



Research Strategies in Proton Therapy: Proving the Promise and Avoiding the Perils

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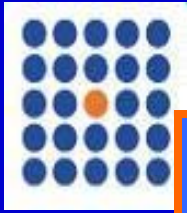


Research Strategies in Proton Therapy: Objectives

- **Promise**
- **Perils**
 - Clinical (3)
 - Ethical
 - Health Care Cost
- **Suggested Research Strategies**



The Promise of Proton Therapy



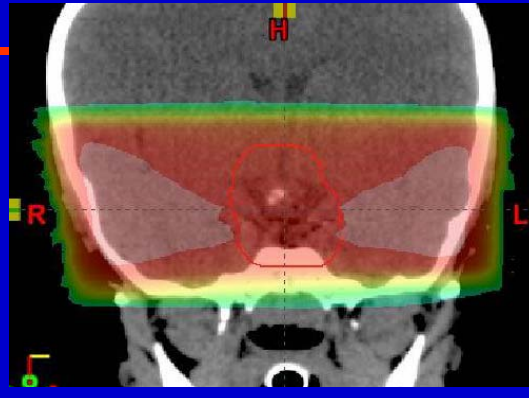
Radiation Therapy Basics

- Radiation damage is non-specific.
- Response probability *dose-related* and *volume-related*.
- Dose distribution key to outcome.

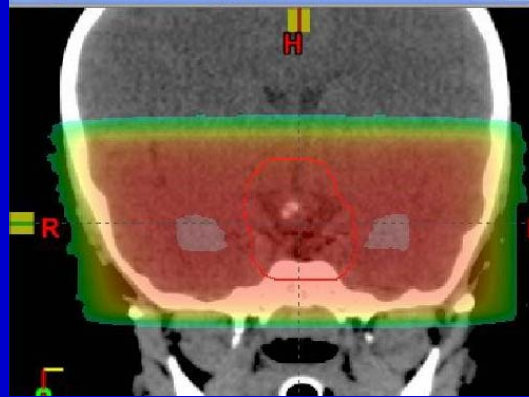


Improvements in Photon Dose Distribution

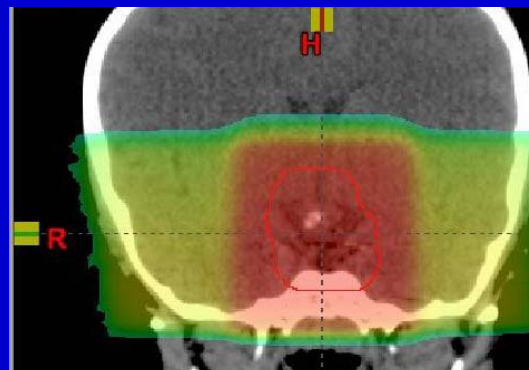
1. ~1980
Opp 6X



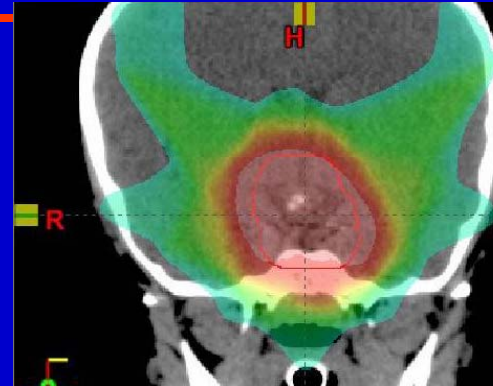
2. ~1985
Opp 15X



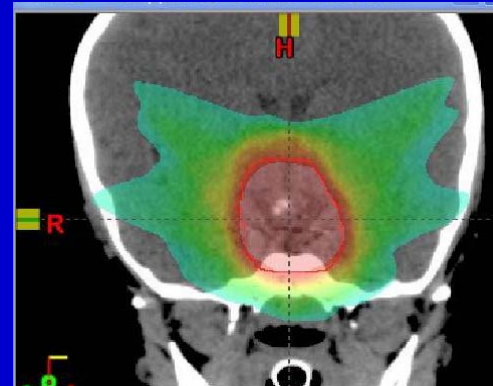
3. ~1990
Vertex
Field



4. 3D
Con-
formal
~1995



5. IMRT
~2005



~105% to ~20%
red = 100%
aqua = 20%

Courtesy:
D Louis,
D Yeung,
Z Li, C Li



Improving Dose Distribution with photons

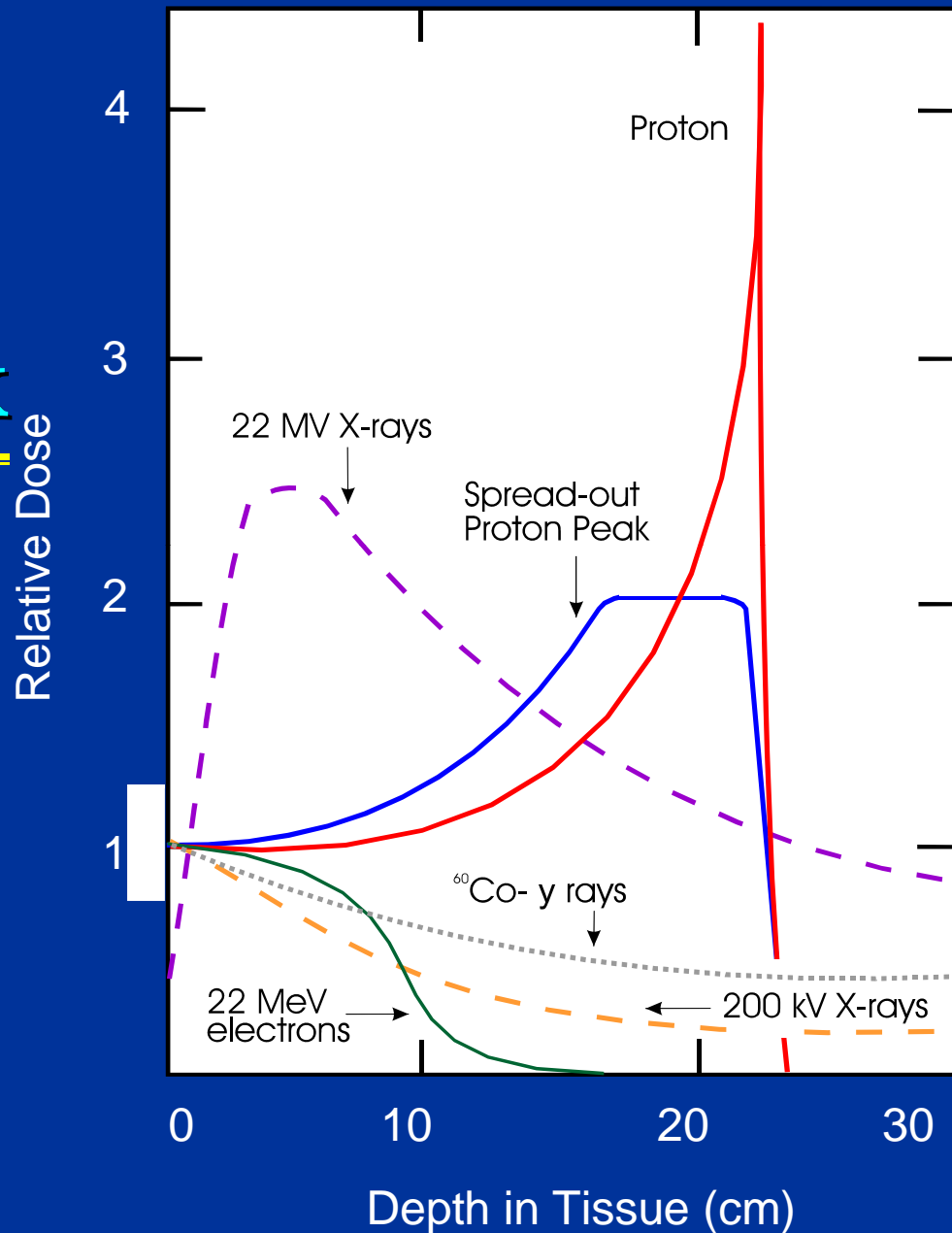
- Changes in photon energy
- Intersection and modulation of multiple photon beams overlapping over target *
- These solutions* have resulted in significant and favorable *redistribution* of *integral dose***.
- We may have reached the limit in our ability to improve dose distribution with X rays and to improve outcomes through the *redistribution of integral dose*.

*Gamma Knife, SRS, SRT, IMRT, Arc IMRT, Tomotherapy, Cyberknife.

