NTCP modelling – re-irradiation challenges

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Clinical challenge

- A patient who received previous radiation treatment comes with a second primary tumour in or near the previously treated area or a recurrence in the previously treated area.

- Options:
  - Surgery (not all patients are operable or their tumours can be resected)
  - Chemotherapy (generally a palliative approach)
  - Re-irradiation (could offer disease control)

- Challenge: Find the dose (distributions) that would allow the control of the second tumour while avoiding significant acute and late morbidity.
  - Use the tool of modelling the complication probabilities in the normal tissues taking into account both treatments.

Modelling

- To simulate a process, a concept or the operation of a system (commonly with the aid of a computer).
  - Starting from ground principles and processes (mechanistic modelling)
  - Starting from observations (empirical modelling)
  - Combining observations and principles (semi-empirical/semi-mechanistic modelling)

- The aims of modelling the process leading to complications could be:
  - To describe it
  - To predict its outcome

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NTCP models

- Lyman-Kutcher-Burman (LKB) model:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx,$$

  - where $t = \frac{D - D_{50}}{m D_{50}}$

- Logit model:

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

- Relative seriality (RS) model:

$$NTCP = \left\{1 - \prod_{i=1}^{M} [1 - P(D_i)^s]^{\Delta v_i}\right\}^{1/s},$$

  - where $P(D_i) = exp\left[-e^{e\gamma - (D_i/D_{50})(e\gamma - lnln2)}\right]$

NTCP models

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Non-mechanistic

Generally assume uniform irradiation

- Logit model:

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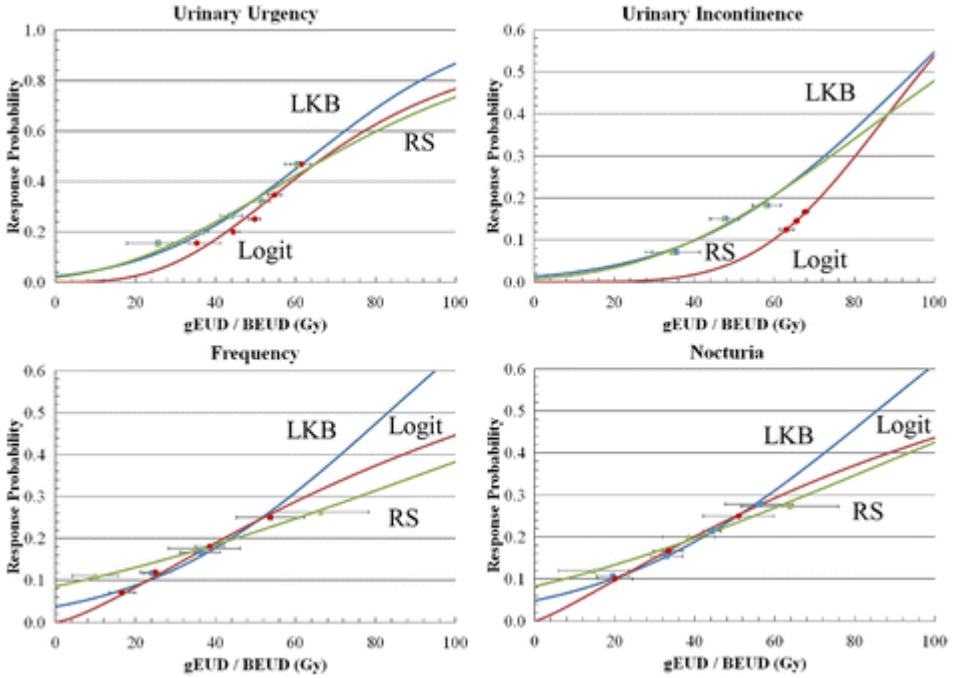
NTCP models

- The NTCP models have different shapes.



Mavroidis et al (2018)

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Applying NTCP models

- What are the relevant OaR?
  - Model parameters: α/β, D_{50}, m, k, s
- How are the dose distributions in an organ?
  - Could we use DVH reduction to find the equivalent uniform dose?
- In case of multiple plans, how was the dose deposited in the two treatments?
  - Do the hotspots coincide in the two plans?

Dose distributions in radiation therapy

- Normal tissue irradiation is seldom uniform.

