Rationale For, and Advances in Clinical Charged Particle Therapy

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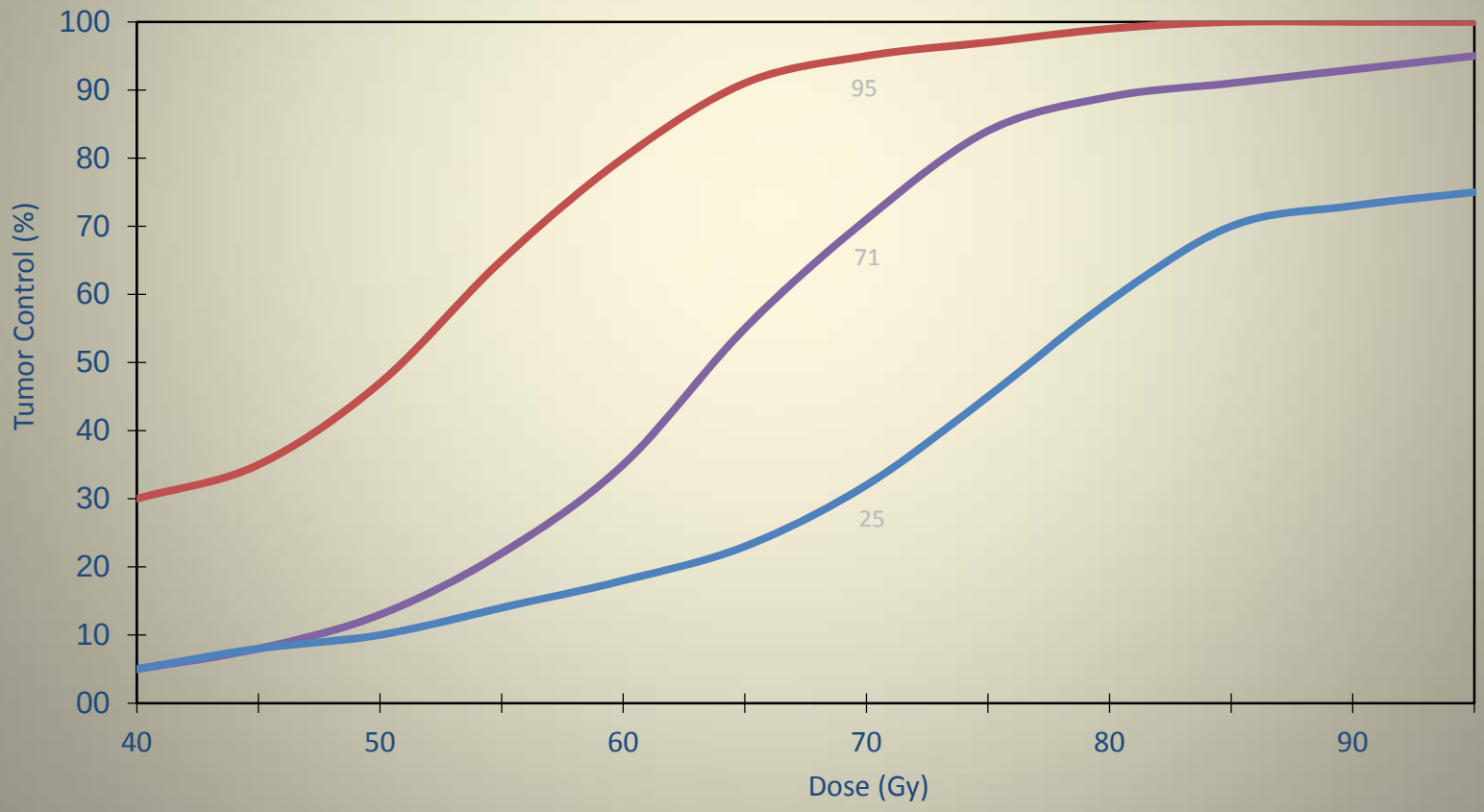
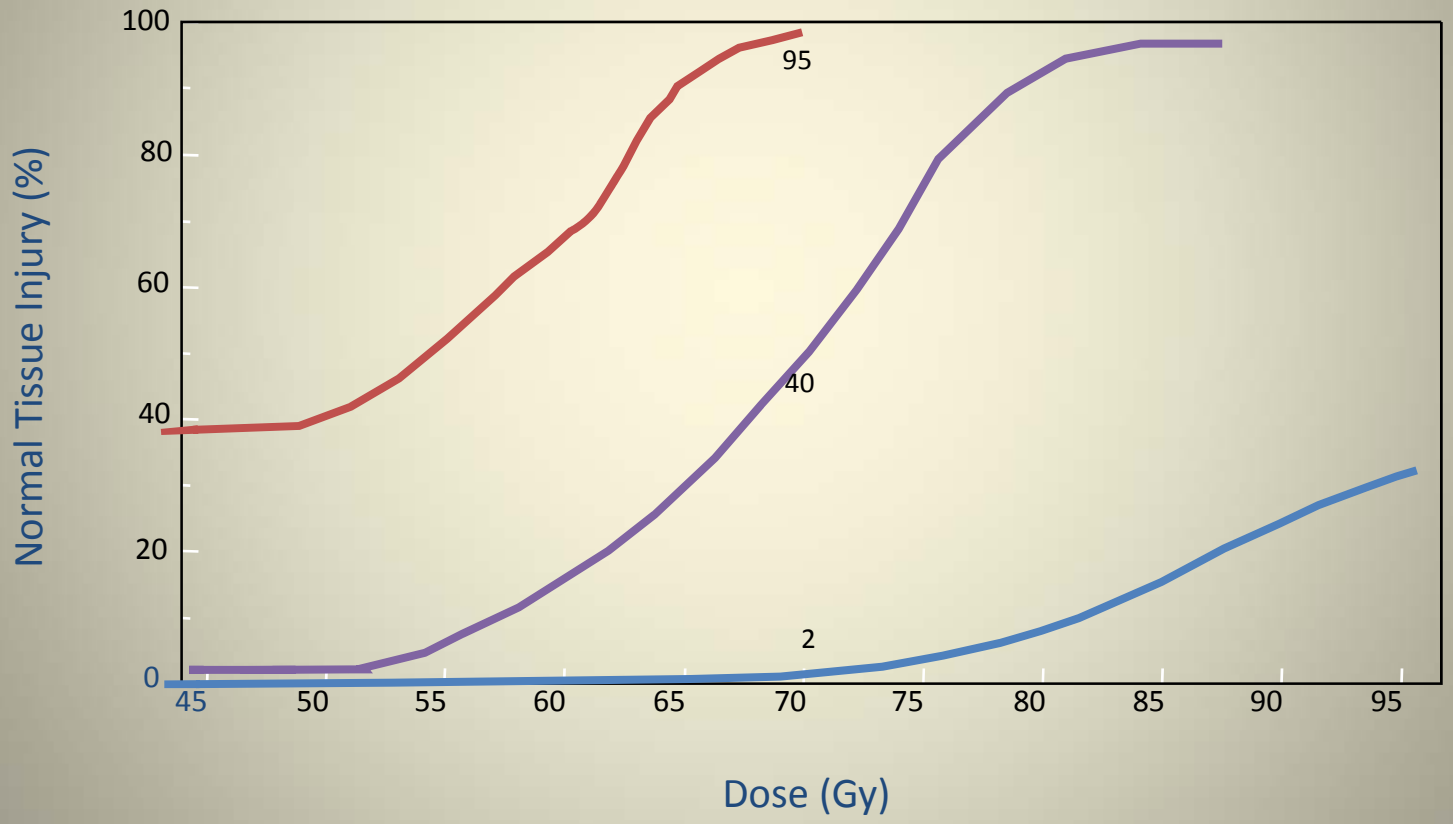
Evolving Role of Radiation in Cancer Treatment

