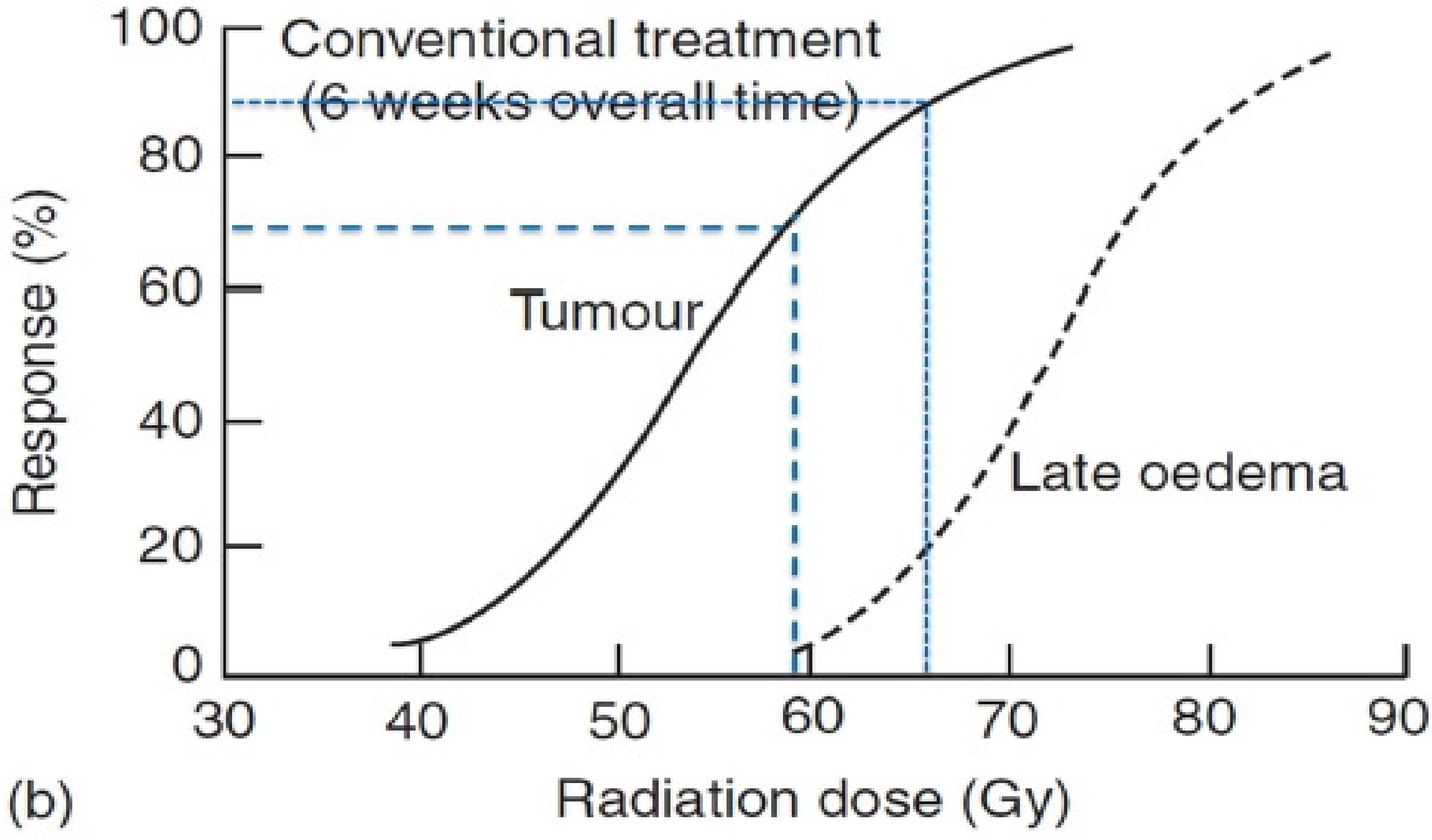
Radiotherapy:
Accuracy and uncertainties

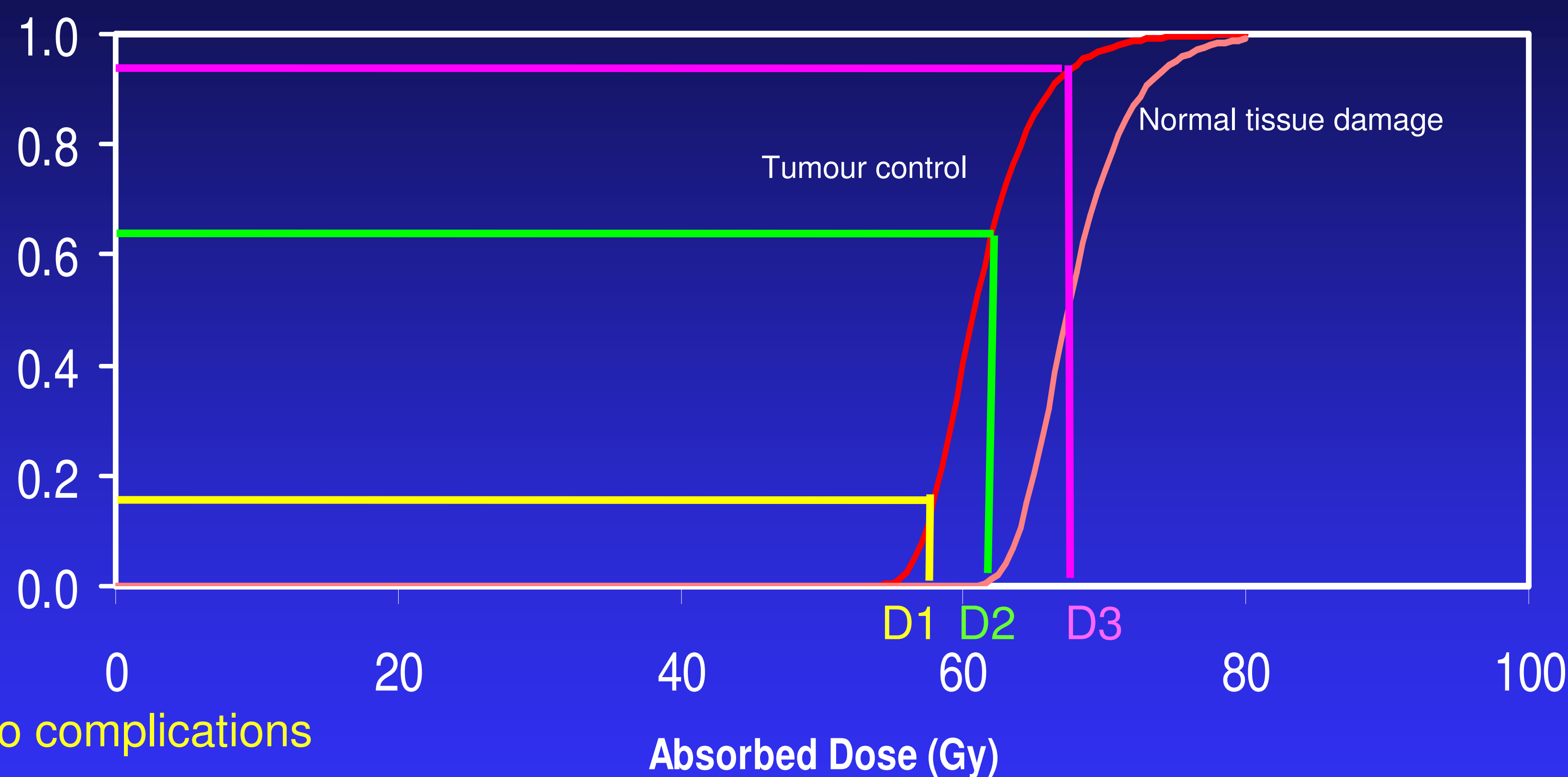
Ben Mijnheer

Tumour control vs complications



From Basic clinical radiobiology 4th Edition Van der Kogel

Tissue response vs absorbed dose



D1 = Low cures, no complications

D2 = Moderate cures, minimal complications

D3 = High cures high complications

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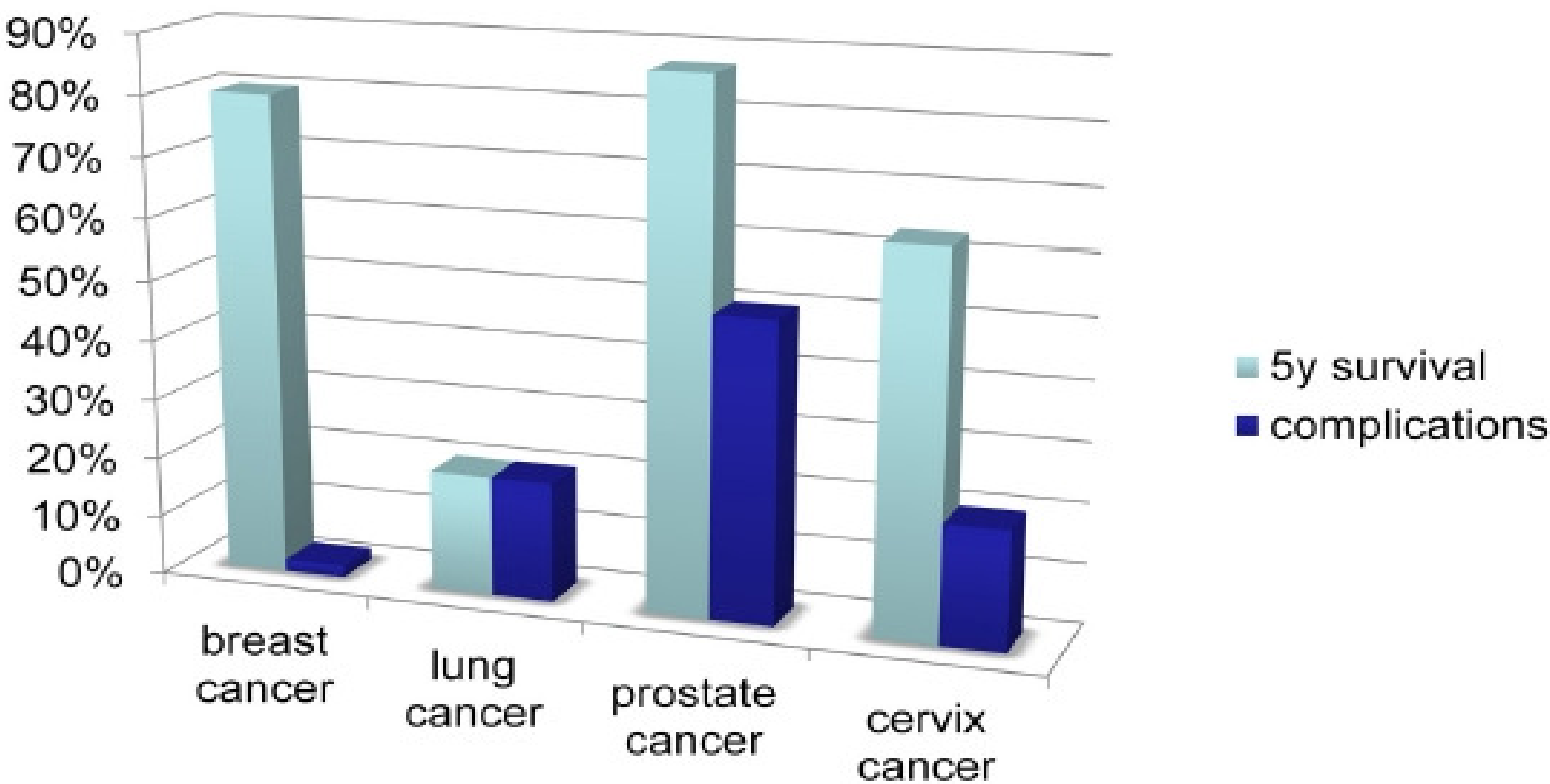
Therapeutic ratio in radical radiotherapy

