Outcomes Modeling (Tumor Control, Response Modeling, Clinical Decision Making)

Review of Normal Tissue Complication Probability models for H&N radiotherapy

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Dose-response Relationships

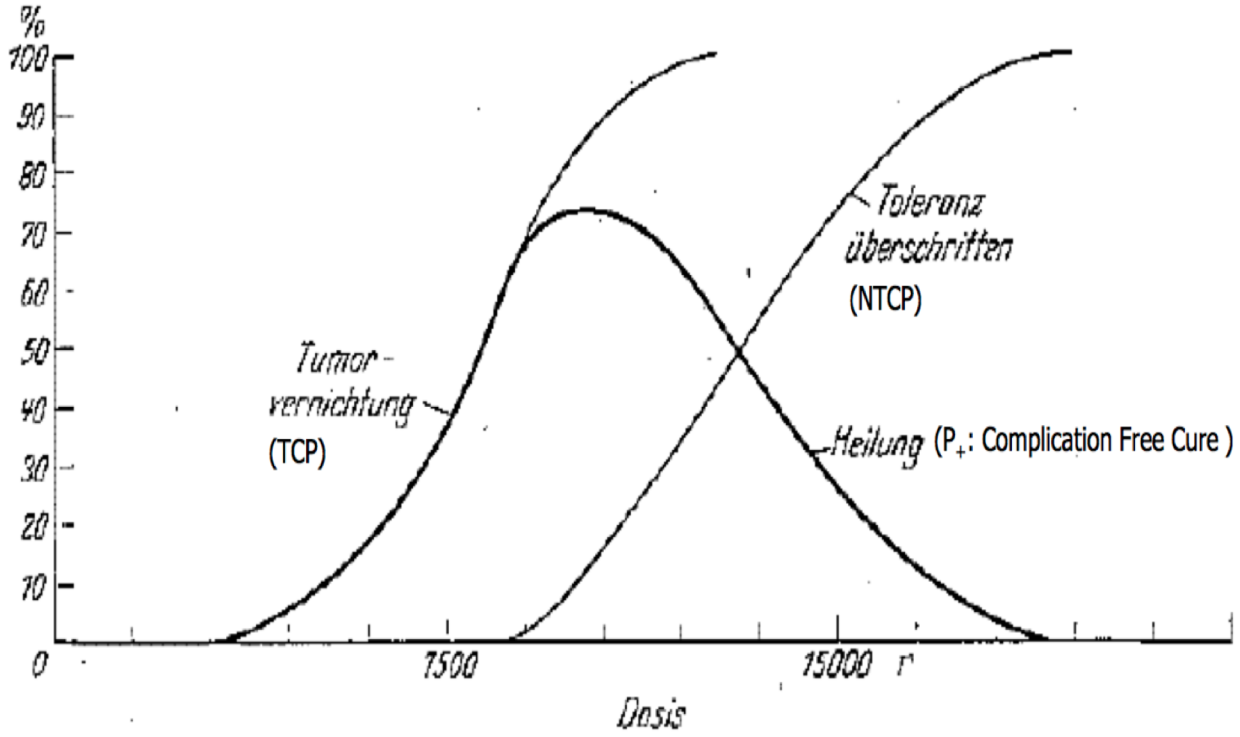
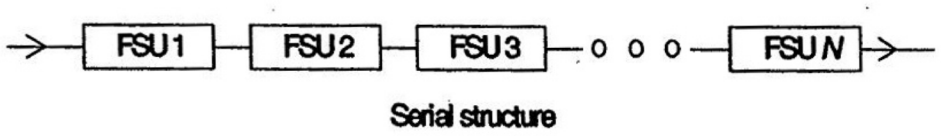


Figure 2.1: Sigmoid shape dose-response curves for tumor control and normal tissue complications. Adapted from Holthusen [Holthusen, Strahlentherapie, 1936].

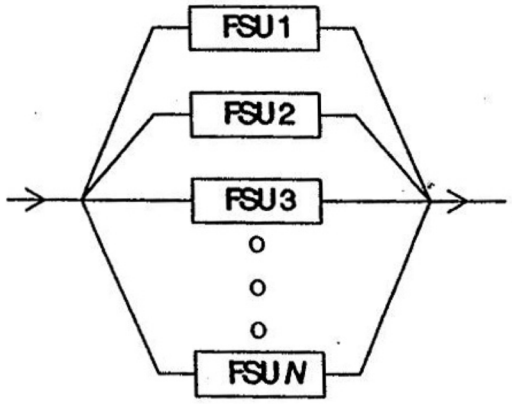
Functional Subunits

Two basic distinct architectures for Structures are considered in modelling:



Serial structure

Probability of incurring a Complication is driven by the Maximum Dose (D_{max})



Parallel structure

Probability of incurring a Complication is driven by the Mean Dose (D_{mean})

The Lyman Model for NTCP calculation

- Two parameter model
- Assumes uniform irradiation of whole or partial organ

The Lyman equations are:

$$NTCP(v,D) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(\frac{-x^2}{2}\right) dx$$

Cumulative Distribution Function of the Normal Distribution

with

$$t = \frac{D - D_{50}(v)}{m \;\; D_{50}(v)}$$

and

$$D_{50}(v) = D_{50}(1)v^{-n}$$

The Lyman Model for NTCP calculation

D_{50}: is the dose that results in a 50% complication probability for some specified complication endpoint.

$D_{50}(1)$: is the dose of 50% complication probability if the entire organ is irradiated.

$D_{50}(v)$: is the dose of 50% complication probability if the fractional volume v of the organ is irradiated. *If* $v < 1$ *then* $D_{50}(v) > D_{50}(1)$.

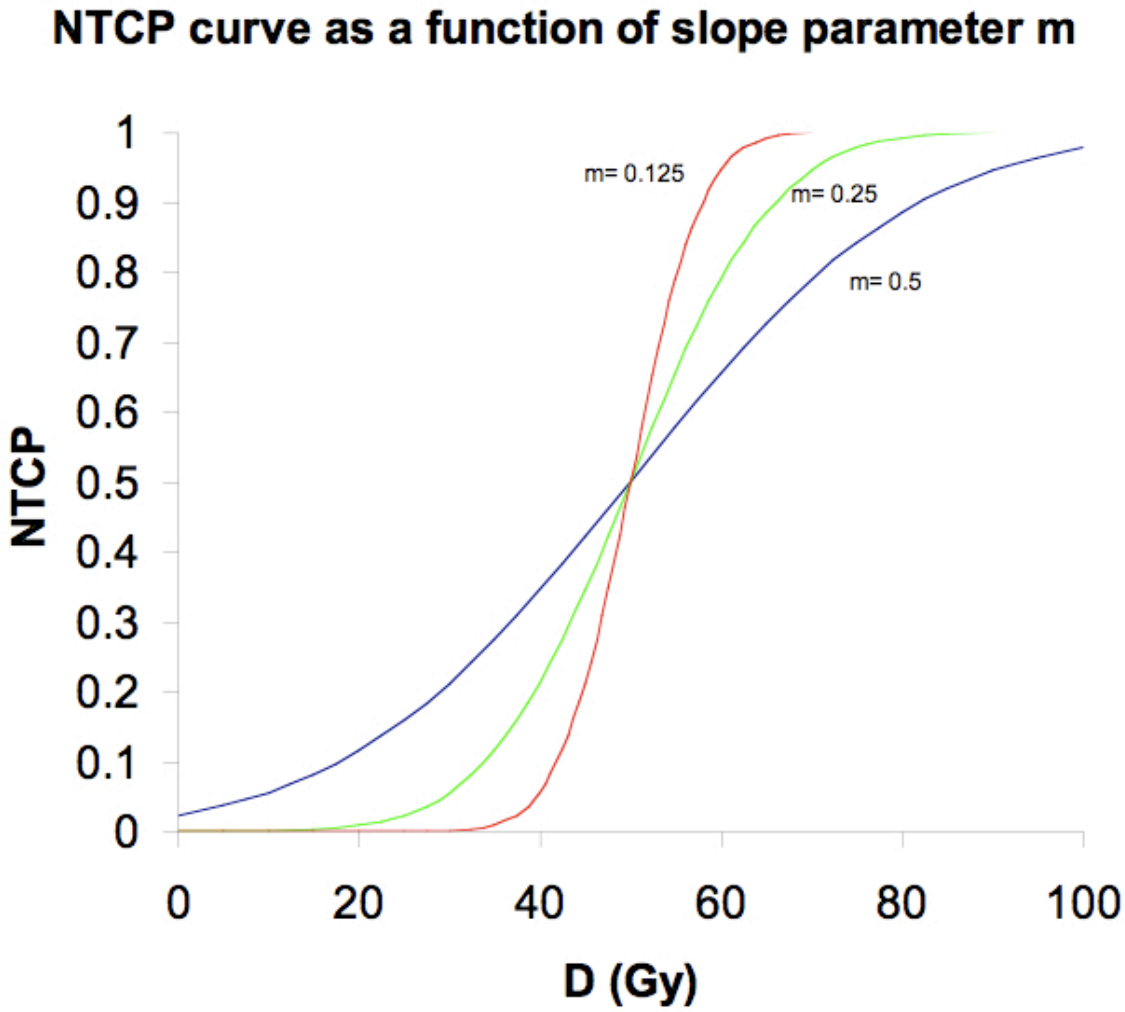
m: Governs the slope of the NTCP curve.

