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Evidence-based accuracy requirements in radiation oncology – tumor focus

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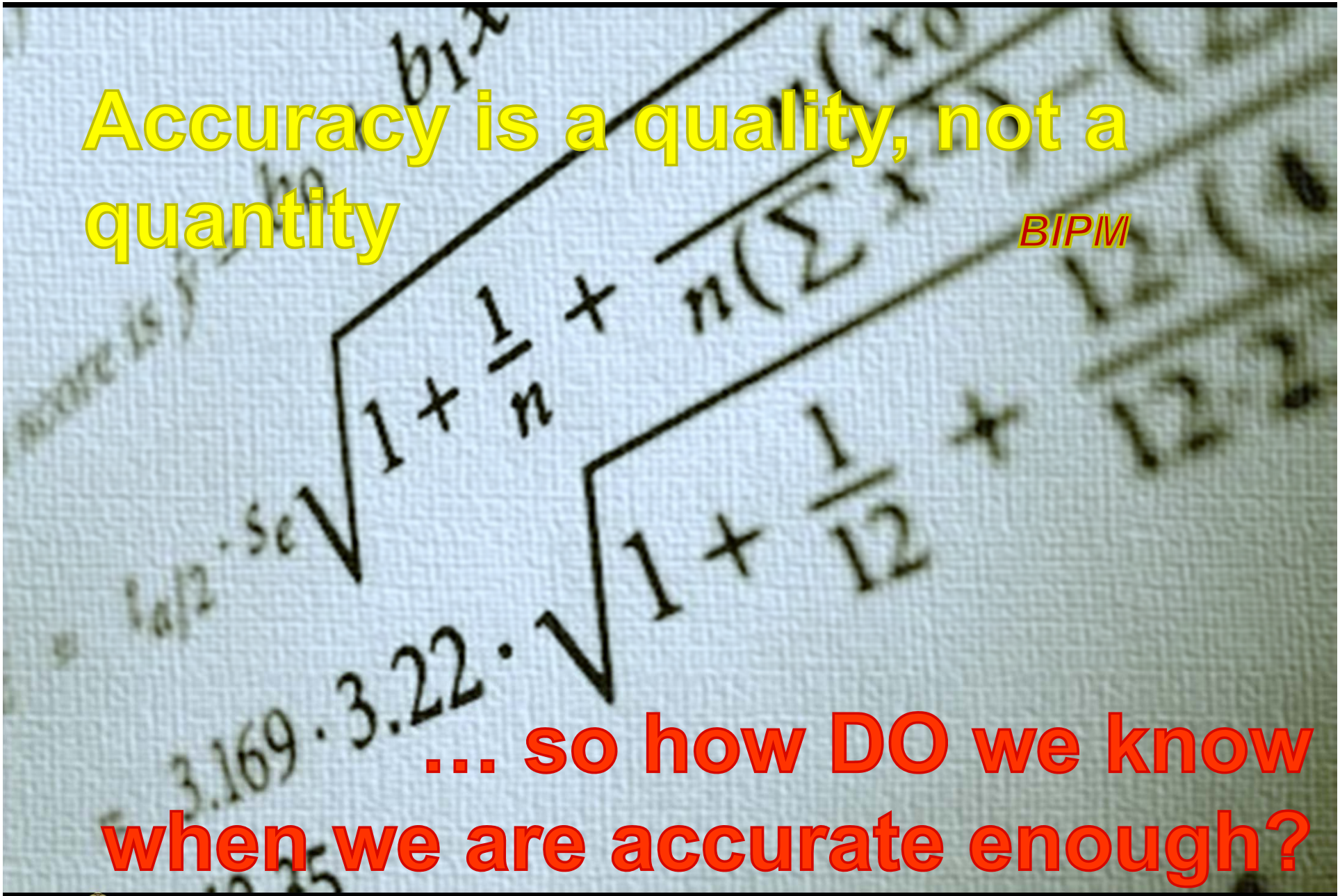


Accuracy is a quality, not a quantity

BIPM

… so how DO we know when we are accurate enough?

Evolution of RT Data Collection Required for Advanced Technology Clinical Trials

Prior to 3DOG/ RTOG 9406

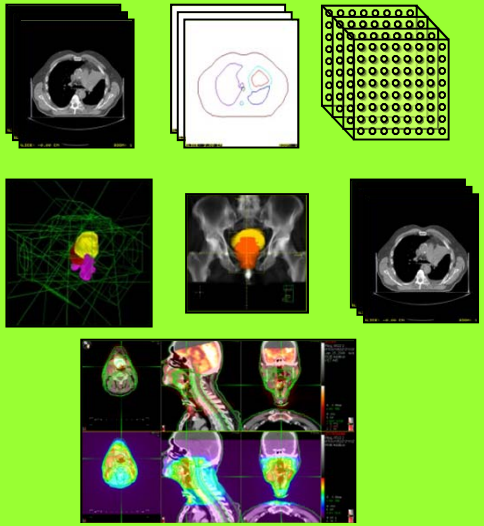
- Film, paper forms (CRFs).
- Postal

☺ Thanks to Jim Purdy

3DOG/RTOG 9406 to present

- Data objects (typical patient accrual digital data set ~ 100 MB)
  - Volumetric, digital images (planning CT)
  - Contours (TV, OAR)
  - 3D dose distributions (fractionation)
- Participants mostly submit data digitally

2010+ Protocols



- Additional data objects needed for 2010 trials
  - Diagnostic imaging studies (pre- & post, MRI, MRS, PET/CT,…)
  - Treatment verif. images (planar, kV CBCT, MV CT, Calypso,…)
  - Treat. plans (parameters for dose recalc.

2011 AAPM Summer School
Uncertainties in External Beam Radiation Therapy
immediately following the Joint AAPM/COMP Meeting
August 4 - 9, 2011 • Simon Fraser University • Burnaby, BC

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Welcome!

Who Should Attend?

This topic is extremely important for all those clinical physicists, radiation oncologists, and radiotherapy equipment manufacturers who are striving to improve the precision and accuracy of modern day radiotherapy.

Why Attend?

1. Radiotherapy is under scrutiny for mistreatments. What are you doing to better expend your quality management resources so that it doesn't happen at your facility? The SS is a cost-effective choice.

2. What has the IAEA on IMRT said about how dose prescriptions should be reported? If you don't know, you should attend the Summer School.

3. Rank the following in terms of likely impact to patient outcome. *Correct answers in parentheses*:

- dose calculation accuracy (3)
- calibration accuracy (4)
- setup uncertainty (2)
- uncertainty in contouring the gross tumor volume (1)

If you hesitated in your answer, you should attend the Summer School.

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3. Rank the following in terms of likely impact to patient outcome.

- dose calculation accuracy (3)
- calibration accuracy (4)
- setup uncertainty (2)
- uncertainty in contouring the gross tumor volume (1)

Precision and accuracy: the target analogy

Not precise, NOT ACCURATE

[in metrology the blue darts would be seen as "accurate" = unbiased]

Precise (i.e. reproducible), but biased = NOT ACCURATE

Precise AND unbiased = <u>ACCURATE</u>

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/SMB 09/11

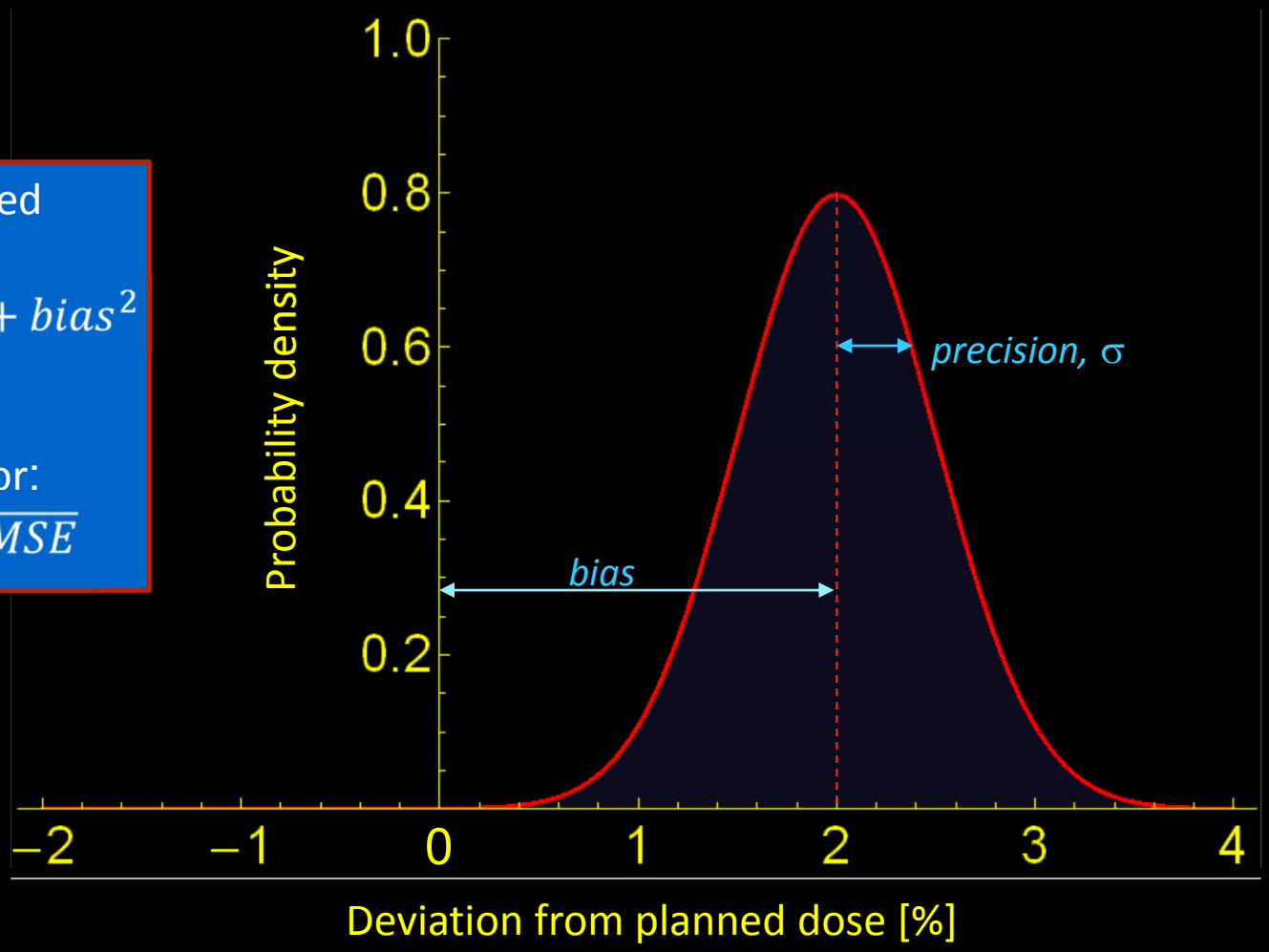
Statistics of radiation delivery

Mean Squared Error:

$$MSE = \sigma^2 + bias^2$$

Root Mean Squared Error:

$$RMSE = \sqrt{MSE}$$



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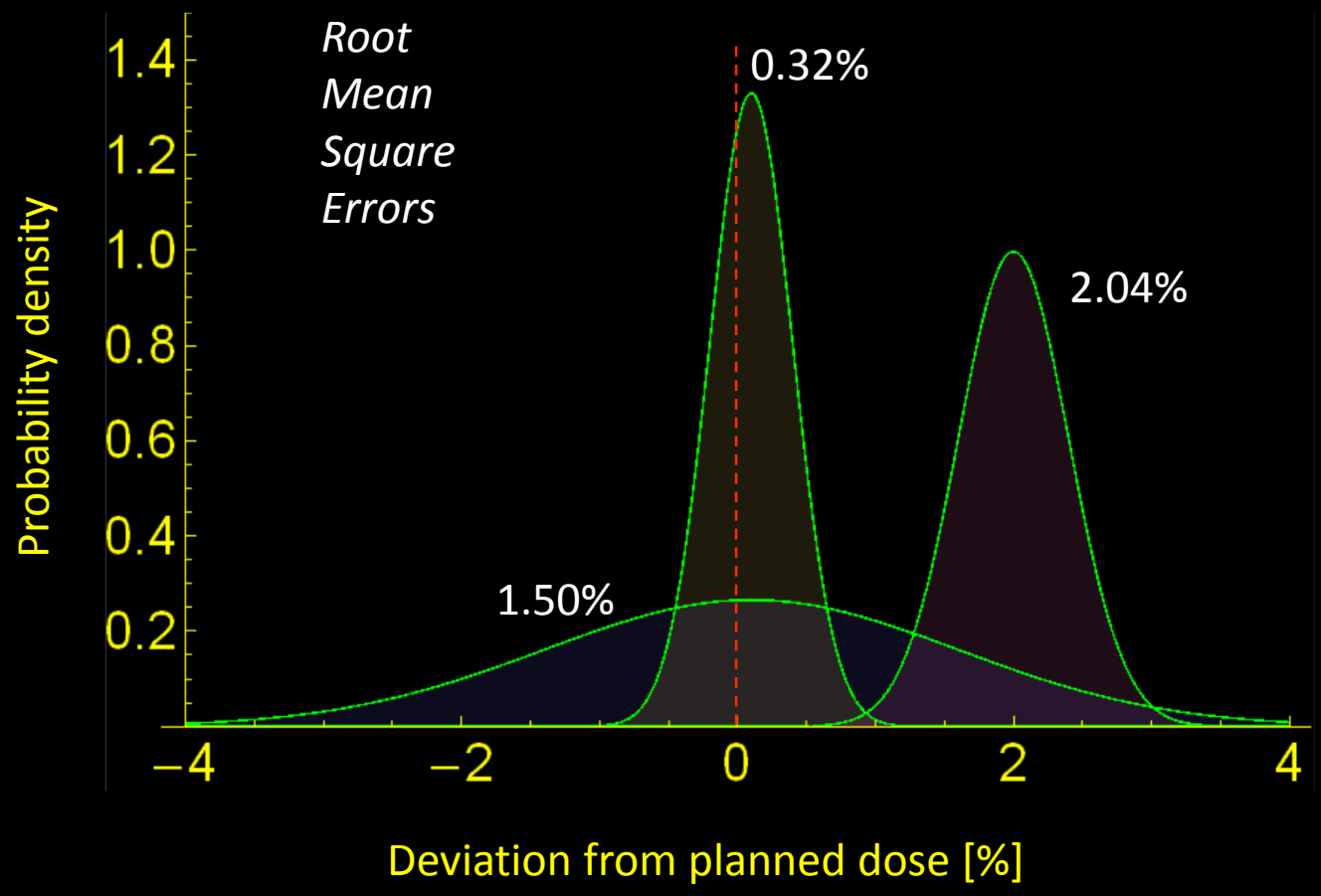
Comparing radiation dose deliveries



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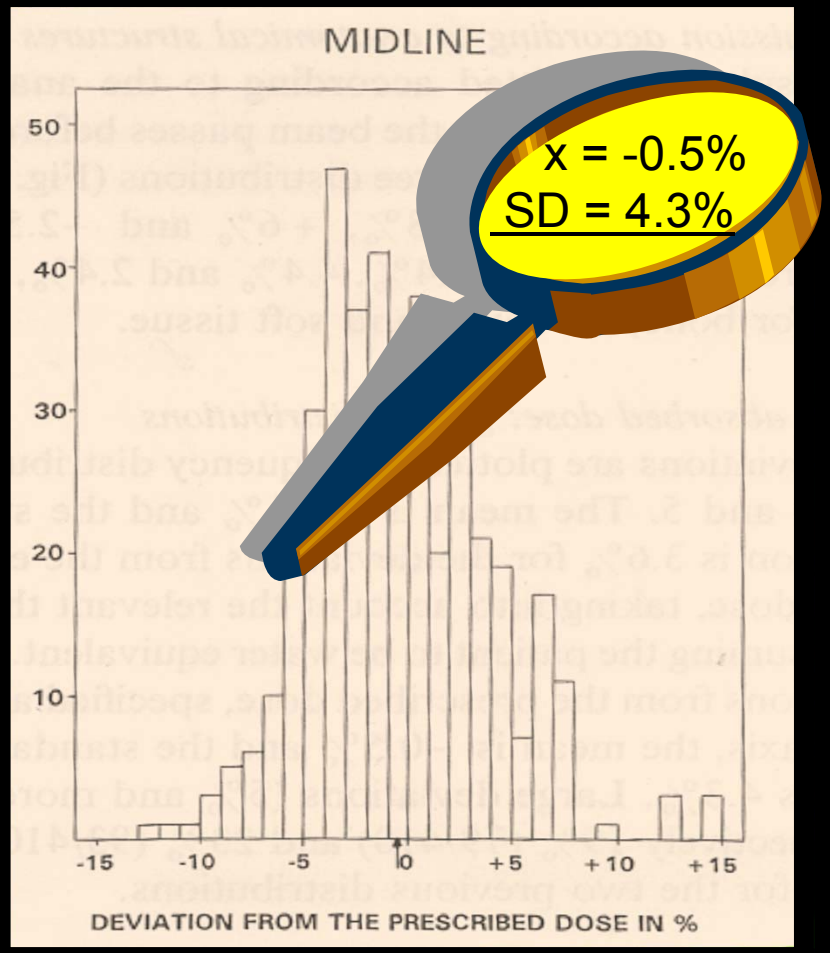
Dosimetric precision *in vivo*

Entrance and exit
Si diode measurements
in 11 patients with
HNSCC



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Leunens,…, van der Schueren, *R&O* 25: 242 (1992)

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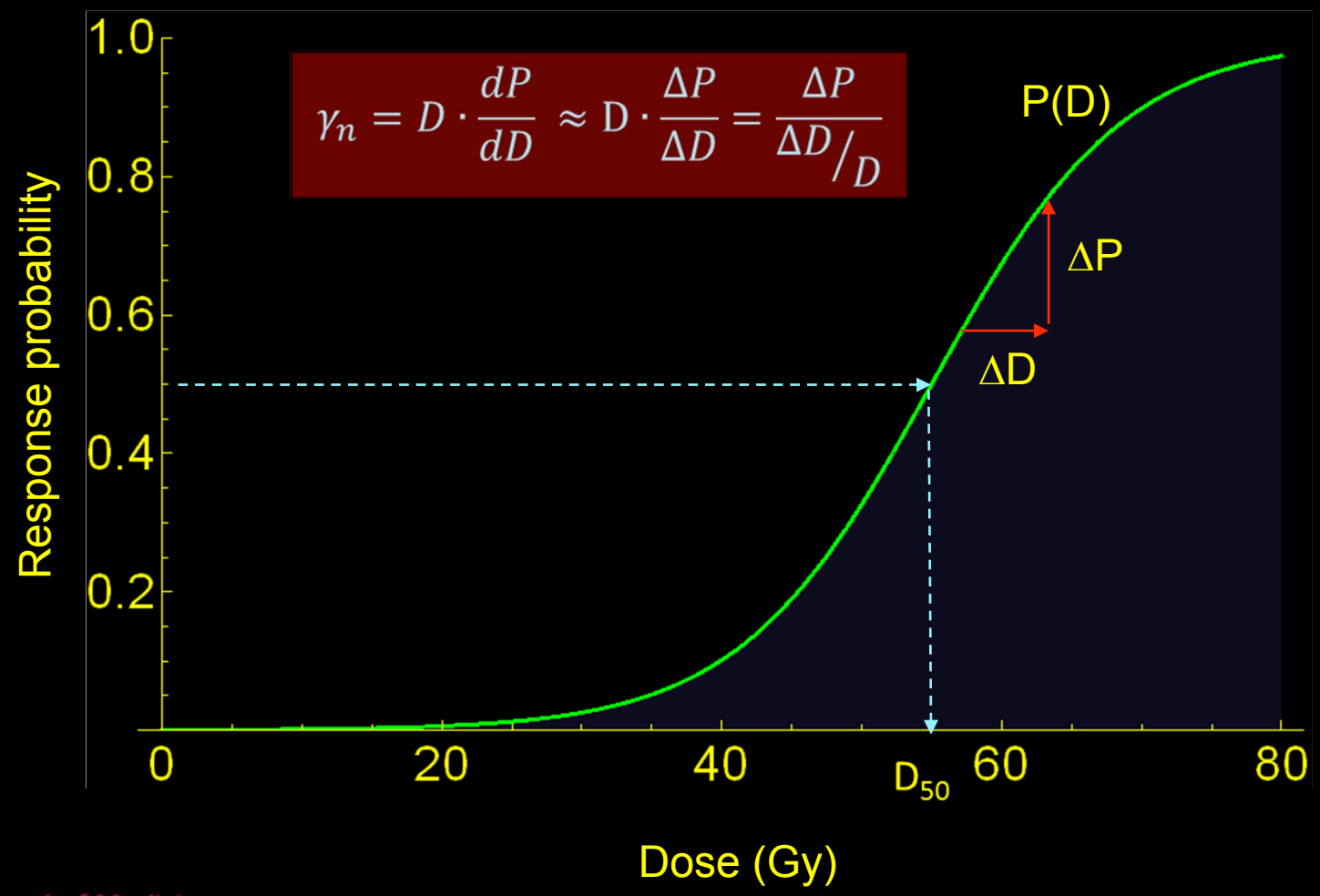
DISCLAIMER

"I guess I should warn you that if I turn out to be particularly clear, you've probably misunderstood me."

