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Metrology for clinical implementation of dosimetry in molecular radiotherapy

NTCP uncertainties

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Outline

- Normal tissue complication probability (NTCP) curves
- Objective of study
- NTCP models
- From uncertainty budgets to
  - GUM results
  - Monte Carlo results
- Comparison
- Conclusions

NTCP curves

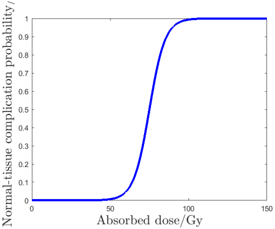
Challenge of treatment planning: quantitatively correlate absorbed dose with clinical outcomes

Today only partly addressed: limited availability of data

Guidelines needed on predicted safety of proposed treatment plans

NTCP: parameter used in radiation therapy for estimating risk of harmful side effects

NTCP curve: relationship between absorbed dose to normal tissue and complication probability



Objective of study

Investigate effects of absorbed dose uncertainty on NTCP

Obtain acceptable level of uncertainty for absorbed dose for MRT

Account for major sources of uncertainty:

- Data on which NTCP curve is based
- Model used for NTCP curve

NTCP models

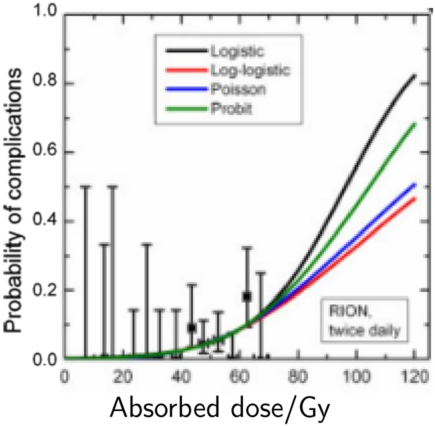
No widely accepted theoretical basis for relationship between NTCP p and absorbed dose D

Use suitable empirical model:

- Logistic function (Niemierko model)
- Gaussian distribution function (Lyman-Kutcher-Burman or LKB model)
- Other models sometimes

Models tend to compare well in regions of concern (low to moderate NTCP values)

Lack of sufficient reliable data



Dangers in extrapolation (Moiseenko, 2011) — even if model fits data tolerably well

However, higher probabilities not of primary clinical interest

Uncertainty budgets — widely used in metrology

Uncertainty budget for caliper to measure a length

Source of Uncertainty	Value a_i	Units	Probability Distribution	Divisor	Sensitivity Coefficient c_i	Standard Uncertainty $U_i(y)$ (mm)
Calibration Uncertainty	0.01	mm	Normal (k=2)	2	1	0.005
Resolution	0.005	mm	Triangular	√6	1	0.002
Cosine error	3	deg	Rectangular	√3	0.046	0.080
Temperature	2	C	Rectangular	√3	0.0023	0.003
Repeatability	0.02	mm	Normal (k=1)	1	1	0.020
					Combined Standard Uncertainty $u_c(y)$	**0.082**
					Expanded Uncertainty (k=2, 95% confidence) U	**0.165**

Measurement model $\longrightarrow$ sensitivity coefficients c_i

Probability distributions $\longrightarrow$ standard uncertainties $u_i(y)$

The c_i and $u_i(y)$ $\longrightarrow$ law of propagation of uncertainty (LPU) of the GUM $\longrightarrow$ combined standard uncertainty

Anything wrong?

Caliper to measure a length

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What's wrong? Two aspects:

1. Probability distributions used no more after forming the $u_i(y)$
2. Normal distribution assumed for output

Alternative: GUM Supplement 1 (Monte Carlo) to propagate distributions (rather than uncertainties) $\longrightarrow$ probability distribution for output

Bonus: sensitivity coefficients (partial derivatives not required)

JCGM-WG1: GUM S1 the 'gold standard' for uncertainty evaluation

Uncertainty propagation principles

GUM (LPU)

1. Calculate partial derivatives $\longrightarrow$ sensitivity coefficients
2. Linearize model about absorbed dose estimate
3. Obtain standard uncertainties from input probability distributions
4. Apply law of propagation of uncertainty
5. Assume normality of NTCP
6. Calculate 95 % confidence interval for NTCP

GUM Supplement 1 (Monte Carlo)

1. Sample many times from input probability distributions
2. Calculate model value for each set of samples
3. Prepare histogram of model values
4. Derive probability distribution for output from histogram
5. Calculate 95 % confidence interval for NTCP

Caliper to measure a length

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Uncertainties

$\sim 10\,\%$ standard uncertainty sometimes claimed in absorbed dose estimate

What influence on NTCP?

Standard uncertainty in D propagates to a standard uncertainty in p, which is much greater in steeper parts of the curve

Left-hand tail important — where we want to be

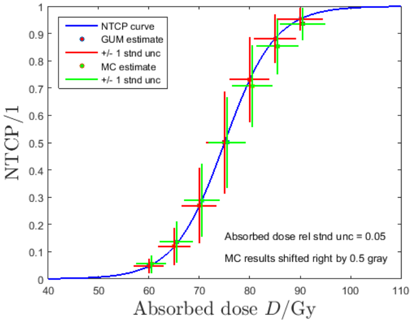


Figure shows $\pm\, u_{\rm rel}(D) = \pm\, 5\,\%$

MC results shifted right by 0.5 Gy for display purposes

GUM and MC results comparable

What's the problem?

