University of Maryland
Department of Radiation Oncology

Radiation Oncology
Recent Advances & New Challenges

Cedric Yu

University of Maryland School of Medicine

Medical (Radiological) Physics

- An applied branch of physics concerned with the application of the concepts and methods of physics to the diagnosis and treatment of human disease.
- ~5000 medical physicists in North America
  - **Therapeutic Radiological Physics** (Radiation Oncology – 76%)
  - Diagnostic Radiological Physics (Radiology ~11%)
  - Medical Nuclear Physics (Nuclear Medicine ~7%)
  - Medical Health Physics (Radiation Safety ~6%)

Therapeutic Radiological Physics

- Introduction and Basics of Radiation Oncology (Physics, Biology)
- Recent Advances: IMRT, IGRT, SBRT
- Challenges

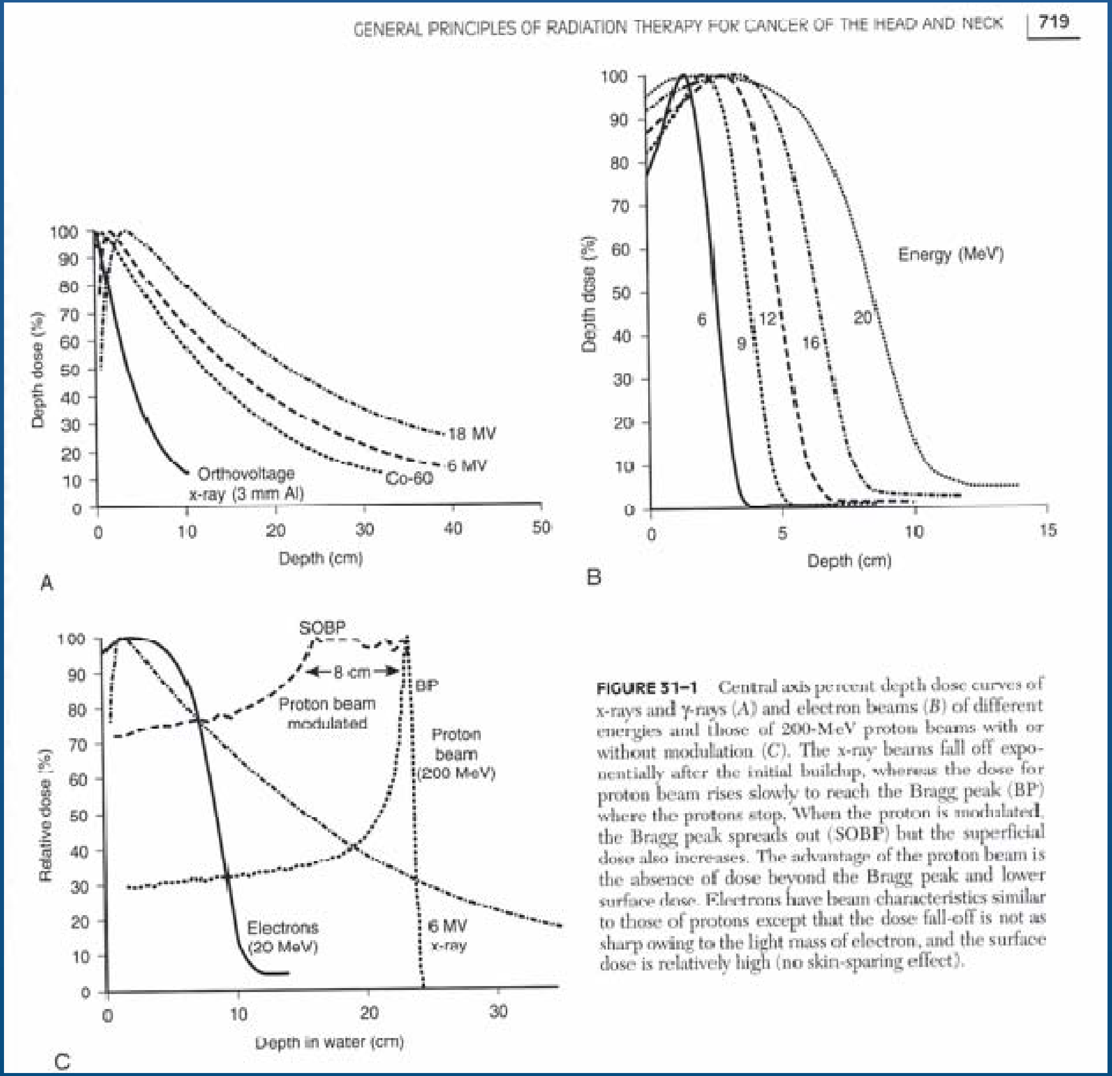
Radiation Physics

- Basis – ionizing particles interact with cellular molecules
- Relies on transfer of energy created by secondary charged particles (usually electrons)
- Break chemical bonds
- External beam vs. Brachytherapy

External Beam Irradiation

- Dual-energy linear accelerators generate:
  - Low energy megavoltage x-rays (4-6 MV)
  - High energy x-rays (15-20 MV)
  - Electrons (4-23MeV)
- Particle Radiation (electrons, protons, neutrons)
- Photon therapy advantages
  - Skin sparing, penetration, beam uniformity
- Head and Neck sites – 4-6 MeV x-ray or Co60 gamma ray radiation

External Beam Irradiation



GENERAL PRINCIPLES OF RADIATION THERAPY FOR CANCER OF THE HEAD AND NECK 719

FIGURE 31–1 Central axis percent depth dose curves of x-rays and γ-rays (*A*) and electron beams (*B*) of different energies and those of 200-MeV proton beams with or without modulation (*C*). The x-ray beams fall off exponentially after the initial buildup, whereas the dose for proton beam rises slowly to reach the Bragg peak (BP) where the protons stop. When the proton is modulated, the Bragg peak spreads out (SOBP) but the superficial dose also increases. The advantage of the proton beam is the absence of dose beyond the Bragg peak and lower surface dose. Electrons have beam characteristics similar to those of protons except that the dose fall-off is not as sharp owing to the light mass of electron, and the surface dose is relatively high (no skin-sparing effect).

Linear Accelerator

Brachytherapy

- Radioactive source in direct contact with tumor
    - Interstitial implants, intracavitary implants or surface molds
- Greater deliverable dose
- Continuous low dose rate
- Advantage for hypoxic or slow proliferators
- Shorter treatment times with high dose rate

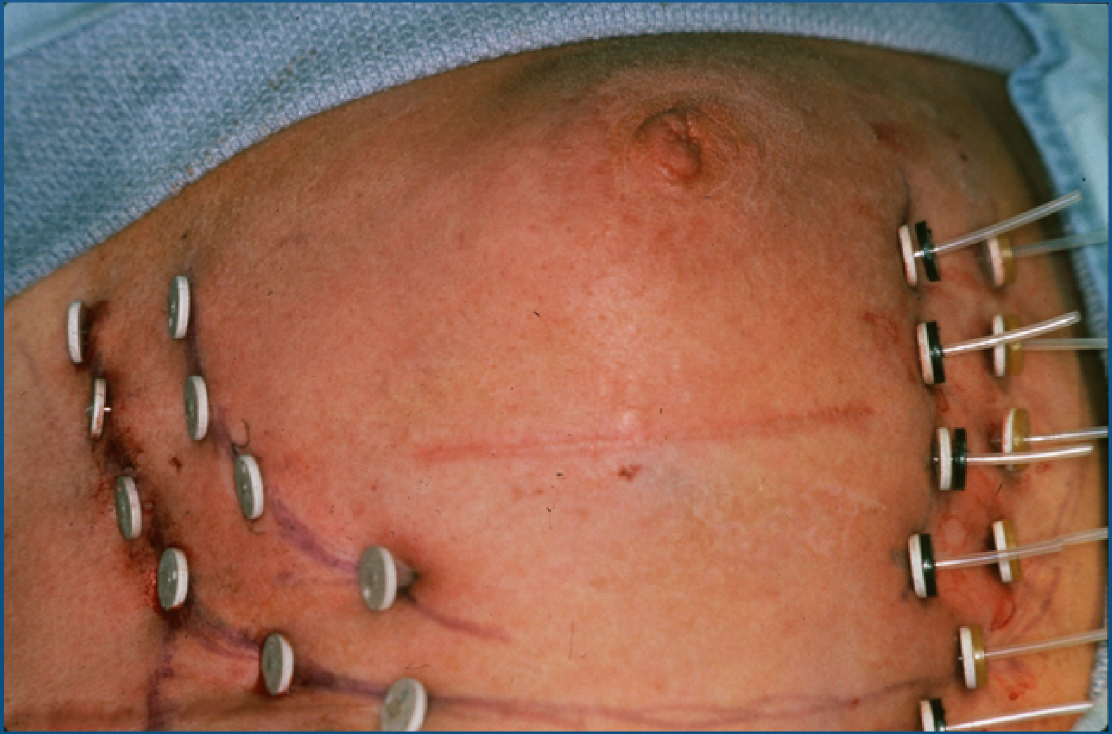
Brachytherapy

Cancer treatment using radioactive materials

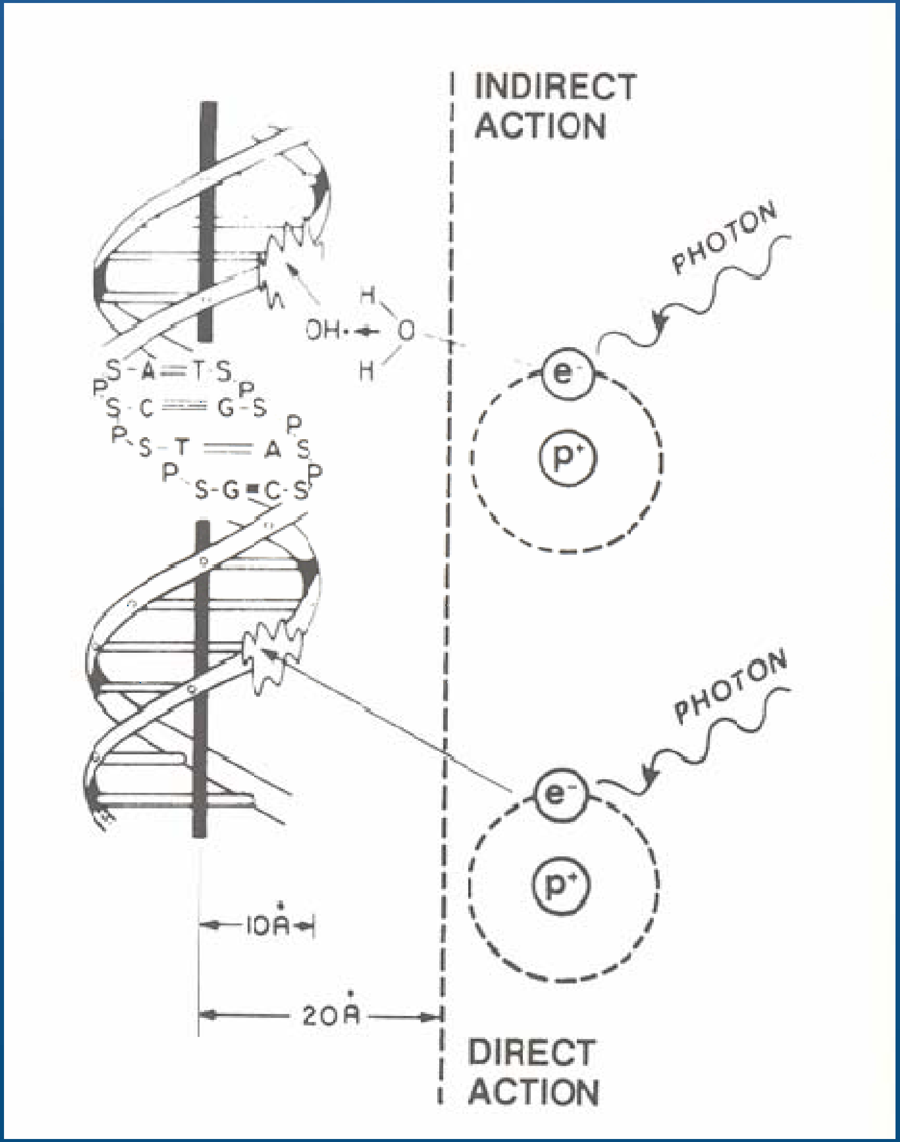
Intracavitary

Brachytherapy

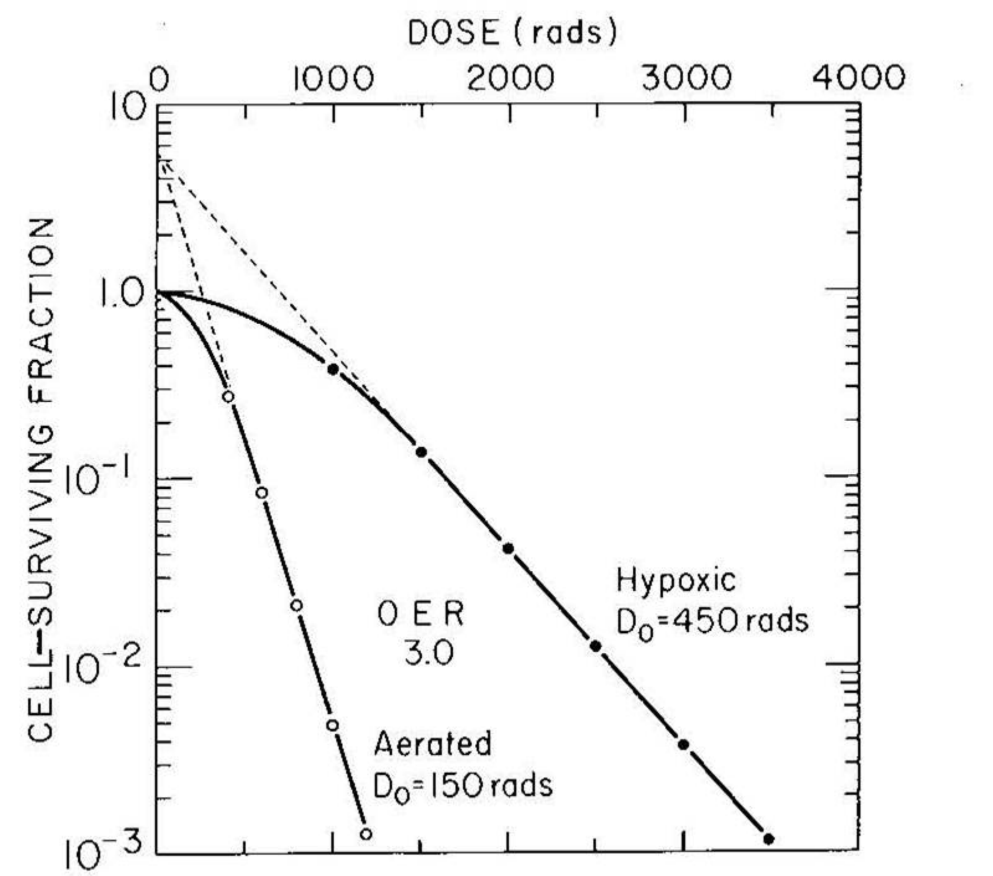
Interstitial



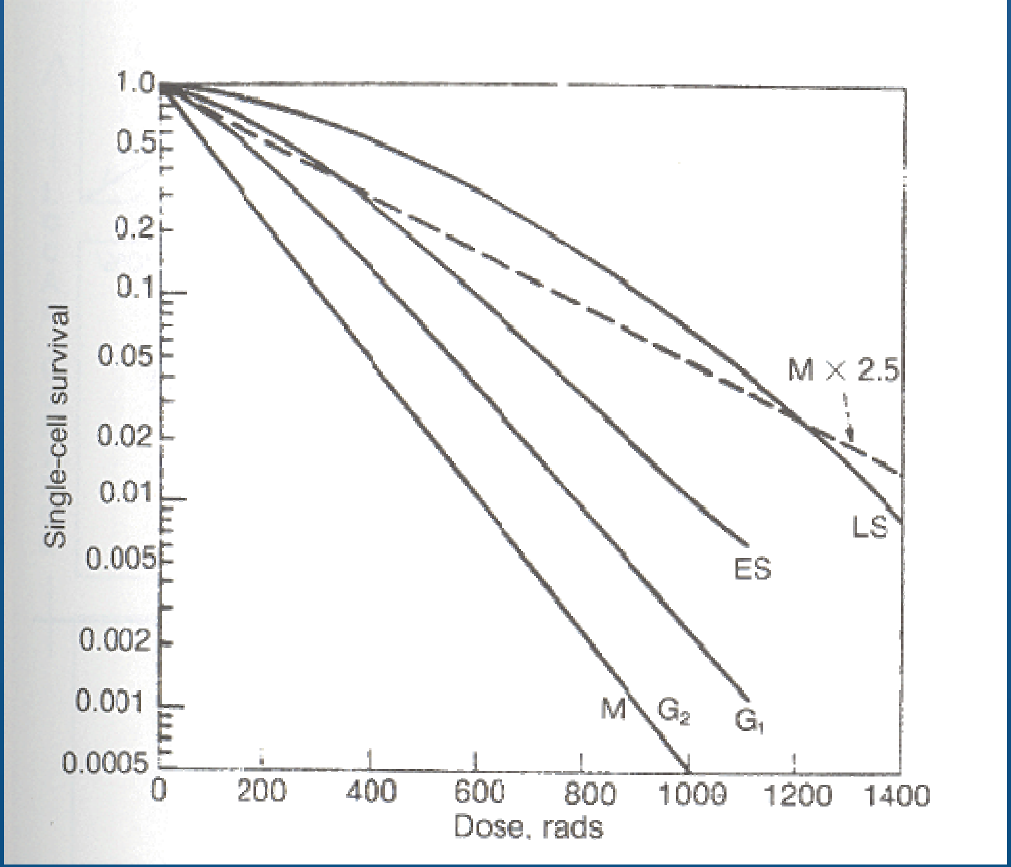
Radiobiology



Dose-Response Curves



Rediosensitivity and Cell Cycle



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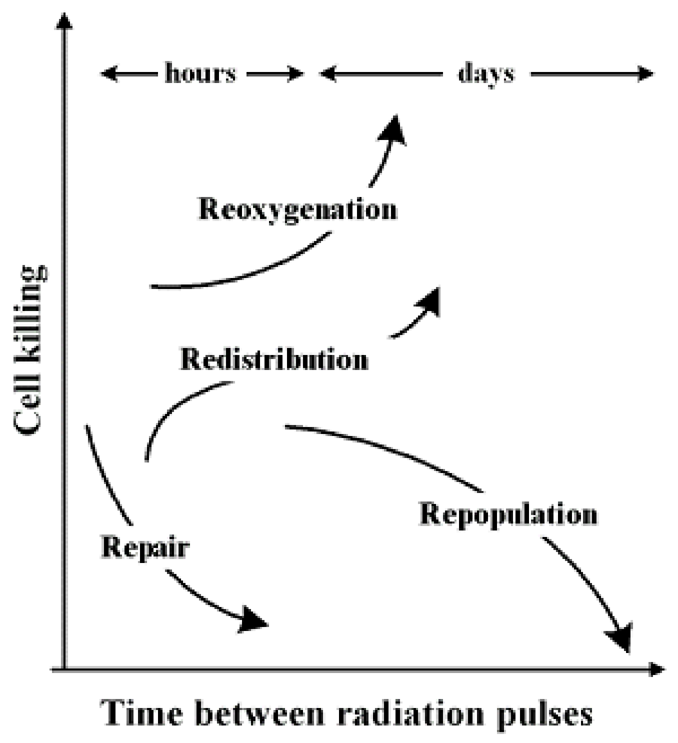
4 R's of radiation biology

- Repair of cellular damage
- Reoxygenation of the tumor
- Redistribution within the cell cycle
- Repopulation of cells



Goals of Radiation Therapy

- Eradication of the tumor.
- Avoidance of damage to healthy tissue and organs near the tumor.

Search for the highest therapeutic ratio

Fractionation

- Allow normal tissue to repair sublethal damage
- Allow tumor cells in S phase to progress to G2-M
- Allow reoxygenation to hypoxic regions in tumor
- Tumor also has chance to repair sublethal damage
- Accelerated proliferation

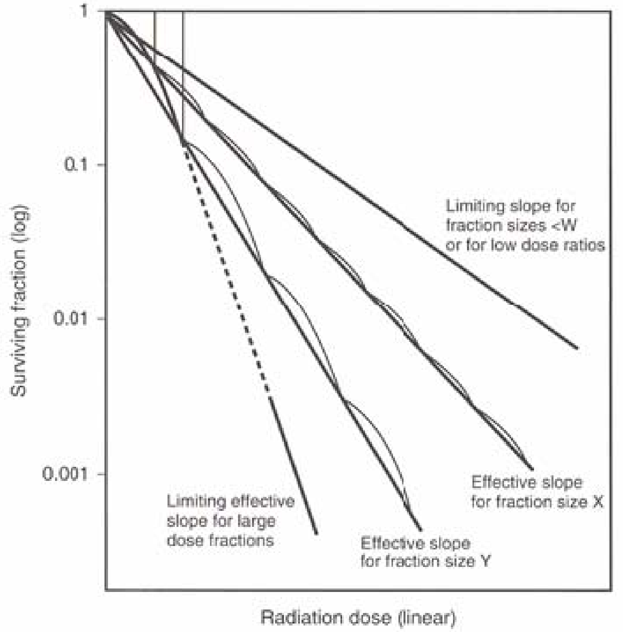
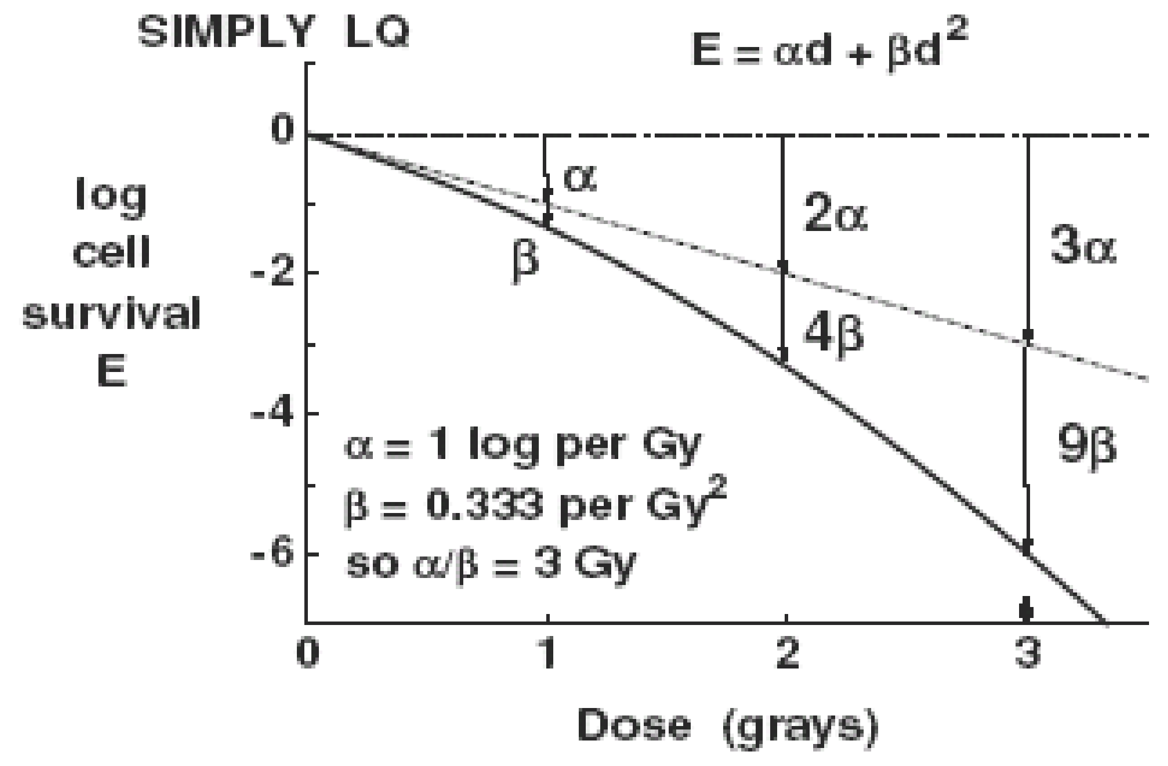


FIGURE 31–5 Survival curves of fractionated radiation delivered in equal doses per fraction separated by time interval, allowing complete repair from SLD to elapse. The curves become exponential as a function of radiation dose. The slope of each curve is defined by the respective "effective" D_0 [$D_{0(eff)}$] for a particular fraction size. The $D_{0(eff)}$ can never exceed ${}_1D_0$, because this denotes single-hit killing that results from irreparable damage.