- “Acceptable” complications depend on
  - Rate of complications
  - Organ concerned
  - Severity of effect
- The risk level may differ between clinicians and patients
  - Usual acceptable level is 5%
    - Lower levels are accepted for serious complications *e.g.* spinal myelitis

Clinical indications and outcome



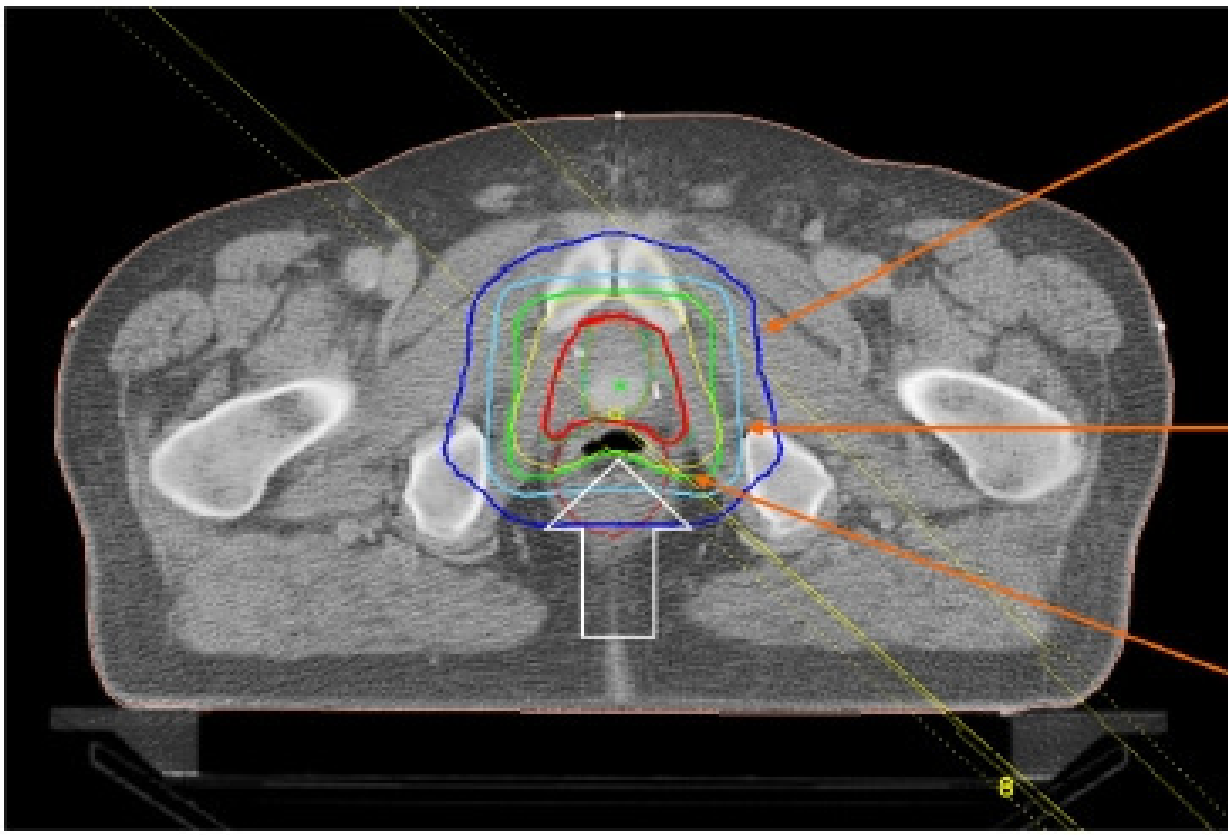
Clinical indications and outcome

- Radiation delivery can be improved to allow for higher tumour dose at no additional cost for normal tissue.

  OR

- Radiation delivery can be improved to obtain a similar tumour control at a lower cost in normal tissue tolerance.

