# The Science behind Proton Beam Therapy


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# Principles underlying Radiotherapy

- Radiation related complications do not occur in un-irradiated tissues

- Normal tissue irradiation does not benefit patient

- One can optimize the therapeutic ratio by maximizing radiation dose to the tumor and minimizing normal tissue dose

# History of Radiation Oncology

- Understanding of radiation biology

- Improvements in imaging:

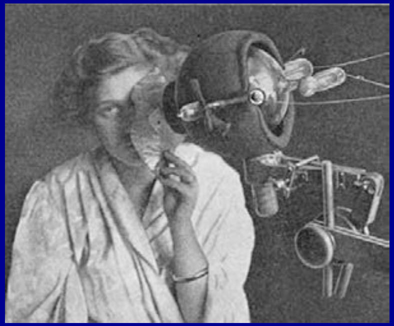
- For visualizing normal tissues and tumor
- For planning
- For on-treatment verification

- Improvements in computing power:

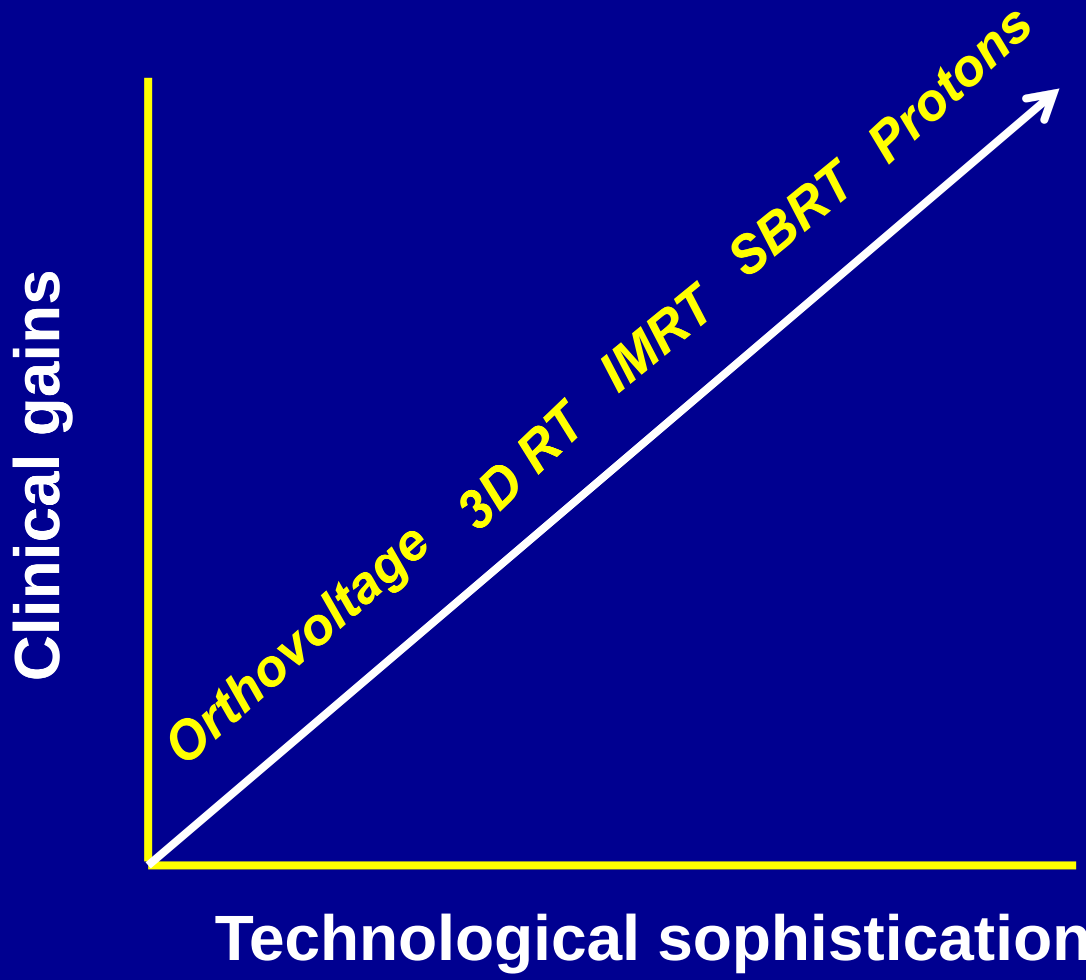
- 3-D planning
- Intensity modulation

- Improvements in delivery systems

# A century of “delivery tools” in radiation oncology



# The “arrow of progress”

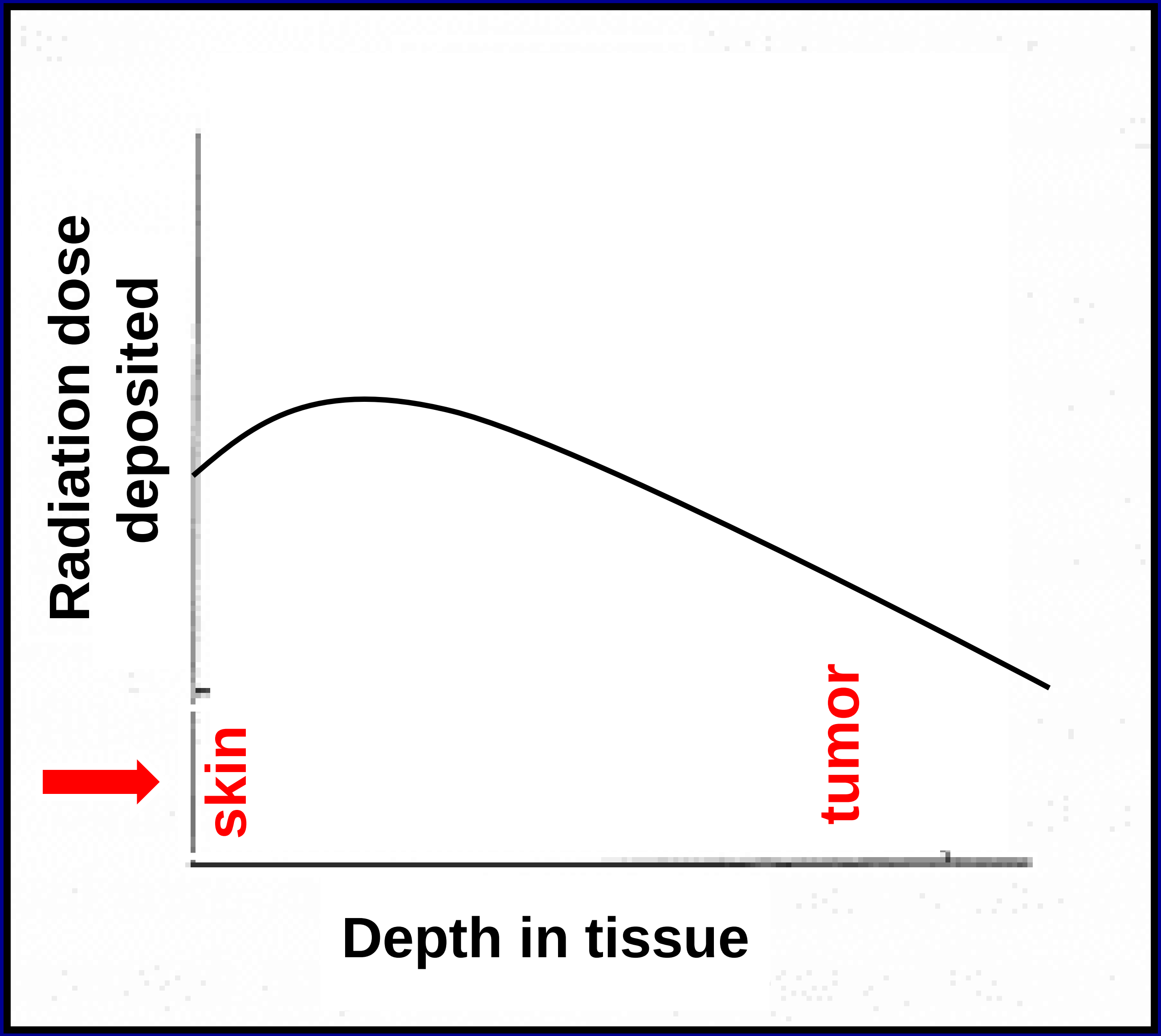


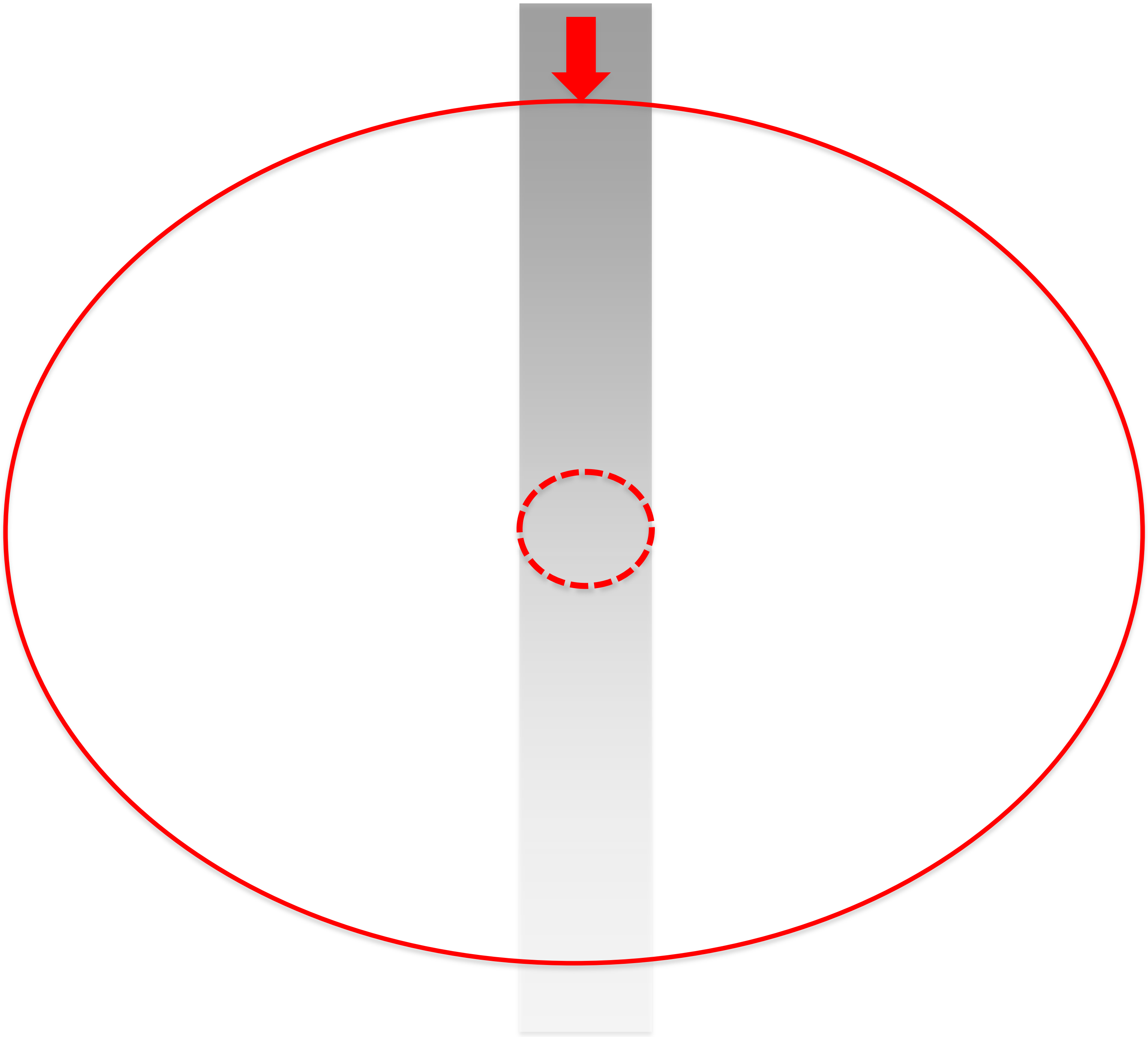
# Protons – “The Point of the Arrow”

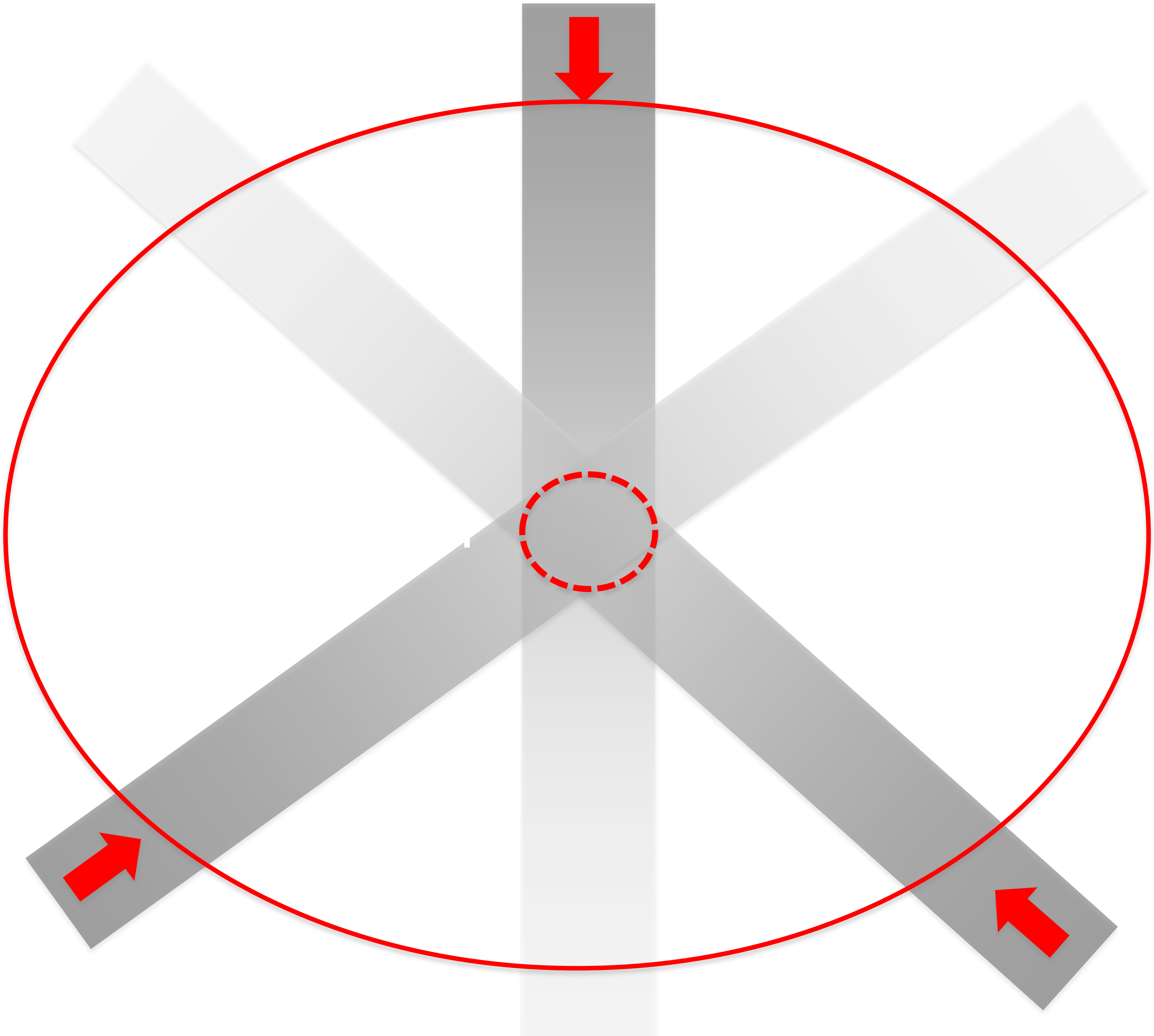
- Traditional X-rays (photons)
  - Attenuate progressively with depth
    - Continue to deposit dose beyond target
      - Unwanted dose to normal tissue