Fractionation Schedules

- Conventional
  - 1.8 to 2.0 Gy given 5 times/week
  - Total of 6 to 8 weeks
  - Effort to minimize late complications
- Accelerated fractionation
  - 1.8 to 2.0 Gy given bid/tid
  - Similar total dose (less treatment time)
  - Minimize tumor repopulation (increase local control)
  - increased acute complications

The Linear-Quadratic model



$$E = n(\alpha d + \beta d^2)$$
$$E/\alpha = nd(1 + d/(\alpha/\beta))$$

Therapeutic Radiological Physics

- Introduction and Basics of Radiation Oncology (Physics, Biology)
- Recent Advances: IMRT, IGRT, SBRT
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Goals of Radiation Therapy

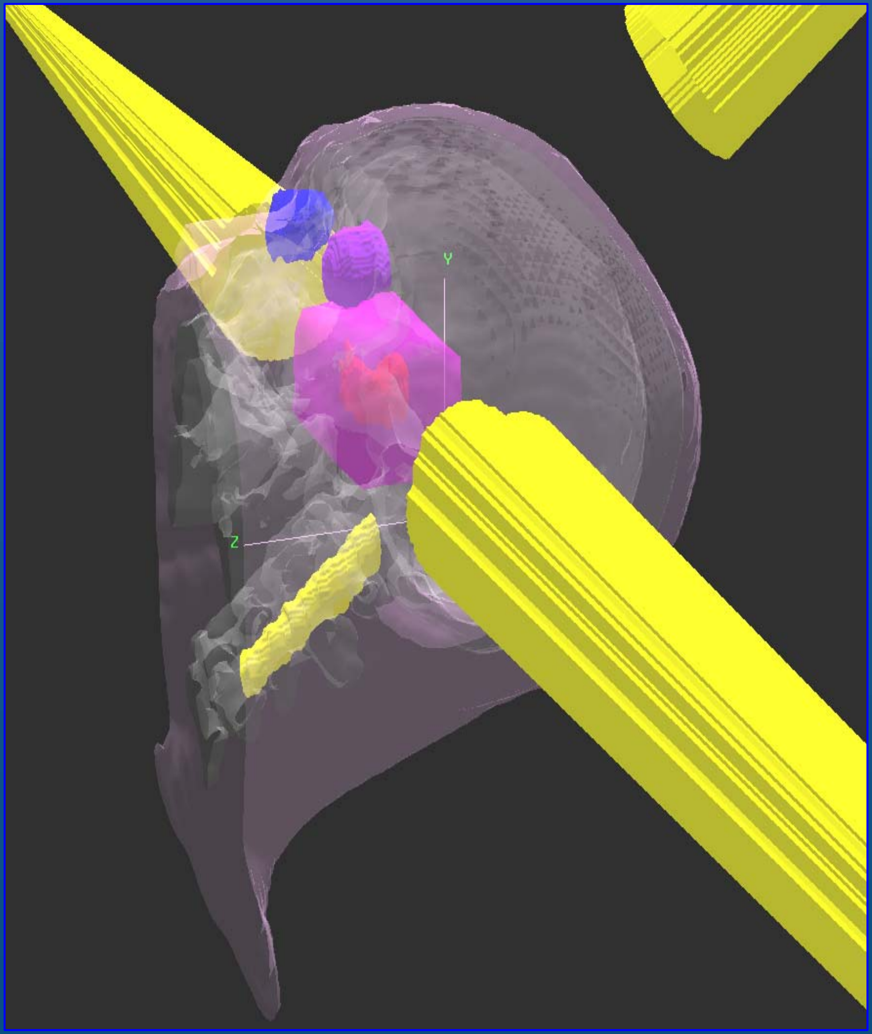
- Eradication of the tumor.
- Avoidance of damage to healthy tissue and organs near the tumor.

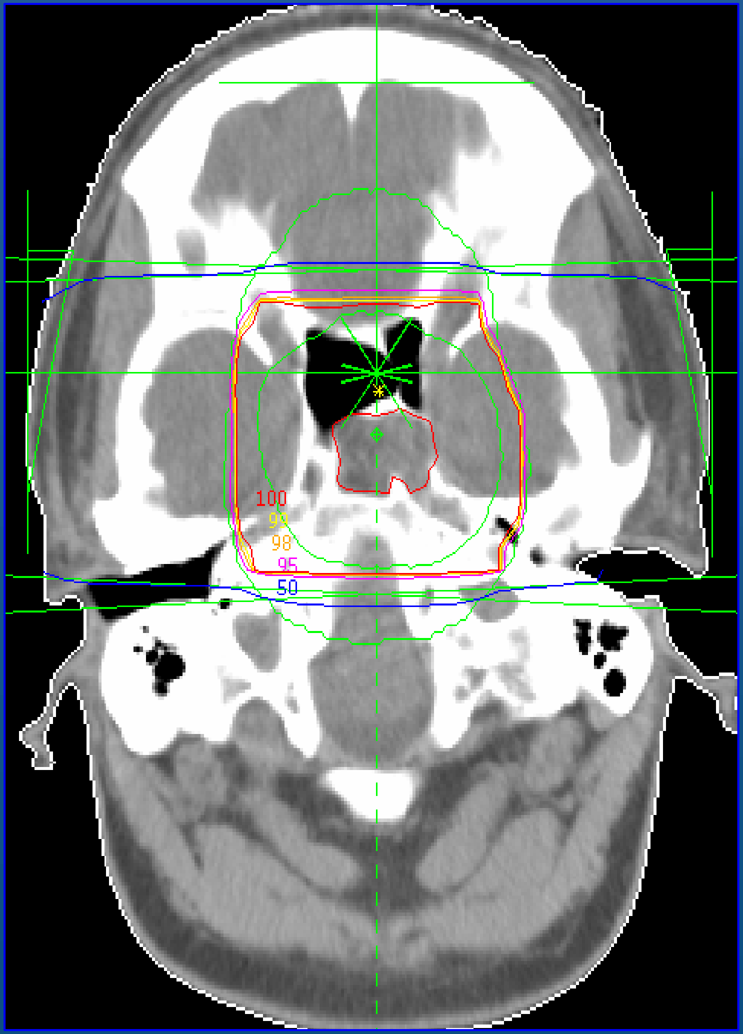
Search for the highest therapeutic ratio

How to achieve the goal

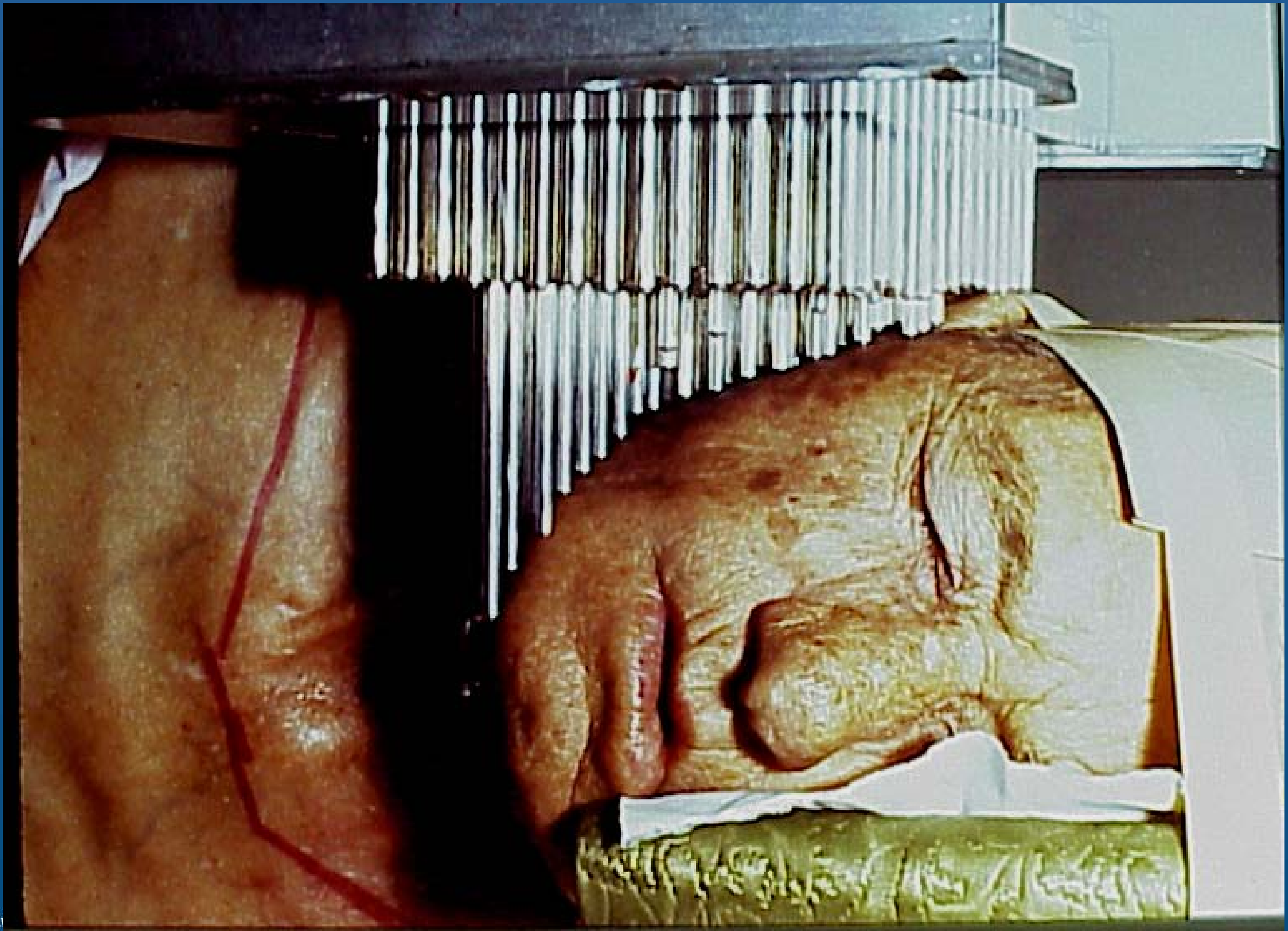
1. Better treatment design
2. Improve the radiation machine to provide greater degrees of freedom in plan design
3. Use heavy particles (Protons, light ions – different physics of interactions)
4. Improve geometric accuracy using imaging guidance
5. Reduce dosimetric uncertainty
6. Better understanding of tumor biology/genetics.

Technology of the ‘80s

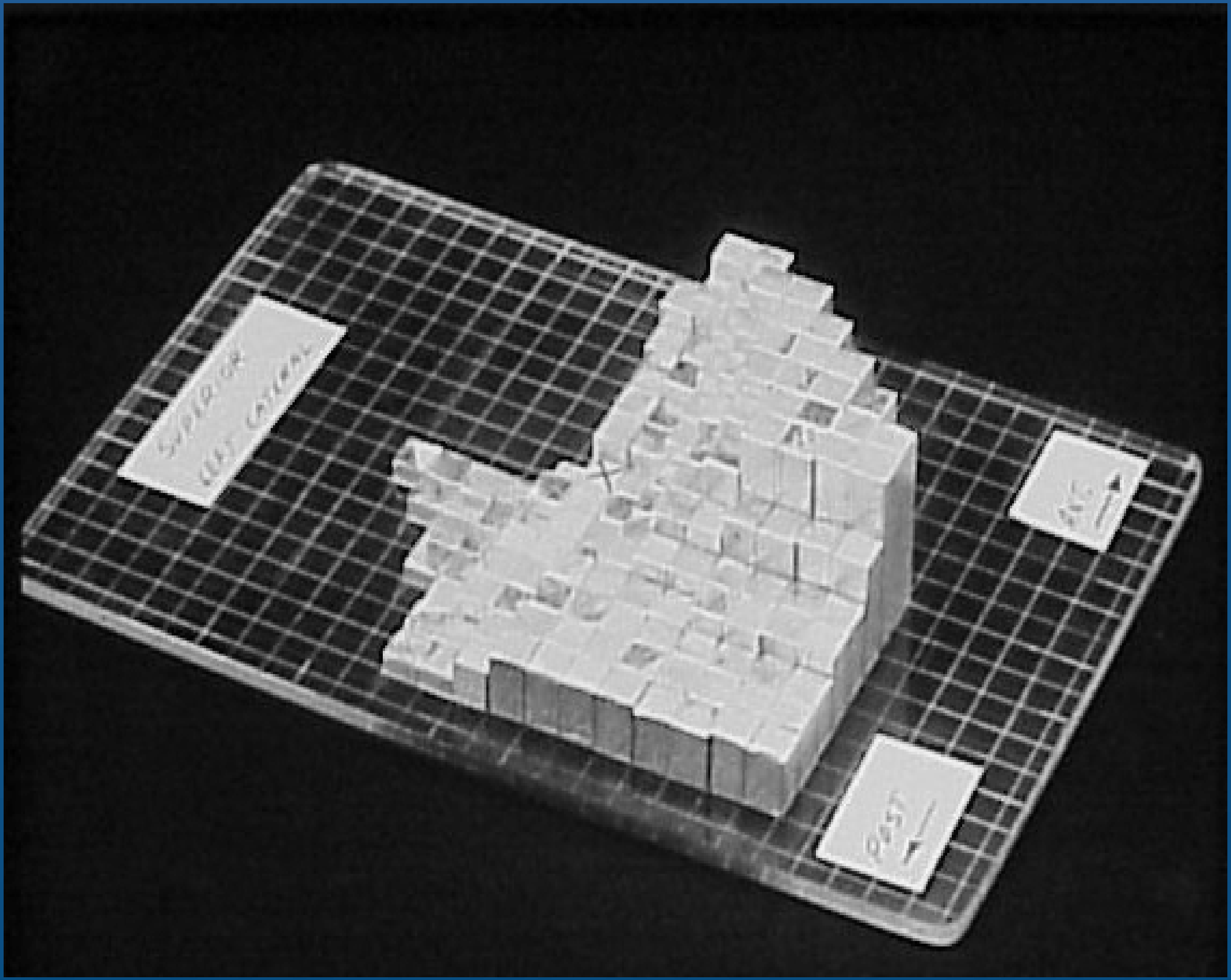




Intensity Modulated Radiotherapy?



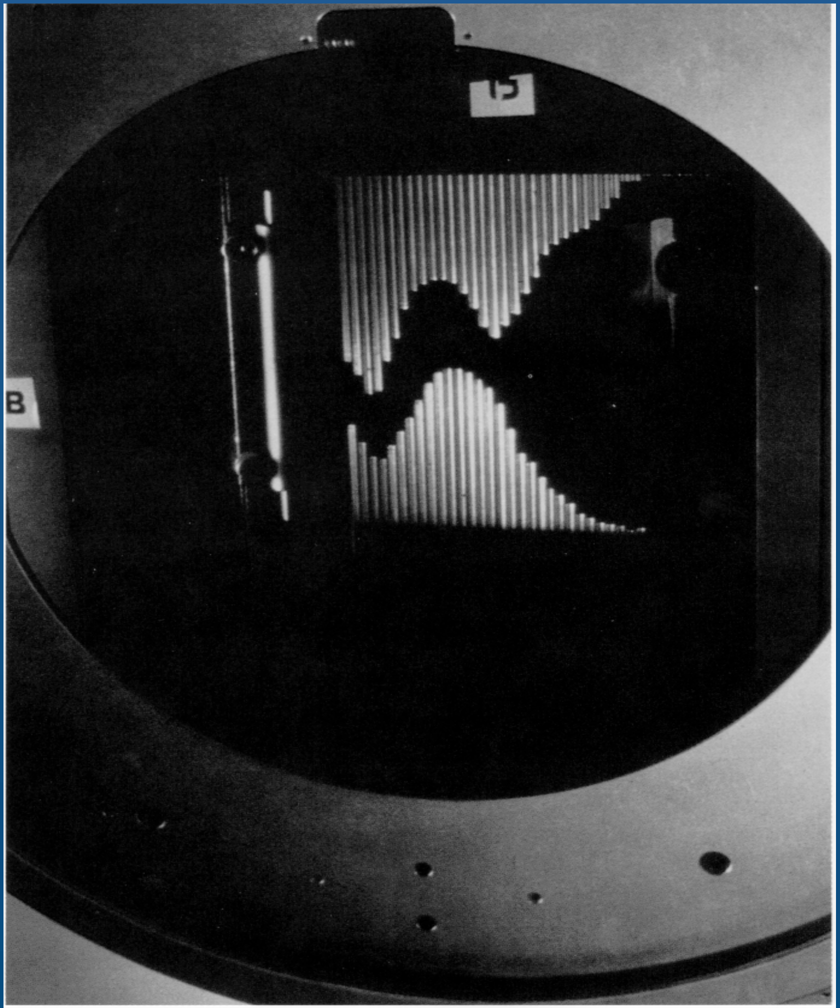
Intensity Modulated Radiotherapy?

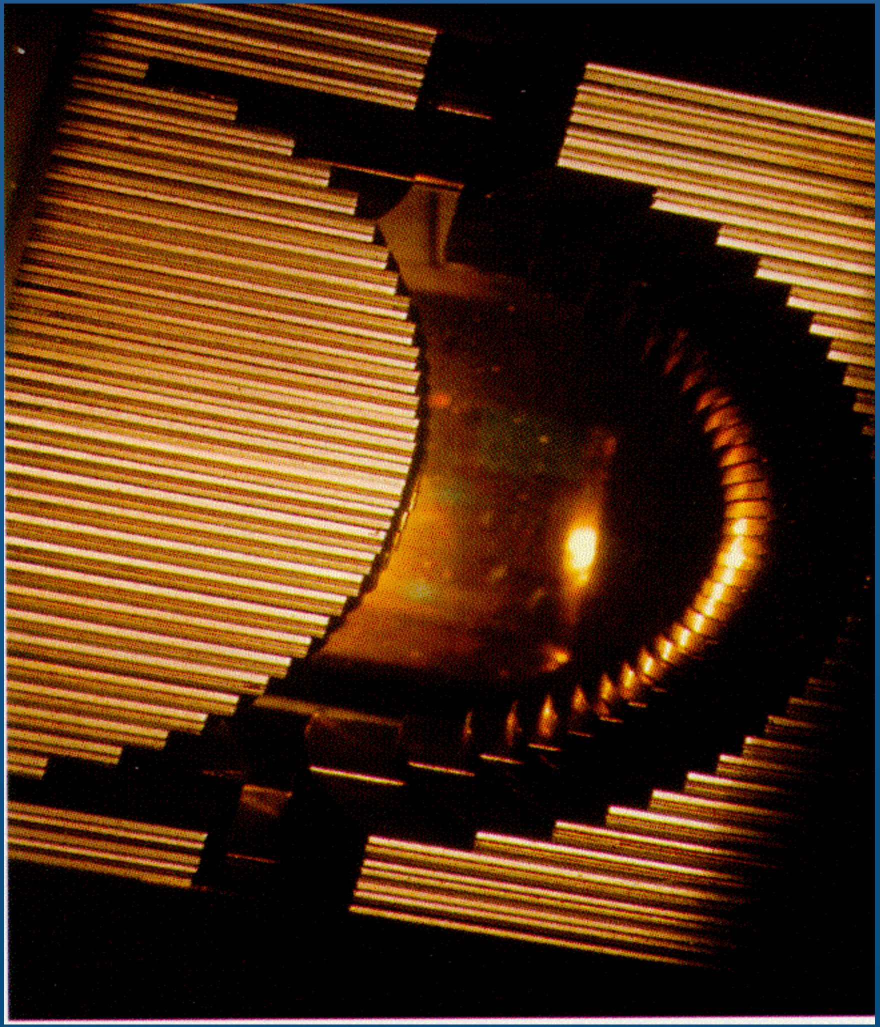


“The Age of Gizmos”

- MLC (1990)
- Inverse planning (1990)
- IMRT (1993)
- Tomotherapy (1993)
- Cyber Knife (1992)
- CBCT (2000)
- Novalus (2000)
- IGRT (2004)
- Clypso (2004)
- MammoSite (2005)
- Synergy (2006)
- Trilogy (2006)
- Protons (1990 -)
- ……

Muli-Leaf Collimator

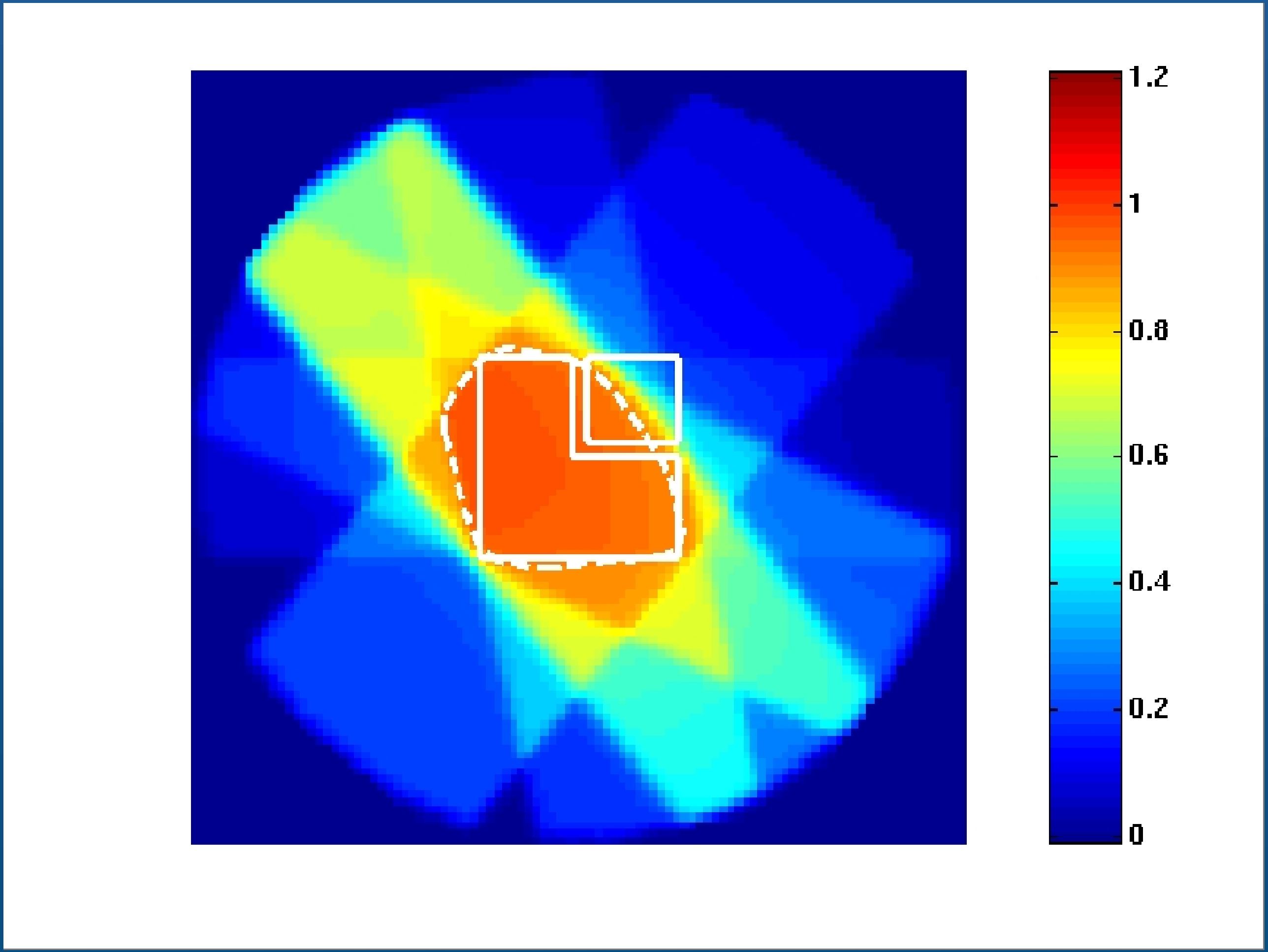




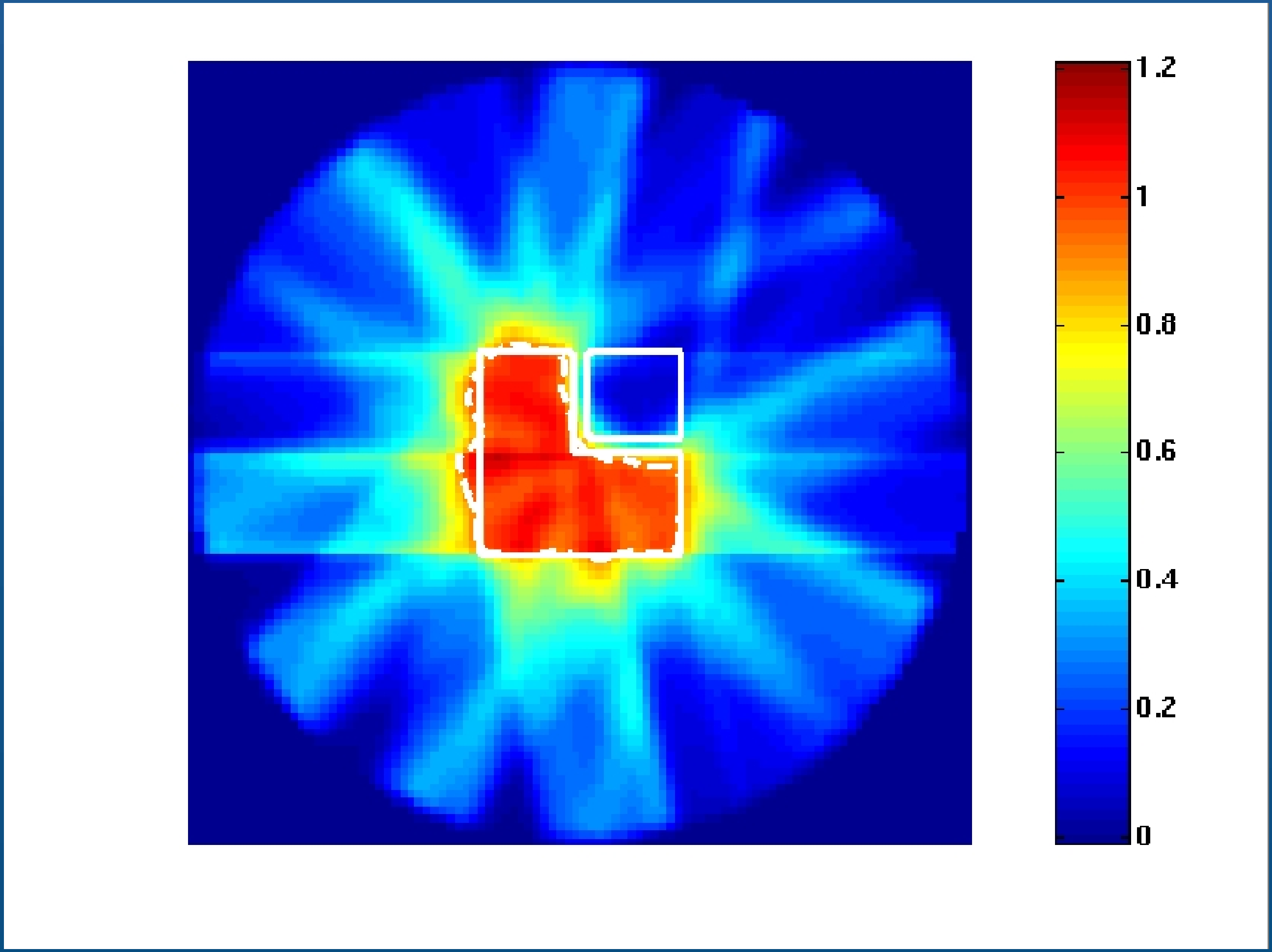
Intensity Modulated Radiation Therapy (IMRT)

