Radiotherapy: Accuracy and uncertainties

Ben Mijnheer
Tumour control vs complications

Conventional treatment
(6 weeks overall time)

Tumour

Late oedema

Response (%)

Radiation dose (Gy)

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
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

- Breast cancer
- Lung cancer
- Prostate cancer
- Cervix cancer

5y survival
Complications
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

PSA >10 ng/ml

Fraction free of failure

78 Gy

70 Gy

p = 0.012

Months after radiotherapy
Demonstration of the concepts “accuracy” and “precision”

- Poor precision, poor accuracy
- Good precision, poor accuracy
- Good precision, good accuracy
Comparing radiation dose deliveries

- Root Mean Square Errors
  - Deviation from planned dose [%]
    - 0.32% (0)
    - 1.50% (-2.5)
    - 2.04% (2.5)
Statistics of radiation delivery

Mean Squared Error:

\[ MSE = \sigma^2 + \text{bias}^2 \]

Root Mean Squared Error:

\[ RMSE = \sqrt{MSE} \]

- Probability density
- Deviation from planned dose [%]
- Precision, \( \sigma \)
- Bias
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
\[ \Delta D = 10\% \text{ in } 80\% \text{ of the cases} \]
\[ \Delta D = 20\% \text{ in } 90\% \text{ of the cases} \]

Turesson and Notter, 1976: skin erythema
\[ \Delta D = 7 - 10\% \text{ could be measured} \]

Dutreix, 1984: unexpected skin reactions and diarrhoea in patients with gynaecological tumours due to an arithmetic error
\[ \Delta D = 7 - 10\% \]
Accuracy requirements

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

Goitein, 1983: $\pm 3.5\%, 1 \text{ SD}$ ($\pm 5\%$ from ICRU should be considered as 1.5 standard deviation, SD)

Brahme, 1984: $\pm 3.3\%, 1 \text{ SD}$ (steepness of dose-effect curves)

Mijnheer et al, 1986: $\pm 3.5\%, 1 \text{ SD}$ (steepness of dose-effect curves and other clinical observations)
Dose-effect curves

Steepness parameter
\( \gamma = D \cdot \frac{dP}{dD} \)
(Typical value: 2 to 4)

\( P_B \) is the probability of tumour control
\( P_I \) is the probability of normal tissue complications
The normalized dose-response gradient

\[ \gamma_n = D \cdot \frac{dP}{dD} \approx D \cdot \frac{\Delta P}{\Delta D} = \frac{\Delta P}{\Delta D/D} \]
### Relative steepness, expressed as the normalized dose-response gradient $\gamma$, for local tumour control

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

- Larynx
- Head & Neck
- Supraglottic
- Pharynx
- Neck nodes

Institutions and references include:
- Hjelm-Hansen
- Cohen
- Slevin
- Overgaard
- Stewart & Jackson
- Thames
- Tokars & Giem
- Stewart & Jackson
- Bentzen
- Mench & Philips
- Thames
- Taylor
- Thames
- Ghosein
- Ghosein
- Thames

Citation: 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

\[ \gamma_{50} \]

- **Fixed dose/F**
- **Fixed no. F**

Influenced by dose inhomogeneity (?)

- Laryngeal edema
- Frozen shoulder
- Subcutaneous fibrosis
- Telangiectasia
- Lung, early
- Lung, late
- Recto-sigmoid

UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Bentzen R&O 32: 1 (1994) /SMB
1984-2001
2-D to 3-D CRT era

- 3.5% (1 σ) at specification point and 5% at other points in PTV 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 – 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

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)

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

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Dose Uncertainty (k=1)</th>
<th>Spatial Uncertainty (k=1)</th>
<th>Action Level** (k=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Lung - SBRT</td>
<td></td>
<td>2-5 mm</td>
<td>+</td>
</tr>
<tr>
<td>- Breast</td>
<td></td>
<td>2-10 mm</td>
<td>+</td>
</tr>
<tr>
<td>- Abdomen</td>
<td></td>
<td>5-15 mm</td>
<td>+</td>
</tr>
<tr>
<td>- Prostate</td>
<td></td>
<td>3-15 mm</td>
<td>+</td>
</tr>
<tr>
<td>- Pelvis</td>
<td></td>
<td>7-15 mm</td>
<td>+</td>
</tr>
<tr>
<td>- Extremities*</td>
<td></td>
<td>3-5 mm</td>
<td>+</td>
</tr>
<tr>
<td><strong>EBRT end-to-end in phantom</strong></td>
<td>5%</td>
<td>4 mm</td>
<td>3%/3 mm</td>
</tr>
<tr>
<td><strong>EBRT end-to-end in patient</strong></td>
<td>5-10%</td>
<td>5 mm</td>
<td>5%/4 mm</td>
</tr>
</tbody>
</table>

* Expert consensus

**Action level = maximum permissible error

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

<table>
<thead>
<tr>
<th>Region</th>
<th>Confidence Limit*</th>
<th>Action Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose, low dose gradient</td>
<td>±3%</td>
<td>±5%</td>
</tr>
<tr>
<td>High dose, high dose gradient</td>
<td>10% or 2 mm DTA</td>
<td>15% or 3 mm DTA</td>
</tr>
<tr>
<td>Low dose, low dose gradient</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Dose fall off (d_{90-50%})</td>
<td>2 mm DTA</td>
<td>3 mm DTA</td>
</tr>
</tbody>
</table>

*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.
Many thanks for your attention

and special thanks to
Jake Van Dyk and Søren Bentzen
for borrowing some of their slides