ITV AND PTV MARGINS IN THE IGRT ERA

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Outline

- PTV margin recipes
  - Systematic and random uncertainties
- ITV
- Delineation uncertainties
- CTV margin recipe
- Combined margin recipe
- Summary / conclusions

PTV margin recipes (ICRU 50/62/83)

Table 4.4. Summary of various published recommendations for margins around target volumes (CTV) and OAR (modified from van Herk, 2004).

Author	Region	Recipe	Comments
Bel *et al.* (1996)	PTV	0.7σ	Statistical uncertainties only (linear approximation)—Monte Carlo.
Antolak and Rosen (1999)	PTV	1.65σ	Statistical uncertainties only, block margin?
Stroom *et al.* (1999a)	PTV	$2\,\Sigma + 0.7\sigma$	95 % absorbed dose to on average 99 % of CTV tested in realistic plans.
van Herk *et al.* (2000)	PTV	$2.5\,\Sigma + 0.7\,\sigma$ (or more correctly): $2.5\Sigma + 1.64\,(\sigma - \sigma_e)$	Minimum absorbed dose to CTV is 95 % for 90% of patients. Analytical solution for perfect conformation.
McKenzie (2000)	PTV	$2.5\,\Sigma + \beta + (\sigma - \sigma_e)$	Extension of van Herk *et al.* (2000) for fringe dose due to limited number of beams. The factor β depends on the beam organization.
Parker *et al.* (2002)	PTV	$\Sigma + \sqrt{(\sigma^2 + \Sigma^2)}$	95 % minimum absorbed dose and 100 % absorbed dose for 95 % of volume. Probability levels not specified.
van Herk *et al.* (2002)	PTV	$2.5 + \Sigma + 0.7\sigma + 3$ mm (or more correctly): $\sqrt{2.7^2\Sigma^2 + 1.6^2\sigma^2} - 2.8$ mm	Monte Carlo based test of 1 % TCP loss due to geometrical errors for prostate patients, fitted for various σ and Σ.

Symbols: Σ, standard deviation of systematic uncertainties; σ, standard deviation of statistical (random) uncertainties; σ_e, describes width of beam penumbra fitted with a Gaussian function; A, peak-to-peak amplitude of respiration.

Patient group characterization by Σ and σ

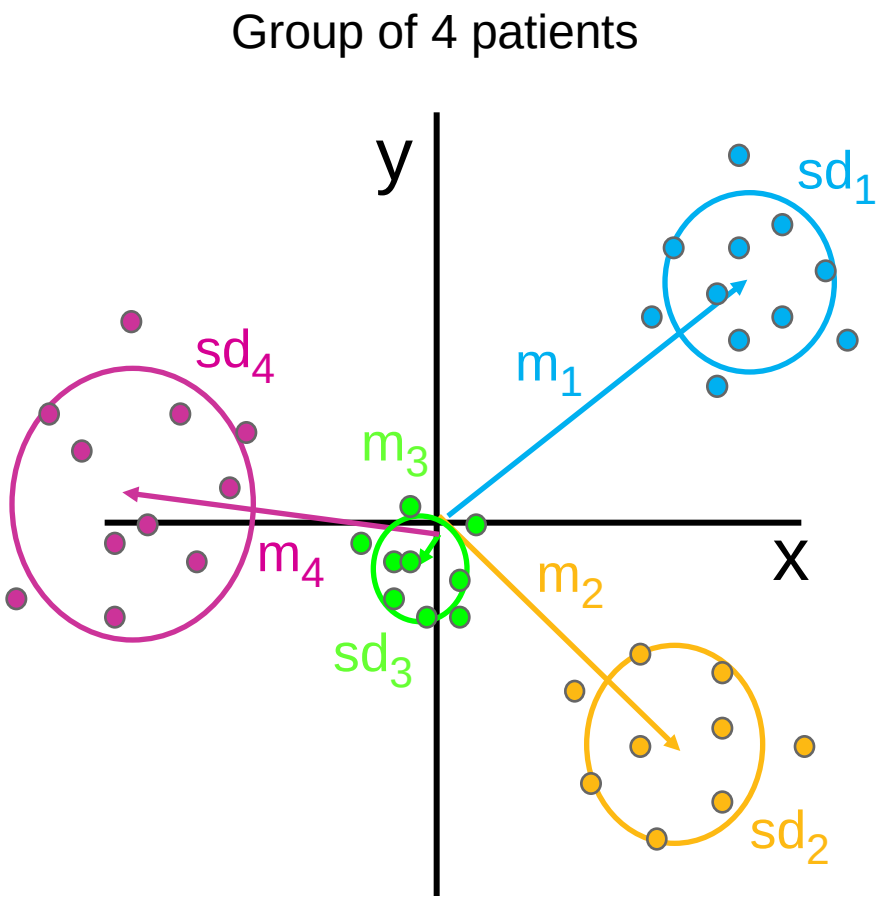
mean of means
M: $< m_i > \approx 0$

systematic deviation

Σ : sd (m_i)