**Integral dose is dose to non-targeted tissues.

Proton Dose Distribution: The Bragg Peak

- 200 KV
- 60Cobalt
- 22 MV X-rays
- 22 MEV Electrons
- Proton Bragg Peak
- Spread Out Proton Peak





Protons vs. Ext Beam Photons

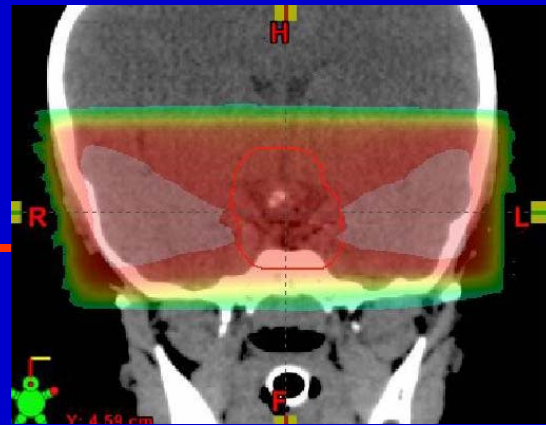
No matter how many beams are used and how much 2-dimensional static or dynamic field shaping occurs. . .

- **Photons:** *most of radiation dose is wasted as integral dose deposited in non-targeted tissues, i.e., an external photon beam is an inefficient¹ and inaccurate² means of radiation therapy with few prospects for further improvements.*
- **Protons:** *most of radiation dose is target dose, deposited in targeted tissues, i.e., an external proton beam is a much more efficient and accurate means of radiation therapy with great potential for future improvement.*

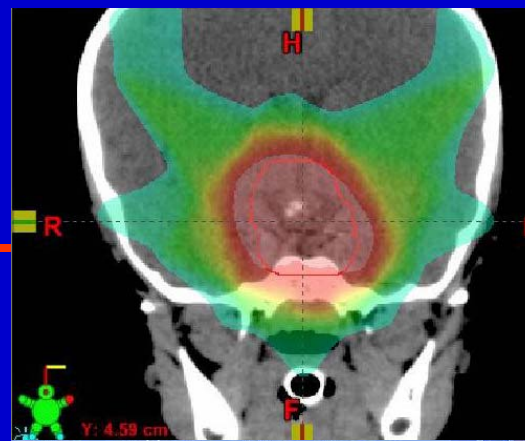
¹ Inefficient in that most dose is wasted.

² Inaccurate in that most dose is placed outside the target.

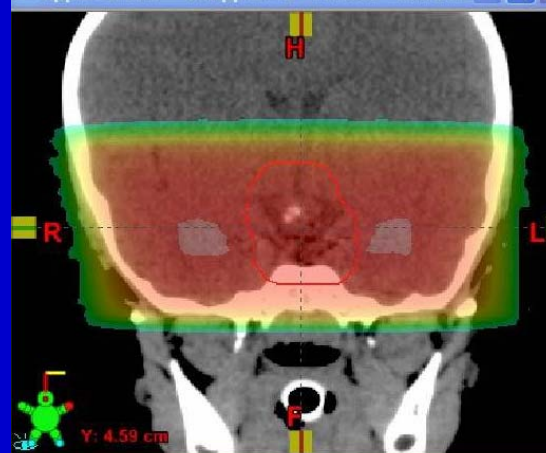
Opp 6X
~1980



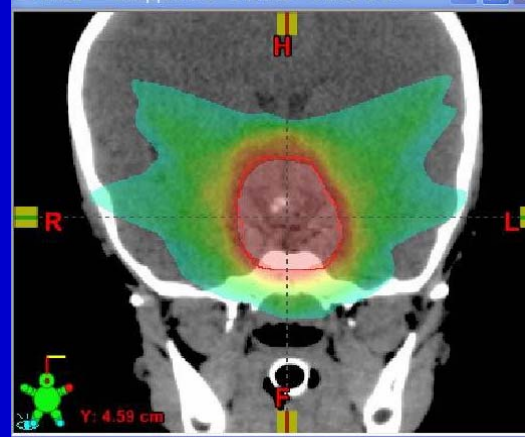
3D Con-
formal
~1995



Opp 15X
~1985

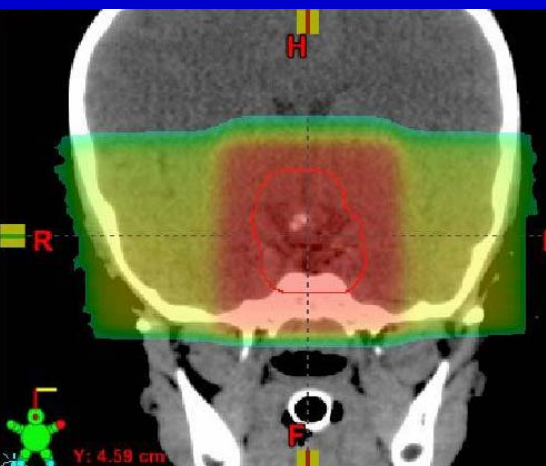


IMRT
~2005

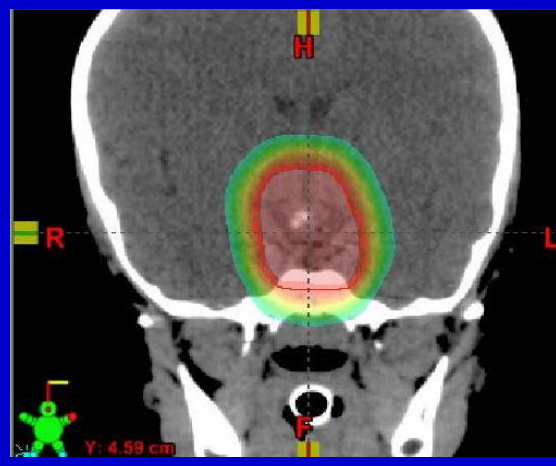


~105% to
~20%
red = 100%
aqua = 20%

3 Field
Vertex
~1990



Proton
~2009



Courtesy:
D Louis,
D Yeung,
Z Li, C Li



Research Strategies in Proton Therapy: The Promise

The promise of proton therapy is that a reduction in integral dose can be leveraged to:

1. Reduce toxicity
2. Permit dose escalation/intensification to improve cancer control
3. Ultimately reduce overall health care costs*



Some Perils of Clinical Research Proton Therapy: Clinical Issues



#1:

Failure to recognize
the importance of
integral dose

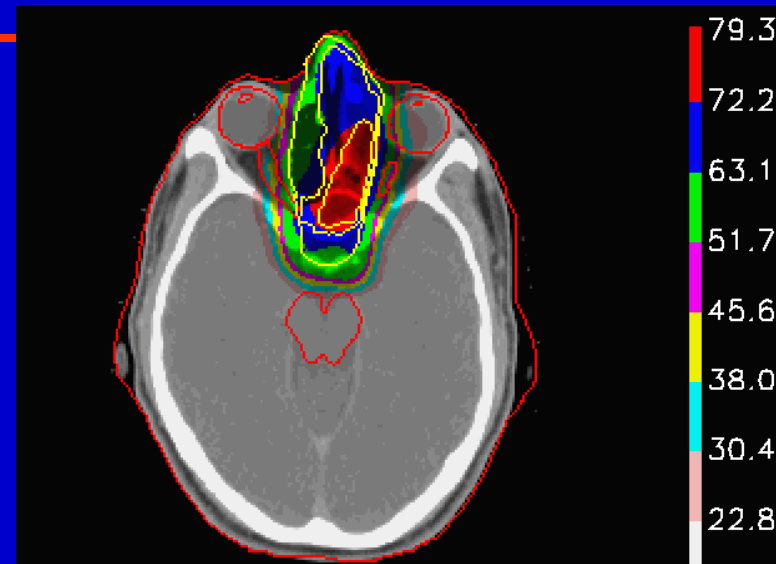
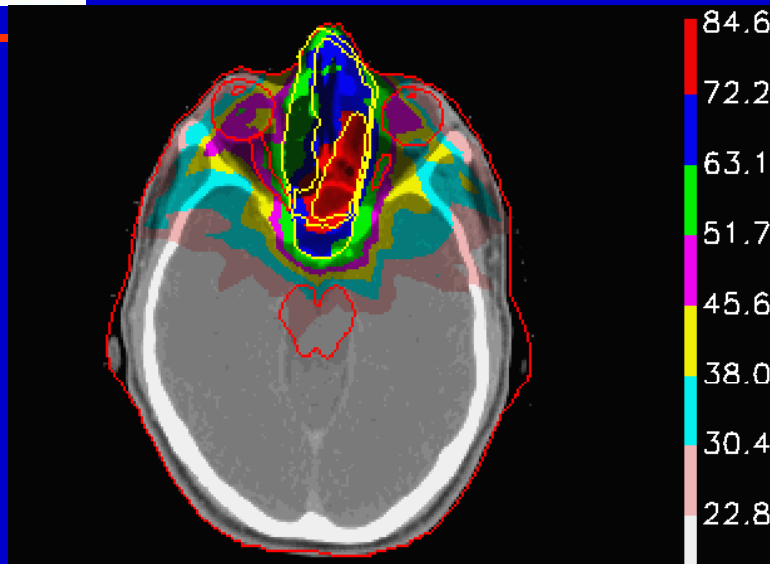
AKA: The Concept of a
“Safe Threshold Dose”