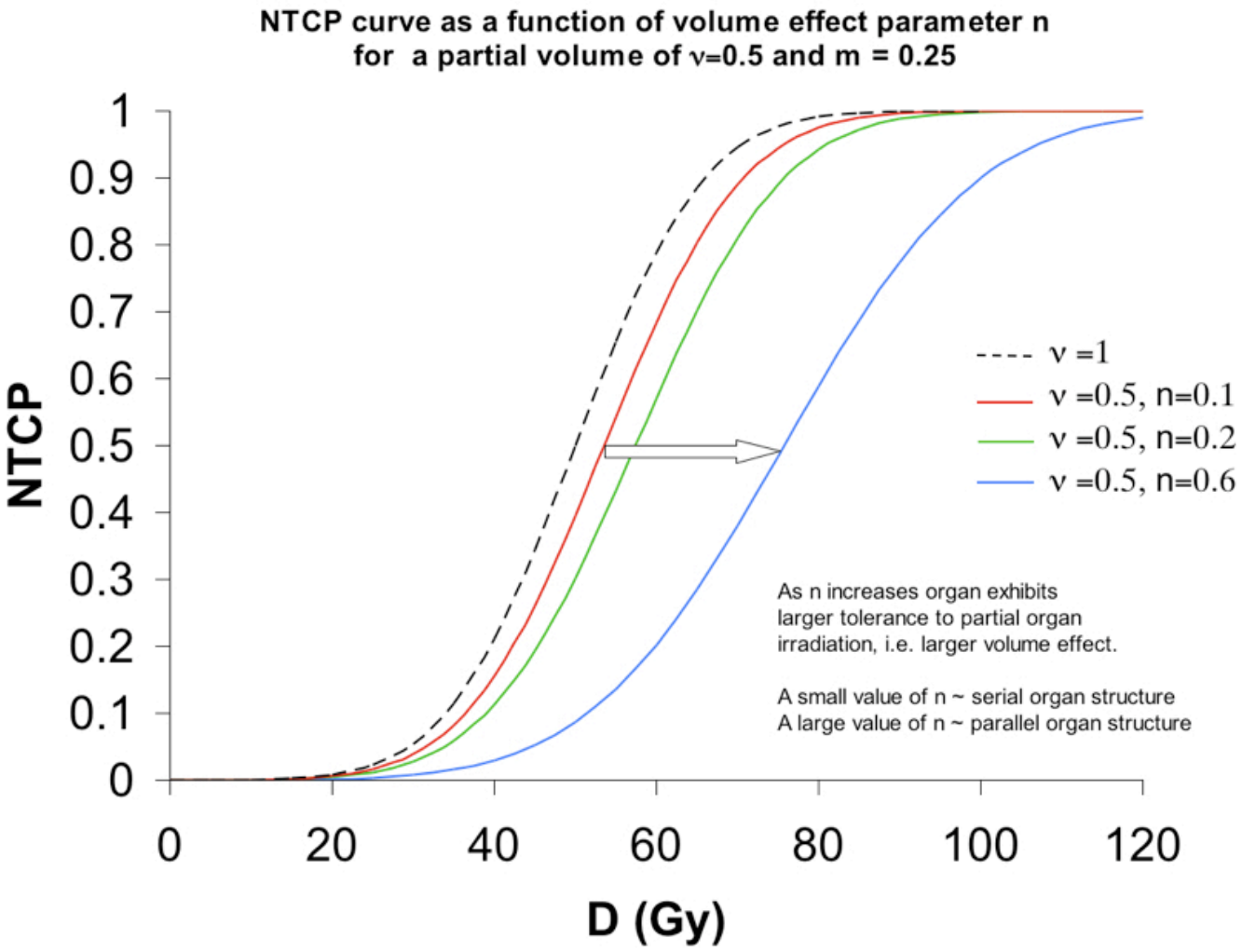
n: Is the volume effect parameter

(Lyman, J.T. *Radiat. Res. Suppl.* 8, **104**, S 13—19 (1985)

Can also be written in closed form making use of the error function, erf(x), as follows:

$$NTCP(v, D) = \frac{1}{2}\left[\, 1 + \mathrm{erf}\left(\frac{D - D_{50}(v)}{\sqrt{2}\, m\, D_{50}(v)}\right)\right], \text{ where } \mathrm{erf}(x) = \frac{2}{\sqrt{\pi}} \int_0^x e^{-t^2} dt$$


NTCP curve as a function of slope parameter m
NTCP
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
D (Gy)
m= 0.125
m= 0.25
m= 0.5


NTCP curve as a function of volume effect parameter n
for a partial volume of ν=0.5 and m = 0.25
NTCP
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
D (Gy)
ν =1
ν =0.5, n=0.1
ν =0.5, n=0.2
ν =0.5, n=0.6
As n increases organ exhibits
larger tolerance to partial organ
irradiation, i.e. larger volume effect.
A small value of n ~ serial organ structure
A large value of n ~ parallel organ structure