random deviation

σ : $< sd_i >$



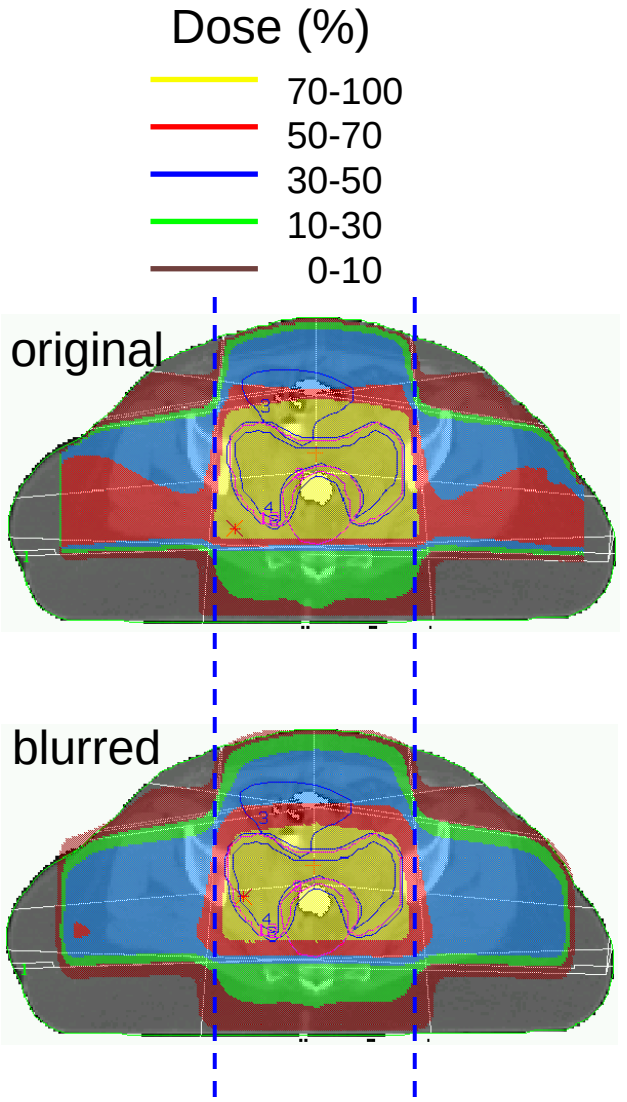
Two types of uncertainties

Systematic	Random
Mean difference with the planning (i.e. same for all fractions)	Day-to-day (multi-fraction) difference with the planning situation
Characterized by Σ: the standard deviation of the mean differences per patient in the group	Characterized by σ: the mean of the standard deviation per patient
Examples: delineation uncertainties, organ motion, setup error	Examples: organ motion, setup error, breathing
Total systematic uncertainty by quadratic addition of components	Total random uncertainty by quadratic addition of components
Dosimetric effect: shift	Dosimetric effect: blurring

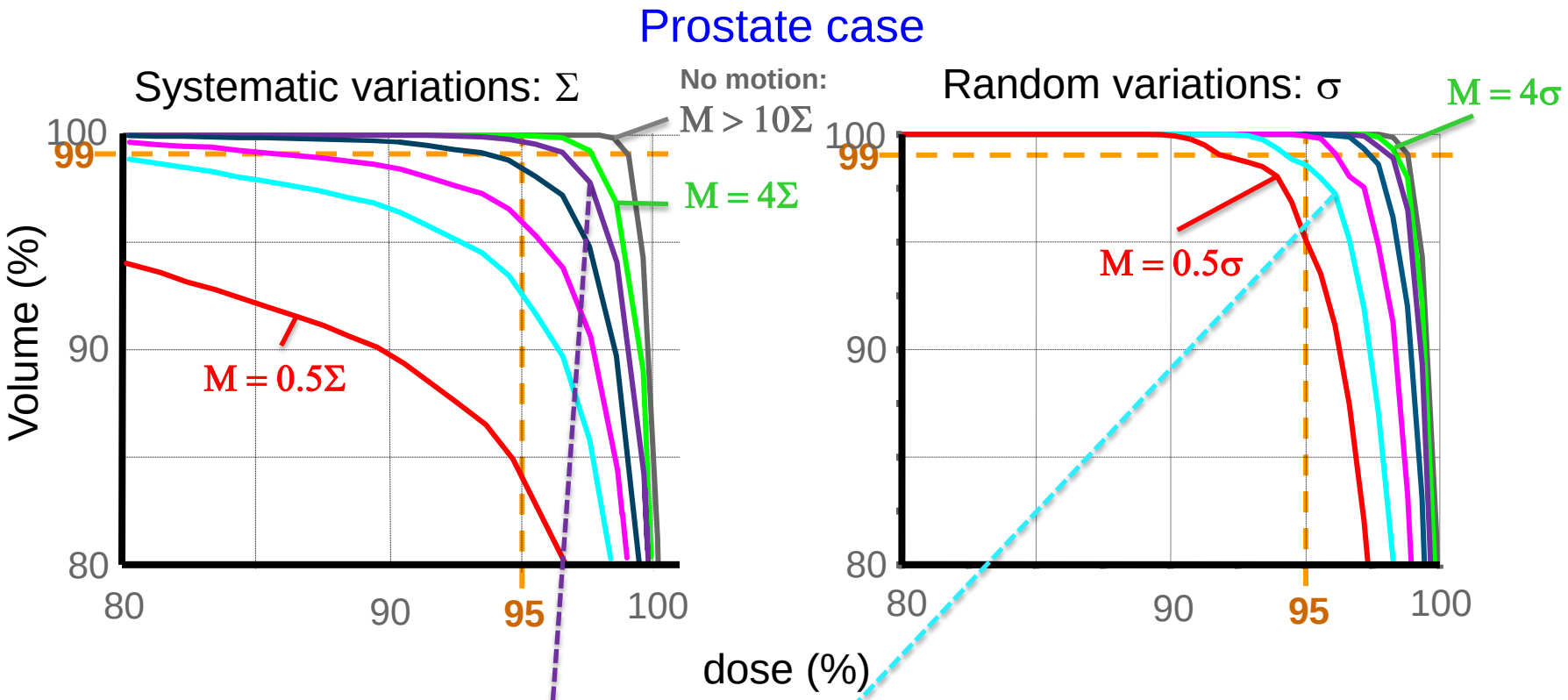
NB: also valid in the IGRT era!

