School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON

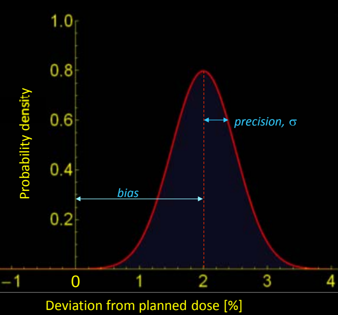
Radiobiological rationale for accuracy considerations in RT

Søren M Bentzen, Ph.D., D.Sc.
Departments of Human Oncology; Medical Physics; Biostatistics and Medical Informatics,
University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, USA
bentzen@humonc.wisc.edu

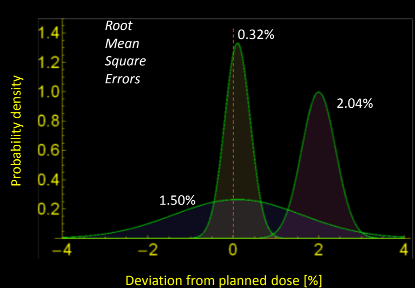
Statistics of radiation delivery

Mean Squared Error:
$MSE = \sigma^2 + bias^2$

Root Mean Squared Error:
$RMSE = \sqrt{MSE}$

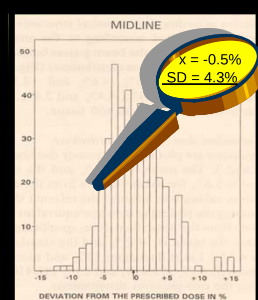


Comparing radiation dose deliveries



Dosimetric precision *in vivo*

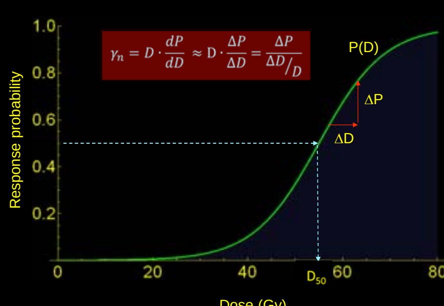
Entrance and exit Si diode measurements in 11 patients with HNSCC



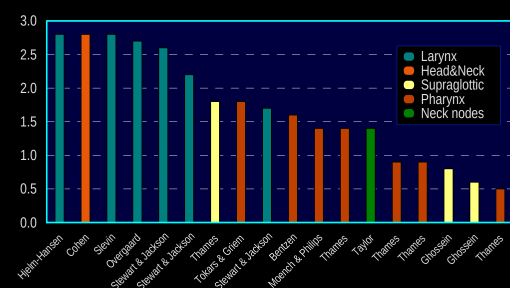
Leunens,..., van der Schueren, *R&O* 25: 242 (1992)

The normalized dose-response gradient

$$\gamma_n = D \cdot \frac{dP}{dD} \approx D \cdot \frac{\Delta P}{\Delta D} = \frac{\Delta P}{\Delta D / D}$$

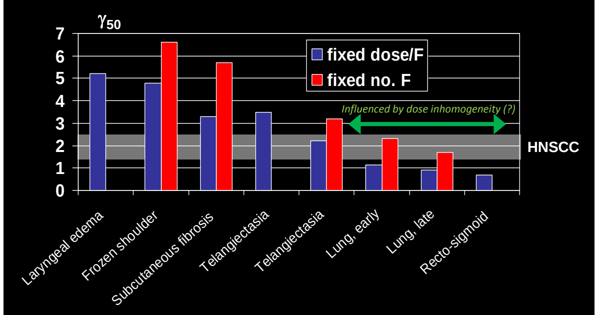


Steepness of DR curves for HNSCC



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

Steepness of normal-tissue dose-response curves

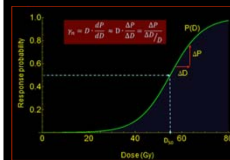


UNIVERSITY OF WISCONSIN SCHOOL OF MEDICINE AND PUBLIC HEALTH

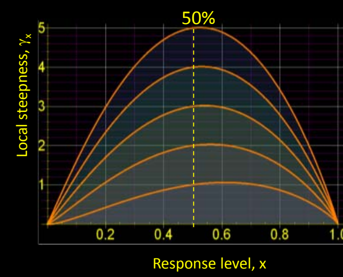
Bentzen *R&O* 32: 1 (1994)

/SMB

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 parameterized in terms of D_{50} and γ_{50}
- However, in most situations the local γ-value should be applied



School of Medicine and Public Health UNIVERSITY OF WISCONSIN-MADISON

/SMB 8/13

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 $\Longrightarrow \gamma_N = 1.5 \cdot \gamma_d$
d_r = 6 Gy $\Longrightarrow \gamma_N = 1.75 \cdot \gamma_d$

- Two asymptotic results are

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

School of Medicine and Public Health UNIVERSITY OF WISCONSIN-MADISON

Bentzen *Acta Oncol* 44: 825 (2005)

