Update on Normal Tissue Injury: What us new since Emami?

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Emami

- Terrific Paper
- Dose Volume Guidelines
  - Referenced and misquoted often
- Survey
- Extensive literature review
  - 3D provided information
  - We needed to know how to act on the knowledge
- Tremendously useful: early 3D era & today

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What is new since Emami?

- The Hope: "3D information will set us free"
  - Partly true: Major Progress
  - DVH → outcome (many organs)
  - Good but NOT perfect
- Another Reality: "We don't know what we want to measure and the information overload is killing us"
  - Recognition of shortcomings of DVHs
    - Mathematical, anatomic/physiologic
  - Clarification of endpoints (clinical vs subclinical)
  - Moving target as technology advances
    - 1990's: 2 Gy/fx, QD mostly, opposed beams, limited chemo
    - 2000's: IMRT, chemo, BID, etc

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Clear Progress
3D Dose/Volumes → Outcome

- Liver (Michigan)
- Lung (many places)
- Parotid (MIR)
- Rectum (several, MSKCC)
- Brain (U Pitt)

Physicians have a lot more information to guide us!!
Thank you! Really.

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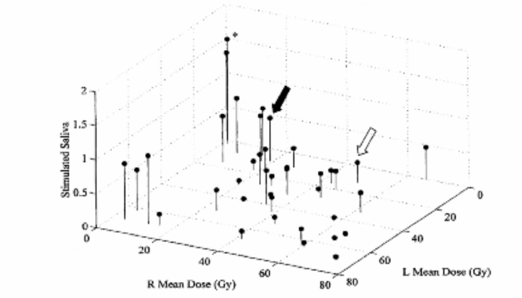
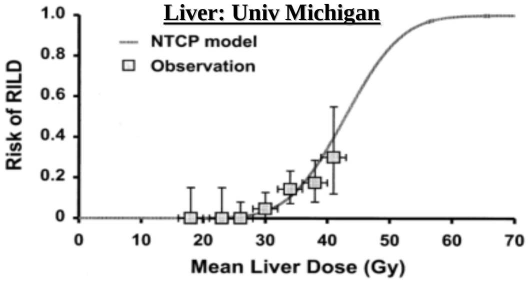
Parotid dose → dry mouth



From Chao, Mallivckrodt, IJROBP 49; '01

Liver: Univ Michigan



Observed and predicted NTCP, according to the LKB NTCP model vs. mean liver dose (in 1.5 Gy *b.i.d.*). Observed NTCP calculated from patients grouped in 4-Gy bins, with 80% confidence intervals displayed. Predicted NTCP based on the LKB NTCP model, with *n* = 1.1, m = 0.18, and $TD_{50}(1)$ = 43.3 Gy.

Dawson *et al. IJROBP* 53:810-821, 2002

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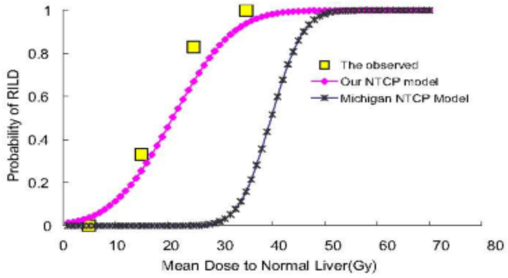
Exportability of predictive models from one university to another: Challenging

Michigan vs. China: Grade A RT-induced liver disease. China: Primary liver Ca vs. Michigan: metastases



Xu *et al. IJROBP* 65:193, 2006

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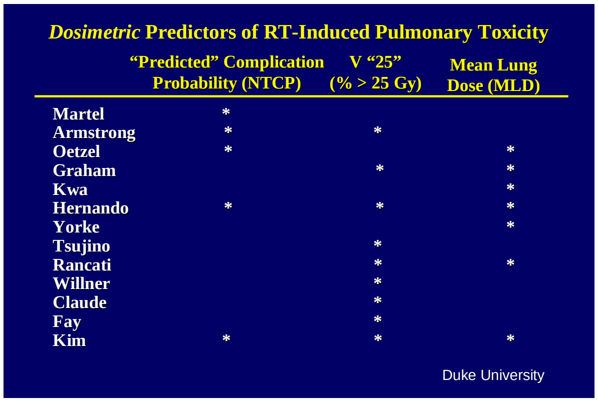

Dosimetric Predictors of RT-Induced Pulmonary Toxicity

	"Predicted" Complication Probability (NTCP)	V "25" (% > 25 Gy)	Mean Lung Dose (MLD)
Martel	*		
Armstrong	*	*	
Oetzel	*		*
Graham		*	*
Kwa			*
Hernando	*	*	*
Yorke			*
Tsujino		*	
Rancati		*	*
Willner		*	
Claude		*	
Fay		*	
Kim	*	*	*

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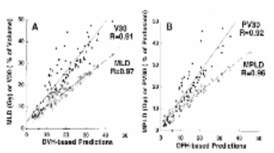
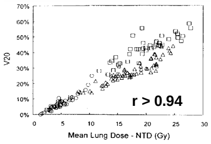
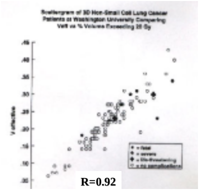
Fan, JCO 19(2):543, 2001, Duke Univ.