Effect of σ on dose distribution

- Random errors vary from fraction to fraction
  - Or within fraction
- Effect on final dose:
  - Smoothing or blurring of the dose
  - Low dose regions grow
  - High dose regions shrink
    - MARGIN



Mean DVHs for “moving” CTVs



Use these curves to determine margin recipe (1999):

1. criterion: $D99_{<CTV>} > 95\%$ (somewhat arbitrary!)
2. recipe: $M(\Sigma,\sigma) = 2\Sigma + 0.7\sigma$

See also: Stroom et al. , IJROBP 43, 905-919,1999

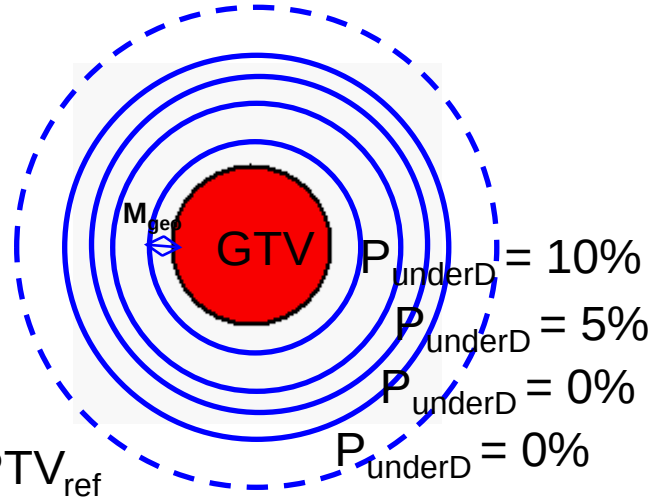
Margin recipes allowing P_{underD} = 10%

Criterion:

- **# patients with under-dose, P_{underD} <= 10%** (also arbitrary!)
- **under-dose: D_{min}< 95%**

Geometric errors

e.g.: Σ_{geo} = 3 mm , σ_{geo} = 3 mm



→ P_{underD} = 0%

Repeat for N_{pat} = 1000, all (Σ_{geo}, σ_{geo})

⇩

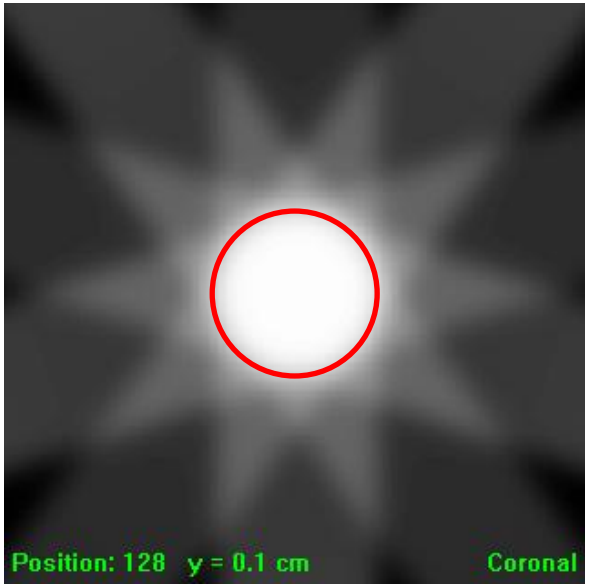
$M_{geo} = a\Sigma_{geo} + b\sigma_{geo}$

We found: $M_{geo} = 2.1\Sigma_{geo} + 0.8\sigma_{geo}$

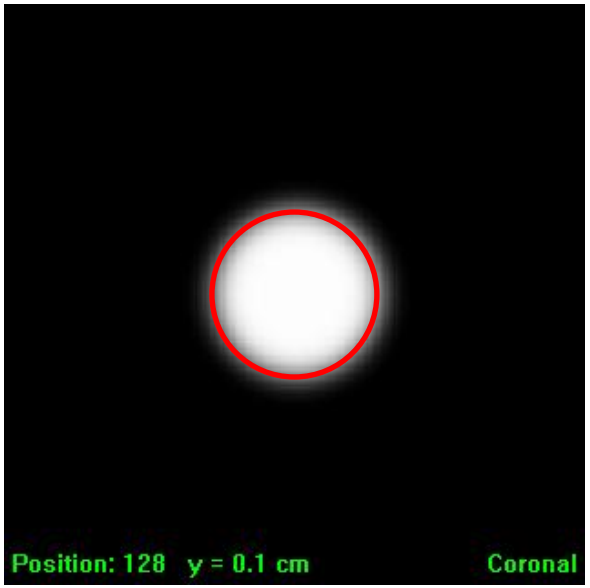
See also: van Herk et al., IJROBP 47, 1121-1135, 2000

Margins and Conformity Index (CI)

5 equi-angular beams, CI = 1.25



Ideal dose, CI = 1.0



$$M_{geo} = \mathbf{a}\Sigma_{geo} + \mathbf{b}\sigma_{geo}.$$

5-field conformal				ideal dose			
a	SD(a)	**b**	SD(b)	**a**	SD(a)	**b**	SD(b)
2.1	0.1	**0.8**	0.2	**2.5**	0.0	**0.9**	0.2

Stroom 1999/2014

Van Herk 2000

PTV: quadratic addition of uncertainties

- $M = 2.1\Sigma + 0.8\sigma$
  - $\Sigma = \sqrt{(\Sigma_{delineation}^2 + \Sigma_{setup}^2 + \Sigma_{organmotion}^2 + \ldots)}$
  - $\sigma = \sqrt{(\sigma_{setup}^2 + \sigma_{organmotion}^2 + \ldots)}$

- Example:
  - $\Sigma_{setup} = 0$, $\Sigma_{organmotion} = 3 \rightarrow M = 6.3$
  - $\Sigma_{setup} = 3$, $\Sigma_{organmotion} = 0 \rightarrow M = 6.3$
  - $\Sigma_{setup} = 3$, $\Sigma_{organmotion} = 3 \rightarrow M = 8.9 < 12.6$

Margin calculation procedure

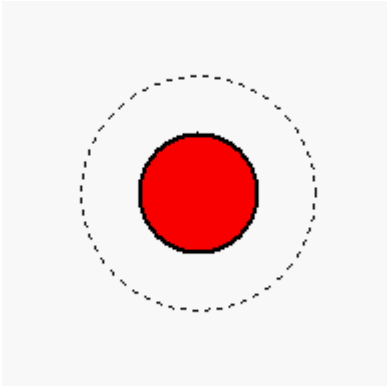
- determine all geometrical errors
  - own data or from literature
- determine overall Σ and σ
  - $\Sigma = \sqrt{(\Sigma_{su}^2 + \Sigma_{om}^2 + \Sigma_{del}^2)}$, $\sigma = \sqrt{(\sigma_{su}^2 + \sigma_{om}^2)}$
- apply margin rule: $M = 2\Sigma + 0.7\sigma$ (1999):

site	type	Σ x	Σ y	Σ z	σ x	σ y	σ z
prostate	Setup	1.2	1.0	1.1	2.1	1.8	2.0
	Organ motion	0.5	2.5	2.7	0.6	2.8	2.5
	Delineation	2.5	2.5	2.5	-	-	-
	Total	2.8	3.7	3.8	2.2	3.3	3.2
	M (mm)	**7**	**10**	**10**			

NB: 10 mm was the clinically applied prostate safety margin before 1999!