Alan Greenspan at his 1988 confirmation hearings

The normalized dose-response gradient



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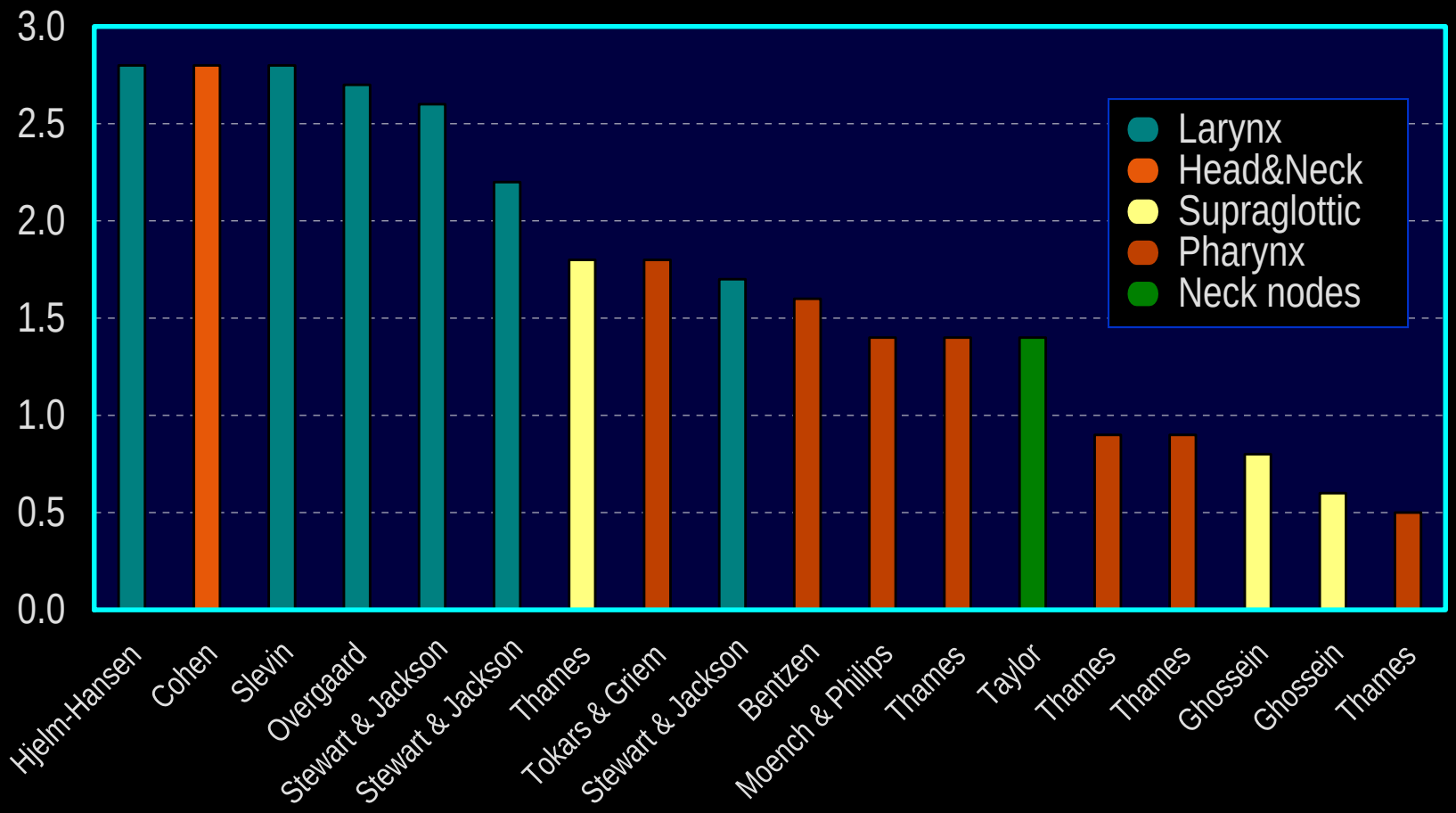
Steepness of DR curves for HNSCC



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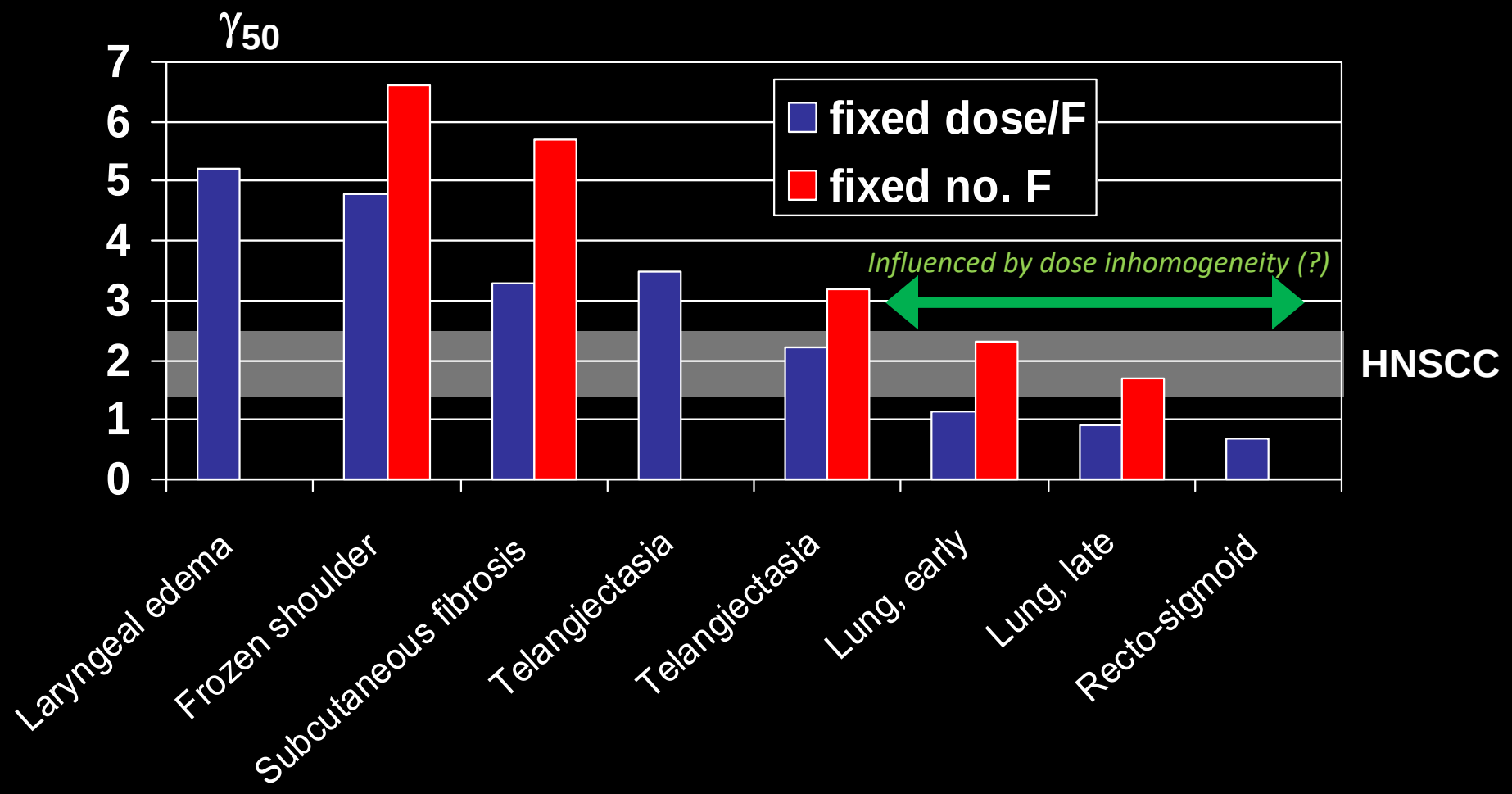
Bentzen *R&O* 32: 1 (1994)

/SMB

Steepness of normal-tissue dose-response curves



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Bentzen *R&O* 32: 1 (1994)

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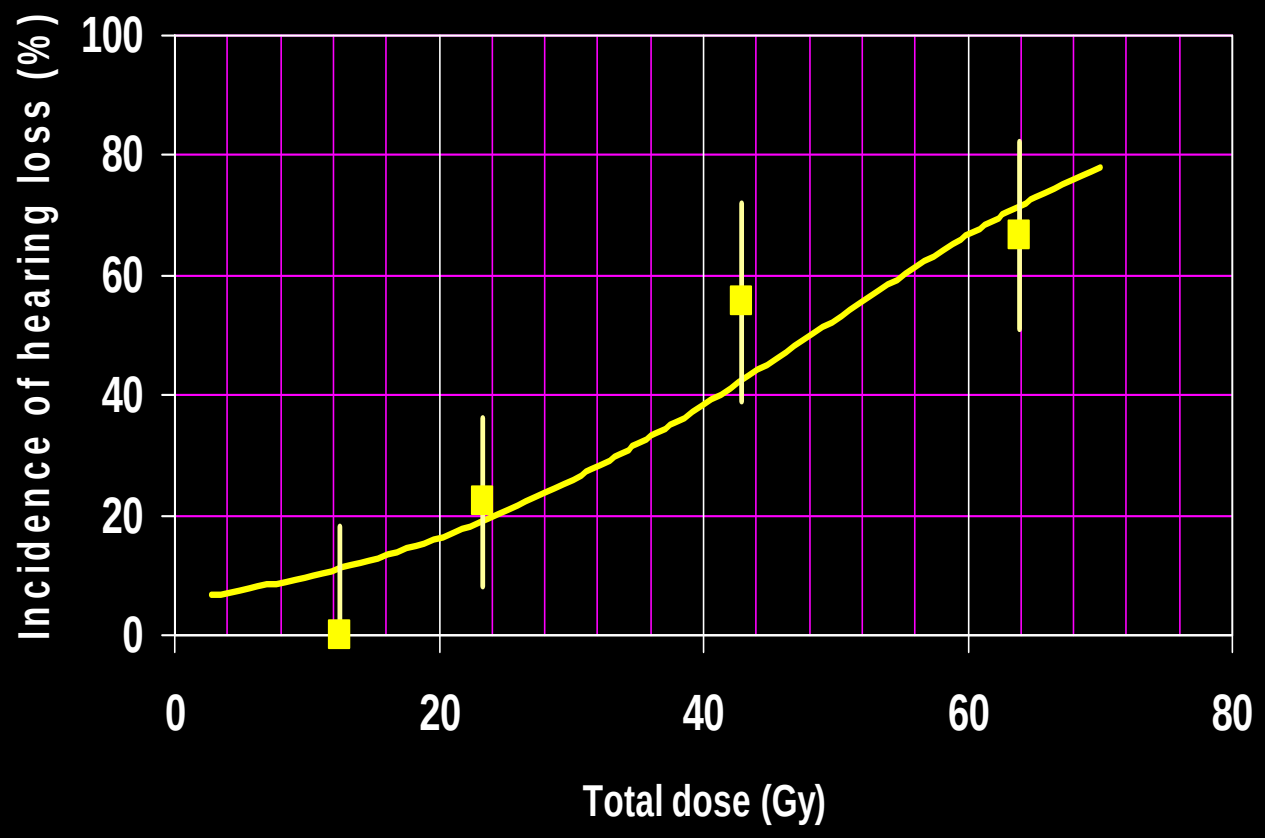
Sensori-neural hearing loss

γ_{50} = 0.70 with 95% CI (0.22; 1.18)