From Steppenwolde & Lebesque
Sem Rad Oncol 11:247, 2001



From Graham IJROBP 1999
Washington University

High correlation is technique dependent

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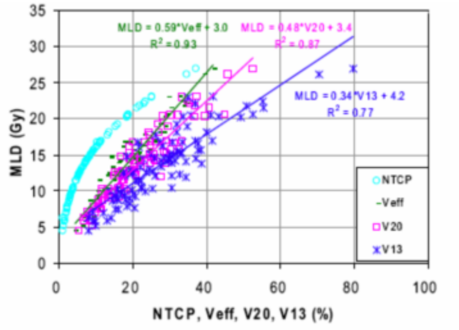

Kong, U Mich, IJROBP 2006

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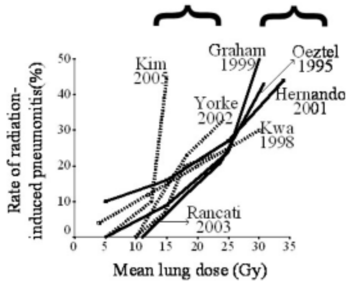
Low Risk Group:
70% of pts. x
15% risk RP = 10.5%

High Risk:
30% of pts. x
40% risks = 12%



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U Mich Data, Dose Escalation

- 109 patients
  - 1992-2002, excellent FU data
- RT dose per V eff
- ≈ 15% pneumonitis rate
- Predictors of lung injury
  - MLD, V20, NTCP, etc

Kong IJROBP 65:1075, 2006

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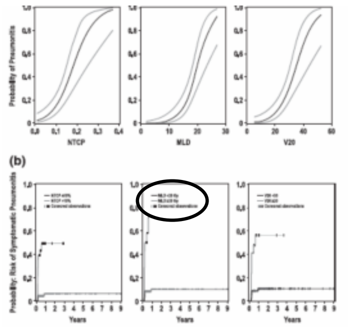

Kong, U Mich, IJROBP 2006

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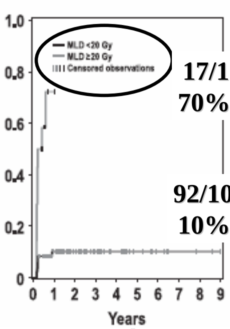

17/109 with MLD >20
70% x 17 = <u>12 patients</u>

92/109 with MLD < 20
10% x 92 = <u>9 patients</u>

Kong, U Mich, IJROBP 2006

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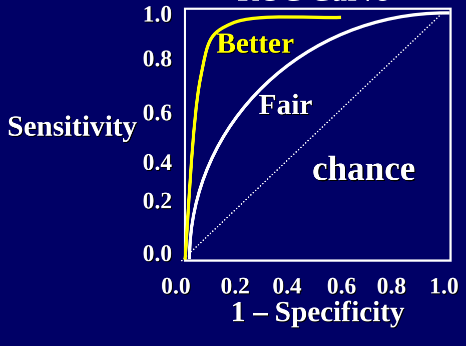
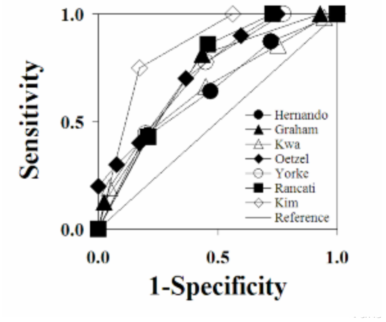
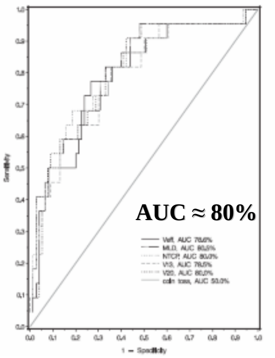
ROC Curve



ROC areas typically ≈ 0.55-0.75 for Mean Lung Dose





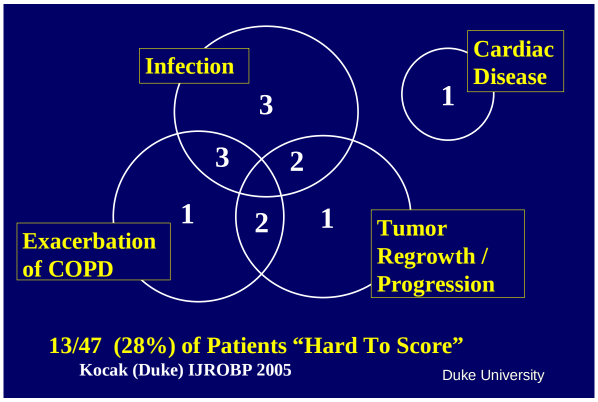
Kong, U Mich, IJROBP 2006

Functional Factors Pollute Lung Analysis

- Tumor shrinkage
- Baseline low PFT --> more SOB
  - Yes: Marks, Choi, Monson, Robnett
  - No: Graham, Sunyach, Kong
- Distribution of “functioning” lung
  - SPECT perfusion > CT volumes
  - Duke, NKI, Choi, Curran
- Exercise capacity ?
  - Miller, IJROBP 2005