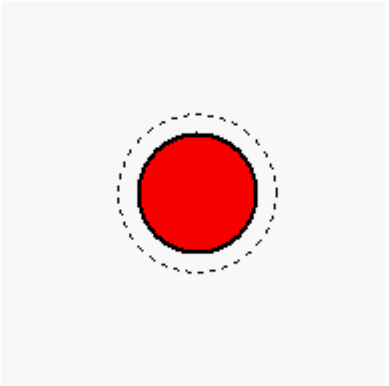
Consequences of recipe: CTV outside PTV

Systematic: M = 2 Σ



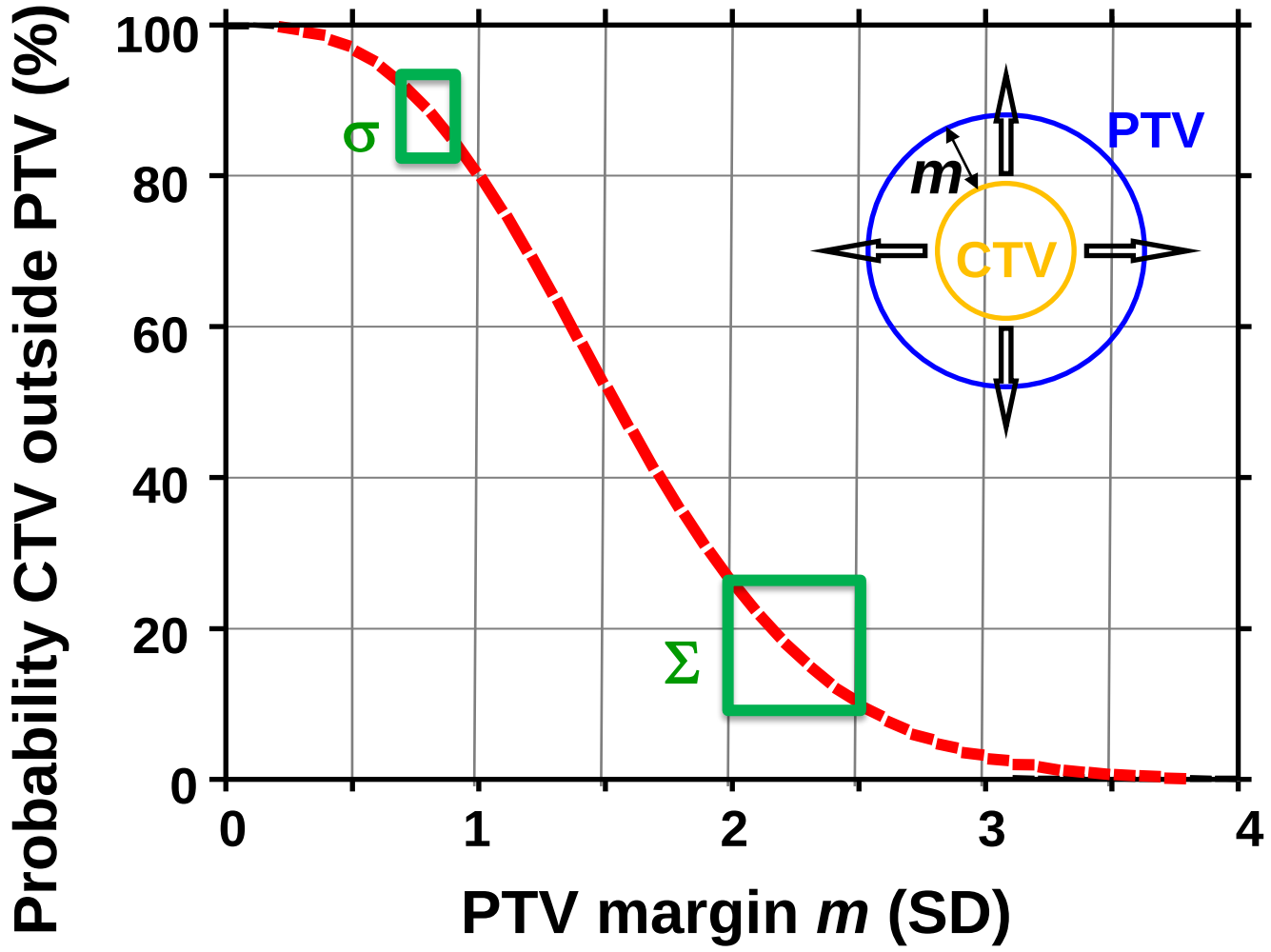
P(CTV outside PTV) = 25%

Random: M = 0.7 σ



P(CTV outside PTV) = 90%!