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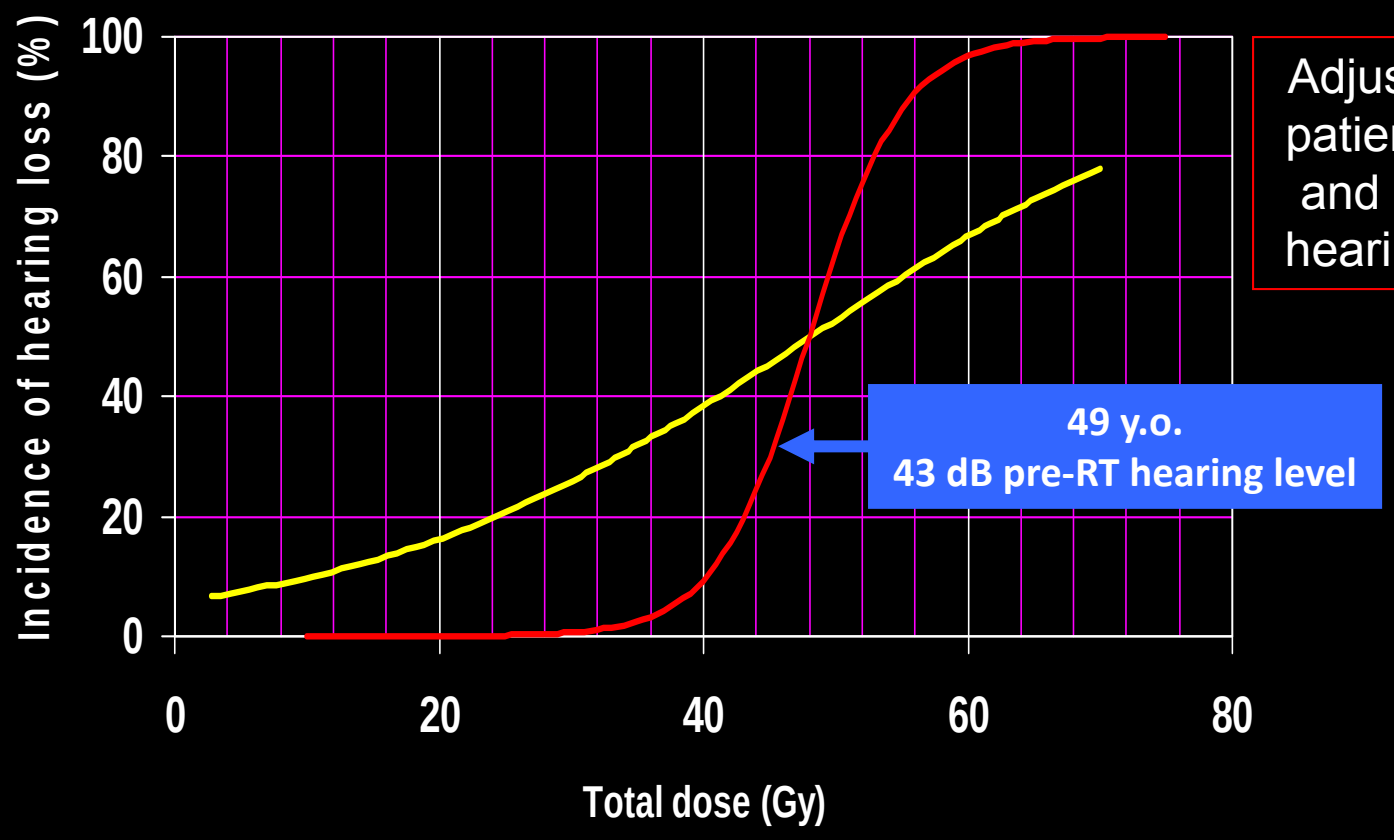
AND PUBLIC HEALTH

Honore et al. *R&O* 65: 9 (2002)

/SMB

Sensori-neural hearing loss

γ_{50} = 3.4 with 95% CI (0.3; 6.5)



Adjusting for patient's age and pre-RT hearing level

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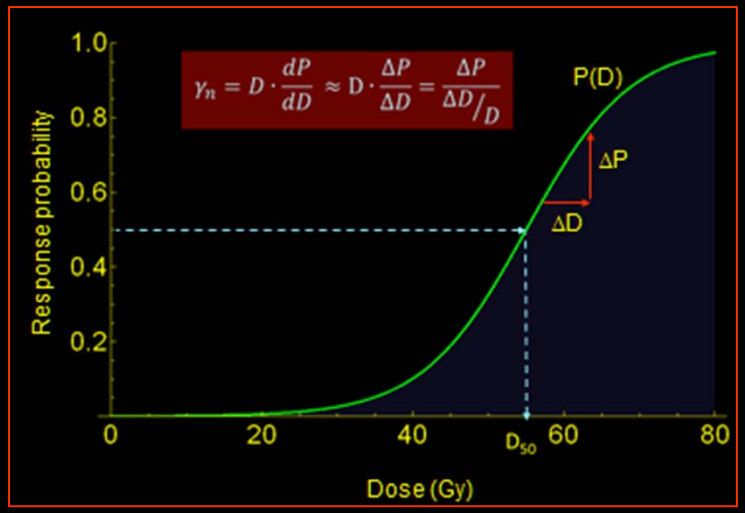
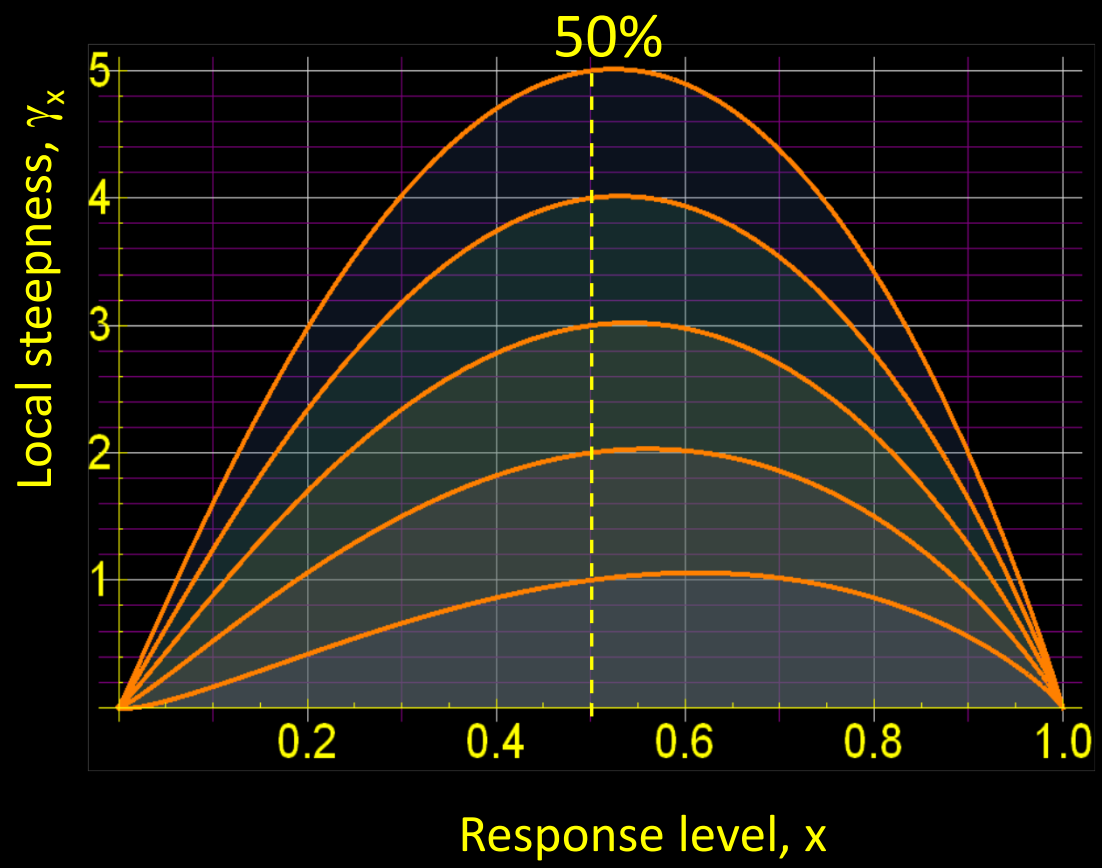
AND PUBLIC HEALTH

Honore et al. *R&O* 65: 9 (2002)

γ_{50} vs. local γ-value



- γ varies with position on the dose-response curve, i.e. with the response level.
- The curve is still <u>parameterized</u> in terms of D_{50} and γ_{50}
- However, in most situations the local γ-value should be applied



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γ-value for dose-per-fraction escalation

- At a reference dose per fraction of d_r the relationship between γ_N and γ_d is

$$\gamma_N = \gamma_d \cdot \frac{\alpha/\beta + 2 \cdot d_r}{\alpha/\beta + d_r}$$

EXAMPLE:
Assume α/β = 2 Gy
d_r = 2 Gy □ $\gamma_N = 1.5 \cdot \gamma_d$
d_r = 6 Gy □ $\gamma_N = 1.75 \cdot \gamma_d$

- Two asymptotic results are

$$\lim_{d_r \to \infty} \gamma_N = 2 \cdot \gamma_d \qquad \lim_{d_r \to 0} \gamma_N = \gamma_d$$

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Bentzen *Acta Oncol* 44: 825 (2005)

Uncertainty components

The delivered dose can be decomposed as:

$$\hat{D} = D_P + b + \varepsilon$$

Effect of BIAS on outcome

where D_P is the planned (intended or acceptable to the physician) dose, b is the bias, and ε is a random error

Bentzen, IAEA report (in preparation)

Estimating the clinical effect of imprecision

The expectation value of P(D) in the presence of variability in dose is

(( )) ( )

The change in P(D) due to imprecision in dose delivery is

( ) ( )

