CLINICAL TRIALS

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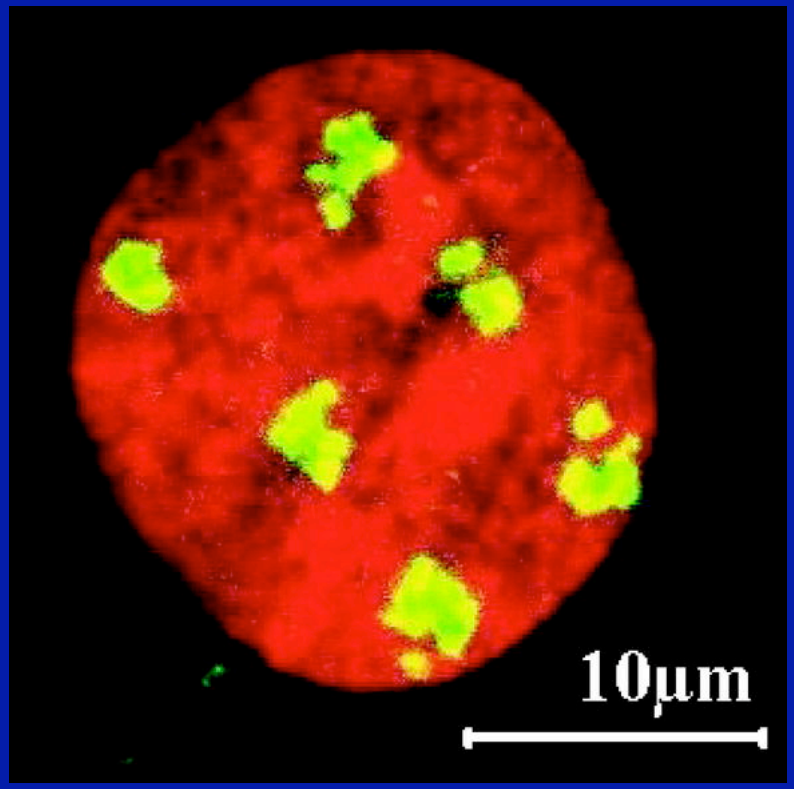
TOMORROW

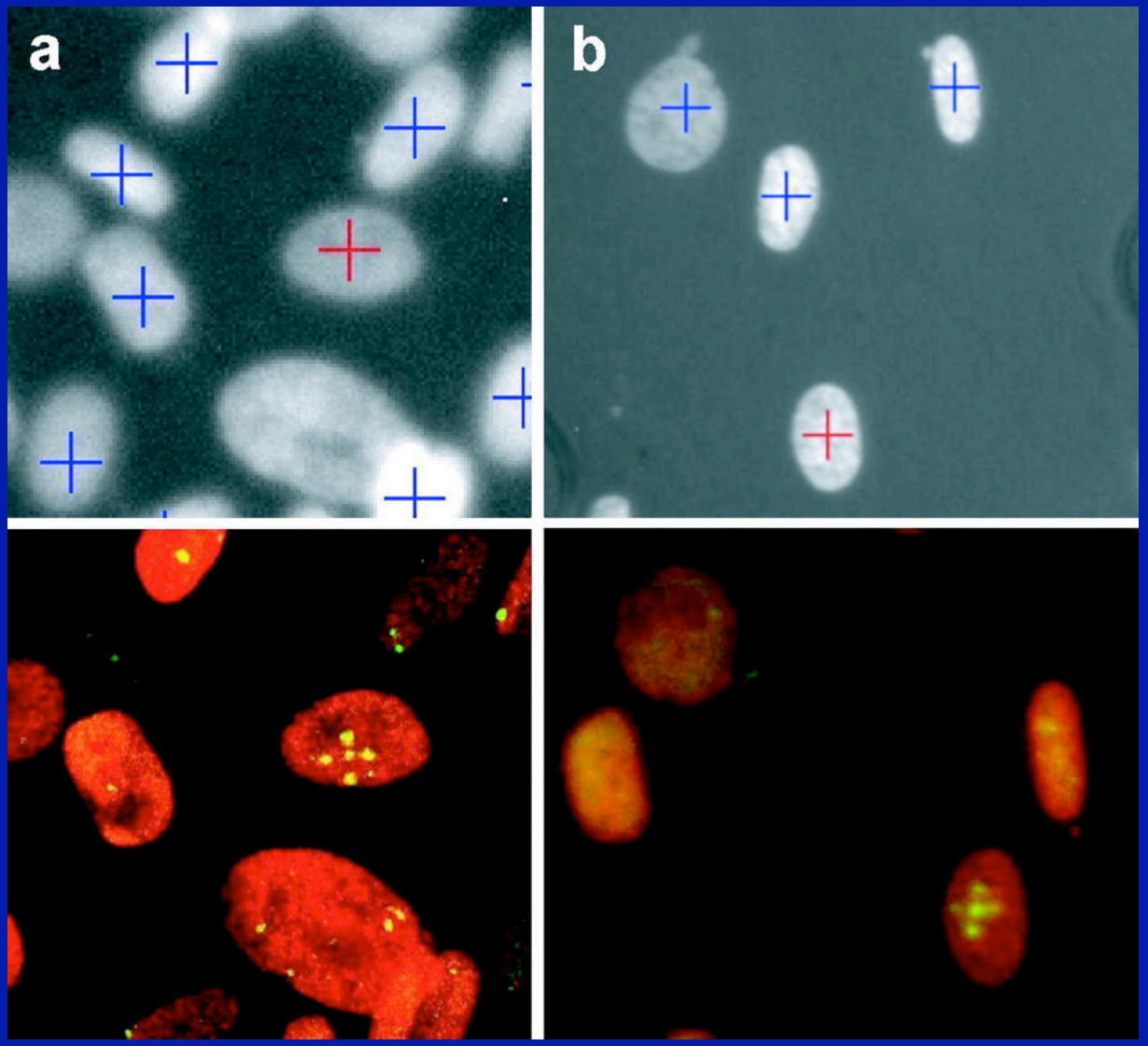
CARBON-ION RIF IN A HUMAN FIBROBLAST NUCLEUS