- First utilized in 1896 for cancer therapy
- Improvements in equipment and delivery capabilities over the last 50 years led to radiation therapy being one of the most effective curative treatments for local / regional cancer
- The increase in cancer cures with radiation over the last century are directly related to:
    - the ability to target and deliver higher doses to the tumor while
    - reducing the damage to surrounding normal tissues

Radiation Sensitivity
Tumor



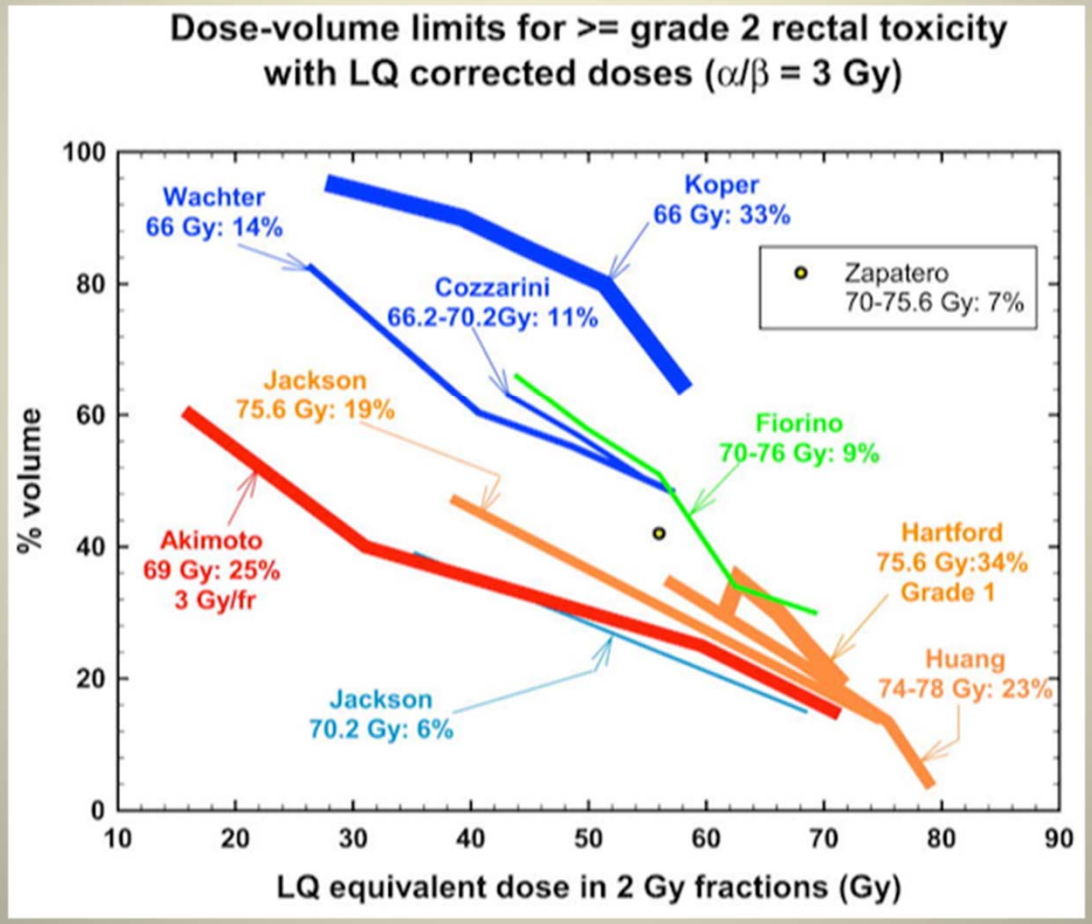
Radiation Sensitivity
Normal Tissue Dose Effect



