Margins and margin recipes

Marcel van Herk

On behalf of the image guidance group

The Netherlands Cancer Institute
Amsterdam, the Netherlands
Classic radiotherapy procedure

Tattoo, align and scan patient

Align patient on machine on tattoos and treat (many days)

Draw target and plan treatment on RTP

In principle this procedure should be accurate but …
Things move: geometrical uncertainties

Organ motion: largest error in prostate RT

Baseline shift: largest error in lung RT

In the past large safety margins had to be used
Example IGRT system: Elekta Synergy

- 1997: proposed by David Jaffray and John Wong
- 2004: prototype in clinical use at NKI
- 2005: Released for clinical use worldwide
- 6 at NKI, more than 500 worldwide

Over 100,000 scans made at NKI – 200 GByte scans per week
With such a system, this is no longer needed to precisely irradiate a brain tumor.
We can use this instead: focus on patient stability, but let computer position the patient with better than one mm precision

Accuracy registration: 0.1 mm SD
Accuracy table: 0.5 mm SD
Intra-fraction motion: 0.3 mm SD

v Beek et al, in preparation
IGRT – The good, the bad, and the ugly

- **Good**: IGRT gives unprecedented precision of hitting any *clearly defined* point in the body

- **Bad**: This precision may give us overconfidence in the total chain accuracy: *tumors are rarely clear*

- **Ugly**: we may have to find this out from our clinical mistakes
Nomenclature

- **Gross error**: mistakes, transcription errors, software faults:
  - must be caught by QA

- **Error**: difference between planned value and its true value during treatment, however small

- **Uncertainty**: the fact that unpredictable errors occur – quantified by standard deviations

- **Variation**: the fact that predictable or periodic errors occur
EPID dosimetry QA to catch gross errors: used for all curative patients at NKI

Reconstructed EPID dose (VMAT case)

EPID movie

Gantry = -138

-140°  140°

Precision: within few %, enough to catch gross errors

Mans et al, 2010
Gross errors detected in NKI

0.4% of treatments show a gross error (>10% dose)

9 out of 17 errors would not have been detected pre-treatment!!

Mans et al, 2010
What happens in the other 99.6%?

- There are many small unavoidable errors (mm size) in all steps of radiotherapy
  - In some cases many of these small errors point in the same direction
  - I.e., in some patients large (cm) errors occur(ed)

- This is not a fault, this is purely statistics

- What effect does this have on treatment?
  - We do not really know!
Motion counts? Prostate trial data (1996)

N=185 (42 risk+)

N=168 (52 risk+)

Risk+: initial full rectum, later diarrhea

Heemsbergen et al, IJROBP 2007
The major uncertainties not solved by IGRT

- Target volume definition
  - GTV consistency
  - GTV accuracy
  - CTV: microscopic spread

- Inadequacy of surrogate used for IGRT

- Motion that cannot be corrected
  - Too fast
  - Too complex
Delineation variation: CT versus CT + PET

CT (T2N2)
SD 7.5 mm

CT + PET (T2N1)
SD 3.5 mm

Consistency is imperative to gather clinical evidence!

Steenbakkers et al, IJROBP 2005
Effect of training and peer collaboration on target volume definition

Material collected during ESTRO teaching course on target volume delineation
Glioma delineation variation (Beijing 2008)

<table>
<thead>
<tr>
<th></th>
<th>SD (mm)</th>
<th>SD (mm) outliers removed</th>
<th>Margin (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homework</td>
<td>3.6</td>
<td>2.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Groups</td>
<td>1.3</td>
<td>1.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Validation</td>
<td>2.6</td>
<td>2.3</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Delineation uncertainty is a systematic error that should be incorporated in the margin. Consistency is imperative to gather clinical evidence.
Other remaining uncertainties

- Is the surrogate appropriate?
Are prostate markers perfect?

Apex
Base
Sem. Vesicles

→ +/-1 cm margin required

Best: combine markers with low dose CBCT

van der Wielen, IJROBP 2008
Smitsmans, IJROBP 2010
Intra-fraction motion: CBCT during VMAT
Intra-fraction motion: CBCT during VMAT

This amount of intra-fraction motion is rare for lung SBRT.
Error distributions

- Central limit theorem:
  - the distribution of the sum of an increasing number of errors with arbitrary distribution will approach a Normal (Gaussian) distribution

- Large errors happen sometimes if all or most of the small sub-errors are in the same direction

- Normal distribution:
  - mean = 0
  - s.d. = 1
  - N = 10000
  - -2..2 = 95%
Definitions (sloppy)

- CTV: Clinical Target Volume
  The region that needs to be treated (visible plus suspected tumor)

- PTV: Planning Target Volume
  The region that is given a high dose to allow for errors in the position of the CTV

- PTV margin: distance between CTV and PTV

- Don’t use ITV for external beam! (SD adds quadratically)
Time-scales for errors

• Compare $X_{\text{planned}}$ with $X_{\text{actual}}$

• $X_{\text{planned}} - X_{\text{actual}} = \varepsilon_{\text{group}} + \varepsilon_{\text{patient, group}} + \varepsilon_{\text{fraction, patient, group}}$