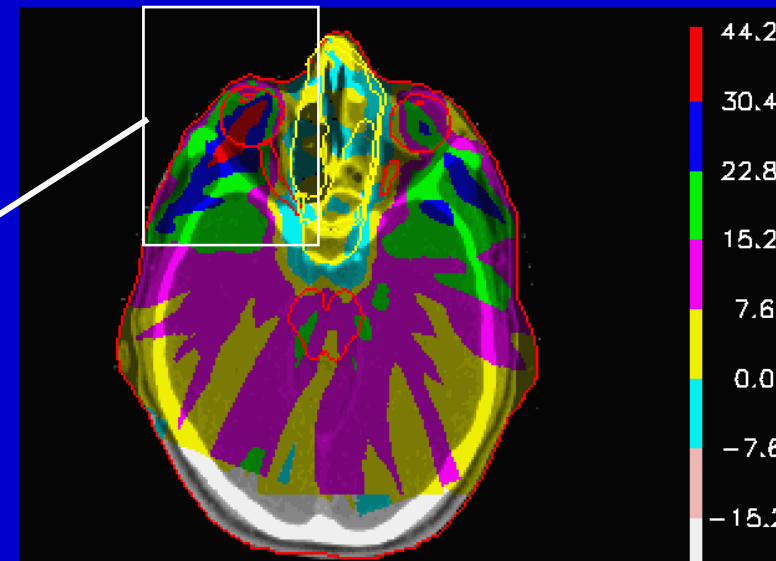
Paranasal Sinus

IMXT


IMPT



Dose
Difference →



PSI



Modeling Radiation Dosimetry to Predict Cognitive Outcomes in Pediatric Patients with CNS Embryonal Tumors Including Medulloblastoma

Merchant et al, IJROBP - 2006

- **Results**

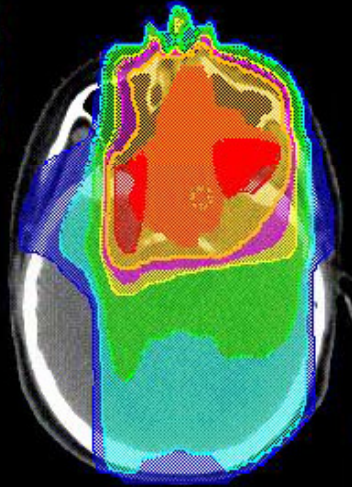
- Exposure to supratentorial brain had significant impact on long-term IQ and cognitive function
- Each Gy of exposure had a similar effect

- **NO DOSE THRESHOLD**

Additional studies by same group indicating exquisite relationship between radiation dose and neuroendocrine function

Juvenile Angiofibroma: IMRT vs. Protons

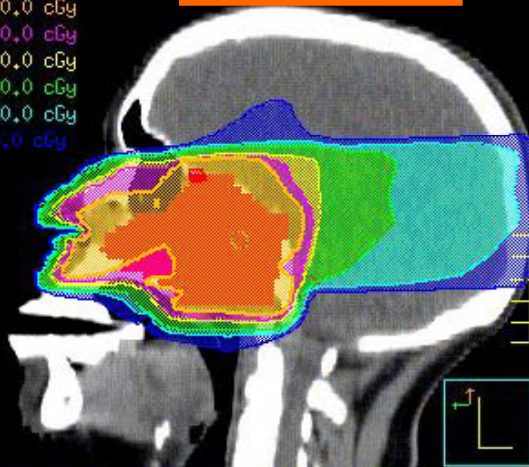
conformal
Absolute
4100,0 cGy
3600,0 cGy
3240,0 cGy
2880,0 cGy
1800,0 cGy
1260,0 cGy
720,0 cGy



Slice 40; Z = -34,55

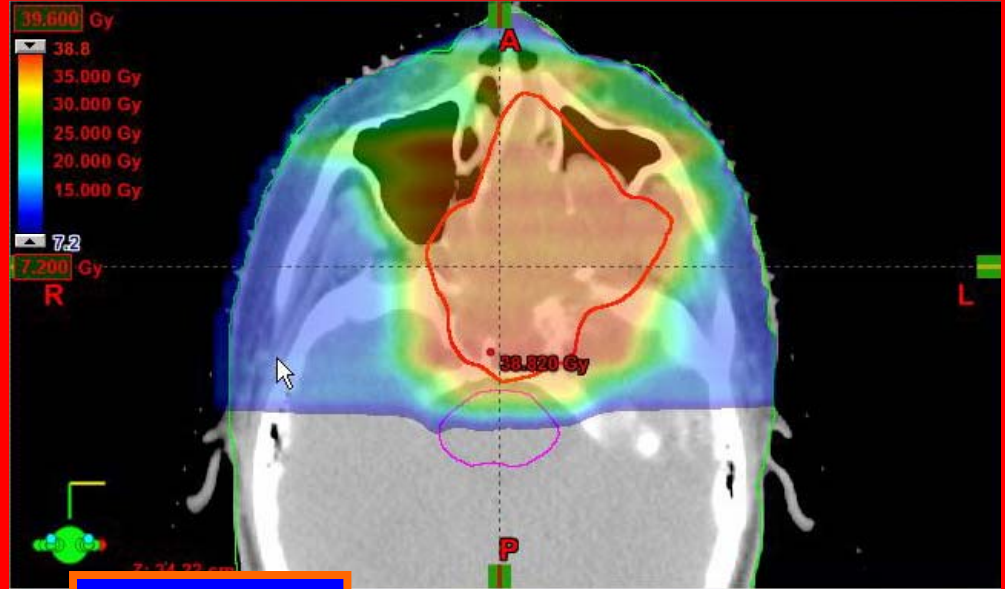
V20 = 50%
V10 = 71%

conformal
Absolute
4100,0 cGy
3600,0 cGy
3240,0 cGy
2880,0 cGy
1800,0 cGy
1260,0 cGy
720,0 cGy

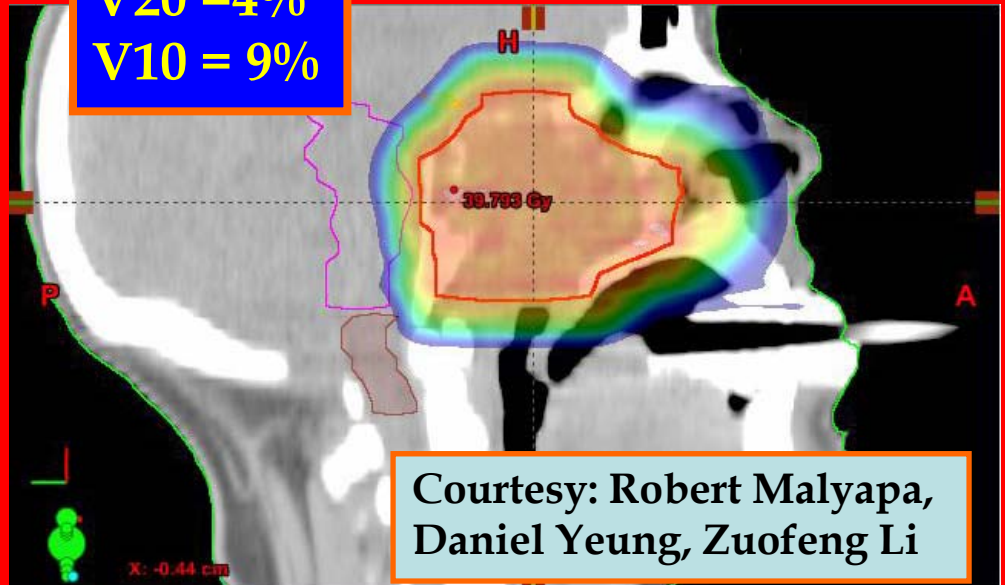


Slice 262; X = 0,591

39,600 Gy
38,8
35,000 Gy
30,000 Gy
25,000 Gy
20,000 Gy
15,000 Gy
7,2
7,200 Gy



V20 = 4%
V10 = 9%



Courtesy: Robert Malyapa,
Daniel Yeung, Zuofeng Li



Are low integral
doses relevant in
adults?