Pneumonitis is subjective and inexact

- 1991-2003
- 47/251 (19%) grade ≥2 pneumonitis
- 13/47 confounding issues
- Kocak, IJROBP 2005



13/47 (28%) of Patients "Hard To Score"

Kocak (Duke) IJROBP 2005

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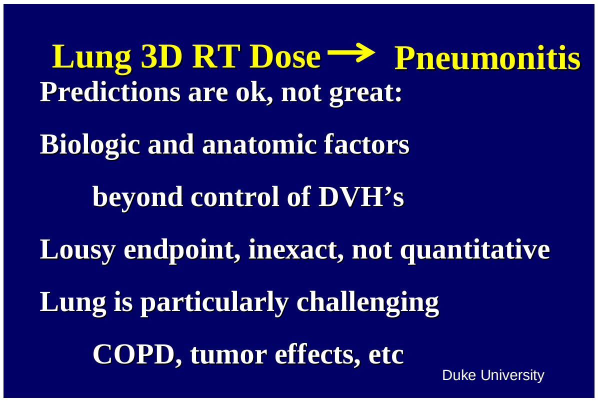

Lung 3D RT Dose → Pneumonitis

Predictions are ok, not great:

Biologic and anatomic factors

beyond control of DVH's

Lousy endpoint, inexact, not quantitative

Lung is particularly challenging

COPD, tumor effects, etc

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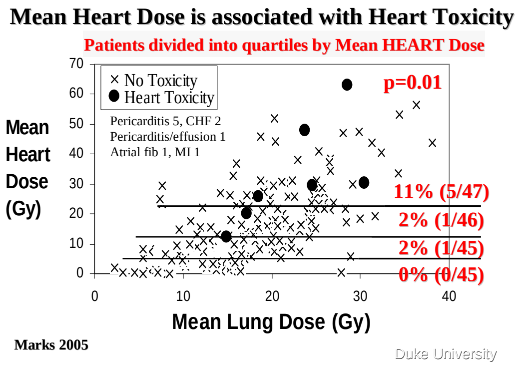

Mean Heart Dose is associated with Heart Toxicity

Patients divided into quartiles by Mean HEART Dose

Marks 2005

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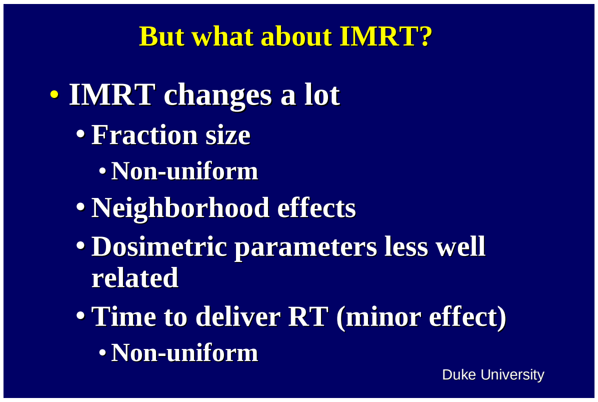

But what about IMRT?

- IMRT changes a lot
  - Fraction size
    - Non-uniform
  - Neighborhood effects
  - Dosimetric parameters less well related
  - Time to deliver RT (minor effect)
    - Non-uniform

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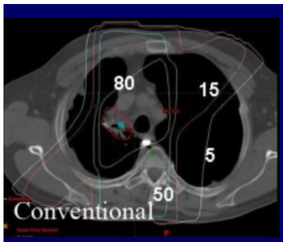
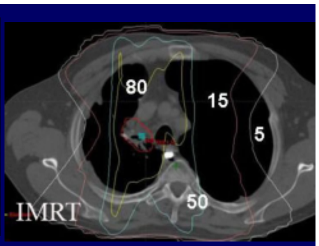
IMRT delivers highly variable fraction sizes to normal tissues

Fraction-size corrected DVH’s

Assumes we know how to correct!



APPA, and then LAO/RPO, beams treated <u>sequentially, ≈ 2 Gy/day everywhere</u>



Multiple beams treated <u>concurrently, variable fraction sizes</u>

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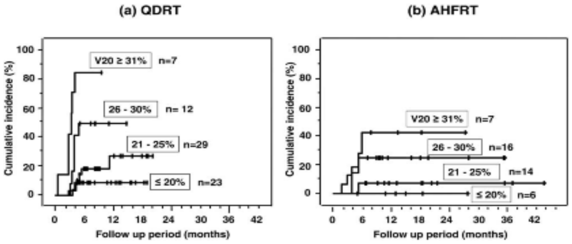
Fractionation rears it ugly head



Cumulative incidence ≥ Grade 2 RT pneumonitis

Non-randomized comparison.