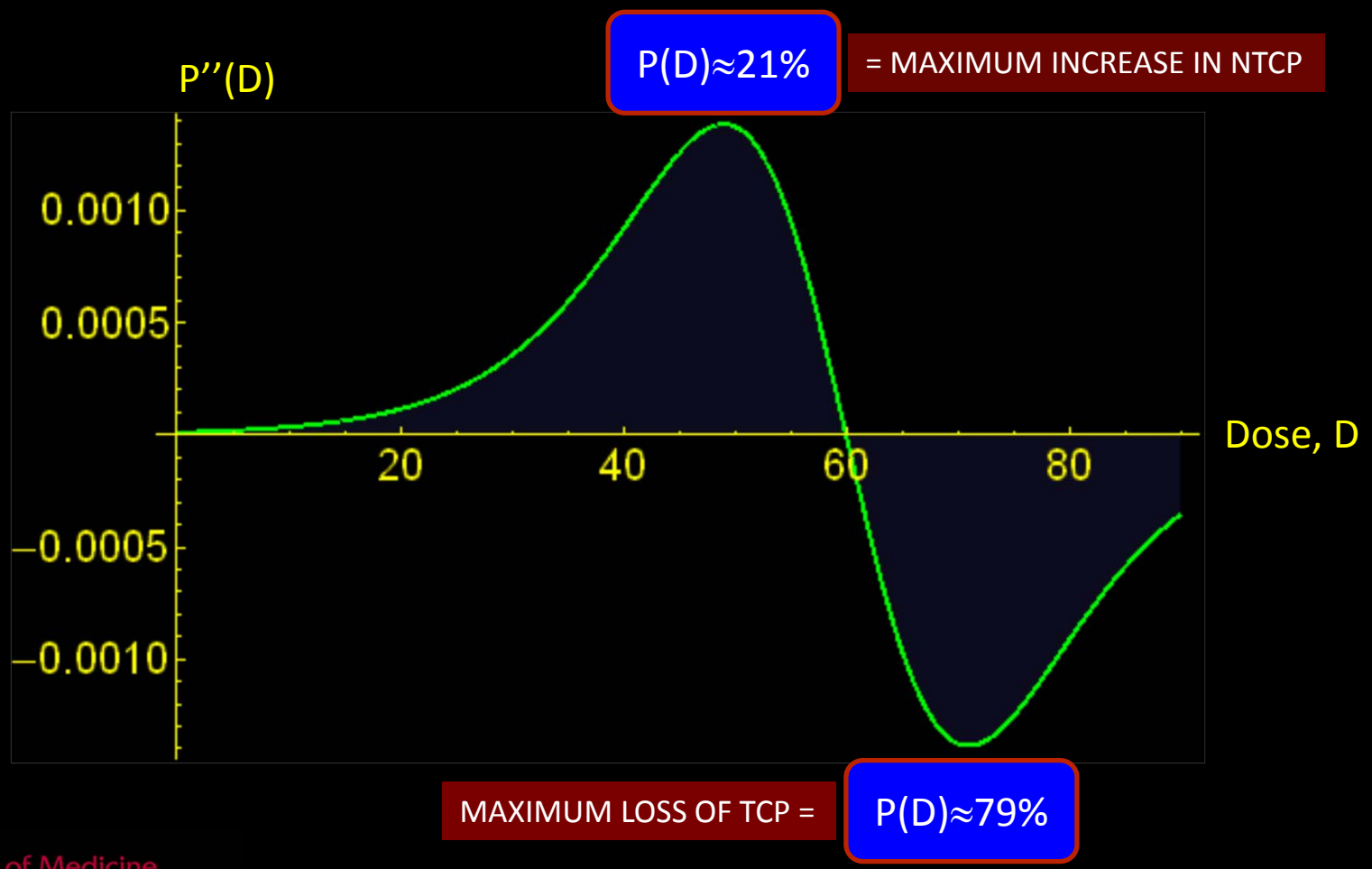
The Taylor expansion of P(D) is

( ) ( ) ( ) ( ) – ( ) ( )

The first order term cancels out in the convolution integral due to the symmetry of the p.d.f.

Second derivative of dose-response function

- Logistic dose-response curve: D_{50}=60 Gy, γ_{50}=1.8



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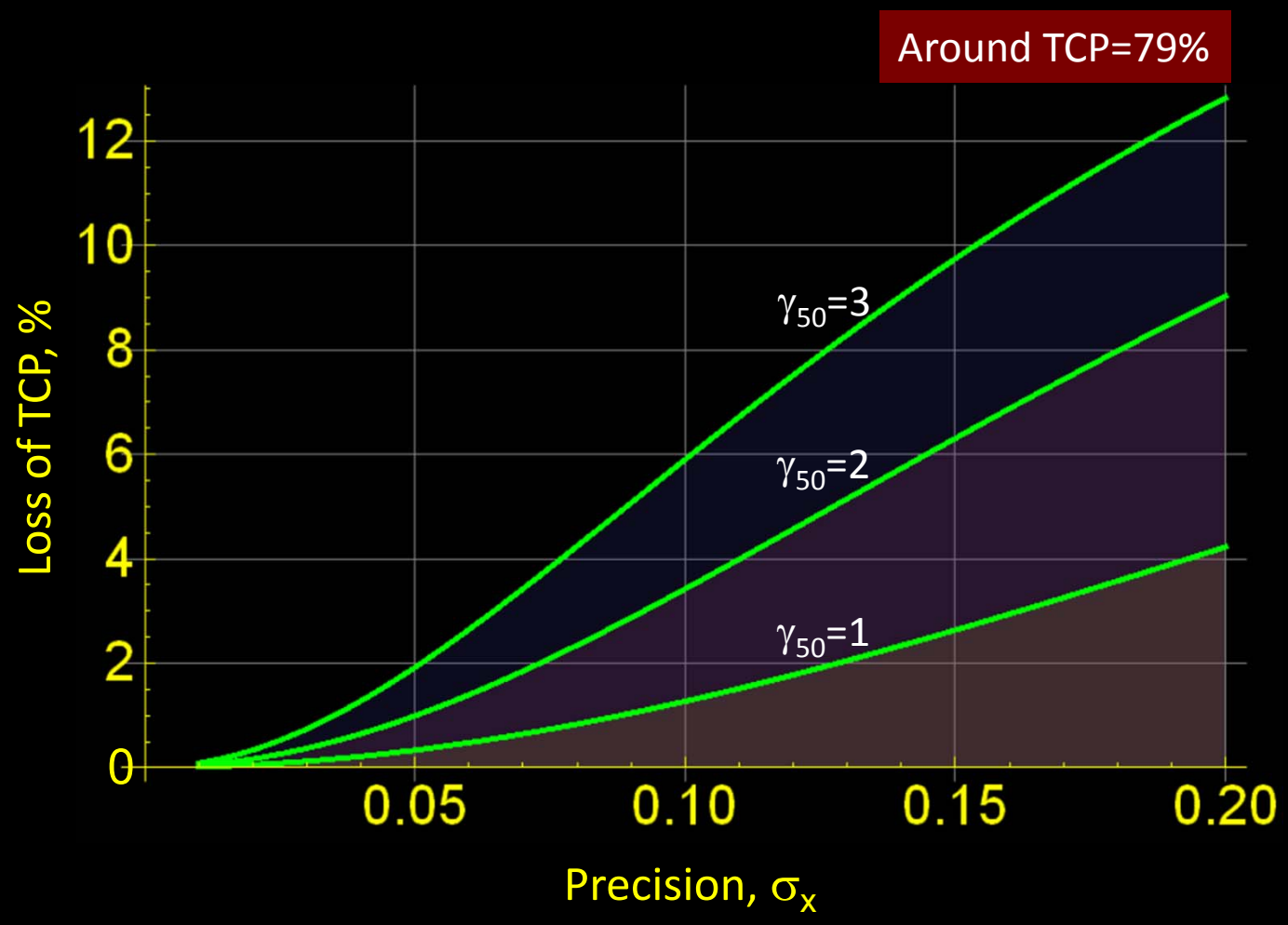
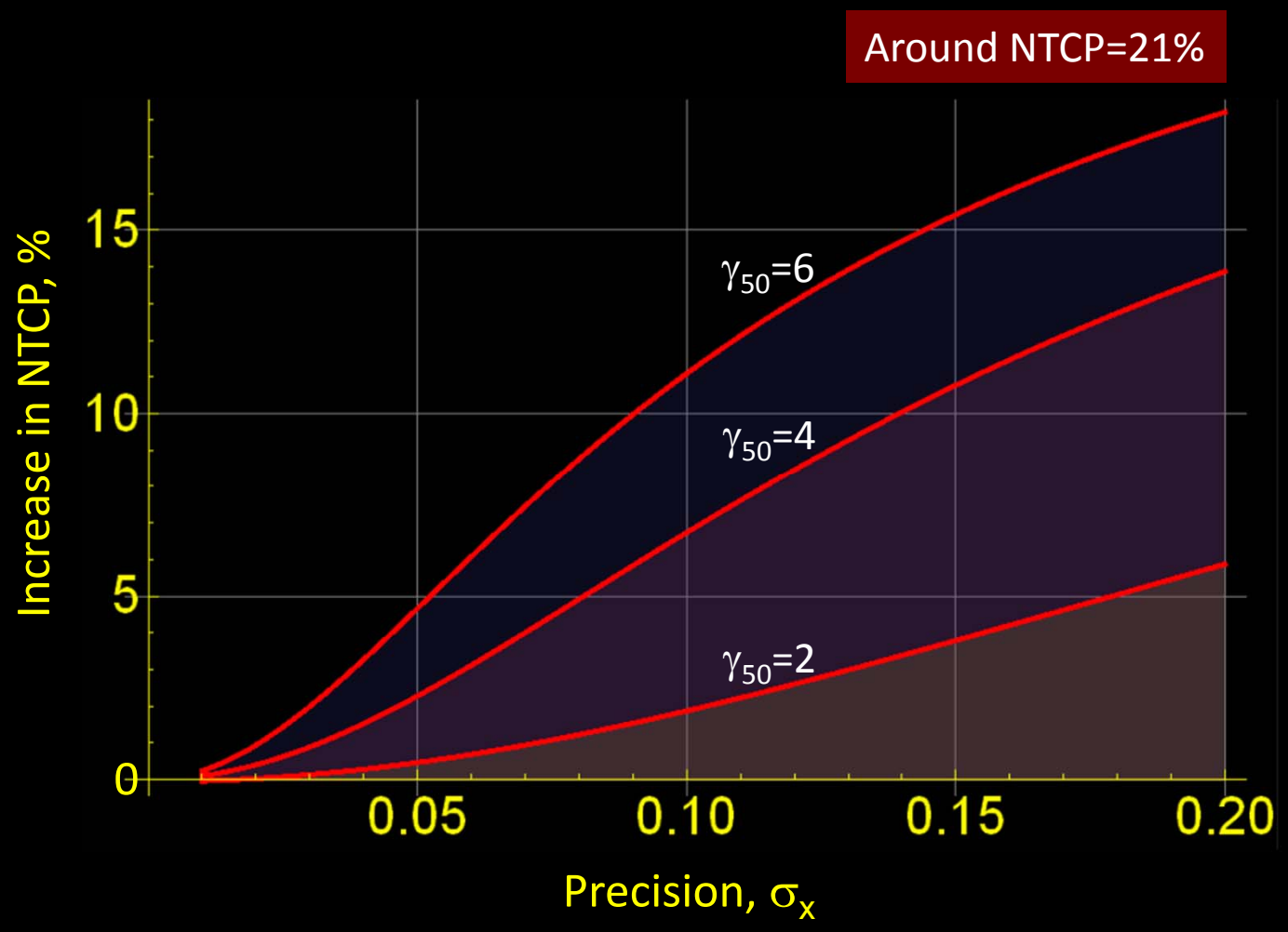
Bentzen, IAEA report (in preparation)

Loss of TCP with reduced precision



Increase in NTCP with reduced precision



So, what's the accuracy target then?

Tumor control

- **GOAL:** lack of accuracy results in <5% loss of tumor control probability
- **ASSUMPTION:** $\gamma_{50,N}=3$
- What is γ at the 80% level where the precision requirement is tightest?