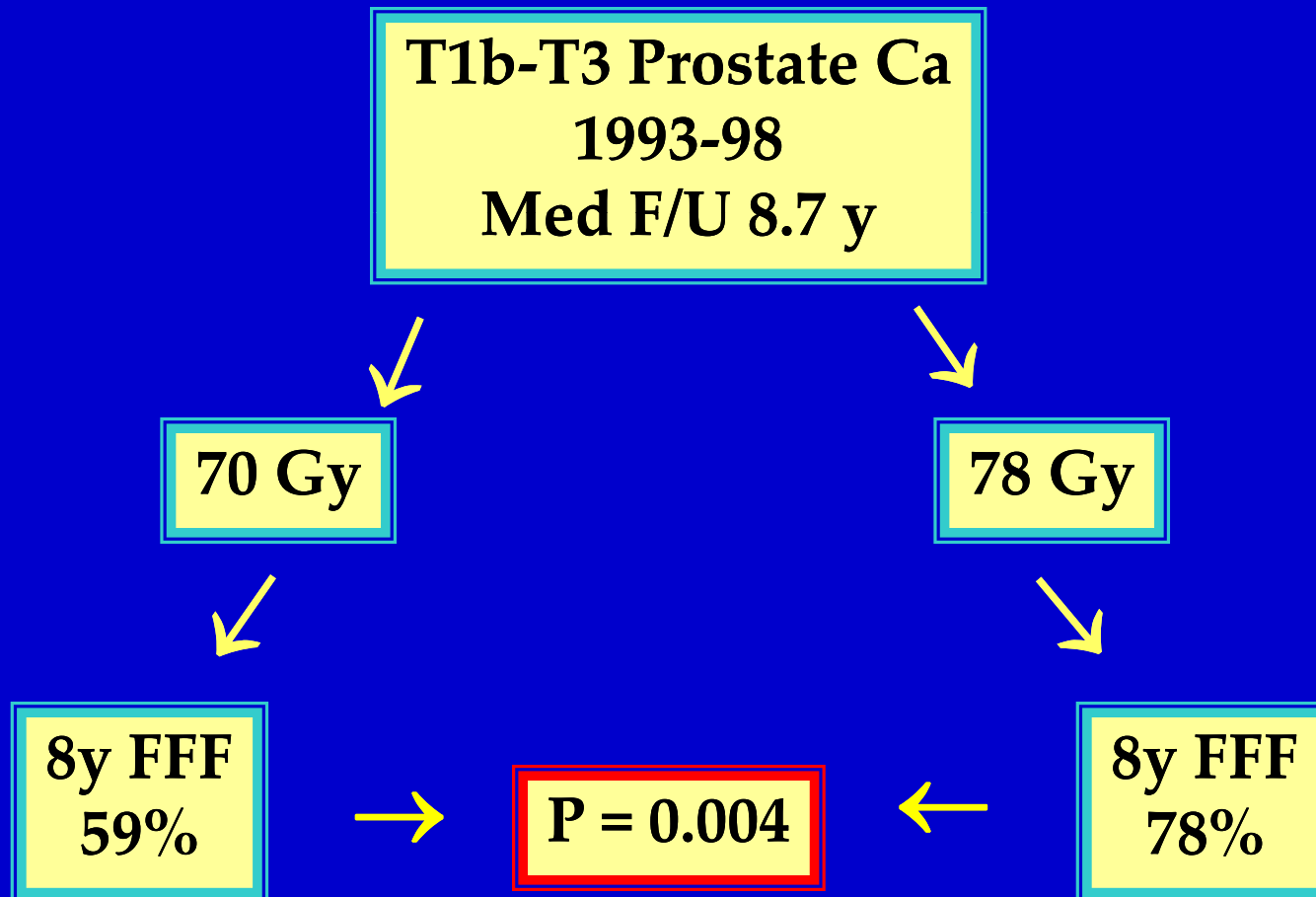


“Safe Threshold Dose”





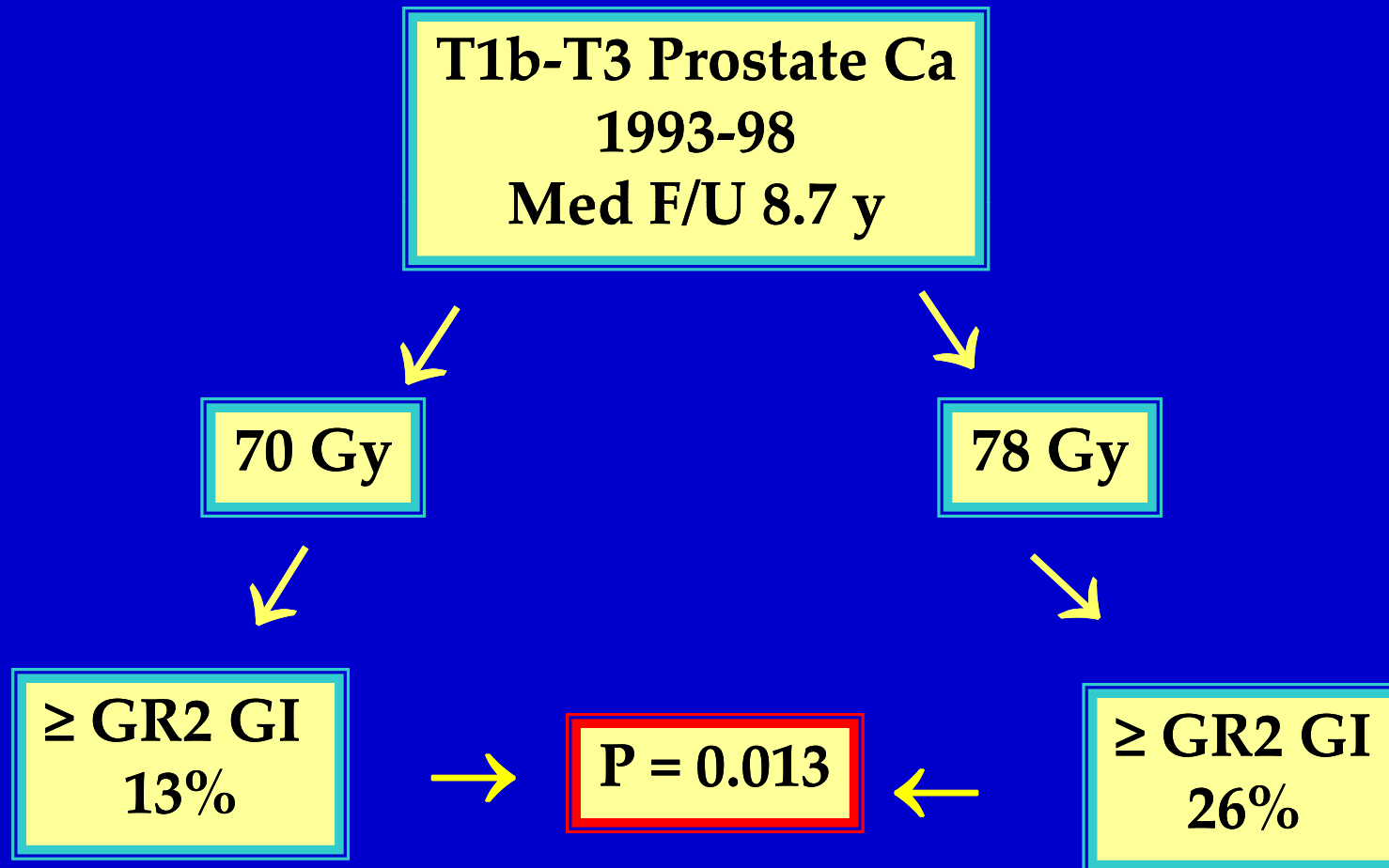
Dose Escalation in Prostate Cancer with X rays at MDACC



*Kuban et al, IJROBP,70:67-74, 2008.



Dose Escalation in Prostate Cancer: What about toxicity? MDACC



*Kuban et al, IJROBP,70:67-74, 2008.