Tsujino, *et al* *IJROBP* 64:1100,2006

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Tsujino *et al.* *IJROBP* 64:1100-1105, 2006

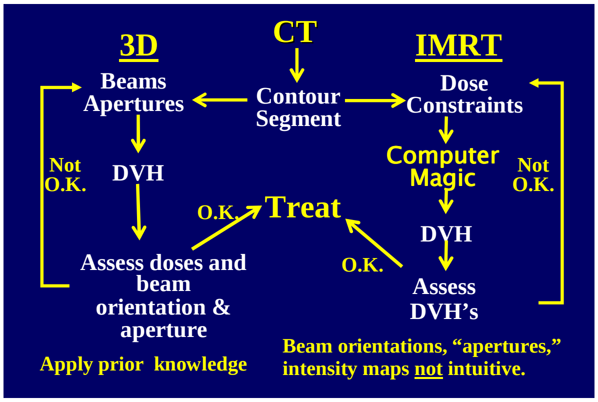
Planning in the post-Emami era

Using 3D doses to predict outcome
data derived pre-IMRT
is it applicable?

3D and IMRT are BOTH DVH-based planning exercises

But, 3D
- "conventional" dose distributions
- beam orientations are "usual"
- we can rely on pre-3D knowledge

IMRT
- unusual dose distributions
- we are DEPENDENT on the DVH



Apply prior knowledge

Beam orientations, "apertures," intensity maps <u>not</u> intuitive.

DVH Shortcomings

- DVH vs. DFH
- Spatial information discarded
- Fraction size (can correct)
- Volume?

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What is Volume?

- External Contour
- Functional vs. Anatomic
  - Lung Kidney
- Expanding/Contracting tissues
  - Esophagus Rectum
- Organ Heterogeneities
  - Lung Kidney
  - Bone

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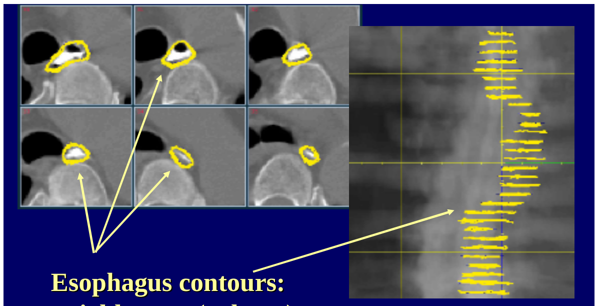

Esophagus contours:
variable area (volume)

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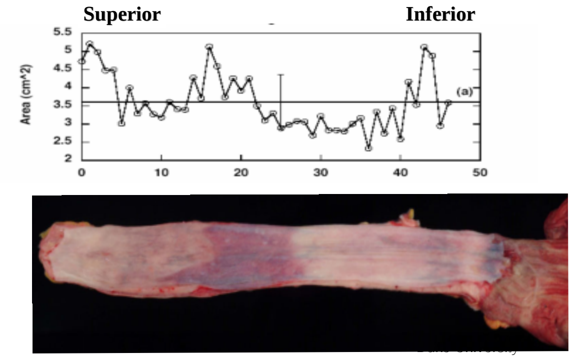
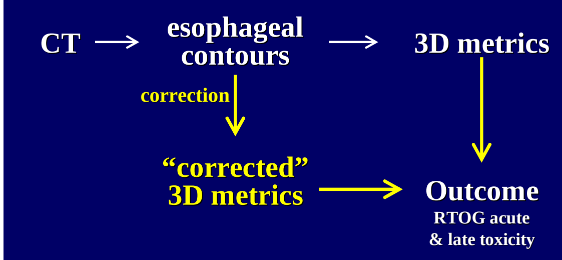


Univariate and Multivariate Analyses



CT → esophageal contours → 3D metrics

esophageal contours → correction → "corrected" 3D metrics

"corrected" 3D metrics → Outcome

3D metrics → Outcome

Outcome
RTOG acute
& late toxicity

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Toxicity = f (Dosimetric Parameters)
p-values

	V 50 Uncorrected	V 50 Corrected
Acute ≥ grade 2	0.008	0.005
Acute ≥ grade 3	0.05	0.003
Late ≥ grade 1	0.14	0.08

Adapted from Kahn *et al.* 2004 (Duke)