Spherically symmetric case



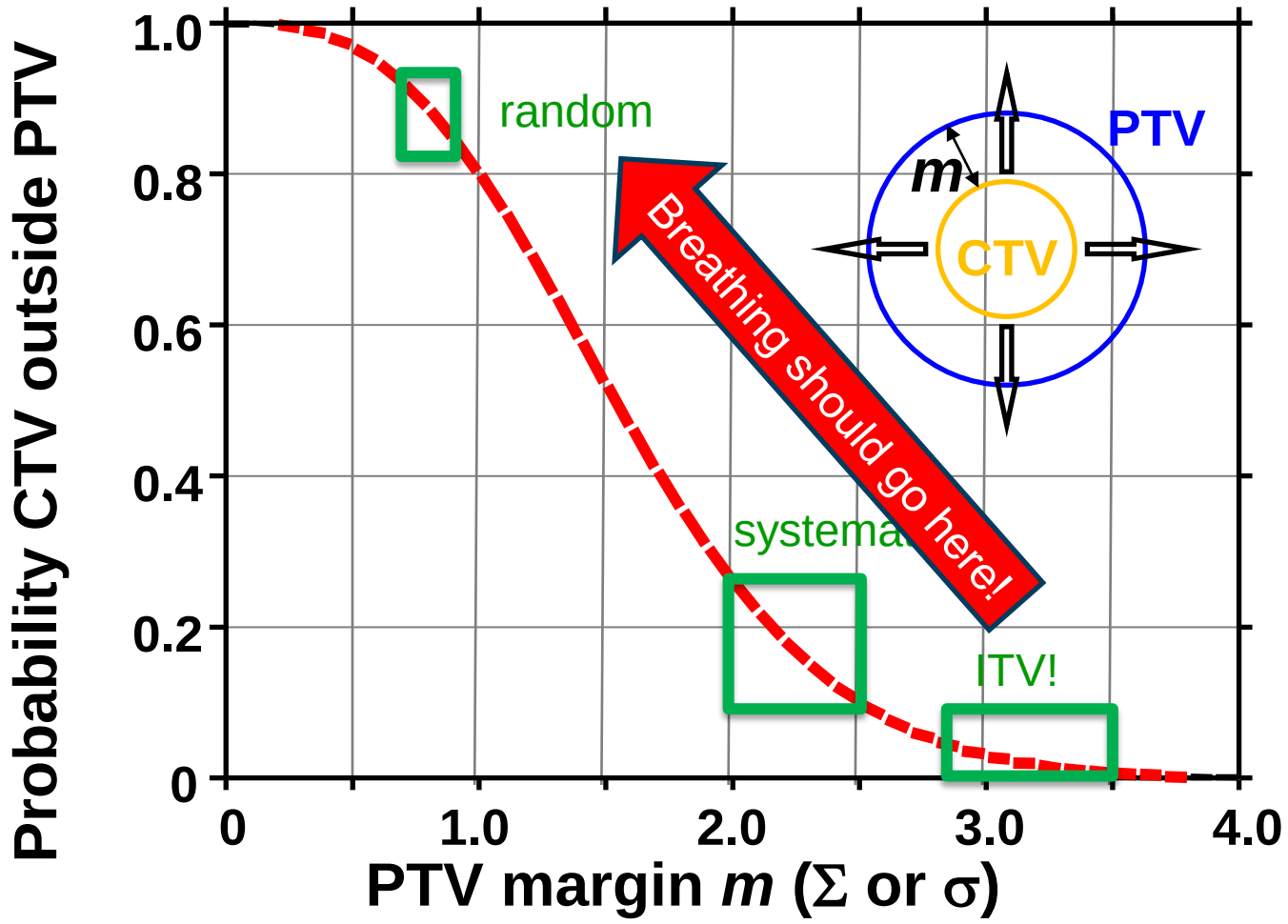
Stroom et al. (IJROBP 43, 905, 1999)

Breathing motions (ITV?)

- Systematic or random?
  - Mostly random!
  - Dose will be blurred
- Approximate amplitude (A) by standard deviation
  - $\sigma_{breathing} \approx A / 3$ *
  - $\sigma_{tot} = \sqrt{(\sigma_{setup}^2 + \sigma_{organmotion}^2 + \boldsymbol{\sigma_{breathing}^2} + \ldots)}$

*** Van Herk et al, IJROBP 2003**

Separate ITV overestimates margins!



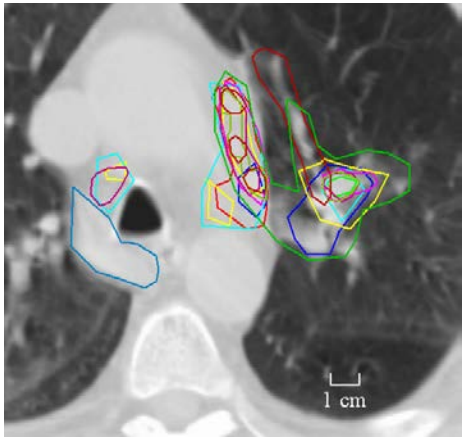
Delineation uncertainty of GTV

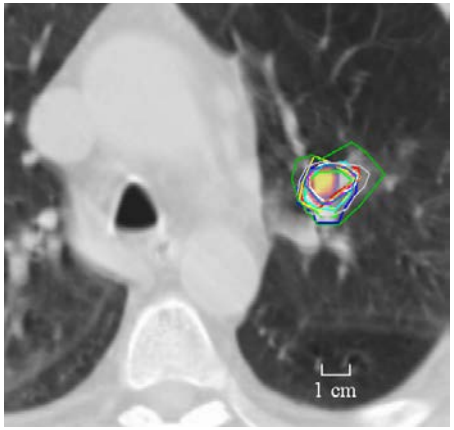
- Visible and/or palpable tumor
- Reduction by new imaging techniques
  - CT, MRI, PET
- Multi-observer studies
  - Pathology is the gold standard!
- $\Sigma_{delineation}$ should go in PTV margin!

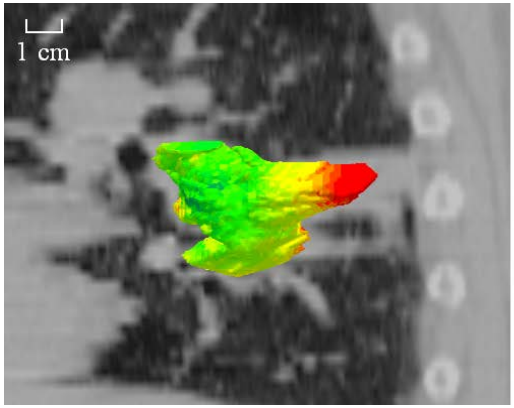
Multi-observer study lung

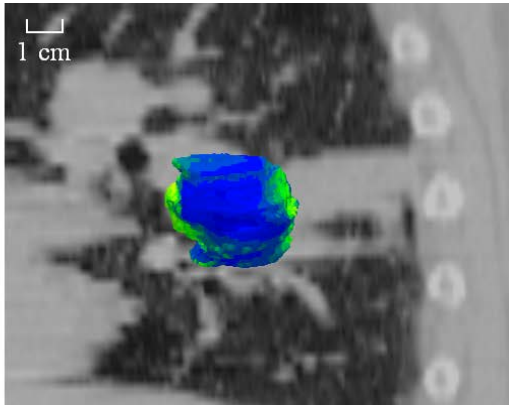
Without PET

With PET









SD ($\Sigma_{delineation}$) projected on the median delineated surface **(from dark blue (SD < 0.1 cm)** to **red (SD > 1.5 cm)**

With PET less random errors, but… What is the truth?