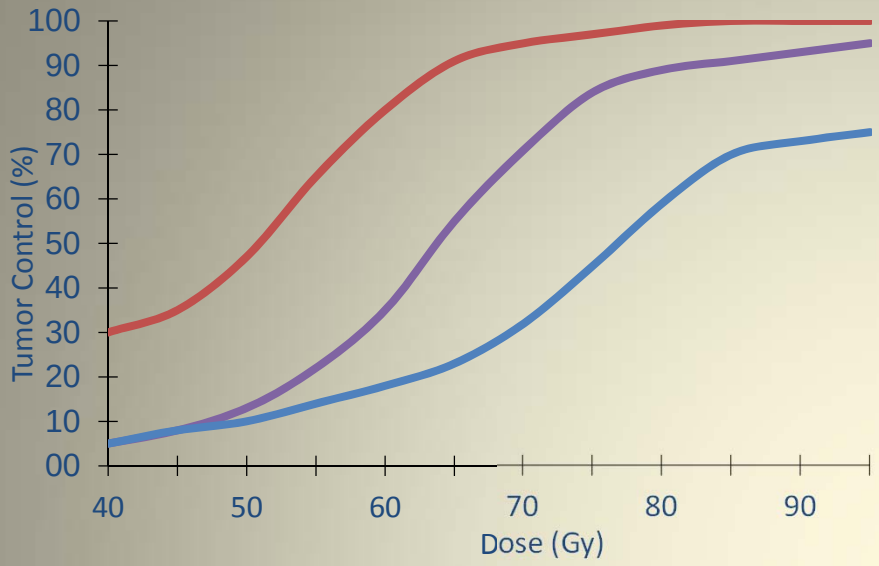
Modifiers of Therapeutic Ratio

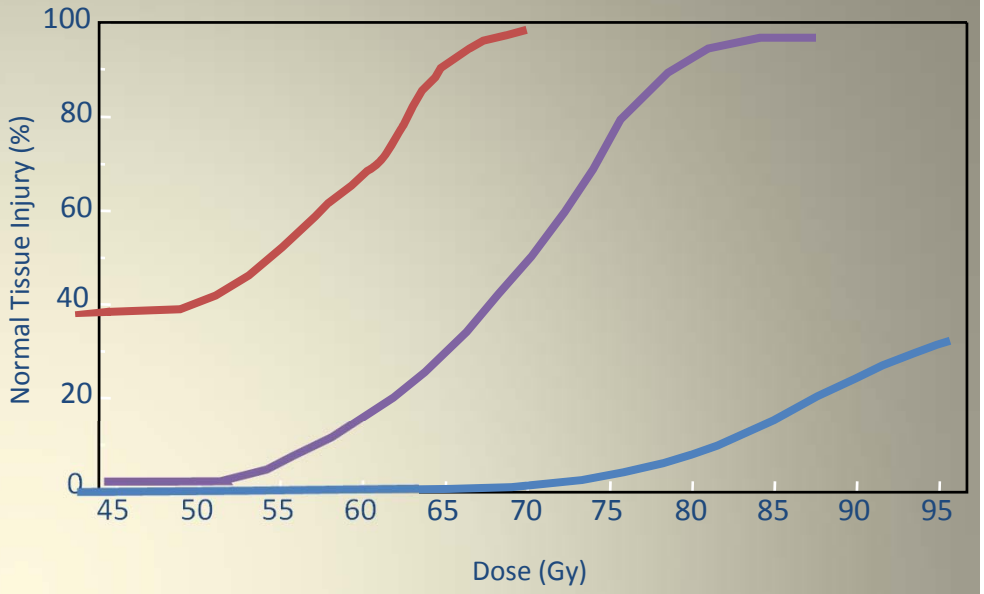
- Radiation Sensitizers
- Radiation Protectors
- Fractionation
- Volume of normal tissue

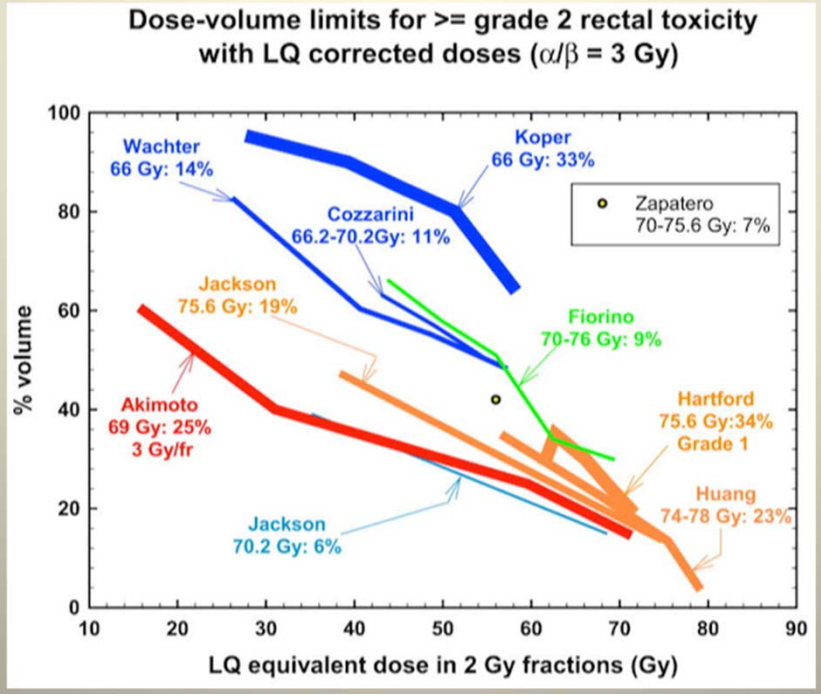
Radiation Sensitivity
Normal Tissue Volume Effect



Michalski et al. IJROBP 3:2010


Tumor Control (%)
100
90
80
70
60
50
40
30
20
10
00
40
50
60
70
80
90
Dose (Gy)


Normal Tissue Injury (%)
100
80
60
40
20
0
45
50
55
60
65
70
75
80
85
90
95
Dose (Gy)


Dose-volume limits for >= grade 2 rectal toxicity
with LQ corrected doses (α/β = 3 Gy)
% volume
LQ equivalent dose in 2 Gy fractions (Gy)
Wachter
66 Gy: 14%
Koper
66 Gy: 33%
Cozzarini
66.2-70.2Gy: 11%
Zapatero
70-75.6 Gy: 7%
Jackson
75.6 Gy: 19%
Fiorino
70-76 Gy: 9%
Akimoto
69 Gy: 25%
3 Gy/fr
Hartford
75.6 Gy:34%
Grade 1
Huang
74-78 Gy: 23%
Jackson
70.2 Gy: 6%