Clinical indications and outcome

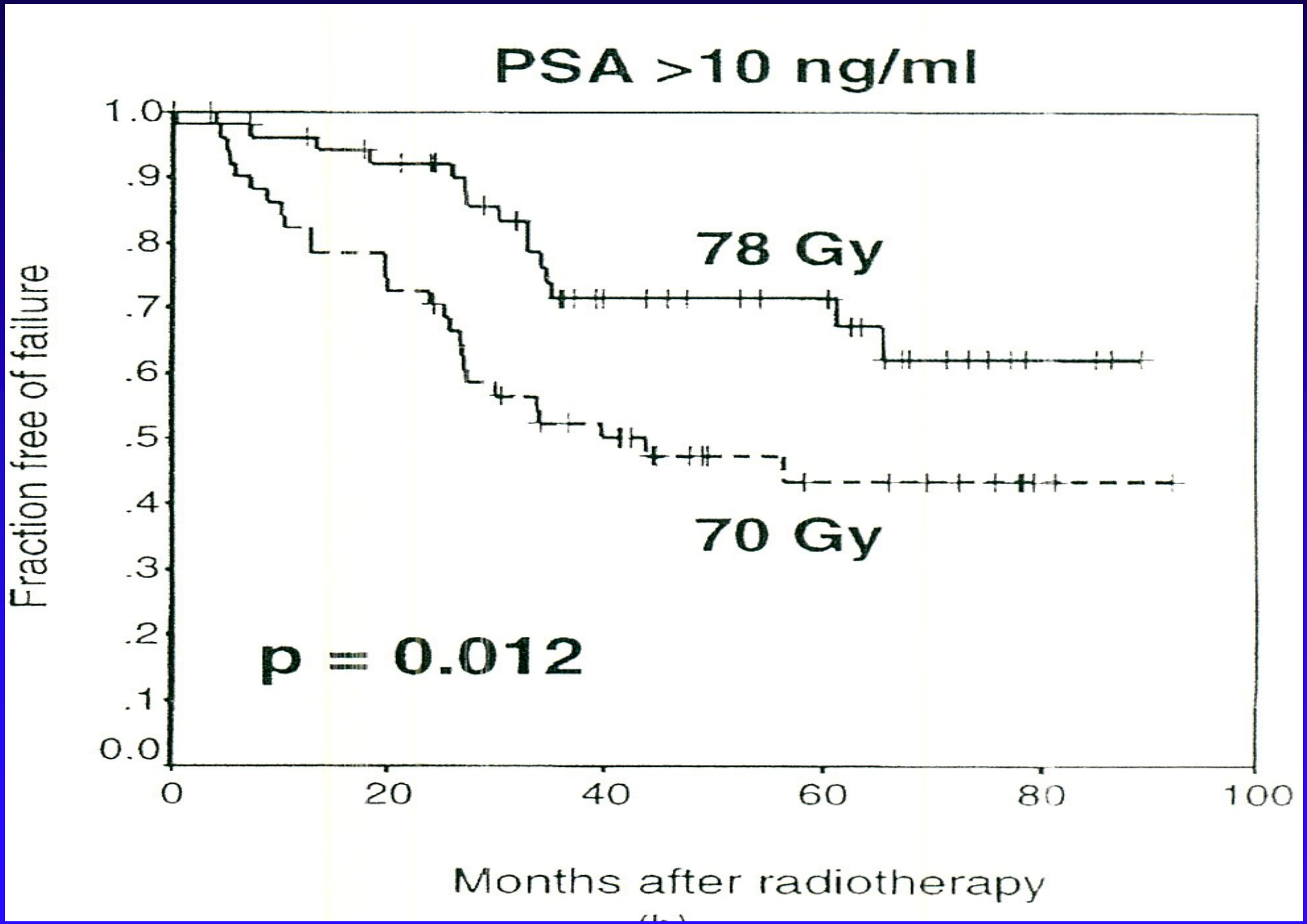


Conventional 2D
(1970 – 1993)
60 Gy

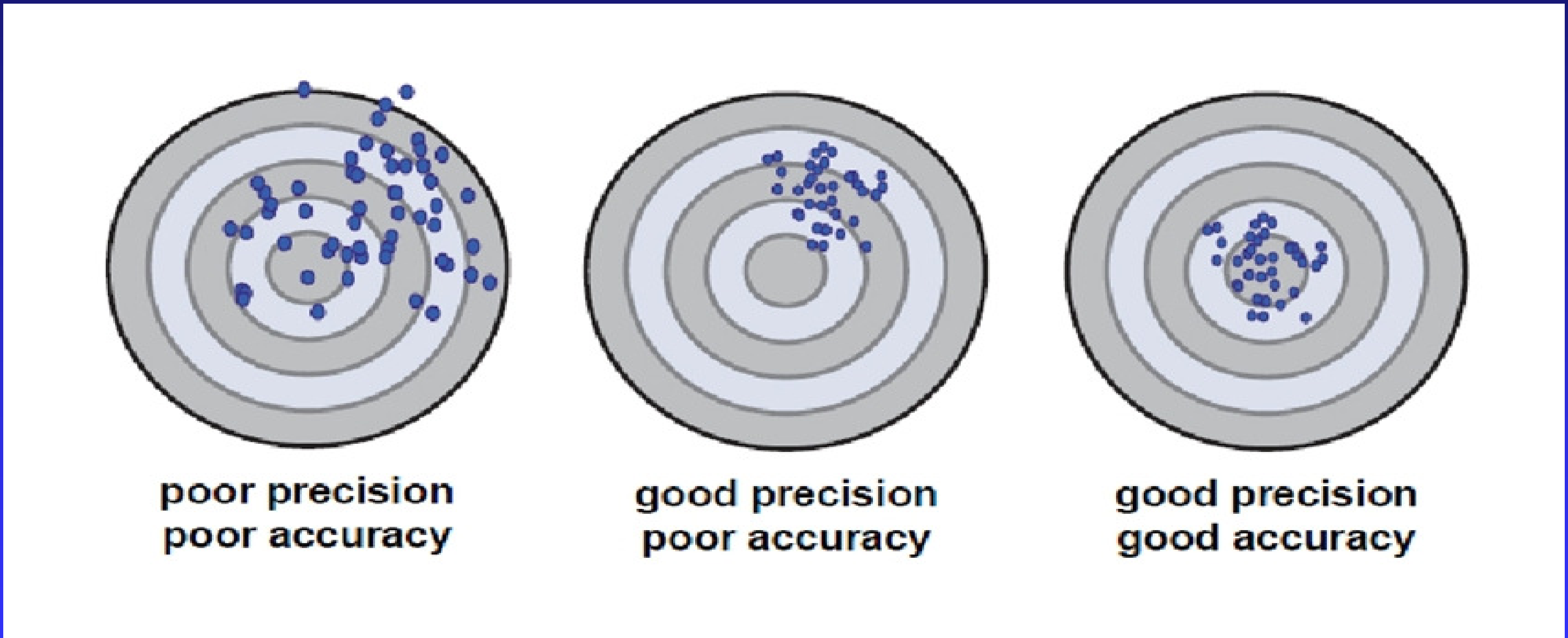
3D CRT
(1993 - 1999)
70 Gy

Segmented 3D
(2000 ⟶)
74 Gy

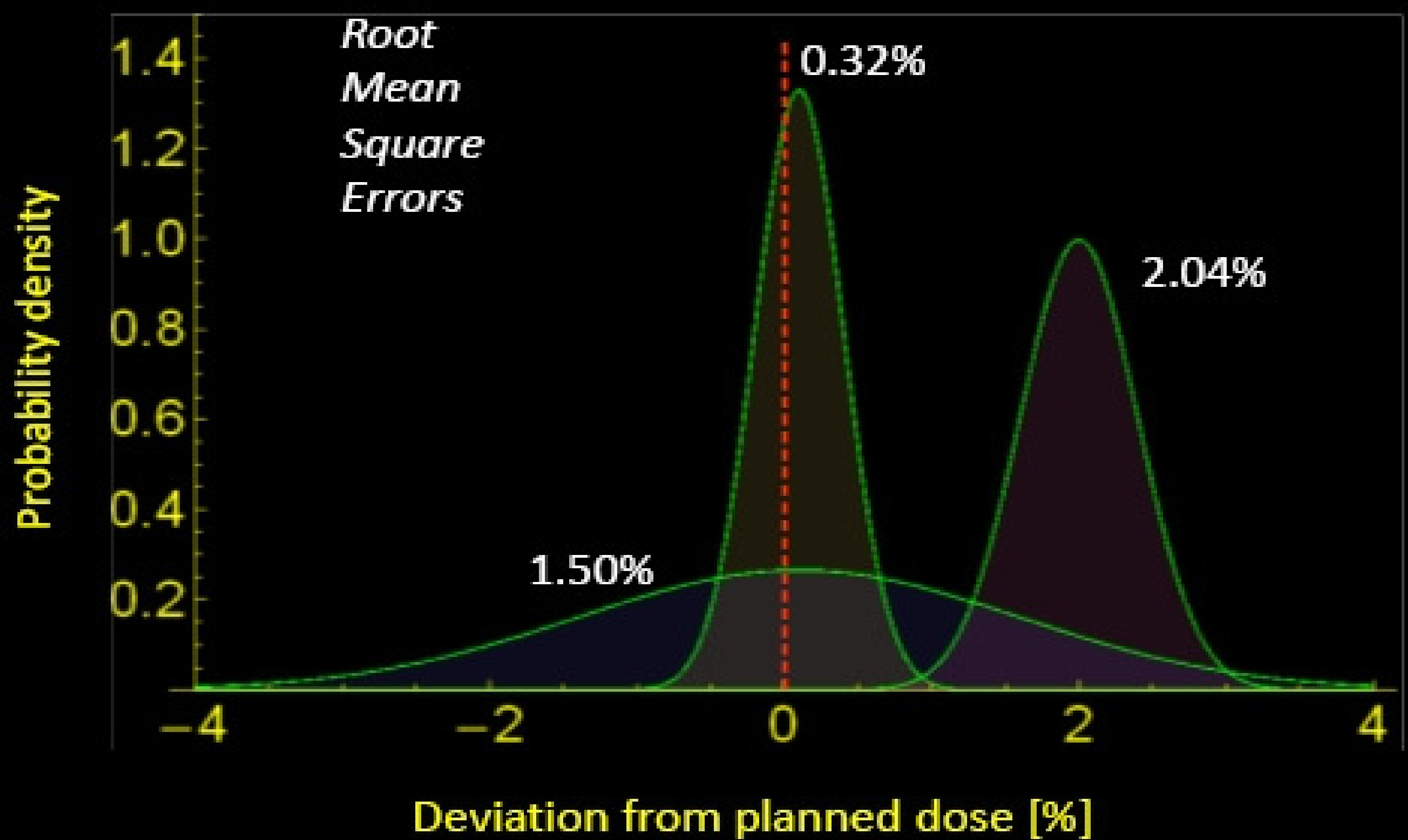
Results clinical trial prostate cancer treatment



Demonstration of the concepts "accuracy" and "precision"



Comparing radiation dose deliveries



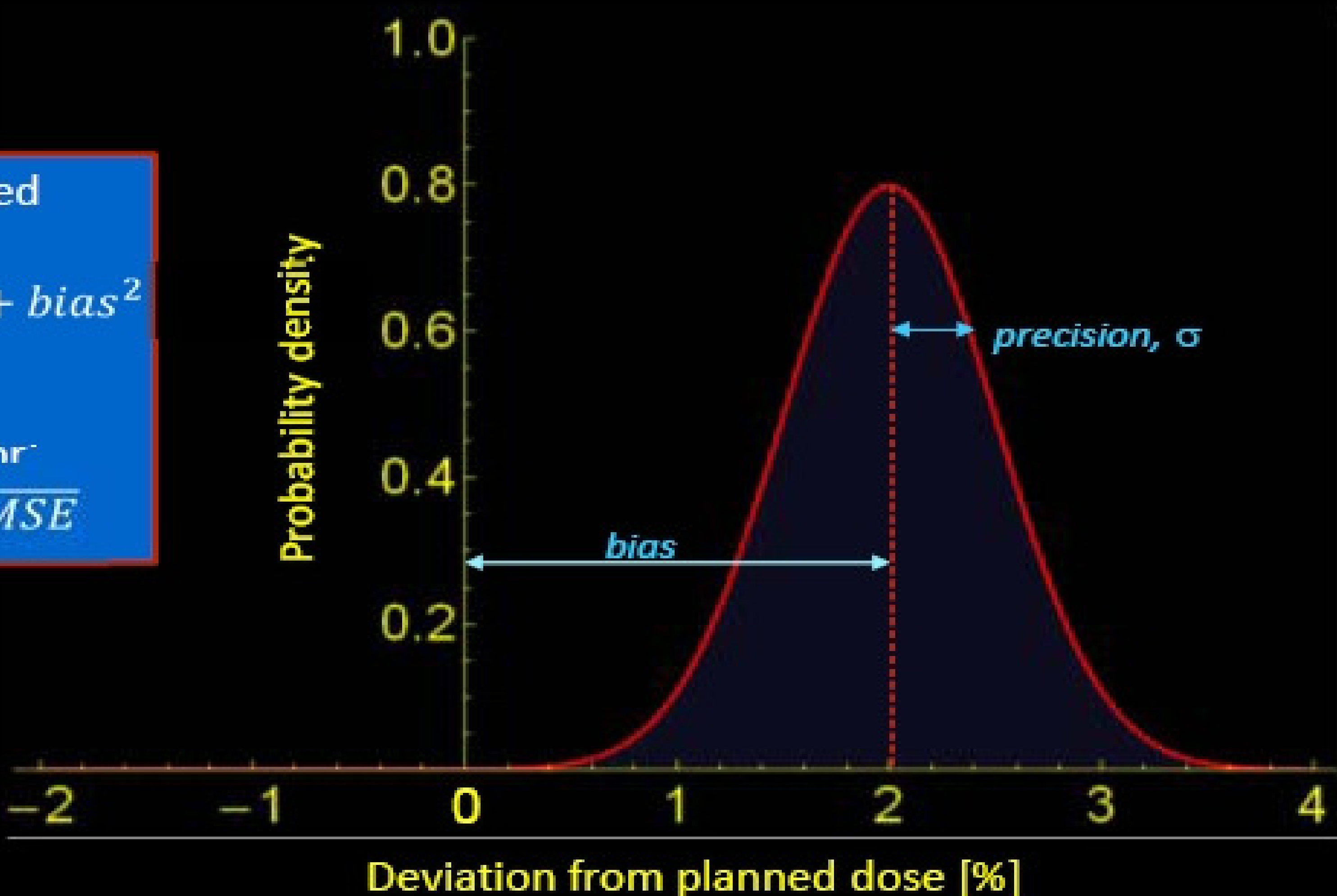
Statistics of radiation delivery

Mean Squared Error:

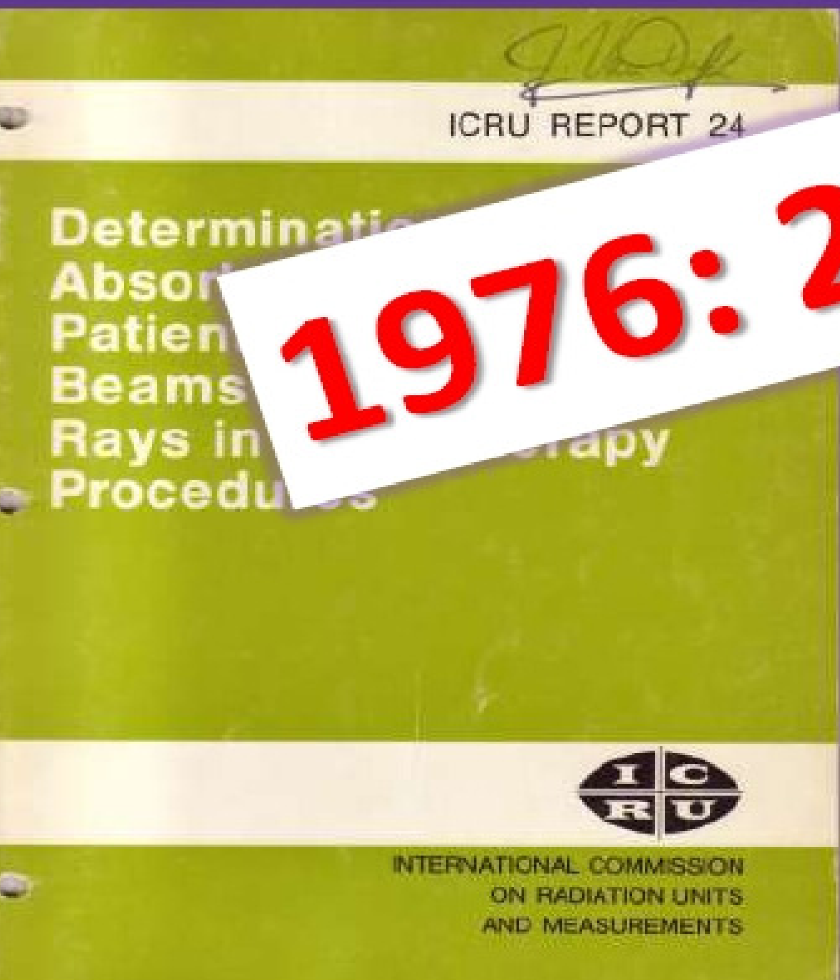
$$MSE = \sigma^2 + bias^2$$

Root Mean Squared Error:

$$RMSE = \sqrt{MSE}$$



History



1976: 2-D RT era

"… need for an accuracy of ±5% the in the delivery of an absorbed dose to a target volume …"

Accuracy requirements

Using the limited information available in 1975 on clinical dose-effect curves it was concluded in ICRU Report 24 (1976) that "although it is too early to generalize, the available evidence for certain types of tumor points to the need for an accuracy of ± 5% in the delivery of an absorbed dose to a target volume if the eradication of a the primary tumor is sought". Note that ICRU Report 24 continues: " Some clinicians have requested even closer limits such as ± 2%, but at the present time it is virtually impossible to achieve such a standard".

Clinical observations

Wambersie et al., 1974 : skin reactions after electron irradiation
ΔD = 10% in 80% of the cases
ΔD = 20% in 90% of the cases

Turesson and Notter, 1976 : skin erythema
ΔD = 7 - 10% could be measured

Dutreix, 1984 : unexpected skin reactions and diarrhoea in patients with gynaecological tumours due to an arithmetic error
ΔD = 7 - 10%

Accuracy requirements

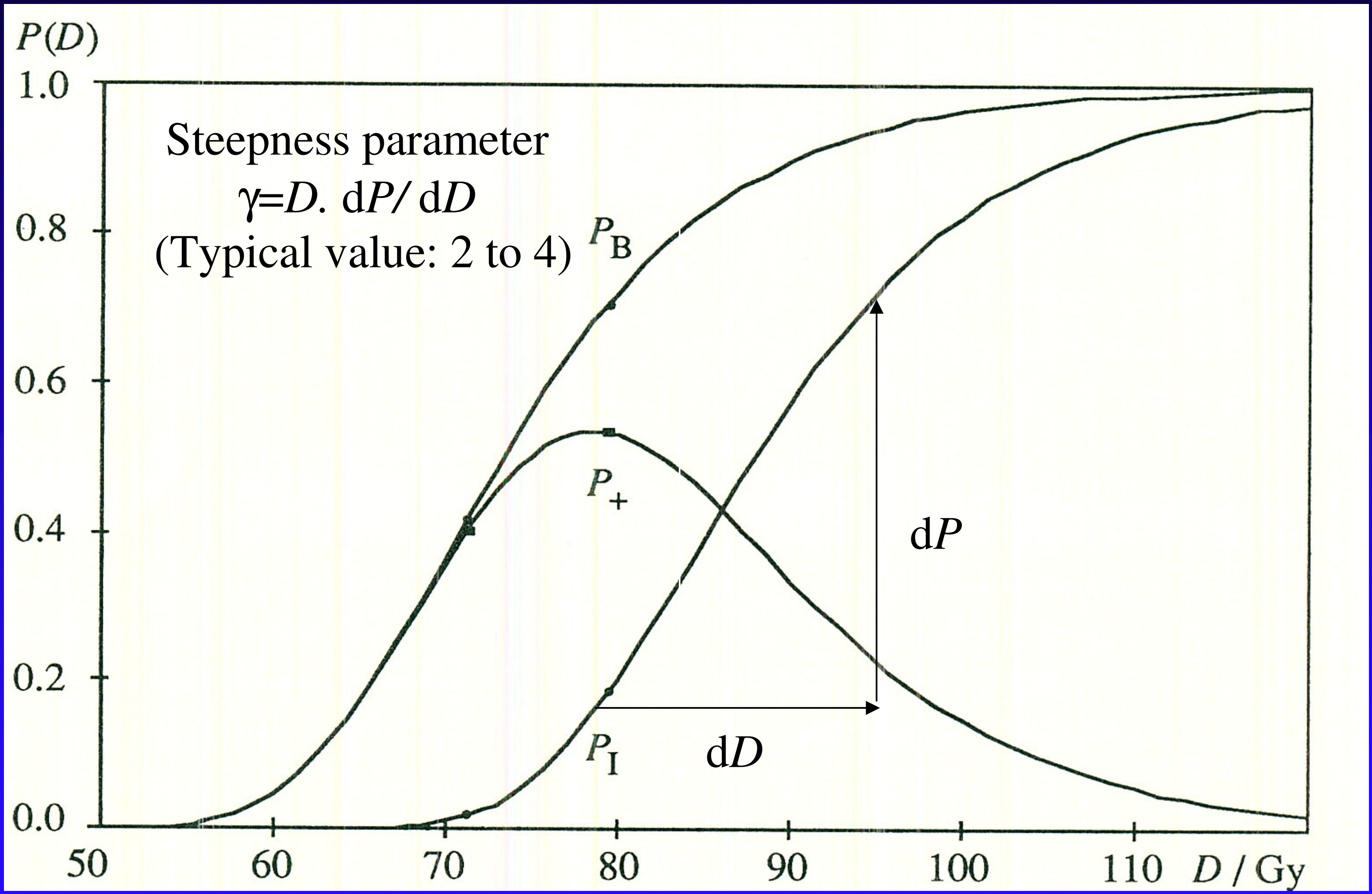
ICRU, 1976 : ± 5% (in the delivery of an absorbed dose to a target volume)

Goitein, 1983 : ± 3.5%, 1 SD (± 5% from ICRU should be considered as 1.5 standard deviation, SD)

Brahme, 1984: ± 3.3%, 1 SD (steepness of dose-effect curves)

Mijnheer et al 1986 : ± 3.5%, 1 SD (steepness of dose-effect curves and other clinical observations)