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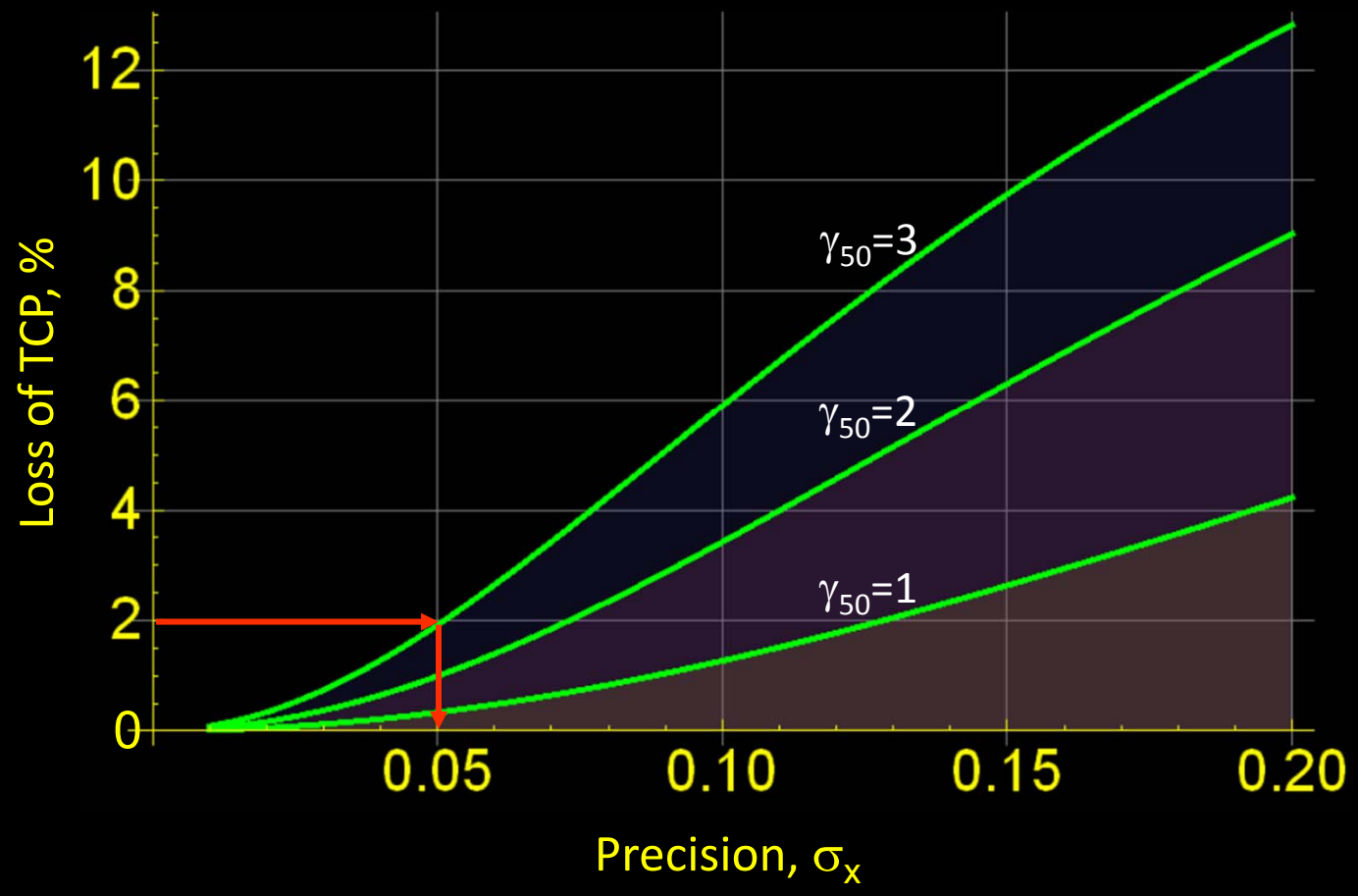
- **ASSUMPTION:** $\gamma_{50,N}=3$
- What is γ at the 80% level where the precision requirement is tightest?
- Answer: $\gamma_{80,N}\approx 2.1$
- Accepting a maximum loss due to bias of 3% □ bias□1.5%
- This caps the loss due to imprecision at 2%

Loss of TCP with reduced precision

NOTE: These curves refer to γ_{50} **NOT** the local γ



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- What is γ at the 80% level where the precision requirement is tightest?
- Answer: $\gamma_{80,N}\approx 2.1$
- Accepting a maximum loss due to bias of 3% □ *bias*□1.5%
- This caps the loss due to imprecision at 2% □ σ_{ε}□5%
- If treatment is delivered in, say, 30F this could be split as
- σ_{course}□4.5%
- σ_{Fx}□2.2% □ σ_{fx}□12%

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So, what if we gave 15 Gy x 3 instead?

Tumor control

- **GOAL:** lack of accuracy results in <5% loss of tumor control probability
- **ASSUMPTION**: tumor α/β = 8 Gy, $\gamma_{50,d}$ = 2.5 □ $\gamma_{50,N=3}$=4.1
- At the 80% level where the precision requirement is tightest $\gamma_{80,N}\approx 2.9$
- Accepting a maximum loss due to bias of 3% □ *bias*□1%
- This caps the loss due to imprecision at 2% □ σ_{ε}□3.9%
- As treatment is delivered in 3F this now yields

σ_{course}□3.5%

σ_{Fx}□1.7% □ σ_{fx}□3.0%

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So, what about the NT accuracy target?

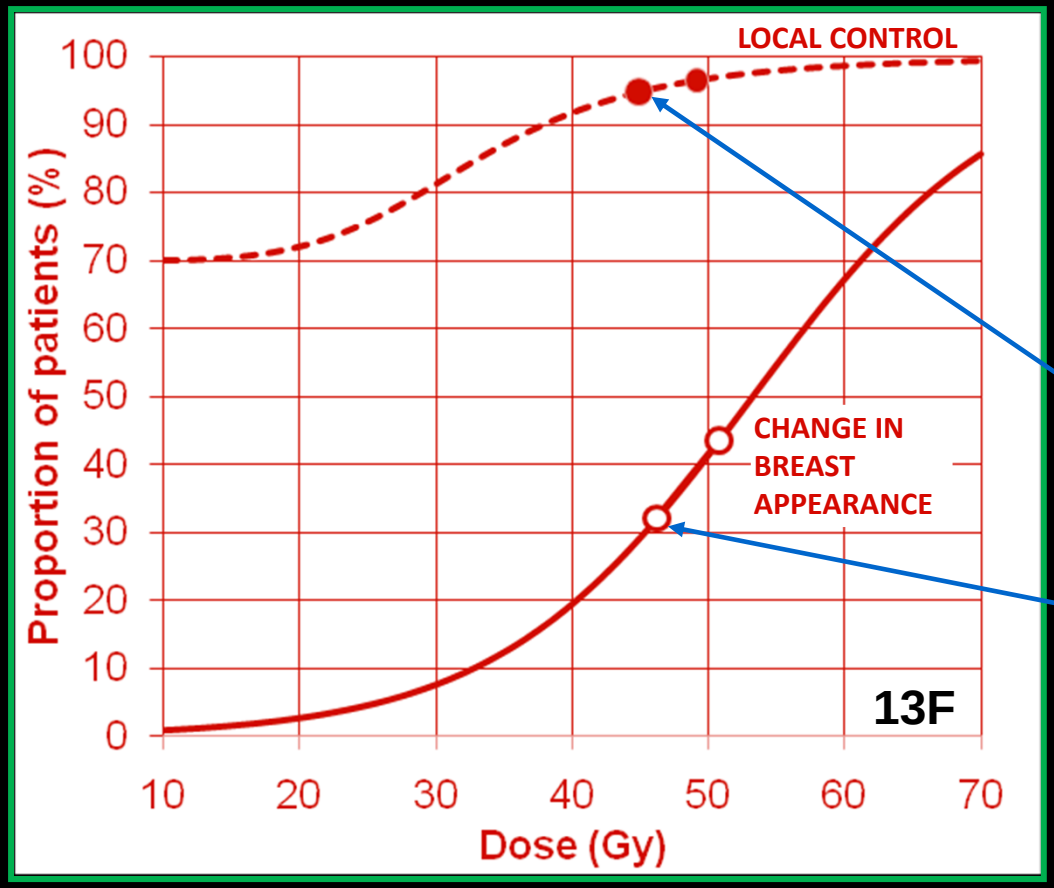
NTCP

- **GOAL:** lack of accuracy results in <5% increase in NTCP
- **ASSUMPTION**: $\gamma_{50,N}=4$
- At the 20% level where the precision requirement is tightest $\gamma_{20,N}\approx 2.3$
- Accepting a maximum loss due to bias of 3% □ *bias*□1.3%
- This caps the loss due to imprecision at 2% □ σ_{ε}□4%
- If treatment is delivered in, say, 30F this could be split as

σ_{course}□3.5%

σ_{Fx}□1.9% □ σ_{fx}□10.6%

Special consideration – subclinical breast cancer



Clinical outcome data from 1487 patients in the two 13F test arms of the START A trial

Lancet Oncol 9: 331 (2008)

$\gamma_{eff} = 0.2$

$\gamma_{30} = 1.7$

…without adjusting for age, chemotherapy, tamoxifen, breast size, and surgical deficit

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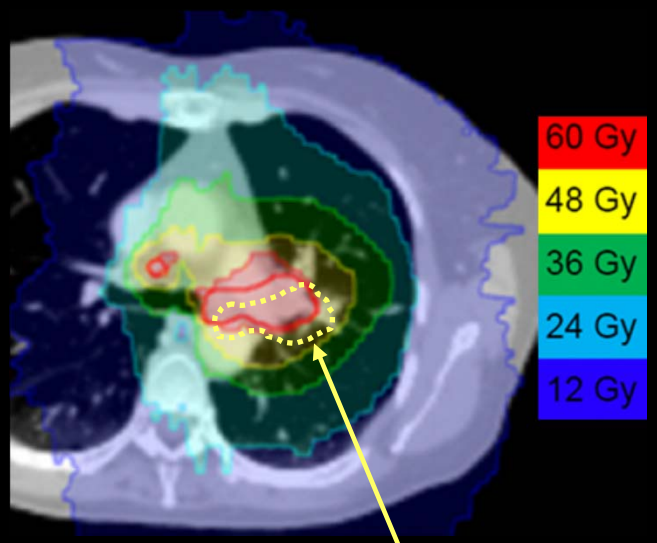
Yarnold, Bentzen et al. *IJROBP* 79:1 (2011)

Missing a fraction of D_p to a fractional volume



Target moved
(or dose distribution moved)

TAKEHOME MESSAGE:

IF YOU MAKE MISTAKES,

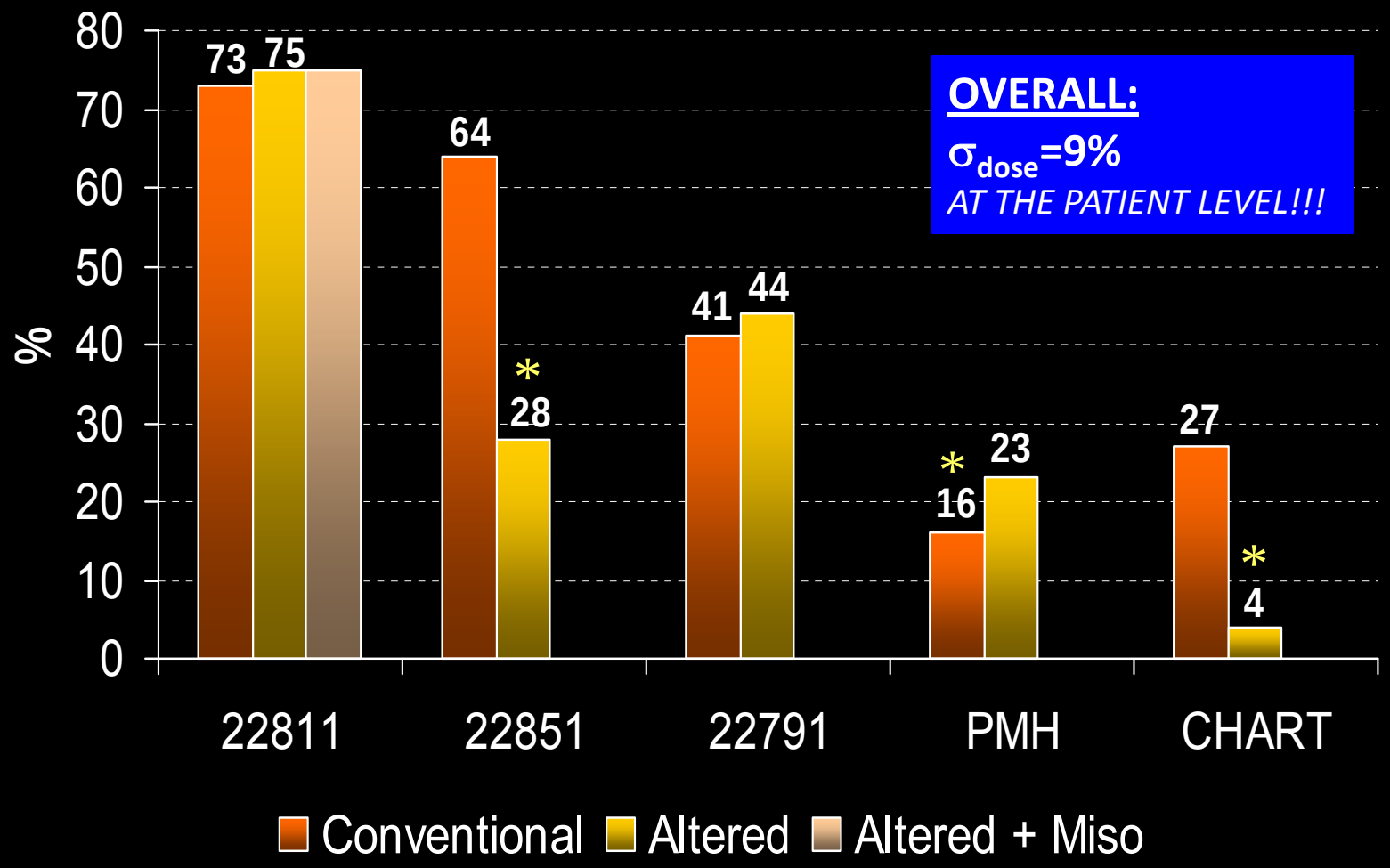
MAKE SURE TO MAKE THEM RANDOMLY!

3. Rank the following in terms of likely impact to patient outcome.

- dose calculation accuracy (3) 2
- calibration accuracy (4) 1
- setup uncertainty (2) 3
- uncertainty in contouring the gross tumor volume (1)

EPILOGUE: Accuracy in a (humbling) perspective

% of patients who lost >3 Gy due to poor compliance



OVERALL:

σ_{dose}=9%

AT THE PATIENT LEVEL!!!

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Khalil et al. *IJROBP* 55: 568 (2003)

*I*SMB

EPILOGUE: Accuracy in a (humbling) perspective

Co-factors in the expression of RT effects

Endpoint	Risk factor	OR	Ref.
Various	Connective tissue disease	2.0	Hoelscher
Telangiectasia of the skin	Moist desquamation during RT	3.0	Bentzen
Radiological lung fibrosis	Tamoxifen during RT	3.2	Bentzen
Pneumonitis	Non-smokers/smokers	4.2	Liao
Sensori-neural hearing loss	5 years increment in patient's age	10	Honore
Gastrointestinal injury RT for Hodgkin's Disease	Previous laparotomy	12	Cosset

*γ_{50}=3, D=70 Gy, p_0=10%

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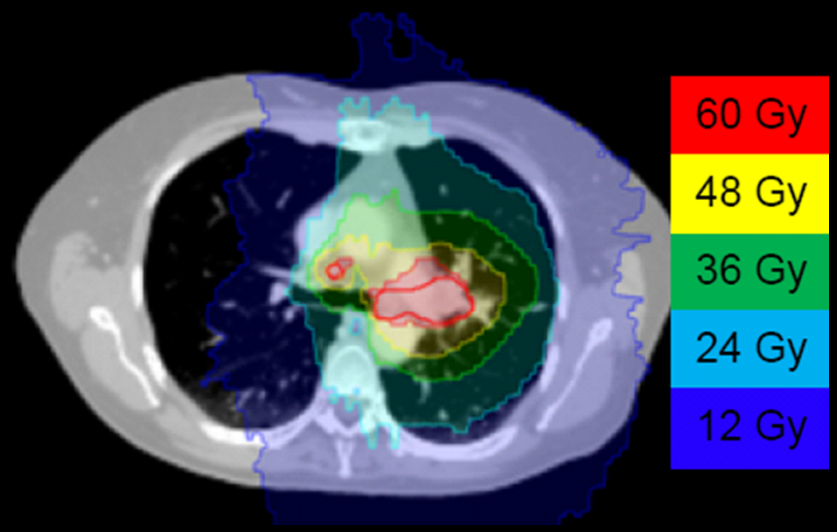
EPILOGUE: Accuracy in a (humbling) perspective

Variation in Mean Equivalent Lung Dose

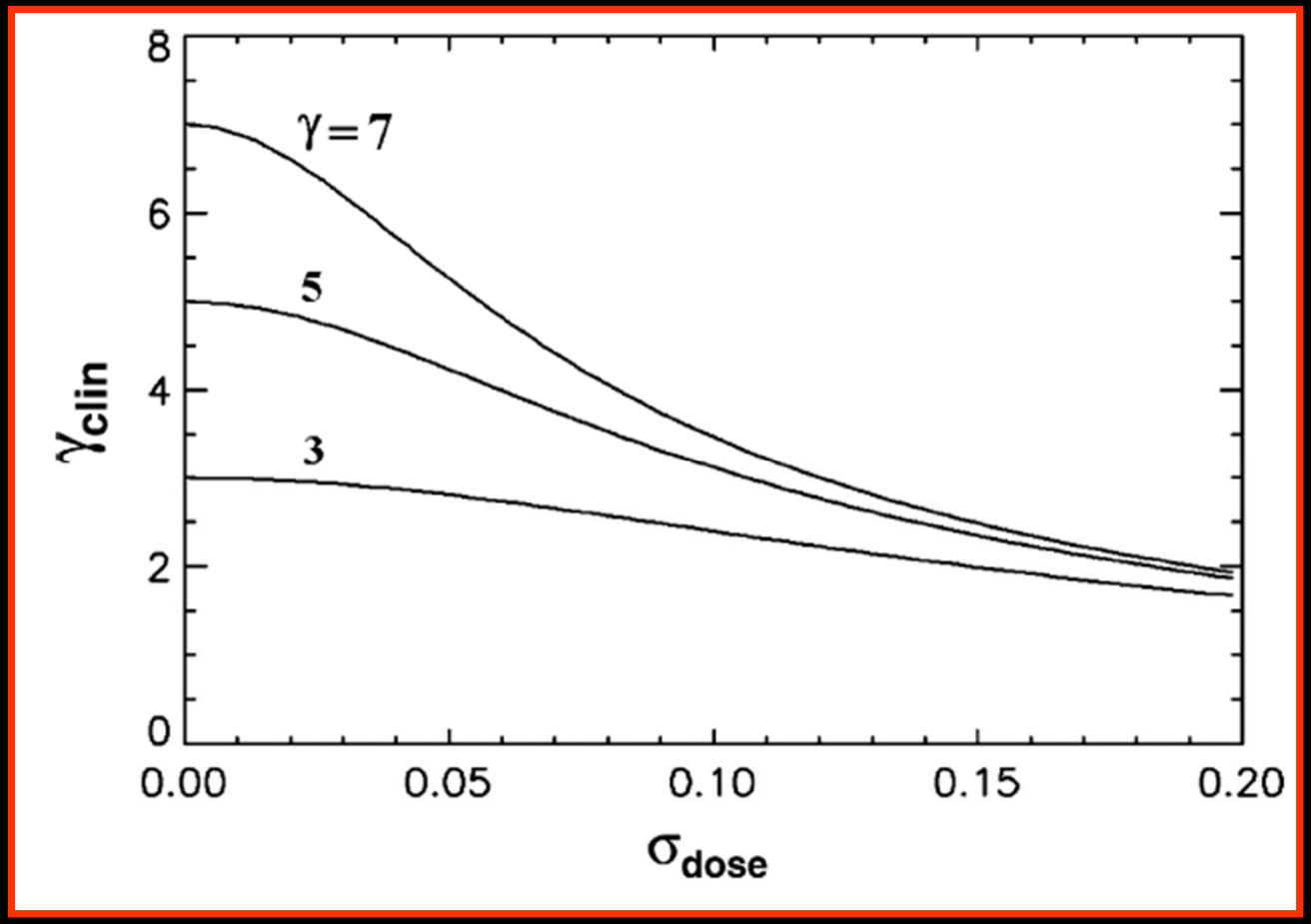
Tomotherapy



- 18 patients with NSCLC receiving chemo-RT
- Average MELD=10.2 Gy
- CV_{MELD}=42%

Thanks to *Fridtjof Nüsslin, Jan-Willem Leer, Jacques Bernier & Jake van Dyk* for inspiring discussions on aspects of this topic

Influence of dosimetric variation on γ_{50}



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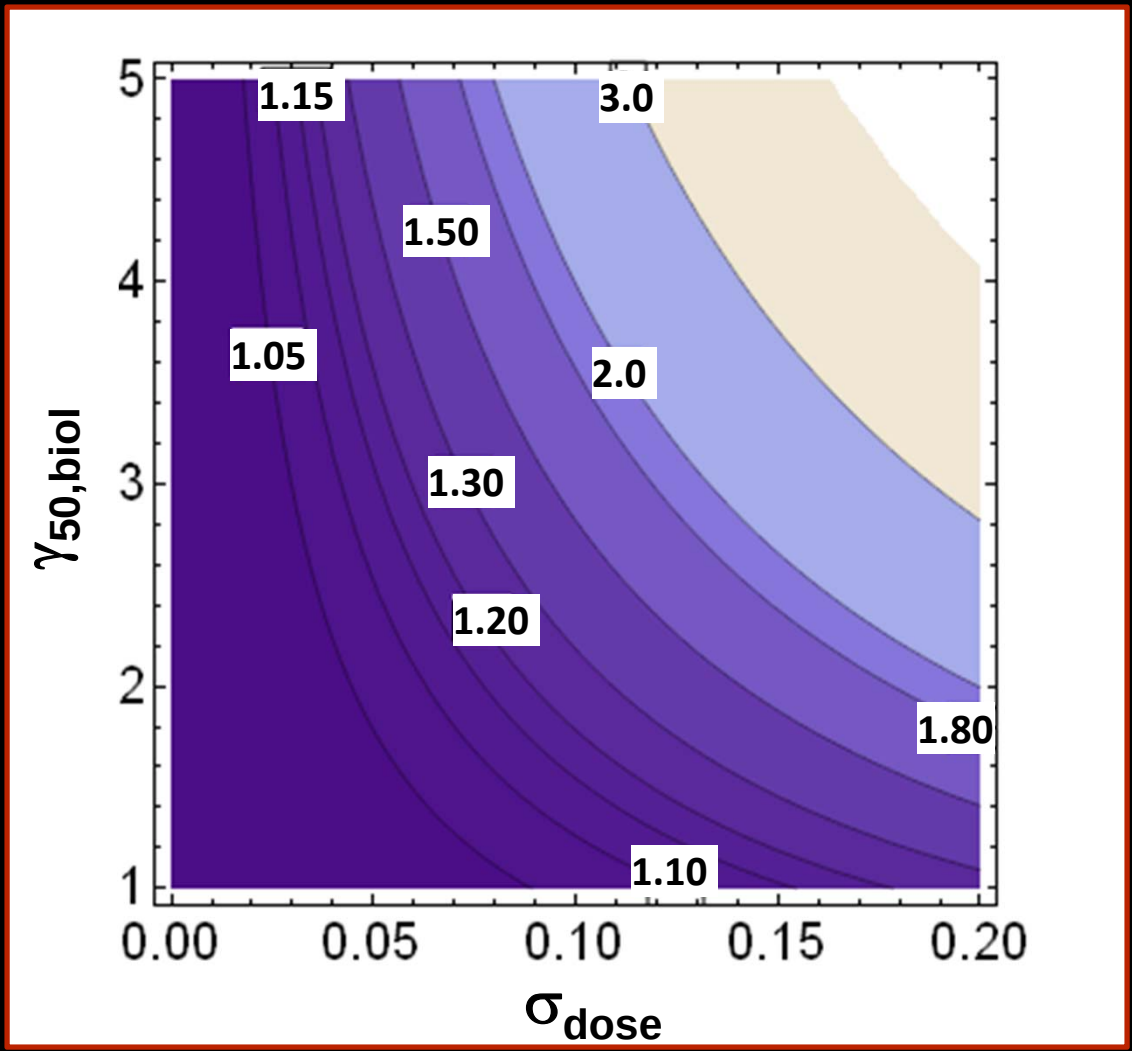
Pettersen et al. *R&O* 86: 195 (2008)