Steenbakkers, IJROBP 2006, p435

Overview delineation uncertainties

Who	Year	Tumor Site	#cases	#doctors	Images	SD(mm)	Reference
Steenbakkers	2006	Lung	22	11	CT / CT+PET	**10 / 4**	IJROBP 64, p435
Petric	2013	Cervix	6	10	MRI	**4**	RadOnc 107, p6
Rasch	1999	Prostate	18	3	CT / MRI	**3 / 3**	IJROBP 43, p57
Van Mourik	2010	Breast (boost)	8	13	CT / CT + clips	**7 / 5**	RadOnc 94, p286
Rasch	2005	Head&Neck (nasoph.)	18	10	CT / CT+MRI	**4 / 3**	Semin Radiat Oncol 15:136
Nijkamp	2012	Rectum	8	11	CT+MRI / + guideline	**10 / 6**	RadOnc 102, p14

Weakest link in radiotherapy?

Ignoring delineation errors

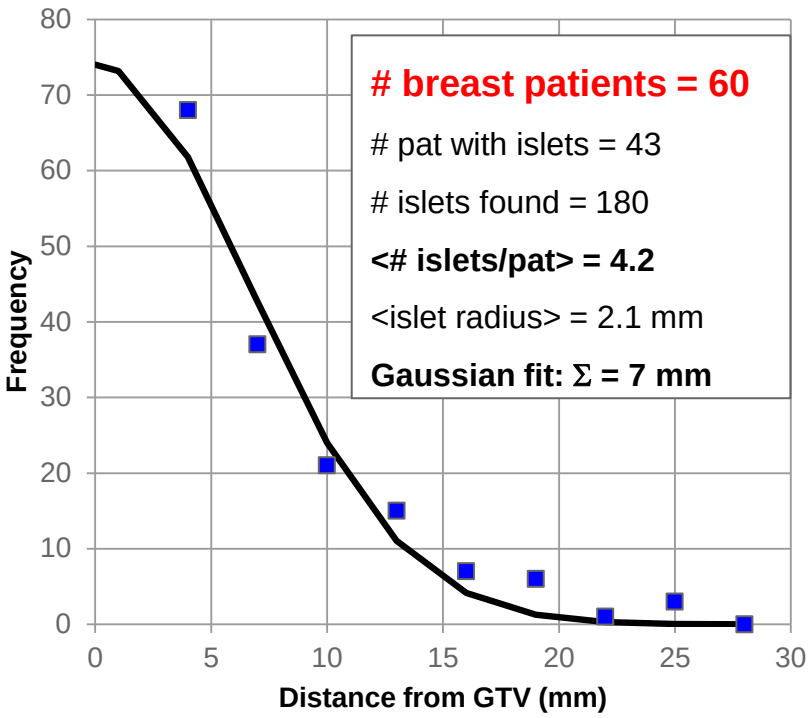
- Frequently, delineation errors are ignored in margin calculations
- But, TCP is not too bad
- This means that either:
  - Too large margins for other factors are applied accidently compensating for delineation errors
  - There is an overall mean error in delineating, i.e., all delineations are too large (“better safe than sorry”)
    - See e.g. Daisne et al, Radiology. 2004, p93-100
    - NTCP can be improved by proper margins
  - TCP can really be improved by proper margins

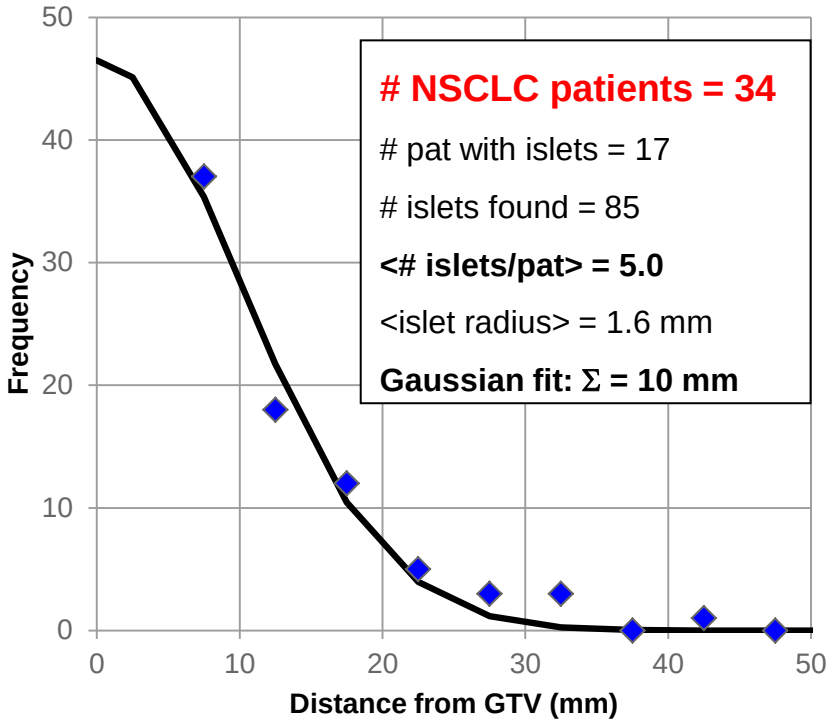
CTV (Clinical Target Volume)

- Microscopic disease:
  - By definition not directly visible
  - Microscope required to measure this

- Relatively few histopathology studies have been performed
  - Low # patients
  - Low sampling frequency