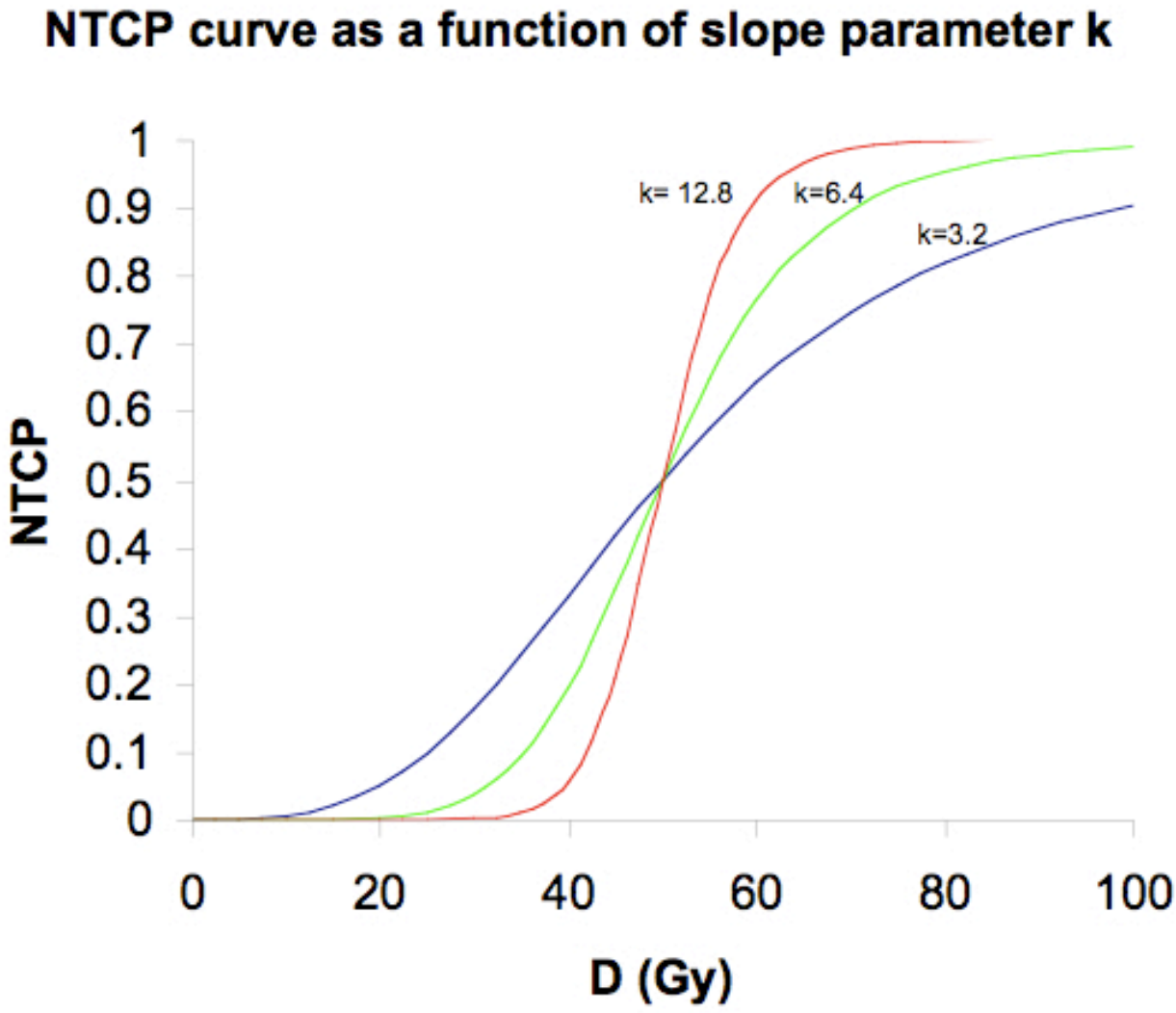
The Logistic Model

- One parameter model
- Assumes uniform whole organ irradiation

$$NTCP(v=1,D)=\frac{1}{\left[1+\left(\frac{D_{50}}{D}\right)^{k}\right]}$$

D_{50}: is the dose that results in a 50% complication probability for some specified complication endpoint.

k: Governs the slope of the NTCP curve.


NTCP curve as a function of slope parameter k
NTCP
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
D (Gy)
k= 12.8
k=6.4
k=3.2

Relationship between the Lyman Model and the Logistic Model

Since both models generate sigmoidal curves, one can demonstrate the equivalence of the Lyman Model and the Logistic Model by matching the dose gradient at D = D_{50}.

Lyman:

$$\gamma_{50} = D_{50} \left. \frac{dNTCP}{dD} \right|_{D_{50}} = \frac{1}{\sqrt{2\pi}\ m}$$

Logistic:

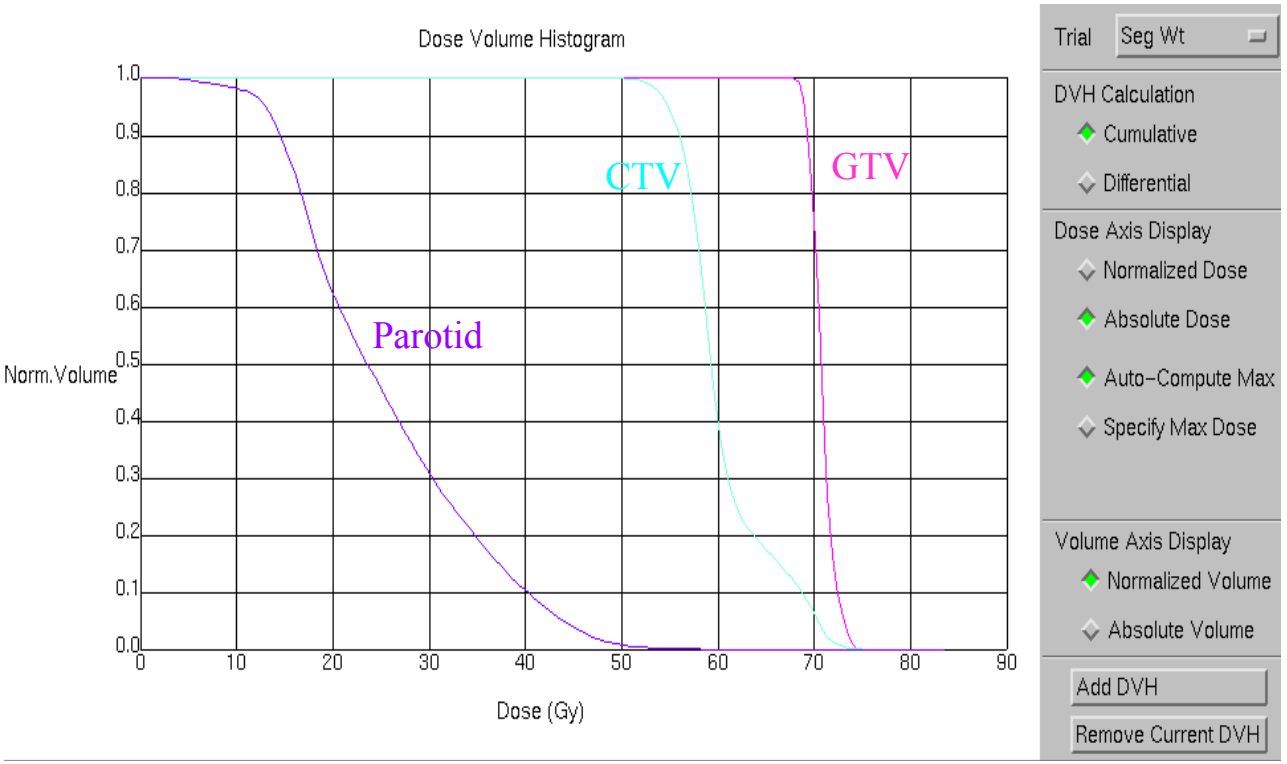
$$\gamma_{50} = D_{50} \left. \frac{dNTCP}{dD} \right|_{D_{50}} = \frac{k}{4}$$

Therefore:

$$k = 4\gamma_{50} = \left. \frac{4}{\sqrt{2\pi}\ m} \right| \approx \frac{1.6}{m}$$

Calculation of NTCP using the Lyman Model for Non-Uniform Normal Tissue Irradiation: The Effective Volume Method.

In general modern treatment planning yields highly non-uniform dose distributions in normal structures, and hence non-uniform dose volume histograms.



Calculation of NTCP using the Lyman Model for Non-Uniform Normal Tissue Irradiation: The Effective Volume Method.

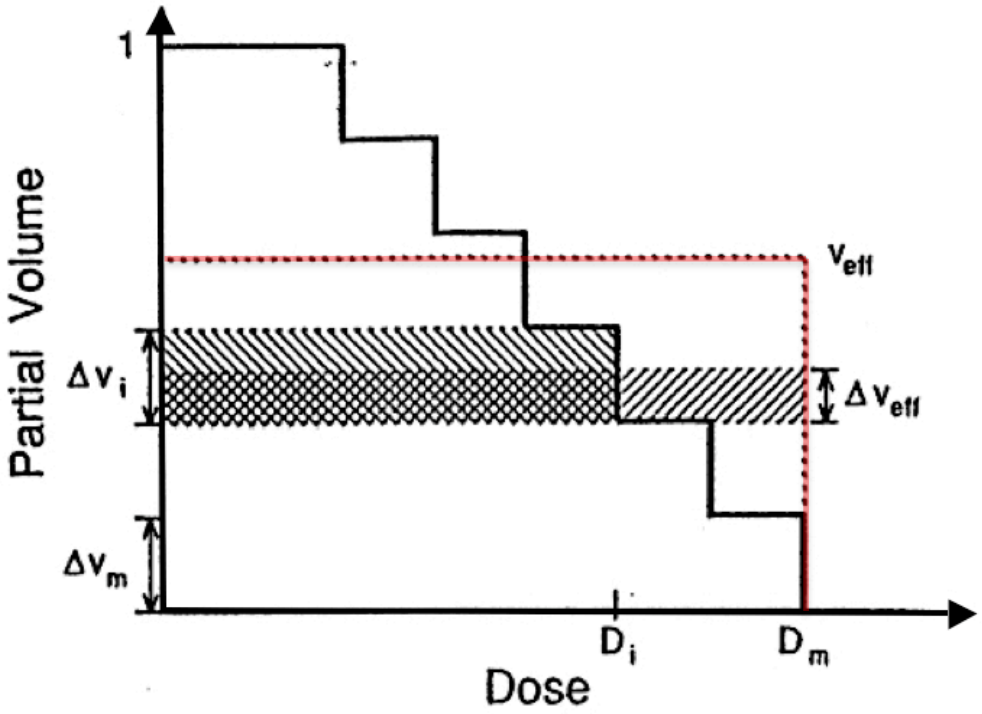
Since, in the Lyman Model includes partial volume as a parameter a reduction scheme that reduces the non-uniform cumulative DVH into a uniform DVH in which an effective volume v_{eff} is irradiated to a reference dose D_{ref} can be found. Kutcher and Burman (Int. J. Radiat. Onc. Biol. Phys. **16** (1989), 1623—1630) have suggested the following volume reduction scheme.