• The appropriate average of each $\varepsilon$ is zero $\rightarrow$

$X_{\text{planned}} - X_{\text{actual}} = M_g +/- \sigma_g +/- \sigma_p +/- \sigma_f$
# The nomenclature hell

<table>
<thead>
<tr>
<th>Proposed to ICRU</th>
<th>Bel et al.</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_g$</td>
<td>Mean group error</td>
<td>$M$ Mean group error bias (fraction) Systematic error</td>
</tr>
<tr>
<td>$\sigma_g$</td>
<td>Intra-group uncertainty</td>
<td>$\Sigma$ Inter-patient uncertainty</td>
</tr>
<tr>
<td>$\sigma_p$</td>
<td>Intra-patient uncertainty</td>
<td>$\sigma$ Inter-fraction uncertainty (fraction) Random error</td>
</tr>
<tr>
<td>$\sigma_f$</td>
<td>Intra-fraction uncertainty</td>
<td></td>
</tr>
</tbody>
</table>
Analysis of uncertainties
Keep the measurement sign!

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction 1</td>
<td>0.5</td>
<td>0.0</td>
<td>0.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Fraction 2</td>
<td>0.6</td>
<td>-0.5</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Fraction 3</td>
<td>0.9</td>
<td>0.2</td>
<td>0.2</td>
<td>-0.4</td>
</tr>
<tr>
<td>Fraction 4</td>
<td>1.3</td>
<td>-1.1</td>
<td>0.3</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

| Mean       | 0.8       | -0.4      | 0.3       | 0.1       |
| SD         | 0.3       | 0.6       | 0.1       | 0.5       |

\[ M = \text{mean group error (equipment)} \]
\[ \Sigma = \text{standard deviation of the inter-patient error} \]
\[ \sigma = \text{standard deviation of the inter-fraction error} \]
\[ \sigma_f = \text{standard deviation of the intra-fraction motion} \]

van Herk et al, Sem Rad Onc 2004
Demonstration – errors in RT

- Margin between CTV and PTV: 10 mm

- Errors:
  - Setup error:
    - 4 mm SD (x, y)
  - Organ motion:
    - 3 mm SD (x, y)
    - 10 mm respiration
  - Delineation error: optional
What is the effect of geometrical errors on the CTV dose?

Random: Breathing, intrafraction motion, IGRT inaccuracy

Systematic: delineation, intrafraction motion, IGRT inaccuracy
Analysis of CTV dose probability

• Blur planned dose distribution with all execution (random) errors to estimate the cumulative dose distribution

• For a given dose level:
  - Find region of space where the cumulative dose exceeds the given level
  - Compute probability that the CTV is in this region
Computation of the dose probability for a small CTV in 1D

In the cumulative (blurred) dose, find where the dose > 95%

..and compute the probability that the average CTV position is in this area
What should the margin be?

Typical prostate uncertainties with bone-based setup verification
Simplified PTV margin recipe for dose - probability

To cover the CTV for 90% of the patients with the 95% isodose (analytical solution):

$$ \text{PTV margin} = 2.5 \sum + 0.7 \sigma $$

$\sum =$ quadratic sum of SD of all preparation (systematic) errors
$\sigma =$ quadratic sum of SD of all execution (random) errors

(van Herk et al, IJROBP 47: 1121-1135, 2000)

*For a big CTV with smooth shape, penumbra 5 mm*
2.5Σ + 0.7σ is a simplification

- Dose gradients (‘penumbra’ = \( σ_p \)) very shallow in lung \( → \) smaller margins for random errors

\[
M = 2.5Σ + 1.64\sqrt{(σ_p^2 + σ^2)} - 1.64σ_p^2
\]

- Number of fractions is small in hypofractionation
  - Residual mean of random error gives systematic error
  - Beam on time long \( → \) respiration causes dose blurring

- If dose prescription is at 80% instead of 95%:

\[
M = 2.5Σ + 0.84\sqrt{(σ_p^2 + σ^2)} - 0.84σ_p^2
\]

(van Herk et al, IJROBP 47: 1121-1135, 2000)
Practical examples
Prostate: $2.5 \sum + 0.7 \sigma$

<table>
<thead>
<tr>
<th></th>
<th>systematic errors</th>
<th>squared</th>
<th>random errors</th>
<th>squared</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>delineation</td>
<td>0.25</td>
<td>0.0625</td>
<td>0</td>
<td>0</td>
<td>Rasch et al, Sem. RO 2005</td>
</tr>
<tr>
<td>organ motion</td>
<td>0.3</td>
<td>0.09</td>
<td>0.3</td>
<td>0.09</td>
<td>van Herk et al, IJROBP 1995</td>
</tr>
<tr>
<td>setup error</td>
<td>0.1</td>
<td>0.01</td>
<td>0.2</td>
<td>0.04</td>
<td>Bel et al, IJROBP 1995</td>
</tr>
<tr>
<td>intrafraction motion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total error</td>
<td>0.40</td>
<td>0.16</td>
<td>0.37</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>times 2.5</td>
<td></td>
<td>times 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>error margin</td>
<td>1.01</td>
<td></td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total error margin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.27</td>
</tr>
</tbody>
</table>
Prostate: $2.5 \Sigma + 0.7 \sigma$
Now add IGRT