10 hits per position, 7 microns apart



[Heiss M, Rad Res 165: 231-9, 2006]

ARGON-ION RIF, 3 MICRONS APART



TODAY

THE DEBATE OVER PROTONS

- **The debate is not about the money.**
- **We do not know if patients treated by protons live longer or better than those treated without protons.**
- ***Without comparative trials we do not know that they will even do as well as those treated without protons!***

NCI WORKSHOP ON ADVANCED TECHNOLOGIES IN RADIATION ONCOLOGY

DECEMBER 2006

LEVEL 1 EVIDENCE OF SUPERIORITY OVER 3D-CRT

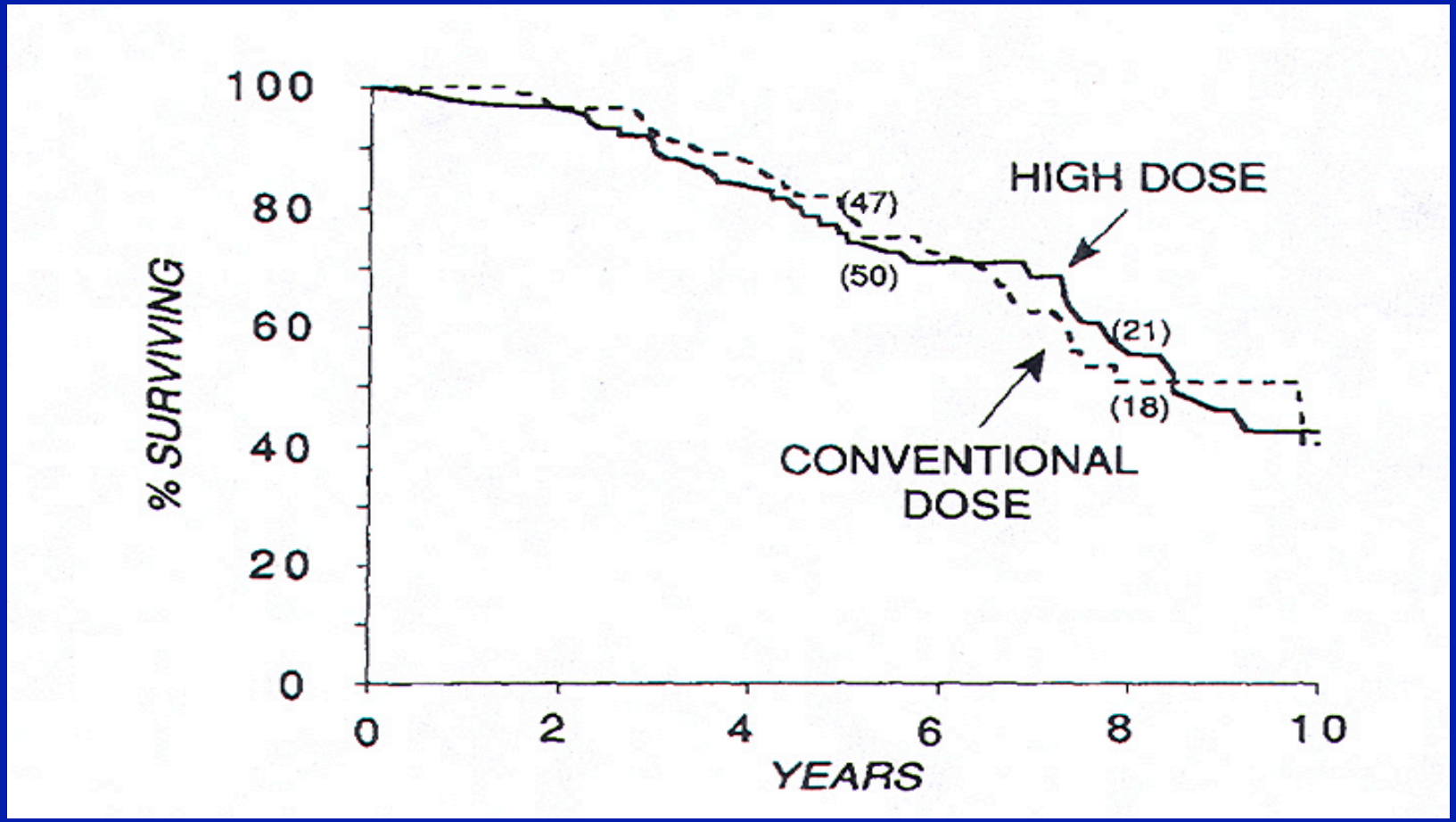
	LESS TOXIC		*BETTER SURVIVAL*	
	PROTONS	***C-IONS***	***PROTONS***	***C-IONS***
Brain	No	No	No	No
H&N	No	No	No	No
Breast	No	No	No	No
Lung	No	No	No	No
Colorectal	No	No	No	No
Prostate **	No	No	No	No
Cervix	No	No	No	No

CA PROSTATE: SUMMARY OF THREE RANDOMIZED TRIALS

- **Patients treated with protons suffered worse toxicity than those treated without protons.**
- **Patients receiving high dose RT (>75 Gy by photons, protons or both) suffered worse toxicity than those receiving a standard dose (~70 Gy).**
- **Patients treated with protons or high doses *did not* live any longer, even after 8-25 years follow-up.**