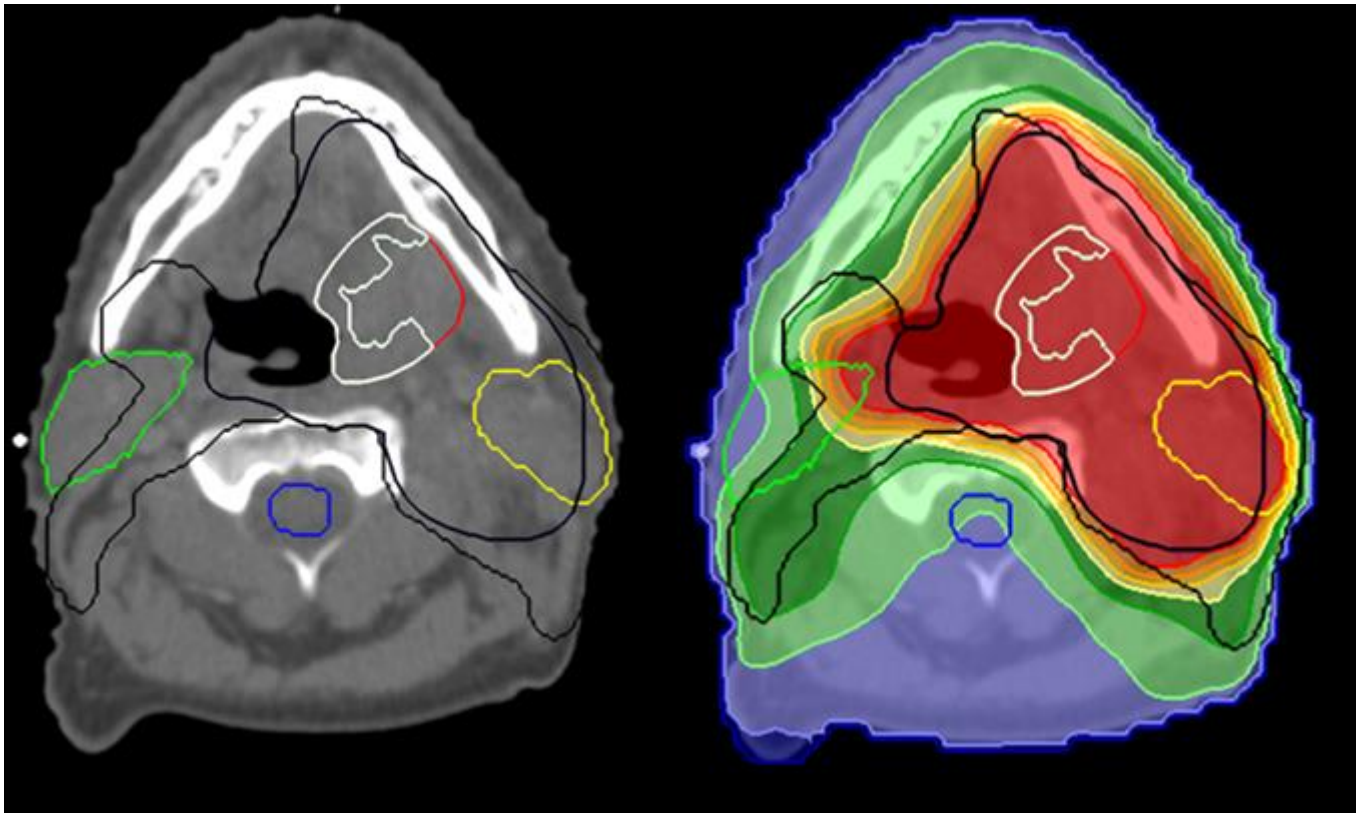
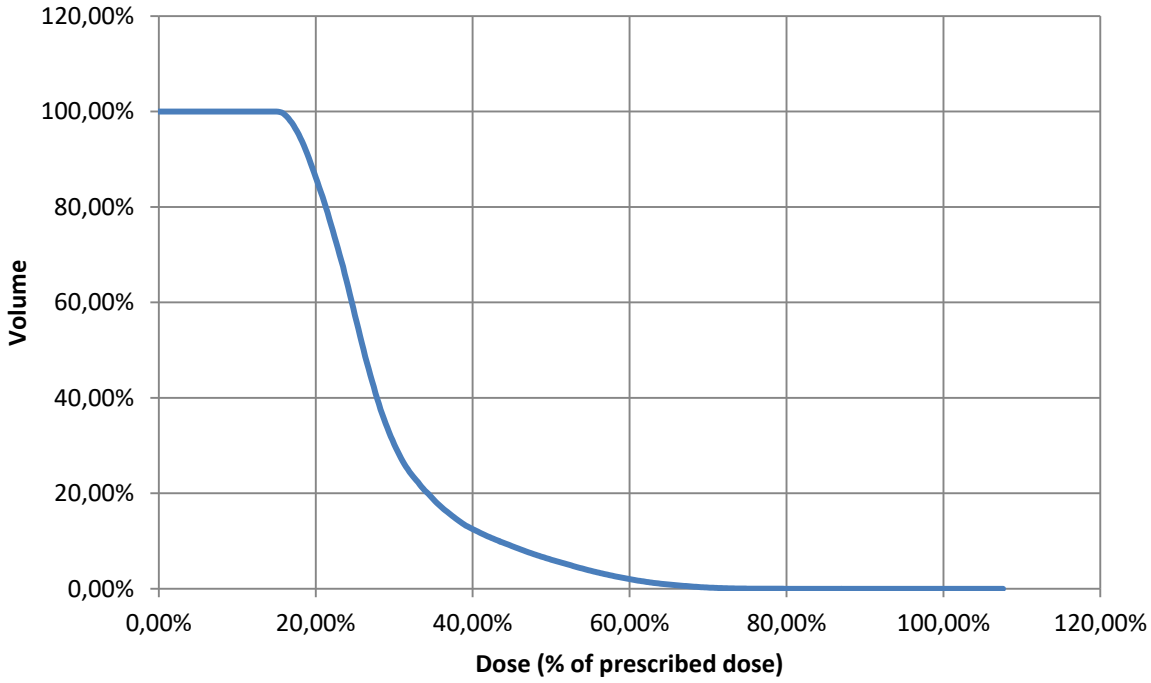


Image courtesy of M. Lazzeroni

Dose volume histogram (DVH)

- Irradiation heterogeneity is quantified by the DVH.