$$v_{eff} = v_{ref} + v_1\left(\frac{D_1}{D_{ref}}\right)^{\frac{1}{n}} + v_2\left(\frac{D_2}{D_{ref}}\right)^{\frac{1}{n}} + \cdots + v_m\left(\frac{D_m}{D_{ref}}\right)^{\frac{1}{n}} + \cdots = \sum_i v_i\left(\frac{D_i}{D_{ref}}\right)^{\frac{1}{n}}$$

In fact, v_{eff} is a dose weighted volume average. For *n=1*, v_{eff} the equal to the mean dose received by the structure divided by the reference dose. In the original Kutcher and Burman paper the $D_{ref} = D_{max}$. However, other dose values for the reference dose can and have been chosen.

Calculation of NTCP using the Lyman Model for Non-Uniform Normal Tissue Irradiation: The Effective Volume Method.

The fraction of an organ irradiated to a given dose can be characterized by a cumulative DVH.



Calculation of NTCP using the Lyman Model for Non-Uniform Normal Tissue Irradiation: The Effective Volume Method.

- This method is somewhat empirical but Kutcher and Burman have shown that it has many desirable features:
  - It reduces to same NTCP for uniform irradiation as is used for the input data.
  - When small hot or cold spots are introduced to an otherwise uniformly irradiated volume, the NTCP marginally rises or falls respectively, the magnitude of the change depending on the value for n.
  - For small n the max dose drives NTCP, while for large n mean dose drives NTCP.

Normal Tissue DVH-Reduction using generalized EUD

Rancatti et al. (Radiotherapy and Oncology 2004;73:21-32) have proposed a normal tissue DHV reduction schema that is based on generalized EUD (gEUD) and this is equivalent to the Kutcher-Burman DVH reduction schema. Niemierko has defined generalized EUD as:

$$gEUD = \left(\sum_i v_i D_i^{1/n} \right)^n$$

Recall that in the Kutcher-Burman DVH reduction formalism the final NTCP formula is given by:

$$NTCP(D_{ref}, v_{eff}) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{u^2}{2} \right) du$$

$$t = \frac{D_{ref} - D_{50}(v_{eff})}{m D_{50}(v_{eff})}; \qquad D_{50}(v_{eff}) = D_{50}(1) v_{eff}^{-n}$$

Normal Tissue DVH-Reduction using generalized EUD

Using this we can write t as follows:

$$t = \frac{D_{ref} v_{eff}^{n} - D_{50}(1)}{m D_{50}(1)}$$

Now let us look at the expression $D_{ref} v_{eff}^{n}$:

$$D_{ref} v_{eff}^{n} = D_{ref} \left(\sum_i v_i \left(\frac{D_i}{D_{ref}} \right)^{\frac{1}{n}} \right)^n = \left(\sum_i v_i D_{ref}^{\frac{1}{n}} \left(\frac{D_i}{D_{ref}} \right)^{\frac{1}{n}} \right)^n = \left(\sum_i v_i D_i^{\frac{1}{n}} \right)^n = gEUD,$$

where n is the volume effect parameter of the Lyman model.

Normal Tissue DVH-Reduction using generalized EUD

Therefore, the NCTP for an inhomogeneously irradiated volume in terms of *gEUD* becomes:

$$NTCP(gEUD) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{u^2}{2}\right) du$$

$$t = \frac{gEUD - D_{50}(1)}{mD_{50}(1)}; \quad gEUD = \left(\sum_i v_i D_i^{\frac{1}{n}}\right)^n \text{; where } n \text{ is the volume effect parameter}$$

This is a very natural expression of NTCP for an inhomogeneously irradiated volume. Note, that n here is not used in the way defined by Niemierko, but is the volume effect parameter of the Lyman model.

Advantages and Disadvantages of these Models

Disadvantages:

- *No real Biological Basis for models. Models are chosen for their ability to describe the observed dose response curves for normal tissues.*
- *The effect of partial irradiation of organs is inadequately modeled (partial volume v for Lyman Model) or cannot be handled (Logistic Model assumes entire organ is irradiated)*
- *Strictly applicable only to homogeneously irradiated organs. However, normal tissue DVHs are very inhomogeneous. Rescue is to reduce the DVH to a homogenous DVH that has an effective volume irradiated to a reference dose D_{ref} (Lyman Model) or that assumes that the entire organ is irradiated to an effective dose D_{eff} (Logistic Model). Therefore, Lyman Model places an emphasis on the Hot Spot in the organ, while in Logistic Model the Hot Spots are de-emphasized.*

Advantages:

- Because of their simple mathematical form these models can be easily fitted to clinical data.

Example: NTCP prediction using the Lyman Model for Parotid Irradiation (D_{50}=28.4Gy, n = 1.0, m = 0.18)