MGH Ca Prostate trial: Photons +/- Protons

Shipley W, IJROBP 32:3-12, 1995



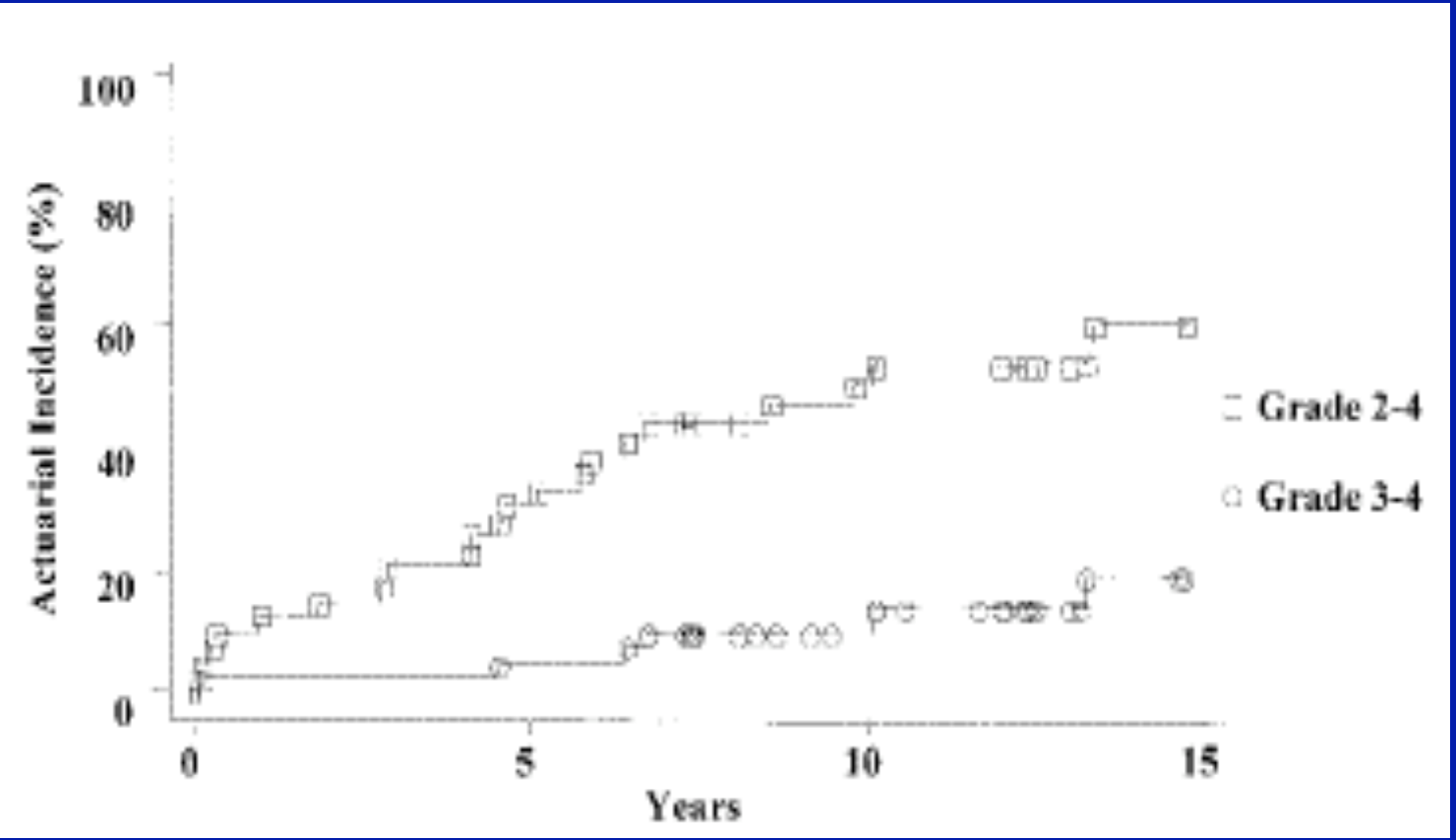
MGH CaP trial: 3DCRT +/- Protons

Shipley W, IJROBP 32:3-12, 1995

	Urethral Strictures	Rectal Bleeding
CRT *N=99*	8%	12%
CRT+PRT *N=103*	19% (p=0.07)	32% (p=0.002)