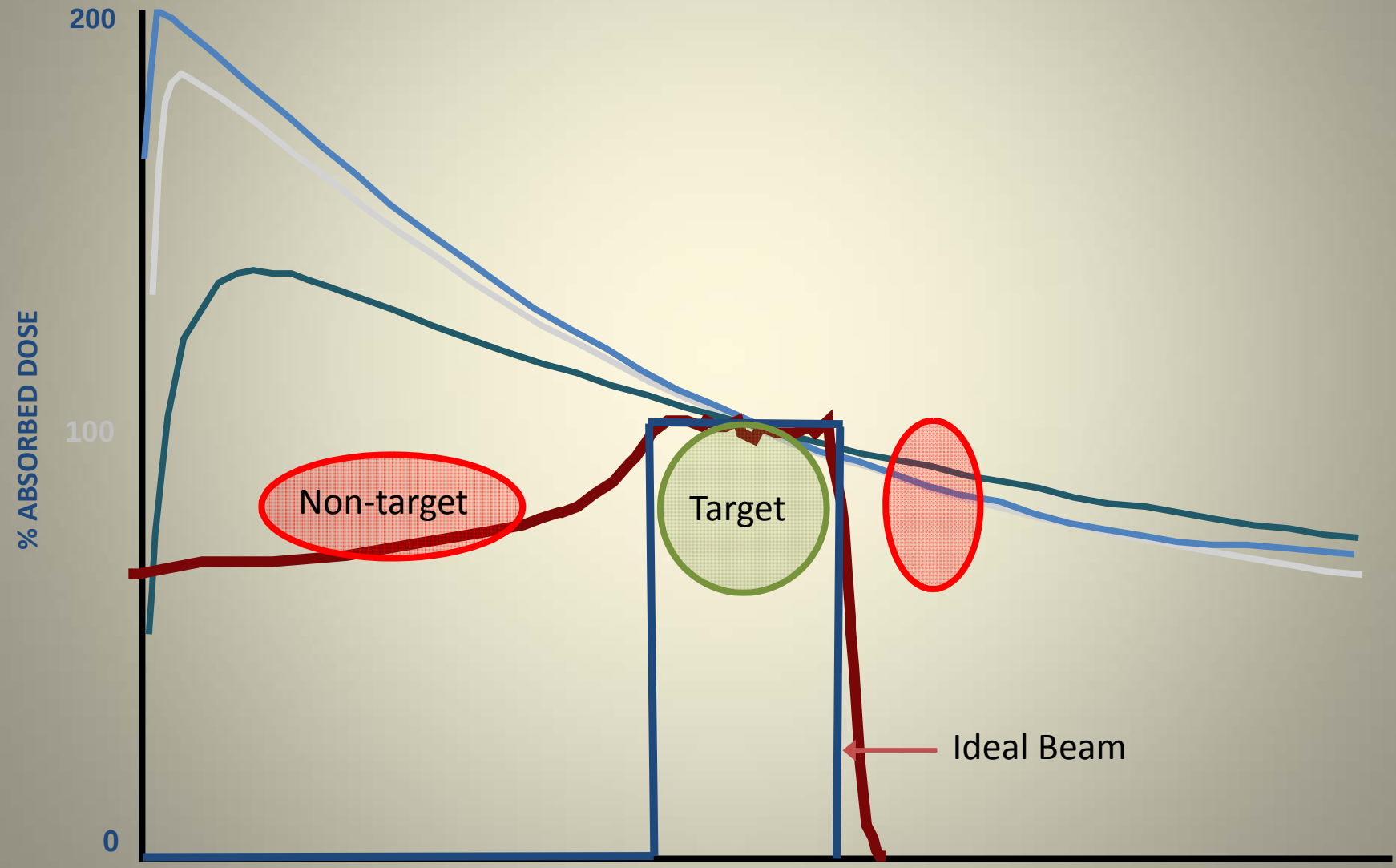
Types of Radiation Used Clinically

- Photons (x-rays and gamma rays)
- Particles (subatomic)

Why Particle Therapy?

- Fundamental principles of radiation delivery have not changed despite technical changes
  - The primary goal of radiation oncology has always been to hit the target and eliminate radiation to non-target tissues
  - There is no known threshold dose *below* which radiation becomes potentially harmless
- Brachytherapy – early 1900's
- Ortho-Megavoltage x-rays – 1930's
- Particle Therapy – 1950's

Fundamental Tools of Radiation Oncology



TCP and NTCP

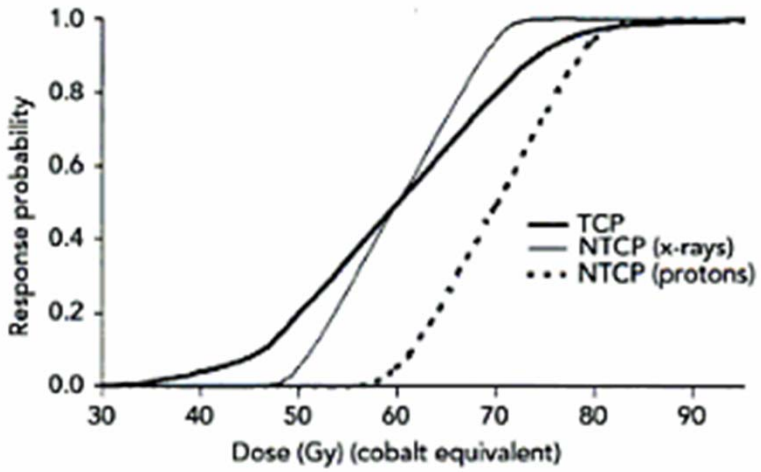


Figure 1.5 Dose–response curves for tumor control probability (TCP) (thick solid line) and for normal tissue complication probability (NTCP) (a thin solid line for large volume treatment and a dotted line for a reduced volume of irradiated normal tissues.)

Suit and Chu 2008
From Delaney and Kooy eds.

Evolution of Radiation Delivery

- Within each modality, radiation biology and physics have found ways to improve delivery over time
- Brachytherapy
  - Surface, intracavitary, interstitial, low and high dose rate
- Megavoltage
  - High energy, 3D conformal, IMRT etc
- Charged particles
  - 3D planning, ‘IGRT’, match, patch, and stack Bragg peaks, IMPT etc

Particles

- The controllability of particles depends primarily on 3 factors
  - Stability
  - Mass
  - Charge
    - Electrons
    - Protons
    - Neutrons
    - Heavy Ions
    - Pi Mesons

Selecting The Optimum Radiation Type

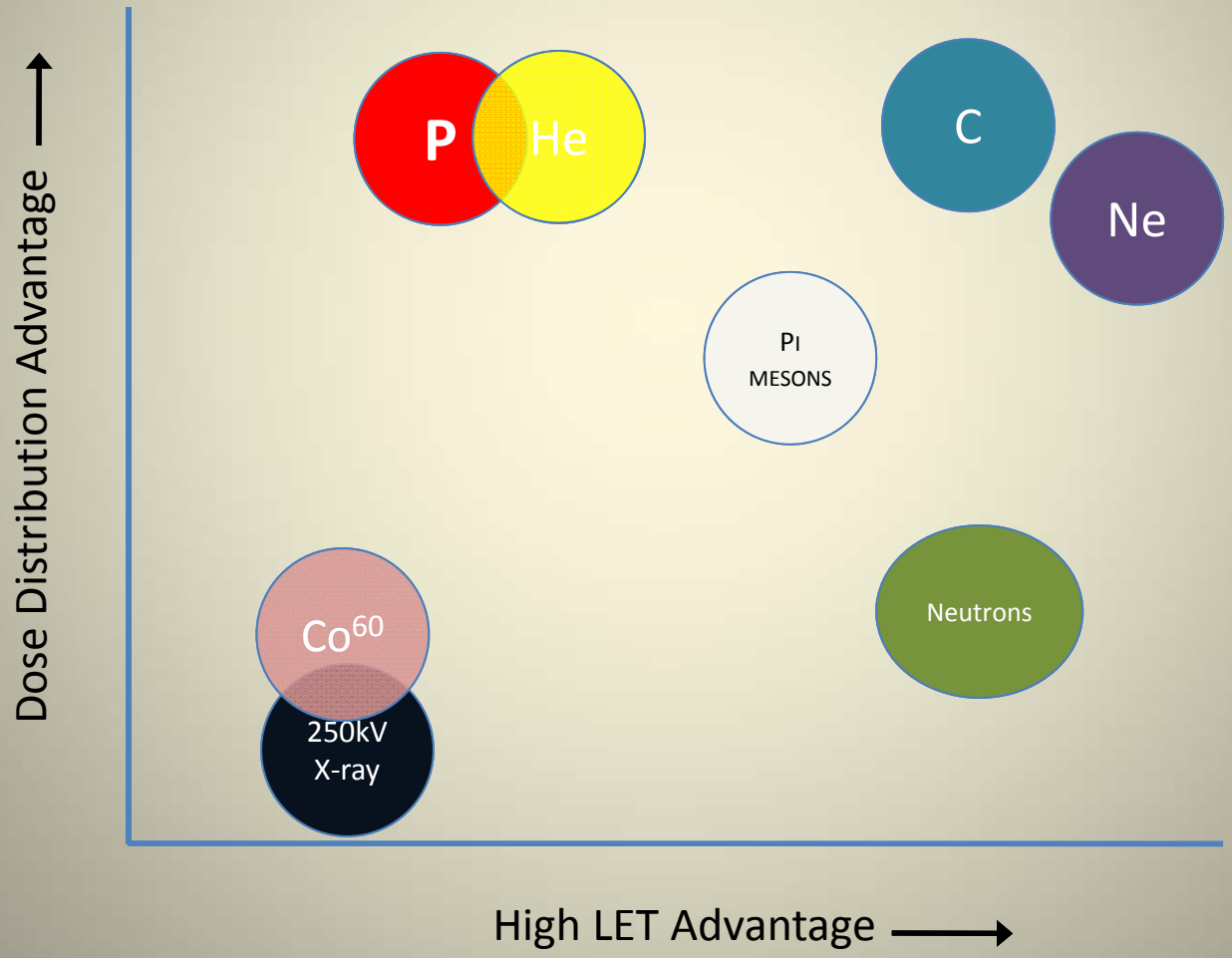
- Controllability of radiation beam
- Biologic effect
- Cost of delivery

- Is there an ideal beam?