Dose Escalation in Prostate Cancer MDACC

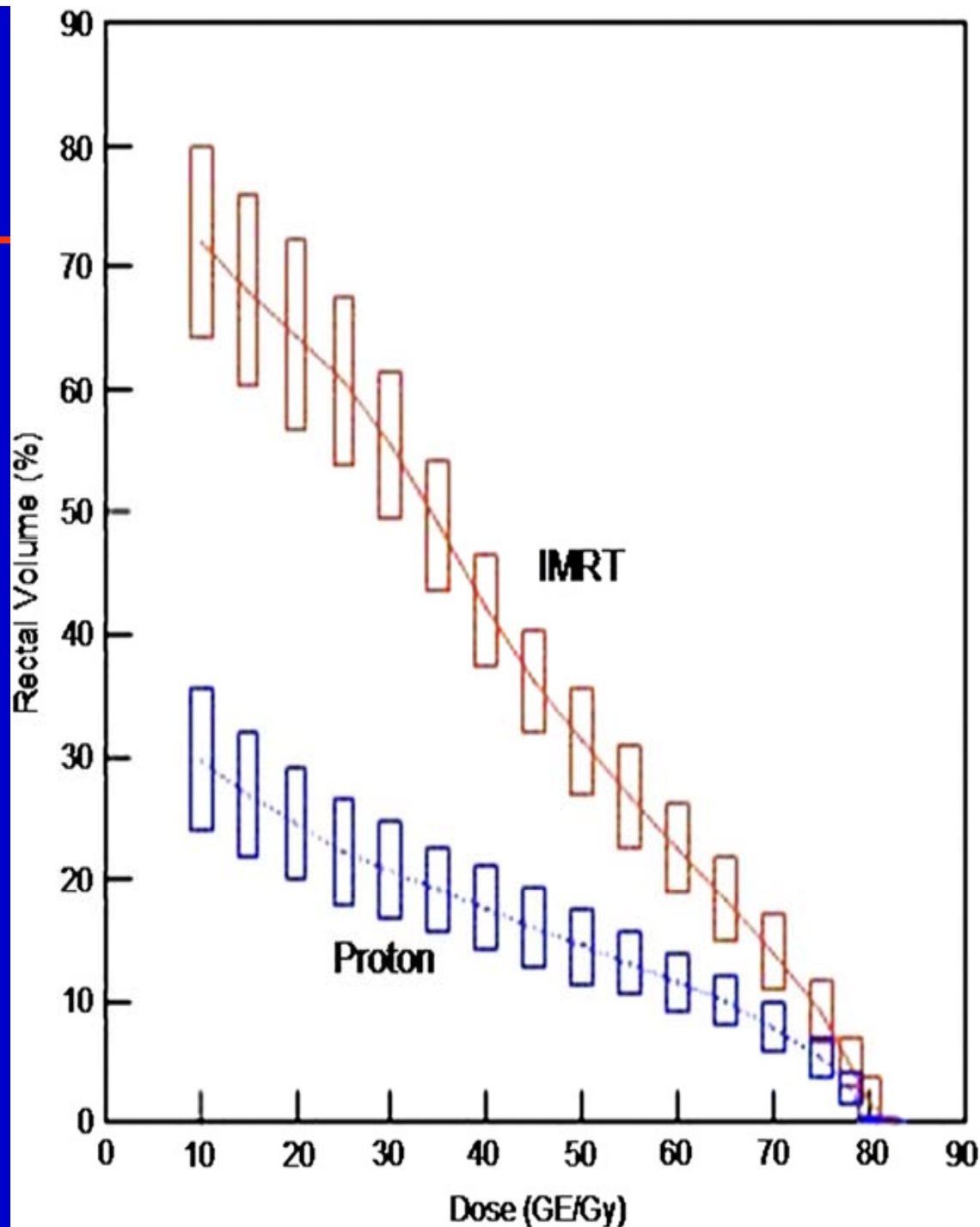
- Kuban et al have reported that the volume of rectum receiving lower doses (35 Gy to 60 Gy) is even more significantly predictive of future rectal injury than volumes receiving doses of 70 Gy+.

Kuban et al, IJROBP,70: 67-74, 2008.



Vargas et al, in a comparison of IMRT and proton plans for prostate cancer patients treated at UFPTI, have demonstrated significant reductions in the volumes of non-targeted tissues receiving a full range of doses (10-80 Gy/CGE) with protons.

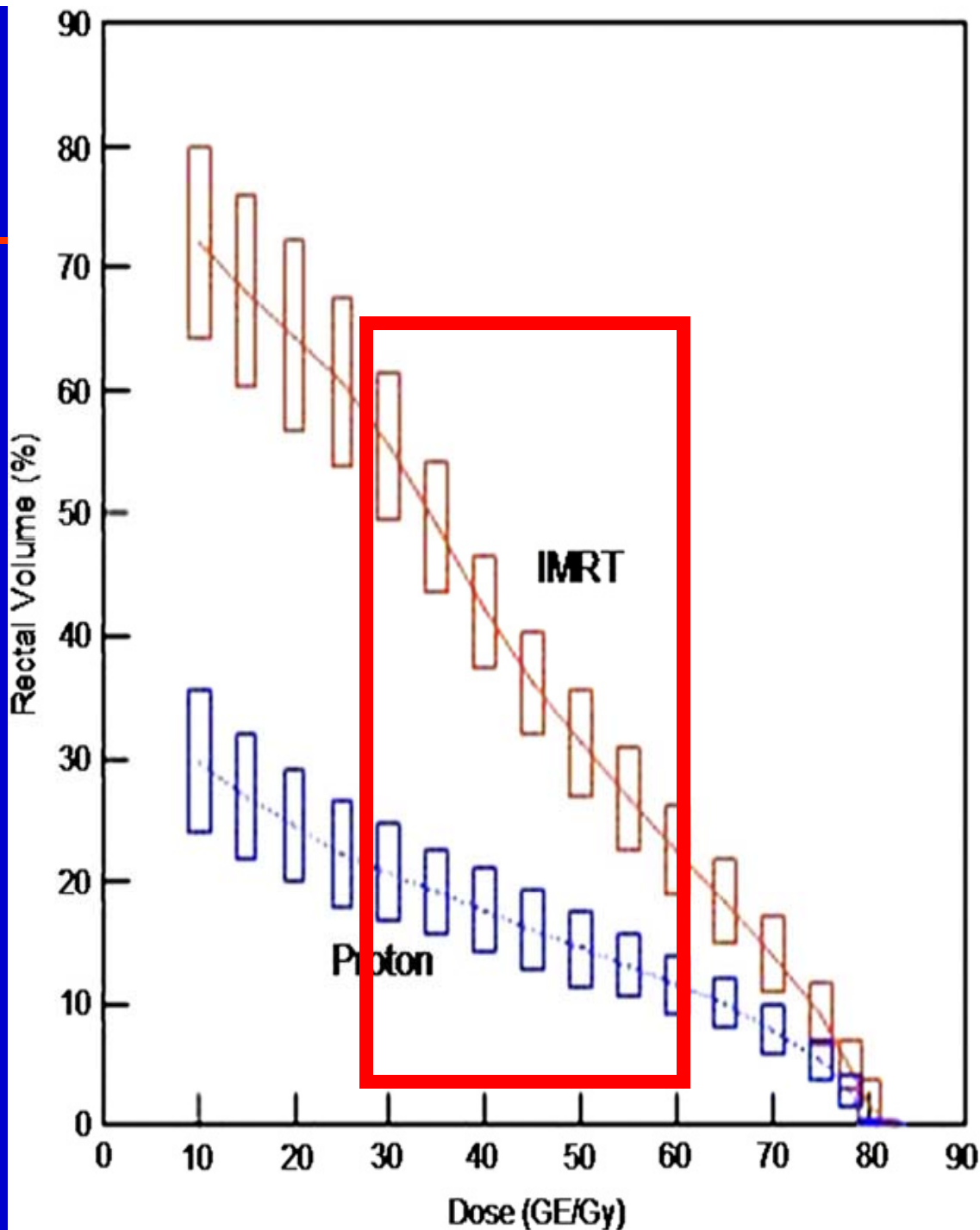
Vargas et al, IJROBP
70: 744-751, 2008





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Vargas et al, IJROBP
70: 744-751, 2008





Concept of “Safe Threshold Dose”

- **Necessary compromises with X ray dosimetry:**
 - Decreased cure rates to avoid early and/or overt toxicity.
 - Assumptions that low integral doses below the threshold for early and/or overt toxicity were safe.
- **Increased survivorship and sophisticated tools refute the concept of “safe dose.”**
- **Historical Examples:**
 - ↑ Cardiac disease in breast cancer survivors offset survival benefit of XRT.
 - Infertility, cardiac and thyroid disease in CSI survivors[†]
- **No published literature does not excuse us, as clinicians, from our responsibility to our patients**



Clinical Research Strategies in Proton Therapy

- Studies must be designed that do not knowingly subject patients to unnecessary integral dose radiation.





#2:

Failure to control for
confounding variables
affecting trial execution
and subject selection



Trial Execution: The importance of target definition and treatment delivery

- Because the vast majority of dose deposited goes into the targeted area, proton therapy may be more sensitive to errors in target definition and treatment delivery.
- Imaging must be high quality and patterns of subclinical disease spread must be understood, to create an accurate CTV expansion.
- Otherwise a trial may yield the answer to a targeting or delivery question rather than a comparative effectiveness question.