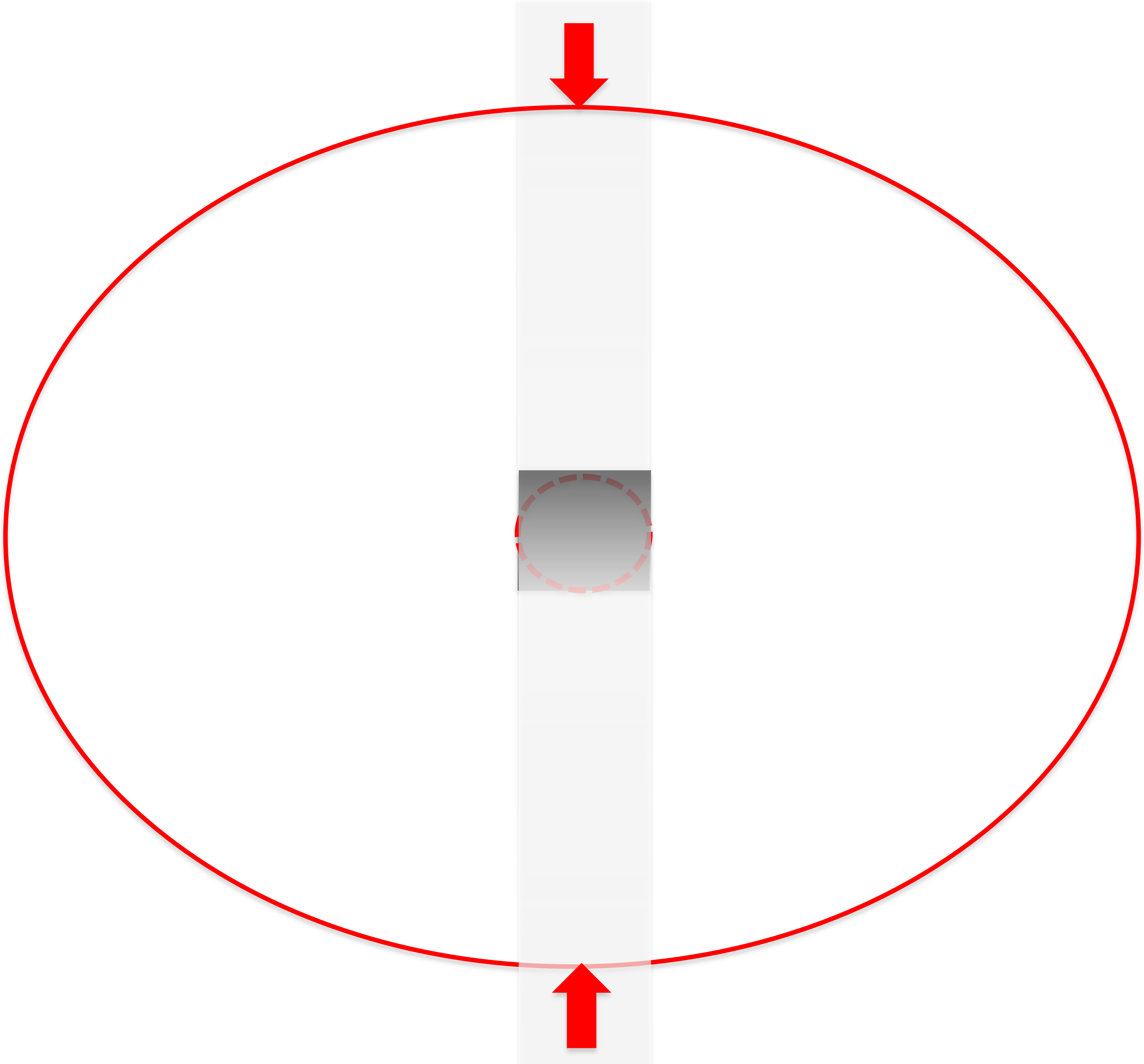
- Particles with charge and mass
  - Defined range in tissue
    - Proportional to energy
    - Deposit dose in sharp Bragg Peak
      - No dose delivered beyond that point

# Radiation deposition in tissue for radiation beams









# Proton Radiation Therapy

- **1929:** Cyclotron invented by Ernest Lawrence as a way to accelerate nuclear particles to very high speeds.

- **1946:** Robert Wilson, professor of physics at Harvard first proposes using protons for the treatment of cancer.

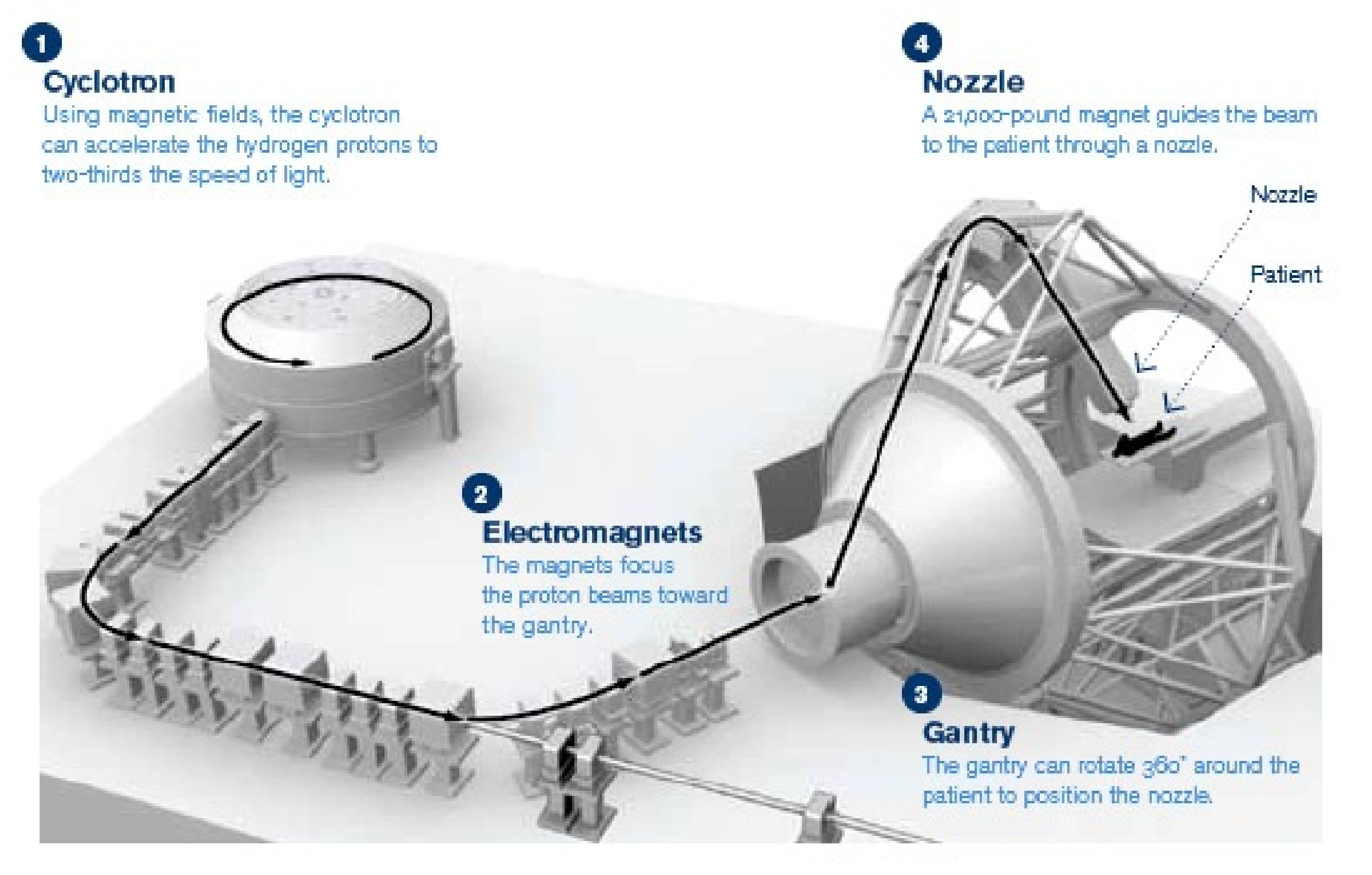
- **1954:** J. Lawrence treats first patient with protons at Berkeley for pituitary tumor

- **1957:** First European proton Rx in Uppsala, Sweden.