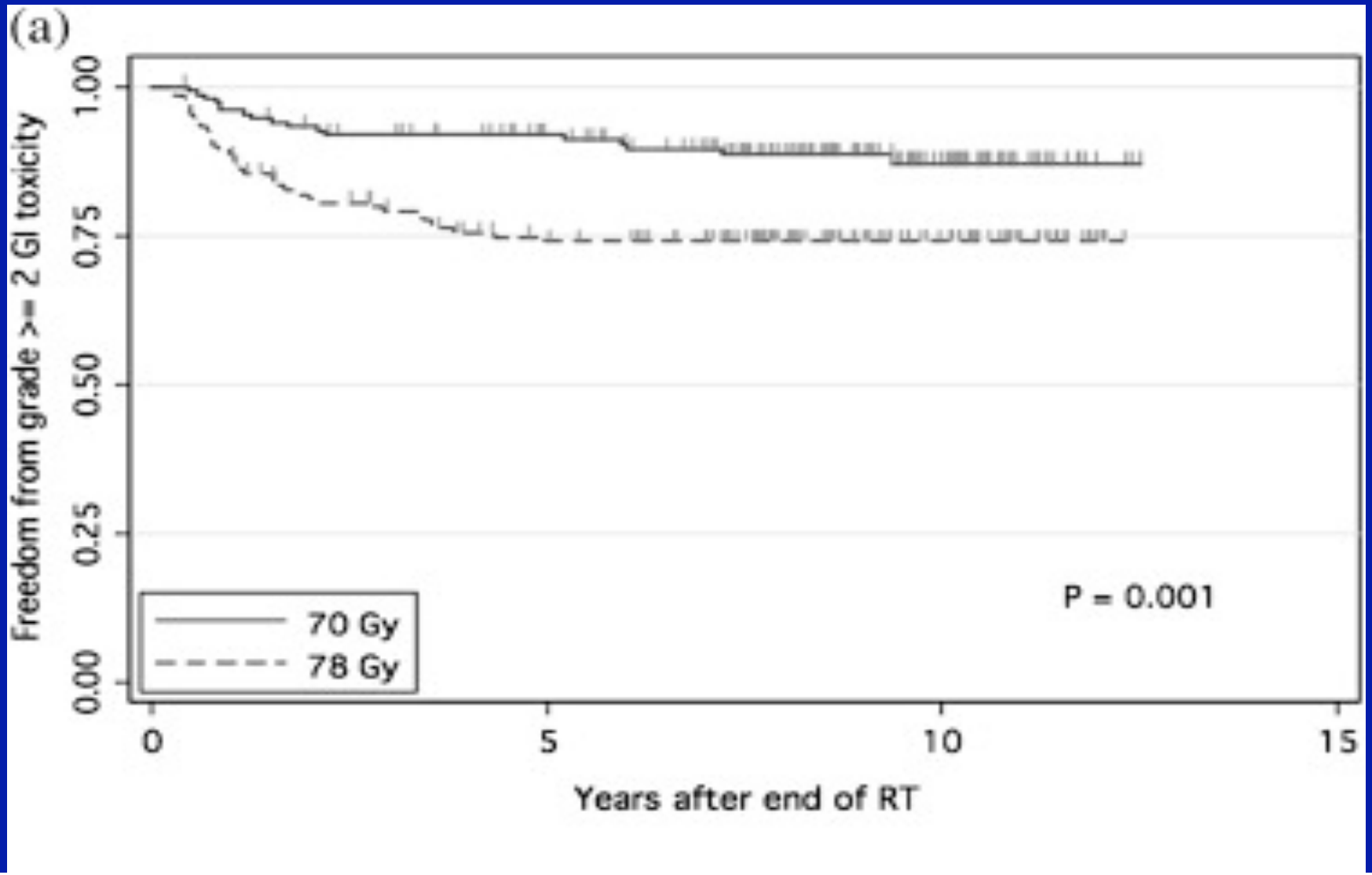
MGH trial – GU toxicity

Gardner. J Urol,167:123,2002



MDACC CaP TRIAL: 1993-98