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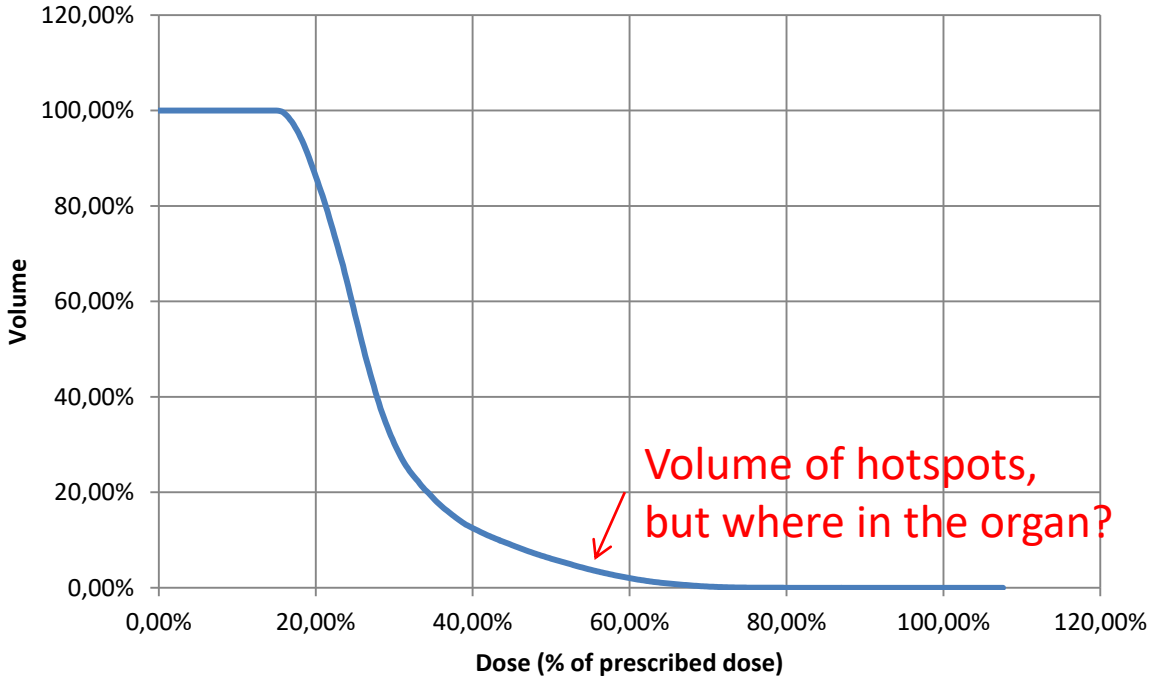
Dose volume histogram (DVH)

- Irradiation heterogeneity is quantified by the DVH.
- Spatial distribution is lost.



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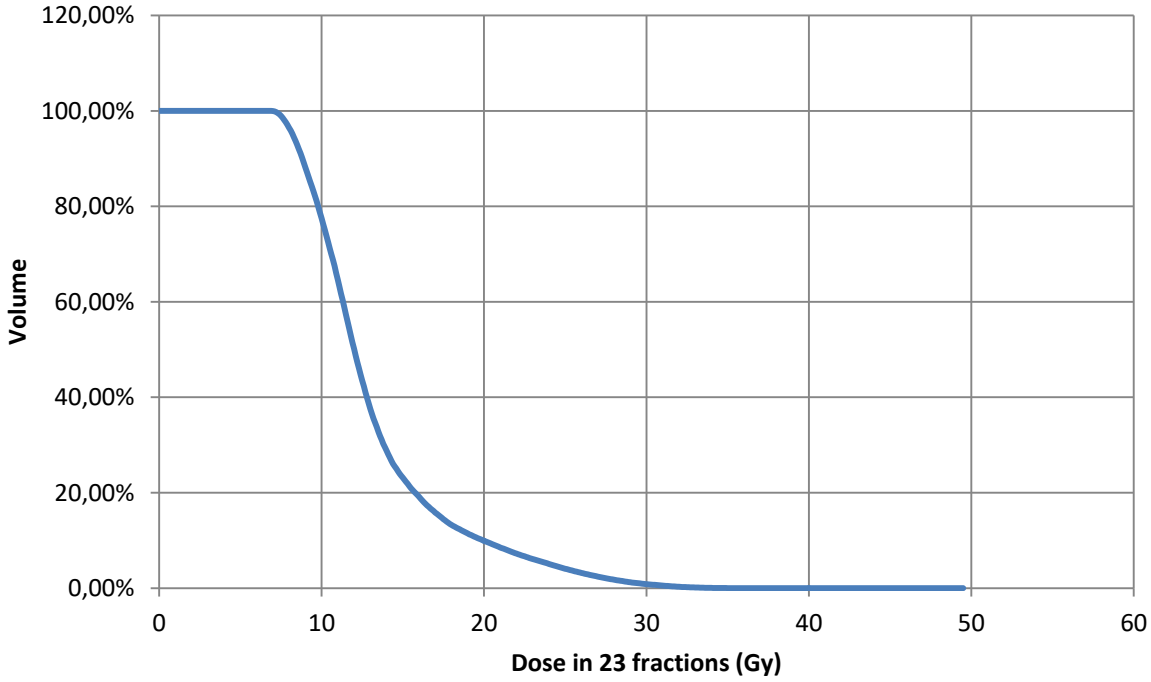
Dose volume histogram (DVH)

- Describe dose delivery with various doses per fraction.
- A conversion is needed to relate the doses to known thresholds.



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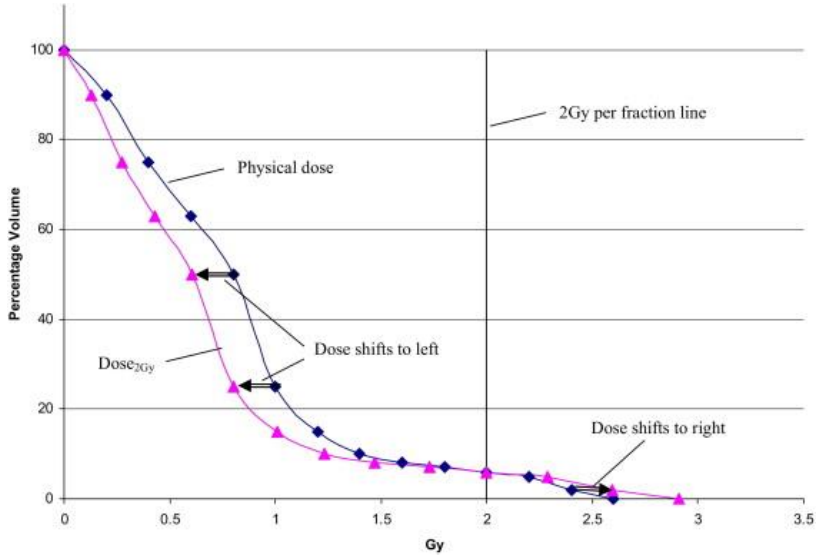
EQD_2 (equivalent dose in 2 Gy fractions)

- Each bin (D_i) in the DVH could be converted to the equivalent dose in 2 Gy per fraction, $(EDQ_2)_i$.

$$(EQD_2)_i = D_i \frac{\left(1+\frac{d_i}{\alpha/\beta}\right)}{\left(1+\frac{2}{\alpha/\beta}\right)} \qquad \text{or} \qquad (EQD_2)_i = D_i \frac{\left(1+\frac{D_i/n}{\alpha/\beta}\right)}{\left(1+\frac{2}{\alpha/\beta}\right)}$$



Leung et al (2011)

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gEUD (generalized Equivalent Uniform Dose)

- The DVH could be further compressed into the gEUD.