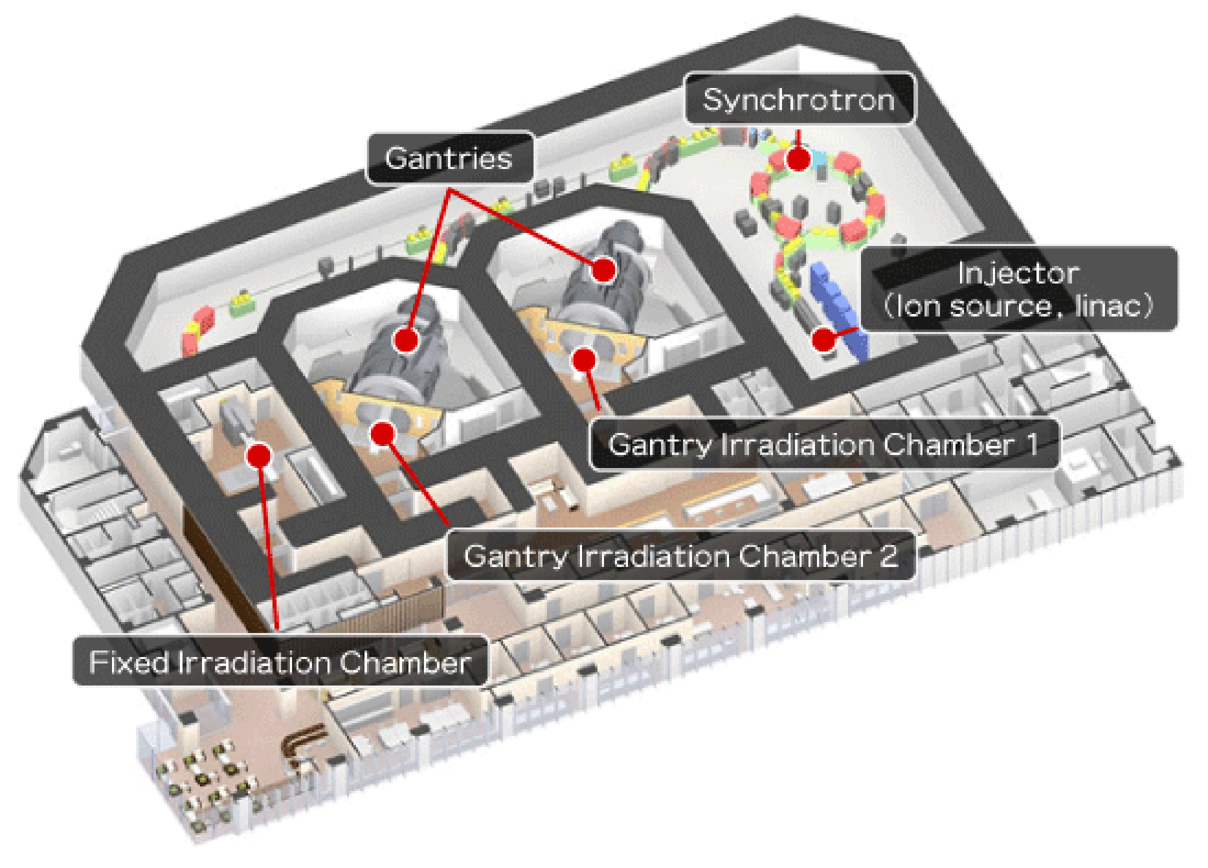
# Proton Radiation Therapy

- **1961:** First patient treated at Harvard Cyclotron by Kjellberg
- **1974:** MGH protons for cancers including eye, skull base, prostate
- **1988:** FDA approves protons for selected cancers
- **1990:** Loma Linda Medical Center synchrotron opens
- **2001:** Francis H. Burr Proton Therapy Center opens
- **2004-2015:** Multiple new facilities built, planned
- **2015:** 42 operating centers worldwide

# How are clinical proton beams generated?



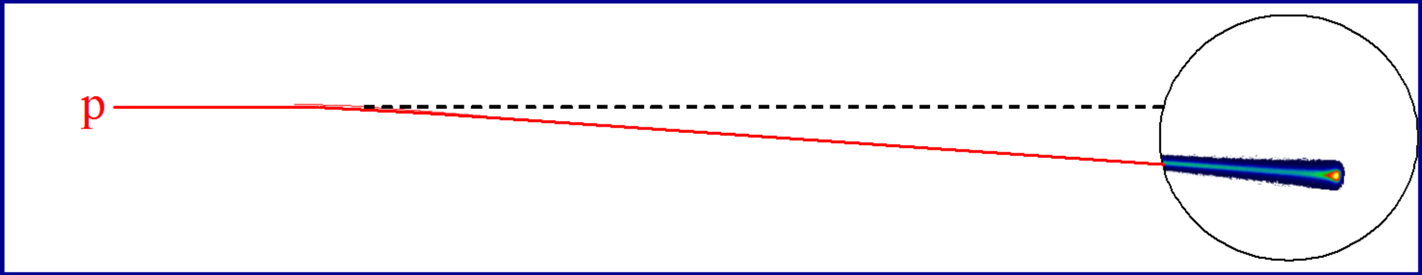
# How are clinical proton beams generated?

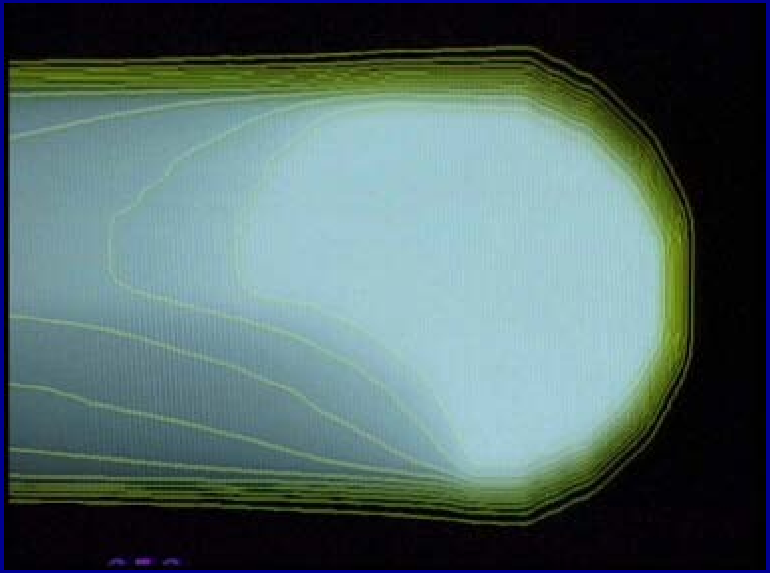



**Cost: $30-180M**

# "Spot scanned" beams – the new wave

**The dynamic application of scanned and modulated proton pencil beams**



Images courtesy of Eros Pedroni

# Proton beam therapy – US treatment centers


**Over 20 more in planning stages**

# Protons: Potential Clinical Advantages

## Lower integral dose and absence of exit dose:

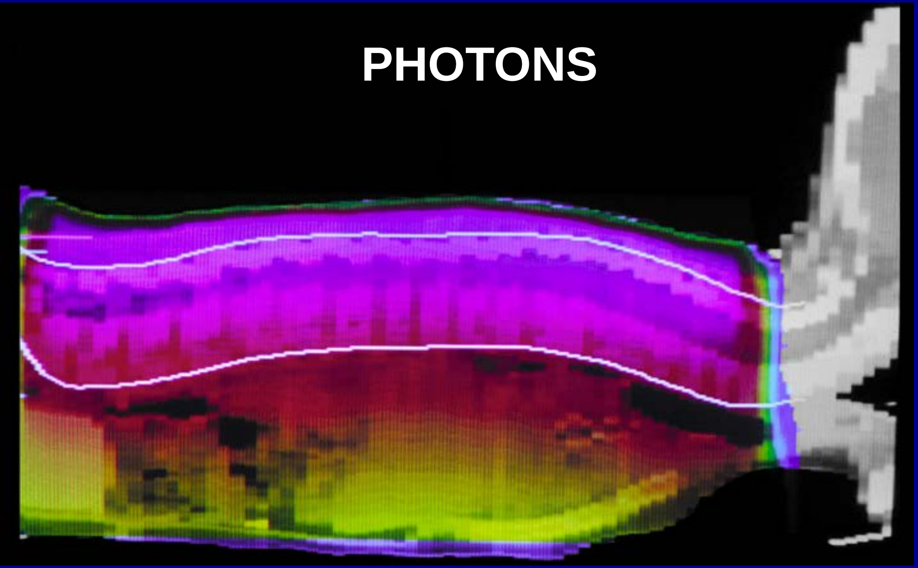
- Improve acute treatment tolerance:
  - Allows integration with systemic chemotherapy
  - Allows delivery of higher radiation doses
- Reduce late effects

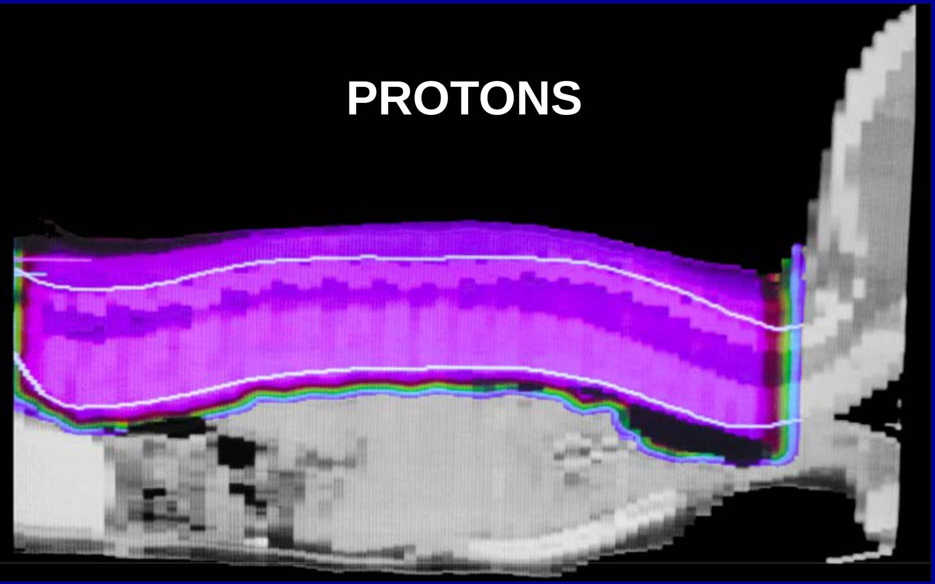
# Pediatric cancers – the very best indication for proton beam

Children are uniquely sensitive to radiation:

