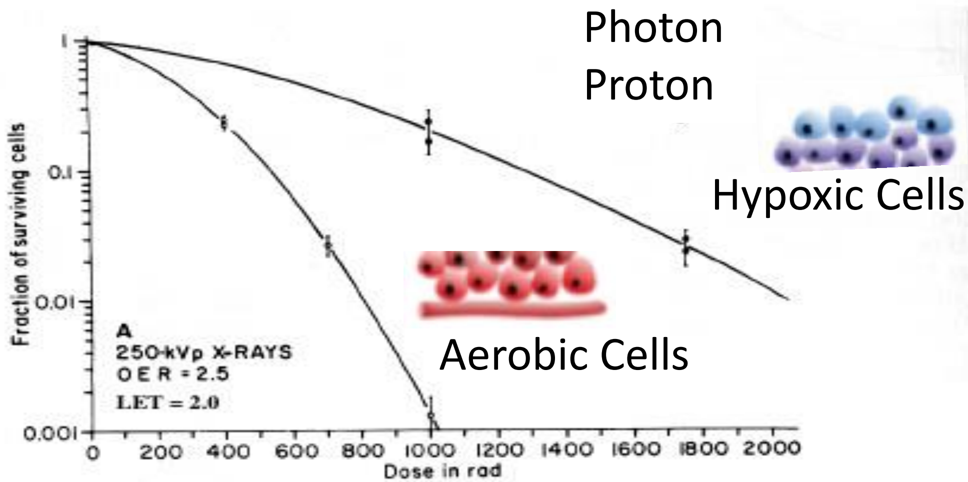
Hypoxic tumors show:

- Increased aggressiveness
- Resistance to therapy
- Increased metastasis
- Poor patient prognosis

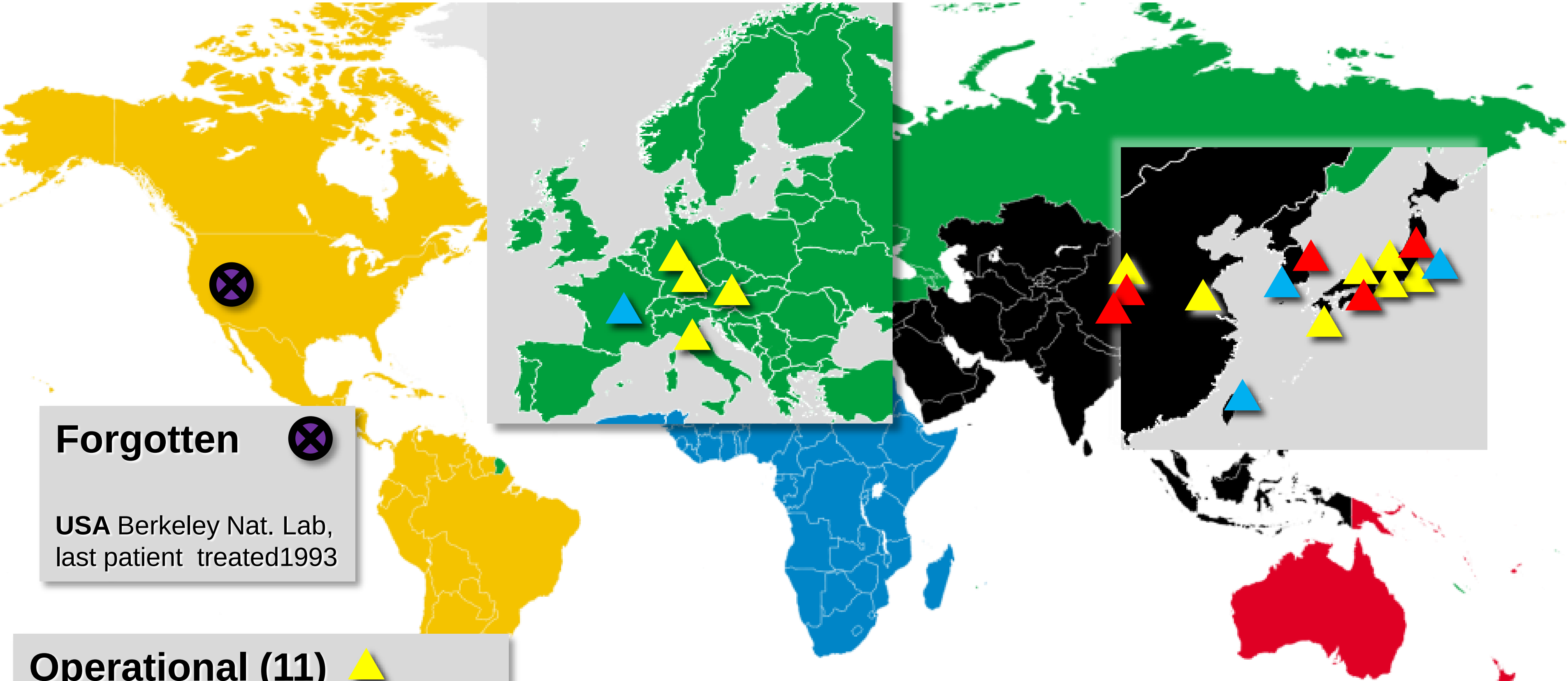
Heavy charged particles can overcome radioresistance due to hypoxia