Distribution of Microscopic disease



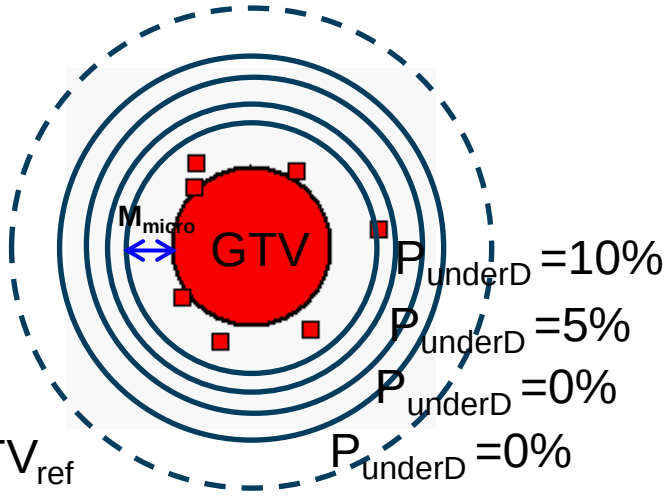


See Stroom et al. Combined Recipe for Clinical Target Volume and Planning Target Volume Margins. IJROBP. 2014 Mar 1;88(3):708-14

Margin recipes allowing $P_{underdose}$ =10%

Microscopic disease

e.g.: N_{pat} = 1000, $N_{islet/pat}$ = 5, Σ_{micro} = 6 mm



Repeat for all (N_{islet}, Σ_{micro})

⇩

$$M_{micro} = (d + e\log(N_i)) \times \Sigma_{micro}$$

5-field conformal			ideal dose		
d	e	SD (d,e)	d	e	SD (d,e)
1.4	0.8	0.2	1.7	0.8	0.0

Discussion CTV margins

- Assumed in simulations
  - Microscopic disease are islets
  - Radio-sensitivity of Islets equal to GTV

Review
Trends in Molecular Medicine January 2012, Vol. 18, No. 1
Cell Press

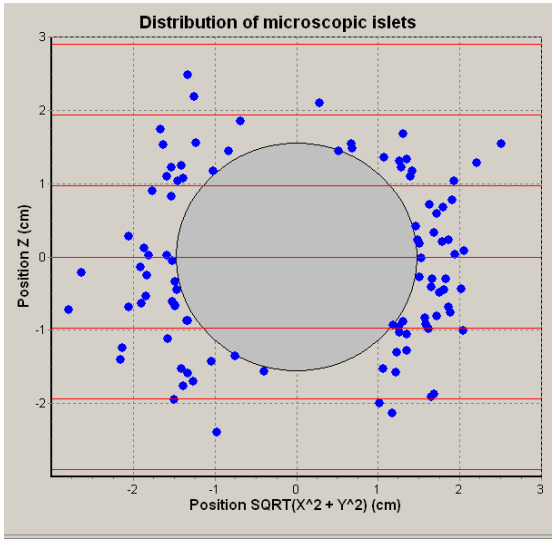
Feature Review

Cancer invasion and resistance: interconnected processes of disease progression and therapy failure

Stephanie Alexander[1,2] and Peter Friedl[1,2,3]

[1] Department of Dermatology and Rudolf Virchow Center, DFG Research Center for Experimental Biomedicine, University of Wuerzburg, Wuerzburg, Germany
[2] David H. Koch Center for Applied Research of Genitourinary Cancers, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[3] Microscopical Imaging of the Cell, Department of Cell Biology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

- Where are all the real microscopic islets (<< 1mm)?



- CTV margin often ignored altogether
  - See discussion delineation errors

- Undersampling at pathology ignored

Combining PTV and CTV margins

- Geometric uncertainties:
  - $M_{geo} = 2.1\Sigma_{geo} + 0.8\sigma_{geo}$
- Microscopic uncertainties:
  - $M_{micro} = (1.4+0.8\log(N)) \times \Sigma_{micro}$
- M_{micro} is systematic in nature:
  - Add quadratically with Σ_{geo}?

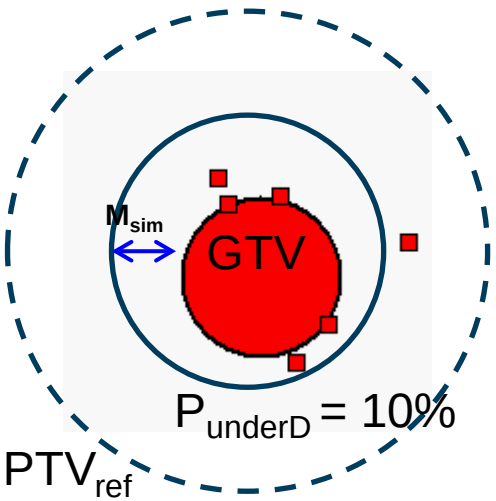
→ $M_{GTV\text{-}PTV}=\sqrt{((2.1\Sigma_{geo})^2 + ((1.4+0.8\log(N_i))\Sigma_{micro})^2)} + 0.8\sigma_{geo}$

Verification of combined formula

1) $M_{GTV\text{-}PTV} = \sqrt{((2.1\Sigma_{geo})^2 + ((1.4+0.8\log(N_i))\Sigma_{micro})^2)} + 0.8\sigma_{geo}$

2) Simulate both geometric and microscopic uncertainties

e.g.: N_{pat} = 1000, Σ_{geo} = 3 mm, σ_{geo} = 3 mm, $N_{islet/pat}$ = 5, Σ_{micro} = 6 mm



Repeat some
(Σ_{geo}, σ_{geo}, N_{islet}, Σ_{micro})
for verification

⇩

$M_{simulation}$

See Stroom et al. Combined Recipe for Clinical Target Volume and Planning Target Volume Margins. IJROBP. 2014 Mar 1;88(3):708-14

GTV to PTV: verification for 54 cases

Σ_{geo}=(2,4mm), σ_{geo}=(0,2,4mm), Σ_{micro}=(3,6,9mm), N_i=(3,15,75).