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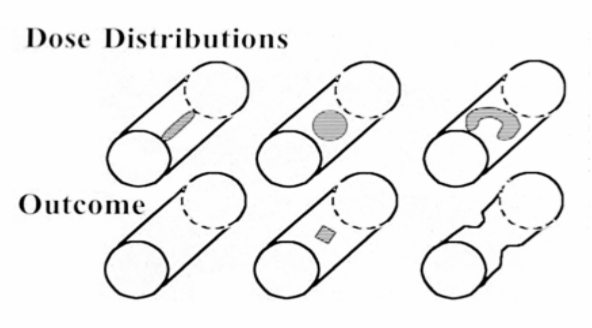

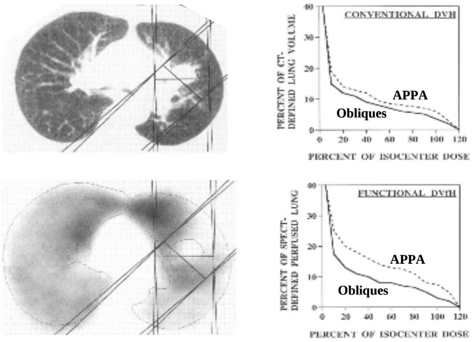

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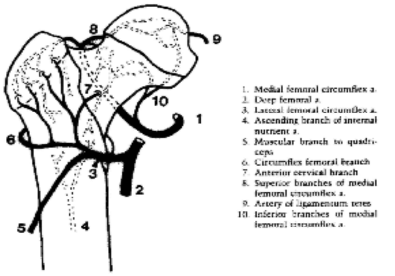

Fig. 4. Diagram illustrating the vascular supply of the proximal femur. The majority of blood to the proximal femur is delivered via the medial circumflex artery [1]. This artery passes medially and posterior to the femoral neck as it supplies the neck and head. The secondary vessel is the lateral femoral circumflex artery [3]. Both of these are branches off of the femoral artery [2]. If radiation-induced damage to the femur occurs secondary to damage to the vasculature, the position of these vessels and their branches relative to the XRT beams might be important. Reproduced with permission from (20).

Marks *IJROBP* 34:1168, 1996

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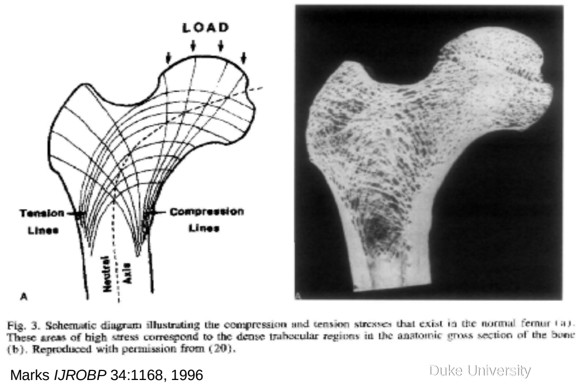

Fig. 3. Schematic diagram illustrating the compression and tension stresses that exist in the normal femur (a). These areas of high stress correspond to the dense trabecular regions in the anatomic gross section of the bone (b). Reproduced with permission from (20).

Marks *IJROBP* 34:1168, 1996

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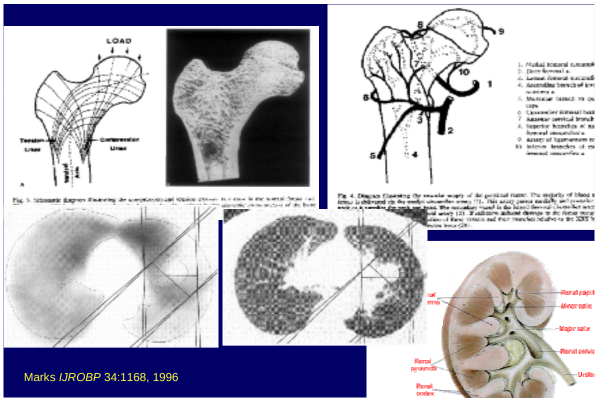
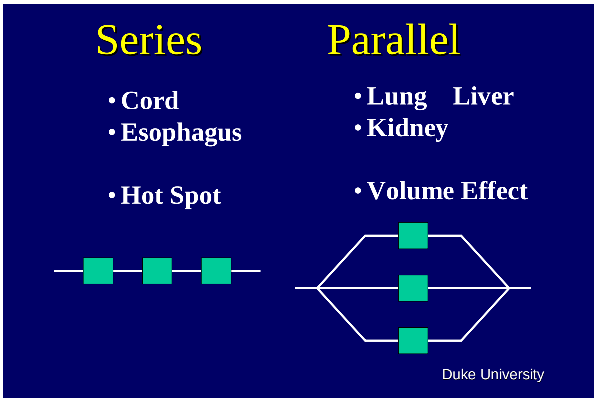