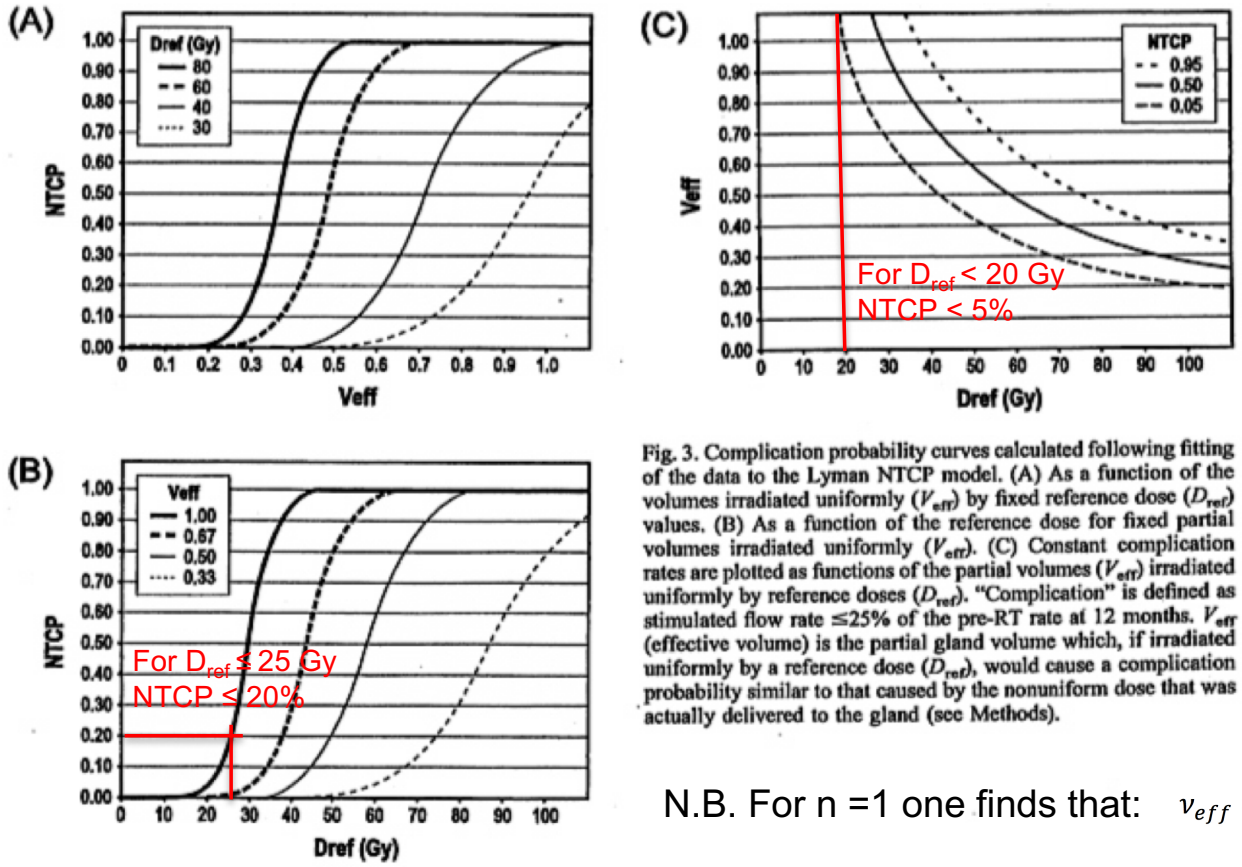


Fig. 3. Complication probability curves calculated following fitting of the data to the Lyman NTCP model. (A) As a function of the volumes irradiated uniformly (V_{eff}) by fixed reference dose (D_{ref}) values. (B) As a function of the reference dose for fixed partial volumes irradiated uniformly (V_{eff}). (C) Constant complication rates are plotted as functions of the partial volumes (V_{eff}) irradiated uniformly by reference doses (D_{ref}). "Complication" is defined as stimulated flow rate ≤25% of the pre-RT rate at 12 months. V_{eff} (effective volume) is the partial gland volume which, if irradiated uniformly by a reference dose (D_{ref}), would cause a complication probability similar to that caused by the nonuniform dose that was actually delivered to the gland (see Methods).

N.B. For n =1 one finds that: $v_{eff} = \sum_i v_i \left(\frac{D_i}{D_{ref}}\right) = \frac{D_{mean}}{D_{ref}}$

Eisbruch et al. Int. J. Radiat. Onc. Bio. Phys Vol. 45(3) 577-587

RADIOTHERAPY DOSE–VOLUME EFFECTS ON SALIVARY GLAND FUNCTION

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Publications relating parotid dose–volume characteristics to radiotherapy-induced salivary toxicity were reviewed. Late salivary dysfunction has been correlated to the mean parotid gland dose, with recovery occurring with time. Severe xerostomia (defined as long-term salivary function of <25% of baseline) is usually avoided if at least one parotid gland is spared to a mean dose of less than ≈20 Gy or if both glands are spared to less than ≈25 Gy (mean dose). For complex, partial-volume RT patterns (*e.g.*, intensity-modulated radiotherapy), each parotid mean dose should be kept as low as possible, consistent with the desired clinical target volume coverage. A lower parotid mean dose usually results in better function. Submandibular gland sparing also significantly decreases the risk of xerostomia. The currently available predictive models are imprecise, and additional study is required to identify more accurate models of xerostomia risk.

Xerostomia, salivary parotid glands, submandibular salivary glands, radiotherapy, dose–volume effects.

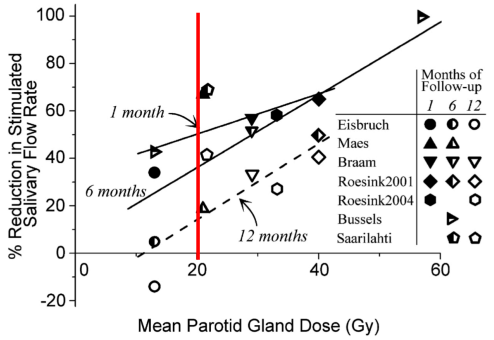

Fig. 2. Mean percentage of reduction in stimulated salivary flow rate vs. mean parotid gland dose for different follow-up durations (8, 10, 12, 14, 15, 16). Follow-up durations of 1, 6, and 12 months represent ranges of 1–1.5, 6–7, and 12 months, respectively. Linear fits of data from different follow-up intervals shown. Dose–response effect appears present at all times, with shift of data to right with time, suggesting functional repair or regeneration.

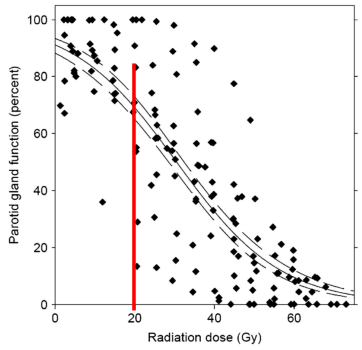

Fig. 4. Population-based dose vs. local function response (salivary function at rest) from imaging study by Buus *et al.* (2). Local functional decline in metabolic clearance of parotid salivary glands vs. local dose, according to voxel-by-voxel estimated time-activity curves of intravenously injected C11-methionine. Data points from 12 patients shown, along with best-fit curve and 95% confidence intervals of curve fit. Individual gland curves reported by Buus *et al.* (2) deviated significantly from this population average curve (reproduced from Buus *et al.* [2], used with permission.) This population curve demonstrated functional decline in salivary function even at low doses.

Review of post-QUANTEC dose-response models for HN RT toxicity

International Journal of Radiation Oncology biology • physics
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Critical Review

Systematic Review of Normal Tissue Complication Models Relevant to Standard Fractionation Radiation Therapy of the Head and Neck Region Published After the QUANTEC Reports

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Madhur K. Garg, MD,*,†,‡,§ Chandan Guha, MD, PhD,*,†,§,‖
and Wolfgang A. Tomé, PhD, FAAPM, FASTRO*,†,¶

Brodin NP, Kabarriti R, Garg MK, Guha C, Tomé WA. Int J Radiat Oncol Biol Phys. 2018 Feb 1;100(2):391-407. Review. PMID: 29353656

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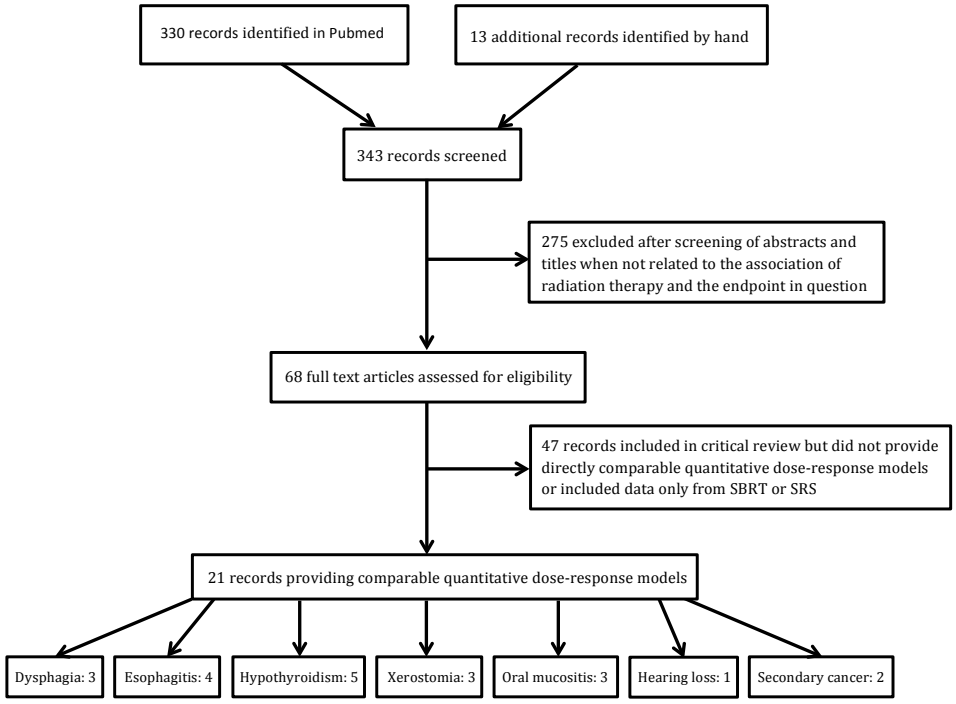
Review of post-QUANTEC dose-response models for HN RT toxicity