$M_{simulation} - M_{recipe}$ (mm)			
5-field conformal		ideal dose	
mean	SD	**mean**	SD
0.2	0.8	**0.1**	0.7

Comparison with linear ICRU approach (GTV, CTV, PTV)

$M_{ICRU} - M_{new\ recipe}$ (mm)			
5-field conformal		ideal dose	
mean	SD	**mean**	SD
4.5	1.4	**5.4**	1.6

Summary: over/underestimation PTV

- No clin. validation margin criteria: OVER/UNDER
- Assuming perfect dose conformance: OVER
- Using a separate ITV: OVER
- Ignoring error sources (e.g. delineation): UNDER
- “Better safe than sorry” delineations: OVER
- Separate CTV and PTV margins: OVER
- Ignore undersampling @pathology: UNDER
- Unknown radiosensitivity Σ_{micro}: OVER/UNDER

- **Total: 0?**

Conclusions

- GTV and CTV delineation may be largest uncertainty in RT
- Margin factors are to some extent arbitrary
  - But systematic errors have more weight
  - ITV is wrong
- CTV and PTV margins should be combined
  - Otherwise margins overestimated by up to 5 mm
- Margins used in the clinic should be consistent and based on uncertainties

TCP-based GTV-PTV margins

- Similar simulations using criterion ΔTCP=1%:

$M_{GTV-PTV}=\sqrt{\{(2.6\Sigma_{geo})^2 + ([1.7+0.7\log(N_i)]\Sigma_{micro})^2 + (1.8\sigma_{geo})^2\}}$ -3.8mm

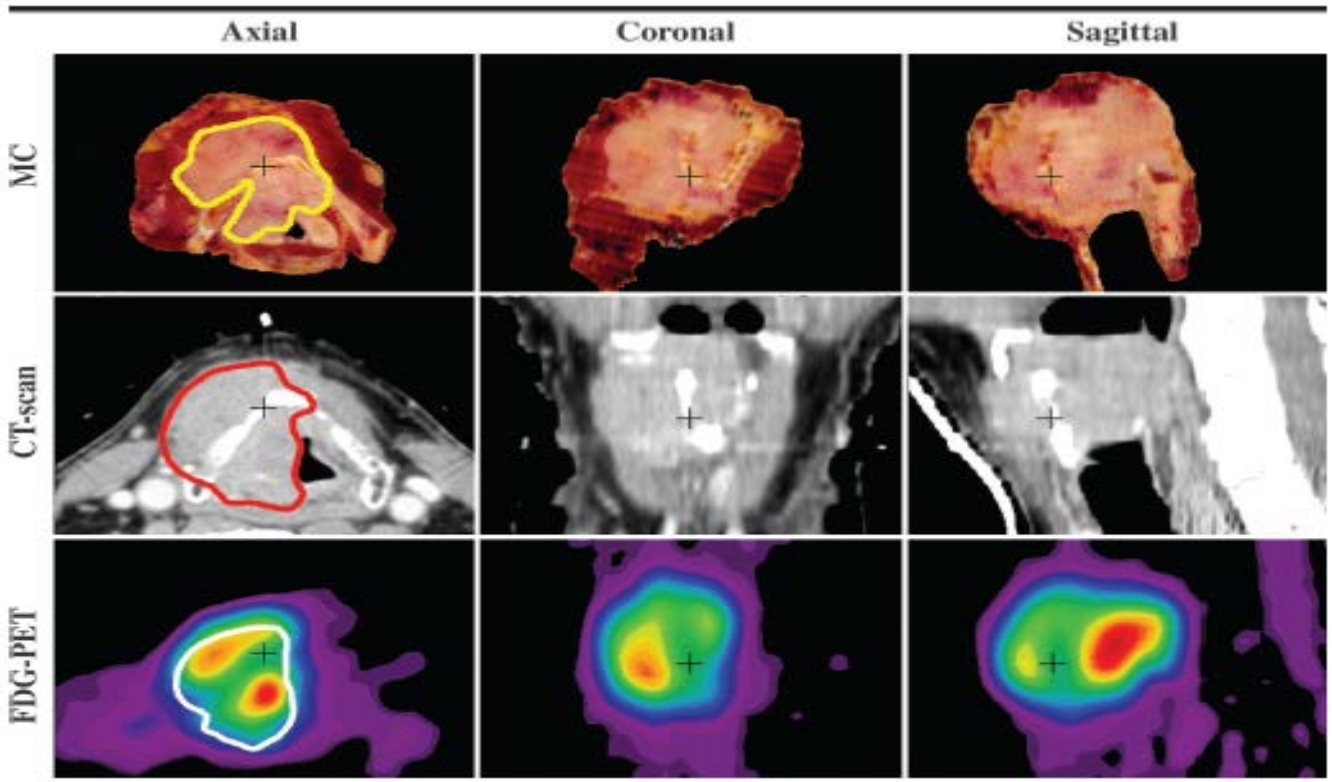
- TCP should be clinically more relevant
- However
  - TCP parameters add extra uncertainty
  - Much more sensitive to tumor size, prescription dose, etc
- Currently preferred: D_{min}-based recipes

See Stroom et al. Combined Recipe for Clinical Target Volume and Planning Target Volume Margins. IJROBP. 2014 Mar 1;88(3):708-14

Combined margin robustness

	Ref. value	Value range		Margin range (%)	
		min	max	Crit: D_{min}	Crit: TCP
Geometry					
penumbra width (SD, mm)	3.2	1	7	92-118	**70-135**
tumor diameter (cm)	3	1	10	-	**74-107**
microscopic islet radius (mm)	2	0.5	4	-	96-102
dose conformity Index	1.25	1	1.3	99-118	95-107
TCP parameters					
<TCP>	0.8	0.25	0.9	-	**75-101**
nfrac	40	25	50		
relative islet radiosensitivity (%)	100	75	150	-	87-109
Plan criteria					
minimal PTV dose (%)	95	95	95	102-112	95-112
PTV coverage (%)	100	90	100		
Margin criteria					
$P(D_{min} < 95\%) < X\%$	10	1	25	**85-137**	-
$\Delta TCP < Y\%$	1	0.1	10	-	**35-145**

GTV validation: surgical specimens



1. Pharyngolaryngeal SquamousCell Carcinoma: CT, MRI, PET, Surgical specimen
2. **All imaging volumes are too large, PET closest to surgery**
3. Microscopic disease invisible with imaging
4. Daisne et al, Radiology. 2004, p93-100.