<table>
<thead>
<tr>
<th></th>
<th>systematic errors</th>
<th>squared</th>
<th>random errors</th>
<th>squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>delineation</td>
<td>0.25</td>
<td>0.0625</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>van Herk et al, IJROBP 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>organ motion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bel et al, IJROBP 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>setup error</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>intrafraction motion</td>
<td></td>
<td></td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>total error</td>
<td>0.25</td>
<td>0.06</td>
<td>0.10</td>
<td>0.01</td>
</tr>
<tr>
<td>times 2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>times 0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>error margin</td>
<td>0.63</td>
<td></td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>total error margin</td>
<td>0.70</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Engels et al (Brussels, 2010) found 50% recurrences using 3 mm margin with marker IGRT
CNS: single fraction IGRT for brain metastasis

<table>
<thead>
<tr>
<th></th>
<th>systematic errors</th>
<th>random errors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>squared</td>
<td>squared</td>
</tr>
<tr>
<td>delineation</td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>organ motion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>setup error</td>
<td>0.05</td>
<td>0.0025</td>
</tr>
<tr>
<td>intrafraction motion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total error</td>
<td>0.11</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>times 2.5</td>
<td>times 0.7</td>
</tr>
<tr>
<td>error margin</td>
<td>0.28</td>
<td>0.02</td>
</tr>
<tr>
<td>total error margin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tightest margin achievable in EBRT ever due to very clear outline on MRI
Planning target volume concepts

- Convention Free-breathing CT scan
- Internal Target Volume
- Gating @ exhale
- Mid-Ventilation /Position

Time-averaged mean position

Margin ?

GTV/ITV CTV PTV

Crap Too large
Image *selection* approaches to derive representative 3D data

4D CT

Exhale (for gating)

Mid-ventilation

Vector distance to mean position (cm)
Using conventional fractionation, prescription at 95% isodose line in lung

<table>
<thead>
<tr>
<th>all in cm</th>
<th>systematic errors</th>
<th>squared</th>
<th>random errors</th>
<th>squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>delineation</td>
<td>0.2</td>
<td>0.04</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>organ motion</td>
<td>0.3</td>
<td>0.09</td>
<td>0.3</td>
<td>0.09</td>
</tr>
<tr>
<td>setup error</td>
<td>0.2</td>
<td>0.04</td>
<td>0.4</td>
<td>0.16</td>
</tr>
<tr>
<td>Intra-fraction motion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>respiration motion</td>
<td>0.1</td>
<td>0.01</td>
<td>0.3</td>
<td>0.111111</td>
</tr>
<tr>
<td></td>
<td>(0.33A)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>total error</td>
<td>0.42</td>
<td>0.18</td>
<td>0.60</td>
<td>0.361111</td>
</tr>
<tr>
<td>times 2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>difficult equation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(almost times 0.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>error margin</td>
<td>1.06</td>
<td></td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>total error margin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.47</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Using hypo-fractionation, prescription at 80% isodose line in lung
Planned dose distribution: hypofractionated lung treatment 3x18 Gy
Realized dose distribution with daily IGRT on tumor (no gating)

9 mm margin is adequate even with 2 cm intrafraction motion
But what about the CTV?

- By definition disease between the GTV and the CTV cannot be detected.

- Instead, the CTV is defined by means of margin expansion of the GTV and/or anatomical boundaries.

- Very little is known of margins in relation to the CTV:
  - Very little clinical / pathology data
  - Models to be developed.
Hard data: microscopic extensions in lung cancer

30% patients with low grade tumors (now treated with SBRT with few mm margins), have spread at 15 mm distance

Having dose there may be essential!

Slide courtesy of Gilhuijs and Stroom, NKI
Is dose outside the prostate related with outcome? → detect disease spread in historical data

Dose differences due to:
- randomization
- anatomy
- technique

Mapping of planned dose cubes to standard patient
Estimate pattern of spread from response to incidental dose in clinical trial data (high risk prostate patients)

Average dose no failures – average dose failures

≈ 7 Gy

\( p = 0.02 \)

Witte et al, IJROBP2009; Chen et al, ICCR2010
Conclusions

• We defined a margin recipe based on a given probability of covering the CTV with a given isodose line of the cumulative dose

• The margin with IGRT is dominated by delineation uncertainties

• Margins for random uncertainties and respiratory motion in lung can be very small because of the shallow dose falloff in the original plans
Conclusions

• In spite of IGRT there are still uncertainties that need to be covered by safety margins

• Important uncertainties relate to imaging and biology that are not corrected by IGRT

• Even though PTV margins are designed to cover geometrical uncertainties, they also cover microscopic disease

• Reducing margins after introducing IGRT may therefore lead to poorer outcome and should be done with utmost care (especially in higher stage disease)