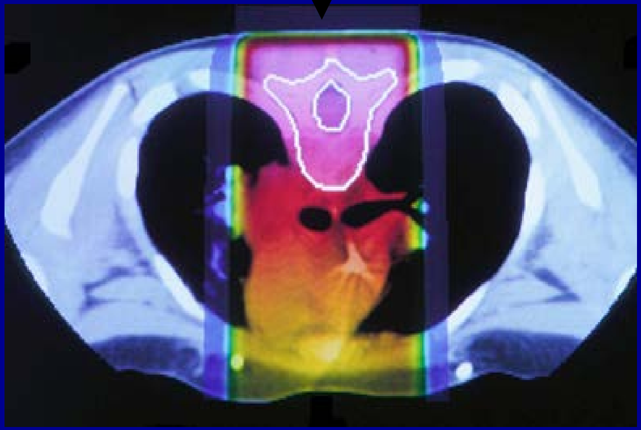
- Profound effects on growth and development
- Substantial risk of radiation-induced cancers

# MEDULLOBLASTOMA



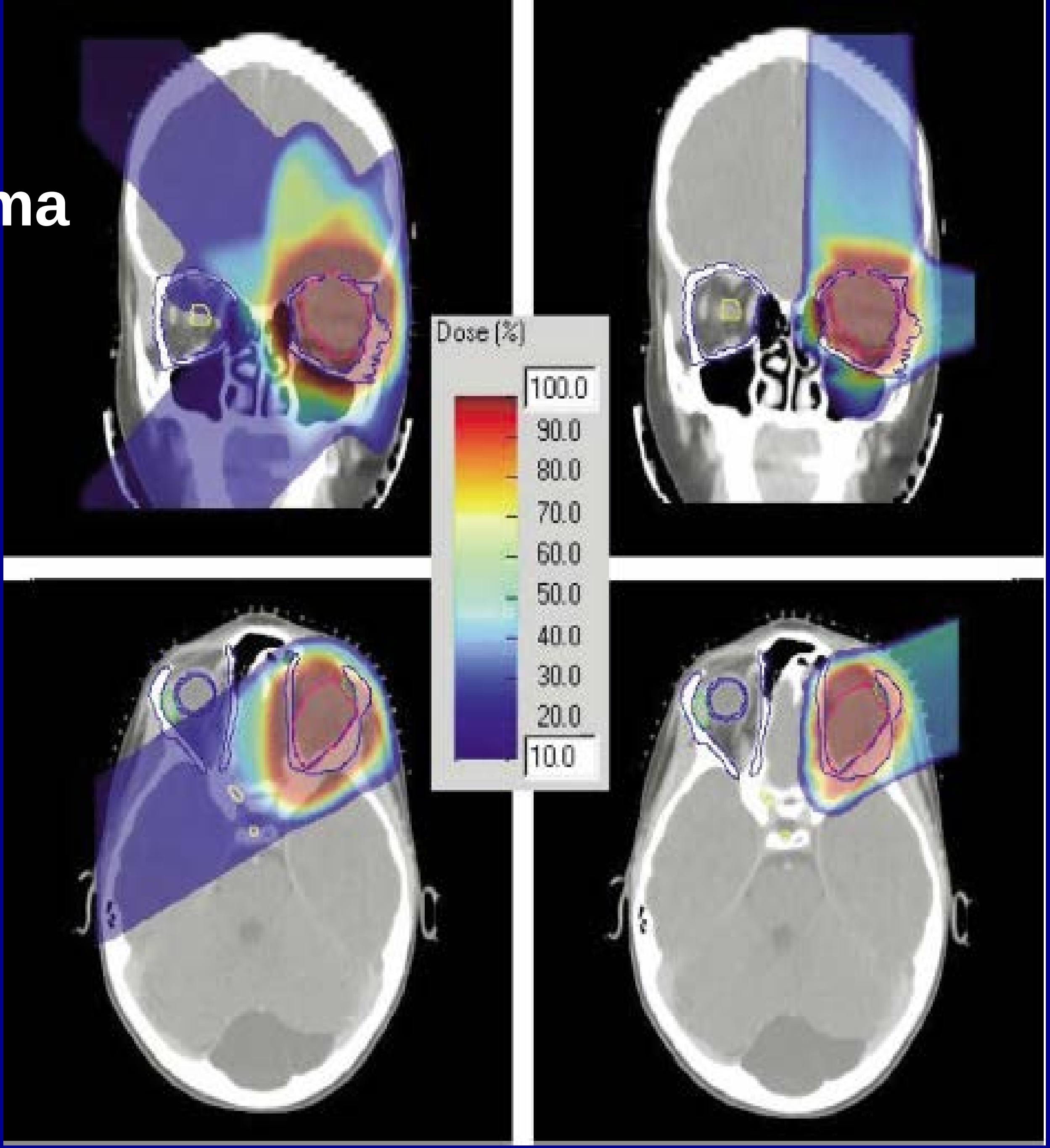

PHOTONS



PROTONS

*Courtesy T. Yock, N. Tarbell, J. Adams*

# Orbital Rhabdomyosarcoma




Photons Protons

**Courtesy T. Yock, N. Tarbell, J. Adams**

# Pediatric Studies

**Traditional Comparative Effectiveness Research does not exist:**

- **No RCTs because no equipoise**
- **Unanimity among radiation oncology community globally**

# Protons: Reduction in Second Malignancies among Pediatric Patients

**Comparative Treatment Planning studies:**

**Protons vs. Photons (Conformal or IMRT)**

- **Rhabdomyosarcoma**
  - **Protons reduce risk 2nd tumors by factor of $\geq$ 2**
- **Medulloblastoma**
  - **Protons reduce risk 2nd tumors by factor of 8-15**

***Miralbell, Lomax et al, Int J Radiat Oncol Biol Phys. 2002;54:284-9***

# Proton beam therapy – UK treatment centers

**Government Commission:**
**1 facility per 30m population**

# Accepted adult indications for protons:

- **Skull base tumors**
- **Eye tumors**
- **Spine and sacral tumors**

**Not that evidence is strong. More that alternatives are unacceptable**

# Adult Cancer Studies

**For more common cancers**

**Do the physical advantages translate into measurable clinical benefit?**

- **Cancer control**
- **Quality of life**
- **Second malignancies**

# The trouble with randomized trials testing proton therapy

- Ethical objections
- Advantages small and trials large
- Advantages late and trials long
- Huge initial investment for protons
- Slow the engine of discovery

# Reducing the incidence of second cancers

- How many patients would one need to demonstrate a significant reduction in 2nd tumors?
  - Assume 60% decrease in 0.5% incidence at 15 y (NCI)
  - For 80% power at p=0.05.

| | 1-sided | 2-sided | |
|---|---|---|---|
| • 5 y average FU | 13509 | 17280 | ( # pts/arm) |
| • 10 y average FU | 6759 | 8646 | |
| • 15y average FU | 4510 | 5768 | |
| • Expected 2nd cancers | 32 | 41 | |
| | 23 | 29 | photons |
| | 9 | 12 | protons |

Sample size smaller by increasing FU from 10 y to 15 y

Courtesy of Beow Yeap, PhD

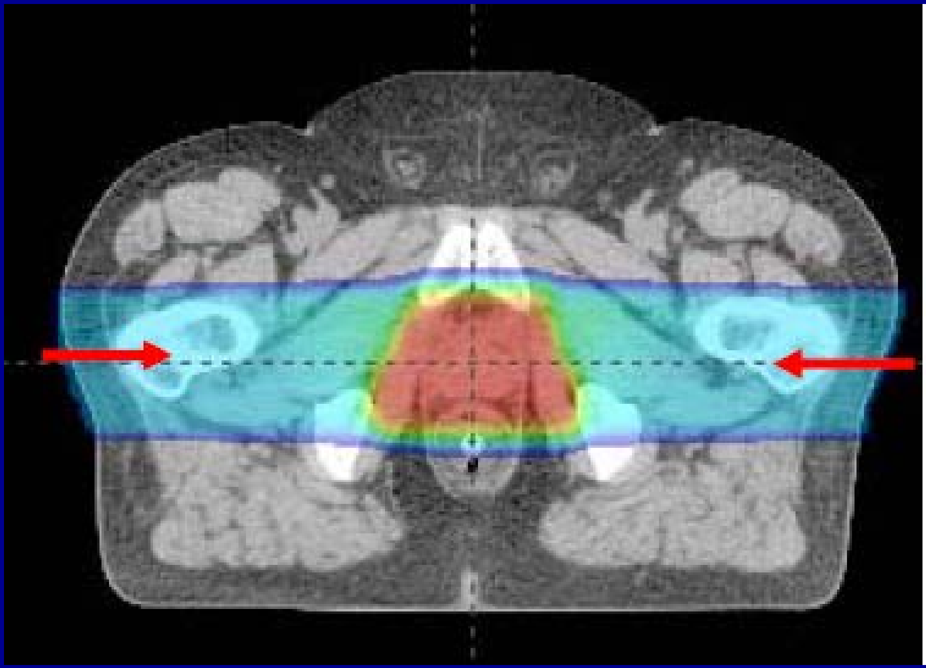
# Second Malignancies in adults

- **Matched retrospective cohort study**
  - **1,450 Harvard proton patients and photon cohort in SEER cancer registry**
  - **Matched 558 HCL proton pts (1972-2001) with 558 SEER pts. Median FU 6 years**
  - **6.4% of proton patients developed another malignancy, versus 12.8% of photon patients**