- Computer optimization of beam intensities – *shaping the dose from 2D to 3D*
- Proposed in 1983 by Anders Brahme
- More research work on computer optimization started in 1990
- First delivery to phantoms - 1994

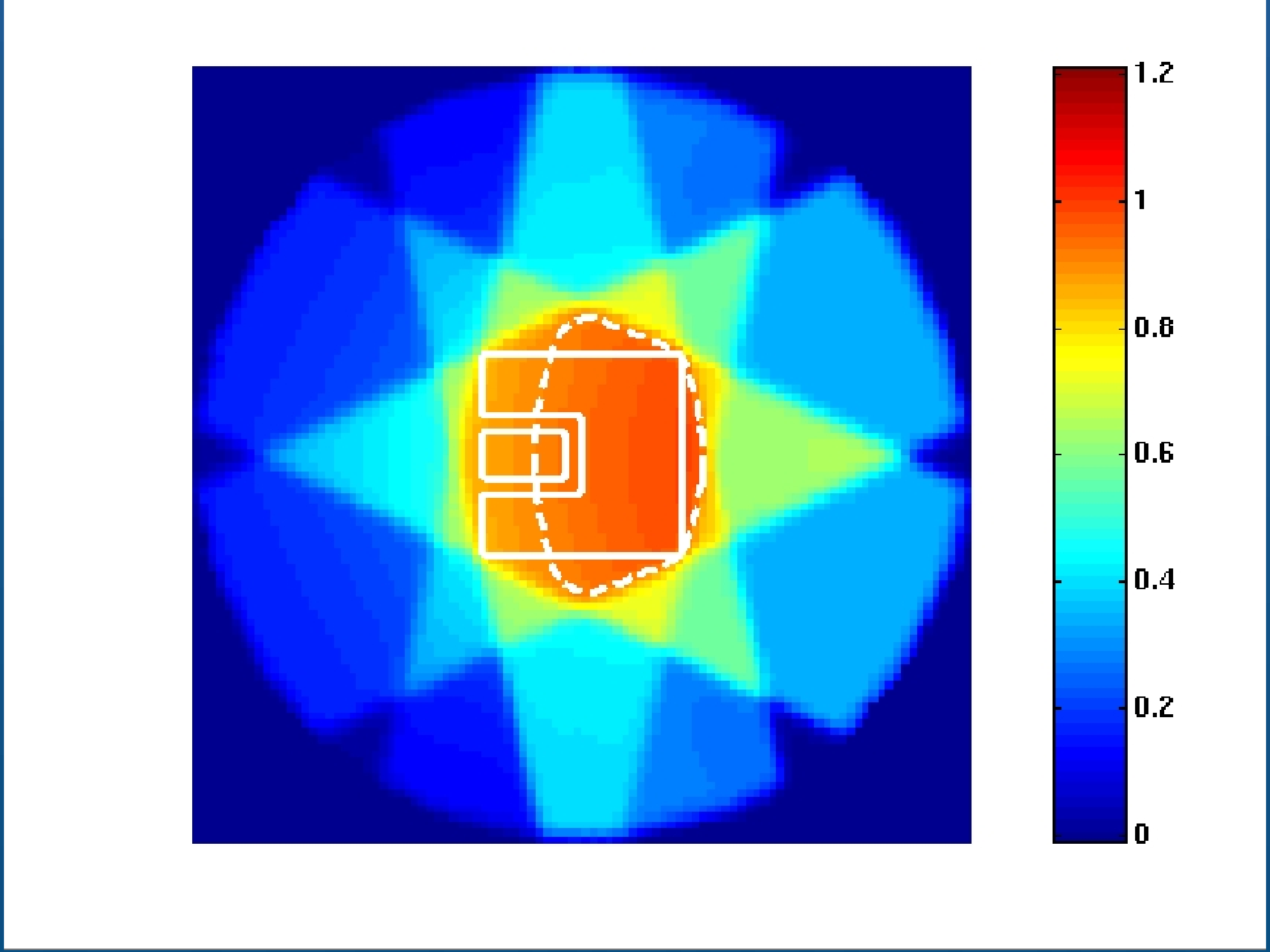
Conventional Treatment with limited number of beams



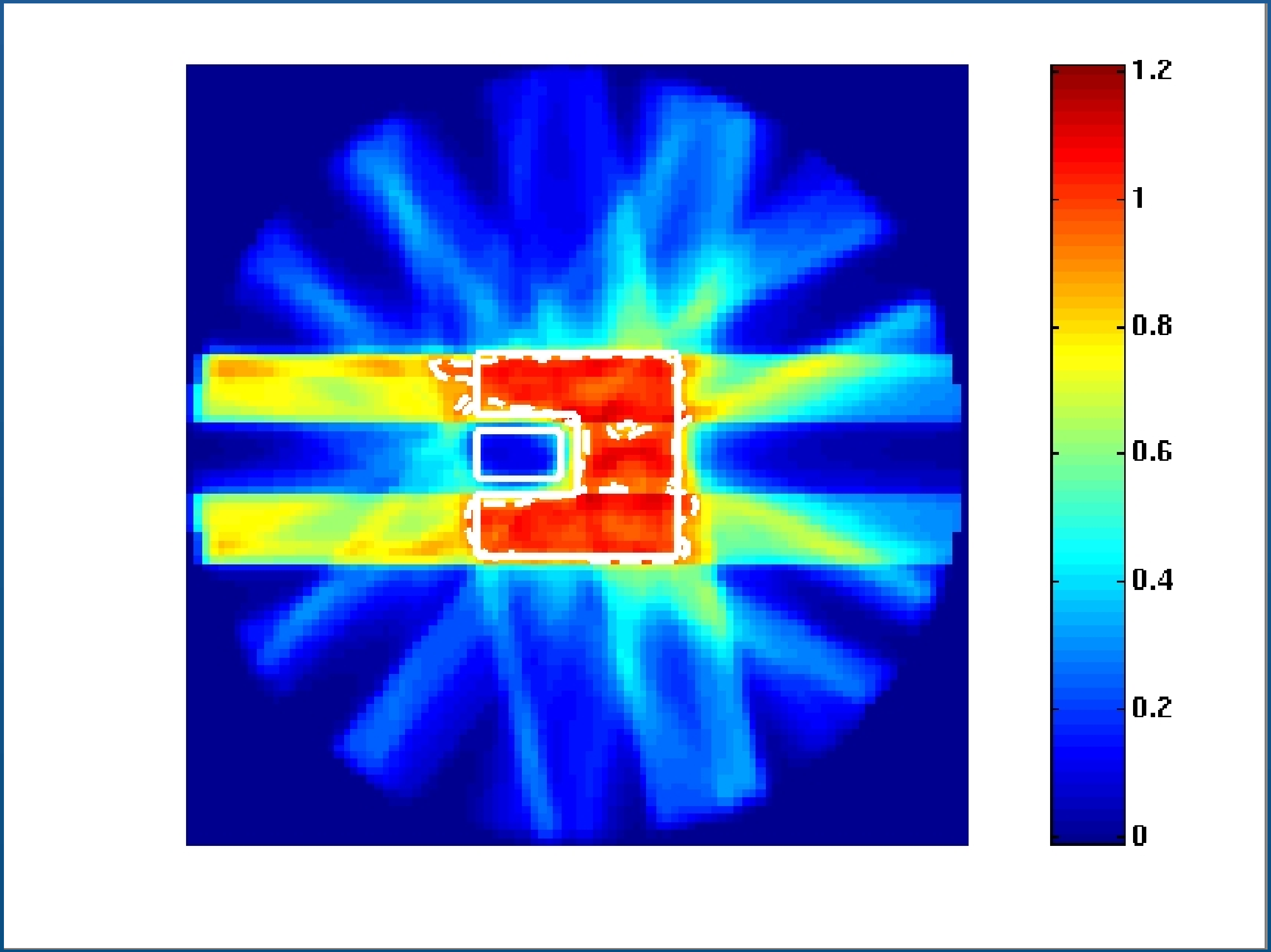
Increase beam direction and optimize beam weighting



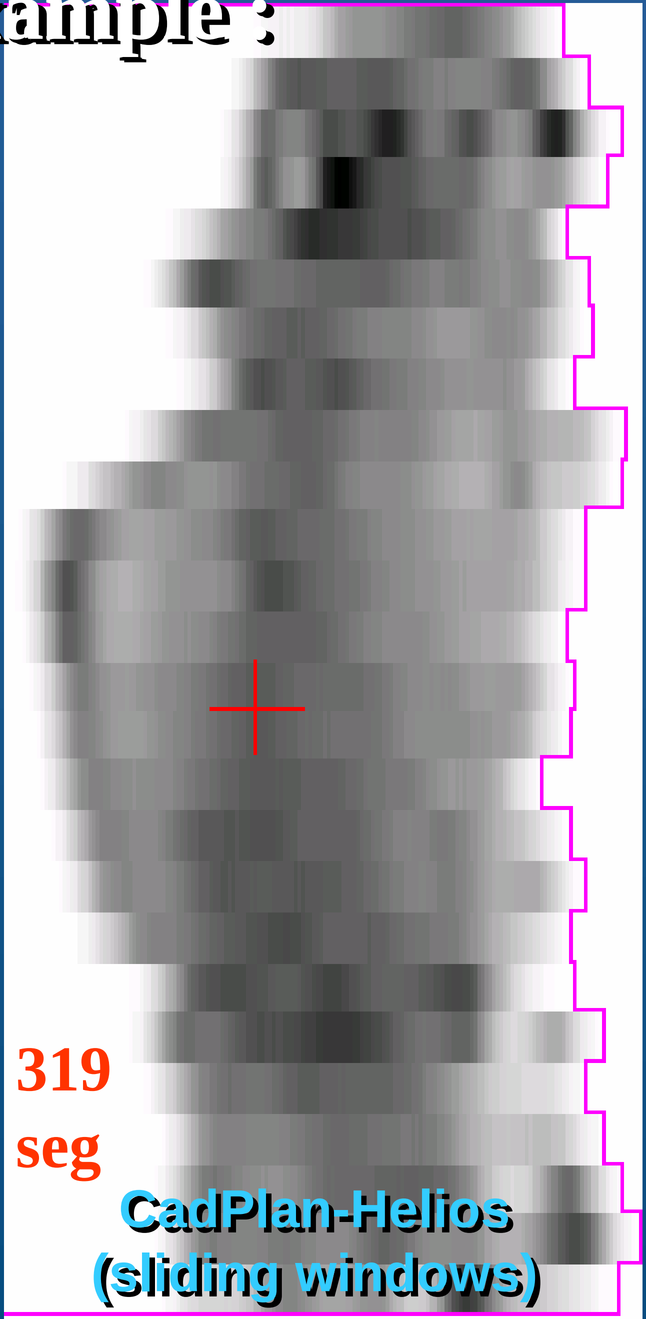
Conventional Treatment



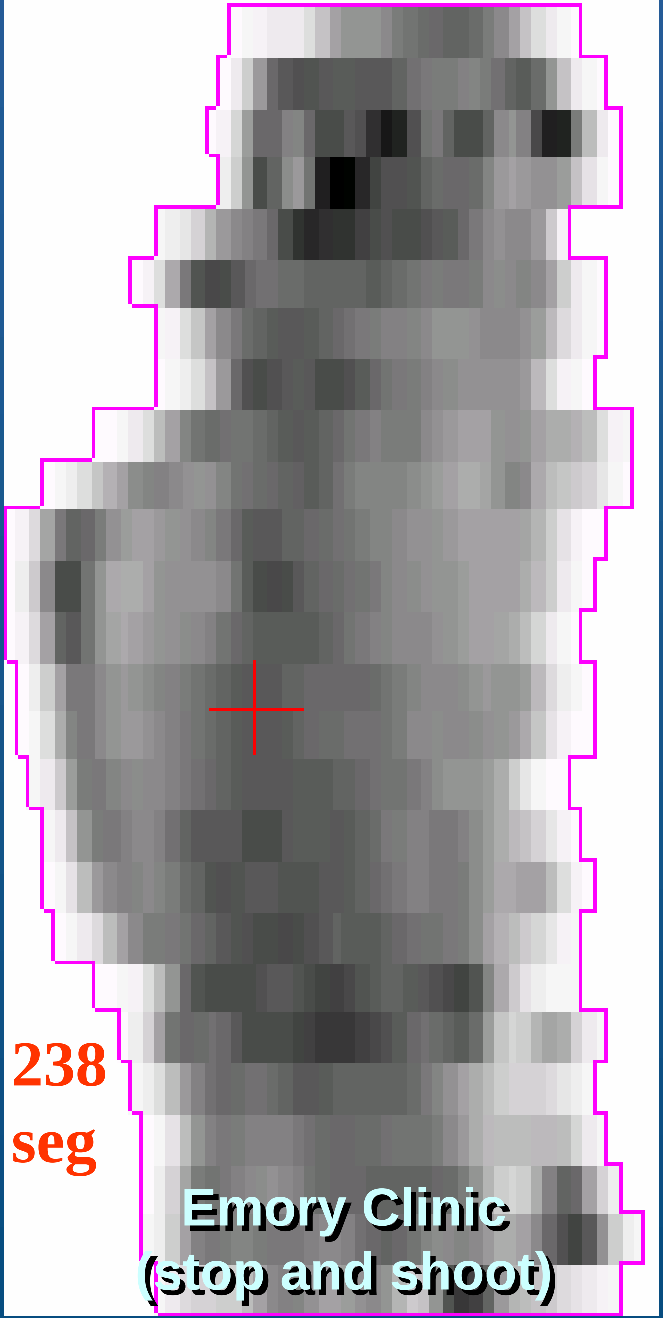
Intensity Modulated



For example :

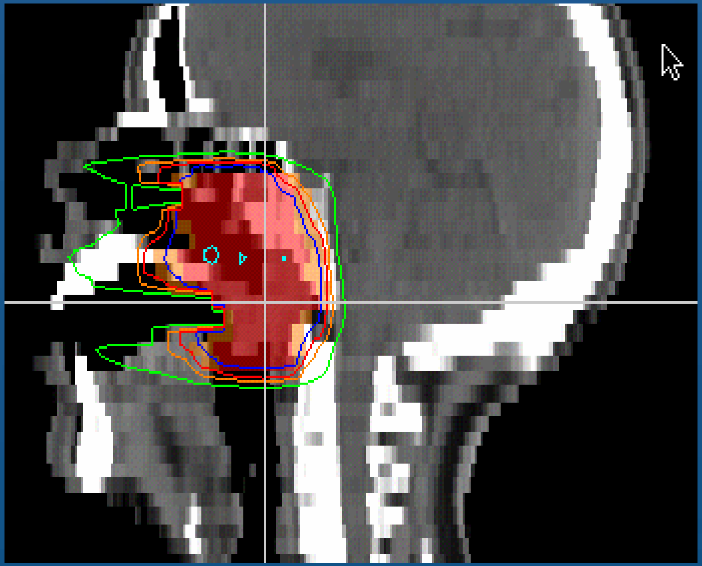


CadPlan-Helios
(sliding windows)



Emory Clinic
(stop and shoot)

Capabilities of IMRT



IMRT

70Gy

60Gy

50Gy

30Gy

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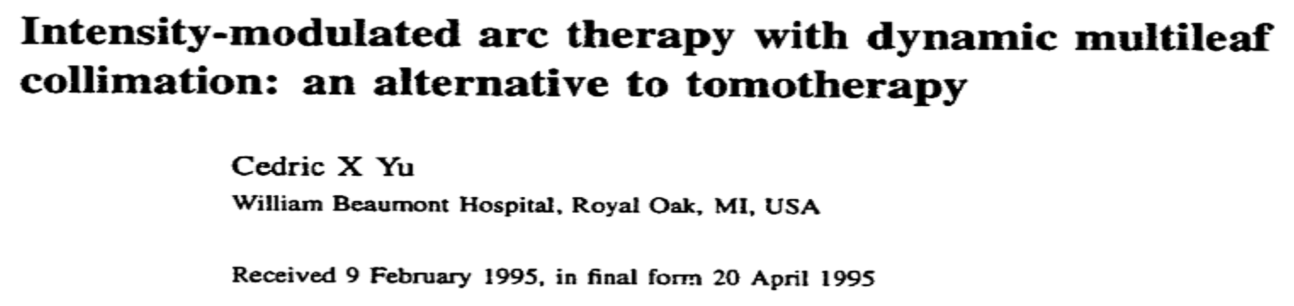
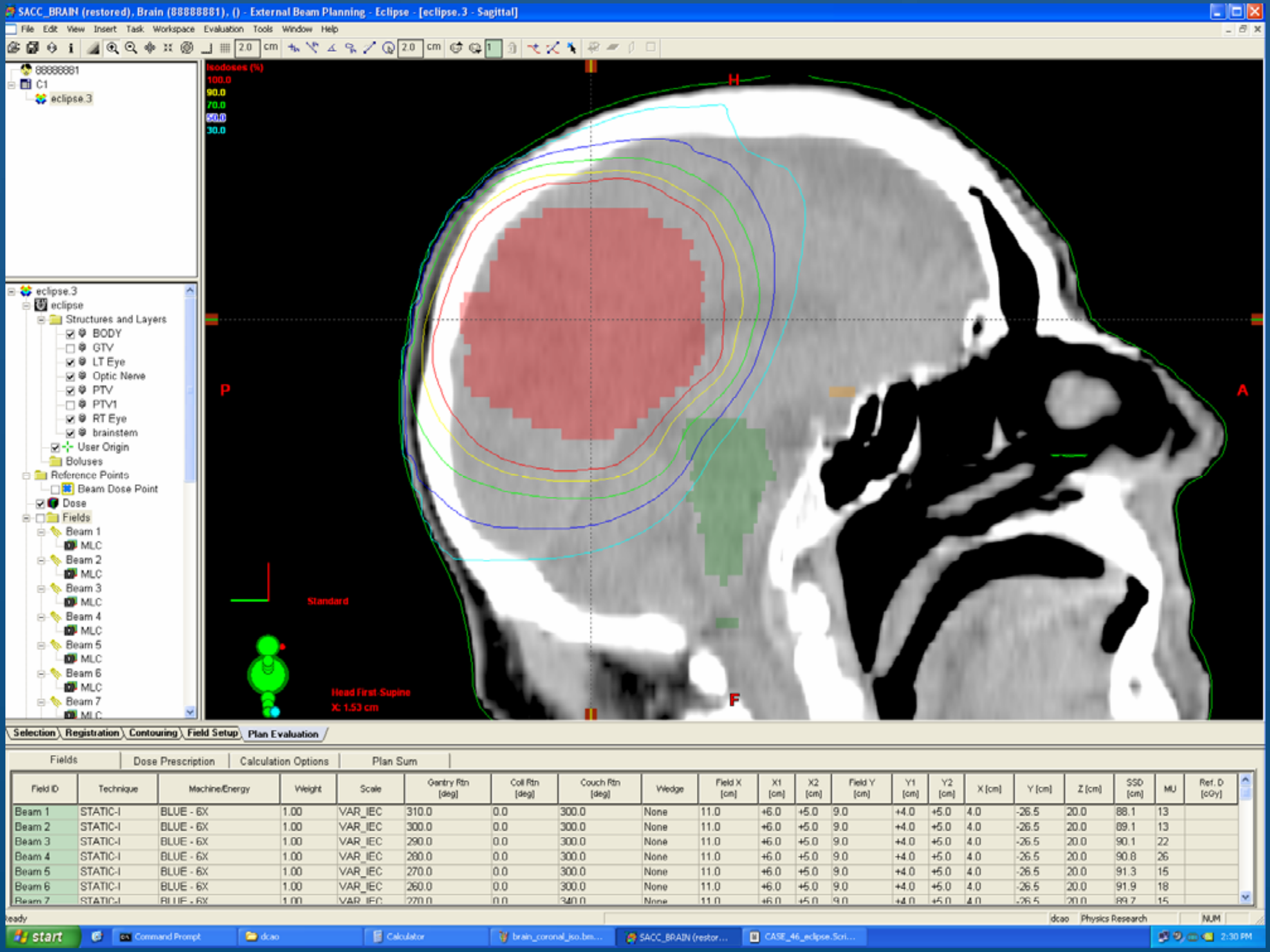


Intensity-modulated arc therapy with dynamic multileaf collimation: an alternative to tomotherapy

Cedric X Yu
William Beaumont Hospital, Royal Oak, MI, USA

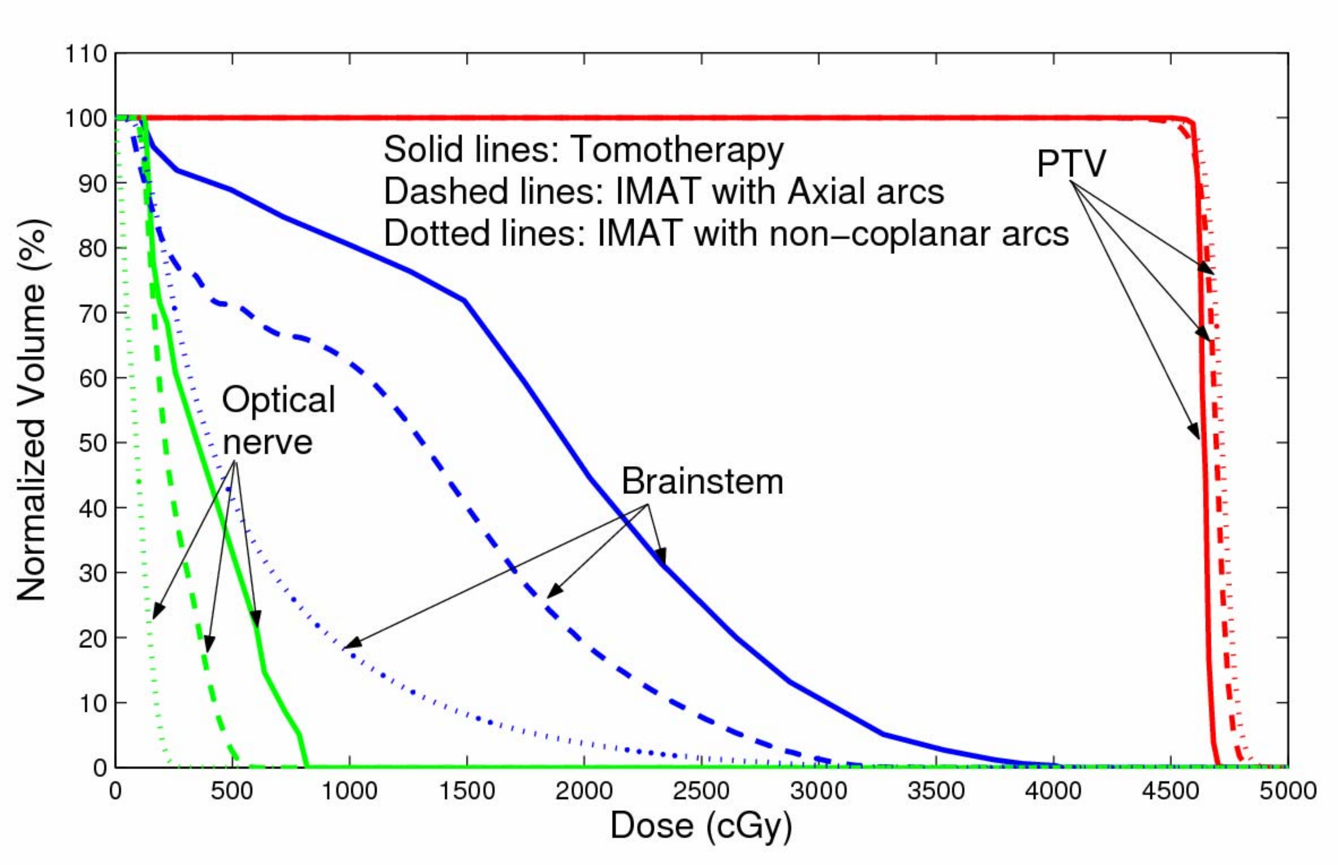
Received 9 February 1995, in final form 20 April 1995

GBM – 4 Non-coplanar Arcs



Field ID	Technique	Machine/Energy	Weight	Scale	Gantry Rtn [deg]	Coll Rtn [deg]	Couch Rtn [deg]	Wedge	Field X [cm]	X1 [cm]	X2 [cm]	Field Y [cm]	Y1 [cm]	Y2 [cm]	X [cm]	Y [cm]	Z [cm]	SSD [cm]	MU	Ref. D [cGy]
Beam 1	STATIC-I	BLUE - 6X	1.00	VAR_IEC	310.0	0.0	300.0	None	11.0	+6.0	+5.0	9.0	+4.0	+5.0	4.0	-26.5	20.0	88.1	13	
Beam 2	STATIC-I	BLUE - 6X	1.00	VAR_IEC	300.0	0.0	300.0	None	11.0	+6.0	+5.0	9.0	+4.0	+5.0	4.0	-26.5	20.0	89.1	13	
Beam 3	STATIC-I	BLUE - 6X	1.00	VAR_IEC	290.0	0.0	300.0	None	11.0	+6.0	+5.0	9.0	+4.0	+5.0	4.0	-26.5	20.0	90.1	22	
Beam 4	STATIC-I	BLUE - 6X	1.00	VAR_IEC	280.0	0.0	300.0	None	11.0	+6.0	+5.0	9.0	+4.0	+5.0	4.0	-26.5	20.0	90.8	26	
Beam 5	STATIC-I	BLUE - 6X	1.00	VAR_IEC	270.0	0.0	300.0	None	11.0	+6.0	+5.0	9.0	+4.0	+5.0	4.0	-26.5	20.0	91.3	15	
Beam 6	STATIC-I	BLUE - 6X	1.00	VAR_IEC	260.0	0.0	300.0	None	11.0	+6.0	+5.0	9.0	+4.0	+5.0	4.0	-26.5	20.0	91.9	18	
Beam 7	STATIC-I	BLUE - 6X	1.00	VAR_IEC	270.0	0.0	340.0	None	11.0	+6.0	+5.0	9.0	+4.0	+5.0	4.0	-26.5	20.0	89.7	15	