Inflation of sample size needed in RCT



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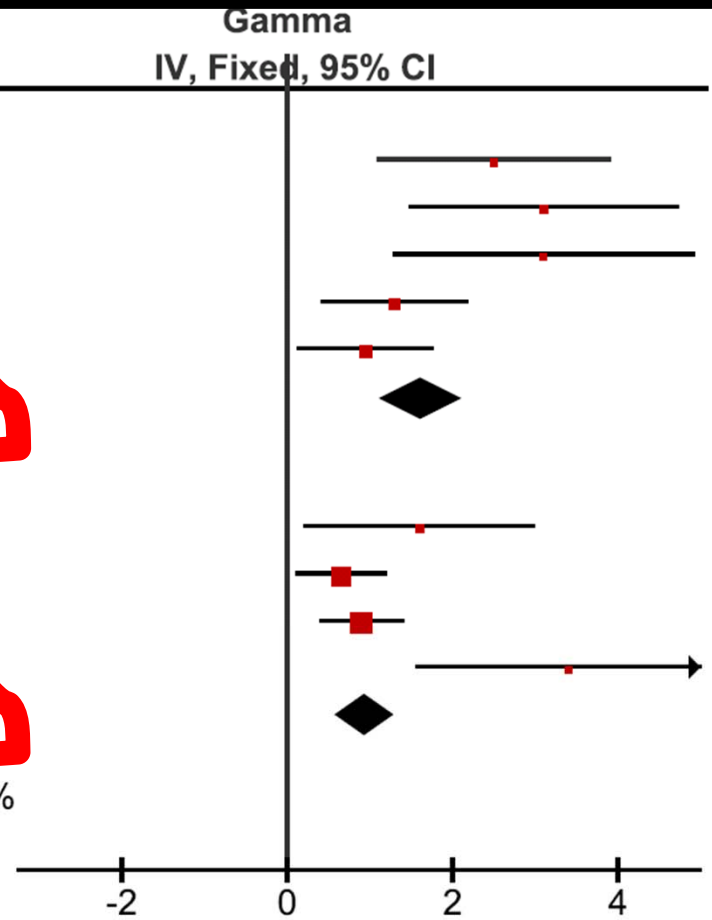
Bentzen (in preparation)

Intermediate/high risk prostate cancer

Study or Subgroup	Weight	Gamma IV, Fixed, 95% CI
Non-randomized studies		
Zelefsky 1998	4.2%	2.50 [1.09, 3.91]
Lyons 2000	3.2%	3.10 [1.47, 4.73]
Pollack 2000	2.5%	3.10 [1.28, 4.92]
Hanks 2000	10.8%	1.30 [0.42, 2.18]
Kupelian 2005	12.4%	[illegible]
Subtotal (95% CI)	**33.1%**	**1.63 [1.13, 2.14]**
Randomized studies		
Zietman 2005	4.3%	1.60 [0.21, 2.99]
Peeters 2006	27.8%	0.65 [0.10, 1.20]
Dearnaley 2007	32.3%	0.90 [0.39, 1.41]
Kuban 2008	2.5%	[illegible]
Subtotal (95% CI)	**66.9%**	**0.93 [0.58, 1.29]**

Test for subgroup differences: Chi² = 4.94, df = 1 (P = 0.03), I² = 79.8%



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Diez, Vogelius, Bentzen *IJROBP* 77: 1066 (2010)

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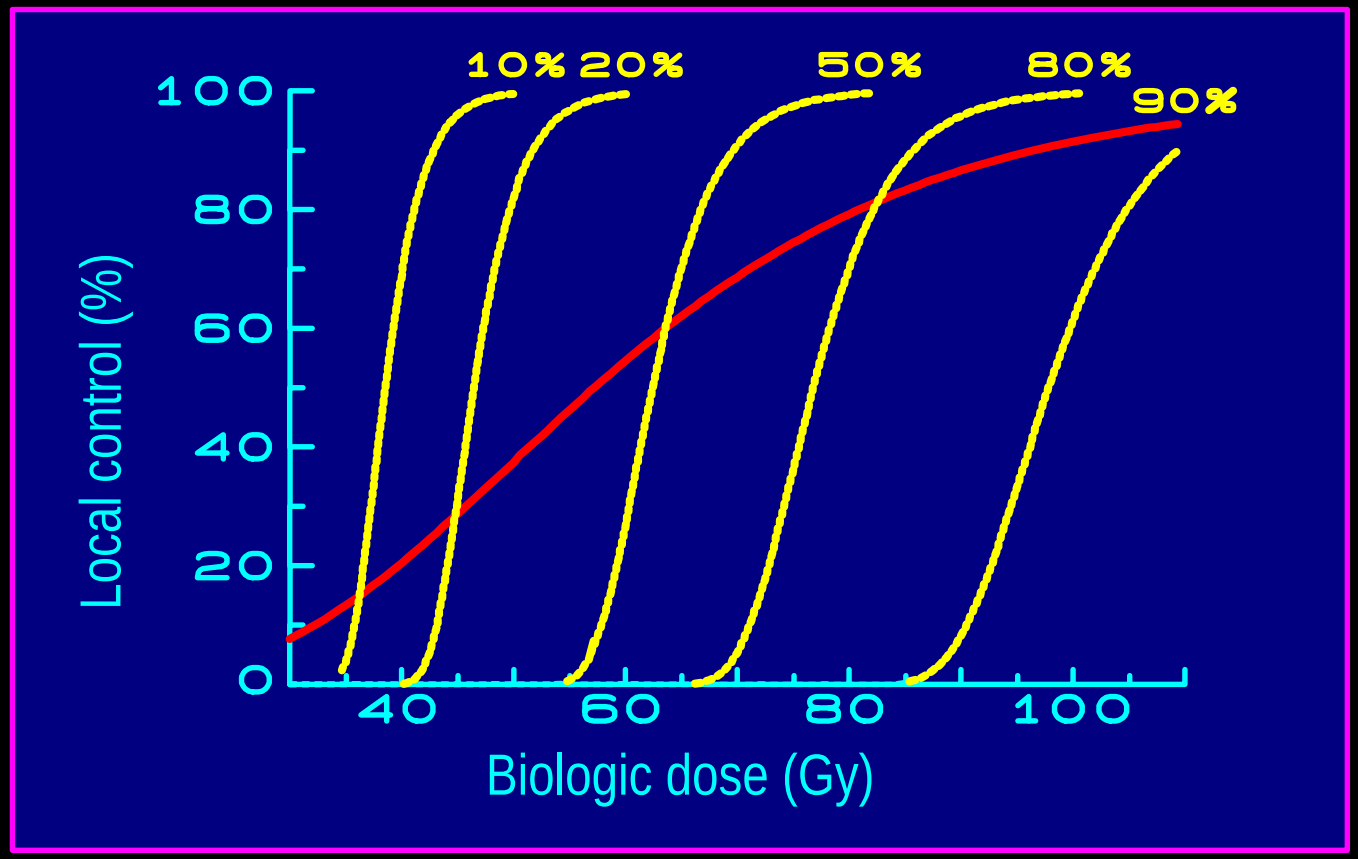
Dose-response stratified for *in vitro* radiosensitivity



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Bentzen *IJRB* 61: 417 (1991)

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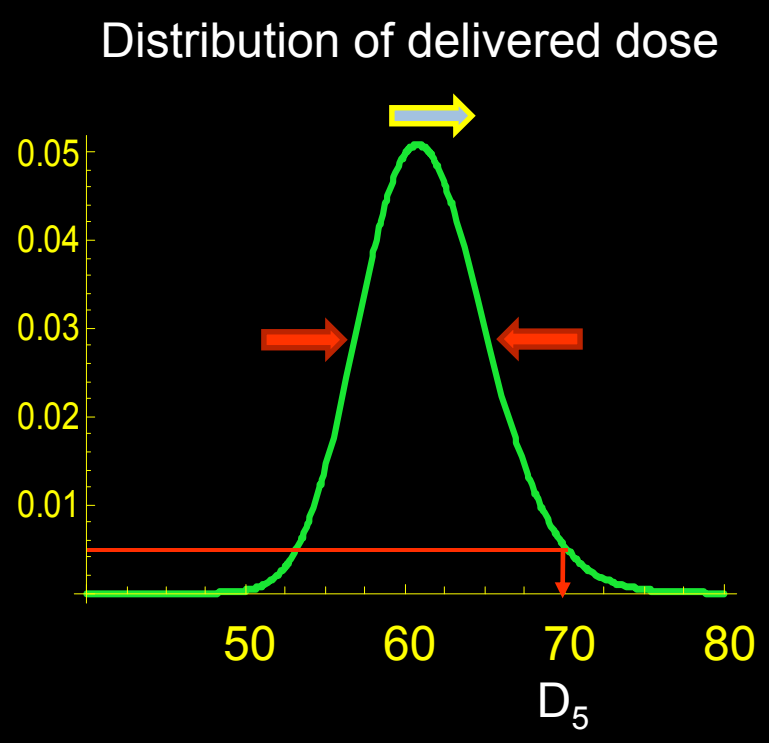
When is dose delivery precise enough?



CV(%)	D_5 (Gy)	TCP
10	68.73	50.0
5	71.76	62.9
2	72.85	67.2
1	73.01	67.9
0.1	73.07	68.1

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Bentzen, *IJROBP* 58: 320 (2004)

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