2. Nature of Radiation





World Wide Heavy Ion Therapy Centers



Forgotten

USA Berkeley Nat. Lab,
last patient treated1993

Operational (11)

Austria MedAustron, Wiener Neustadt
China Fudan Univ CC, Shanghai
China IMP-CAS, Lanzhou
Germany HIT, Heidelberg
Germany MIT, Marburg
Italy CNAO, Pavia
Japan HIMAC, Chiba
Japan HIBMC,Hyogo
Japan GHMC, Gunma
Japan SAGA-HIMAT, Tosu
Japan i-ROCK, Kanagawa

Under Construction(5)

China HITFiL, Lanzhou
China Another Center, Lanzhou
Japan, Osaka
Japan, Yamagata
South Korea KHIMA, Busan

Advanced Planning(4)

Japan Okinawa
Taiwan, CMU
Taiwan, Taichung Univ
South Korea, Yonsei University

Total : 20

AP End of 2015

Ion Beam Initial clinical Trials at LBNL-UCSF, 1975–1992

Prof. Joseph Castro, UC San Francisco conducted the LBNL clinical trials in1975. Almost 3000 patients were treated until 1992.

Prof. T. Phillips

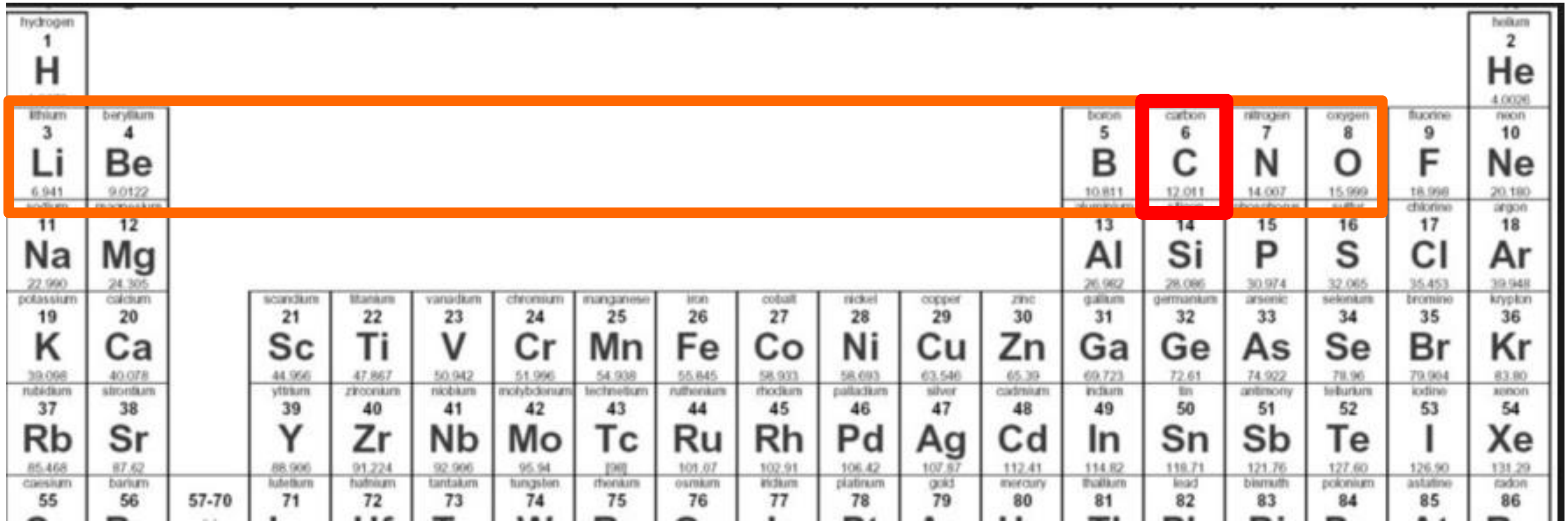
Prof. J. Quibby

Prof. G. Chen

Dr. E. Blakely

Heavy Ion Therapy at LBNL(1975~1992)

- **Heavier ions were the most effective in : salivary, bone & soft tissue, and bile duct tumors. slow growing tumors, hypoxic tumors.**
- **Optimal ion species for clinical use :**
  - **somewhere between lithium and oxygen, and <u>carbon ions might be the best.</u>**



Heavy Ion Therapy at LBNL(1975~1992)

- **Although many proposals for medical accelerator facilities were put forth by Berkeley Lab researchers and their colleagues in the late 1980s and early 1990s, a combination of economic and social factors prevented their realization.**

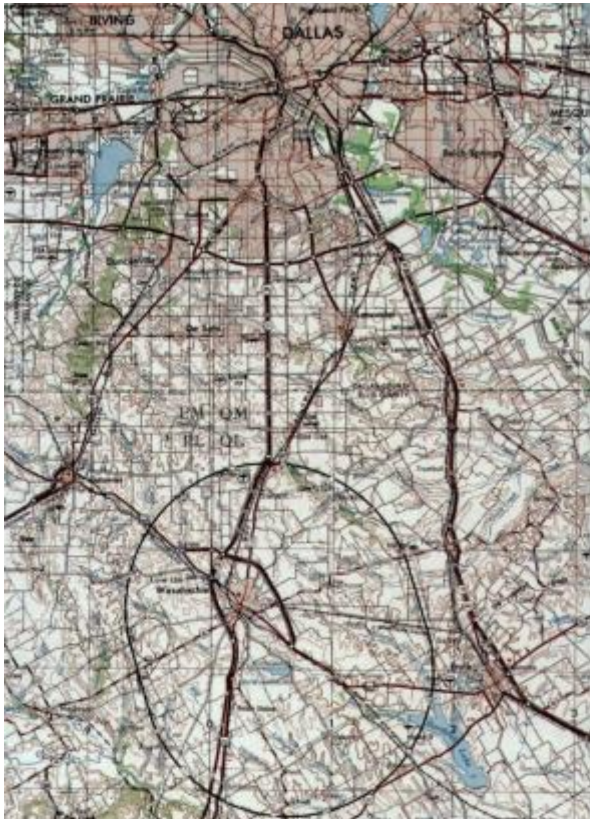
- **The world's first dedicated carbon-ion medical facility, although inspired by the work at Berkeley Lab, was not built in California but in Japan**