Advances in Oncology

- Imaging becomes more important as precision of hitting target increases
- Advances in imaging
  - CT
  - MRI
  - PET
- Accelerators / Computers
- Treatment Planning
- Treatment Delivery
- Sensitizers

Relative Advantage of Particles



Raju et al. 1974

Particle Therapy

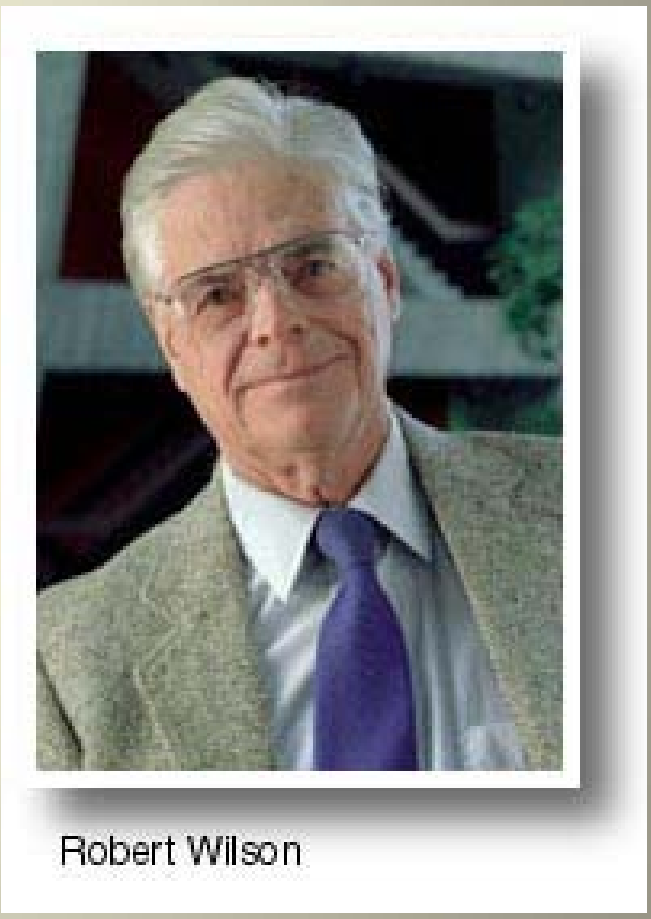
- Neutrons
  - Multiple facilities built in 1980's
  - High toxicity vs tumor control
  - Uncertainty of RBE for different normal tissues

Developmental Process of Particle Therapy Protons

- Theoretical Scientific Rationale
- Scientific Validation
  - 1950's – 1980's
- Technical and Operational, and Clinical Validation
  - 1990's – present

Scientific Rationale: Protons 1940's

- 1946 Robert R. Wilson, PhD proposed protons in the treatment of cancer

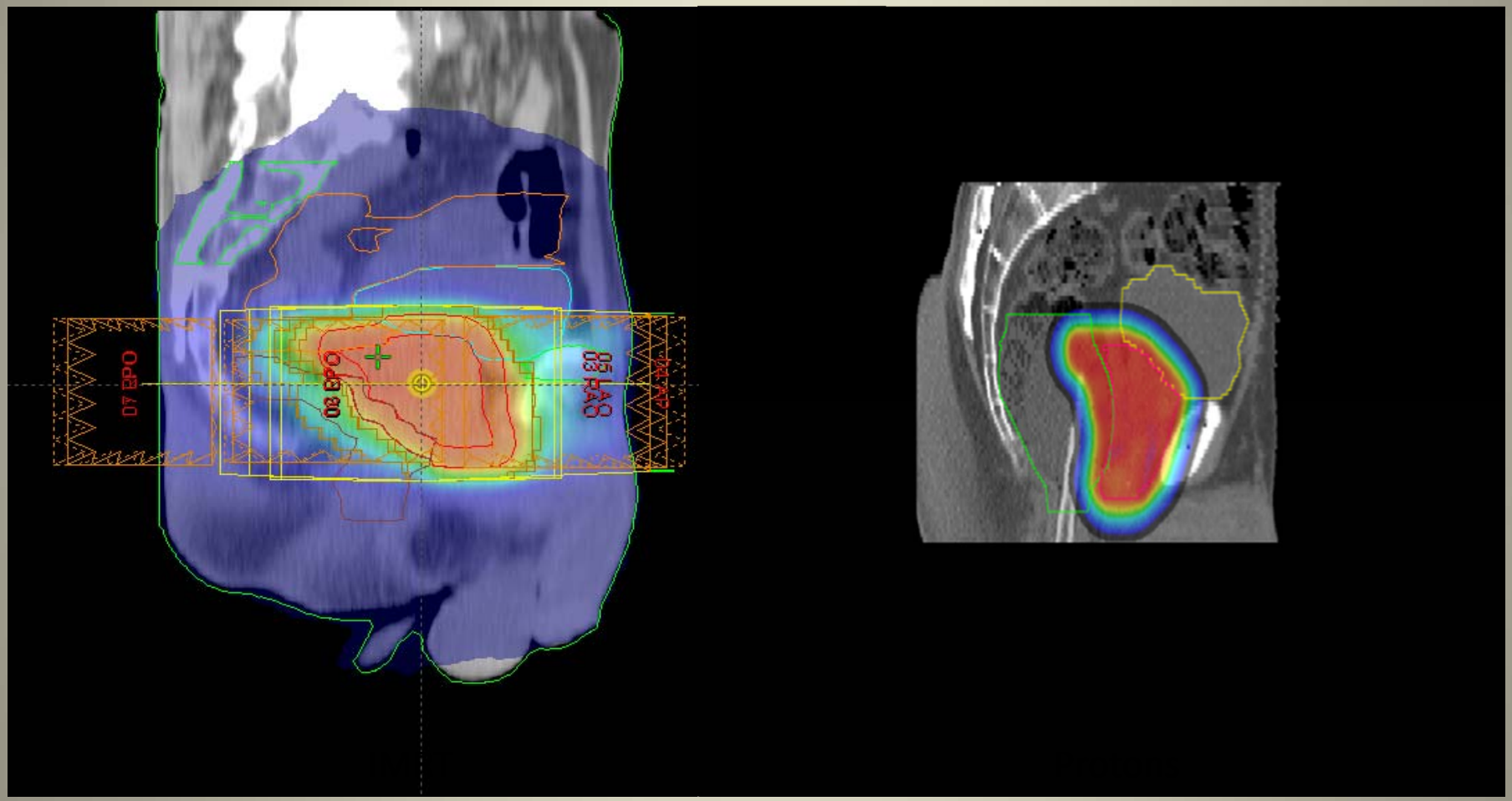


Robert Wilson

Scientific Rationale: Protons

- Experimental data obtained in the 1950's demonstrated that the RBE of SOBP protons as compared to Co^{60} is approximately 1.1.
- Low proton RBE = ease of use in clinical situations - if you can give the dose with x-rays, you can safely do so with protons.
- The physical and biologic basis of protons