DVHs for Brain



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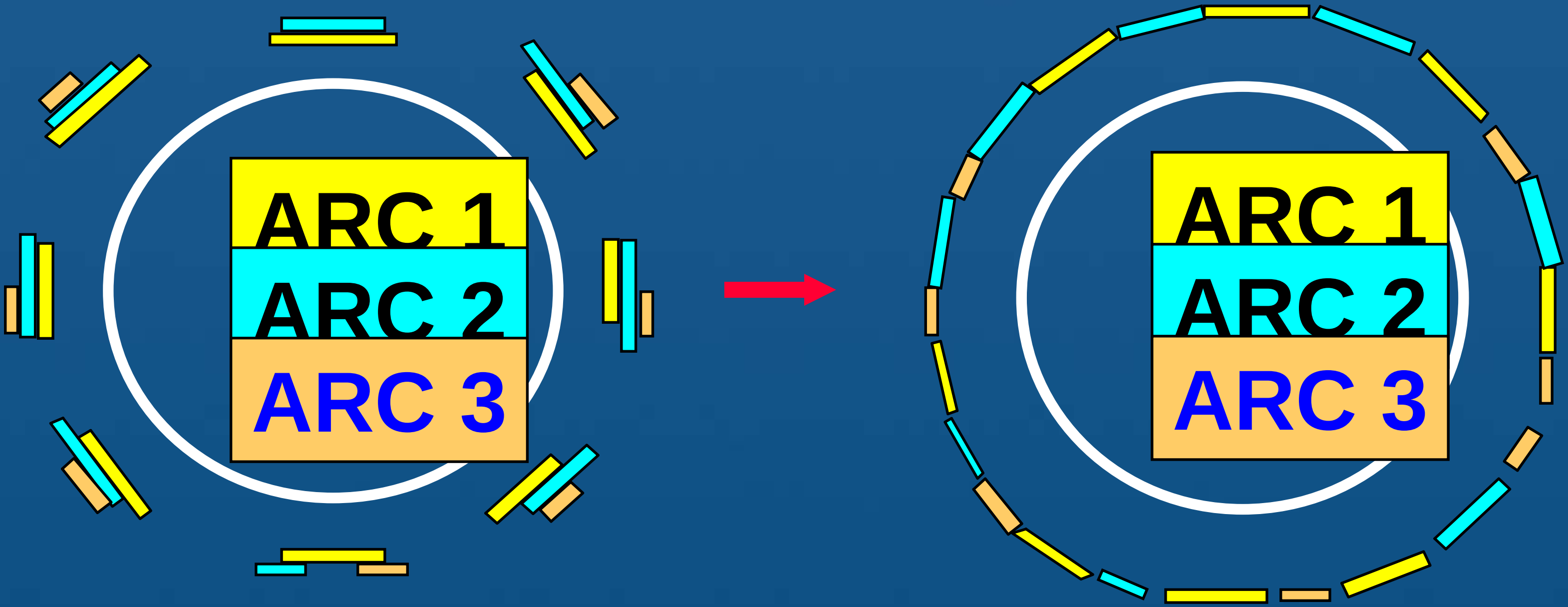
Multi-arc to Single arc



Stacked -> Spaced

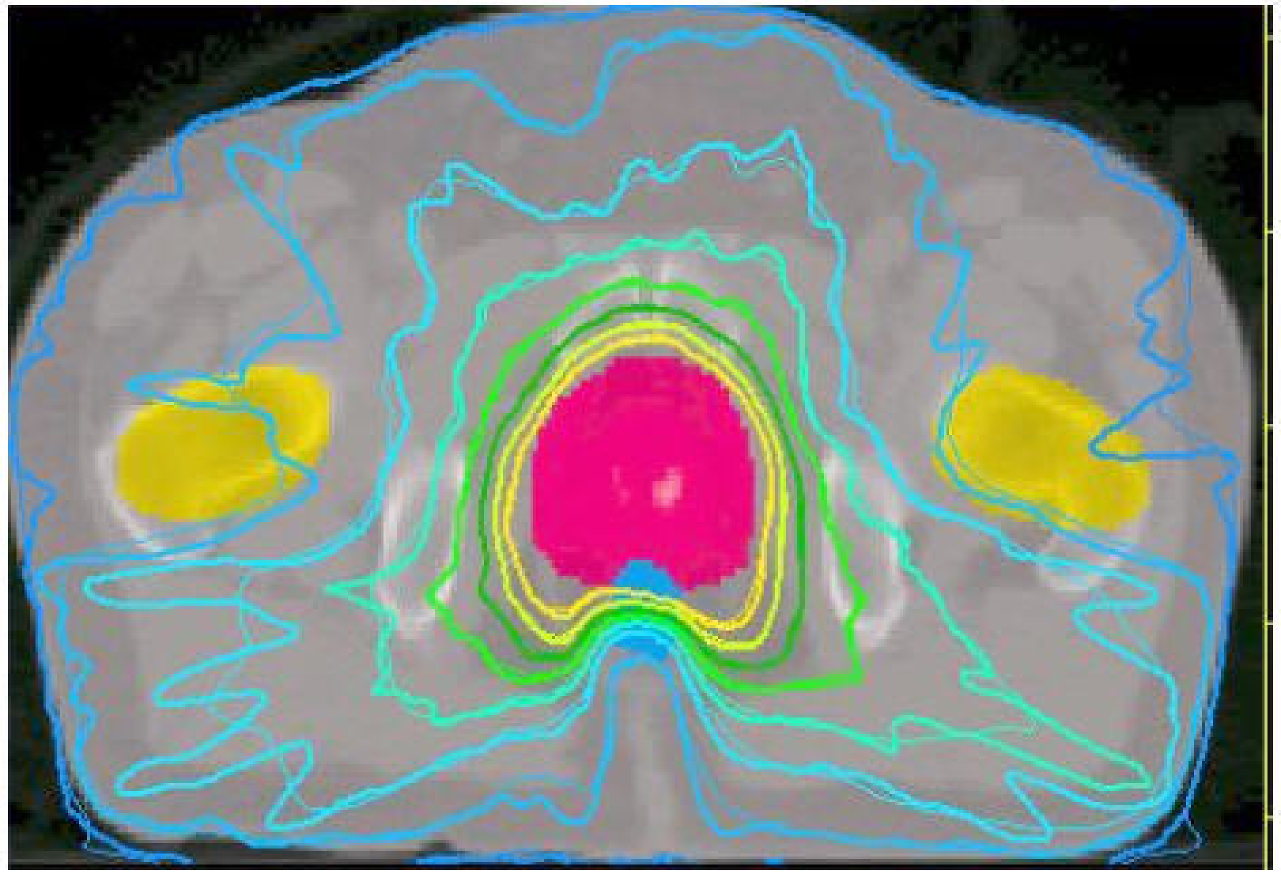


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Image guided Radiation Therapy (IGRT)

- A new trend of the field
- Broad definition with multiple flavors
- Clinical implications are significant

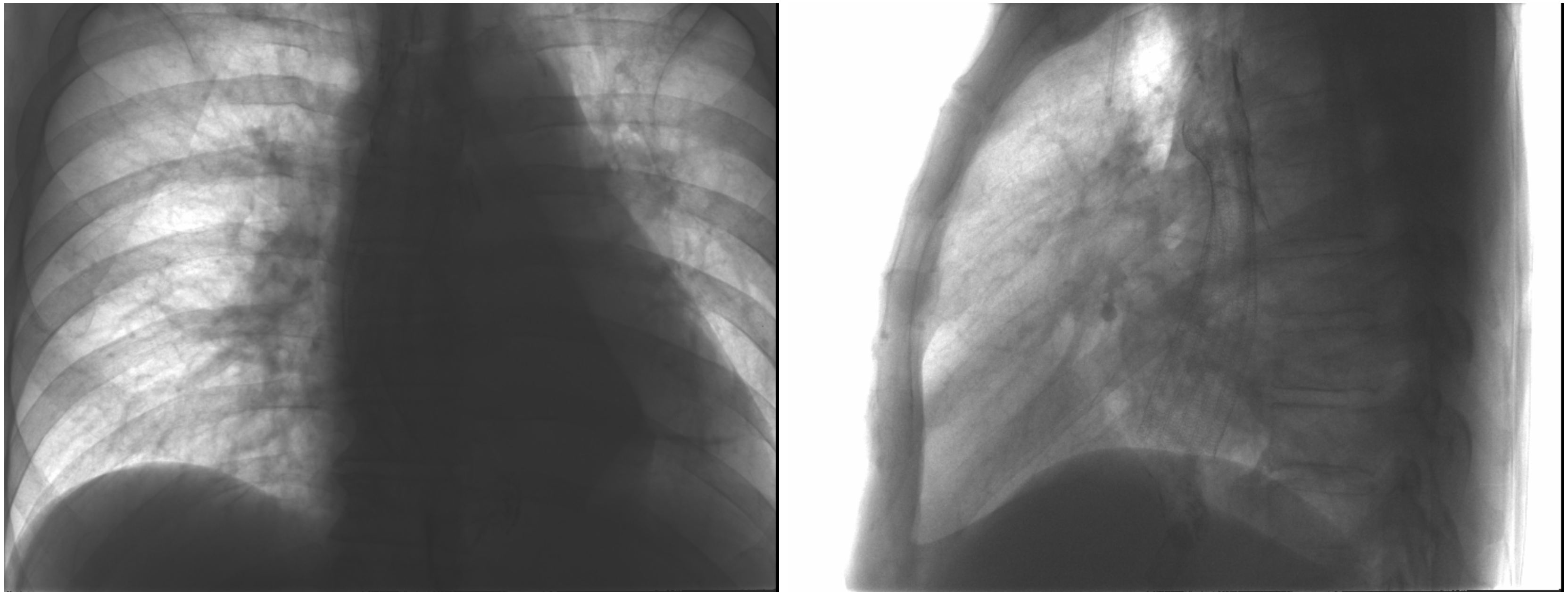
The use of three- and/or four-dimensional multi-modality images to guide target delineation, localization, treatment positioning, verification, and/or continuous adjustment of radiation therapy.

Elekta's Synergy

Varian's OBI and Trilogy

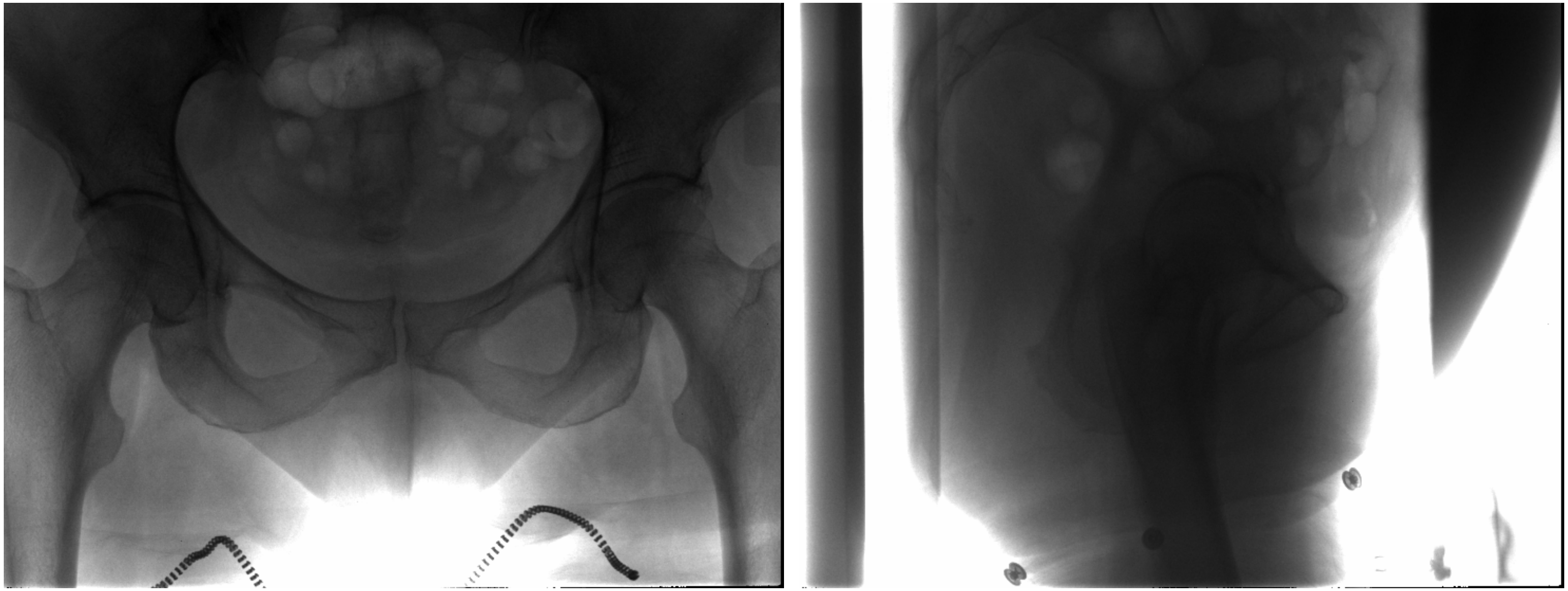
On-Board Imager

Sample images



Images courtesy of Karolinska Medial Center

Sample images



Images courtesy of Karolinska Medial Center

Sample CBCT image

Siemens

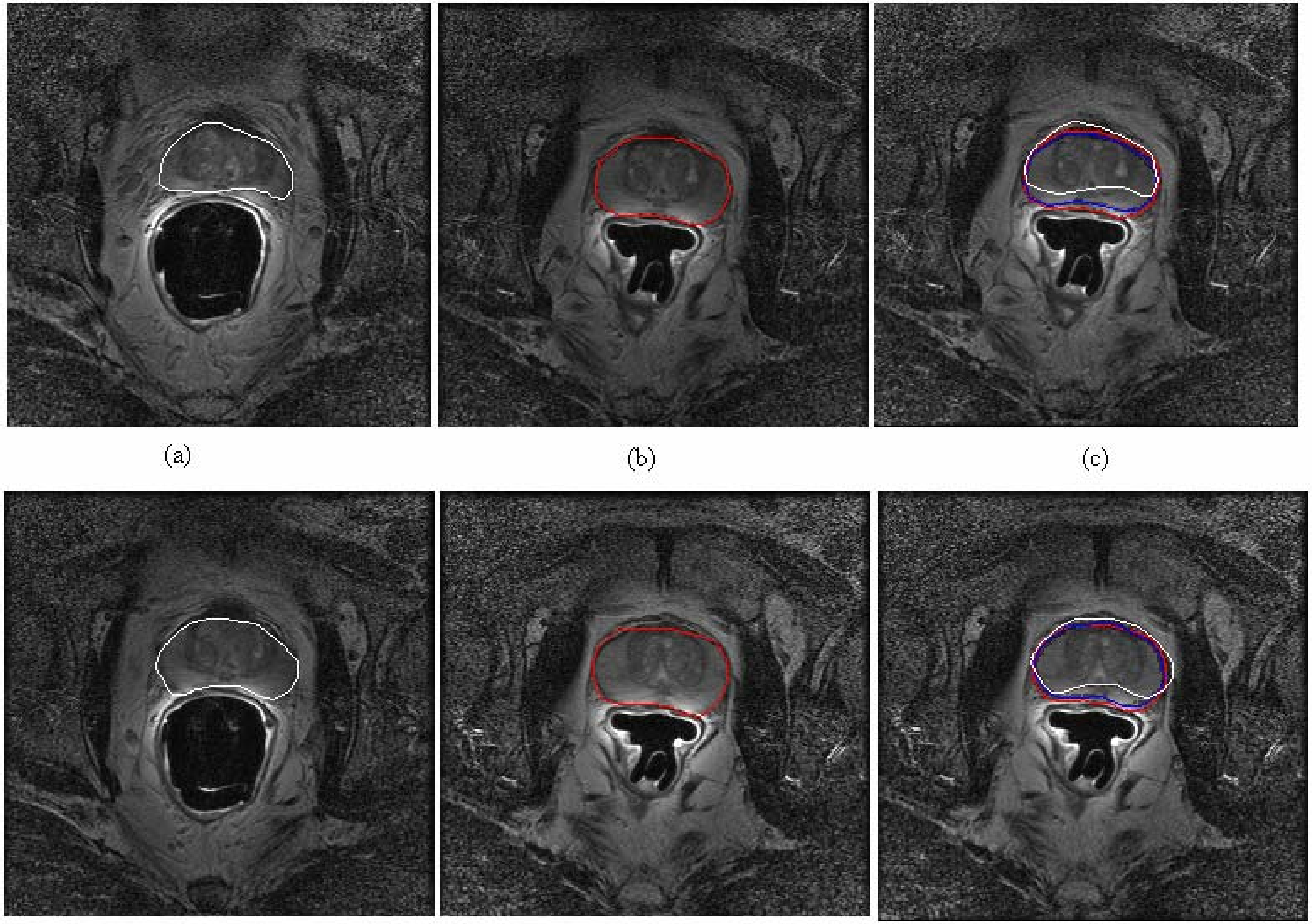
How to use the images?

- Simple shift of the patient
  - Cannot handle deformation
  - Cannot handle organ rotation
  - Cannot consider changes in surrounding structures

To Handle Target Deformation

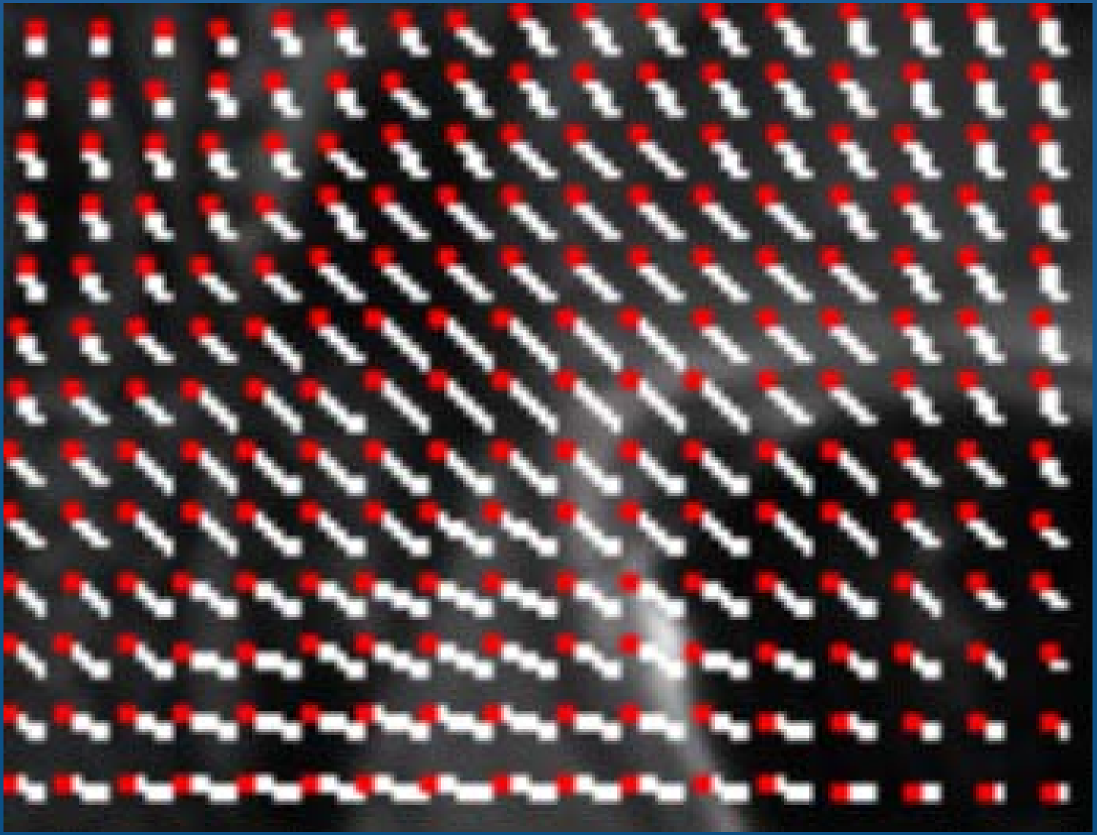
- Re-plan requires 3D target delineation for each CBCT (re-contour) – not realistic if done manually.
- On-line correction – an UMD scheme
- Fast deformable registration as the cornerstone to the effective use of CBCT

auto contouring

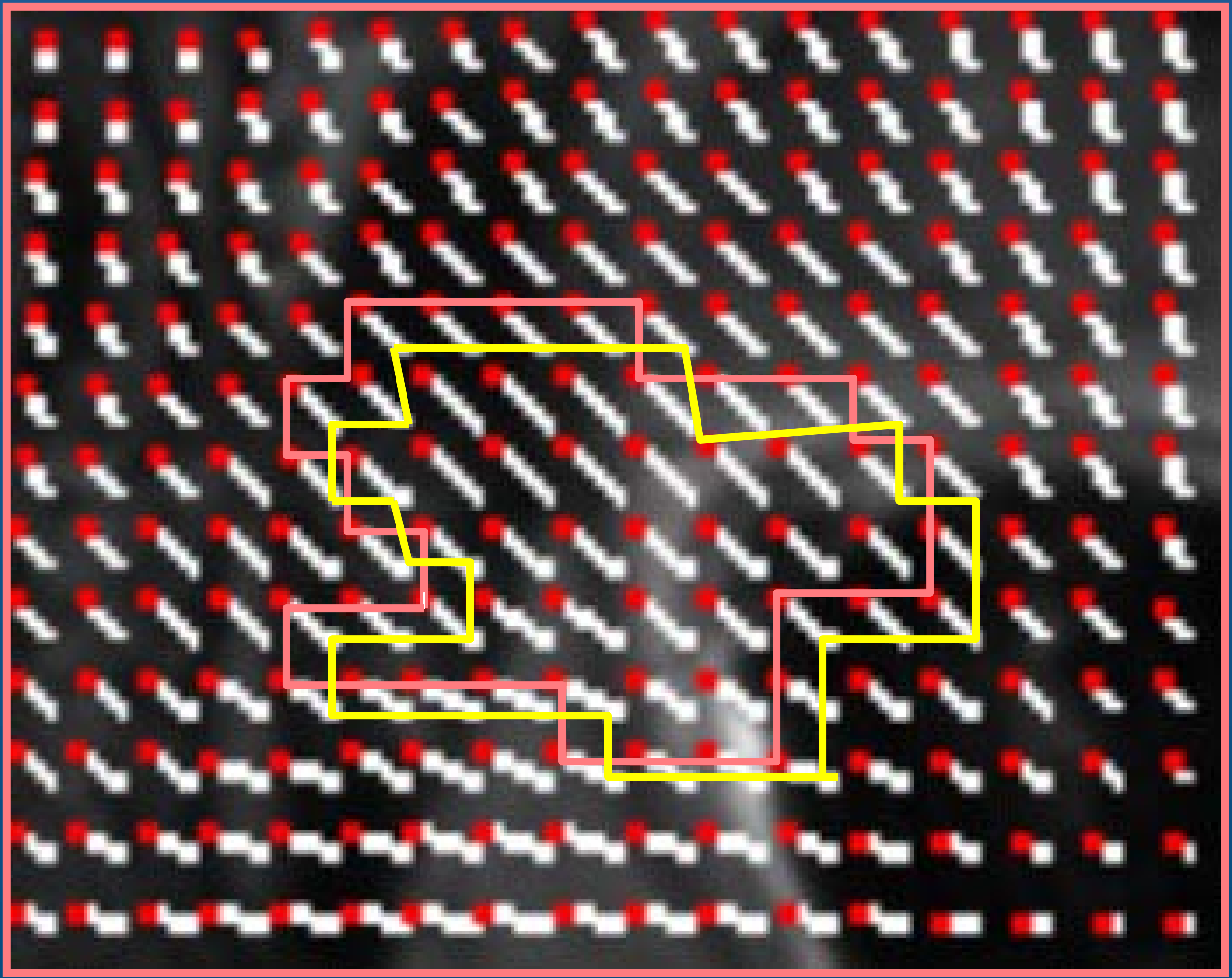

(a) (b) (c)

(d) (e) (f)