OCTOBER 21, 2013 | by TREVOR QUIRK | COMMENTS

How Texas Lost the World's Largest Super Collider

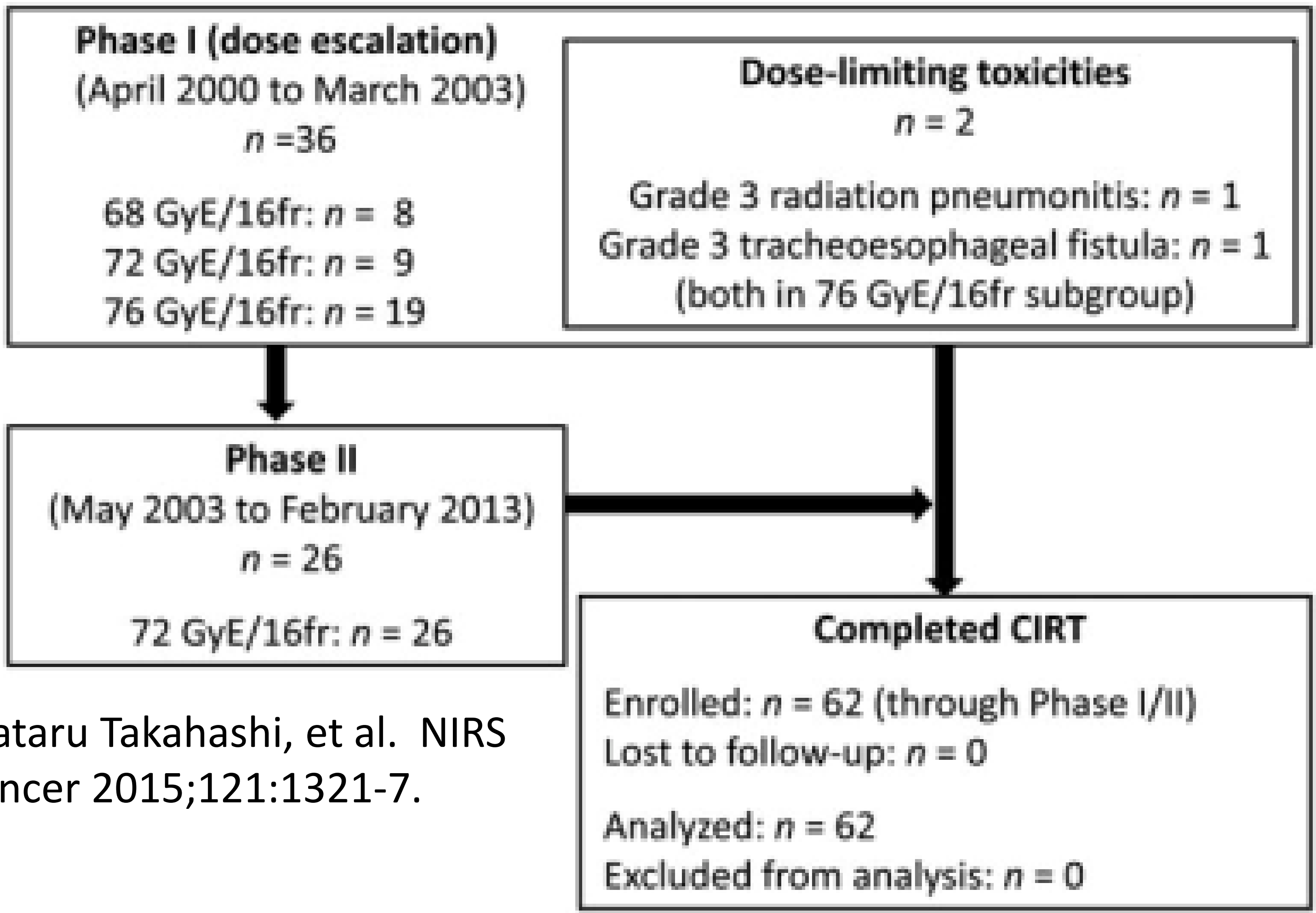
Magnablend, a chemical blending plant, bought the shell of the abandoned SSC last year.
PHOTOGRAPH BY WILL GRAHAM

Texas Super Collider Project (Waxahachie)



- The projected cost of construction:$6 billion
- 16,000 acres
- 52 miles in circumference
- Annual operating budget $600 M
- By the summer of 1993, $2 billion and 12 miles tunnel and Congress decided to stop funding the project.