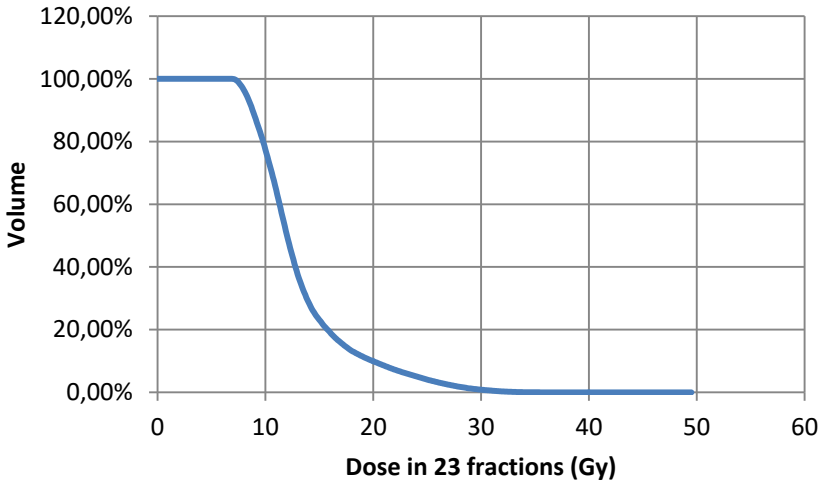
$$gEUD = \left[\sum_{i=1}^{M} (EQD_2)_i^{1/a} \cdot \frac{V_i}{V}\right]^a$$

- The conversion of the DVH into gEUD removes any measure of the heterogeneity since it is a single value.
  - Two different DVH distributions could result in the same gEUD.
  - This is especially problematic for tissues with non-uniform sensitivity.

- gEUD values are used in NTCP models (logit and LKB).

Plan summation

- NTCP calculation often involves plan summation, e.g. main (elective) plan and a boost (or initial plan and re-irradiation plan).



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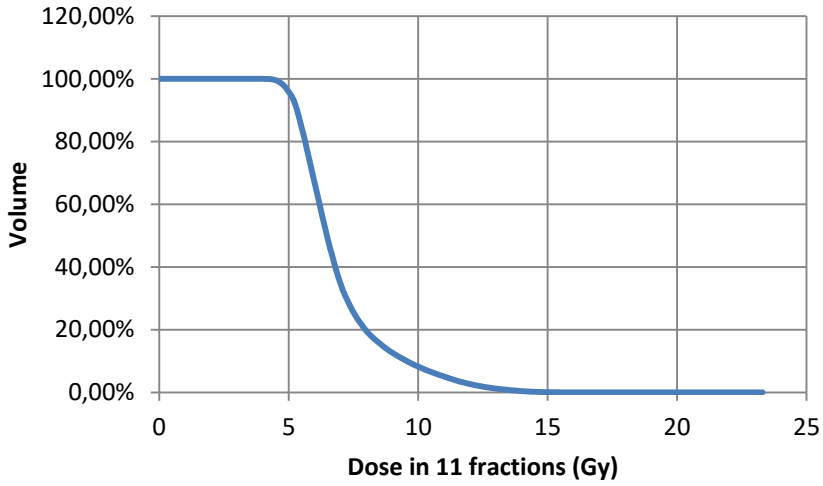

DVH from the elective plan

DVH from the boost plan

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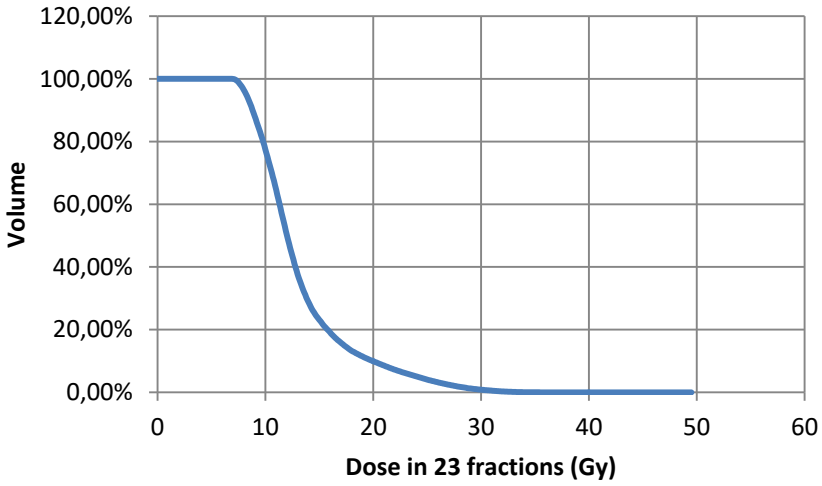
Plan summation

- The DVH of the TPS plan sum has no radiobiological meaning as its bins are sums of physical doses from different fractionations.