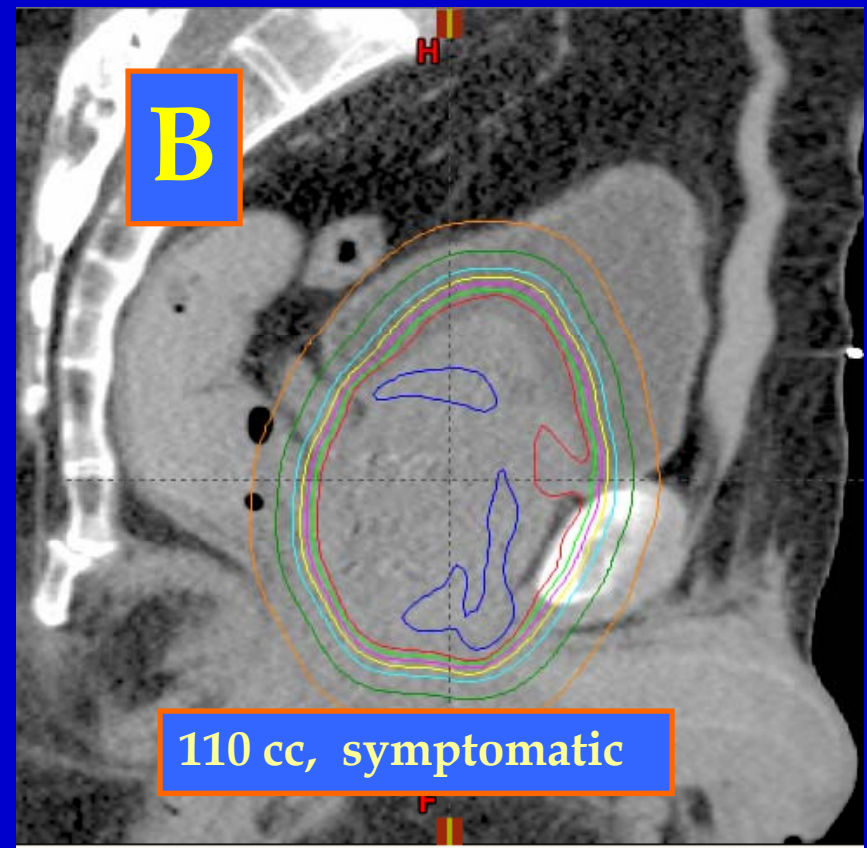
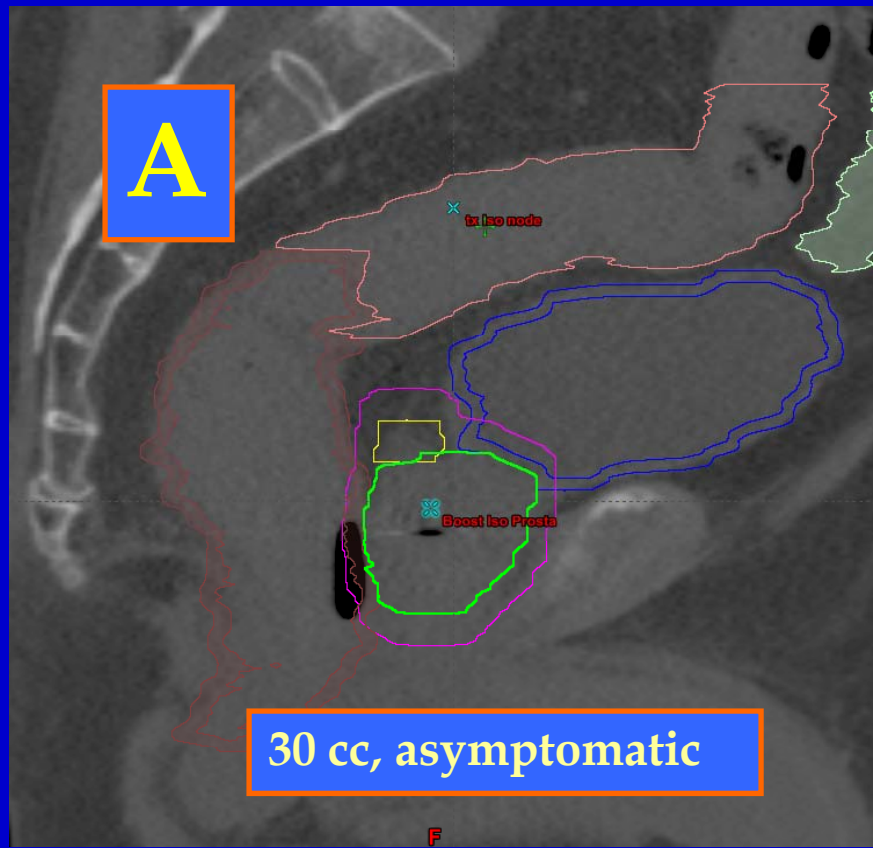
Historical studies in prostate cancer are difficult to compare:

- Different patients receiving surgery, brachytherapy, external beam irradiation
- Different pretreatment conditions
- Clinical staging
- Different thresholds for toxicity intervention





T1C Low Risk Prostate Cancer



- Both candidates for protons and IMRT, only **A** for brachy or surgery
- Dissimilar pretherapy conditions impacting toxicities
- Dependency on clinical exam for prognostic stratification



Future Comparative Effectiveness Research Should

- Compare apples with apples
- Use more objective stratification criteria than clinical exam
- Deal with confounding variables of pretreatment condition, medications, varying thresholds for intervention





#3:

Failure to ask questions for which sufficiently sensitive tools and time are available to measure the important end points

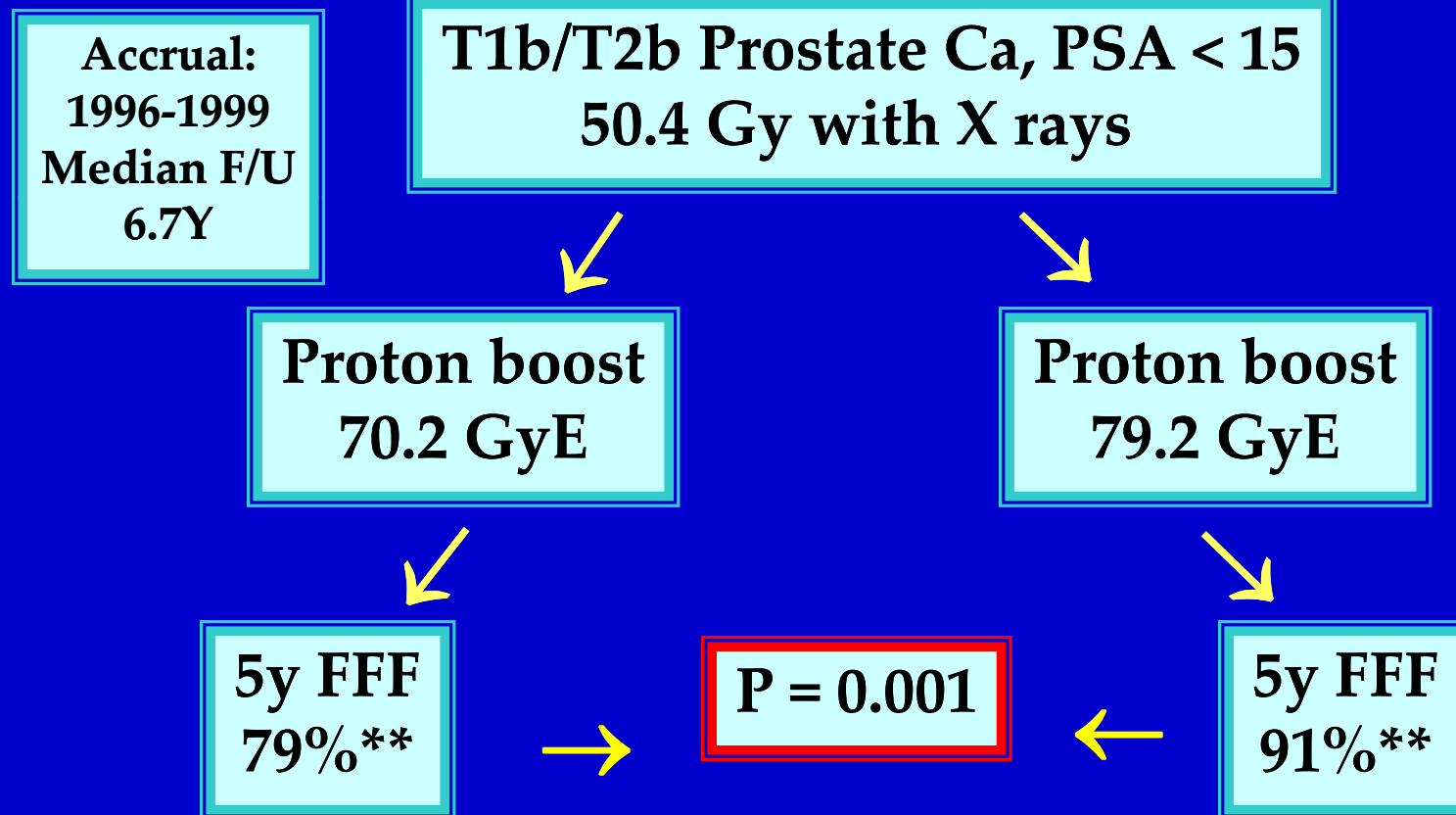


Failure to ask questions for which time and sufficiently sensitive tools are available to measure the important end points