Brodin NP, Kabarriti R, Garg MK, Guha C, Tomé WA. Int J Radiat Oncol Biol Phys. 2018 Feb 1;100(2):391-407. doi: 10.1016/j.ijrobp.2017.09.041. Epub 2017 Sep 29. Review. PMID: 29353656

Common toxicity endpoints

- ***Dysphagia***
  - Grade ≥2 incidence ~60-70% within 6 months of RT
- ***Xerostomia***
  - Grade 4 incidence ~30-40% at 1 year with IMRT, typically ~80% with 3DCRT
- ***Hypothyroidism***
  - Clinical or biochemical hypothyroidism incidence ~20-50% within 2 years after RT
- ***Oral mucositis***
  - Grade ≥3 incidence ~50-70% during or within 8 weeks of RT
- ***Hearing loss***
  - Mild-to-severe hearing loss incidence ~20-30%
- ***Esophagitis***
  - Grade ≥3 incidence ~30-40% (majority of data from lung cancer patients)
- ***Fatigue***
  - Grade ≥2 incidence ~50-60% during or within 3 months of RT

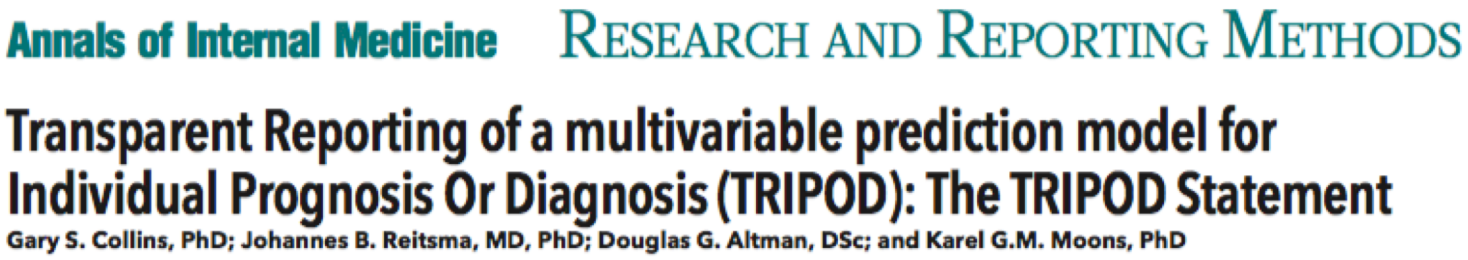
References provided in: Brodin NP, Kabarriti R, Garg MK, Guha C, Tomé WA. Int J Radiat Oncol Biol Phys. 2018 Feb 1;100(2):391-407. doi: 10.1016/j.ijrobp.2017.09.041. Epub 2017 Sep 29. Review. PMID: 29353656

Critical organs-at-risk

- Dysphagia
  - ***Larynx, pharyngeal constrictor muscles***
- Xerostomia
  - ***Parotid glands, submandibular glands***
- Hypothyroidism
  - ***Thyroid, pituitary gland***
- Oral mucositis
  - ***Oral cavity, oral mucosa***
- Hearing loss
  - ***Cochlea, inner ear***
- Esophagitis
  - ***Esophagus***
- Fatigue
  - ***Hypothesized OARs: brainstem, cerebellum, posterior fossa***

Dose-response models reviewed

- Adherence to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement was considered



*simultaneously published in various inter-disciplinary journals

TRIPOD adherence

TRIPOD model development and validation checklist item # related to methods and results

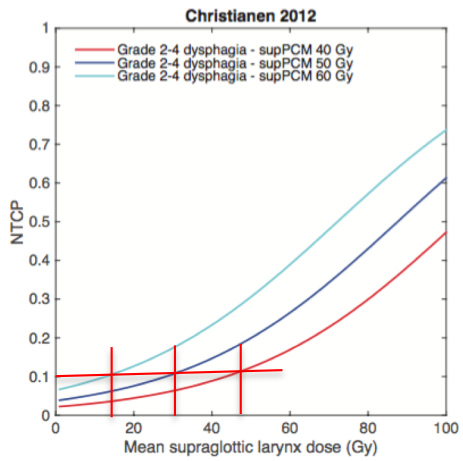
	4ab	5ac	5b	6a	7a	9	10b	10c	10d	11	12	13a	13b	13c	14a	14b	15ab	16	17
Dysphagia																			
Christianen et al. 2012[20]	✔	✔	✔	✔	✔	✔			✔	✔			✔			✔	✔	✔	
Otter et al. 2015[24]	✔	✔	✔	✔	✔	✔			✔			✔	✔		✔		✔	✔	
Bhide et al. 2012[35]	✔	✔	✔	✔	✔	✔			✔								✔		
Esophagitis																			
Huang et al. 2012[26]	✔	✔	✔	✔	✔	✔	✔	✔	✔			✔	✔		✔	✔	✔		
Kwint et al. 2012[27]	✔	✔	✔	✔	✔	✔						✔	✔		✔	✔	✔		
Wijsman et al. 2015[28]	✔	✔	✔	✔	✔	✔	✔	✔	✔			✔	✔		✔	✔	✔	✔	
Wu et al. 2014[29]		✔	✔	✔	✔	✔				✔		✔	✔		✔				
Hypothyroidism																			
Bakhshandeh et al. 2013[43]		✔	✔	✔	✔	✔	✔					✔	✔		✔		✔		
Boomsma et al. 2012[44]	✔	✔	✔	✔	✔	✔	✔	✔	✔			✔	✔		✔	✔	✔	✔	
Cella et al. 2012[49]		✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔		✔		✔	✔	
Rønjom et al. 2015[45]	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔	✔	✔		✔	✔	
Vogelius et al. 2011[50]	✔	✔	✔	✔	✔					✔			✔				✔		
Xerostomia																			
Chen et al. 2013[31]	✔	✔	✔	✔	✔	✔						✔	✔			✔	✔		
Moiseenko et al. 2012[32]	✔	✔	✔	✔	✔	✔		✔			✔	✔	✔		✔		✔		✔
Beetz et al. 2012[30]	✔	✔	✔	✔	✔	✔	✔		✔			✔	✔		✔		✔	✔	
Oral mucositis																			
Dean et al. 2016[36]	✔	✔	✔	✔	✔	✔	✔	✔	✔				✔			✔	✔	✔	
Otter et al. 2015[24]	✔	✔	✔	✔	✔	✔			✔			✔	✔		✔		✔	✔	
Sanguineti et al. 2012[37]	✔	✔	✔	✔	✔		✔		✔	✔		✔	✔			✔		✔	
Bhide et al. 2012[35]	✔	✔	✔	✔	✔	✔			✔								✔		
Hearing loss																			
De Marzi et al. 2015[53]	✔	✔	✔	✔	✔	✔	✔		✔			✔			✔		✔	✔	
Secondary cancer																			
Morton et al. 2012[65]	✔	✔	✔	✔	✔	✔	✔			✔		✔	✔		✔		✔		
Schneider et al. 2011[67]	✔	✔	✔	✔	✔		✔						✔				✔		

The following page provides a short description for each included item, whereas the full checklist can be accessed from: https://www.equator-network.org/reporting-guidelines/tripod-statement/

4ab	Describe source data and specify study dates
5ac	Specify study setting and provide treatment details
5b	Describe eligibility criteria
6a	Define predicted outcome including time of assessment
7a	Define predictor variables including time of measurement
9	Describe handling of missing data
10b	Specify model and model building procedures
10c	Describe prediction calculations in the validation setting
10d	Specify model performance metrics
11	Creation of various risk groups
12	Identify differences between training and validation data
13a	Describe sample size and number of events, preferably with temporal information
13b	Describe patient characteristics and potential missing data
13c	Show comparison of patient characteristics between training and validation data
14a	Specify analyzed sample size and number of events
14b	Report unadjusted associations between predictors and outcome
15ab	Present full prediction model and explain model use
16	Report performance measures with confidence intervals
17	Report results from model updating