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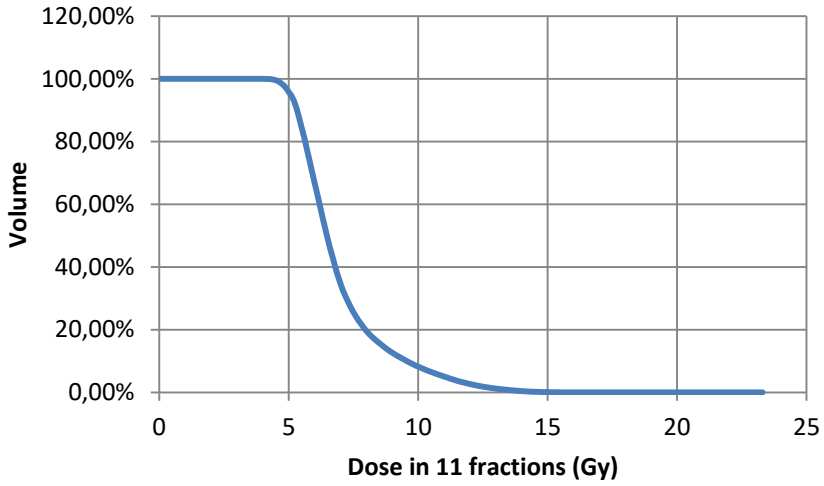

- gEUDs are not additive.
- Summing the hotpots as the worst case scenario

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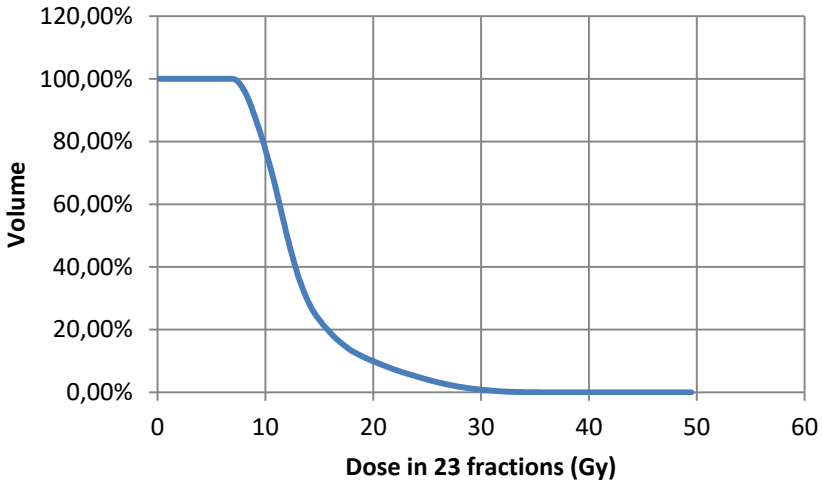

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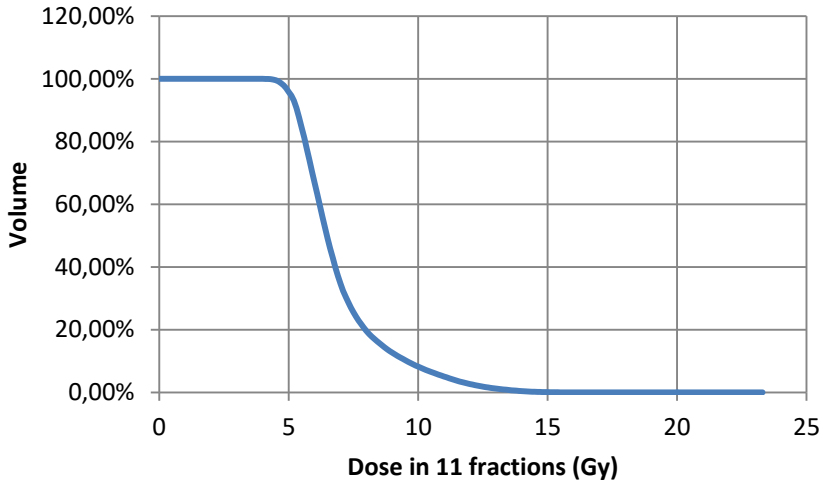

- gEUDs are not additive.
- But EQD_2 are additive.

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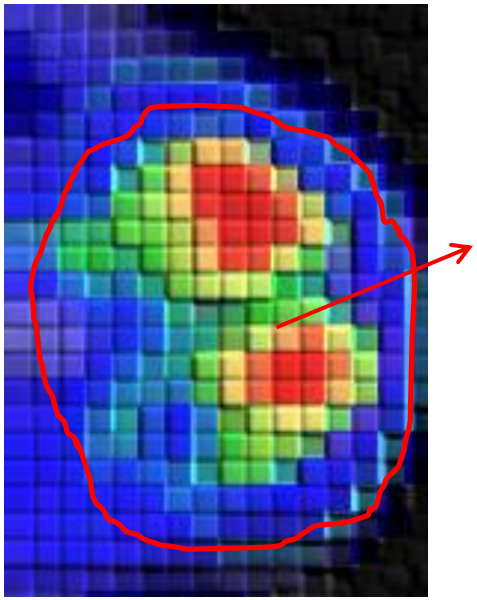
Back to basics!

- Do a voxelwise summation taking into account the fractionation patterns.

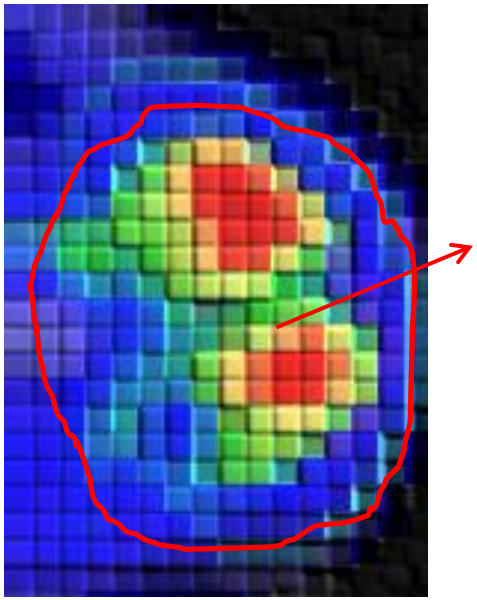


$$(EQD_2)_i = \left[D_i \frac{\left(1 + \frac{d_i}{\alpha/\beta}\right)}{\left(1 + \frac{2}{\alpha/\beta}\right)} \right]_1 + \left[D_i \frac{\left(1 + \frac{d_i}{\alpha/\beta}\right)}{\left(1 + \frac{2}{\alpha/\beta}\right)} \right]_2$$

- One could produce an EQD_2VH to be further used for gEUD and NTCP calculations.