Kuban DA. IJROBP 70:67-74, 2008



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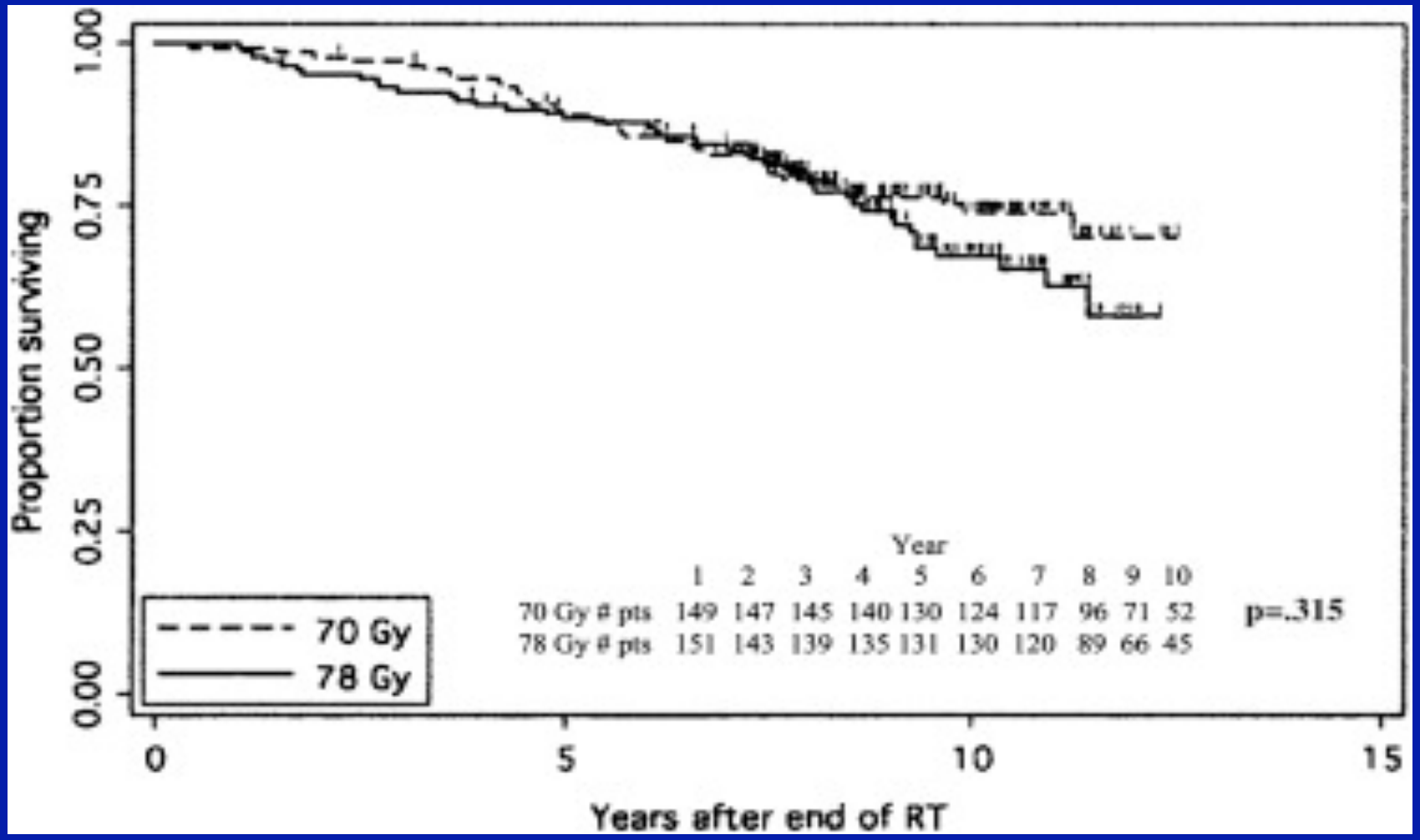