Marks *IJROBP* 34:1168, 1996



Series

- Cord
- Esophagus

- Hot Spot

Parallel

- Lung Liver
- Kidney

- Volume Effect

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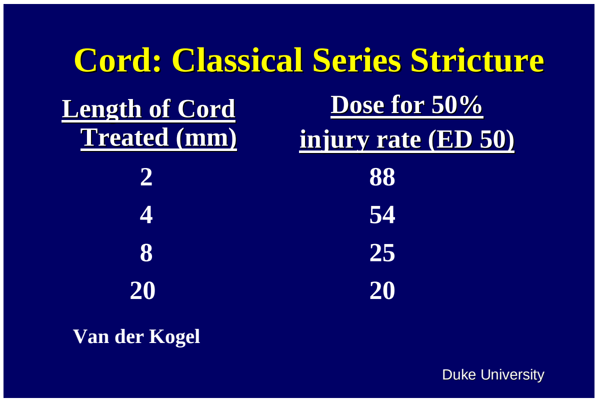

Cord: Classical Series Stricture

Length of Cord Treated (mm)	Dose for 50% injury rate (ED 50)
2	88
4	54
8	25
20	20

Van der Kogel

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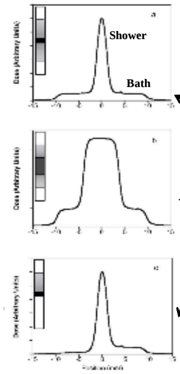

Rat Proton Cord RT

	ED 50 (Gy) to "shower"
No bath (control):	88 (dose in peak)
4 Gy bath, both sides	61
4 Gy bath, one side	69
18 Gy bath, both sides	31
Wide shower, 8 mm	No bath effect

Serial vs. parallel

Less well defined
Migration of stem cells
Cytokine/neighborhood effects
Vascular

Bisl *et al. IJROBP* 64:1204-1210, 2006

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Neighborhood Effects

Rectum: MSKCC, Prostate Cancer

- $V_{70} - V_{77} \rightarrow$ bleeding
  makes sense: local hot spot
- Independent assoc also with V_{46}!
- "large surrounding areas of intermediate dose may interfere with the ability to repair the effects of a central high dose region."

***IJROBP* 49:685,2001**

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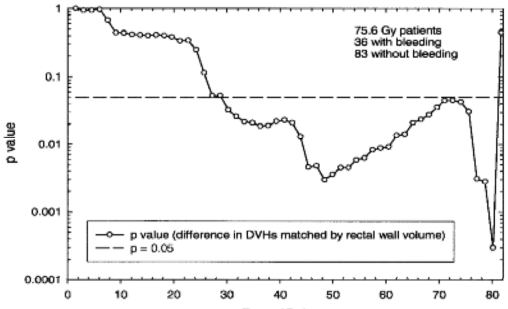
Predictors of Bleeding: Prostate Cancer Treated to 75.6 Gy



***Jackson IJROBP* 49:685,2001**

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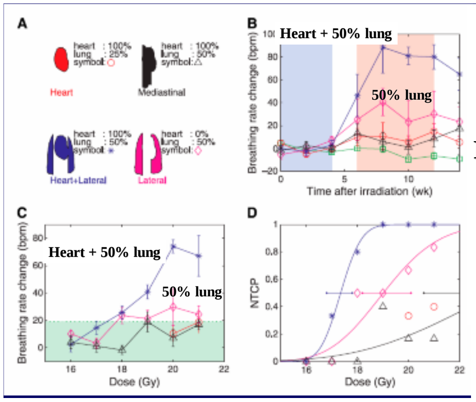
Organ interactions

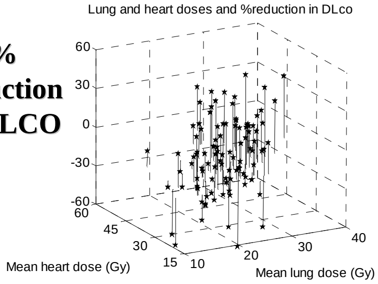


Proton RT in Rats: Resp Rate = f (lung and heart RT)

Luijk Ca Res 65:6509, 2005

Lung and Heart Interactions?

% reduction in DLCO



Jing Zeng 2006, Duke Medical Student

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Current Predictors

- Based on conventional techniques
- Probably NOT applicable with new treatment techniques?
- But may be ok
- Fractionation, chemotherapy, etc

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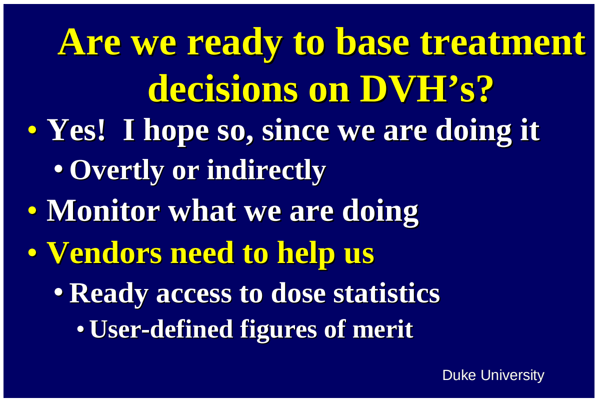

Are we ready to base treatment decisions on DVH's?