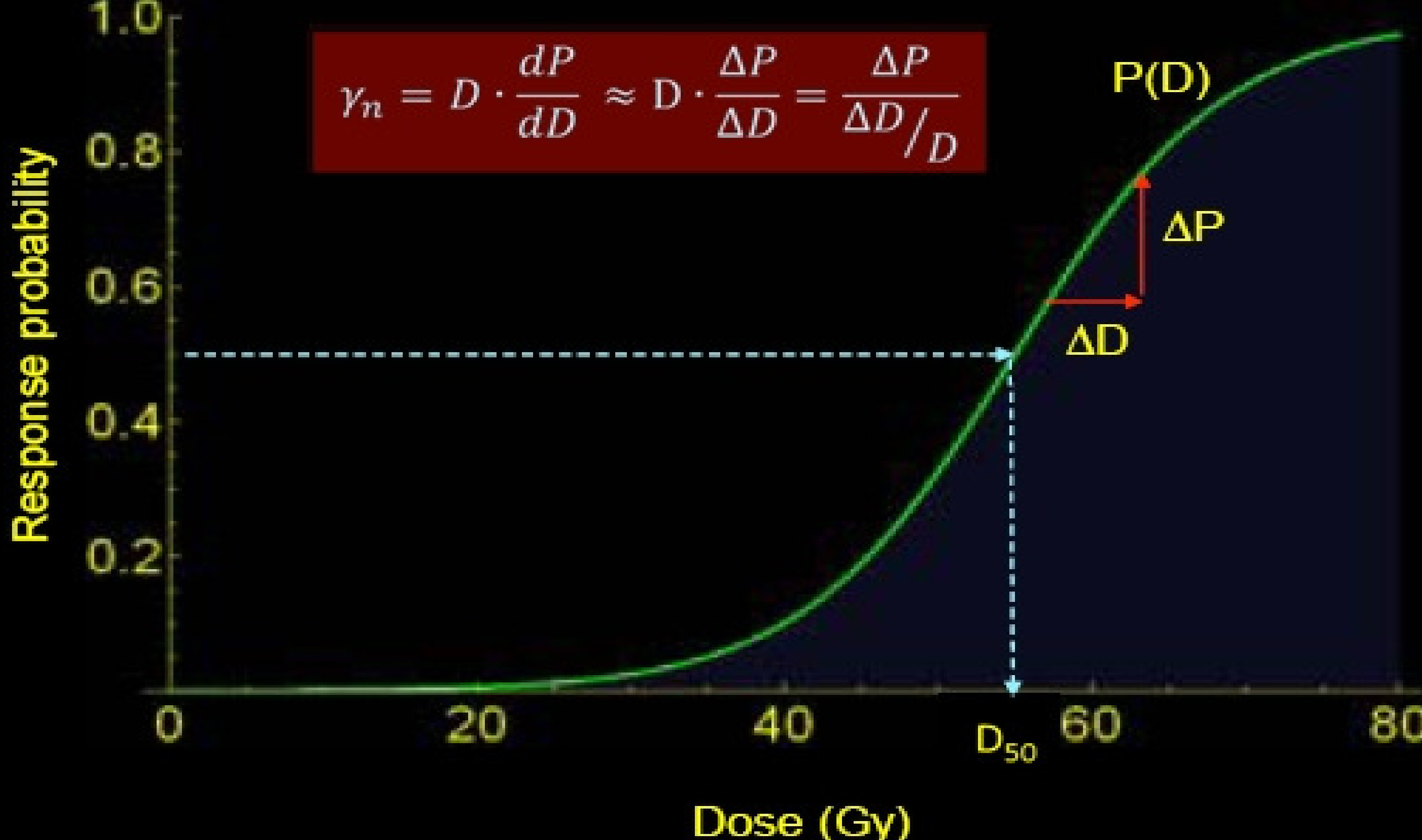
Dose-effect curves



P_B is the probability of tumour control
P_I is the probability of normal tissue complications

The normalized dose-response gradient

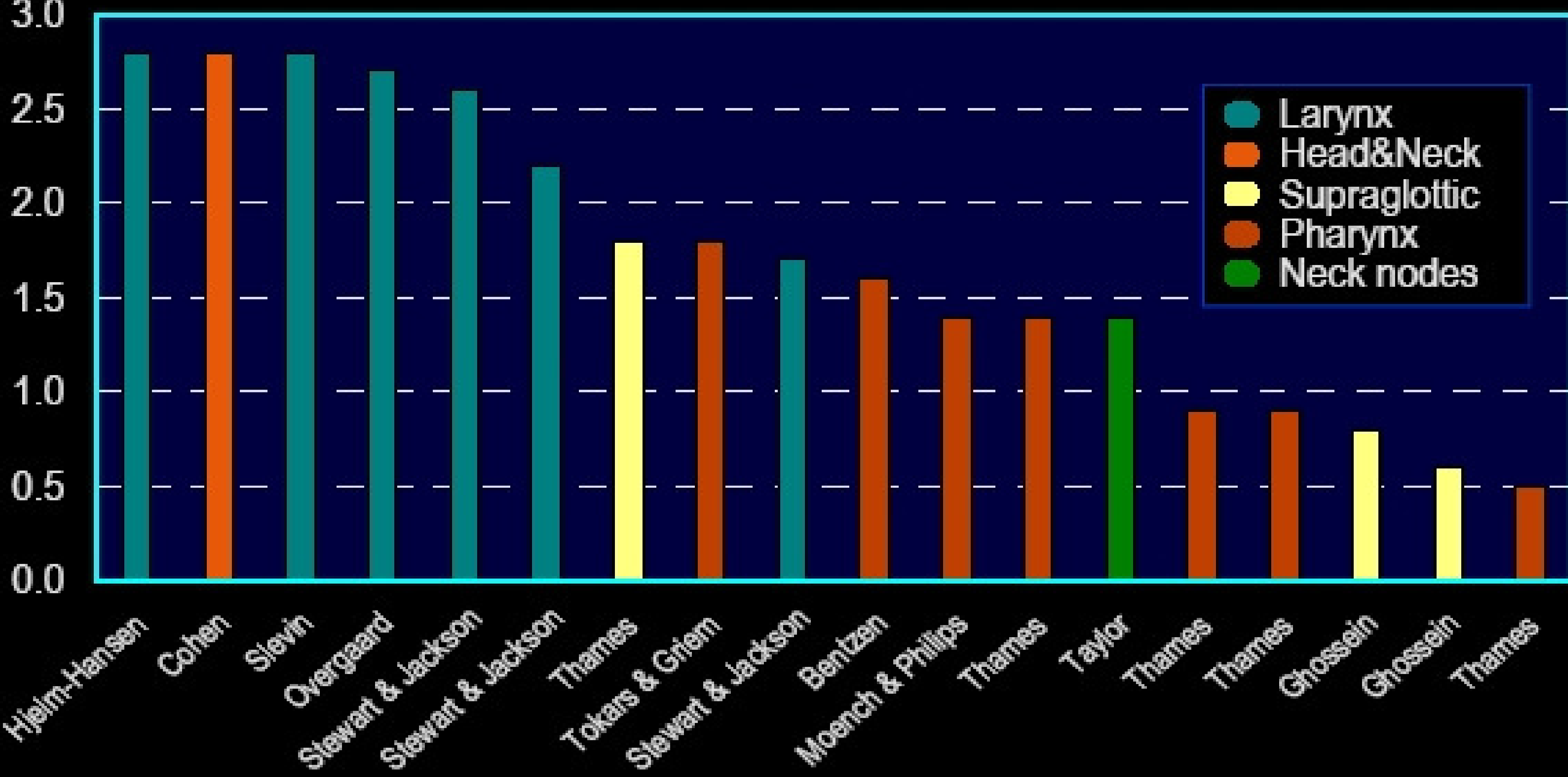
$$\gamma_n = D \cdot \frac{dP}{dD} \approx \mathrm{D} \cdot \frac{\Delta P}{\Delta D} = \frac{\Delta P}{\Delta D / D}$$



Relative steepness, expressed as the normalized dose-response gradient γ, for local tumour control

Site of tumour	Relative steepness, γ
Supraglottic larynx T_2 and T_3 (Shukofsky)	5.0
Larynx T_3 (Stewart and Jackson)	4.2
Supraglottic larynx all stages (Hjelm-Hansen et al.)	2.3
Larynx all stages (Hjelm-Hansen et al.)	2.1
Bladder T_{4B} (Battermann et al.)	1.9
Epidermoid carcinoma head and neck (Cohen)	1.9
Supraglottic larynx T_1 and T_2 (Ghossein et al.)	1.9
Skin and lip (Strandqvist)	1.5
Supraglottic larynx T_2 and T_3, revised analysis	1.5
of the Shukofksy data (Thames et al.)	1.4
Nasopharynx T_1 and T_2 (Tokars and Griem)	1.4
Nasopharynx (Moench and Philips)	1.3
Lymphoma (Fuks and Kaplan)	1.2
Retromolar trigone/anterior faucial pillar	1.2
T_1 and T_2 (Thames et al.)	
Bladder all stages (Morisson)	1.0
Base of tongue T_1 and T_3 (Thames et al.	0.8
Tonsillar forsa T_3 and T_4 (Thames et al.)	0.8
Hodgkin (Kaplan)	0.5

Steepness of DR curves for HNSCC



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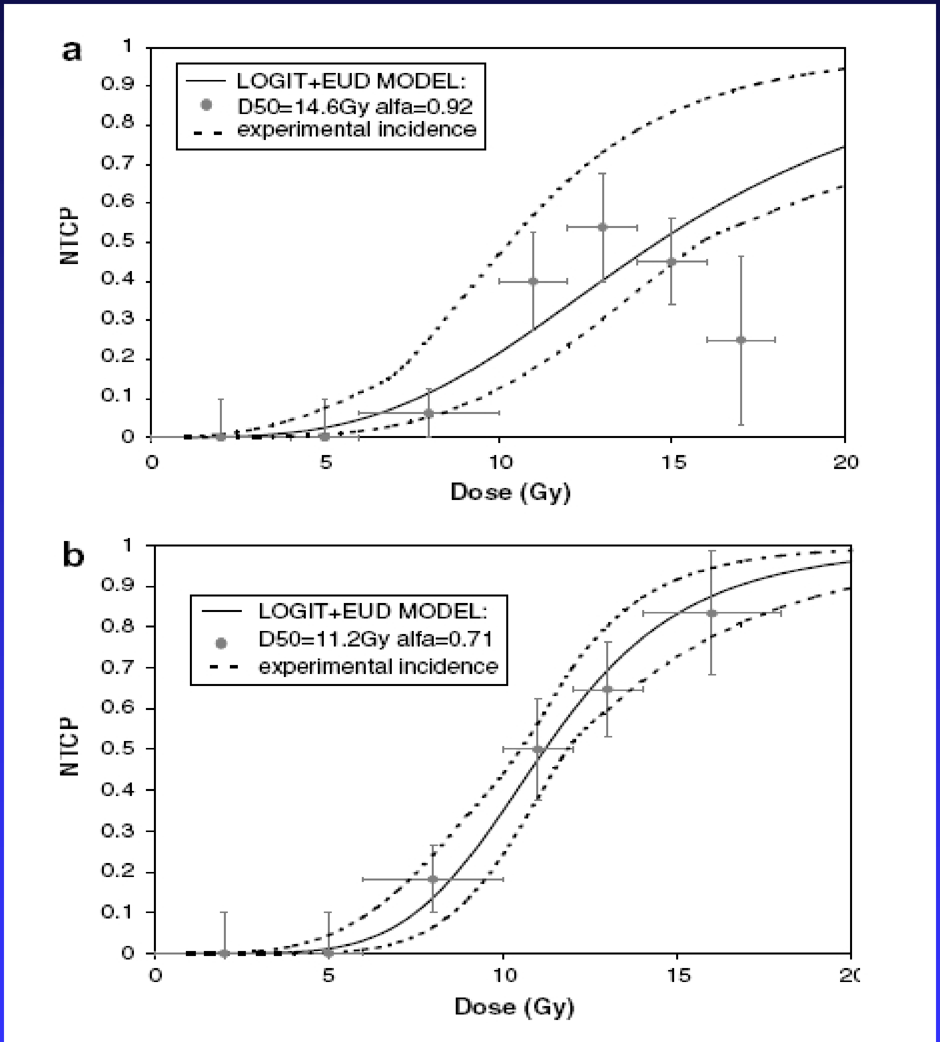
Bentzen *R&O* 32: 1 (1994)