Integral Dose



Era of Scientific Validation

- The physical and biologic basis of protons appeared to make for a modality to investigate for clinical use

- The next natural step was to try and validate the theoretical ideas

Proton Development 1950's Berkeley, USA

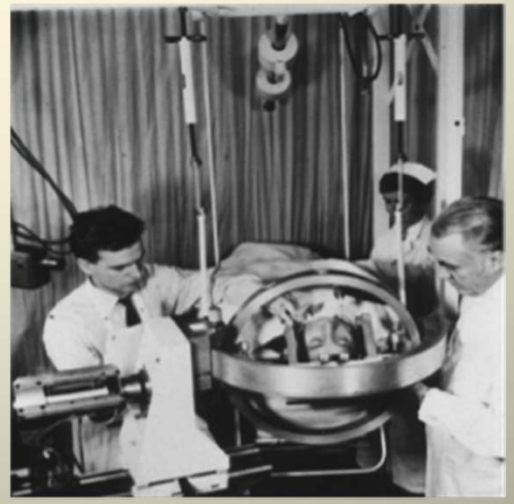
- Drs. Lawrence and Tobias
- 1954-1957
- 30 patients with protons to the pituitary

- Helium and heavy ion program began in 1957 – 1993
  - Drs. Castro and team
- Radiosurgery program
  - Drs. Fabrikant and team

Proton Development 1950's
Uppsala, Sweden

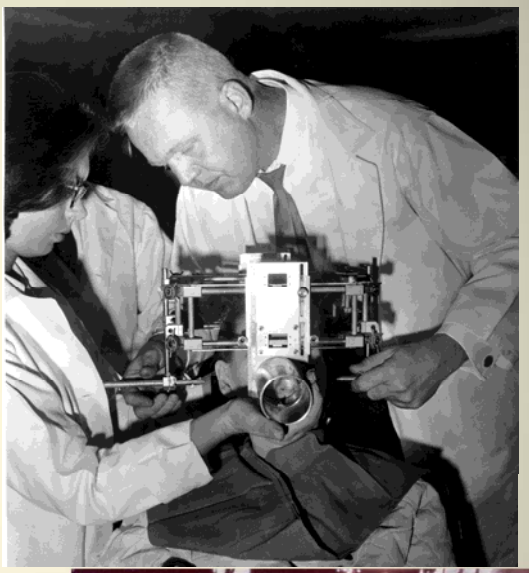
- First patient 1957 for large malignant tumor of pelvis

- Radiosurgery program began in 1958 with Drs. Leksell and Larsson

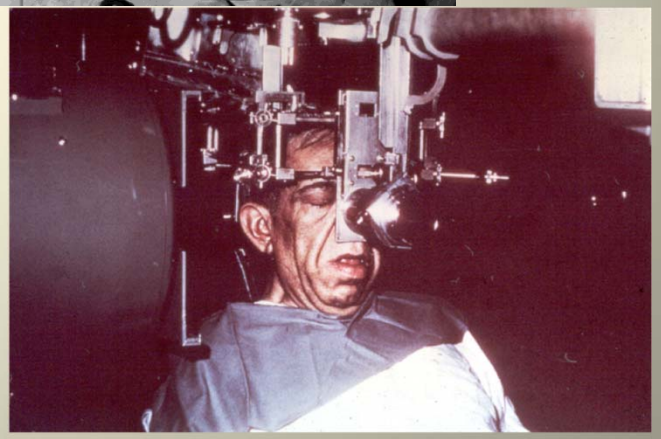


Proton Development 1960's

- 1961 radiosurgery program at MGH/HCL with Dr. Kjellberg
  - NEJM 278:732, 1968
  - NEJM 309:269, 1983



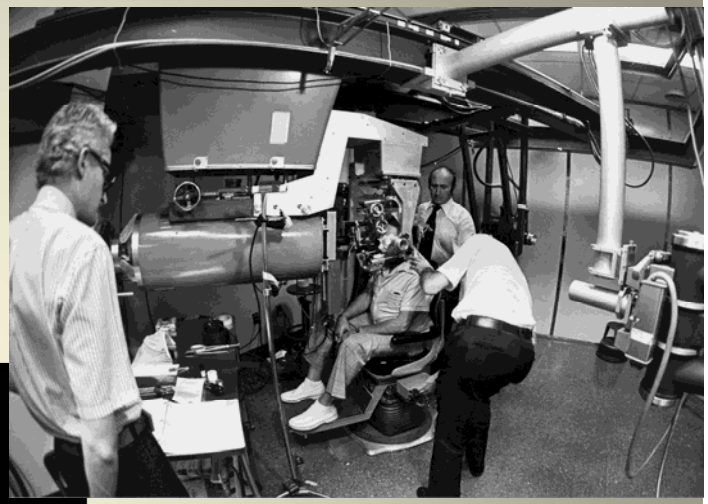
- 1967 proton began in Dubna, Russia
  - Program ran through 1996 with 124 pts
- ITEP in Moscow, Russia began treating in 1969
  - completed 4162 patients through 7/09

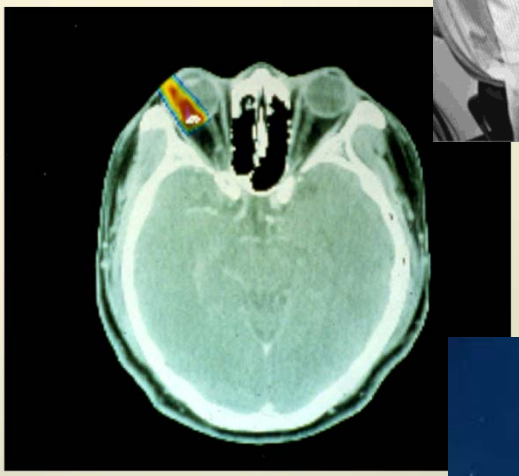


Proton Development 1970's

- Development of ocular melanoma treatments at MGH/HCL
  - Dr. Gragoudas and team
  - Dr. Koehler and team

- 1006 patients treated at MGH/HCL: 1975-1986
  - 96% of patients had tumor controlled in the eye at 5 years*
  - Overall, 89% retained eye, including 97% of small lesions+
  - Greater than 50% of patients retain vision better than 20/100^