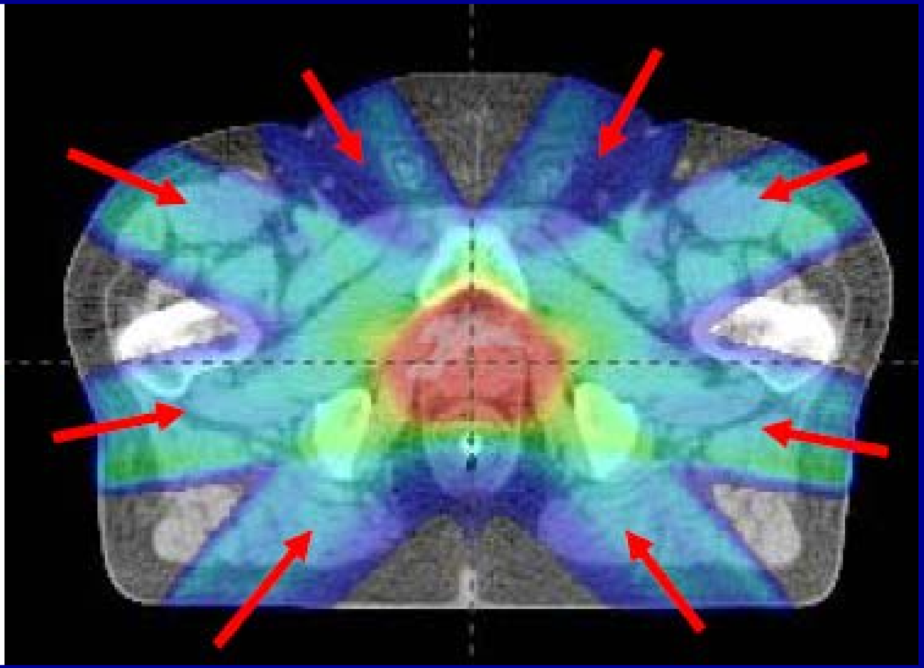
***Chung et al  Int J Radiat Oncol Biol Phys 2014***

# Studies in prostate cancer

**Protons**

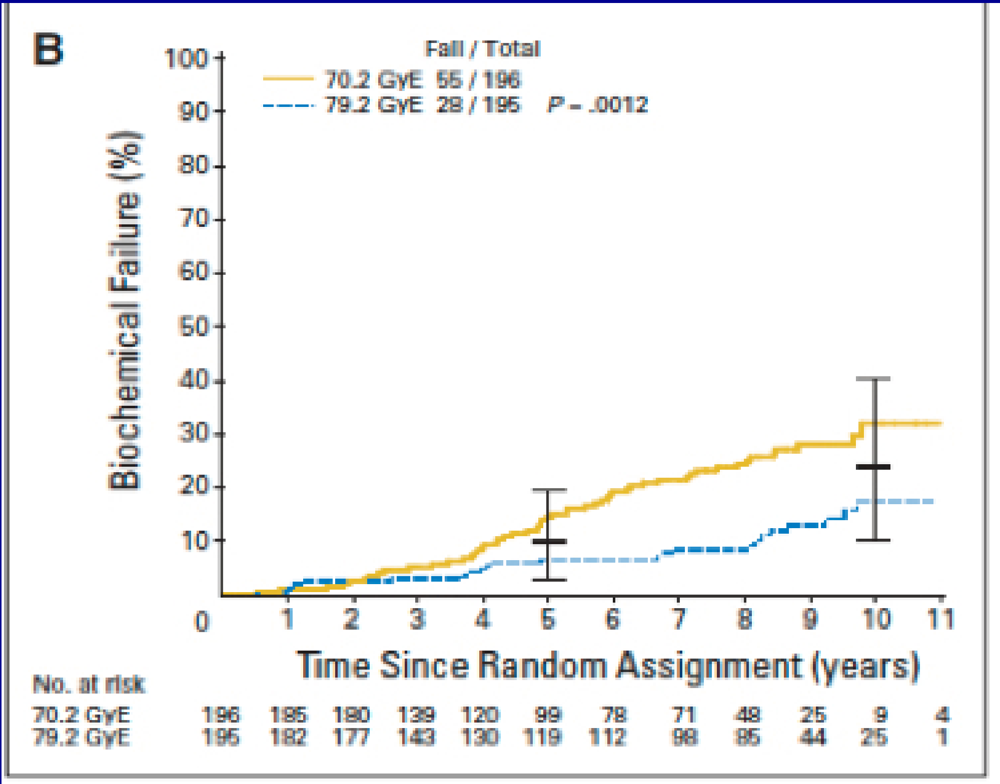


**IMRT**



# Does proton beam cure patients ?

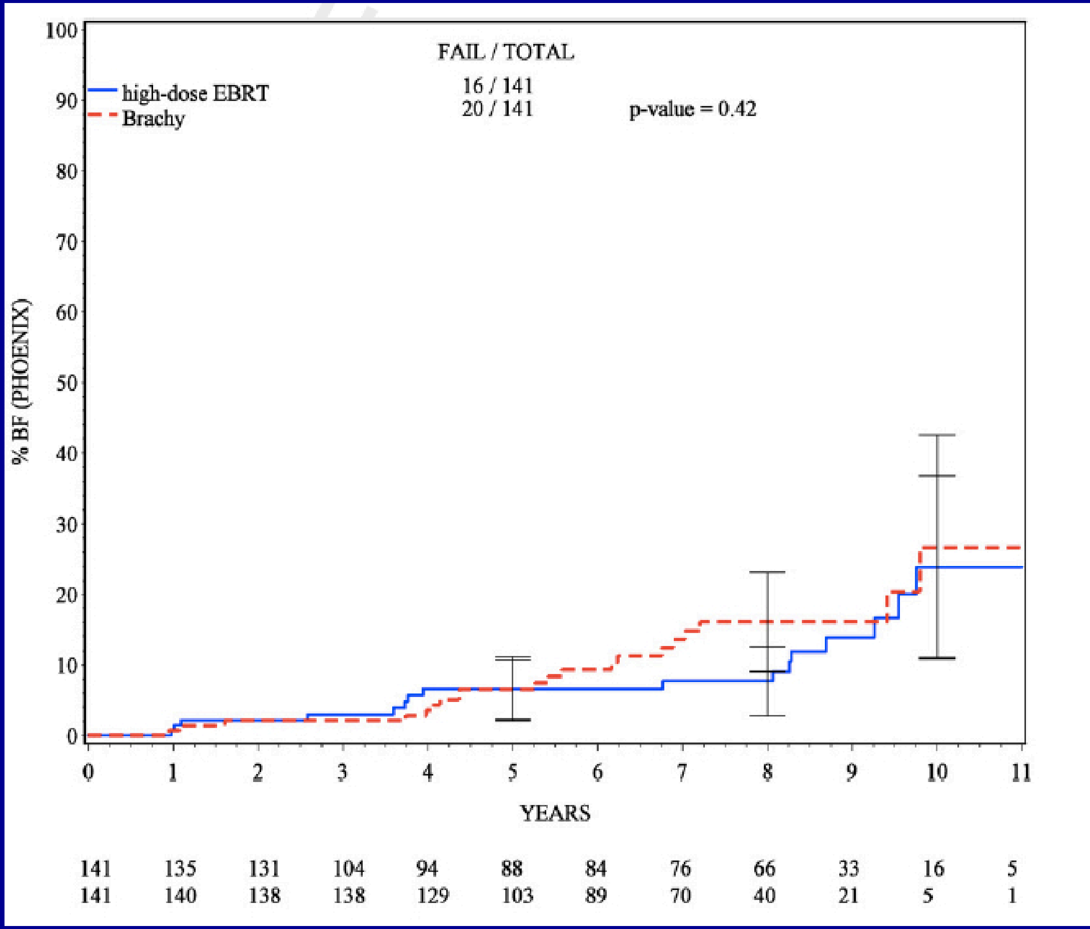
- Randomized trial 393 men T1-2 tumors
- 70 vs. 79Gy    Median FU 8.9 years