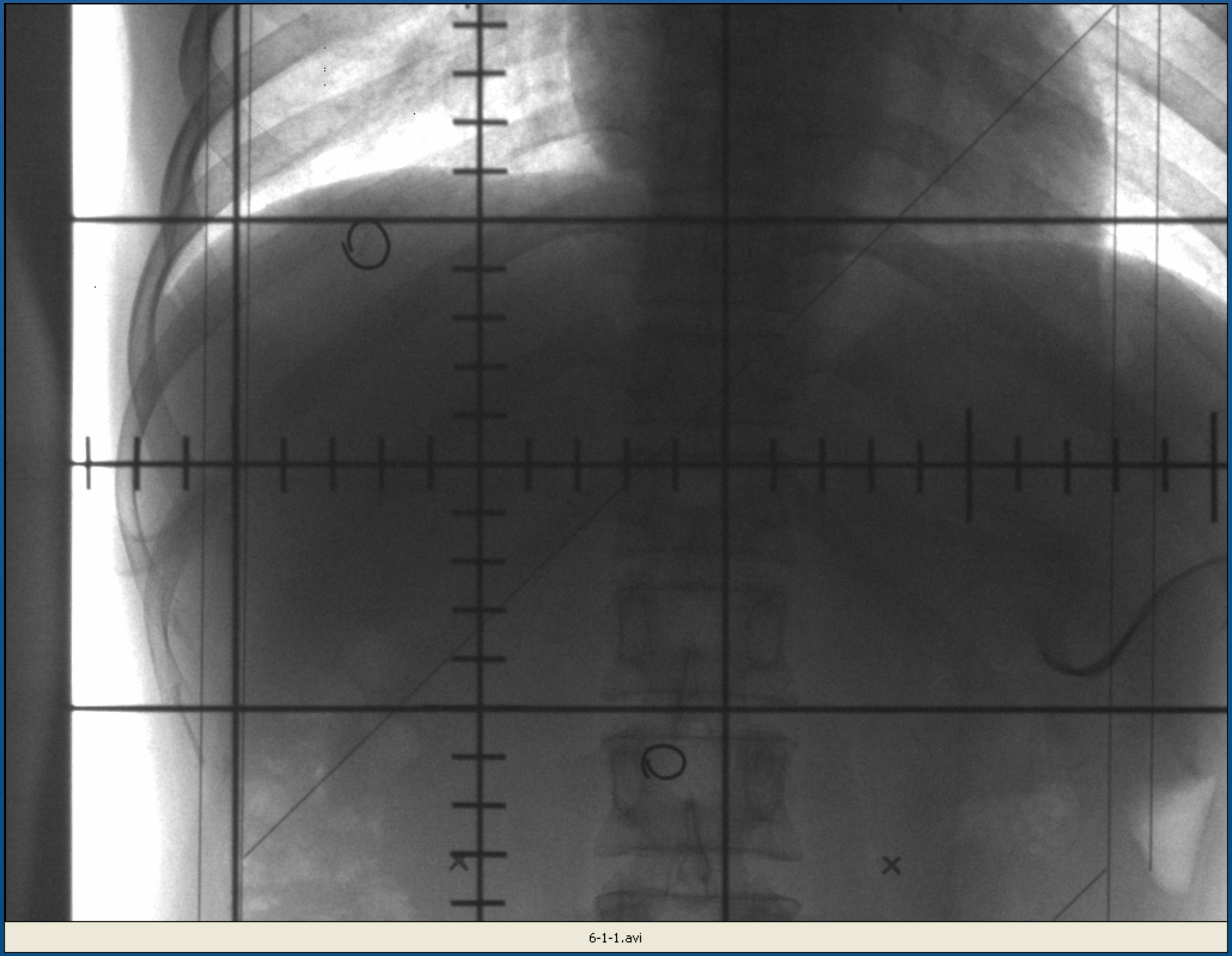
Collapsing the 3D vector to 2D



Morphing the Aperture



Intra-treatment Motion



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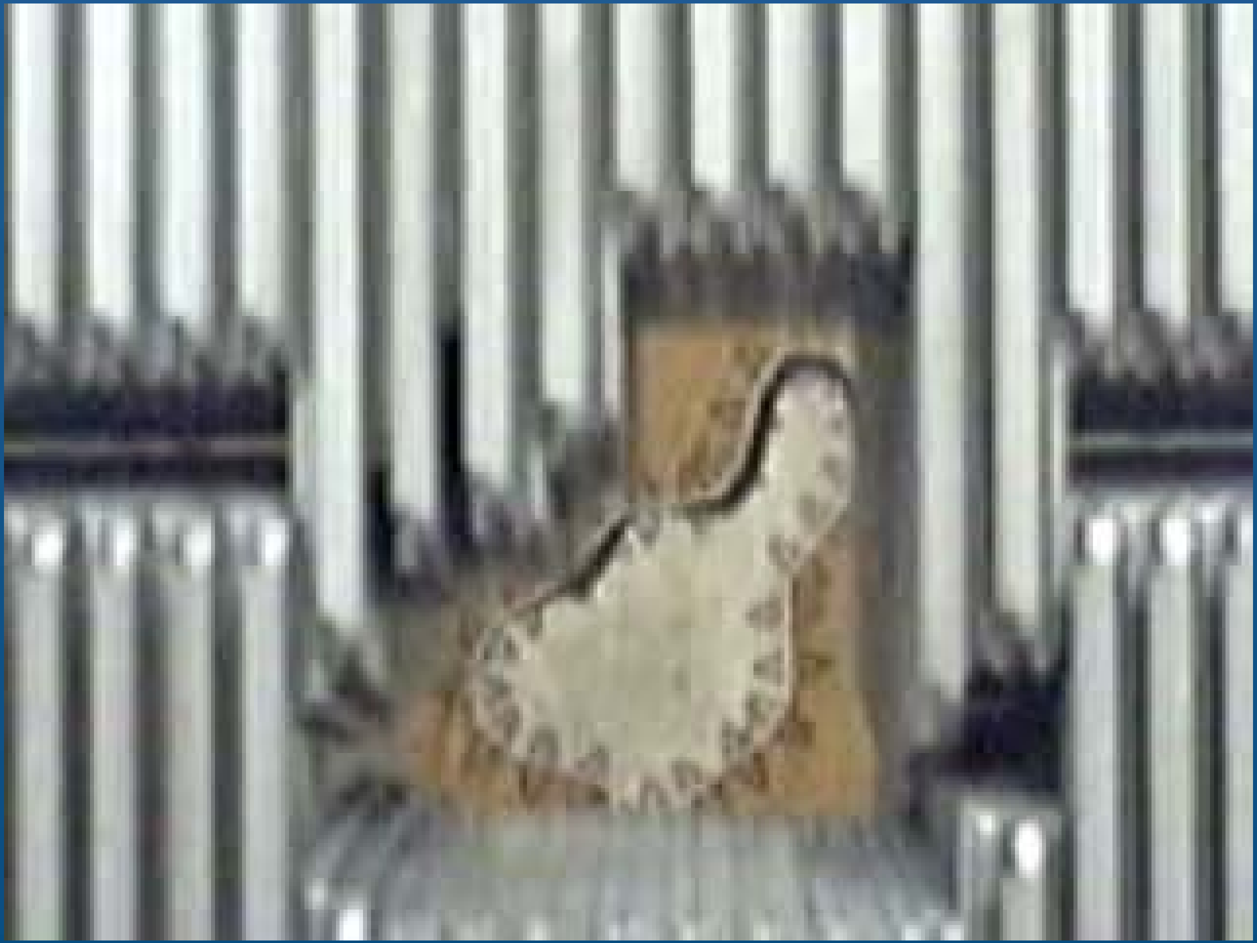
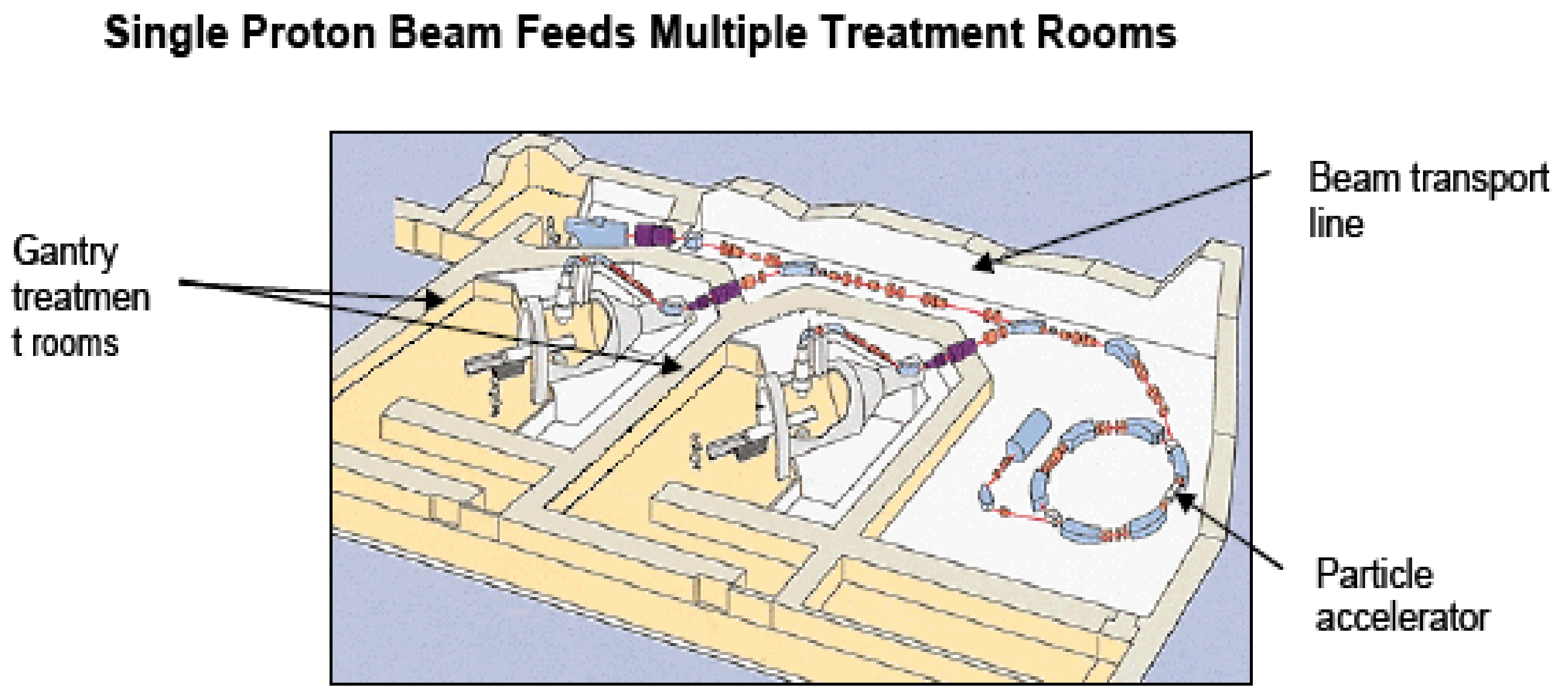
Dynamic Tumor Tracking



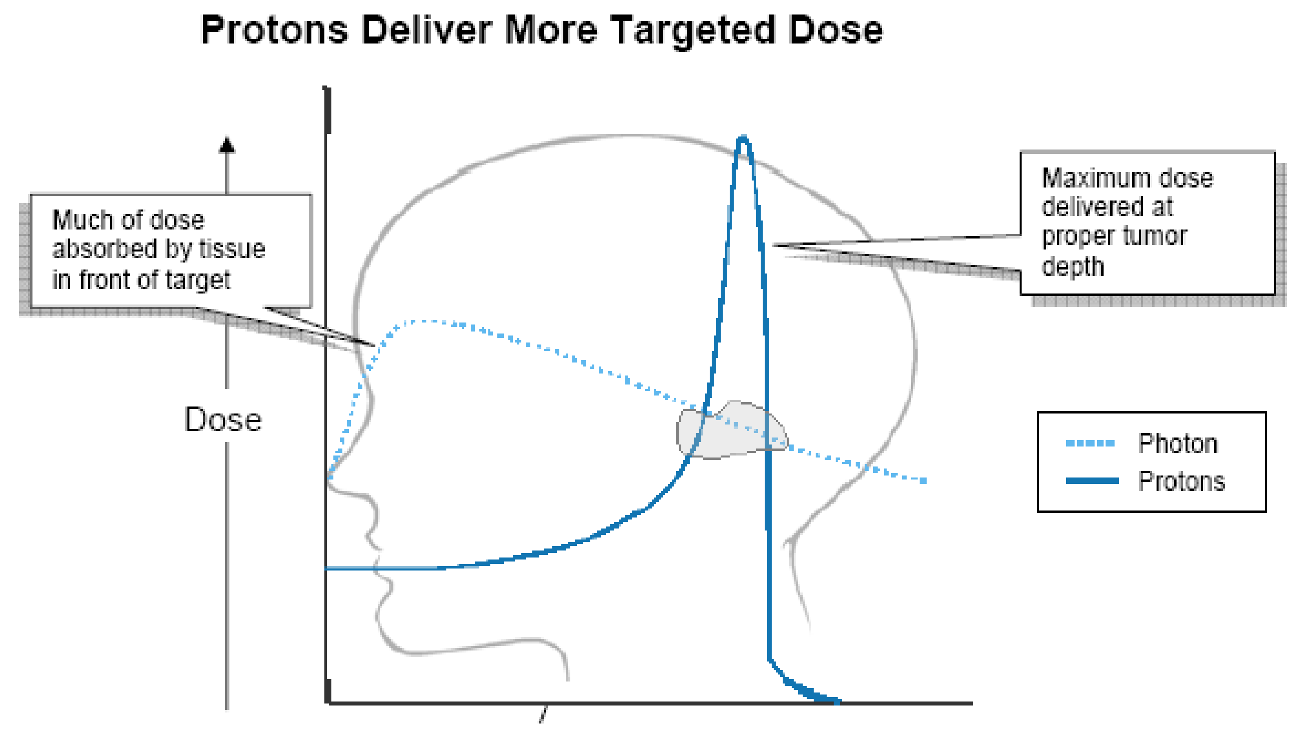
Protons

Proton Site

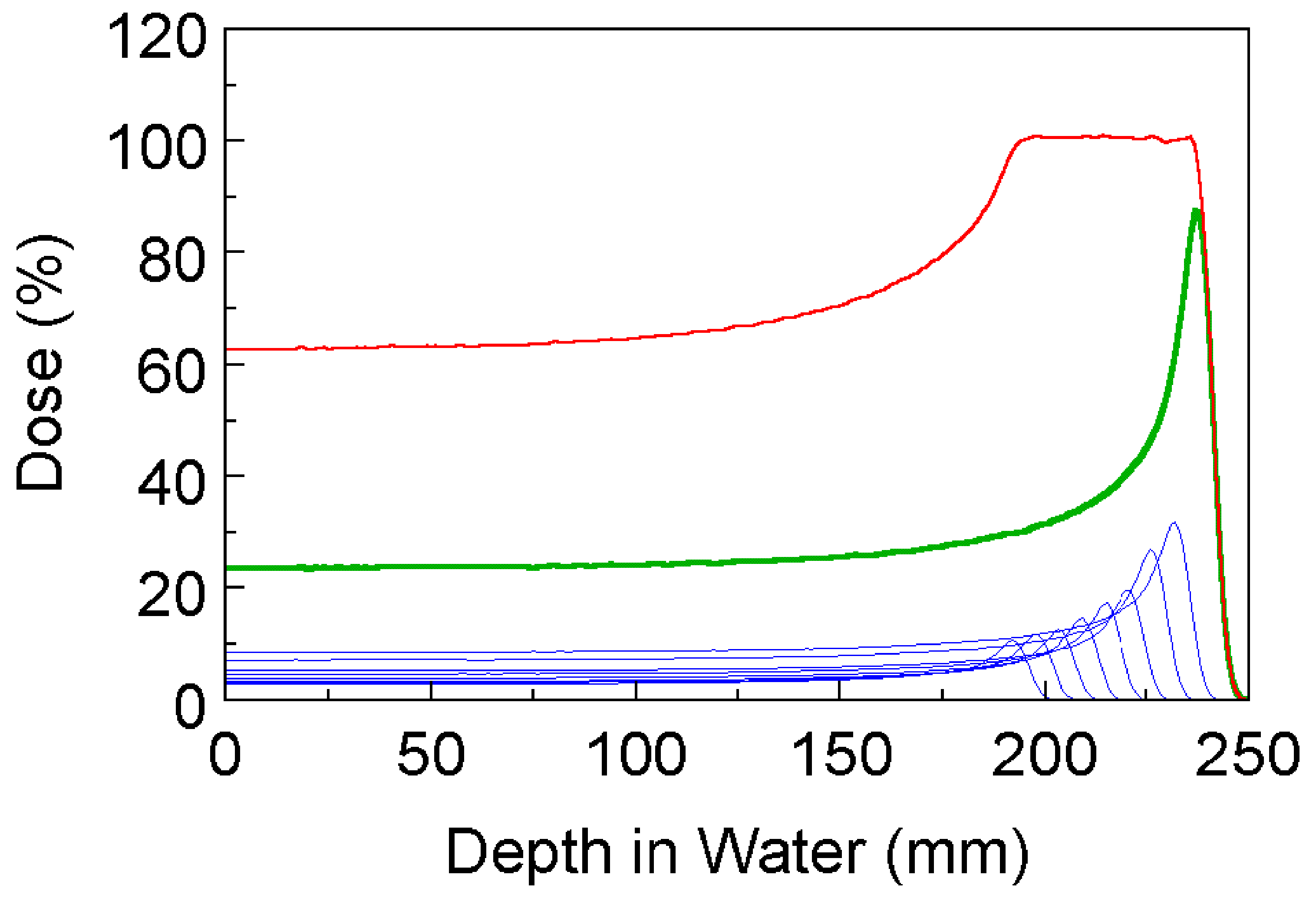


Single Proton Beam Feeds Multiple Treatment Rooms

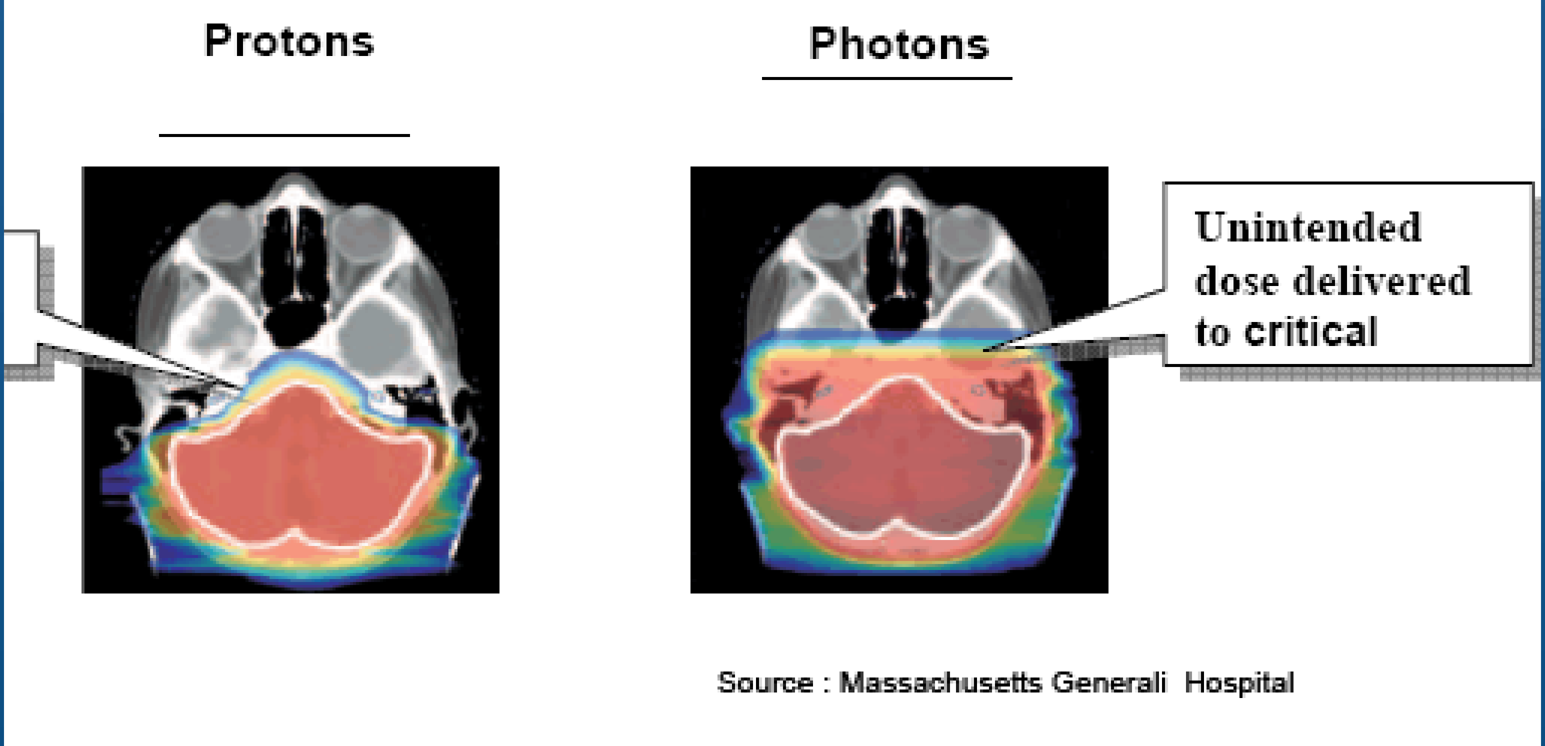
Physics


Protons Deliver More Targeted Dose
Dose
Much of dose absorbed by tissue in front of target
Maximum dose delivered at proper tumor depth
Photon
Protons

Ideal Depth Dose with SOBP



Proton Marketing



Protons

Photons

Unintended dose delivered to critical

Source : Massachusetts Generali Hospital

Therapeutic Radiological Physics

- Introduction and Basics of Radiation Oncology (Physics, Biology)
- Recent Advances: IMRT, IGRT, SBRT
- New Challenges

New Challenges

- Geometric uncertainty
  - Geometric uncertainties are far greater.
- Biological uncertainty
  - Biological understanding of radiotherapy falls far behind physics.
- New treatment techniques based on new biological understanding and new imaging capabilities hold the key to cure.

New Challenges

- Geometric uncertainty
  - Geometric uncertainties are far greater.
- Biological uncertainty
  - Biological understanding of radiotherapy falls far behind physics.
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> “Patient repositioning and patient motion have been a problem in radiation therapy since its inception,”

Connor et al, IJROBP 1975

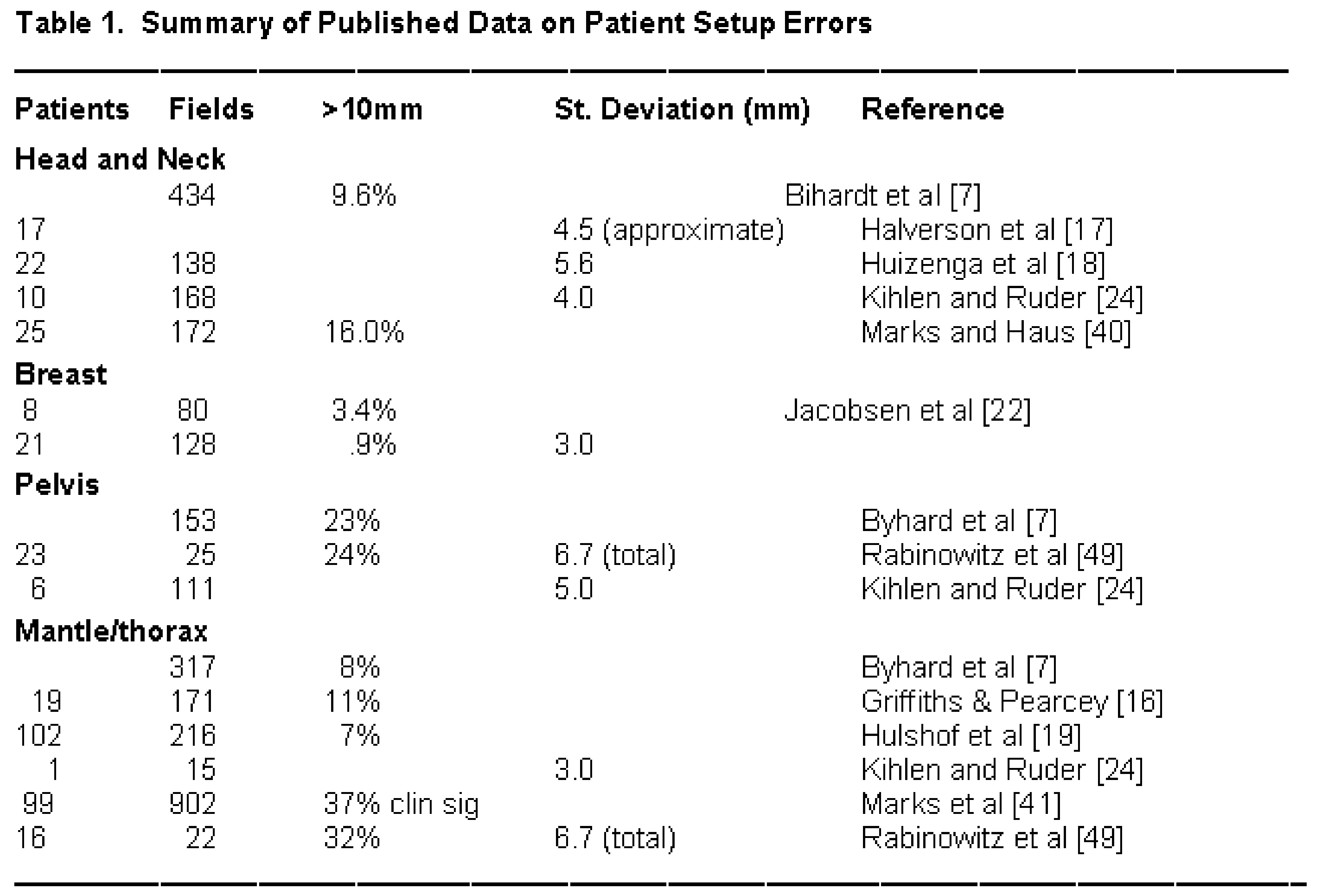
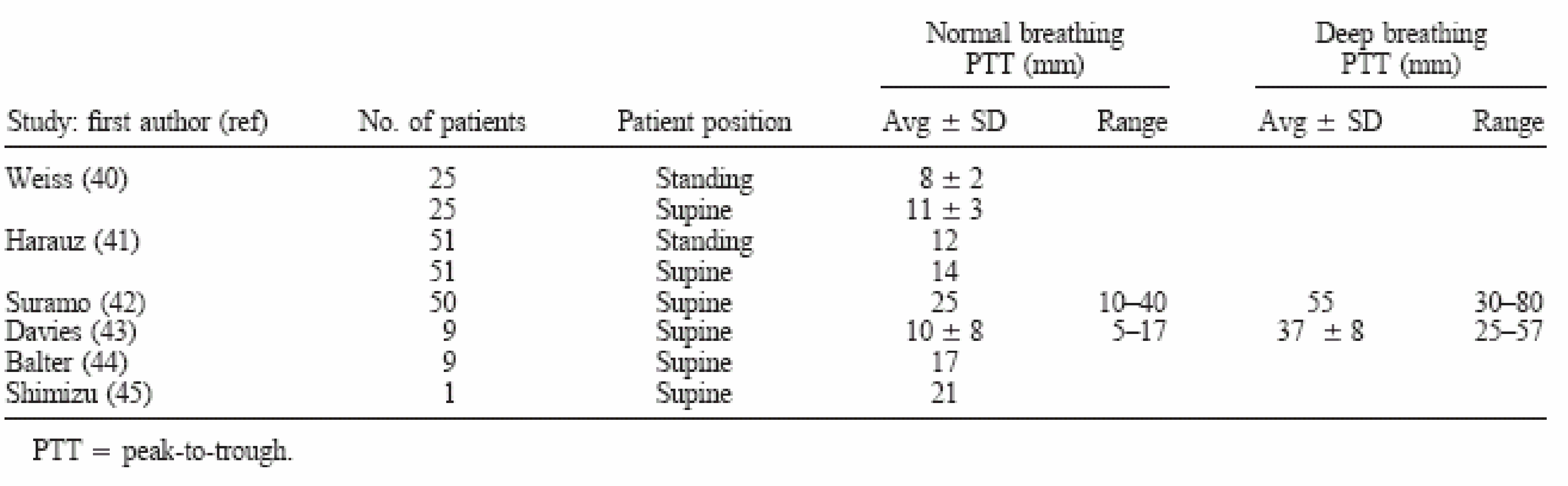