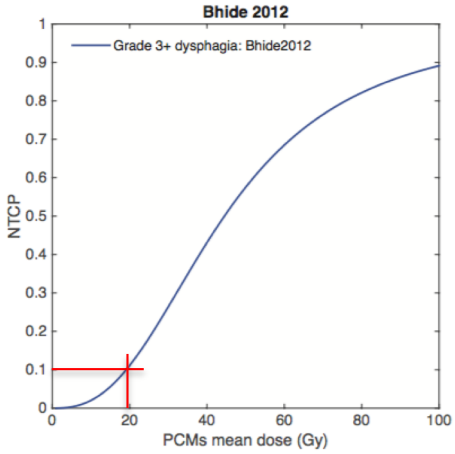
Dose-response models: Dysphagia

NTCP as a function of mean dose to superior pharyngeal constrictor muscles and mean dose to supraglottic larynx



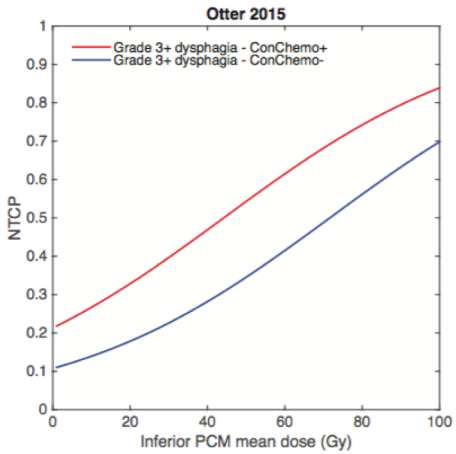
Multivariable
Relevance score: 215
Prospective
IMRT
or
3DCRT

Mean dose to pharyngeal constrictor muscles



Univariable
Relevance score: 170
Prospective
IMRT

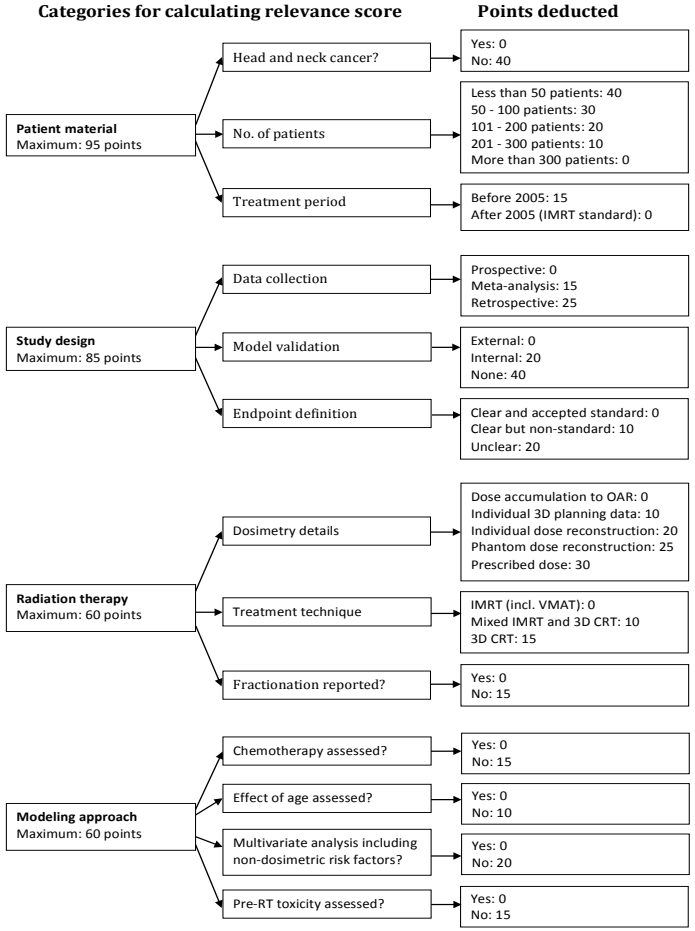
Influence of Chemotherapy



Multivariable
Relevance score: 215
Prospective
IMRT

*Relevance score: Composite measure of the applicability to modern day head and neck cancer patients, higher score = more applicable

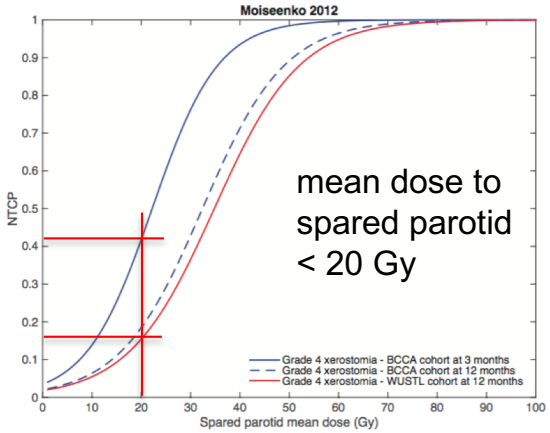
How is the relevance score derived?



Applicable to fractionated head and neck cancer RT, categories should be adjusted to match the specific site of interest

Dose-response models: Xerostomia

Moiseenko and colleagues tested the **validity of the QUANTEC xerostomia recommendations on an independent, prospectively acquired dataset**, and found that the suggested constraints performed well, with a negative predictive value of 94%



Univariable

Relevance score: 150

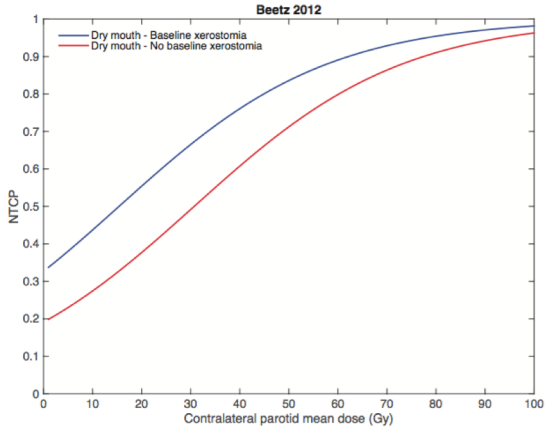
Prospective

IMRT or 3DCRT

NTCP as a function of mean dose @ 6 months to contralateral parotid depending on baseline assessment of xerostomia.

blue curve — baseline xerostomia present

red curve — no baseline xerostomia present



Multivariable

Relevance score: 240

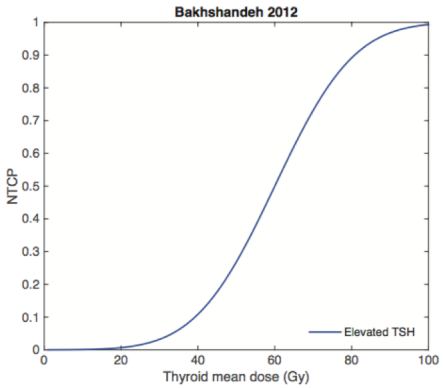
Prospective

IMRT

*Relevance score: Composite measure of the applicability to modern day head and neck cancer patients, higher score = more applicable

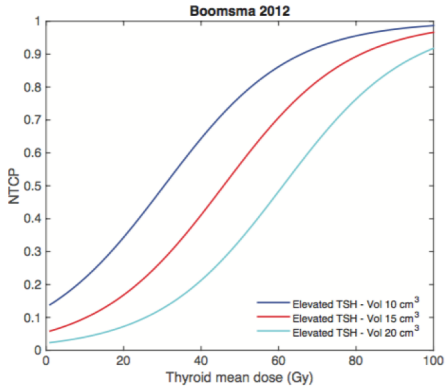
Dose-response models: Hypothyroidism

Risk for elevated Thyroid Stimulating Hormone (TSH) as a function of thyroid mean dose

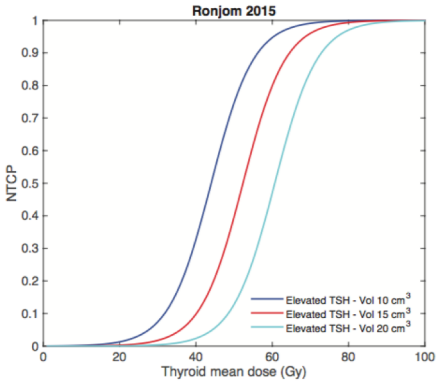


Univariable
Relevance score: 130
Prospective
3DCRT

Risk for elevated Thyroid Stimulating Hormone (TSH) as a function of thyroid volume before treatment and thyroid mean dose