- **Example: Postmastectomy Radiation Therapy (PMRT) Trials**
- Despite the correctness of the now-survival benefit of PMRT, multiple trials involving many thousands of breast cancer patients failed to detect a survival improvement, in part because imaging technology was inadequate for 1) evaluation of the adequacy of treatment delivery and 2) for the detection of the endpoint of concern: local and regional breast cancer recurrence.



Dose Escalation in Prostate Cancer using protons: PROG 95-09*

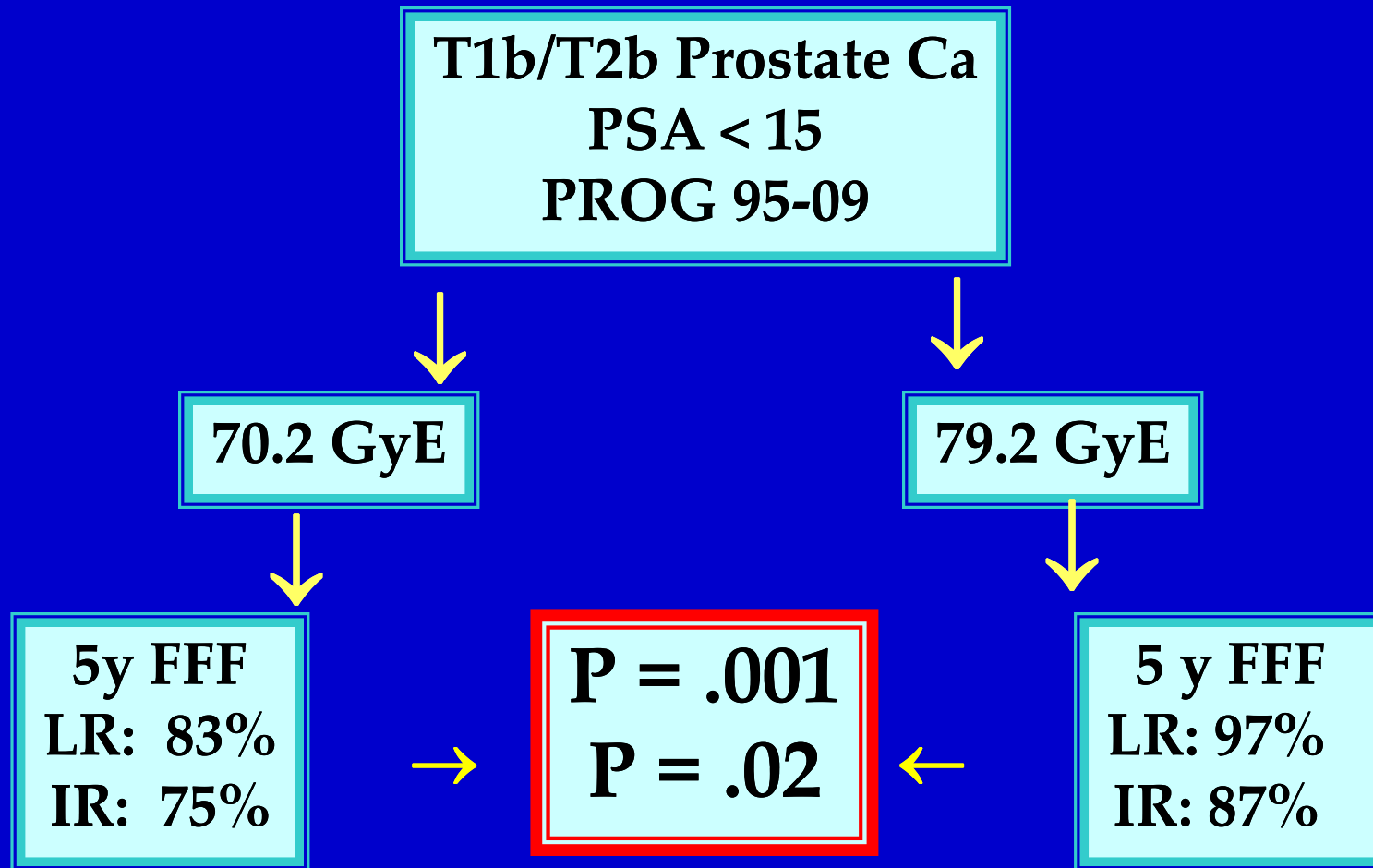


*Zeitman et al, JAMA, September, 2005 and February, 2008

**Originally reported as 63% vs. 81%.



PROG 95-09 Dose escalation using proton therapy in Prostate Cancer



*Zeitman Correction, JAMA, February, 2008.



Dose Escalation in Prostate Cancer PROG 95-09*

T1b/T2b Prostate Ca
PSA < 15, 1996-1999
Median F/U 6.7Y

70.2 GyE

79.2 GyE

GR2(3) GI Toxicity
8(1)%**

P = 0.005
(ND)

GR2(3) GI Toxicity
17(1)%**

*Zeitman et al, JAMA, September, 2005 and February, 2008



Dose Escalation and Quality of Life in Prostate Cancer PROG 95-09*

T1b/T2b Prostate Ca
PSA < 15, 1996-1999
Median F/U 6.7Y

70.2 GyE

79.2 GyE

Q of L GI Late Tox.
7.5%**

ND

Q of L GI Late Toxicity
7.7%**

Talcott, ASCO, 2008. "These results suggest that use of proton radiation boosts may partially mitigate treatment-related toxicity from increased dose."



Trials Based on Quality of Life

- At this point in time, it is unclear that quality of life tools are sufficiently sensitive to detect important differences among treatments despite very different documented toxicity outcomes.
- Trials designed primarily as quality of life studies may not be a wise use of resources at this stage in development of quality of life assessment tools, particularly if the actual treatment itself is a limited resource.



Comparative Effectiveness Trials: BNK 06-01

Courtesy of Dr. Chip Nichols



Bad Newz Kennels Cooperative Group Trial BNK 2006-01

Purpose:

- Determine if pit bulls are better fighting dogs than standard poodles.



Methods and Materials

- “Raoul,” a 2 year old standard poodle faced “Jaws,” a 2 month old pit bull, in a BNK sanctioned match.





Results

- The dogs wagged their tails and sniffed each other for 15 minutes.
- The match was declared a draw.



Conclusion

- Standard Poodles and Pit Bulls are equivalent fighting dogs.



BNK 08-01 Trial

- In 2008, the BNK Cooperative Group, in an effort to validate the results of the BNK 06-01 trial, conducted the BNK 08-01 Trial.
- Methods and Materials: “Raoul” and “Jaws” again faced each other in a BNK sanctioned match.



RESULTS



Raoul



Jaws

Courtesy of Dr. Chip Nichols



Conclusion

- The study design for BNK 06-01 was flawed.
- Early assessments underestimated the mature performance of one arm of the comparative effectiveness trial.



Disclaimer-Conflict of Interest

Have a
family
investment
in canines.





The Perils of Clinical Research in Proton Therapy: Ethical Issues



#4:

Failure to ensure
respect and beneficence
to the patient and
research subject.



Hippocratic Oath*

*Three of the 6 basic tenets of the Hippocratic Oath define the relationship between the physician and patient and inform the nature of “ethical” clinical research.

1. To practice and prescribe to the best of my ability for the good of my patients, and to try to avoid harming them.
2. Never to do deliberate harm to anyone for anyone else's interest.
3. To keep the good of the patient as the **highest priority**.
There may be other conflicting 'good purposes,' such as community welfare, conserving economic resources, supporting the criminal justice system, or simply making money for the physician or his employer that provide recurring challenges to physicians.