*Zietman J Clin Oncol 2010, 28:1106*

# Does it cure more patients than brachytherapy ?

## Case-matched analysis:  n = 141 + 141




*Coen et al IJROBP  2012, 82:201*

# Does it cure more patients than other kinds of external beam ?

**2000-2007**

| | |
|---|---|
| Conformal | 6310 |
| IMRT | 6666 |
| Protons | 684 |

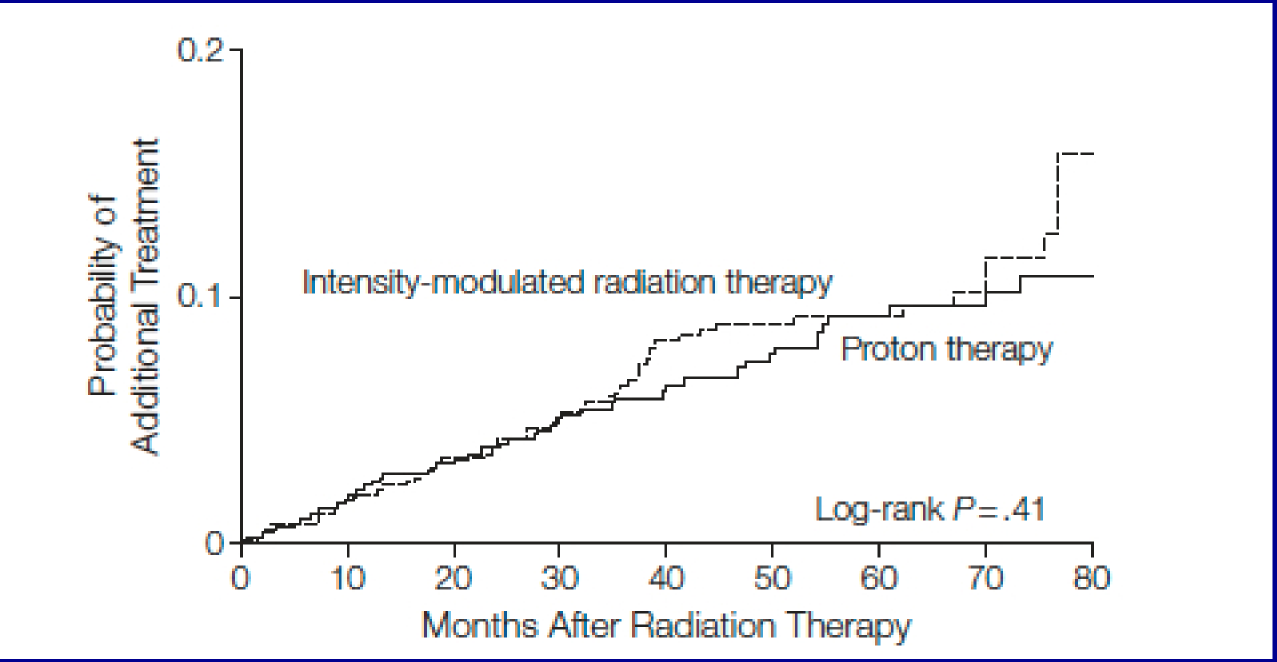
**Min FU 1 year, median 50 months**

**Endpoints: hip fractures, ED, GI morbidity, additional cancer treatment**

***Sheets et al JAMA 2012, 307:1611***

# Does it cure more patients than other kinds of external beam ?

## Likelihood of additional treatment

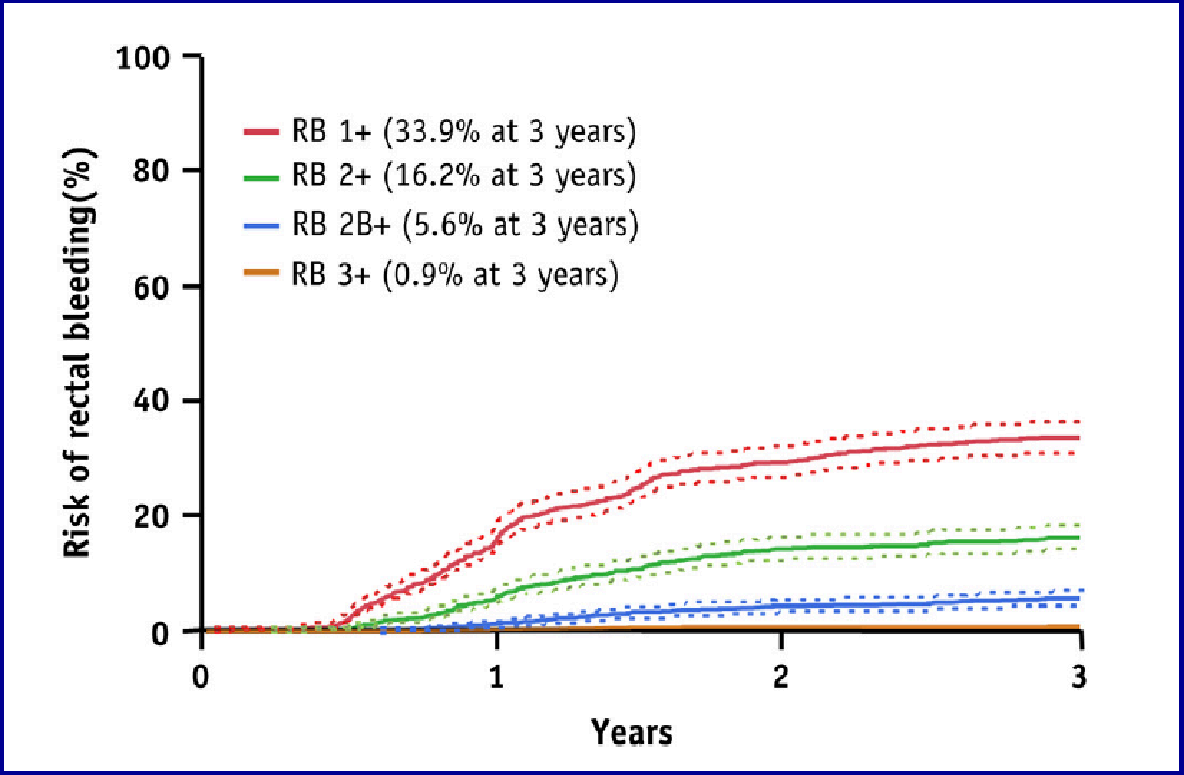



***Sheets et al JAMA 2012, 307:1611***

# Does it reduce morbidity?

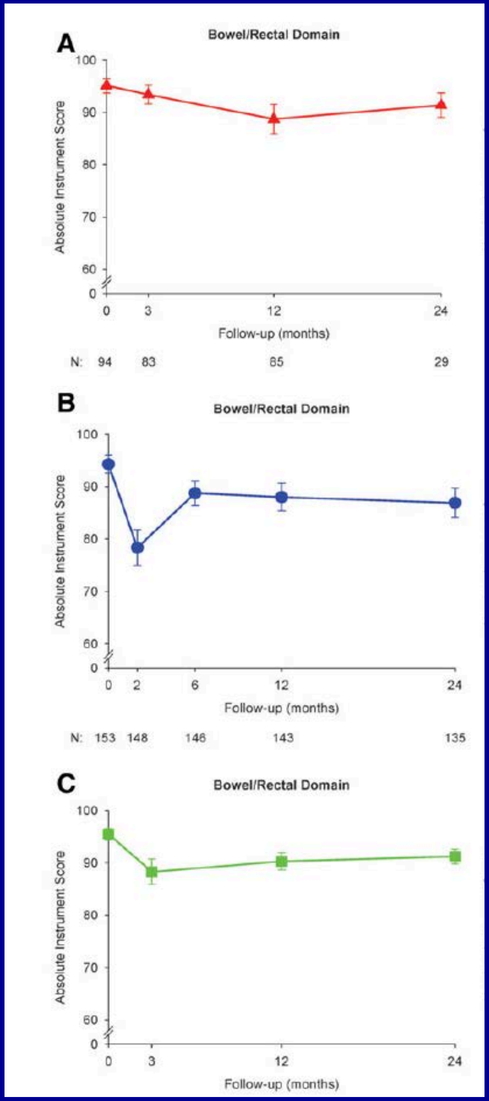
**U Florida**

**1285 patients with median FU 3.5 years**




*Colaco et al IJROBP 2014, 91:172*

# Does it reduce morbidity?




**Data from 3 prospective cohort studies**

***Gray et al cancer 2013, 119:1729***

# Does it reduce morbidity?

**Two contemporaneous cohorts:**

- **Protons 9.4 years**
- **Conventional 5.9 years**

| | Protons | Conventional |
|---|---|---|
| Number | 280 | 97 |
| Age at survey | 76 | 75 |
| Urinary obst/irr | 24.0 | 21.8 |
| Incontinence | 10.2 | 11.2 |
| Bowel problems | 7.8 | 10.6 |
| Sexual problems | 67.1 | 76.3 |