Multivariable
Relevance score: 215
Prospective
IMRT or 3DCRT



Multivariable
Relevance score: 260
Prospective
IMRT

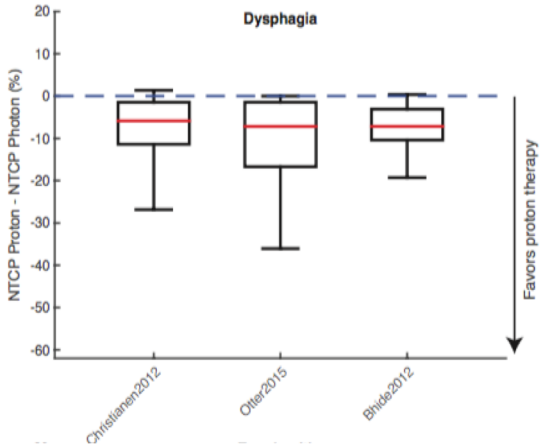
External validation

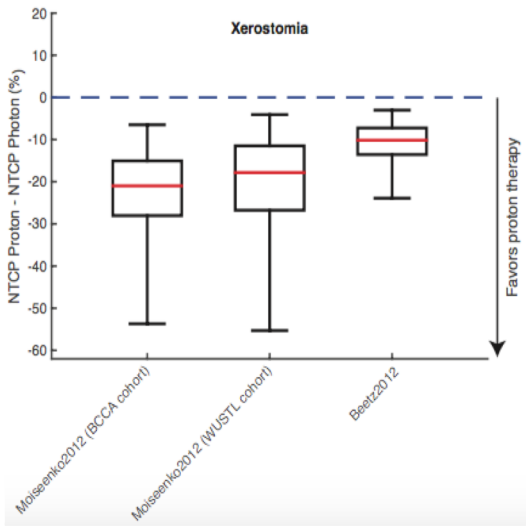
No QUANTEC report on hypothyroidism but systematic review by Vogelius et al. in 2011
Risk factors identified were: female gender; surgery involving the neck or thyroid gland; and Caucasian race

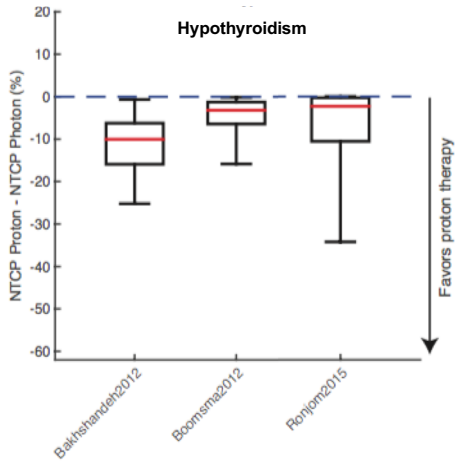
Risk factors for radiation-induced hypothyroidism: a literature-based meta-analysis. Vogelius IR, Bentzen SM, Maraldo MV, Petersen PM, Specht L. Cancer. 2011 Dec 1;117(23):5250-60. doi: 10.1002/cncr.26186. Review.

Agreement between models?

- Tested in a cohort of oropharyngeal head and neck cancer patients by comparing photon IMRT to proton IMPT







Models show considerable variation in estimated NTCP especially in the extremes of the 95% CI (whiskers), but show reasonable agreement in median and inter-quartile range

Brodin et al. Implementation of a Quantitative Clinical Decision-support Strategy to Identify Which Oropharyngeal Head and Neck Cancer Patients will Benefit the Most from Proton Radiation Therapy. Manuscript submitted for publication

Composite estimates from multiple models

- Relevance score (RS) can be used to create weighted composite estimates

$$NTCP_{Composite,i} = \frac{\sum_j NTCP_{i,j} \cdot RS_{i,j}}{\sum_j RS_{i,j}} \text{ where } j \text{ is the number of models for each endpoint } i$$

	Dysphagia	Esophagitis	Hypothyroidism	Xerostomia	Oral mucositis
Photon IMRT	45.9% (30.0 , 71.4%)	52.7% (40.7 , 60.7%)	46.0% (22.0 , 69.1%)	39.8% (29.6 , 50.5%)	57.9% (38.3 , 70.0%)
Proton IMPT	36.4% (24.4 , 58.5%)	42.0% (31.9 , 49.5%)	39.9% (18.5 , 61.9%)	27.5% (20.5 , 36.4%)	54.0% (35.6 , 63.7%)

- Considers the information provided from multiple models rather than assuming that a single model has the correct answer

What we do and do not “know”:

What we know now:

- The QUANTEC criteria for parotid sparing work well and the use of IMRT has brought down the incidence of xerostomia substantially
- There are validated models for hypothyroidism and the field is starting to recognize the importance of patient-reported outcomes
- While IMRT reduces the risk of several H&N complications it may in fact increase the risk of fatigue by inadvertently irradiating parts of the CNS

What we still don’t know:

- Have we reached the ultimate utility of “classical” NTCP models?
- Do we need to move to machine learning methods and models describing non-uniform risk throughout an OAR to improve our estimates and treatment strategies?
- Food for thought, will the improved model complexity outweigh the benefits because of difficult implementations?
- Dose-volume constraints for HNC RT are still evolving in the IMRT era, therefore validation studies and prospective studies evaluating individualized risk-adaptation strategies are needed to make the best use of the rapidly evolving technological capabilities of modern day radiation therapy.

Appendix

Relationship between the Lyman Model and the Logistic Model

Evaluate dose gradient at D_{50} for the Lyman Model:

$$\left.\frac{dNTCP}{dD}\right|_{D_{50}} = \left.\frac{d}{dD}\left\{\frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t(D)}\exp\left(-\frac{u^2}{2}\right)du\right\}\right|_{D_{50}}$$

$$= \left.\left\{\frac{1}{\sqrt{2\pi}}\frac{d}{dD}t(D)\exp\left(-\frac{t^2(D)}{2}\right)\right\}\right|_{D_{50}}$$

$$= \left.\left\{\frac{1}{\sqrt{2\pi}}\frac{d}{dD}\left[\frac{D-D_{50}}{mD_{50}}\right]\exp\left(-\frac{t^2(D)}{2}\right)\right\}\right|_{D_{50}}$$

$$= \left.\left\{\frac{1}{\sqrt{2\pi}}\left[\frac{1}{mD_{50}}\right]\exp\left(-\frac{t^2(D)}{2}\right)\right\}\right|_{D_{50}}$$

$$= \frac{1}{\sqrt{2\pi}}\left[\frac{1}{mD_{50}}\right]\exp\left(-\frac{t^2(D_{50})}{2}\right)$$

$$= \frac{1}{\sqrt{2\pi}}\left[\frac{1}{mD_{50}}\right]\exp(-0)$$

$$= \frac{1}{\sqrt{2\pi}\ m\,D_{50}}$$

Relationship between the Lyman Model and the Logistic Model

Evaluate dose gradient at D_{50} for the Logistic Model:

$$\left.\frac{dNTCP}{dD}\right|_{D_{50}} = \left.\frac{d}{dD}\left\{\left[1+\left(\frac{D_{50}}{D}\right)^{k}\right]^{-1}\right\}\right|_{D_{50}}$$

$$= \left.\left\{-\left[1+\left(\frac{D}{D_{50}}\right)^{-k}\right]^{-2} D_{50}^{k}\frac{d}{dD}\left[D^{-k}\right]\right\}\right|_{D_{50}}$$

$$= \left.\left\{-\left[1+\left(\frac{D}{D_{50}}\right)^{-k}\right]^{-2} D_{50}^{k}(-k)D^{-(k+1)}\right\}\right|_{D_{50}}$$

$$= \left[1+\left(\frac{D_{50}}{D_{50}}\right)^{k}\right]^{-2} D_{50}^{k}kD_{50}^{-(k+1)}$$

$$= [2]^{-2}\frac{k}{D_{50}}$$

$$= \frac{k}{4D_{50}}$$