- Yes! I hope so, since we are doing it
  - Overtly or indirectly
- Monitor what we are doing
- Vendors need to help us
  - Ready access to dose statistics
    - User-defined figures of merit

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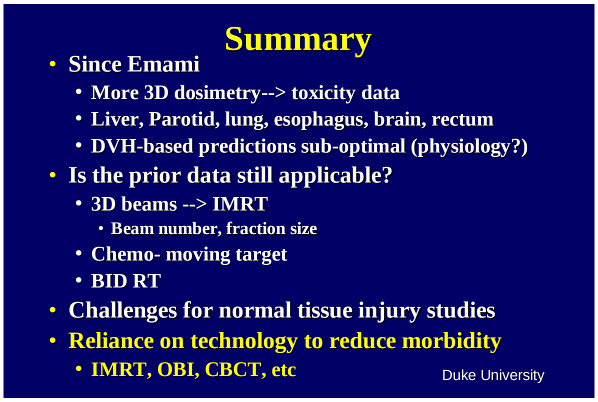

Summary

- Since Emami
  - More 3D dosimetry--> toxicity data
  - Liver, Parotid, lung, esophagus, brain, rectum
  - DVH-based predictions sub-optimal (physiology?)
- Is the prior data still applicable?
  - 3D beams --> IMRT
    - Beam number, fraction size
  - Chemo- moving target
  - BID RT
- Challenges for normal tissue injury studies
- Reliance on technology to reduce morbidity
  - IMRT, OBI, CBCT, etc

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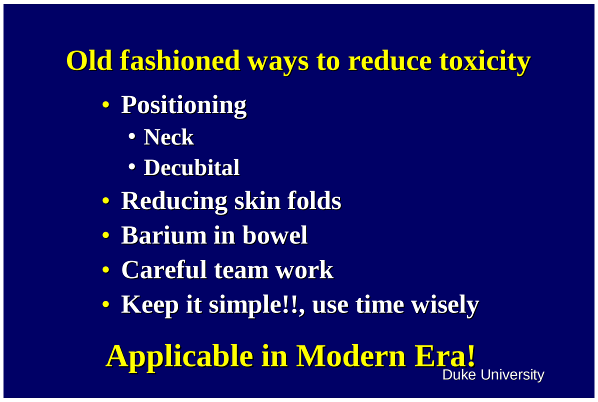

Old fashioned ways to reduce toxicity

- Positioning
  - Neck
  - Decubital
- Reducing skin folds
- Barium in bowel
- Careful team work
- Keep it simple!!, use time wisely

Applicable in Modern Era!

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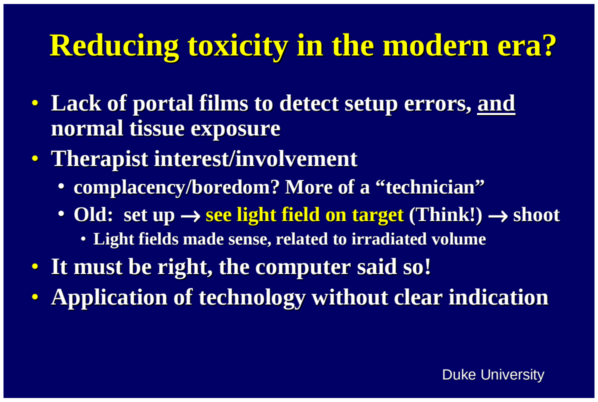

Reducing toxicity in the modern era?

- Lack of portal films to detect setup errors, and normal tissue exposure
- Therapist interest/involvement
  - complacency/boredom? More of a "technician"
  - Old: set up → see light field on target (Think!) → shoot
    - Light fields made sense, related to irradiated volume
- It must be right, the computer said so!
- Application of technology without clear indication

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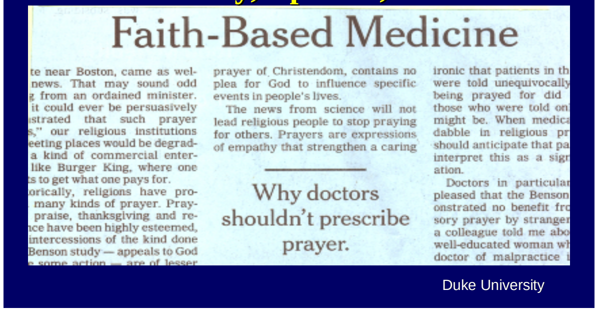
New York Times
Tuesday, April 11, 2006



