Particle (proton) Therapy

Randomized trials vs. Prospective registry

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Should we do randomized trials?	Yes
Are randomized trials needed before accepting protons?	Depends
Is it feasible to do randomized studies comparing XRT vs. protons?	Doubtful

Why proton therapy?

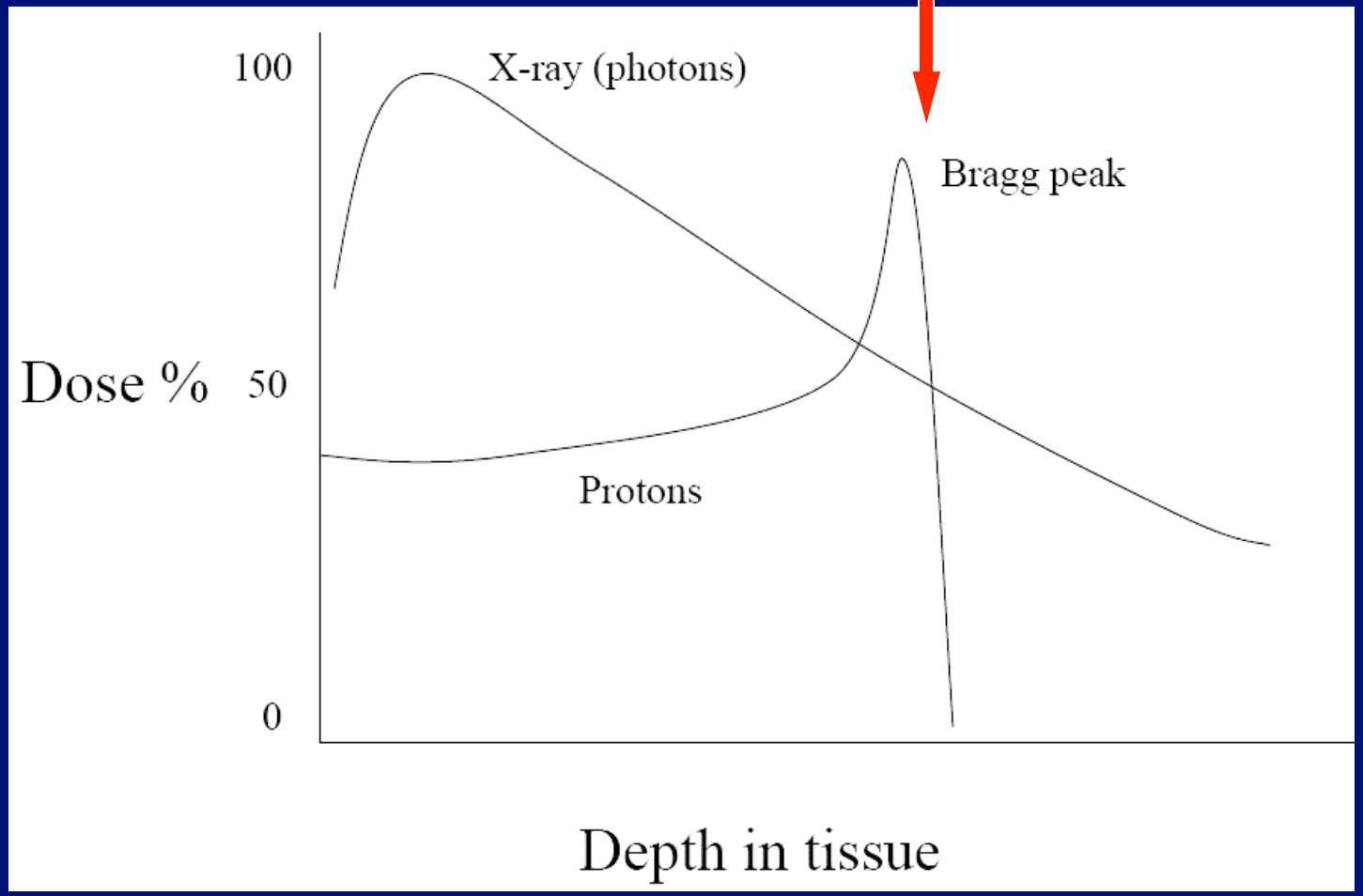
Deliver higher radiation doses accurately

Increase tumor control (only if we can deliver equivalent or higher doses)

Decrease toxicity

How are protons different than x-rays?