Dose-effect curves: Incidence of pneumonitis



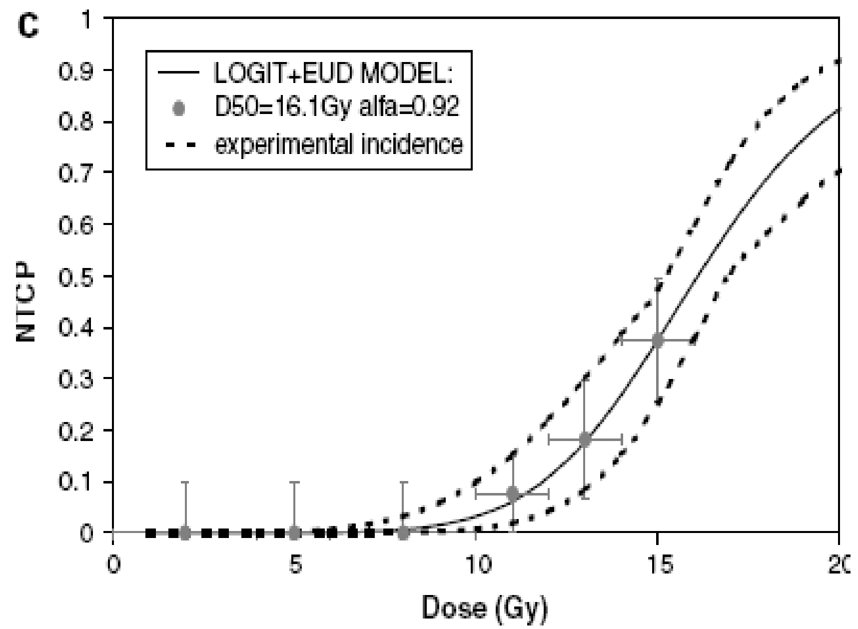
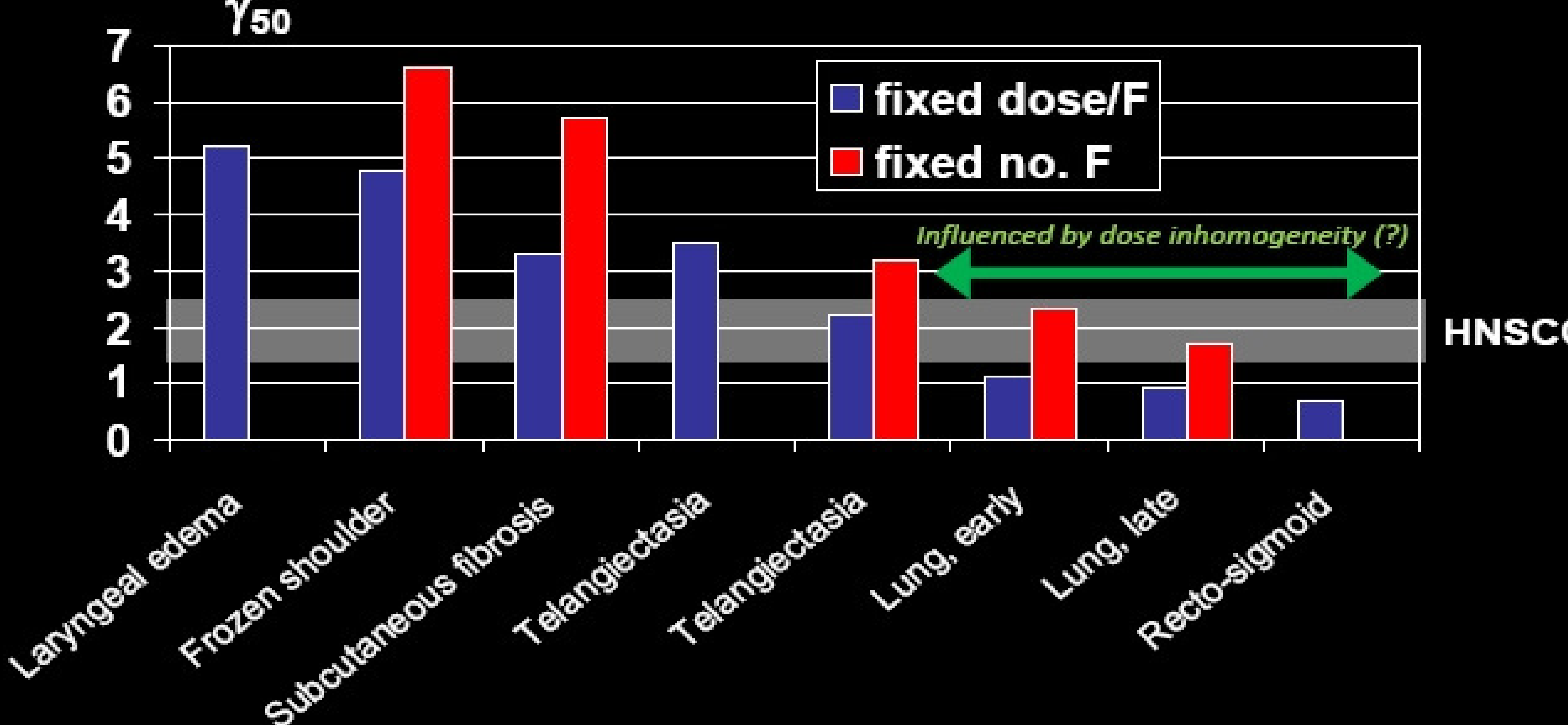


Fig. 2. (a) Incidence of clinical pneumonitis as a function of EUD for the LOGEUD model. (b) Incidence of X-ray assessed pneumonitis as a function of EUD for the LOGEUD model. (c) Incidence of CT assessed pneumonitis as a function of EUD for the LOGEUD model. In all cases observed complication rates [solid symbols] and predicted NTCP curve [continuous line, curve obtained using best estimated parameters] are plotted. The dotted lines depict the two-dimensional 68% confidence region [see the text] for the NTCP curve.

(Rancati *et al.*, Radiother. Oncol. 82: 308-316, 2007)

Steepness of normal-tissue dose-response curves



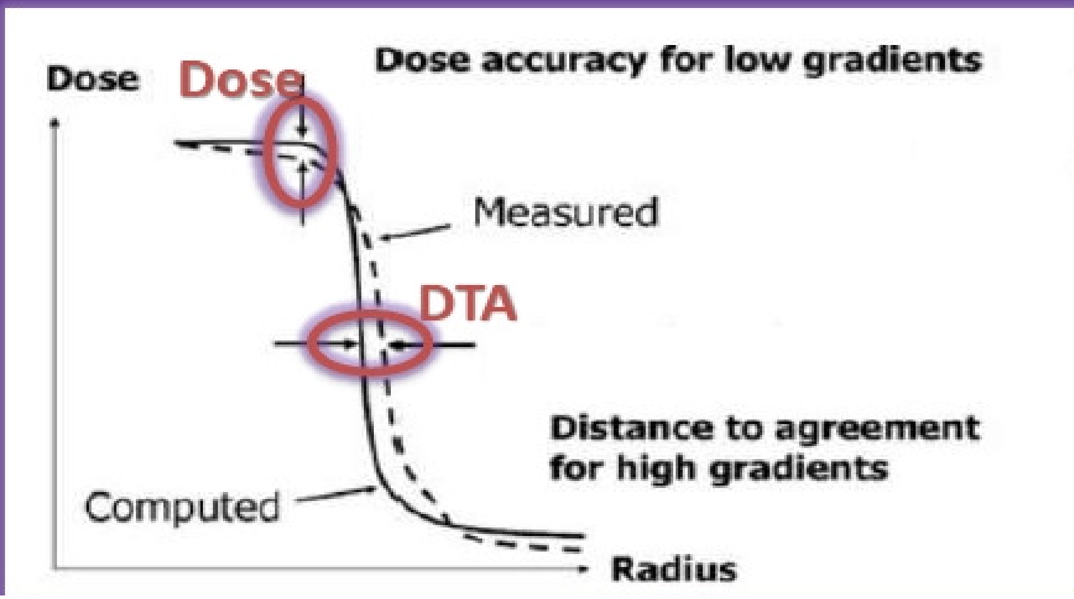
Hist

1984-2001
2-D to 3-D CRT era

- ***<u>3.5% (1 σ) at specification point and 5% at other points in PTV</u>*** for combined Type A and B uncertainties.
- This required accuracy cannot always be achieved even for simple geometries.