STANDARD VS HIGH DOSE PROTON RT

Zietman AL, JAMA 294:1233-39, 2005.

Dose	70 GyE	79 GyE
Survival *(n.s.)*	97%	96%
GI Toxicity *(p=0.004)*	41%	57%
GU Toxicity *(p=0.005)*	8%	17%

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IMPLICATIONS

1. PSA as and end-point.
2. High-dose treatment for prostate Ca.

HOW OFTEN HAS THE "PERCEPTION" BY ACADEMIC CLINICIANS THAT AN EXPERIMENTAL CANCER TREATMENT IS SUPERIOR TO STANDARD TREATMENT BEEN PROVEN CORRECT?

- ***So infrequently as to make us all humble !!***

(Bill Shipley, MGH)

Summary of RCT Outcomes

RTOG: **In 71% of the RCTs the standard treatment was favored.**

COG: **In 53% of the RCTs the standard treatment was favored.**

"The value of new experimental treatments can NOT be confidently predicted in advance."

CaP - TRIAL WORTH DOING

- **Hypothesis: Patients treated by high-dose protons (or IMRT) without androgen-deprivation live as long as patients treated with AD plus 3D-CRT.**

BEFORE ROUTINELY EMPLOYING A NEW TECHNOLOGY

- Head to head trials are needed to show that it helps patients live longer or better.
- If those trials were not part of pre-marketing testing, they must be conducted ASAP after the technology is licensed by the FDA.
- At present, however, the FDA does not demand such trials !

- **The manufacturers can not be relied upon to sponsor those trials voluntarily, because they frequently serve no commercial purpose.**

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- **So, who should twist their arms?**
- ***Who has the financial leverage?***

BOTTOM LINE

- ***Physicians*** **must demand that the manufacturer provides evidence from controlled clinical trials that a new technology didn't just produce pretty pictures but actually helped patients live longer or better!!**
- ***Physicians*** **must participate in clinical trials that generate the evidence.**

STEPS IN EVALUATING A NEW TECHNOLOGY

1. Demonstrate that the dose distribution *in-silico* looks promising.
2. Ensure consistency in planning, optimization and execution by
   - Establishing a credentialing mechanism.
   - Conducting feasibility studies.
3. Demonstrate by controlled clinical trials that patients live longer and/or better.

CAVEATS/LESSONS LEARNED

IMRT, IGRT, SRT, PROTONS

- **Advanced techniques are less tolerant of poor implementation than 'standard' techniques.**
- **Misadministrations are harder to detect and may lead to worse outcomes for patients.**
- **In-vivo dosimetry is not possible at present. There is , therefore, no substitute for analysis of both tumor control and adverse effects.**
- **That is best done by participating in clinical trials.**

LESSON LEARNED SO FAR

- **IMRT, SRT, Protons, etc. pose a *greater* risk of missing the target than 'traditional' techniques of radiation therapy.**

Halperin's Rule

- ***Most tumors are radioresistant if you miss them!***
  - ***Protons may offer many new and expensive ways of missing the tumor.***

‘MISADMINISTRATIONS’ WITH ADVANCED TECHNOLOGIES

- Discrepancies between prescribed dose and planned dose.
- Discrepancies between planned dose and dose delivered ‘to an ideal patient’.
- Discrepancies between planned dose and dose delivered to an actual patient.