X-rays don't stop…protons

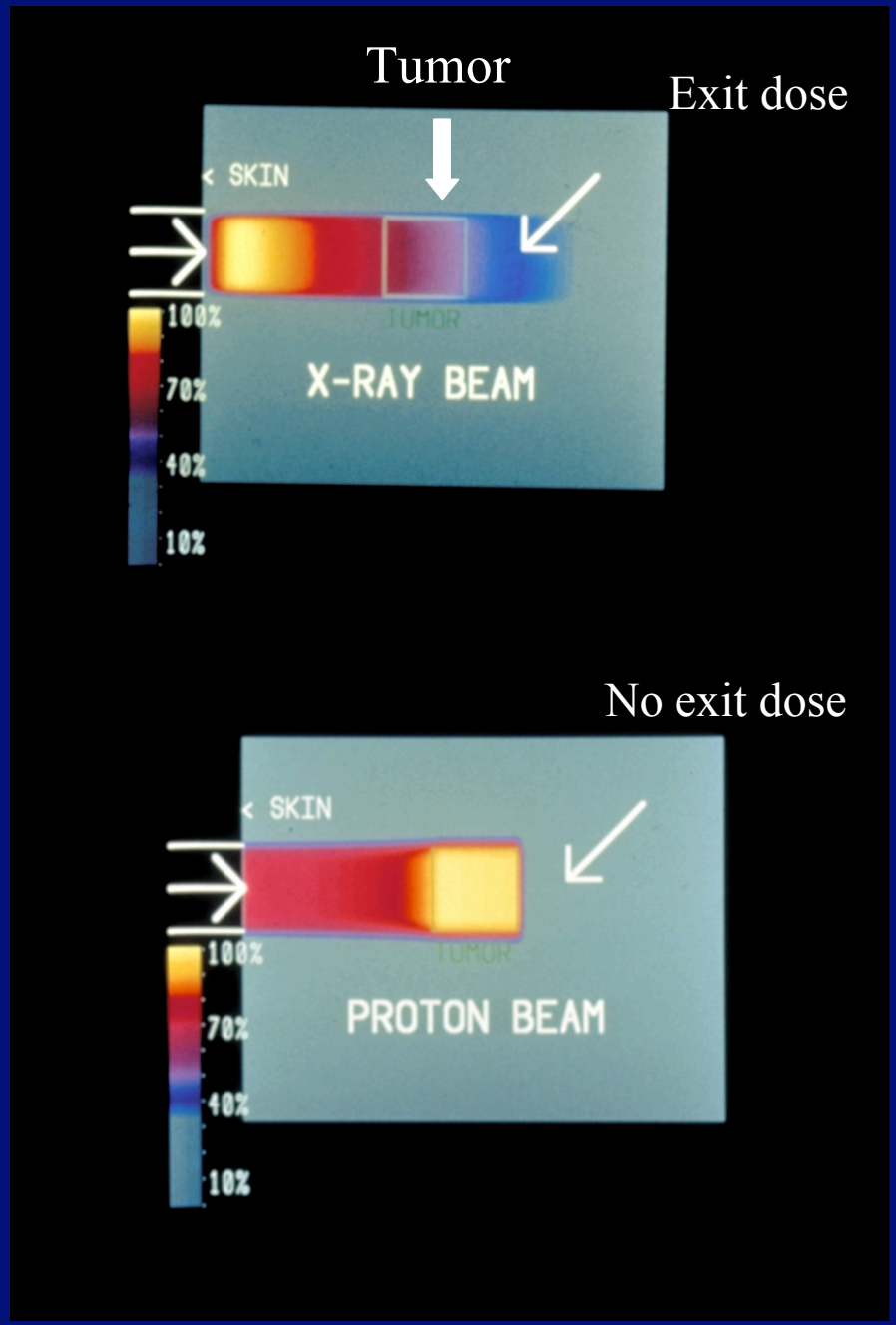


X-RAYS

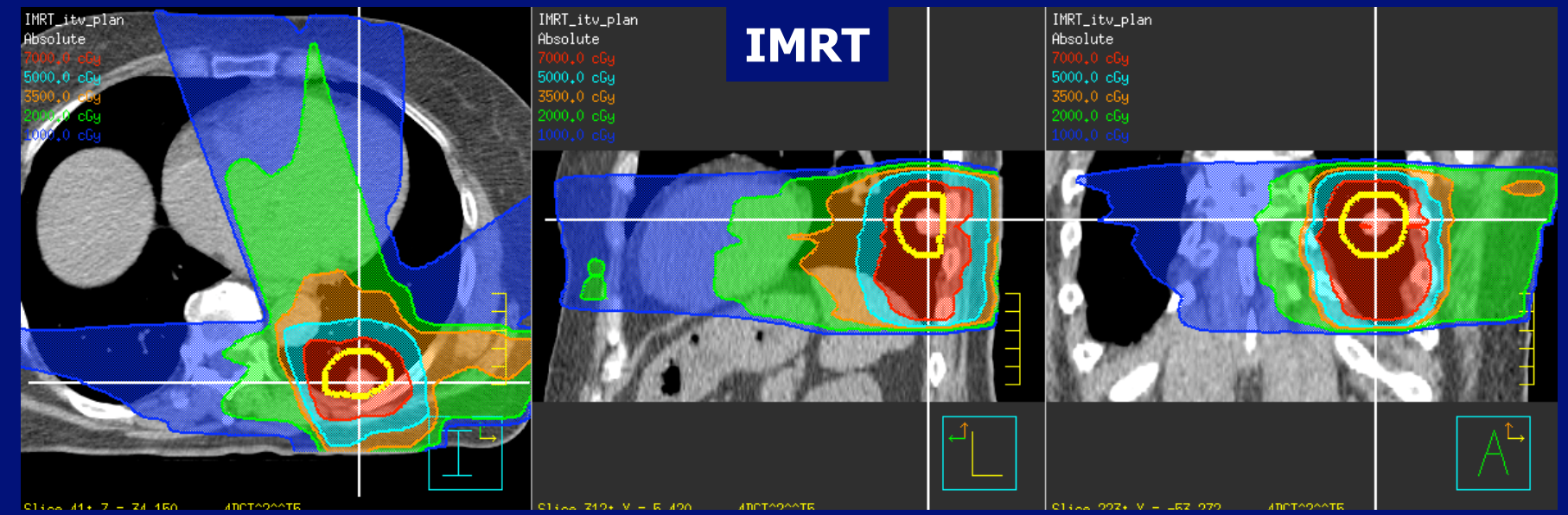
Yellow 100% dose

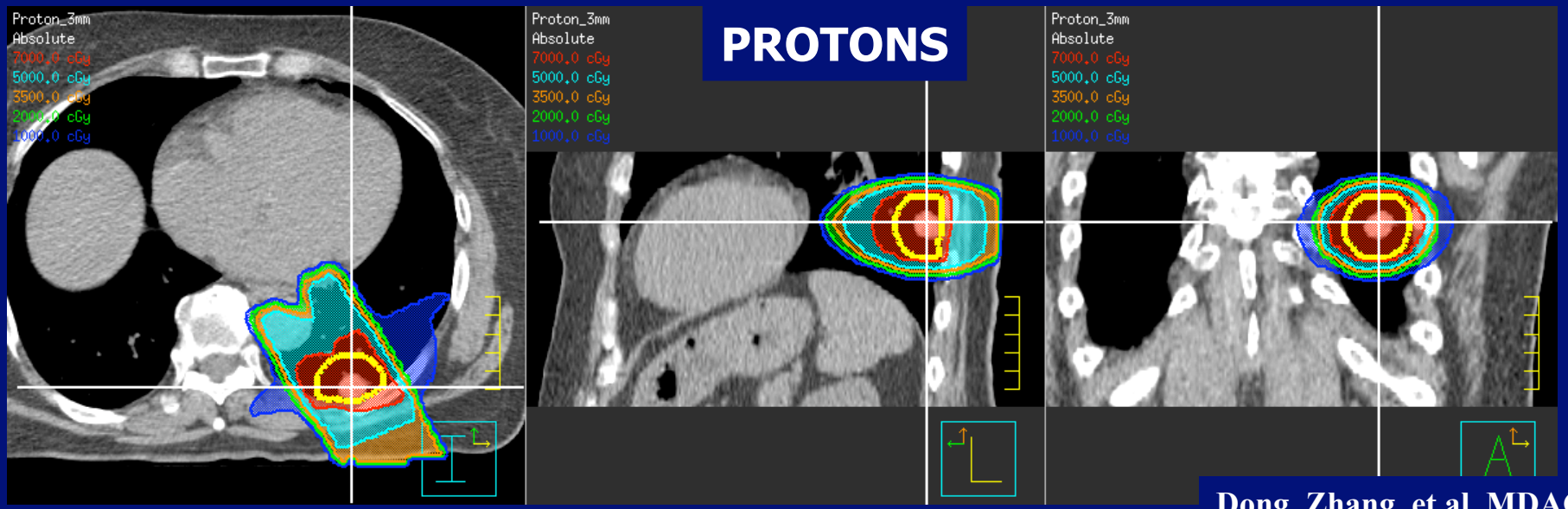
Blue 40% dose

PROTONS



IMRT (x-rays) vs. Protons





Dong, Zhang, et al MDACC

Evidence

- Recent systematic review
- 41 comparative studies
  - Most compared w/ historical controls & one at a different center
  - Few prospective studies
- Only 1 RCT
- Findings regarding local control and overall survival are “generally inconclusive”
- This review indicates sparse clinical data for…

Lancet Oncol 9;2008

IMRT !

IMRT vs. Protons

- Given the total number of patients and facilities involved with each modality, there is actually more evidence to support proton therapy than IMRT

Example: Prostate cancer

- RCT's show dose-escalation improves outcome
- RCT comparing 2D vs. 3D showed no difference in LC but did show less Gr 2-3 proctitis (Lancet 353;1999)

- IMRT adopted as "standard" on the basis of…
  - No RCT comparing 3D vs. IMRT
  - No RCT comparing IGRT: 3D vs. IMRT
  - Single institution retrospective experiences