In 1990s …

- Added distance-to-agreement (DTA) to dose accuracy considerations
  - As part of treatment planning system (TPS) commissioning

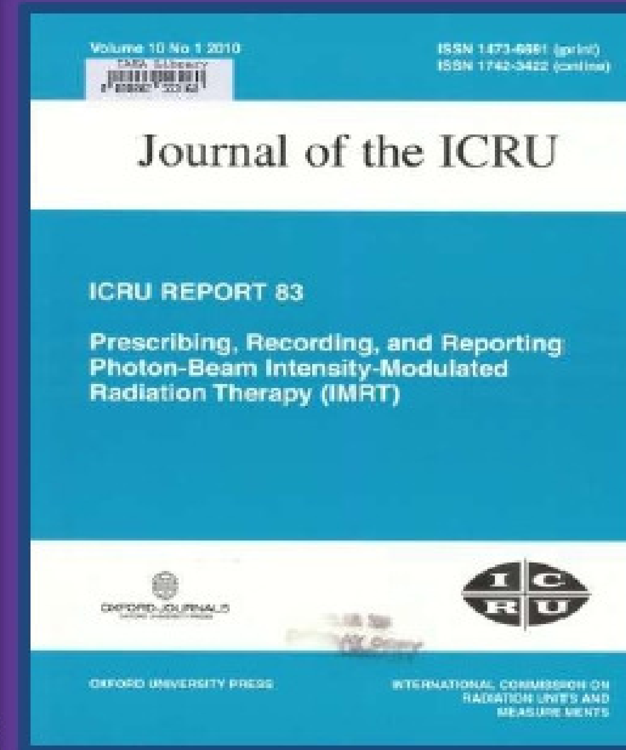


- ICRU 42 (1987) on TPSs suggested a ***goal*** of 2% in relative dose and 2 mm DTA

ICRU 83

2010

ICRU 83 – Dose Accuracy



- More statistical
- Two regions
  - Low dose gradient (<20%/cm)
    - 85% of target volume, dose within 5%
  - High dose gradient (≥20%/cm)
    - Specify distance to agreement
    - 85% of dose samples, within 5 mm

New IAEA Report

- Draft
- Under final review
- To be published in 2013/2014

Accuracy Requirements and Uncertainties in Radiation Therapy, DRAFT 2012-05-31

269 pages!
646 references!

Accuracy Requirements

and

Uncertainties

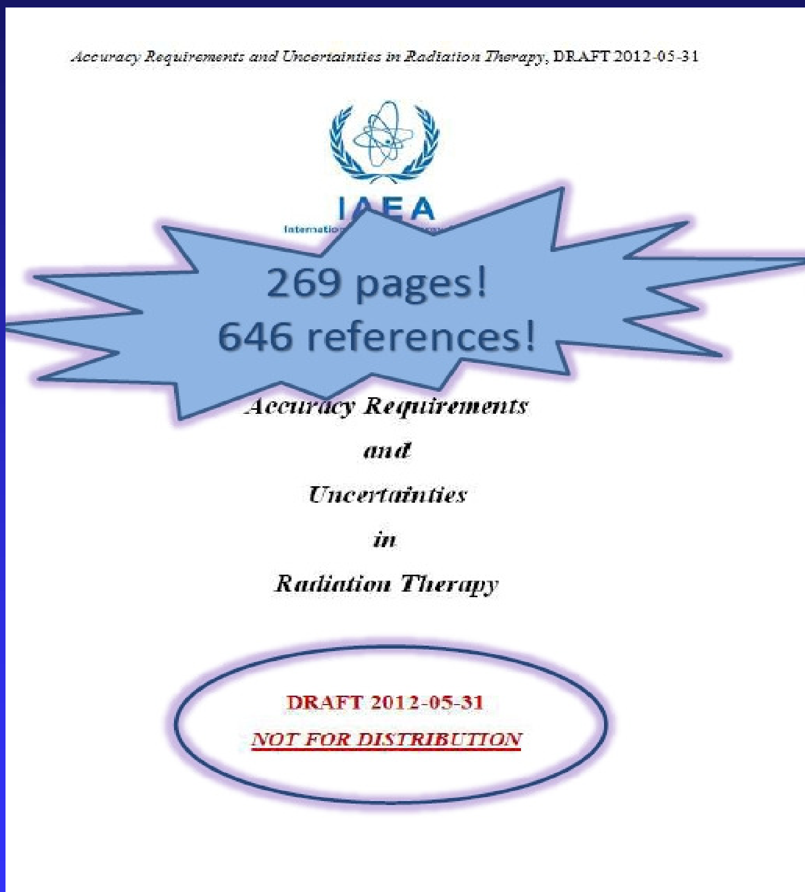
in

Radiation Therapy

DRAFT 2012-05-31

NOT FOR DISTRIBUTION

Objectives of the IAEA Report

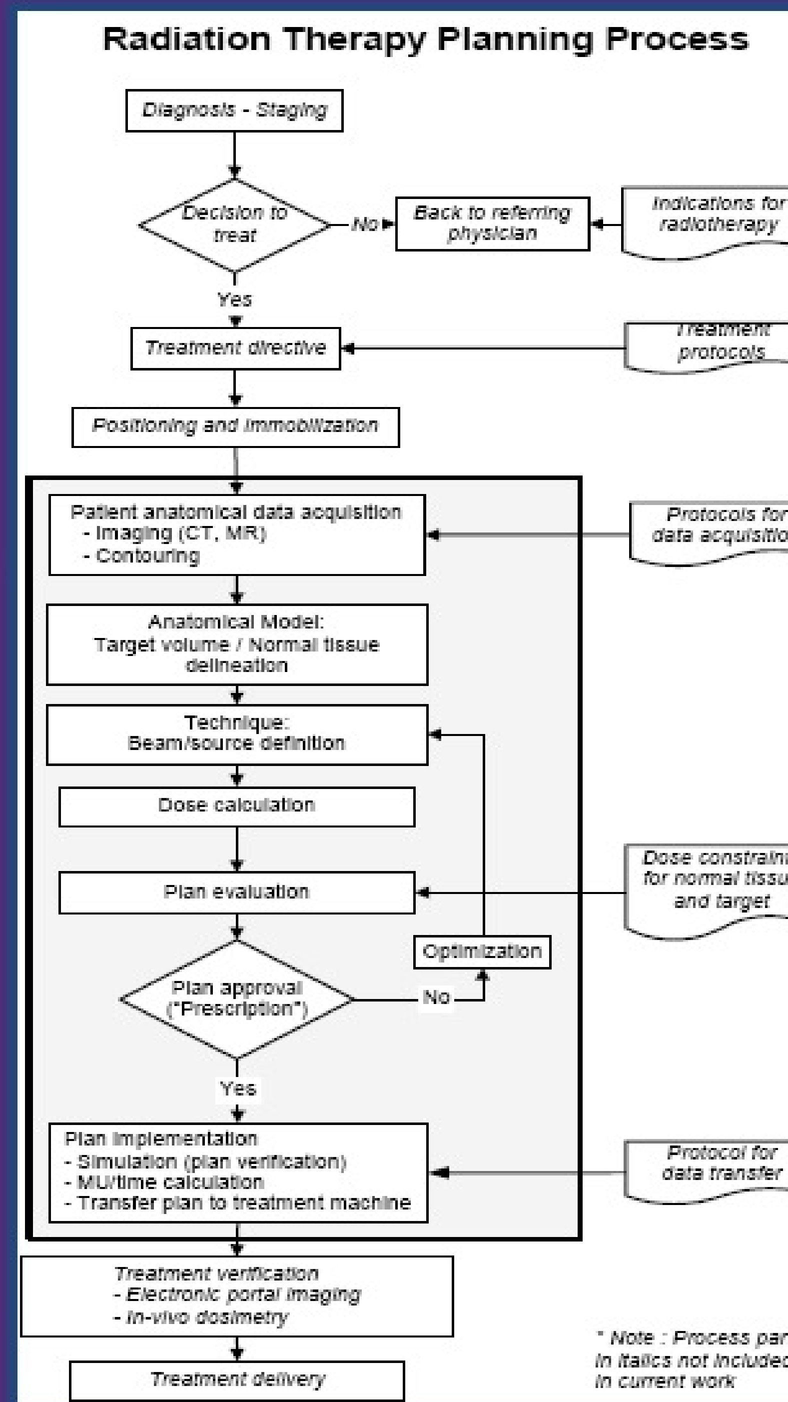


To provide a new international guidance document on accuracy requirements and uncertainties in radiation therapy in order to promote awareness and encourage quantification of uncertainties in order to promote safer and more effective patient treatments

Uncertainties in the Radiation Treatment Process

- Patient immobilization
  - Reproducibility in setup
- Imaging for treatment planning
- Definition of target volume and normal tissues
- Radiation dose measurements
  - Beam commissioning/calibrations
  - For treatment planning systems
- Dose computations
- Treatment plan optimization
  - Forward planning
  - Inverse planning
- Radiobiological considerations/prescription
- Verification imaging
- Patient treatment

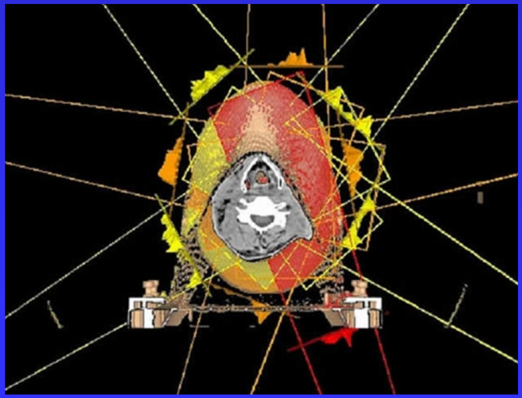
IAEA TRS 430
Fig. 1



Recommendation - 1 in the IAEA Report

- All forms of radiation therapy should be applied As Accurately As Reasonably Achievable (AAARA), technical and biological factors being taken into account

- Two-dimensional radiation therapy with minimal resources, *e.g.* a treatment of a single bone metastasis in a leg, has different accuracy considerations compared to IMRT combined with IGRT, *e.g.* a treatment of a tumour in the head-and-neck region



Uncertainties and action levels for External Beam Radiation Therapy (EBRT)

Quantity	Dose Uncertainty ($k=1$)	Spatial Uncertainty ($k=1$)	Action Level** ($\sim k=2$)
- Lung – SBRT - Breast - Abdomen - Prostate - Pelvis - Extremities*		2-5 mm 2-10 mm 5-15 mm 3-15 mm 7-15 mm 3-5 mm	+ + + + + +
EBRT end-to-end in phantom	5%	4 mm	3%/3 mm
EBRT end-to-end in patient*	5-10%	5 mm	5%/4 mm

* Expert consensus

** Action level = maximum permissible error

\+ Action levels should be determined in individual clinics dependent on the type of immobilization used.

(From the IAEA Report "Accuracy Requirements and Uncertainties in Radiation Therapy")

Uncertainties and action levels for Intensity-Modulated Radiation Therapy (IMRT)

TABLE 15. PROPOSED CONFIDENCE LIMITS AND ACTION LEVELS FOR IMRT TREATMENTS (*from Palta et al. [246]*).