/SMB 8/13

Uncertainty components

The delivered dose can be decomposed as:

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

Effect of BIAS on outcome
$\Delta P = \gamma_x \cdot b/D_p$

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

School of Medicine and Public Health UNIVERSITY OF WISCONSIN-MADISON

Bentzen, IAEA report (in preparation)

/SMB 8/13

Estimating the clinical effect of imprecision

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

$$E(P(D)) = \tilde{P}(\sigma_\varepsilon, D_p) = \int_{-\infty}^{\infty} P(x) \cdot nd(D_p, \sigma_\varepsilon; x)\, dx$$

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

$$\Delta P(\sigma_\varepsilon, D_p) = P(D_p) - \tilde{P}(\sigma_\varepsilon, D_p)$$

The Taylor expansion of P(D) is

$$P(D) = P(D_p) + f'(D_p) \cdot (D - D_p) + \tfrac{1}{2} \cdot D''(D_p) \cdot (D - D_p)^2 + \cdots$$

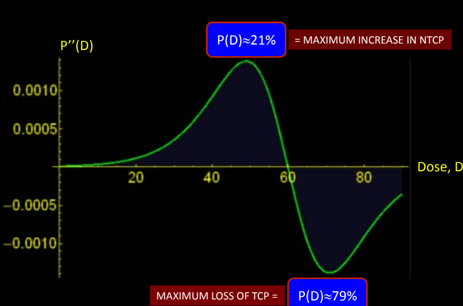
The first order term cancels out in the convolution integral due to the symmetry of the p.d.f.

School of Medicine and Public Health UNIVERSITY OF WISCONSIN-MADISON

/SMB 8/13

Second derivative of dose-response function

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

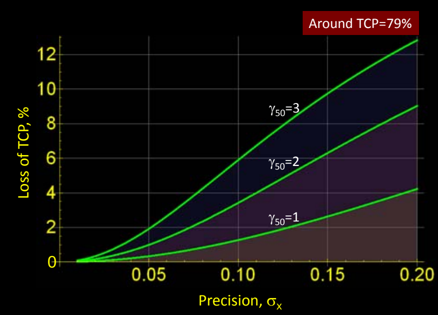


School of Medicine and Public Health UNIVERSITY OF WISCONSIN-MADISON

Bentzen, IAEA report (in preparation)

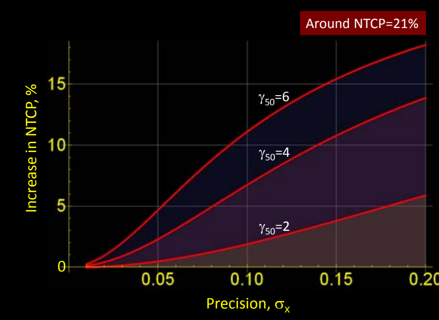
/SMB 8/13

Loss of TCP with reduced precision



School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON
/SMB 8/13

Increase in NTCP with reduced precision



School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON
/SMB 8/13

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?

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON
/SMB 8/13

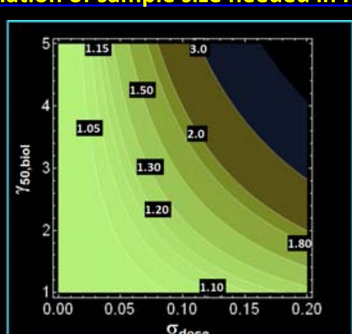
So, what's the accuracy target then?

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?
- Answer: $\gamma_{80,N}\approx 2.1$
- Accepting a maximum loss due to bias of 3% $\Longrightarrow$ bias$\lesssim$1.5%
- This caps the loss due to imprecision at 2%

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON
/SMB 8/13

Inflation of sample size needed in RCT

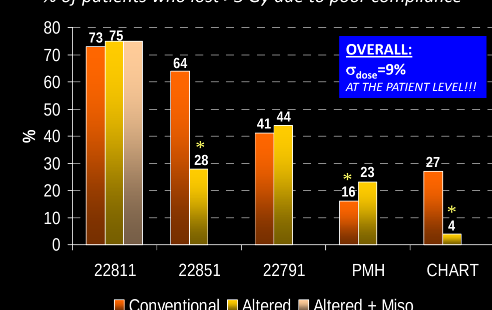


School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON
/SMB 8/13

Bentzen (in preparation)

EPILOGUE: Accuracy in a (humbling) perspective

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



UNIVERSITY OF WISCONSIN SCHOOL OF MEDICINE AND PUBLIC HEALTH

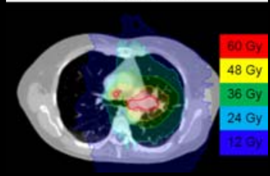
Khalil et al. *IJROBP* 55: 568 (2003)

/SMB

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%

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON

/SMB 8/13