Table 1. Summary of Published Data on Patient Setup Errors

Patients	Fields	>10mm	St. Deviation (mm)	Reference
Head and Neck				
	434	9.6%		Bihardt et al [7]
17			4.5 (approximate)	Halverson et al [17]
22	138		5.6	Huizenga et al [18]
10	168		4.0	Kihlen and Ruder [24]
25	172	16.0%		Marks and Haus [40]
Breast				
8	80	3.4%		Jacobsen et al [22]
21	128	.9%	3.0	
Pelvis				
	153	23%		Byhard et al [7]
23	25	24%	6.7 (total)	Rabinowitz et al [49]
6	111		5.0	Kihlen and Ruder [24]
Mantle/thorax				
	317	8%		Byhard et al [7]
19	171	11%		Griffiths & Pearcey [16]
102	216	7%		Hulshof et al [19]
1	15		3.0	Kihlen and Ruder [24]
99	902	37% clin sig		Marks et al [41]
16	22	32%	6.7 (total)	Rabinowitz et al [49]

Liver Motion

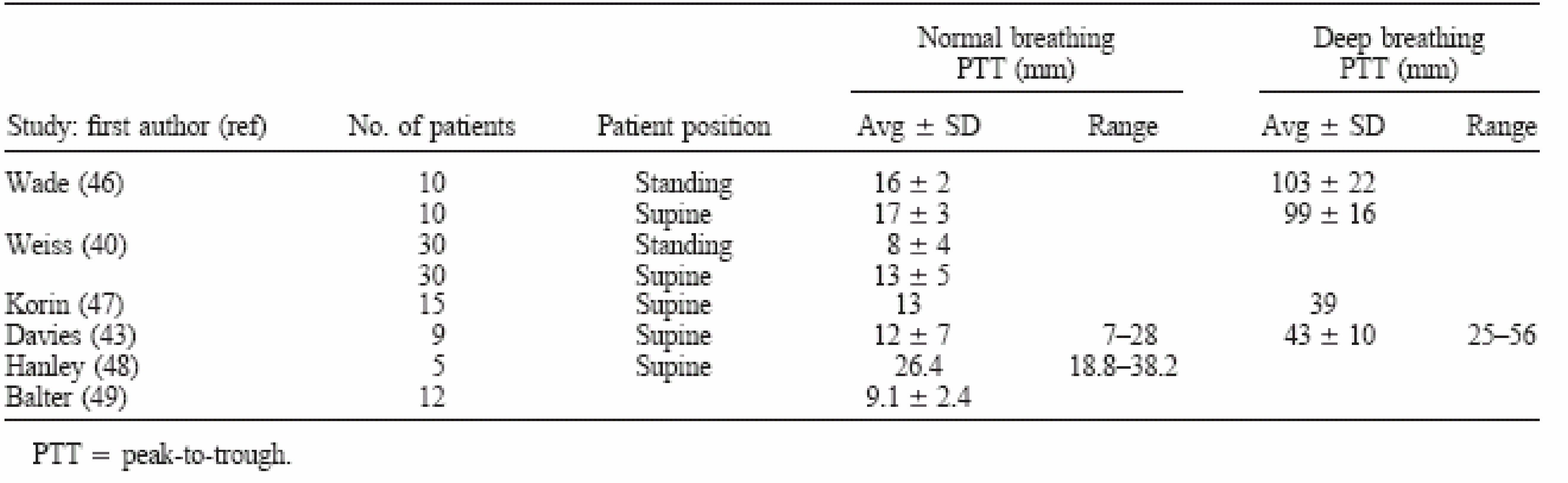


			Normal breathing PTT (mm)		Deep breathing PTT (mm)	
Study: first author (ref)	No. of patients	Patient position	Avg ± SD	Range	Avg ± SD	Range
Weiss (40)	25	Standing	8 ± 2			
	25	Supine	11 ± 3			
Harauz (41)	51	Standing	12			
	51	Supine	14			
Suramo (42)	50	Supine	25	10–40	55	30–80
Davies (43)	9	Supine	10 ± 8	5–17	37 ± 8	25–57
Balter (44)	9	Supine	17			
Shimizu (45)	1	Supine	21			

PTT = peak-to-trough.

Langen Red, 50(1):265–278, 2001

Diaphragm



Study: first author (ref)	No. of patients	Patient position	Normal breathing PTT (mm) Avg ± SD	Normal breathing PTT (mm) Range	Deep breathing PTT (mm) Avg ± SD	Deep breathing PTT (mm) Range
Wade (46)	10	Standing	16 ± 2		103 ± 22	
	10	Supine	17 ± 3		99 ± 16	
Weiss (40)	30	Standing	8 ± 4			
	30	Supine	13 ± 5			
Korin (47)	15	Supine	13		39	
Davies (43)	9	Supine	12 ± 7	7–28	43 ± 10	25–56
Hanley (48)	5	Supine	26.4	18.8–38.2		
Balter (49)	12		9.1 ± 2.4			

PTT = peak-to-trough.

Langen Red, 50(1):265–278, 2001

Gated RT

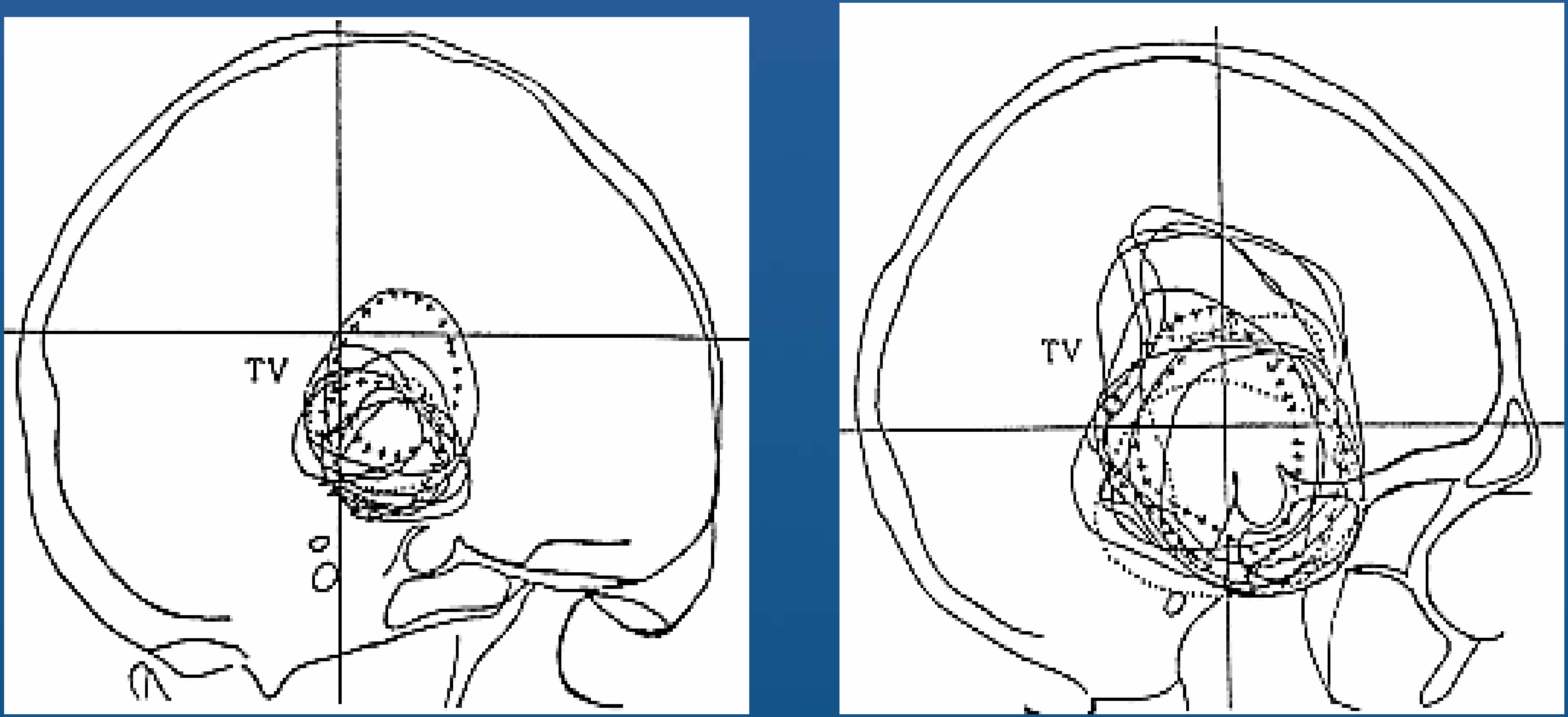
Non-Gated

Gated

Limitations of Imaging

- Tumors consist of $<10^5$ cells cannot be imaged or palpated
- Experience involved in the “guessing game”

Large variations among physicians!



Example of difficulty and risk of disagreement when delineating the Gross Tumor Volume. Schematic drawings on lateral radiographs for two patients with brain tumors, where the Gross Tumor Volume was delineated by:

-8 radiation oncologists (----), - 2 radiologists (·······),
-- 2 neurosurgeons (- - - -).

Adapted from Leunens et al., 1993.

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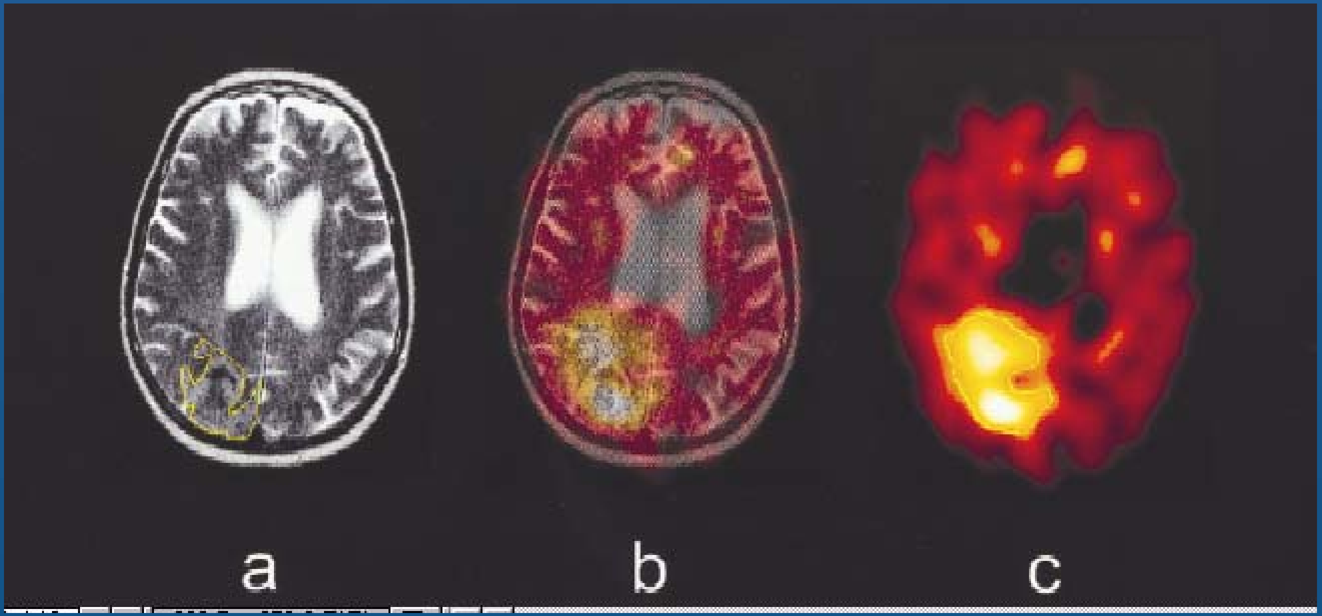
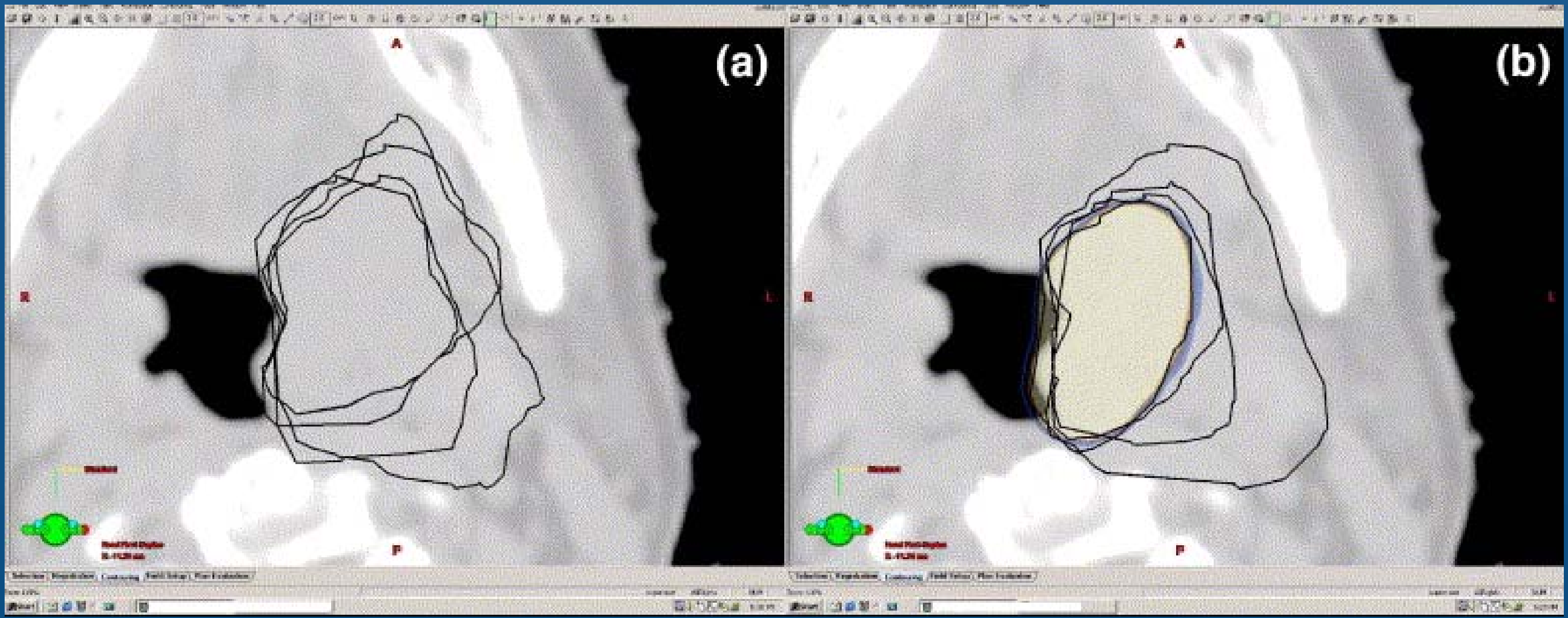
New Imaging Tools May Help



Glioma T2 weighted MRI (a),
IMT(I-123-alpha-methyl tyrosine)-SPECT (c)

IJROBP 47(2) 517, 2000

Riegel AC, et al, Variability of gross tumor volume delineation in head-and-neck cancer using CT and PET/CT fusion, Int J Radiat Oncol Biol Phys. 65(3): 726-32, 2006



- **Logue JP**, et al, Clinical variability of target volume description in conformal radiotherapy planning Int J Radiat Oncol Biol Phys. 1998 Jul 1;41(4):929-31

  In 4 cases of T3 bladder cancer:

    RESULTS: There was a maximum variation ratio (largest to smallest volume outlined) of the GTV in the four cases of 1.74 among radiologists and 3.74 among oncologists.

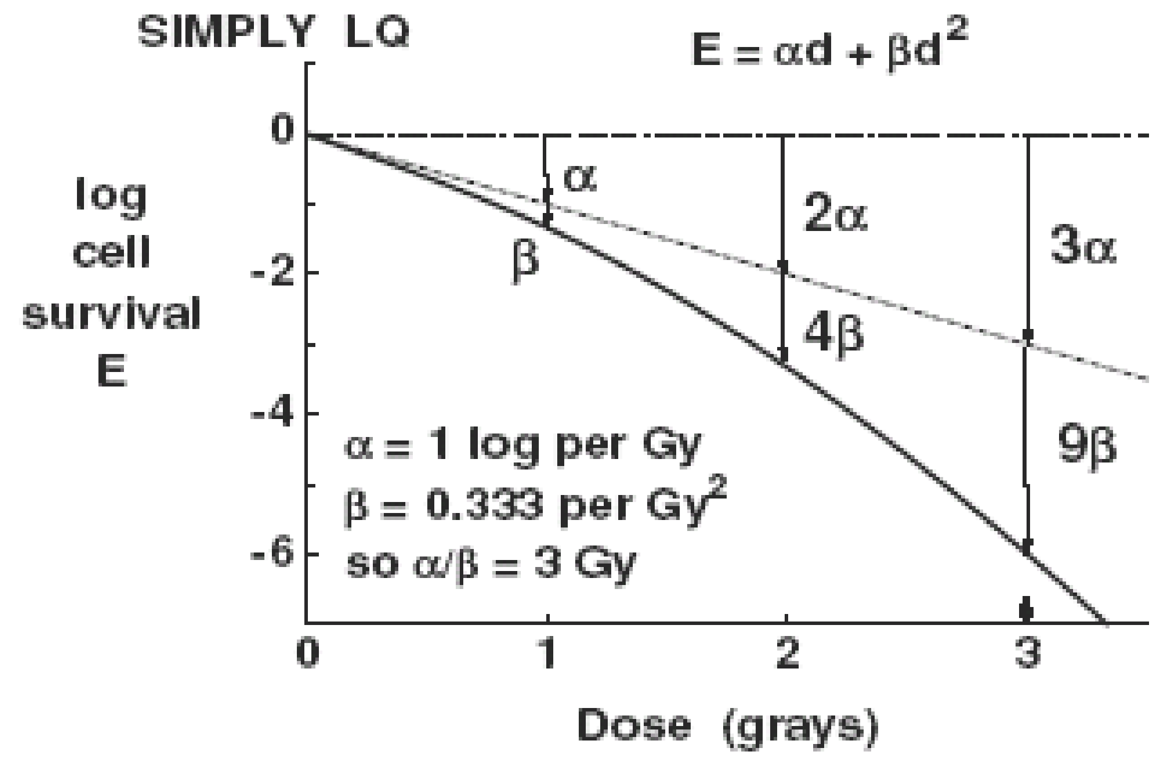
New Challenges

- Geometric uncertainty
  - Geometric uncertainties are far greater.
- Biological uncertainty
  - Biological understanding of radiotherapy falls far behind physics.
- New treatment techniques based on new biological understanding and new imaging capabilities hold the key to cure.

‘When I came into radiotherapy in 1950, I was puzzled that some patients were treated to 3000 rads (cGy) in 3 weeks but others received 4000 in 5 or 6000 in 6 weeks. When I asked why, there were no convincing answers given, except ‘this is what we usually do’.

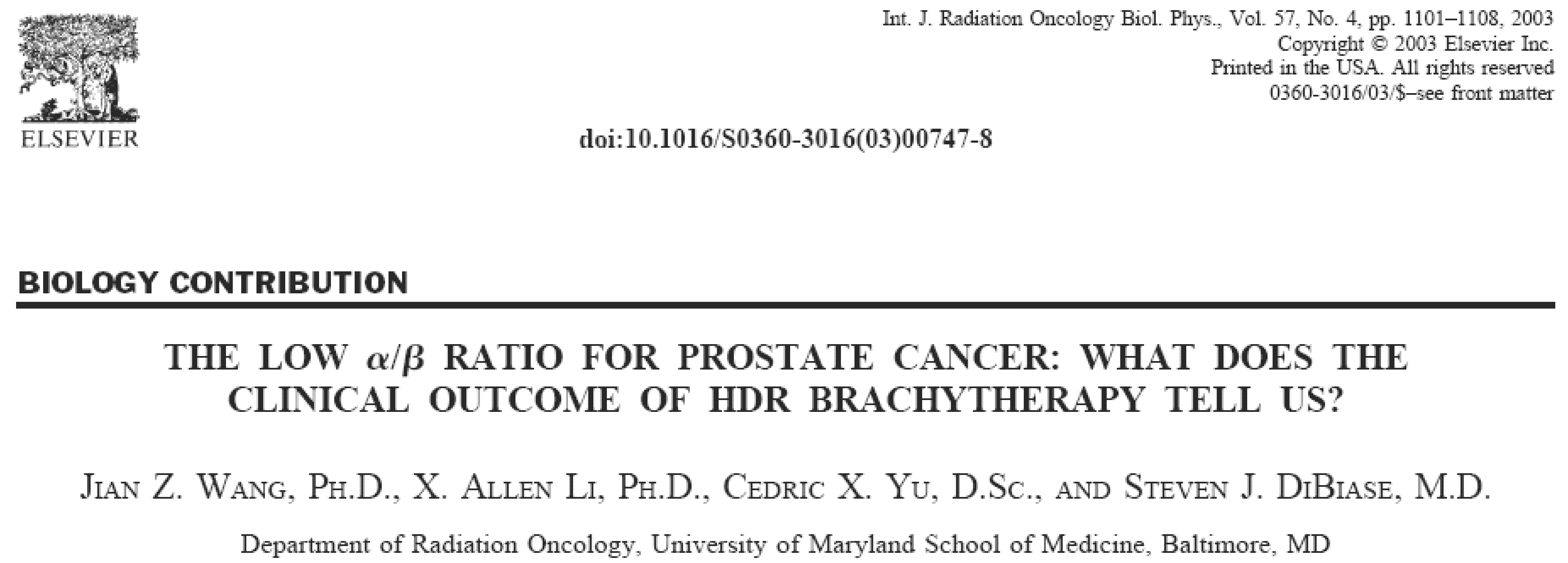
--- Jack Fawler, Phys Med Biol. 51, 2006

The LQ model – Fowler et al



$$E = n(\alpha d + \beta d^2)$$
$$E/\alpha = nd(1 + d/(\alpha/\beta))$$

Actual *α/β is unknown*



Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 4, pp. 1101–1108, 2003

0360-3016/03/$–see front matter

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doi:10.1016/S0360-3016(03)00747-8

BIOLOGY CONTRIBUTION

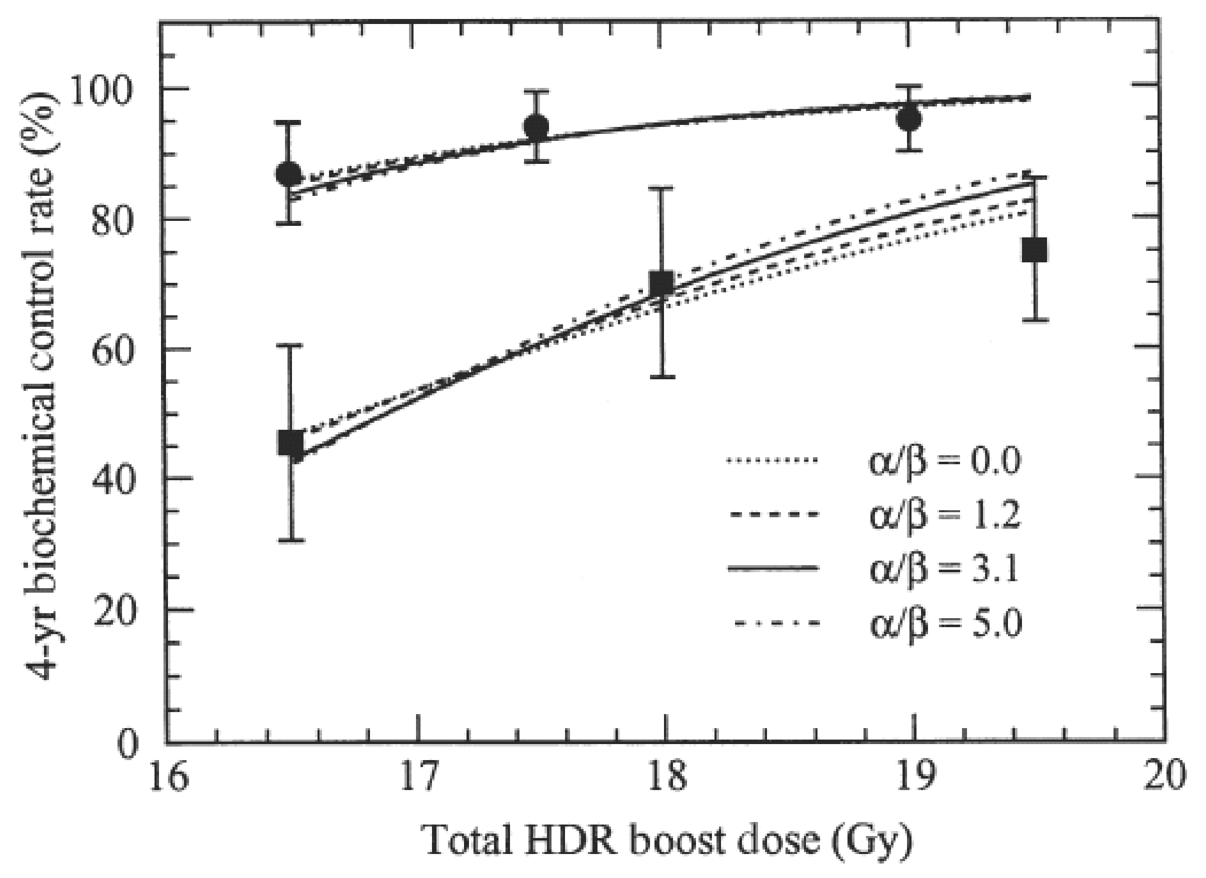
THE LOW α/β RATIO FOR PROSTATE CANCER: WHAT DOES THE CLINICAL OUTCOME OF HDR BRACHYTHERAPY TELL US?