Region	*Confidence Limit**	*Action Level*
High dose, low dose gradient	±3%	±5%
High dose, high dose gradient	10% or 2 mm DTA	15% or 3 mm DTA
Low dose, low dose gradient	4%	7%
Dose fall off ($d_{90-50\%}$)	2 mm DTA	3 mm DTA

* The confidence limit is defined as the sum of the average deviation and 1.96 SD. The average deviation used in the calculation of confidence limit for all regions is expressed as a percentage of the prescribed dose according to the formula: 100% x (D_{calc}-D_{meas}/$D_{prescribed}$).

(From the IAEA Report "Accuracy Requirements and Uncertainties in Radiation Therapy")

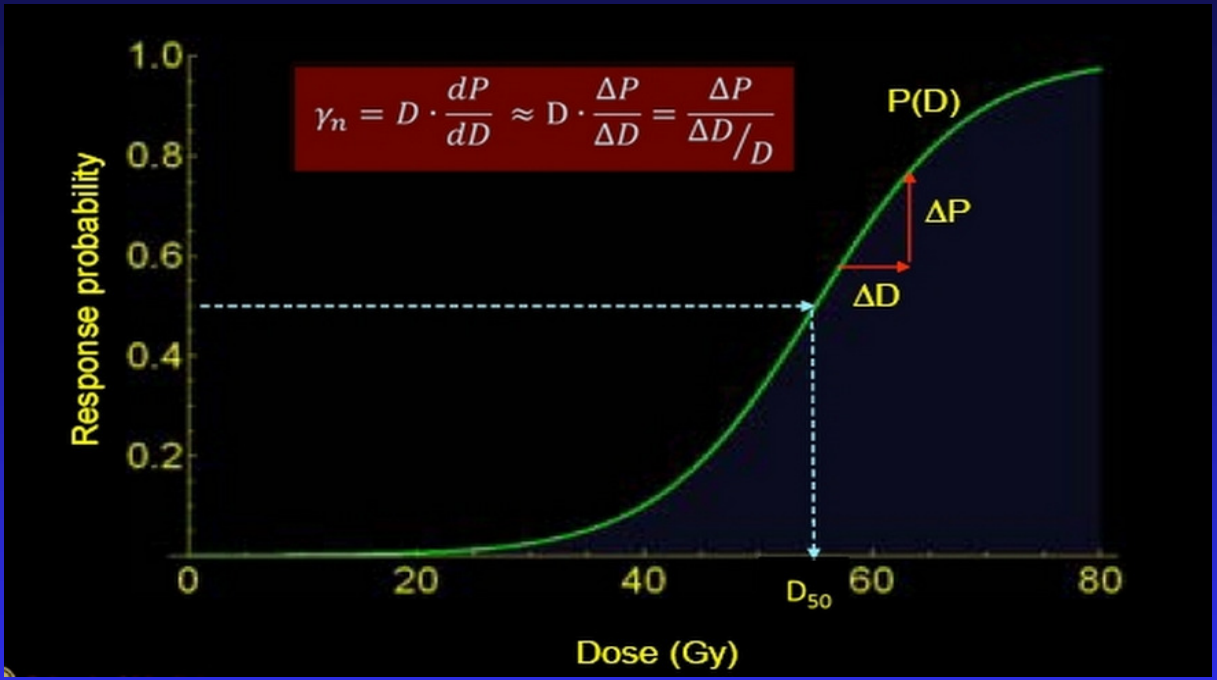
Final remarks in the IAEA Report

- A single statement about accuracy requirements in radiation therapy is an over-simplification

- The accuracy requirements are dependent on both the technological considerations as well as the biological and clinical concerns

- Ultimately, the “cost” in terms of effort, likelihood of possible complications, the possibility of a recurrence, and the impact on other patients in an environment of limited resources must be balanced against “benefit” that will be gained for the patient in terms of cure and improved quality of life.

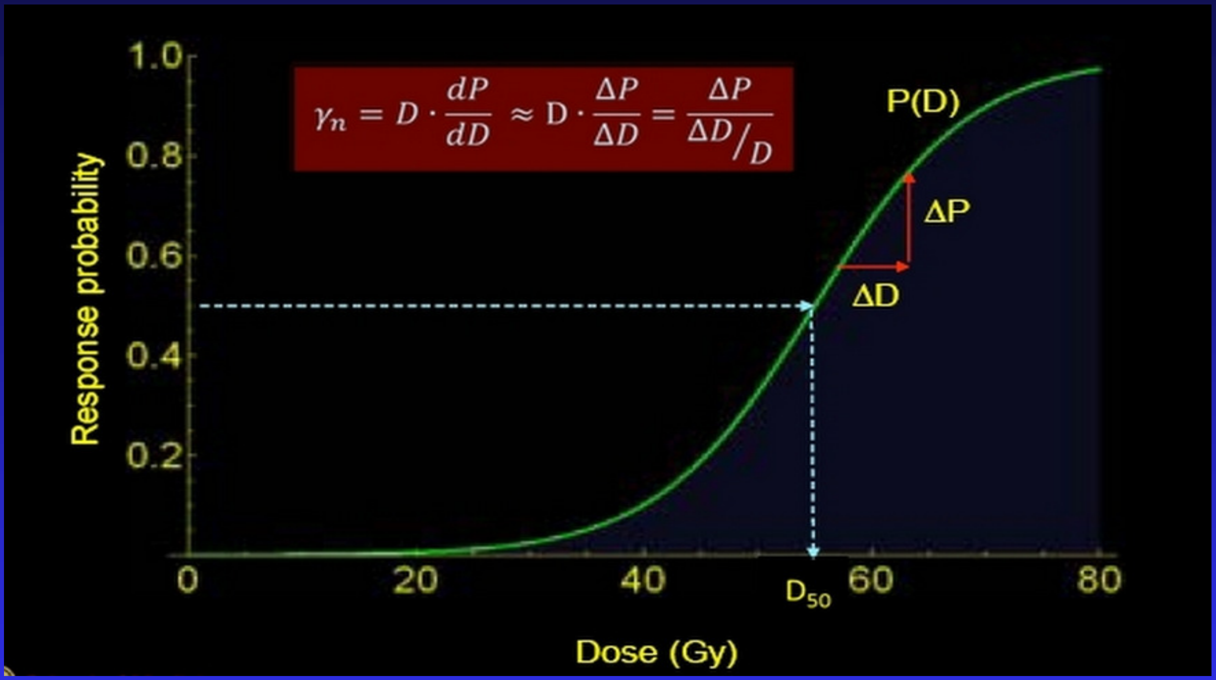
Example 1: Error in dose delivery to a tumour



- An under-dosage of 20% was discovered during the treatment of a tumour which has a slope of the dose-response curve characterised by a $\gamma_n = 1.5$

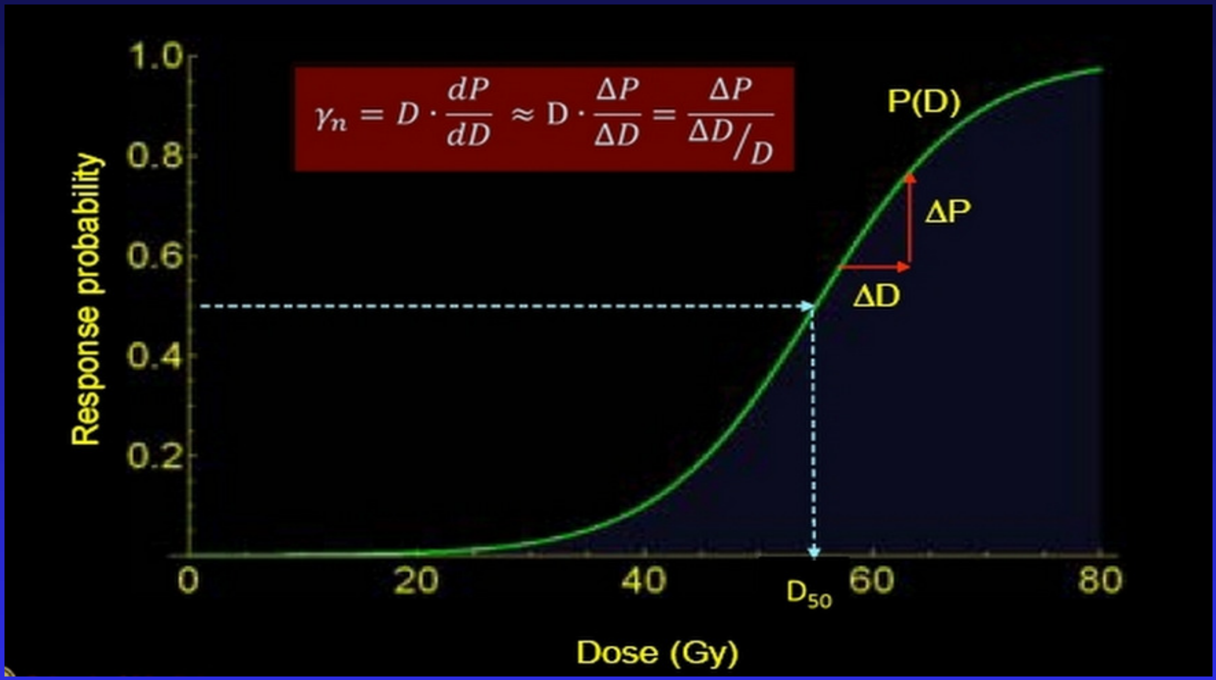
- What is the effect on the tumour control probability?

Example 2: Error in dose delivery to an organ at risk



- An over-dosage of 20% in the dose to an organ at risk was discovered during the treatment of a cancer patient
- The dose-response curve of that organ at risk has a slope with a $\gamma_n = 2.0$
- What is the effect on the normal tissue control probability?

Errors in dose delivery to a tumour or organ at risk



We will discuss actual errors as shown in these examples more extensively in my lecture on “Case histories of radiotherapy accidents & clinical consequences”, and during the group exercises

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Many thanks for your attention

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