Uncertainty propagation: typical results from GUM

Absorbed dose at 50 % complication probability: $D_{50} = 75$ Gy

Steepness parameter: $\gamma = 0.05$

$D = 64$ Gy and 70 Gy

$u_{\mathrm{rel}}(D) = 10$ % in both cases

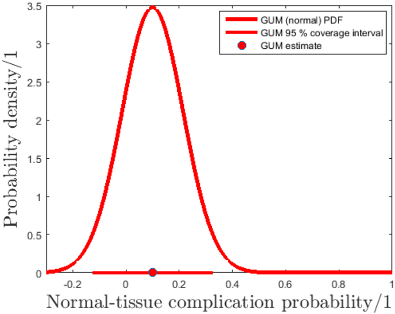
					Confidence interval for p		
D	$u_{\mathrm{rel}}(D)$	p	$u(p)$	$u_{\mathrm{rel}}(p)$	Lower	Higher	Length
64 Gy	0.1	0.10	0.11	1.2	−0.13	0.32	0.45
70 Gy	0.1	0.27	0.28	1.0	−0.27	0.81	1.08

Confidence intervals infeasible

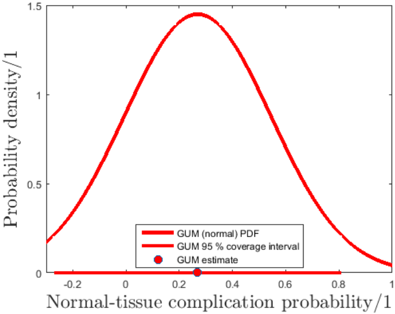
GUM results: $u_{\mathrm{rel}}(D) = 10\,\%$

Filled circles: estimates of NTCP provided by GUM

95 % confidence intervals: horizontal lines



$D = 64\,\mathrm{Gy}$



$D = 70\,\mathrm{Gy}$

Questioning the assumptions made

Two major assumptions made in the use of the GUM:

1. Input uncertainties sufficiently small to be able to linearize the model
2. Normal probability distribution for p

Assumptions often reasonable

They do not hold for typical NTCP calculations as just seen $\Longrightarrow$

- Poor estimates of NTCP
- Invalid standard uncertainties
- Infeasible confidence intervals

Monte Carlo results and comparison with GUM results

						Conf interval for p		
D/Gy	$u_{\mathrm{rel}}(D)$		p	$u(p)$	$u_{\mathrm{rel}}(p)$	Lo	Hi	Len
64	0.1	GUM	0.10	0.11	1.2	−0.13	0.32	0.45
		MCM	0.15	0.15	1.0	0.01	0.58	0.57
70	0.1	GUM	0.27	0.28	1.0	−0.27	0.81	1.08
		MCM	0.32	0.24	0.7	0.02	0.85	0.83

MCM always produces feasible confidence intervals

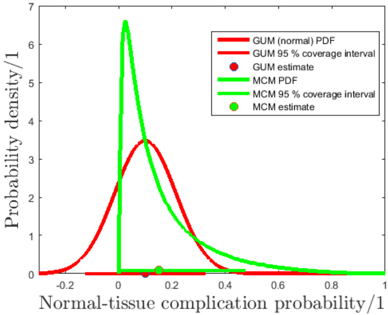
MCM agrees with GUM when $u_{\mathrm{rel}}(D)$ very small, 1 %, say!

Probability distributions for NTCP: $u_{\mathrm{rel}}(D) = 10\,\%$

GUM: red, MC: green

Filled circles: estimates of NTCP provided by GUM and MC

95 % confidence intervals: horizontal lines



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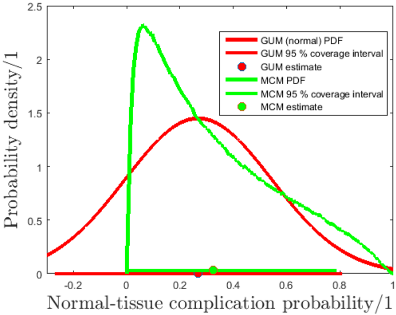

$D = 70\,\mathrm{Gy}$

Amplification factor

From absorbed dose relative standard uncertainty to NTCP relative standard uncertainty, amplification factor

$$K = \frac{u_{\mathrm{rel}}(p)}{u_{\mathrm{rel}}(D)}$$

Typical values of $K \sim 10$

IAEA (2016): at the steepest part of the curve, $K \sim 5$

So, to obtain NTCP value with relative standard uncertainty of 50 % requires absorbed dose uncertainty of $\sim$ 5 % or 10 %

Conclusions

- Traditional "GUM solution" does not guarantee feasible conf interval
- To propagate uncertainties more reliably, use Monte Carlo method
- MC delivers feasible confidence intervals
- MC respects the actual measurement model, however non-linear
- Can use GUM when relative standard uncertainty in D very small, say 1 % — virtually unachievable

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