A Prospective Nonrandomized Phase I/II Study of Carbon Ion Radiotherapy in a Favorable Subset of Locally Advanced Non–Small Cell Lung Cancer (NSCLC)



Wataru Takahashi, et al. NIRS
Cancer 2015;121:1321-7.

A Prospective Nonrandomized Phase I/II Study of Carbon Ion Radiotherapy in a Favorable Subset of Locally Advanced Non–Small Cell Lung Cancer (NSCLC)

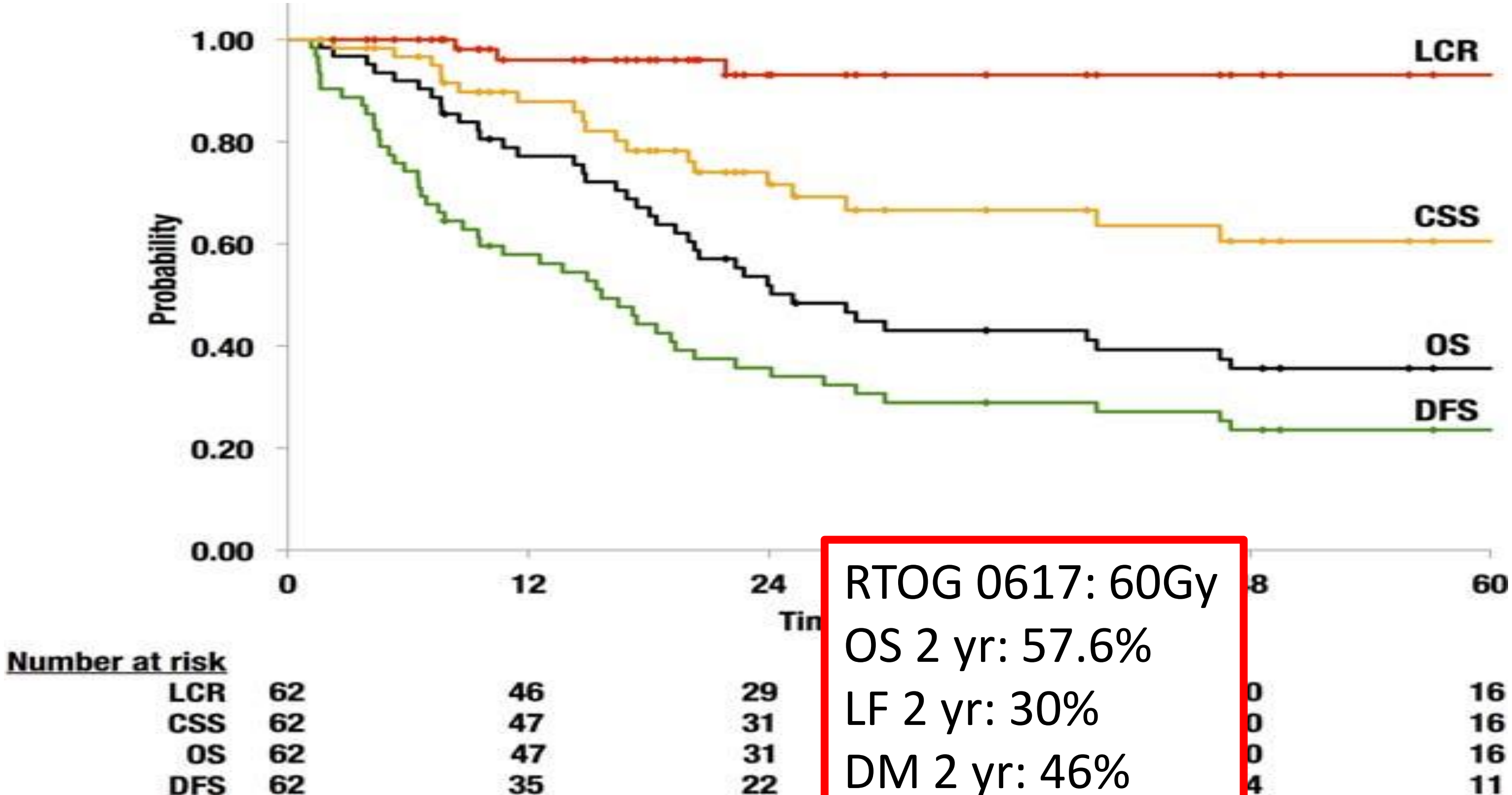


Figure 3. Overall survival (OS), local control rate (LCR), disease-free survival (DFS), and cause-specific survival (CSS) rates in 62 patients with locally advanced non–small cell lung cancer. The 2-year OS, LCR, DFS, and CSS were 51.9%, 93.1%, 35.7%, and 71.7%, respectively.

Wataru Takahashi, et al. NIRS Cancer 2015;121:1321-7.

TABLE 3. Pattern of First Recurrence Sites in 62 Patients

Pattern	n (%)
Local failure (+)	
Local only	0 (0)
+ Distant metastases	2 (3.2)
+ Lymph node[a] + dstant metastases	1 (1.6)
Local failure (-)	
Lymph node	2 (3.2)
Distant metastases	18 (29.0)
Lymph node[b] + distant metastases	5 (8.1)

Wataru Takahashi, et al. NIRS Cancer 2015;121:1321-7.

Review Article

Carbon Ion The,rapy for Early-Stage Non-Small-Cell Lung Cancer

Yusuke Demizu et al.

BioMed Research International
Volume 2014, Article ID 727962, 9 pages

Table 2: Studies of carbon ion therapy for early-stage non-small-cell lung cancer.