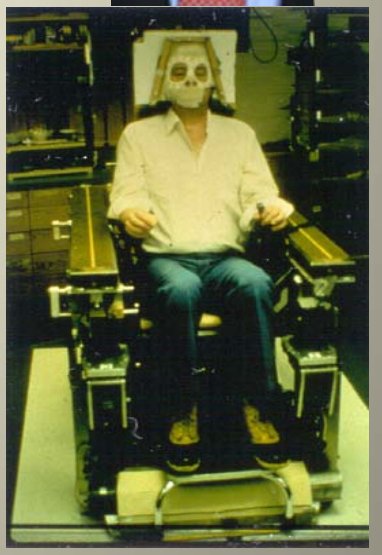




*Munzenrider et al. IJROBP. 17: 493-498
+Munzenrider et al. IJROBP. 15: 553-558
^Gragoudas et al. Ophthalmology. 94: 349-353

Proton Development
1970's – 1980's

- Large field fractionated protons at MGH/HCL
  - Drs. Suit, Goitein, & Munzenrider
  - HCL Staff
  - Chordomas, chondrosarcomas

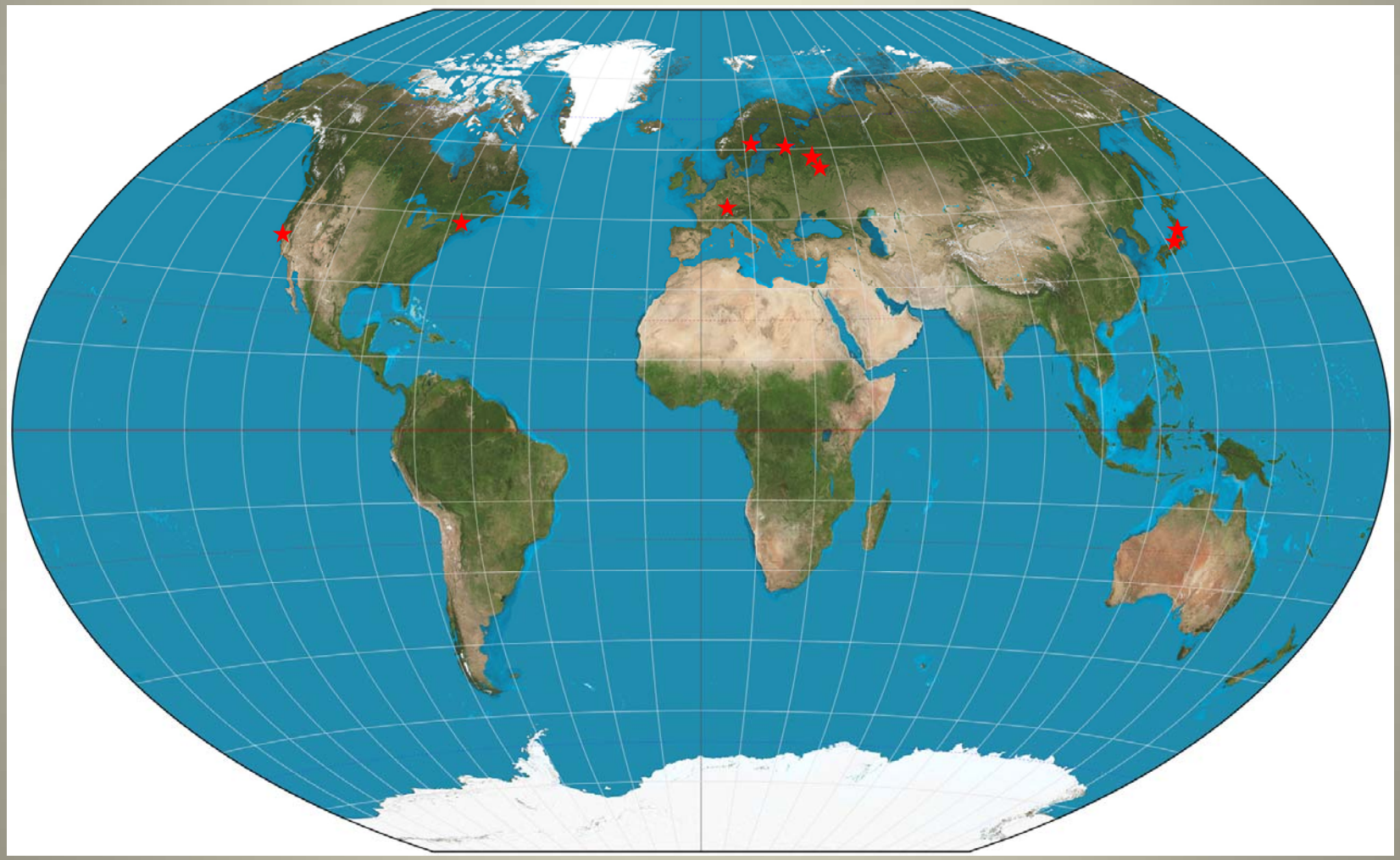


- St Petersburg, Russia
- Chiba and Tsukuba University, Japan

Scientific Validation
Early Results of Proton Therapy

- Dose distribution advantages
- Biologic effects
- Not “experimental”
- Preliminary studies showed clinical effects at least as good if not significantly better that previous approaches

Proton Laboratory Research Facilities
1950's – mid 1980's



Bring Protons into Clinical Facility?

- Technology too great
- Accelerators too large for hospital
- Too many personnel necessary to keep operational
- Too expensive to build
- Too expensive to maintain

Technical, Operational, and Clinical Validation
1990’s - present

Challenges in Integrating Particles into 'Routine Radiation Oncology'

- Challenges of particle therapy in the 1980's
  - Bring this technology into the clinical setting with advantages of hospital infrastructure
  - Develop hardware and software to make this possible
  - Develop facility and infrastructure to make it run as "effortlessly and efficiently" as conventional therapy

- Integrate the technologies, facilities, personnel so that the differences, for the most part, are transparent
  - Modify any preexisting structure to facilitate integration

Integrating Particles into 'Routine Radiation Oncology'

- Hospital based particle therapy
- Loma Linda University
  - James M. Slater, MD, Daniel Miller, PhD and team

Proton Therapy Cooperative Oncology Group (PTCOG)

- PTCOG was started in mid 1980's by James Slater, MD at LLU and Herman Suit, MD at MGH/HCL
- Purpose to bring together an international group to develop requirements for clinical proton facility

Multi institutional Clinical Trials

- Proton Radiation Oncology Group (PROG)
  - NCI-ACR funded
- Chordoma – Chondrosarcoma of Skull Base
  - Dose randomization
  - MGH/HCL, LBL, LLU
- Early Prostate
  - Dose randomization
  - 70.2 vs 79.2 Gy
  - LLU, MGH/HCL
- Oropharynx and Paranasal Sinuses

Clinical Expansion
mid 1990's

- Expanded Clinical Investigations
  - Prostate (early)
  - Oropharynx cancer
  - Macular Degeneration
  - Pediatrics
  - Early lung cancer
  - Primary liver cancer
  - Early breast cancer
  - Locally advanced lung cancer