The Belmont Report

- Belmont Report, April 18, 1979
- Principles and guidelines for the protection of human subjects of research.
- Three underlying principles
 - Respect
 - Beneficence
 - Justice



The Belmont Report

- An *autonomous person* is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. Non-autonomous persons require protection.
- **To show lack of respect for an autonomous agent is**
 - to repudiate that person's considered judgments
 - **to deny** that person the freedom to act on those considered judgments
 - or **to withhold information necessary** to make a considered judgment, when there are no compelling reasons to do so.



Pertinence of Hippocratic Oath and Belmont Report in Consideration of Proton Therapy Trials

- **Assuming that confounding variables mentioned above are accounted for, the only difference between proton therapy and another form of external beam radiation therapy would be the difference in integral dose.**
- **The nature of the trial, then, would be to ask the question of whether integral dose to non-targeted tissue has a harmful effect.**
- **The patient has no potential benefit from such a trial.**
- **Therefore the guiding principles of both the Belmont Report and the Hippocratic Oath are violated.**



The Hippocratic Oath and Belmont Report

- **If the informed consent does not explain the nature of the trial question,**
 - then critical information necessary for autonomous decision has been withheld from the patient, further violating the Belmont principle of respect.
- **It is highly unlikely**
 - that an informed patient would choose to participate in a trial asking the question of whether integral dose might be harmful.
- **It is unlikely**
 - that a treating radiation oncologist, who has taken the Hippocratic Oath and read the Belmont Report, would consider recommending such a trial.



Rights of Patients and the IRB

- The Belmont Report requires respect of the patient's considered judgment.
- Proton therapy is not experimental—efficacy clearly documented.
- IRB unlikely to permit protocols that function as gatekeepers to deny patients access to a particular efficacious treatment by requiring participation in a protocol.



Summary Ethical Concerns

RCT simply comparing proton therapy with other forms of external beam radiation therapy will present significant ethical problems for most physicians familiar with proton therapy and likely be rejected by the informed patient.

The argument might not be that we already have evidence of better outcomes with proton therapy, but that we do not believe that unnecessary exposure of a patient to excess integral dose is in that patient's best interest.



#5

The Competing*
Good of Comparative
Costs of Treatment

**But lower priority*



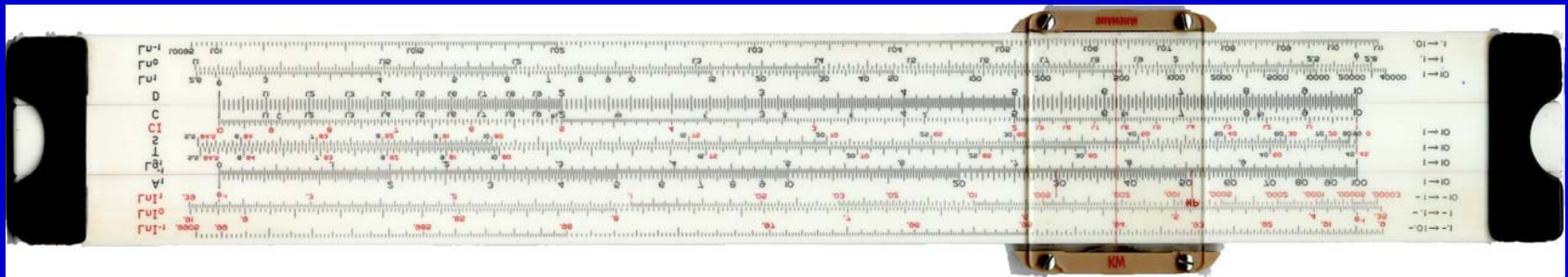
The Slide Rule



February 1, 1972: \$12.50



The Slide Rule



February 1, 1972: \$12.50



May 5, 2009: \$33.00



The Hewlett-Packard HP-35



February 1, 1972: \$399.00



The Slide Rule and The HP-35

Accuracy

Efficiency

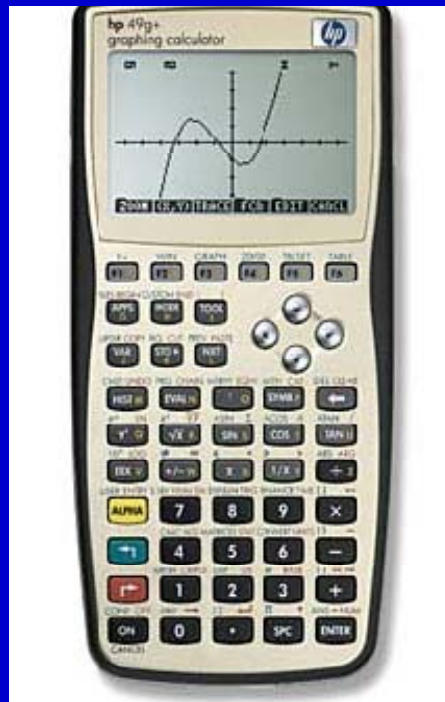
Increased potential for good



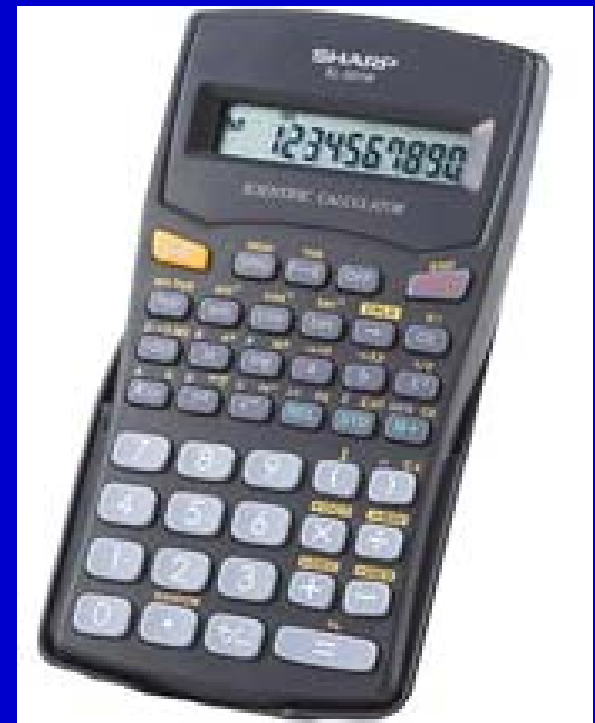
The Hewlett-Packard HP-35



**February 1,
1972:
\$399.00**



**May 4,
2009:
\$79.99**



**Walmart Price
May 4, 2009:
\$7.99**



Comparative Cost Assessment

Invalid if:

it does not account for costs of recurrence, costs of acute and late morbidity, costs of lost social effectiveness... and equipment replacement

Will change with:

increasing operational efficiency, volume, technical development, competition

Highly likely that:

the treatment producing the highest therapeutic ratio will be the most cost effective, and, because of this, competition to provide it will drive down costs, making it increasingly more effective with time.



Suggested Clinical Research Strategies in Proton Therapy*

*In particular as they relate to clinical research.



Suggested research strategies for proton therapy

- **Randomized Controlled Trials** of proton therapy versus another external beam radiation therapy modality present basic ethical issues (as well as practical issues related to the maturity of the technology available, at this point in time, for control of potential confounding variables).



Suggested research strategies for proton therapy

- Dosimetry studies to establish probable improved outcomes.
 - Dosimetry studies have been done in all areas of UFPTI investigation thus far.



Suggested research strategies for proton therapy

- **Prospective Outcome Tracking Trials:** for all patients treated with proton therapy, which is currently a limited resource.
 - 99% of all patients treated at UFPTI thus far have gone on our IRB-approved outcome tracking protocol.
 - This kind of trial can identify unanticipated outcomes that require further study, further technical development, new opportunities.



Suggested research strategies for proton therapy

- **Specific Proton Therapy Trials** as techniques are developed, to ask specific questions and establish specific benchmarks for proton therapy outcomes should be performed.
 - At UFPTI, 3 trials have been completed in low, intermediate, and high risk prostate cancer and 14 trials are currently ongoing in head and neck cancer, brain tumors, pancreas, lung, Hodgkin's, sarcoma, and prostate cancer, additional studies in development in specific pediatric tumors.



Suggested research strategies for proton therapy

- **Virtual Controlled Trials:** based on actual IRB proton therapy trials with a virtual internal control arm created by application of competing radiation therapy technology treatment planning to actual proton target with estimation of virtual outcomes based on peer-reviewed disease control and toxicity models.
- UFPTI proposal made in response to ARRA CER RFP.



Thank You

To AAPM and ASTRO

To The Particle Therapy Community

To my UF and UFPTI colleagues and staff

And to all those who have made it possible for us to investigate the promise of proton therapy.