Plan summation

- The EQD_2 contributions of several relevant plans could be summed up:



$$(EQD_2)_i = \left[D_i \frac{\left(1+\frac{d_i}{\alpha/\beta}\right)}{\left(1+\frac{2}{\alpha/\beta}\right)}\right]_1 + \left[D_i \frac{\left(1+\frac{d_i}{\alpha/\beta}\right)}{\left(1+\frac{2}{\alpha/\beta}\right)}\right]_2 + \left[D_i \frac{\left(1+\frac{d_i}{\alpha/\beta}\right)}{\left(1+\frac{2}{\alpha/\beta}\right)}\right]_3 + \left[D_i \frac{\left(1+\frac{d_i}{\alpha/\beta}\right)}{\left(1+\frac{2}{\alpha/\beta}\right)}\right]_4 + \cdots$$

Plan summation

- Leung et al (2011) compared the maximum organ doses between the summation of the maximum dose and the maximum of the sum of EQD_2 for H&N treatments and found up to 4.2 Gy in differences.

- They also reported that the summation of maximum doses could lead to an overestimation of the NTCP.

- Most studies do not report fractionation-corrected cumulative doses, which could be an issue when data pooling is attempted.

Plan summation in retreatment

- EQD_2VH summation is recommended for accounting the effects of retreatments.

- There are however studies reporting NTCP calculations based on the summation of maximum dose or average OaR dose (e.g., Krauze et al 2017).
  - The lack of clinical data for model validation hampers the filtering out of erroneous approaches.

- Does one have to account for tissue recovery from the previous treatment for the new NTCP calculation?
  - How much time has passed since the previous treatment?
  - How do the radiation-induced changes modulate the response to re-irradiation?

Accounting for increased treatment time

- The effect of breaks could be accounted for with a time factor $f(T)$

$$(EQD_2)_i = \sum_j \left[D_i \frac{\left(1 + \frac{d_i}{\alpha/\beta}\right)}{\left(1 + \frac{2}{\alpha/\beta}\right)} \right]_j - f(T)$$

Time factors in radiation therapy

- This approach is used in isoeffect modelling, and could handle treatment breaks taking several weeks:

- For early reacting tissues (α/β>10 Gy), $f(T) = \frac{\frac{\ln 2 (T - T_k)}{\alpha \quad T_p}}{\left(1 + \frac{2}{\alpha/\beta}\right)}$

- For late reacting tissues (α/β<3 Gy), $f(T) = 0$
  - But is it?

Time factors in radiation therapy

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- For early reacting tissues (α/β>10 Gy), $f(T) = \frac{\frac{\ln 2 (T - T_k)}{\alpha \quad T_p}}{\left(1 + \frac{2}{\alpha/\beta}\right)}$

- For late reacting tissues (α/β<3 Gy):
  - Thames et al (2010) reported the existence of a time factor for prostate tumours (α/β=1.5 Gy), hence $f(T) = \frac{\frac{\ln 2 (T - T_k)}{\alpha \quad T_p}}{\left(1 + \frac{2}{\alpha/\beta}\right)}$ for late reacting tissues as well.
  - The effects of the time factor might be obscured by most primary treatments being ready before the relevant T_k.

Time factors in radiation therapy

- Which leads to an interesting development for NTCP modelling.

$$(EQD_2)_i = \sum_j \left[D_i \frac{\left(1 + \frac{d_i}{\alpha/\beta}\right)}{\left(1 + \frac{2}{\alpha/\beta}\right)} \right]_j - \frac{\frac{ln2}{\alpha} \frac{(T - T_k)}{T_p}}{\left(1 + \frac{2}{\alpha/\beta}\right)}$$

- Most treatments are shorter than T_k.
  - At present we do not have (late reacting) tissue-specific recovery parameters.
- Not yet clear whether time factors are applicable at voxel level.

Time factors for re-irradiation

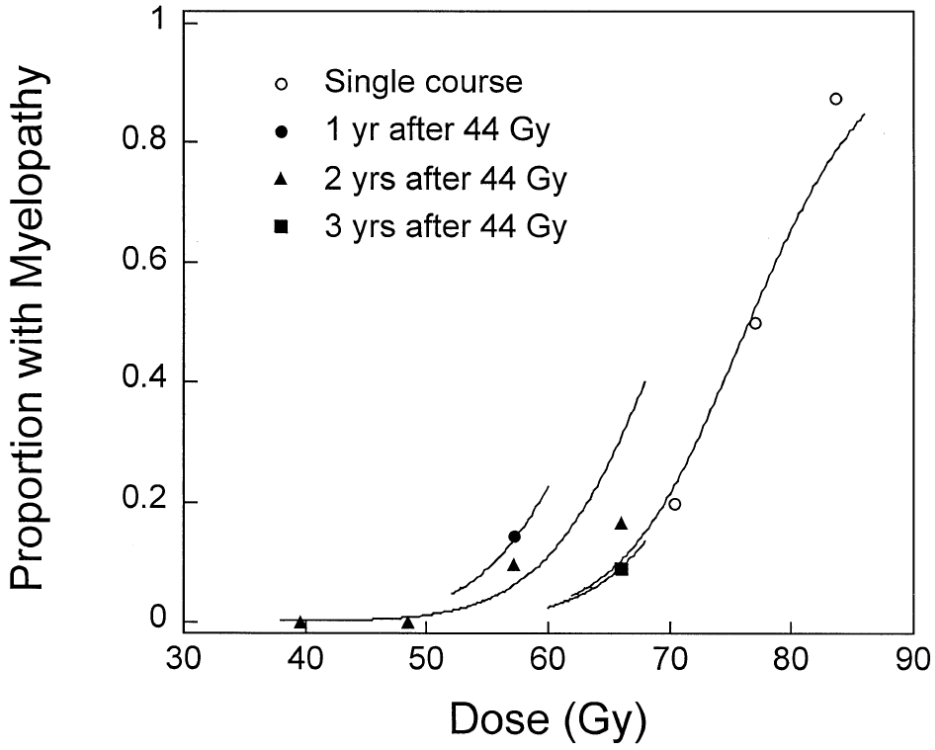
- Can this approach account for all long-time recovery processes?