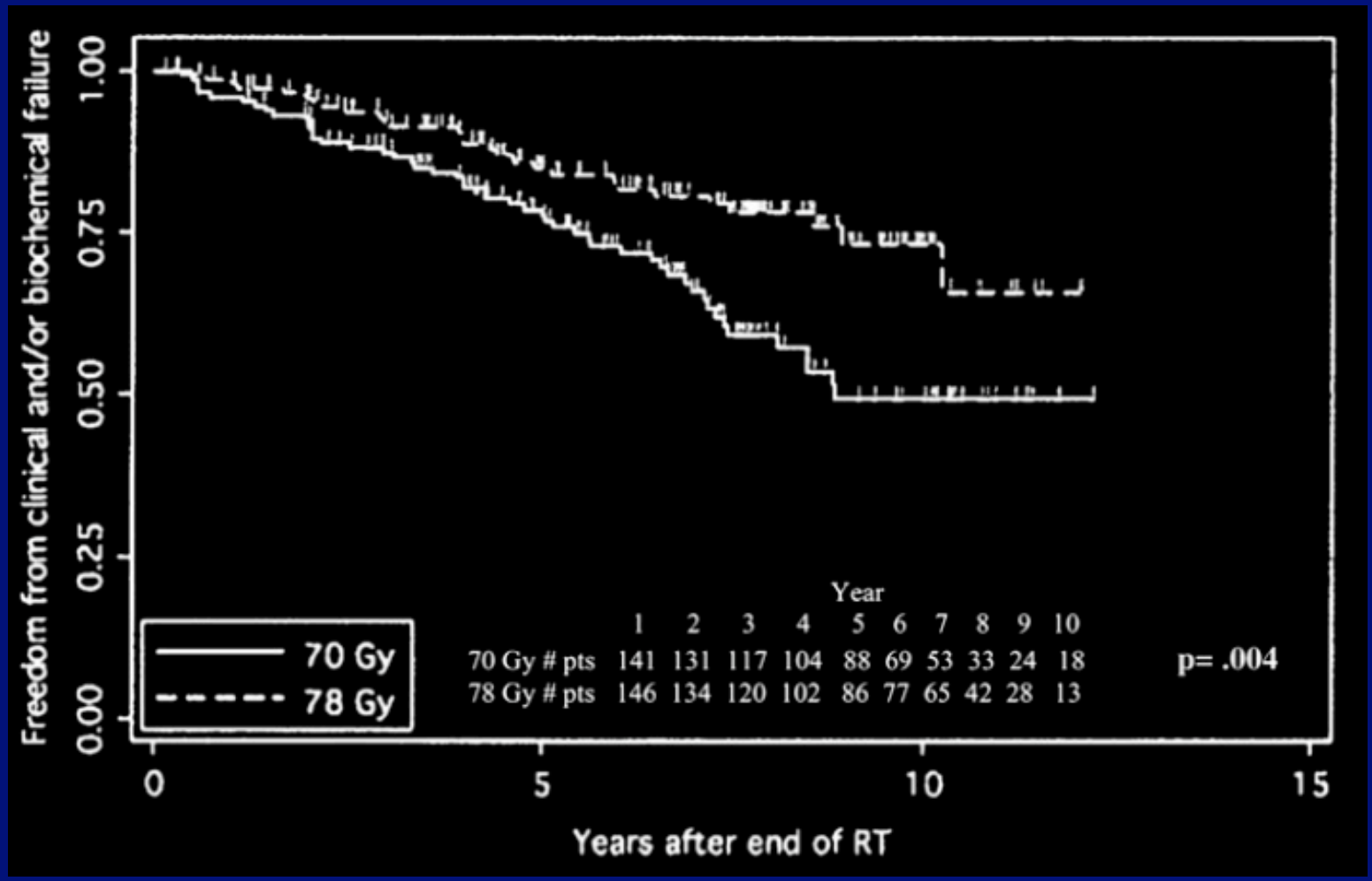
Randomized studies showing benefit to higher dose

- MDACC randomized study of 70 vs. 78 Gy
  - Clinical benefit preferentially for 78 Gy including low risk
  - FFF
  - No difference in DM or OS
    - [JCO 18, 2000] [Updated IJROBP 2008]

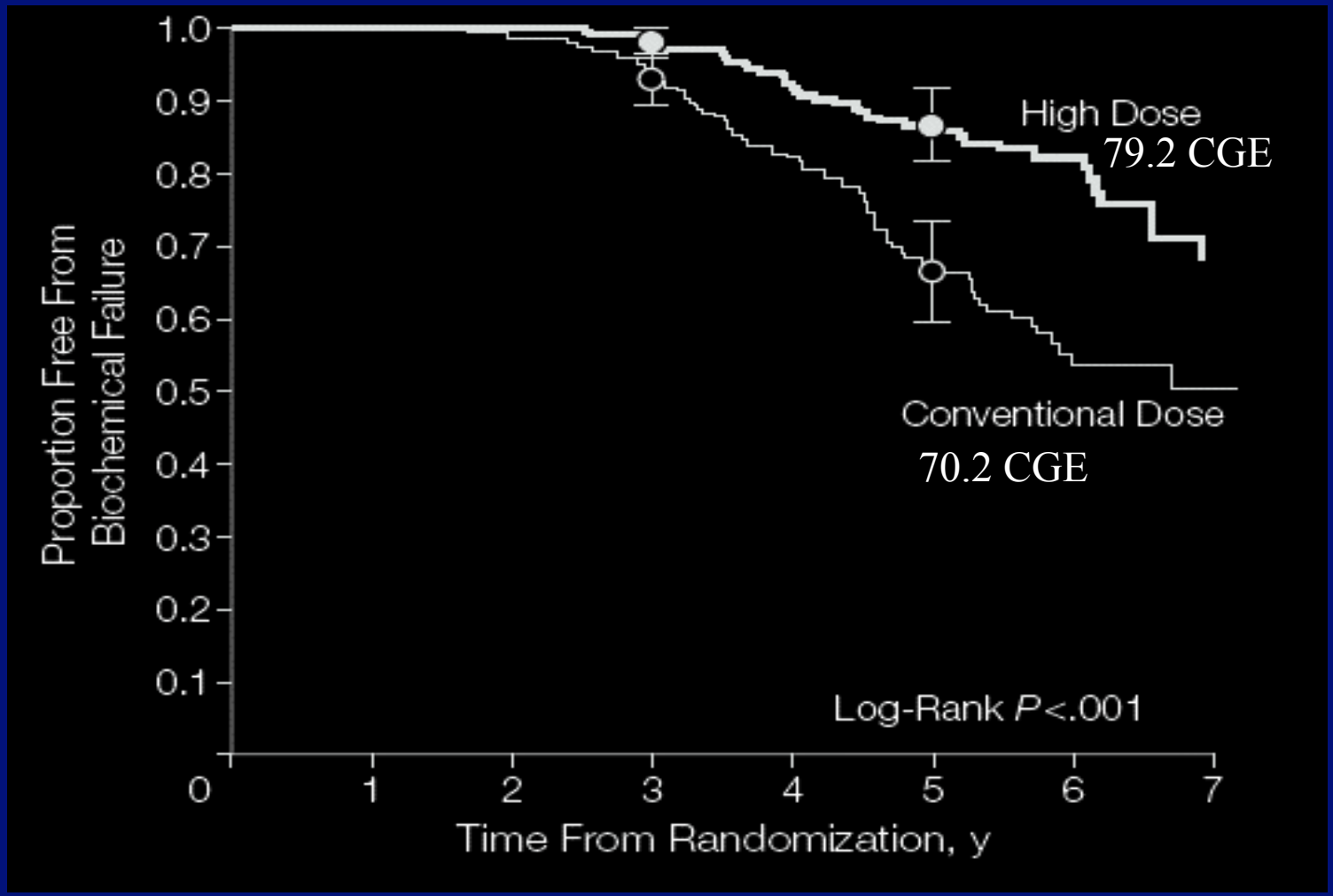
- Proton randomized study LLUMC & MGH
  - 70.2 Gy vs. 79.2 Gy (1.8Gy fxn)
  - Proton boost first 19.8 vs. 28.8 CGE followed by photon 50.4 Gy
  - PSA control benefit in all patients including **low** risk