Jian Z. Wang, Ph.D., X. Allen Li, Ph.D., Cedric X. Yu, D.Sc., and Steven J. DiBiase, M.D.

Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD

Using the same clinical data set, similar methods, we derived an *α/β* of 3.1 for prostate cancer, Branner and Fowler gave an *α/β* of 1.5

Reason: Uncertainty of Analysis



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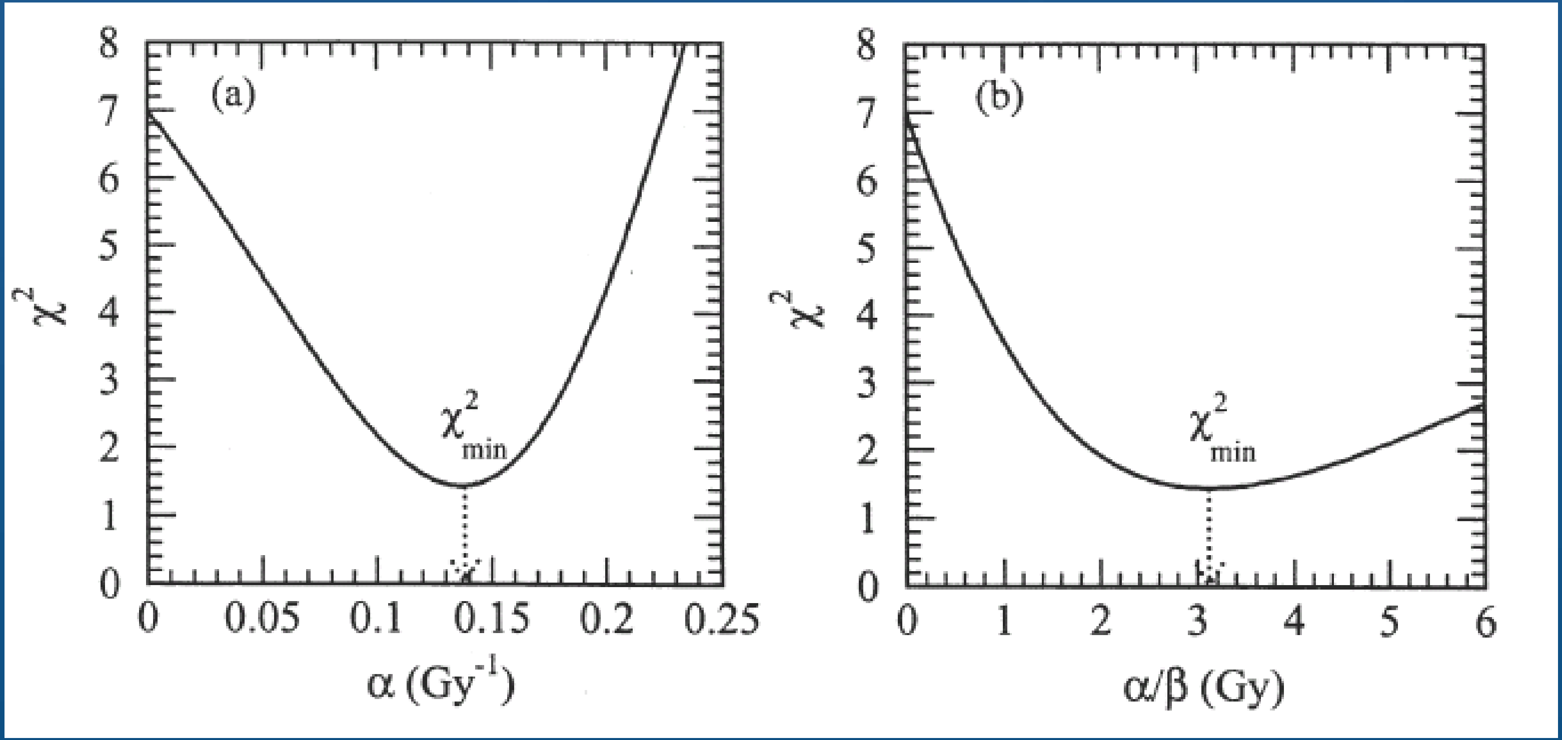
Our Method: Add a control



Practical Impact

- Design clinical trials with different fractionation schemes.
- Predicting TCP and NTCP

Practical Impact

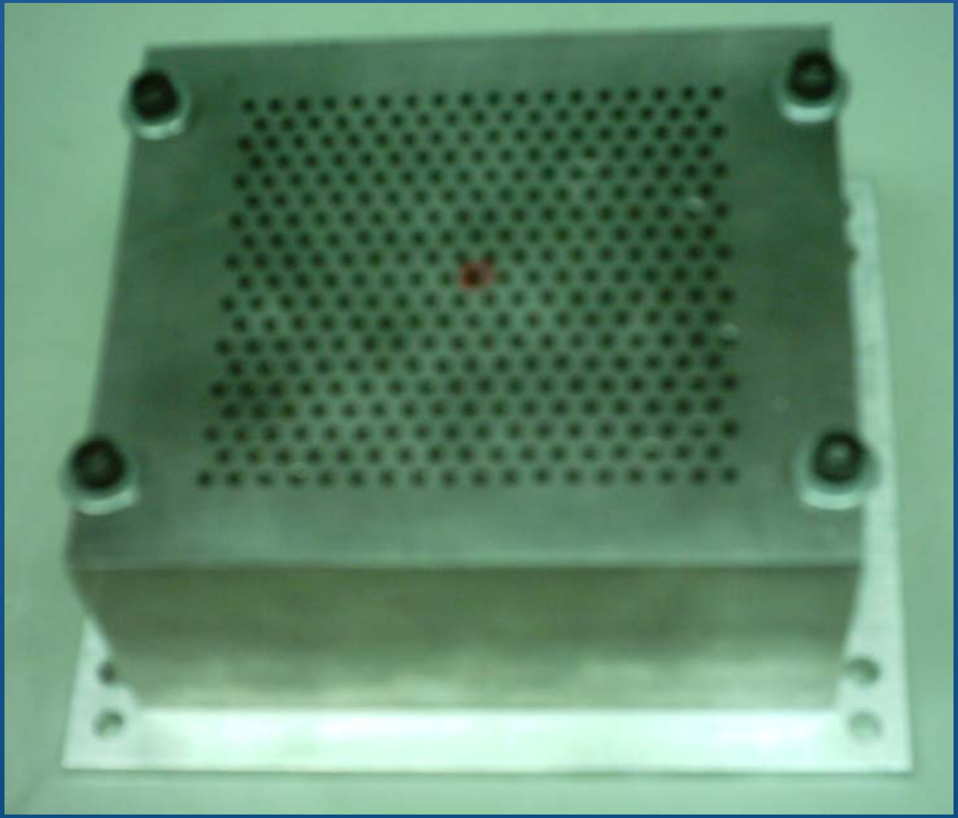
- RTOG 0415: A Phase III study of hypofractionated 3D-CRT/IMRT (70Gy in 28 fractions) v.s. Conventionally fractionated (73.8 Gy in 41 fractions) 3D-CRT/IMRT in patients with favorable risk prostate cancer
  - BED to prostate:

    if $\alpha/\beta = 1.5$, 187Gy v.s. 162Gy BED

    if $\alpha/\beta = 3.1$, 126Gy v.s. 117Gy BED
  - BED to Rectum:

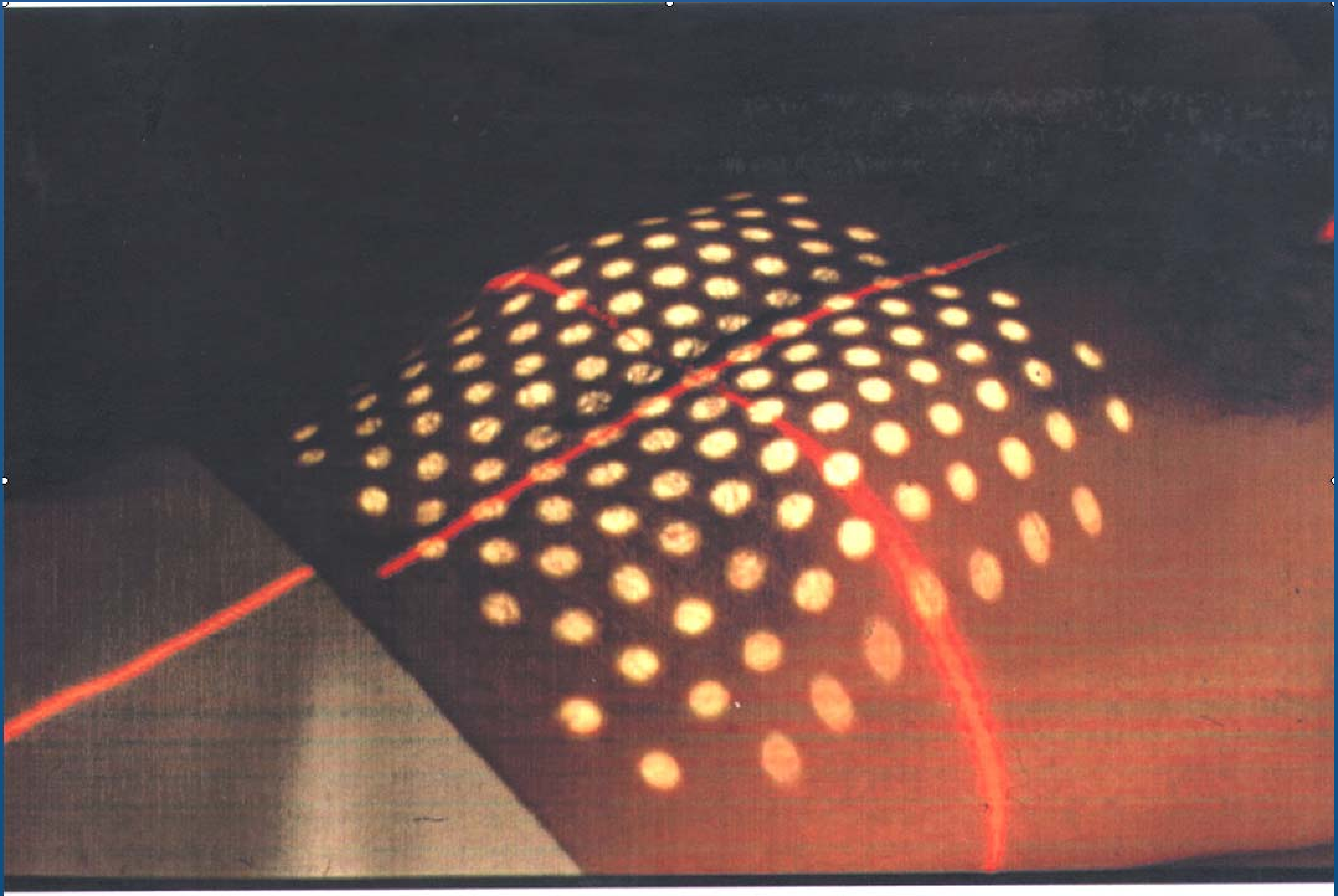
    if $\alpha/\beta = 6.0$, 99.2Gy v.s. 95.9Gy BED

Grid Therapy



- Open-to-Closed Ratio

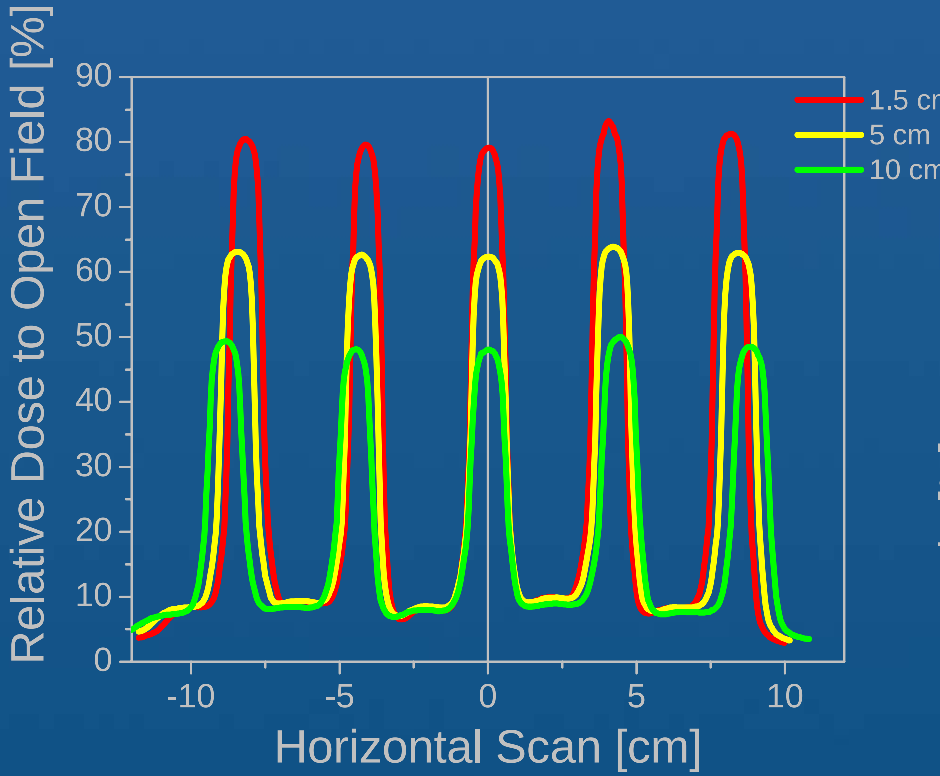
  = 1:3 (~25% open)
- Typical Dose 15 – 20 Gy

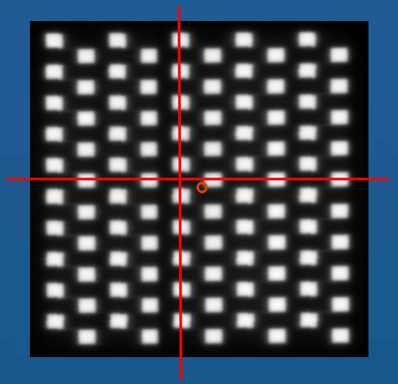


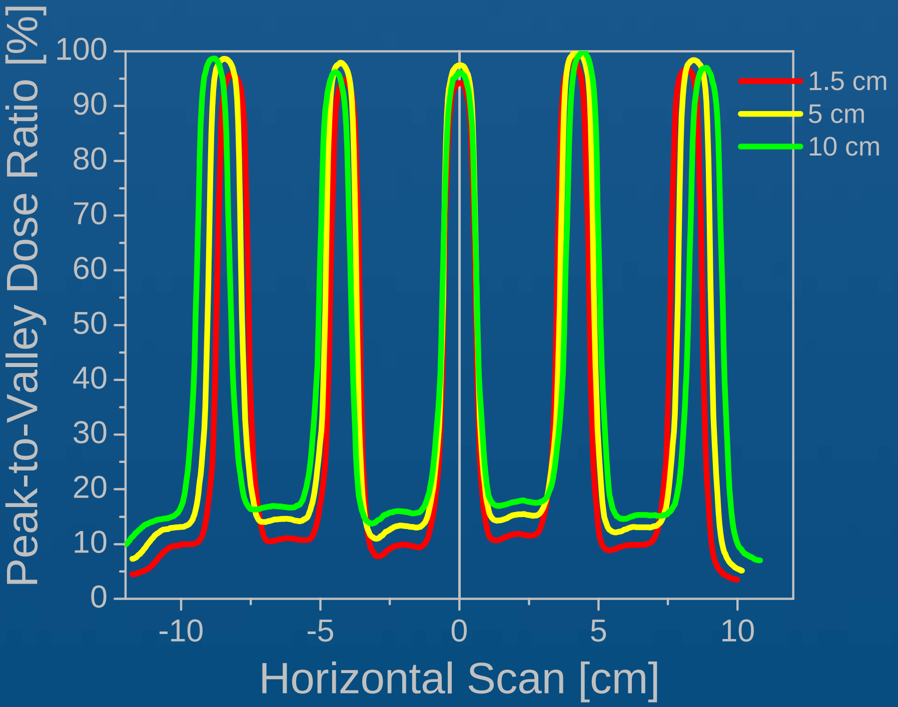
Spatially Fractionated (Grid) Field on Skin

Courtesy of the University of Kentucky

Line Dose Profiles of the 1cm x 1cm Grid







Courtesy of
the University of Kentucky

Clinical Study of Grid Therapy Conducted by the University of Kentucky

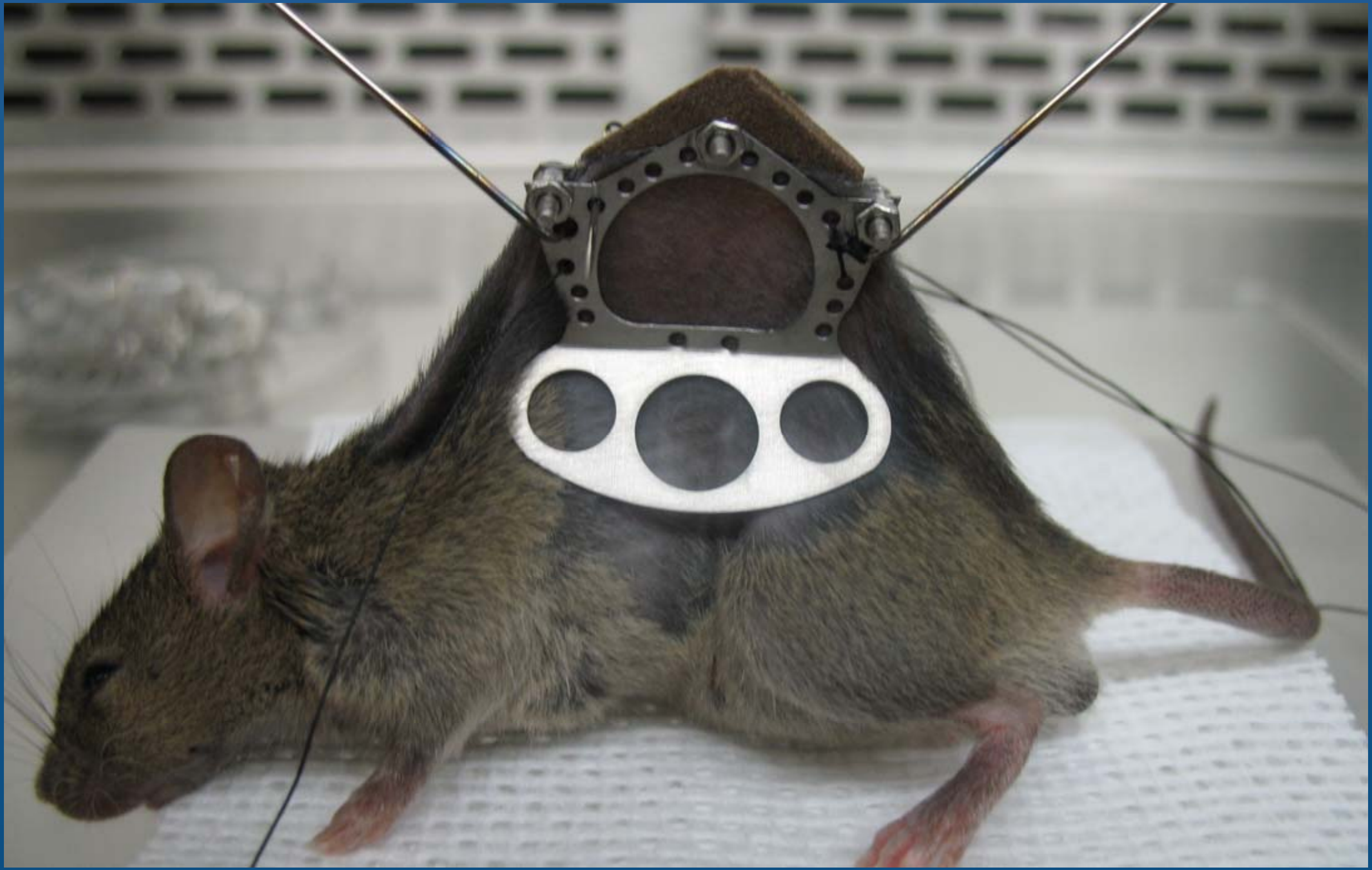
- 71 Patients were admitted in the clinical trial;
- 16% show a complete clinical response;
- 62% show at least a partial clinical response;
- Head and Neck has the most successful rate.

Int. J. Radiation Biol. Phys., Vol. 45, pp. 721-727, 1999.

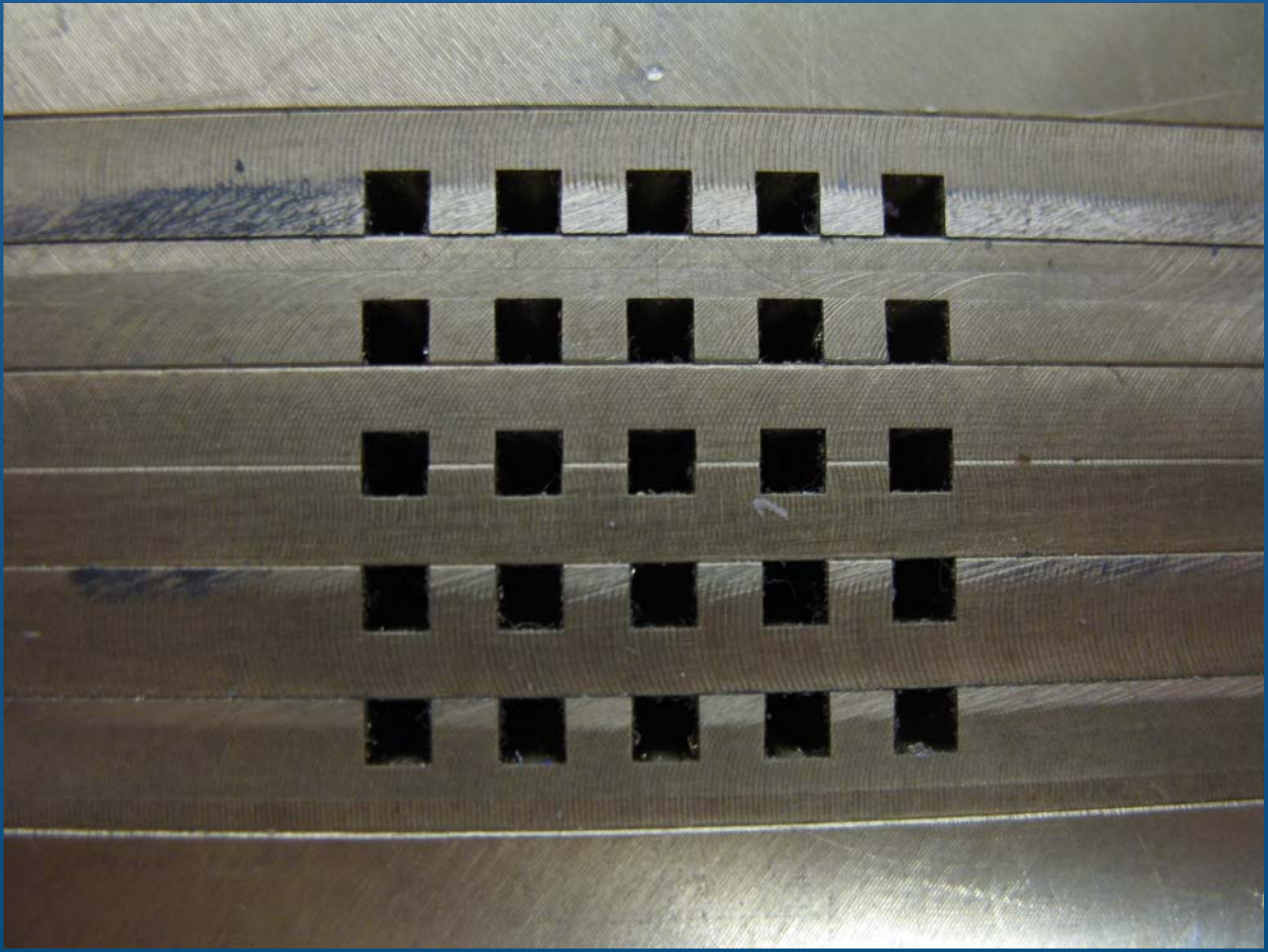
What makes it work?

- No explanation on the lack of normal tissue damage.
  - Different apoptotic pathway with single high dose?
  - Different mechanisms exist between tumor and normal structure in the repair of small regions of damage.
  - Cell mobility and "system control" may play a role.