- Acute reacting tissues usually recover completely after conventional fractionation.
  - Do SBRT treatments activate mechanisms not accounted for by the BED formalism?
  - Does one need to account for voxel-specific recovery?

- Some late reacting tissues (CNS, lung) recover partially after conventional fractionation, while others (heart, kidney) do not.
  - Can this observation be related to the other mechanisms and patterns of recovery from the first treatment course?

Data on recovery after spinal irradiation

- Spinal irradiation in rhesus monkeys.



Ang et al (2001)

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Accounting for tissue recovery at reirradiation

- Woodley et al (2018) defined a recovery function to predict radiation myelopathy after repeated irradiation.
- Start by determining the BED_{NTCP} for a clinically acceptable NTCP, e.g. 1%.
- Assuming that BED_1 and BED_2 are the BEDs for the initial and second treatments, respectively, normalised to the BED_{NTCP}.

$$BED_2 = 100\left(1 - \frac{BED_1}{100}\right)\left[1 + \left(\left(1 - \frac{BED_1}{100}\right)^{\frac{-r(t)}{r(t)+1}} - 1\right) f(BED_1, r(t))\right]$$

- where

$$f(BED_1, r(t)) = \frac{1}{2}\left[1 + \tanh\left[s_0\left(BED_1 - \frac{\overline{BED}}{1 + s_1 \cdot r(t)}\right)\right]\right]$$

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More reirradiation-specific questions

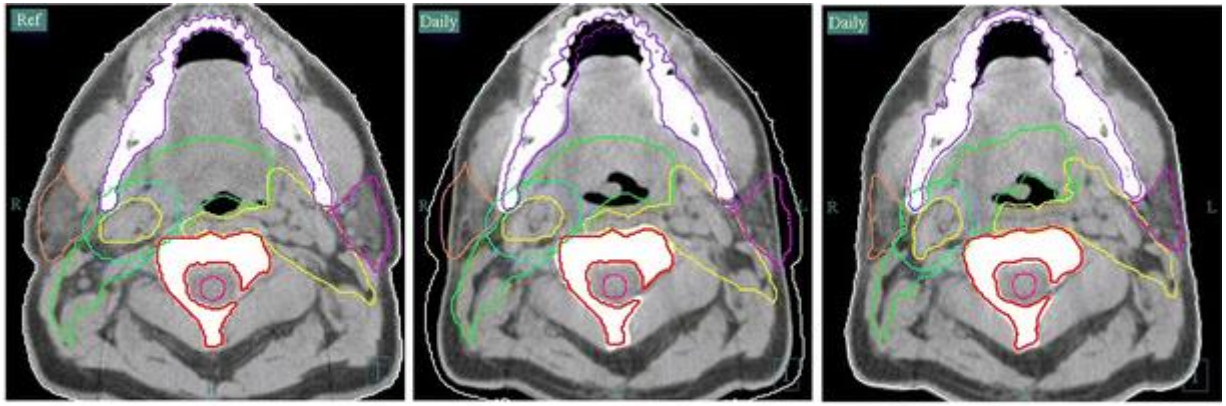
- If the first treatment course induces genetic instability, can we continue using the same parameters for the BED formalism for the re-treatment course?

- In case of heterogeneous irradiations, should tolerance/NTCP calculations be performed at voxel level or rather at TRU level?

- Can we use imaging for voxel-specific quantification of normal tissue function and/or recovery parameters?
  - This leads to the possibility of having voxel-specific recovery parameters.

Patient anatomy changes

- Within one course or between the initial and retreatment courses.



Reference Planning CT | Bone Rigidly Aligned Daily CT | Deformed Contours to Match with the Daily CT

Schwartz (2014)

- Voxel tracking through deformable image registration (DIR) is needed.
  - The DIR algorithm used could introduce a dose uncertainty in the DVH.

- Also relevant for intra-treatment changes (e.g., physiological motion).

Plan availability and calculation algorithms

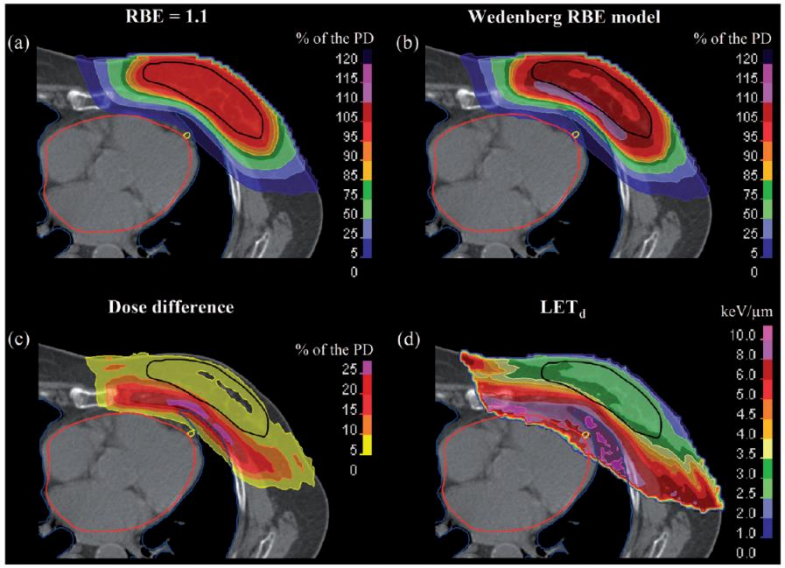
- Candidates for re-irradiation may have received the initial plan more than a decade before.