[JAMA 294:1233-39, 2005]

MDACC 78 vs 70 Gy: Freedom from failure



Proton-photon trial: PSA-Failure free survival



[JAMA 294:1233-39, 2005]

Comments

- Majority of dose given with x-rays 50.4Gy with <29 CGE delivered via protons
- Proton technique may not have been optimal

Late side effects: grade 2-3 rectal

MDACC		Proton-photon	
70 Gy	13%	70.2 CGE	9%
78 Gy	26%	79.2 CGE	18%

Late GU side effects ~15-20% for all arms

Is this a legitimate comparison?

- Only as a basis for exploratory analysis or subsequent clinical studies
- Probably more valid to compare prospective studies than prospective vs. retrospective at different institutions
- Certainly better than doing cross-institutional comparisons of retrospective experiences

Why randomized trials?

- Test hypothesis
- Account for known and unknown confounding factors

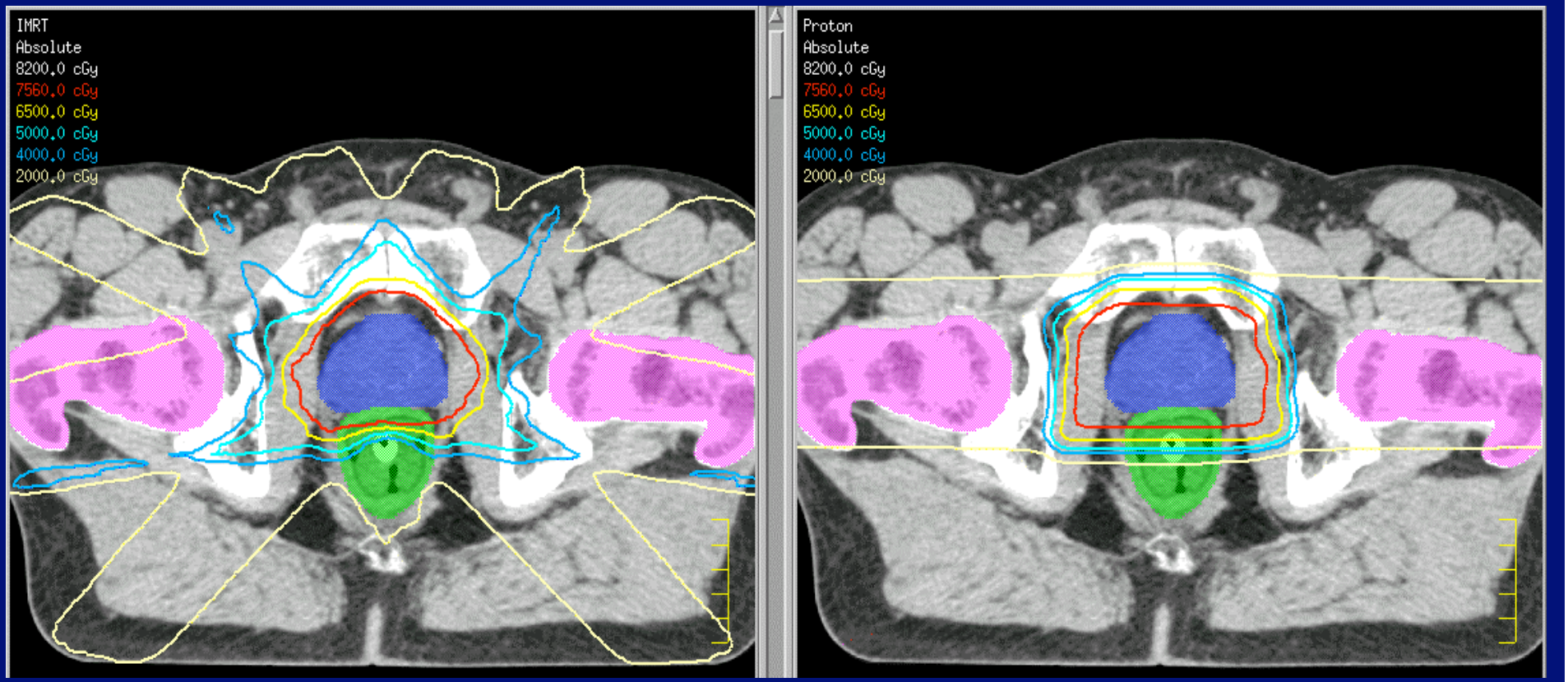
What is needed for RCT?