COUNTRY	WHO, WHERE	PARTICLE	S/C/SC* MAX. ENERGY (MeV)	BEAM DIRECTIONS	START OF TREATMENT	TOTAL PATIENTS TREATED	DATE OF TOTAL
Canada	TRIUMF, Vancouver	p	C 72	1 horiz.	1995	182	Dec-14
Czech Republic	PTC Czech r.s.o., Prague	p	C 230	3 gantries, 1 horiz.	2012	357	Dec-14
China	WPTC, Wanjie, Zi-Bo	p	C 230	2 gantries, 1 horiz.	2004	1078	Dec-14
China	IMP-CAS, Lanzhou	C-ion	S 400/u	1 horiz.	2006	213	Dec-14
China	SPHIC, Shanghai	p	S 250	3 horiz.	2014	13	Dec-14
China	SPHIC, Shanghai	C-ion	S 430/u	3 horiz.	2014	22	Dec-14
England	Clatterbridge	p	C 62	1 horiz.	1989	2626	Dec-14
France	CAL, Nice	p	C165	1 horiz.	1991	5205	Dec-14
France	CPO, Orsay	p	S 250	1 gantry, 2 horiz.	1991	7004	Dec-14
Germany	HZB, Berlin	p	C 250	1 horiz.	1998	2525	Dec-14
Germany	RPTC, Munich	p	C 250	4 gantries, 1 horiz.	2009	2307	Dec-14
Germany	HIT, Heidelberg	p	S 250	2 horiz., 1 gantry**	2009, 2012	824	Dec-14
Germany	HIT, Heidelberg	C-ion	S 430/u	2 horiz., 1 gantry**	2009, 2012	1723	Dec-14
Germany	WPE, Essen	p	C 230	4 gantries***, 1 horiz.	2013	139	Dec-14
Germany	PTC, Uniklinikum Dresden	p	C 230	1 gantry	2014	first patient	Dec-14
Italy	INFN-LNS, Catania	p	C 60	1 horiz.	2002	350	Dec-14
Italy	CNAO, Pavia	p	S 250	3 horiz., 1 vertical	2011	111	Dec-14
Italy	CNAO, Pavia	C-ion	S 480/u	3 horiz., 1 vertical	2012	318	Dec-14
Italy	APSS, Trento	p	C 230	2 gantries, 1 horiz.	2014	5	Dec-14
Japan	HIMAC, Chiba	C-ion	S 800/u	horiz.***, vertical***	1994	8841	Dec-14
Japan	NCC, Kashiwa	p	C 235	2 gantries***	1998	1560	Dec-14
Japan	HIBMC, Hyogo	p	S 230	1 gantry	2001	4652	Dec-14
Japan	HIBMC,Hyogo	C-ion	S 320/u	horiz.,vertical	2002	2146	Dec-14
Japan	PMRC 2, Tsukuba	p	S 250	2 gantries	2001	3416	Dec-14
Japan	Shizuoka Cancer Center	p	S 235	3 gantries, 1 horiz.	2003	1757	Dec-14
Japan	STPTC, Koriyama-City	p	S 235	2 gantries, 1 horiz.	2008	2797	Dec-14
Japan	GHMC, Gunma	C-ion	S 400/u	3 horiz., 1 vertical	2010	1486	Dec-14
Japan	MPTRC, Ibusuki	p	S 250	3 gantries	2011	1317	Dec-14
Japan	Fukui Prefectural Hospital PTC, Fukui City	p	S 235	2 gantries, 1 horiz.	2011	428	Dec-13
Japan	Nagoya PTC, Nagoya City, Aichi	p	S 250	2 gantries, 1 horiz.	2013	627	Dec-14
Japan	SAGA-HIMAT, Tosu	C-ion	S 400/u	3 horiz., vertical, 45 deg.	2013	547	Dec-14
Japan	Aizawa Hospital PTC, Nagano	p	C 235	1 gantry	2014	first patient	Oct-14

Poland	IFJ PAN, Krakow	p	C 60	1 horiz.	2011	85	Dec-14
Russia	ITEP, Moscow	p	S 250	1 horiz.	1969	4368	Dec-14
Russia	St.Petersburg	p	S 1000	1 horiz.	1975	1386	Dec-12
Russia	JINR 2, Dubna	p	C 200****	1 horiz.	1999	1069	Dec-14
South Africa	NRF - iThemba Labs	p	C 200	1 horiz.	1993	524	Dec-14
South Korea	NCC, Ilsan	p	C 230	2 gantries, 1 horiz.	2007	1496	Dec-14
Sweden	Svedberg Lab.,Uppsala	p	C 200	1 horiz.	1989	1431	Dec-14
Switzerland	CPT, PSI, Villigen	p	C 250	2 gantries*****, 1 horiz.	1984, 1996, 2013	7364	Dec-14
USA, CA.	J. Slater PTC, Loma Linda	p	S 250	3 gantries, 1 horiz.	1990	18362	Dec-14
USA, CA.	UCSF, San Francisco	p	C 60	1 horiz.	1994	1729	Dec-14
USA, MA.	MGH Francis H. Burr PTC, Boston	p	C 235	2 gantries***, 1 horiz.	2001	8107	Sep-14
USA, IN.	IU Health PTC, Bloomington	p	C 200	2 gantries***, 1 horiz.	2004-2014	2200	Dec-14
USA, TX.	MD Anderson Cancer Center, Houston	p	S 250	3 gantries***, 1 horiz.	2006	5838	Dec-14
USA, FL.	UFPTI, Jacksonville	p	C 230	3 gantries, 1 horiz.	2006	5376	Dec-14
USA, OK.	ProCure PTC, Oklahoma City	p	C 230	1 gantry, 1 horiz, 2 horiz/60 deg.	2009	1690	Dec-14
USA, PA.	Roberts PTC,UPenn, Philadelphia	p	C 230	4 gantries, 1 horiz.	2010	2522	Dec-14
USA, IL.	Chicago Proton Center, Warrenville	p	C 230	1 gantry, 1 horiz, 2 horiz/60 deg.	2010	1782	Dec-14
USA, VA.	HUPTI, Hampton	p	C 230	4 gantries, 1 horiz.	2010	1200	Dec-14
USA, NY.	ProCure Proton Therapy Center, New Jersey	p	C 230	4 gantries	2012	1168	Dec-14
USA, WA.	SCCA ProCure Proton Therapy Center, Seattle	p	C 230	4 gantries	2013	420	Dec-14
USA, MO.	S. Lee Kling PTC, Barnes Jewish Hospital, St. Louis	p	SC 250	1 gantry	2013	149	Dec-14
USA, TN.	Provision Center for Proton Therapy, Knoxville	p	C 230	3 gantries	2014	100	Aug-14
USA, CA.	Scripps Proton Therapy Center, San Diego	p	C 250	3 gantries, 2 horiz.	2014	220	Dec-14
USA, LA.	Willis Knighton Proton Therapy Cancer Center, Shreveport	p	C 230	1 gantry	2014	28	Dec-14
USA, FL.	Ackermann Cancer Center, Jacksonville	p	SC 250	1 gantry	2015	1	Apr-15