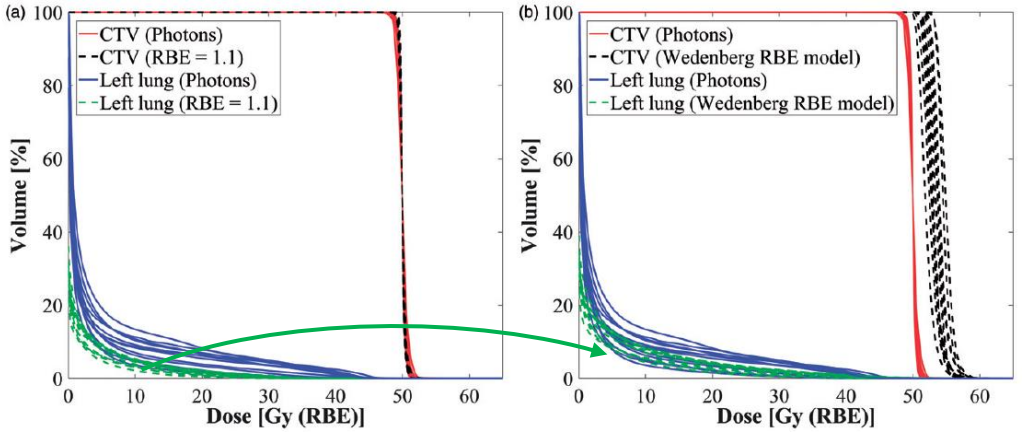
- Is the original plan still available or it has to be reconstructed?
  - Is the CT data set still available?
  - Is the treatment machine still available in the TPS?

- What dose calculation has been used?
  - The accuracy of dose calculation varies between algorithms, with older convolution algorithms being less accurate than newer ones (AAA, CC or MC), especially in heterogeneous media.

What if different radiation modalities are used?

- Particle therapy (a potential candidate for re-irradiation) is characterised by depth and tissue-dependent RBE.
- These variations could be reflected upon the dose distributions (DVHs) used for NTCP calculations.





Ödén et al (2017)

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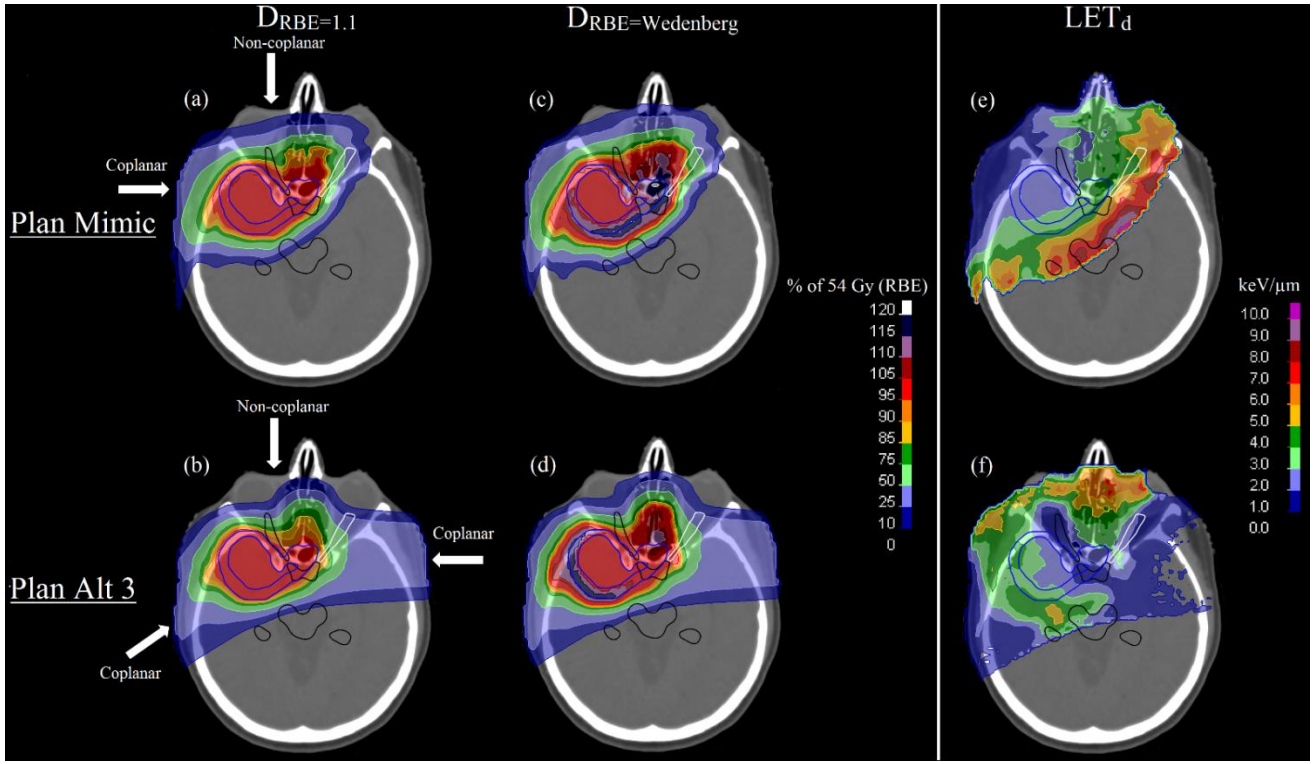
RBE-dependent treatment optimisation

- Accounting for RBE variations for plan evaluation and optimisation is advancing fast.



Ödén et al (2018)

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Conclusions

- Available NTCP models are derived from uniform irradiations.
  - The impact of DVH reduction techniques for tissues with non-uniform sensitivity is not yet explored.
- Plan summation and voxel-tracking techniques are needed to account for real dose distributions in normal tissues.
- Treatment optimisation for particle therapy should account for RBE variations.
- Accounting for tissue recovery between treatment courses is still the most challenging aspect of re-irradiation.

Thank you!

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