Experimental Setup



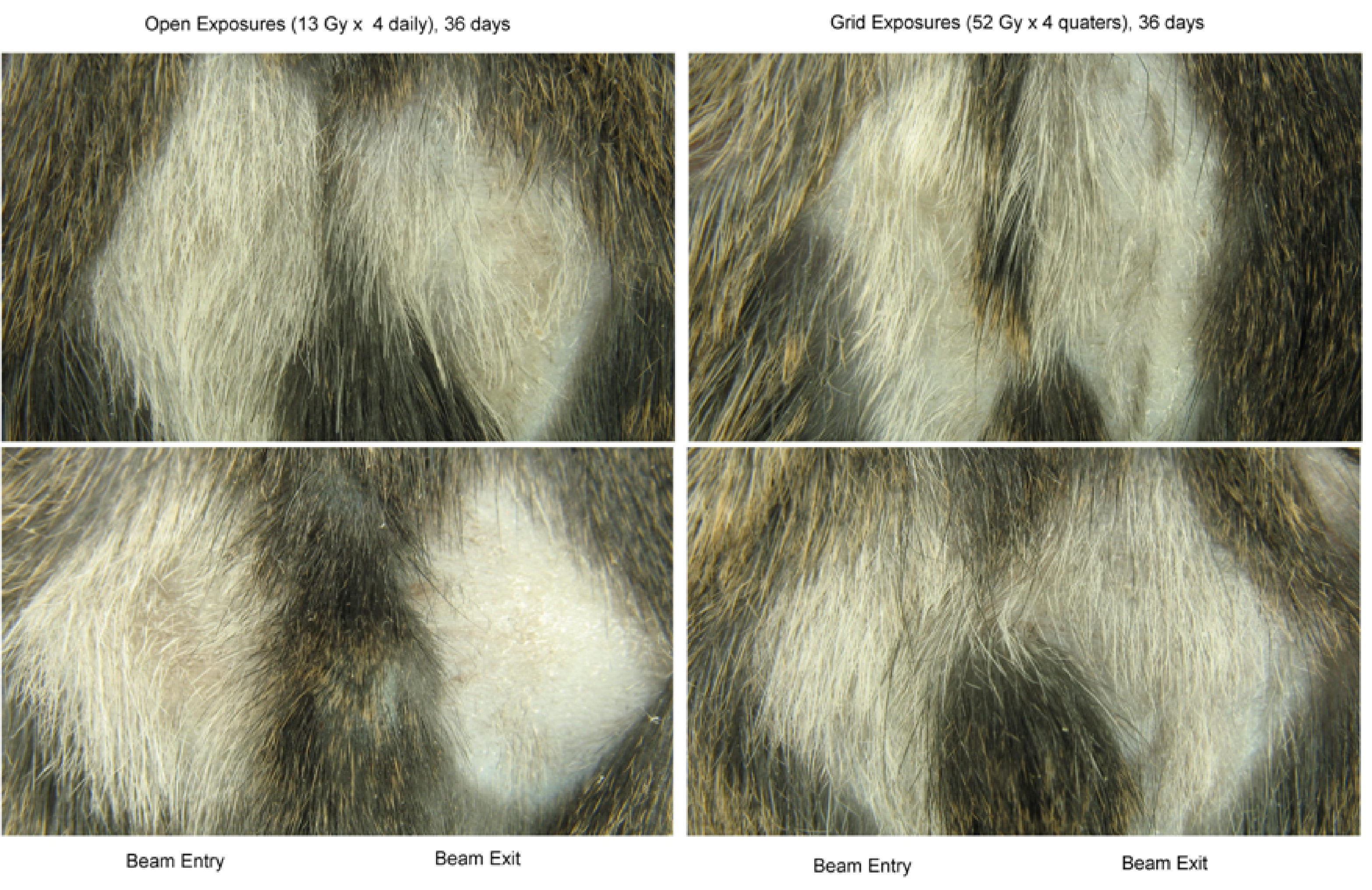
Experimental Setup



Two Groups

- Group1: Open irradiation of 13Gy x 4 days
- Group 2: Grid irradiation of 52Gy, shifting 4 times to unirradiated areas in 4 days

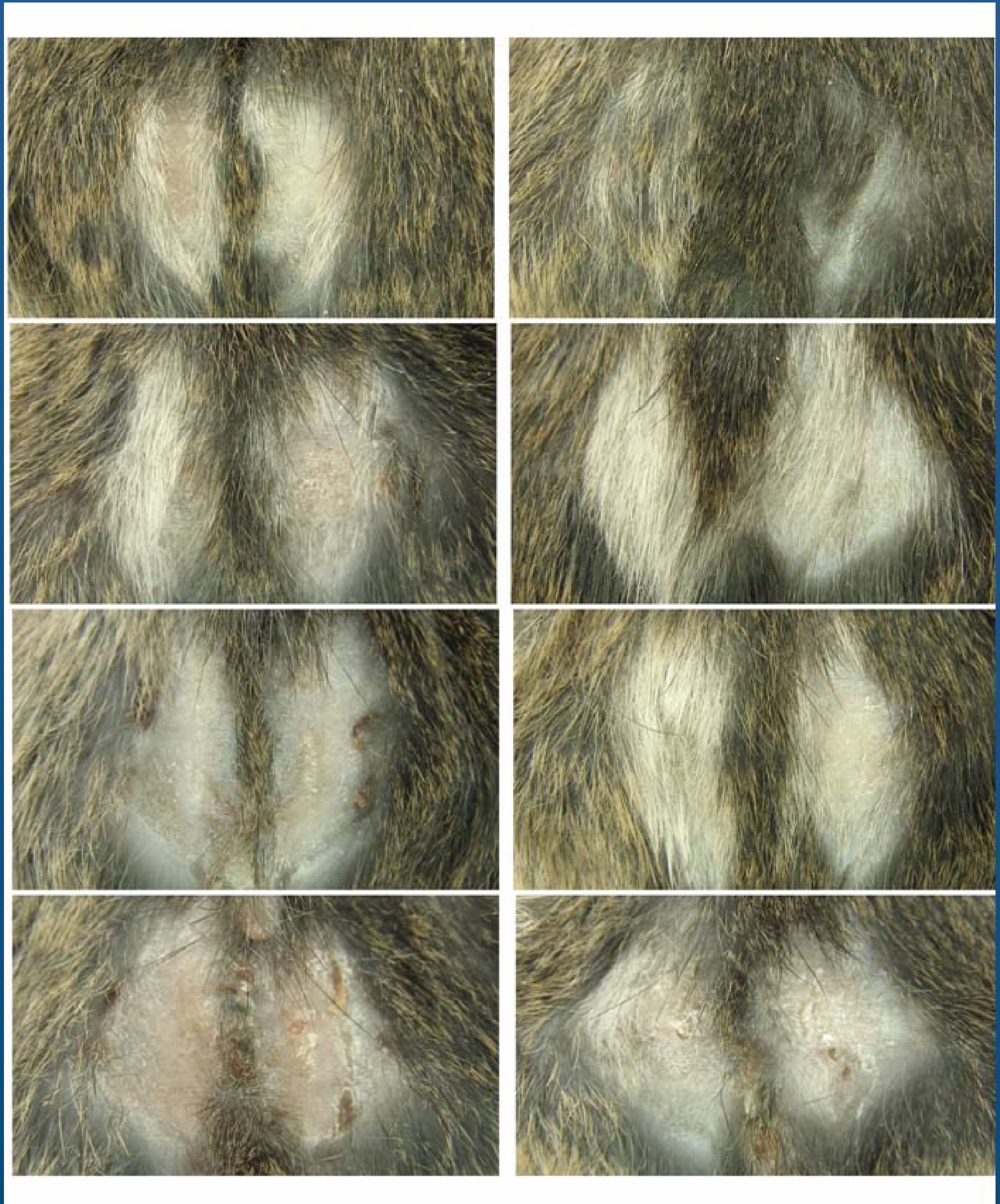
Results



Open Exposures (13 Gy x 4 daily), 36 days

Grid Exposures (52 Gy x 4 quaters), 36 days

More Results



Hair Counts

	Open	Grid	p-value
Entry side	452	860	0.0003
Exit side	223	730	0.0001

- By fractionate spatially, tumor get a more intense assault while normal tissue had less collateral damage.

New Challenges

- Geometric uncertainty
  - Geometric uncertainties are far greater.
- Biological uncertainty
  - Biological understanding of radiotherapy falls far behind physics.
- New treatment techniques based on new biological understanding and new imaging capabilities hold the key to enhance cure.

Breast Cancer

- Pathology
  - DCIS, LCIS
  - Medullary
  - Tubular
  - Lymphatic status
- Hormonal
  - ER, PR
  - Menstrual status
- Other
  - Familial history
  - Age
  - Obesity
- Genetics
  - HER-2
  - P53
  - Basal phenotype
  - Luminal A or B

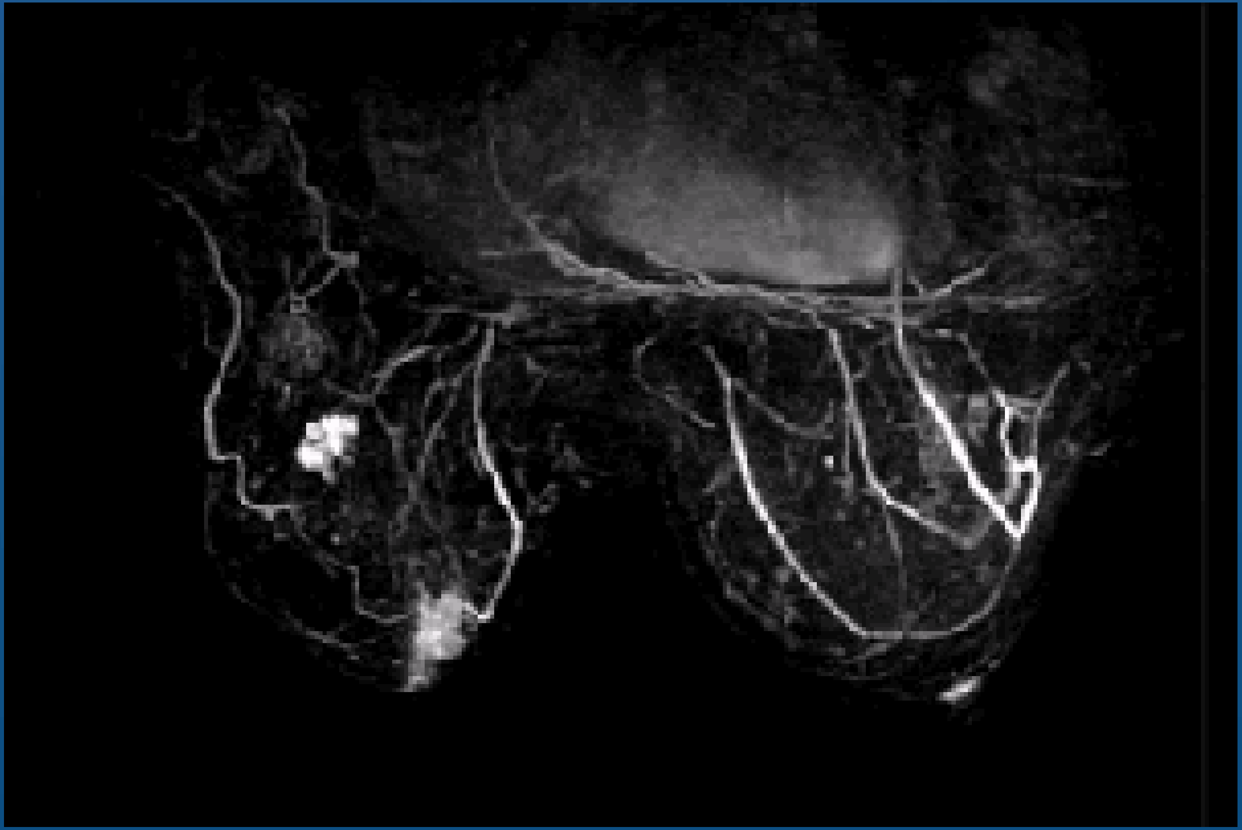
Radiation Therapy

- It is proven that BCT is as effective as mastectomy
- Very high cure rate (95-97%) and very low complication rate
- Dose-fractionation schemes for all comers (BCT) are the mostly the same
- Treatment techniques for all comers are mostly the same
- Distribution of residual tumor foci and the probability of recurrence location is well known, however, dose uniformity remain a dosimetric goal.

What could make a difference?

- Imaging (diagnosis)
  - From mammography to dedicated 3D MRI imaging
- New treatment techniques that can make use of the new diagnostic and delivery capabilities

New MRI capable of fat suppression



MRIs with better resolution

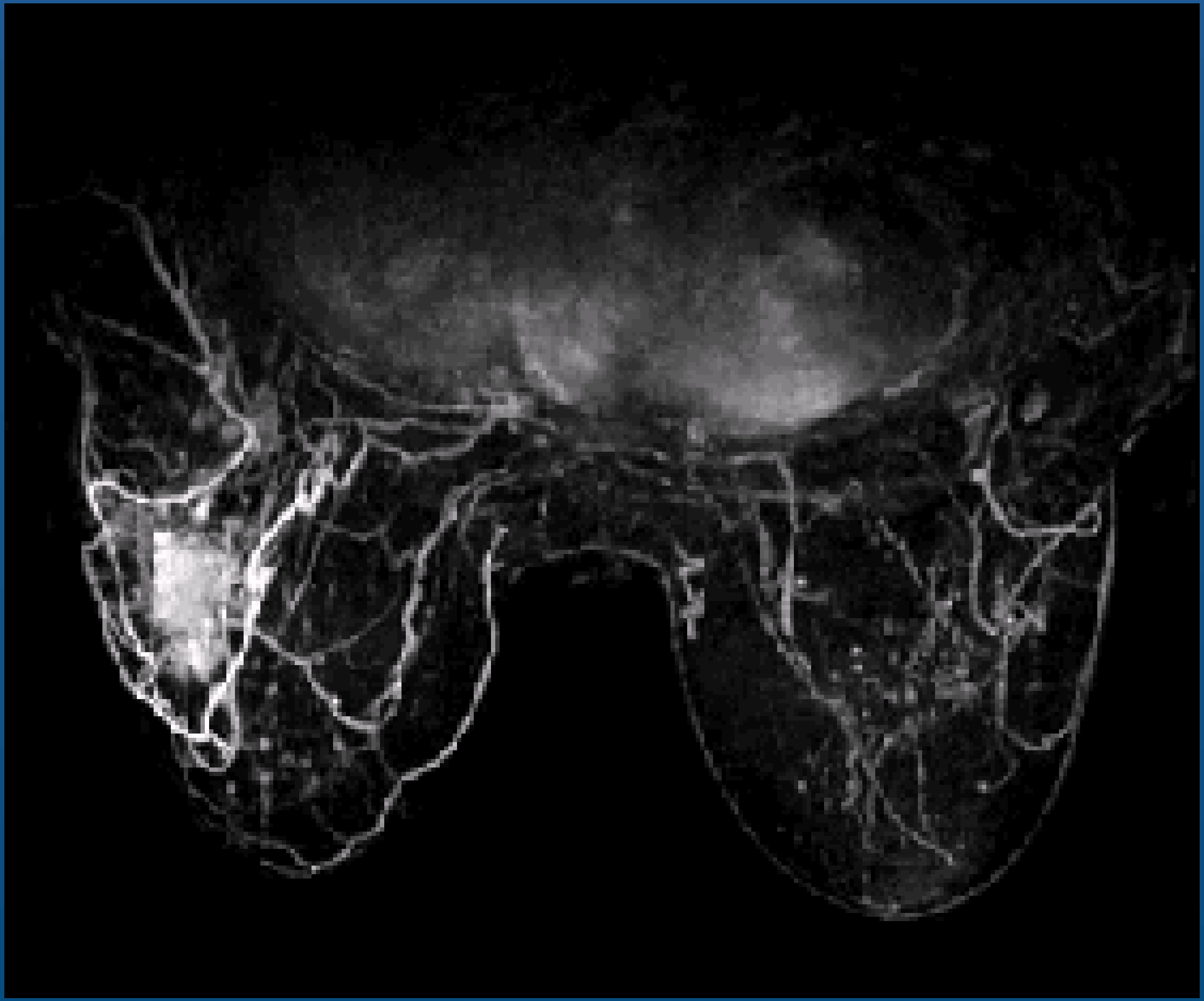


Image guided interventions

- Radiation therapy does not take advantage of these new 3D imaging capabilities
- MRI-guided interventions include RF ablation, and cryosurgery
- There is room for radiotherapy improvement

Lung Cancer

- Poor prognosis for non-operable patients
  - About 30% 3-5 year survival (radiation therapy)
- Conventional radiation therapy
  - 45-55 Gy in 1.8 – 2.0 Gy fractions

New Directions

Timmerman R et al: J Clin Oncol. 2006 Oct 20;24(30):4833-9

> "All 70 patients enrolled completed therapy as planned and median follow-up was 17.5 months. The 3-month major response rate was 60%. Kaplan-Meier local control at 2 years was 95%".

In late 2004, RTOG 0236 using SBRT for medically inoperable patients with clinical stage I non-small cell lung cancer (NSCLC) was activated for accrual.

Japanese SBRT Experience

- **Hiraoka M, Nagata Y: Int J Clin Oncol. 2004 9(5):352-5.**

> “In tumors which received a BED of more than 100 Gy, overall survival at 3 years was 91% for operable patients, and 50% for inoperable patients.”

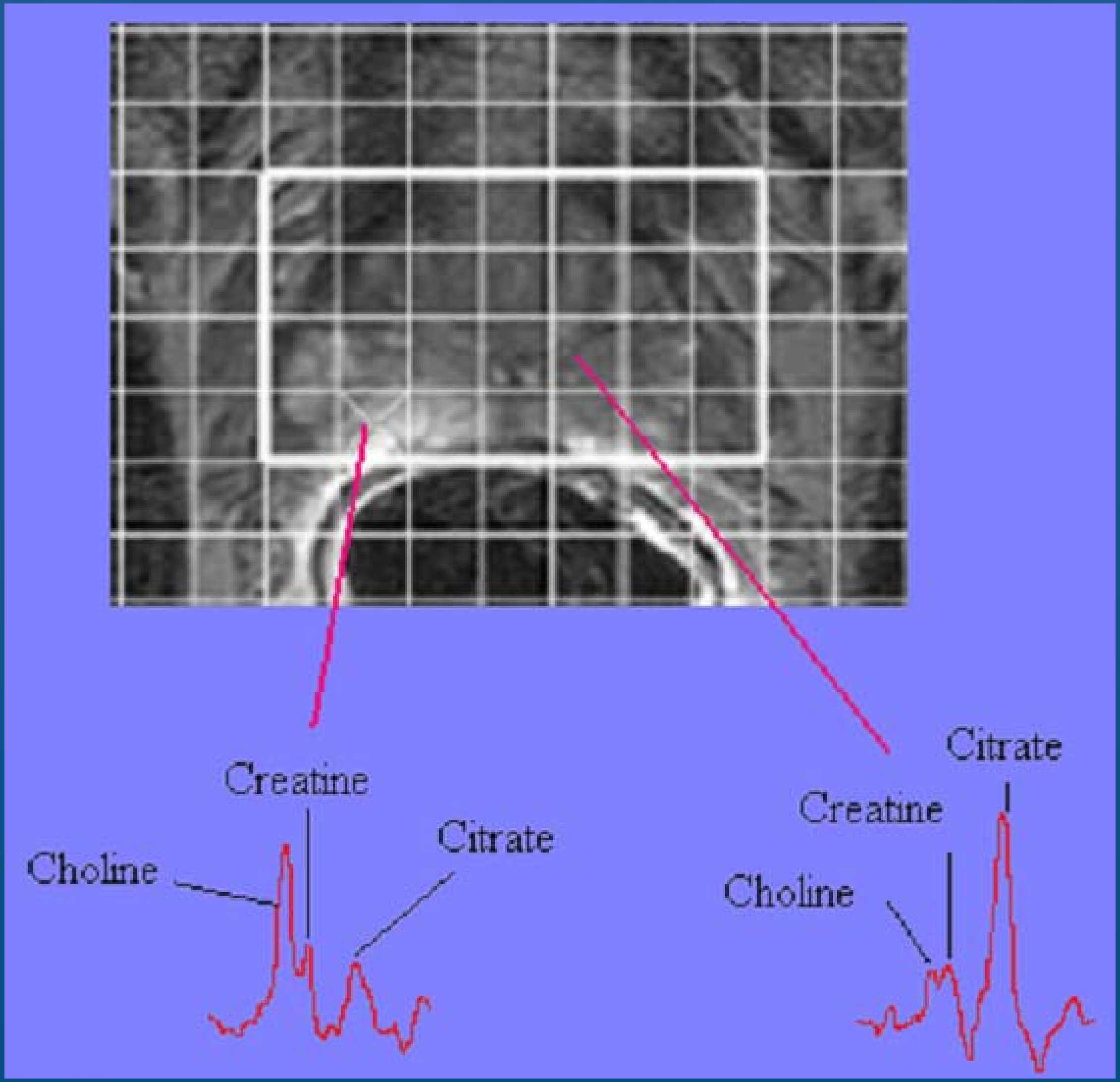
What make this possible

- Imaging guidance
  - On-board fluoro and x-ray imaging
- New delivery techniques
  - Gating
  - IMRT
  - Stereotactic localization
- Most importantly: New thinking based on new biological understanding and new technological capabilities.

Using New biological understanding

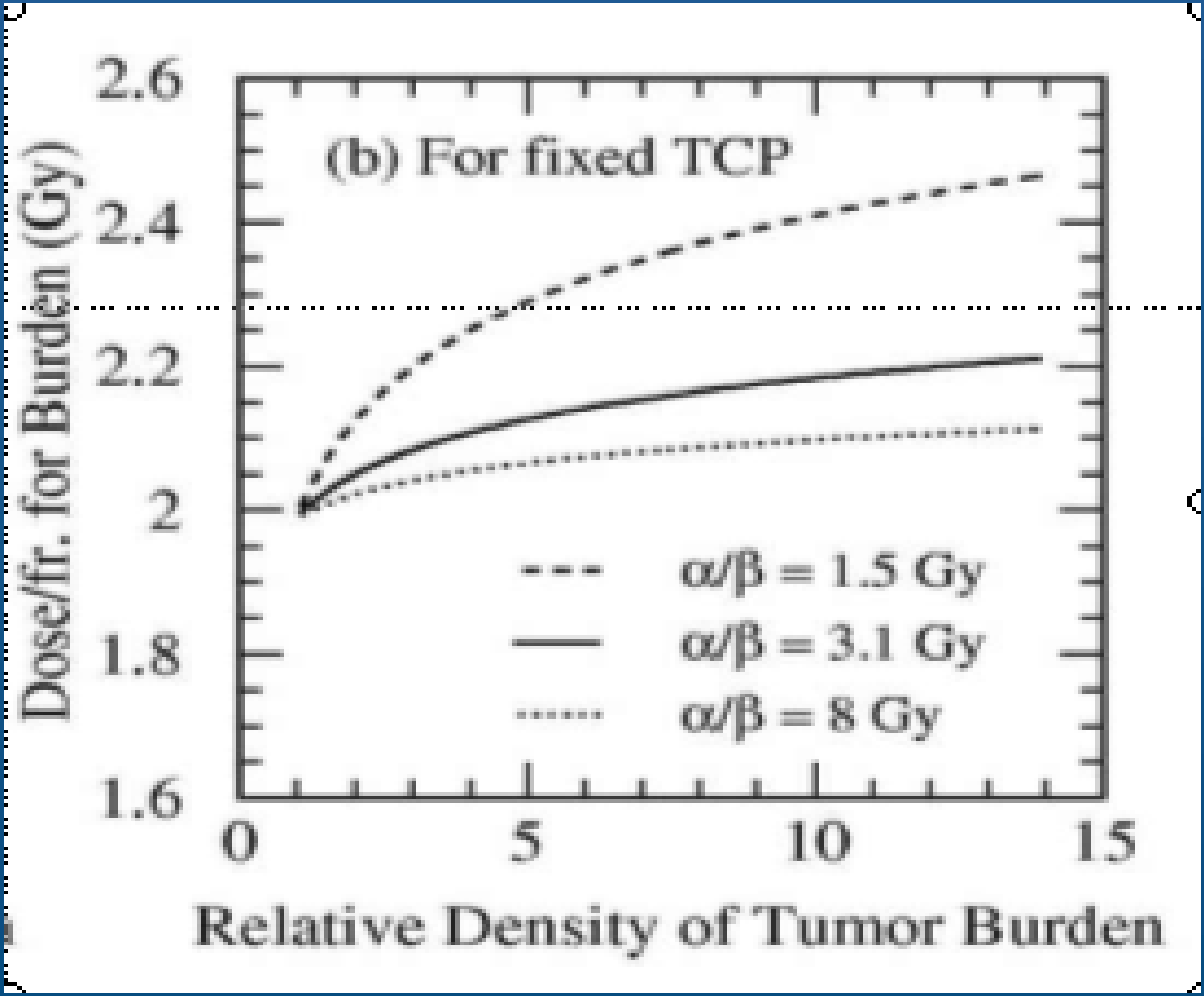
- Some exciting new biological understandings:
  - By-stander effect
  - Tumor stem cells
  - Effects of single high dose
  - Different responses by tumor and normal structures on small fields - high doses

MRSI for Detecting Cancer in Prostate



T2-weighted axial MR image obtained by using an endorectal coil

Preferential Dose Escalation



Status

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CLINICAL INVESTIGATION **Prostate**

MAGNETIC RESONANCE SPECTROSCOPIC IMAGING–GUIDED BRACHYTHERAPY FOR LOCALIZED PROSTATE CANCER

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RICHARD B. ALEXANDER, M.D.,‡ AND CEDRIC YU, PH.D.*

Departments of *Radiation Oncology, †Radiology, and ‡Surgery, University of Maryland Medical Center, Baltimore, MD

- New trial 1: HDR brachy
- New trial 2: EXRT with target in target

Conclusion

- Accelerated technical advancements in last 20 years
- Dosimetric < Geometric < Biological
- New treatment techniques based on new biological understanding and new imaging capabilities hold the key to enhance cure.