- Valid hypothesis
- Measurable endpoint
- “Equipoise” between arms
- Sufficient sample size (power)
- Willing subjects
- Willing investigators

One MD's experience trying to enroll onto a RCT…

IMRT

Protons



Red is prescription isodose.
Beige is 20 Gy

Typical patient responses

"That's great doc…when can I start protons."

"Why would anyone want IMRT when they can have protons?"

"Can I just choose protons and not get randomized?"

I have more people enrolled on MDACC active surveillance protocol than selecting IMRT.

What happens after RCT?

- Results are ***positive*** and superior arm is adopted
- Results are ***positive*** and superior arm is ignored b/c of bias or difficulty in performing Rx

- Results are ***negative*** and people say that arms are either "equivalent" (incorrect assumption) or study was under-powered

- New therapy comes along and the RCT is no longer relevant

- Other data or pressures result in poor accrual and ultimate failure of study to be completed (e.g. SPIRIT)

Does that mean we don't have to do randomized trials?

Randomized trials and Prospective registries

- Prospective data collection at a minimum
- Phase I & II
- Phase III when feasible
  - Only handful of centers would be able to perform these trials currently

- In the meantime, should we have more proton centers?

It's already happened…

- 5 in U.S. in operation with 10 more on the horizon
- I would never have believed that 10 years ago
- Embrace and integrate rather than compete

Advantages to more centers

- More access for patients
- Opportunity for collaborations & larger scale cooperative research

- Competition will motivate innovation (and probably reduce cost)
- Economies of scale (bring down per unit cost)

- Probably only way to make large RCT feasible
  - Not relying on few institutions to bare burden
  - $ + $ + $ +$ vs. $$$$

Disadvantages

- $$$$
- Requires technical expertise
- Quality control
  - Don’t speed…”this stuff is complicated.”
  - “If we make a mistake, then we may affect more than our center but rather the field of proton therapy.”

Innovation vs. $$

- 3D-CRT
- MLC
- SRS
- IMRT
- IGRT
- Tomotherapy
- Cyberknife
- Dynamic arc therapy

We’re not alone

	Annual Sales
• $645,000,000	leuprolide (Lupron)
• $1,008,000,000	goserelin (Zoladex)

Table 2. Top 15 Clinic Drug Expenditures[11]

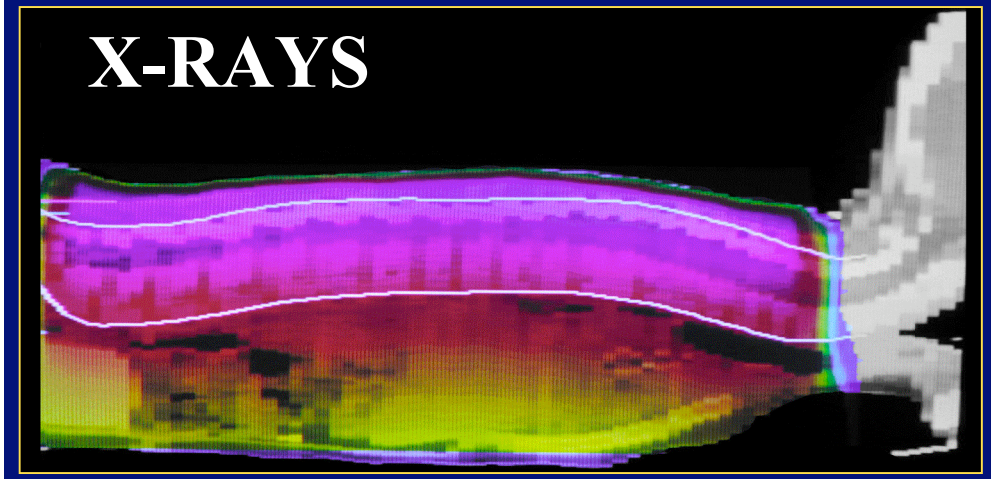
Drug	Total 2004 Expenditures ($ in thousands)	Percentage of Total 2004 Clinic Expenditures
Epoetin alfa	3,901,126	17.7
Darbepoetin	1,214,297	5.5
Pegfilgrastim	1,160,429	5.3
Infliximab	1,269,004	5.8
Rituximab	950,981	4.3
Oxaliplatin	541,014	2.5
Docetaxel	635,990	2.9
Zoledronic acid	466,887	2.1
Trastuzumab	364,762	1.7
Gemcitabine	420,510	1.9
Paricalcitol	349,728	1.6
Pneumococcal vaccine, diphtherla conjugate	349,836	1.6
Irinotecan	327,023	1.5
Filgrastim	227,999	1.0
Carboplatin	317,603	1.4