Author	Institute	Year	Number of patients	Age (years)	Number of lesions	T1	T2	Total dose [Gy (RBE)]	Number of fractions	Median FU (months)	Local control	Overall survival	Toxicity (≥grade 3)
Miyamoto et al. [21]	NIRS	2003	81	Mean 72	82	41	41	59.4–95.4	9–18	52.6	76% (5-yr)	42% (5-yr)	Lung 3.7%
Miyamoto et al. [22]	NIRS	2007	50	Mean 74.1	51	30	21	72	9	59.2	94.7% (5-yr)	50.0% (5-yr)	Skin 2%
Miyamoto et al. [23]	NIRS	2007	79	Mean 74.8	80	42	37	52.8–60	4	38.6	90% (5-yr)	45% (5-yr)	0%
Sugane et al. [24]	NIRS	2009	28	Mean 82*	29	12	17	52.8–72	4–9	NA	95.8% (5-yr)	30.7% (5-yr)	0%
Takahashi et al. [25]	NIRS	2014	151	Mean 73.9	151	91	60	36–50	1	45.6	79.2% (5-yr)	55.1% (5-yr)	0%
Iwata et al. [17]	HIBMC	2010	23	Median 75	23	15	8	52.8	4	30.5†	86% (3-yr)	86% (3-yr)	0%
Iwata et al. [19]	HIBMC	2013	27	Median 75‡	27	0	27	52.8–68.4	4–10	44†	75% (4-yr)§	55% (4-yr)§	Lung 7%, skin 7%‖
Fujii et al. [20]	HIBMC	2013	41	Median 76	41	26	15	52.8–70.2	4–26	39	78% (3-yr)	76% (3-yr)	Lung 5%, skin 4%

Gy: gray; RBE: relative biological effectiveness; FU: follow-up; NIRS: the National Institute of Radiological Sciences; yr: year; NA: not available; HIBMC: Hyogo Ion Beam Medical Center.

International Symposium on Ion Therapy

Emphasis on the "Heavy Ion"

2014

1st International Symposium on Ion Therapy

2015

2[nd] International Symposium on Ion Therapy

http://www.iwptr.org

2016: Nov 3/4th

3rd International Symposium on Ion Therapy

"Even if you're on the right track, you'll get run over if you just sit there"

Will Rogers