Faith-Based Medicine

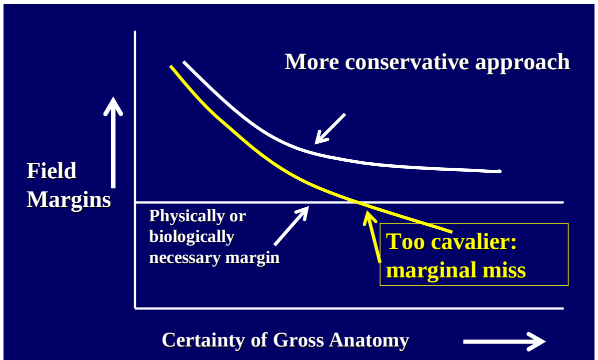
te near Boston, came as wel-
news. That may sound odd
g from an ordained minister.
it could ever be persuasively
istrated that such prayer
s," our religious institutions
eeting places would be degrad-
a kind of commercial enter-
like Burger King, where one
ts to get what one pays for.
orically, religions have pro-
many kinds of prayer. Pray-
praise, thanksgiving and re-
nce have been highly esteemed,
intercessions of the kind done
Benson study — appeals to God
e some action — are of lesser

prayer of Christendom, contains no plea for God to influence specific events in people's lives.

The news from science will not lead religious people to stop praying for others. Prayers are expressions of empathy that strengthen a caring

Why doctors shouldn't prescribe prayer.

ironic that patients in th
were told unequivocally
being prayed for did
those who were told on
might be. When medica
dabble in religious pr
should anticipate that pa
interpret this as a sign
ation.
Doctors in particular
pleased that the Benson
onstrated no benefit fro
sory prayer by stranger
a colleague told me abo
well-educated woman wh
doctor of malpractice i



More conservative approach

Field Margins

Physically or biologically necessary margin

Too cavalier: marginal miss

Certainty of Gross Anatomy

Radiation Oncology:
Lawrence Marks, M.D.
Zafer Kocak, M.D.
Stephanie Yu, M.D.
Ming Fan, M.D.
Roxanne Woel
Bari Levinson
Melahat Garipagaoglu, M.D.
Mitchell Anscher, M.D.
Tim Shafman, M.D.
Pehr Lind, M.D., Ph.D.
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Nuclear Medicine:
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- **Stop here**

IMRT Technical Issues: MD

- Segment (contour) everything (hours)
- Anatomy knowledge (atlases)
- Dose/volume limits
- Plan review
- Beam placement is easier
  - Planning will reduce weights of "bad" beams
- Less QA (for MD); only set-up films
  - No portal films of each field

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IMRT Technical Issues: Therapists

- Therapist complacency/boredom?
  - More of a "technician" than before (vs. therapist)
  - Old: set up → see light field on target (Think!) → shoot
    - Light fields made sense, related to irradiated volume
  - IMRT: set up → shoot
    - Set up iso-center may NOT relate exactly to target
- Treatment time (increased beam on time)
- Personnel dose: radiation safety
- Machine life
- Longer time slots (at first), then decline
  - IMRT can be very fast
    - Set-up and shot. Techs do NOT go into room between beams

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IMRT Technical Issues: Physics/Dosimetry

- Planning times (hours)
- Vague MD direction (we do not know what to ask for). Fang-Fang Yin- Fuzzy Logic apporach
- QA (faith) (hours)
- Storage of data
- Reduces opportunity for creativity
  - Old: geometry, weighting, dose gradients, art
  - <u>IMRT</u>: computer takes care of it.
    - poor plan, no problem, adjust constraints and re-optimize
    - Good solutions often not intuitive
    - I miss the 3D planning exercise

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Shortcomings/Limitations of IMRT

- Dosimetric: dose goes somewhere
- Biologic: low dose volume increases
- Work Flow
  - Physician: hours, anatomy
  - Therapists: exposure, boredom
  - Dosimetrist/Physicist: intuition gone?
- Machine Issues: longevity, dose
- Resources: money, time
- QA: challenging

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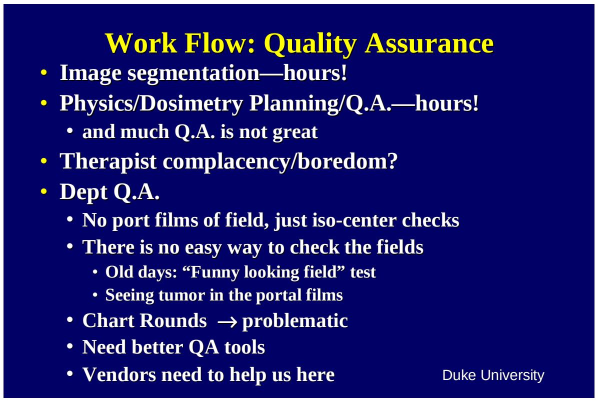

Work Flow: Quality Assurance

- Image segmentation—hours!
- Physics/Dosimetry Planning/Q.A.—hours!
  - and much Q.A. is not great
- Therapist complacency/boredom?
- Dept Q.A.
  - No port films of field, just iso-center checks
  - There is no easy way to check the fields
    - Old days: “Funny looking field” test
    - Seeing tumor in the portal films
  - Chart Rounds → problematic
  - Need better QA tools
  - Vendors need to help us here

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