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IMRT: PRESCRIBED vs. PLANNED DOSE

Das I. JNCI, 100:300-7, 2008

- Studied 803 patients at five institutions.
- Treatment plans were done by experienced physicists (>50 IMRT cases each).

IMRT: PRESCRIBED vs. PLANNED DOSE

Das I. JNCI, 100:300-7, 2008

RESULTS:

- In 46% of patients the plan delivered to the CTV a maximum dose more than 10% higher than prescribed by the MD (worst case: 40% higher).
- In 63% of patients the plan delivered to the CTV a minimum dose more than 10% lower than prescribed (worst case: 100% lower = zero).

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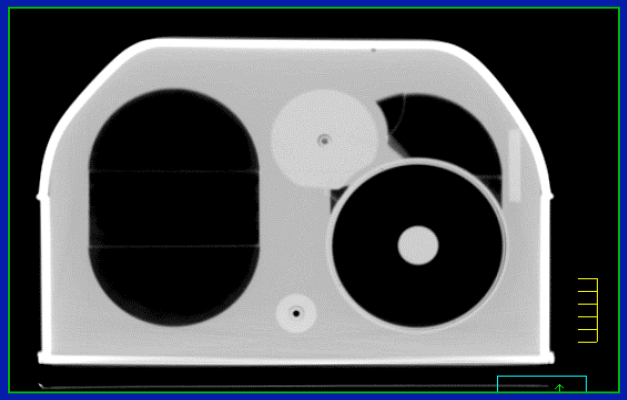
THE IDEAL PATIENT

- We know the CTV precisely.
- There is absolutely no voluntary or involuntary movement.
- There is absolutely no change in the position, size or shape of the CTV or the OAR.

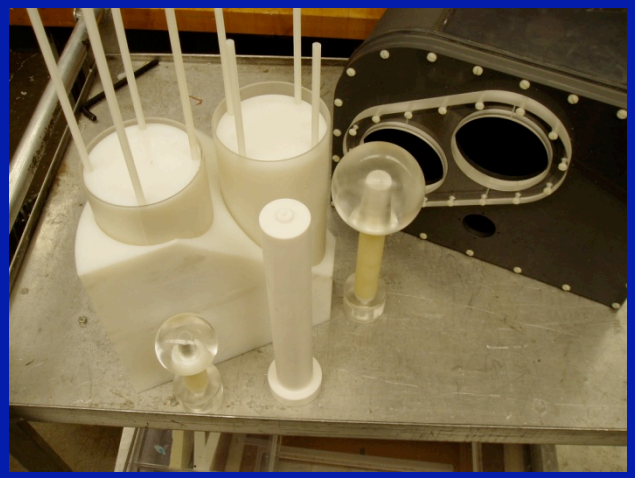
RPC Phantoms

prostate RTOG 0126 (IMRT)



thorax RTOG 0236 (SBRT)

H&N IMRT
RTOG 0225, 0126;
COG ACNS0331



liver RTOG 0438

IMRT: PLANNED vs. DELIVERED DOSE

Ibbott GS. Technology in Cancer Research and Treatment, 5:481-7, 2006.

- 128 RTOG member institutions imaged a phantom, developed a treatment plan, then treated the phantom.
- Goal: Deliver to the CTV a dose within 7% of the planned dose.
- Results: One-third of the institutions failed the test *(the dose delivered differed from the planned dose by up to 22%; the high dose region was off by up to 15 mm).*

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CHALLENGES POSED BY THE PRECISION OF THE ADVANCED TECHNOLOGIES

Very tight margins (PTV approximates the CTV) make it critical to:

- **Know the correct position, size and shape of the CTV and OAR**
- **Constantly account for (between and within fractions):**
  - ***changes in position***
  - ***changes in size***
  - ***changes in shape (deformation)***

WHAT IS THE TARGET?

- Current imaging tools are often inadequate for determining the ‘correct’ CTV.
- The current state of imaging QA leaves much to be desired.
- The ‘correct’ CTV can vary greatly even among experts.