J Clin Oncol 2007;25

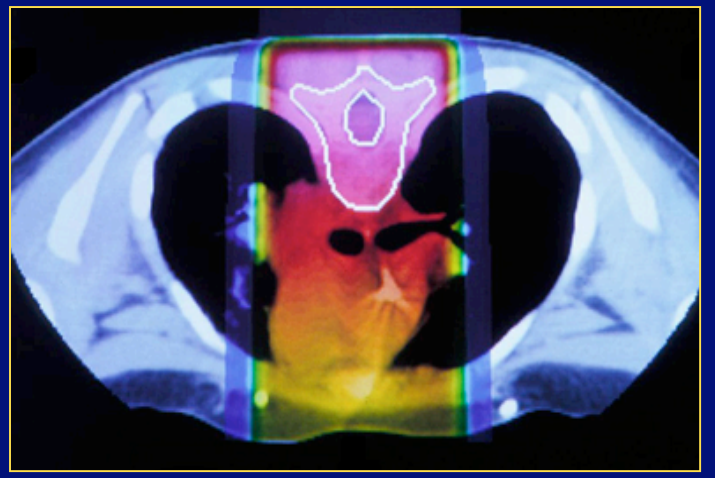
Pediatric Tumors

- Regular x-ray therapy may have side effects even at low doses for young children
  - Growth disturbances
  - Decreased functional outcomes
    - Hearing, vision, neurocognitive, etc.
  - Cosmesis
  - Second cancers

MEDULLOBLASTOMA



Exit dose ~50%!!!

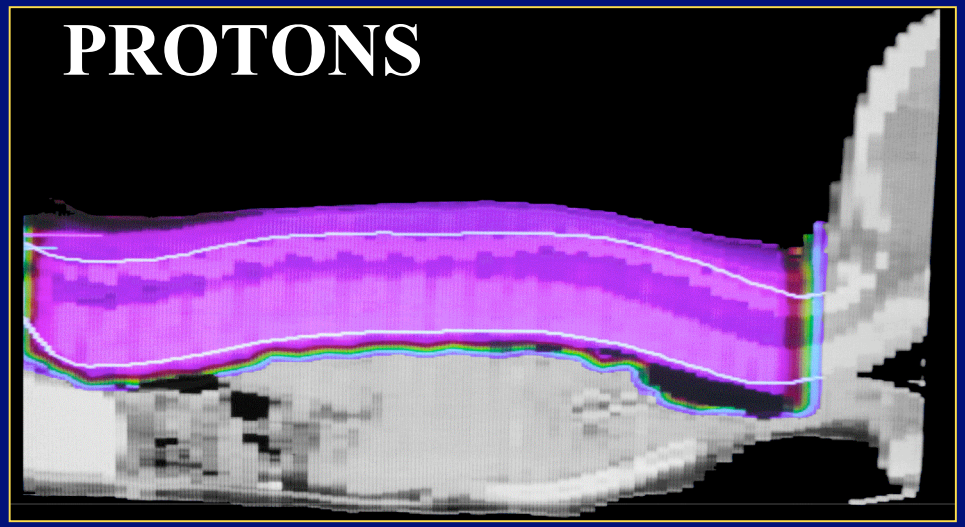


Exit dose ~50%!!!

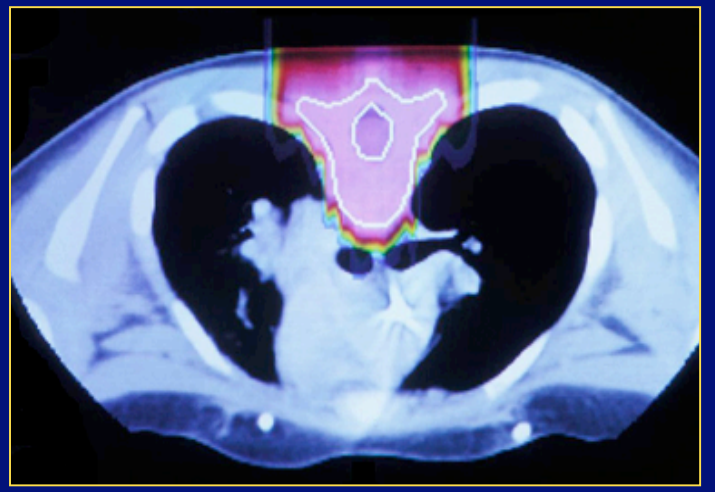
100

60

10



No exit dose



No exit dose

RCT for pediatrics

- Not many willing to do this…"un-ethical"
- Protons allow more dose to target and less dose elsewhere

- Don't we want this for all our patients?

- More importantly, isn't this what our patients want for themselves?