*Talcott et JAMA 2010, 303:1046*

# Does it <u>increase</u> morbidity ?

| IMRT vs Protons | HR |
|---|---|
| GI diagnoses | 0.66 |
| Hip fractures | NS |
| ED | NS |
| Urinary incontinence, diagnoses, and procedures | NS |

*Sheets et al JAMA 2012*

Low-Intermediate Risk Prostate Cancer

RANDOMIZE

N=350

79.2 Gy

IMRT

Proton Beam

79.2 Gy (RBE)

ENDPOINTS

Patient-Reported Quality of Life

Cost-Effectiveness

Physics/Biology

MGH 1811

Penn University of Pennsylvania

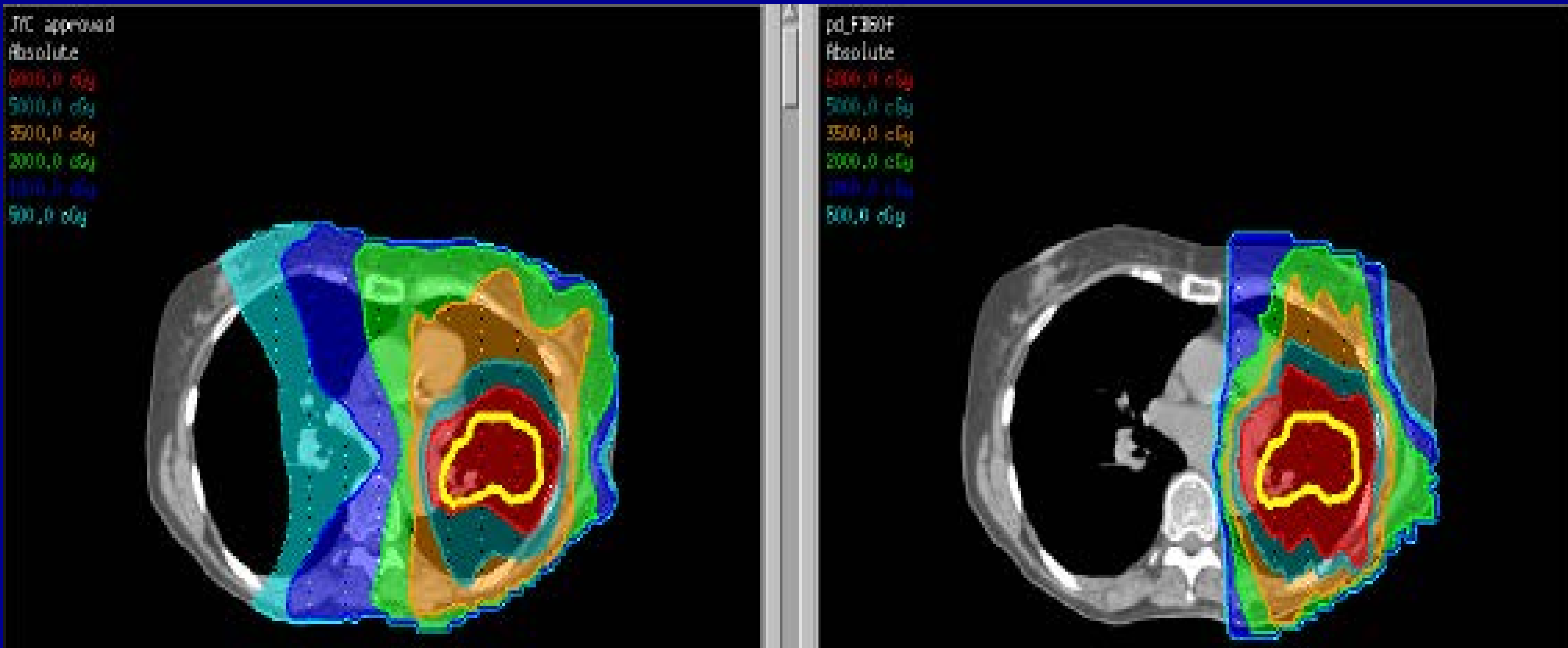
The University of Texas MD Anderson ~~Cancer~~ Center Making Cancer History

Washington University in St. Louis School of Medicine

## New opportunities:

- Left-sided breast cancer
- Pancreas
- Retroperitoneal sarcomas
- Paranasal sinus tumors
- Lung
- Liver

# STAGE III Non-Small Cell Lung Cancer



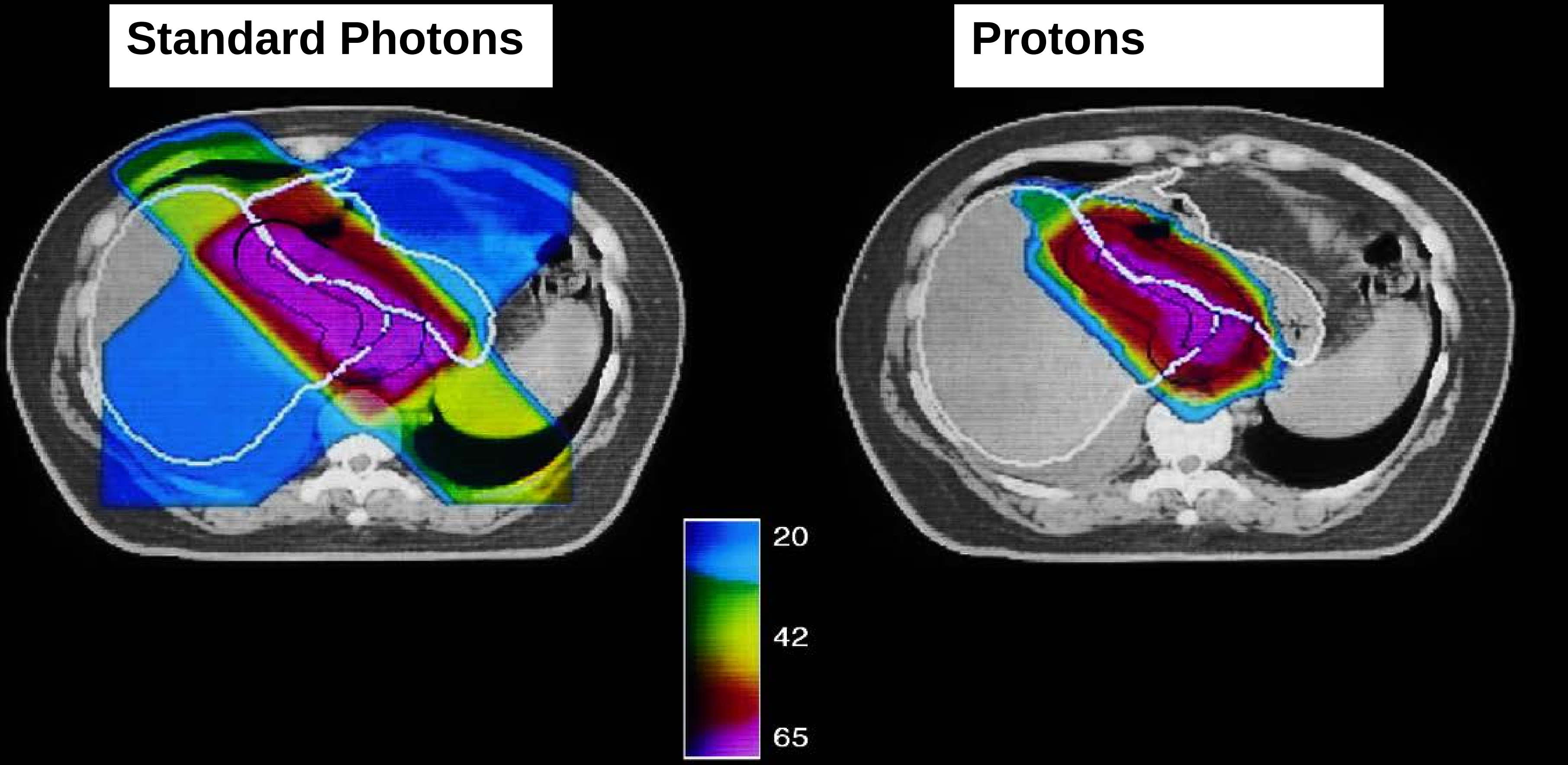

**IMRT** **Protons**

**Randomized Phase II Study in Progress at MDACC/MGH**

**Highest dose that can be achieved: 74 Gy, 66 Gy, (60 Gy) dose levels**

**Image courtesy of Joe Chang MD, MDACC**

# New opportunities- Hepatocellular Cancer




Willett C, Adams J

# Proton Therapy 2015

- Accurate and effective treatment
- Rides the “minimally invasive” wave
- Technical and biological advances: scanned beam biophysical optimization, “personalized” dose
- New centers being established globally

# Proton Therapy 2015

- Treatment of choice for pediatric solid tumors and selected adult tumors
- Relative benefit versus photons in adult patients being studied in randomized, controlled trials
- Cost reduction and efficiency a research priority
- An economic “development trap” exists.