TOP TEN PRIORITIES FOR RADIATION ONCOLOGY

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1. Better imaging
2. Better imaging
3. Better imaging
4. Better imaging
5. Better imaging
6. Better imaging
7. Better imaging
8. Better imaging
9. Better imaging
10. Better targeting

- We have made enormous progress in our ability to hit the target

BUT

- What is the correct target?

HEAD AND NECK

Cooper JS, IJROBP 67:972-5, 2007

- **Overlap between GTVs drawn by 8 'experts' averaged only 50% (in the worst case: 0%).**

BREAST

Li XA. Proc ASTRO 2007. Abstract #127

- ***Bad News:*** **Overlap between CTVs (axilla) drawn by 8 'experts' averaged only 45% (in the worst case: 15%).**
  - ***Good News:*** **Overlap between hearts drawn by 8 'experts' averaged 95% (in the worst case: 45% !!).**

PROSTATE

Lawton C. Proc ASTRO 2007. Abstract #2224

- ***Patient 1:*** **CTVs (iliac nodes) drawn by 11 'experts' ranged from 82 – 877 cc. All of them agreed upon only 30 cc.**
- ***Patient 2:*** **CTVs (iliac nodes) ranged from 60 – 630 cc. All agreed upon only 17 cc.**

ATLASES

- Atlases (created by experts' consensus) in effect propose a hypothesis regarding the 'correct' CTV, that must then be proven or disproven by clinical trials.

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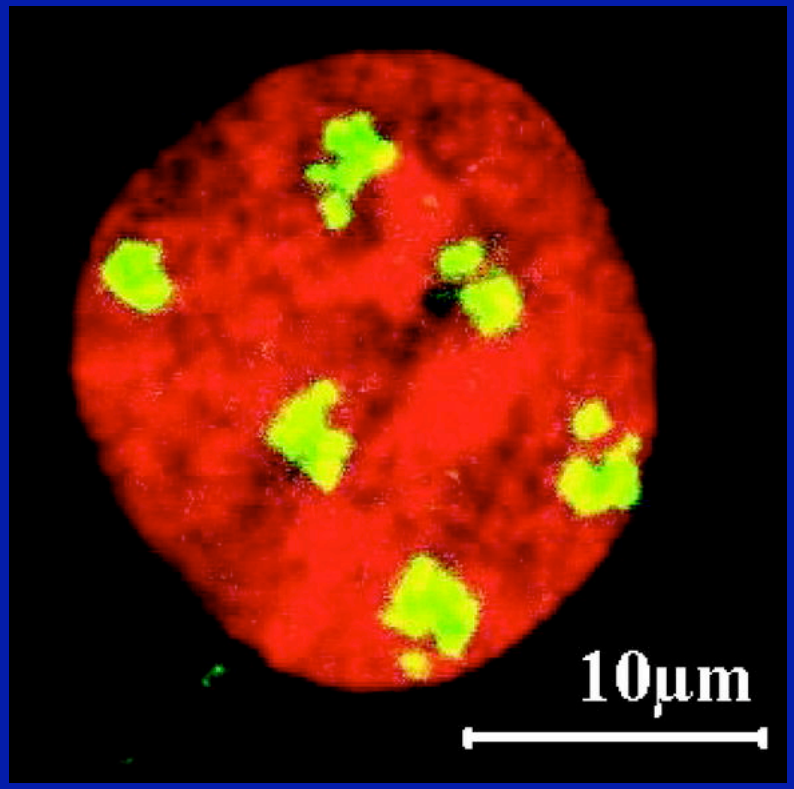

[Heiss M, Rad Res 165: 231-9, 2006]

CREDENTIALING MECHANISM

- NCI in 2004 established minimum standards for protocols that would employ IMRT. Updated in 2006. Protons in 2007.
- Any institution putting a patient on a protocol must be credentialed.
- At present, no such credentialing is required by the FDA or the payers!

SUMMARY-1

- Particle therapy has great potential for helping some patients live longer or better.
- The best way forward is by prospective clinical trials, *underpinned by robust quality assurance*, due to the very demanding QA and the possibility of harm to the patients.

SUMMARY-2

- Institutions participating in NCI-sponsored clinical trials are credentialed for the new technology and must participate in ongoing QA.
- No such safeguards exist for patients not participating in those trials. There are, at present, *no* minimum standards mandated by the FDA or the payers.

SUMMARY-3

- That could delay the fulfillment of the promise of this exciting new technology *and even give it a bad name* unless the profession itself steps up to the plate.

A ‘GOOD’ CLINICAL TRIAL

- Hypothesis.
- Sample size calculation.
- Roles of retrospective analyses.