Proposed RCT for prostate ca

T1-2, Gleason 6-7, PSA <20

Image-guidance, Central QA for CTV & rectum, DVH constraints

IMRT

Protons

3D-CRT

Endpoints

- Grade 2-3 toxicity
  - Equivalence (<10%? <5%? <2%?)
- HRQOL
- PSA outcome
- $$

Is disease-free survival the most important factor for prostate cancer patients?

If patient fails therapy, it may not translate into a meaningful difference in survival

As disease control and survival improves (either cancer-related or other competing risks), quality of life more important

Toxicity vs. Quality of Life

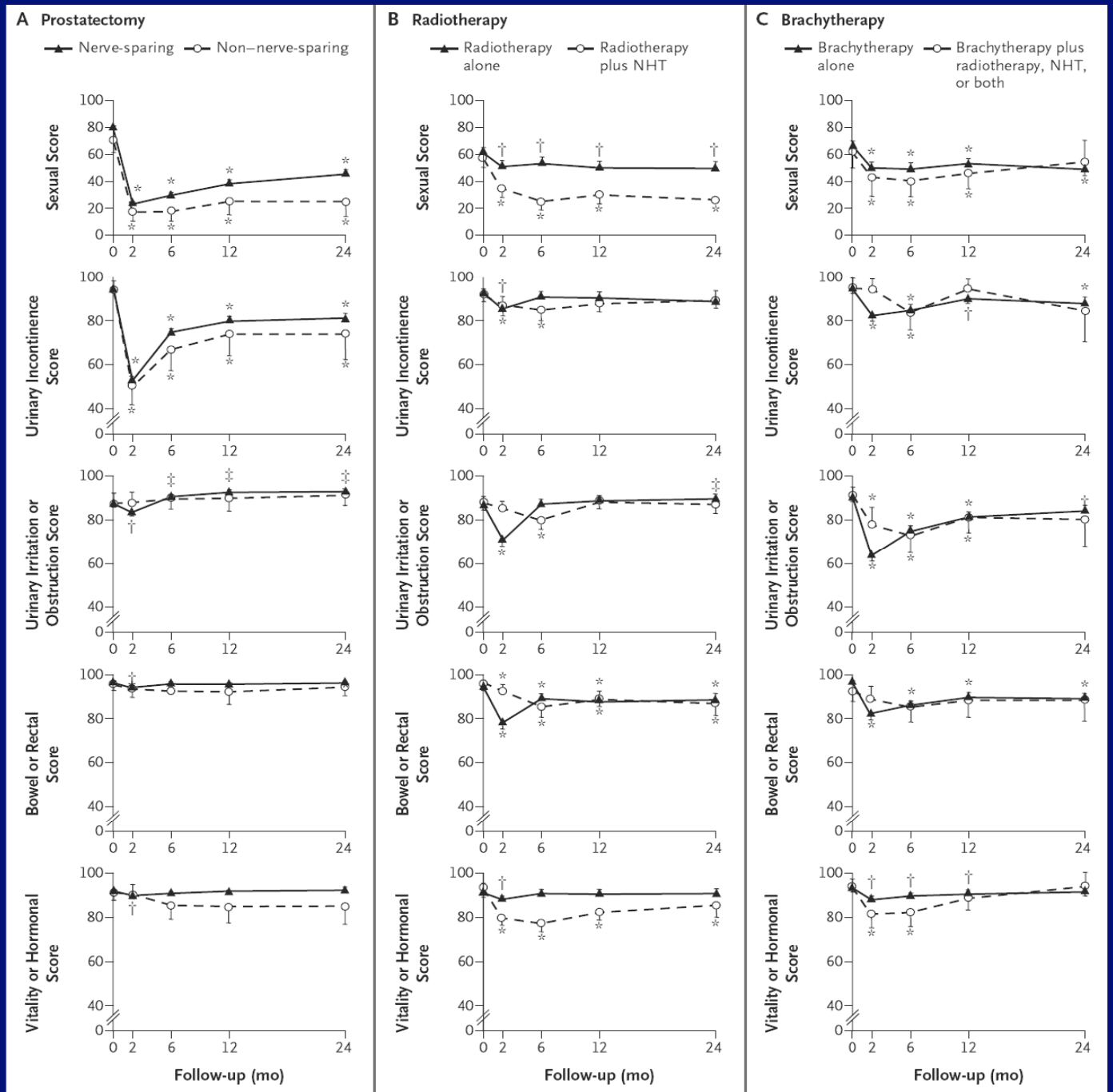
- Rectal bleeding

- My erectile dysfunction *bothers* me

Quality of Life
(Beyond toxicity scales)

- Function vs. Irritation vs. Bother

- Baseline function
- Prospective vs. retrospective
- Patient vs. physician reported
- Validated instrument (e.g. E.P.I.C.)



NEJM 358; 2008

MDACC protocol **2005-0956**

"Prospective evaluation of quality of life after proton therapy for prostate cancer"

- Prospective
- Validated instrument (E.P.I.C.)
- Baseline → During Rx → Periodically post-Rx
- Correlate w/ dosimetric parameters

- Current enrollment 364 (since May 2006)
- Estimated accrual 600 men
  - 3-4 years

Our job:

- Offer safe & effective therapies
- Obtain the information and educate our patients

It is not necessarily to make the choice for them

Thank you