Incorporating clinical and biological factors into (NTCP) models

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Standard phenomenological modelling methodology

\[
\text{EUD} \quad V_x \\
D_{\text{mean}}
\]
Standard phenomenological modelling methodology

Reduce dose distribution to DVH
- Removes all spatial information
- Assumes equal sensitivity/response of all parts of OAR
- Alternatives:
  - Explicitly model local response on voxel-to-voxel basis
  - Divide into anatomical substructures
  - Dose surface histograms
Standard phenomenological modelling methodology

Reduce DVH to limited number of dose metrics

$$EUD = \left( \sum_{k} d_k^a \frac{v_k}{V_{tot}} \right)^{1/a}$$

Mean dose: $$a = 1$$

$$V_x = \sum_{k} E(d_k) v_k$$

$$E(d_k) = \begin{cases} 0 & \text{for } d_k < x \text{ Gy} \\ 1 & \text{for } d_k \geq x \text{ Gy} \end{cases}$$
Standard phenomenological modelling methodology

Generalized approach for calculating “equivalent organ dose/volume” from local response

Standard phenomenological modelling methodology

Reduce DVH to limited number of dose metrics

Dose metrics generally highly correlated

Potential solutions:
- Bootstrapping methodologies
- Principal component analysis (PCA)
Standard phenomenological modelling methodology

Link funktion:
- Logistic (binary outcome)
- Probit (binary outcome)
- Linear model (continuous outcome)
  - Note underlying model assumptions (data not bounded)
- Ordinal logistic (graded outcome)
Standard phenomenological modelling methodology

Logistic regression

\[
\frac{p}{1-p} = \ln(X), \quad X = b_0 + b_1 D
\]

\[
p(X) = \frac{1}{1 + \exp(-X)}
\]
Standard phenomenological modelling methodology

\[ D_{50} = D\bigg|_{p=0.5}, \quad \gamma_{50} = \frac{\partial p}{\partial D} D\bigg|_{p=0.5} \]
Standard phenomenological modelling methodology

Including graded outcome – ordinal logistic regression

\[
\frac{p_{zi}}{1 - p_{zi}} = \ln(X), \quad X = b_{0,i} + \bar{b} \bar{Y}
\]

\[
p_{zi}(X) = \frac{1}{1 + \exp(-X)}
\]
Standard phenomenological modelling methodology

To fit / optimize model: Optimize entire process at once
Lyman-Kutcher-Burman (LKB) model

Effective volume

\[ V_{eff} = \sum_i \left( \frac{D_i}{D_{eff}} \right)^{\frac{1}{n}} \]

Probit link function

\[ NTCP(D_{eff}, V_{eff}) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \exp\left( -\frac{u^2}{2} \right) du \]

\[ t = \frac{D_{eff} - D_{50}(V_{eff})}{mD_{50}(V_{eff})} \quad D_{50}(V_{eff}) = D_{50}(1) V_{eff}^{-n} \]
Modelling including clinical factors

$EUD_x$ $D_{mean}$
Modelling including clinical factors

Assume same dose representation for different risk groups

Treat dose metric and clinical factors as standard regression parameters

Generalised linear model (GLM) framework

\[ g(p) = X = b_0 + b_1 D + b_i Y_i \]

- First order inclusion: Additive
- Second order: Multiplicative (interaction term)
  - "Dose modification factor
Modelling including clinical factors

Assume same dose representation for different risk groups

Treat dose metric and clinical factors as standard regression parameters

Logistic regression – direct relationship with odds ratios (OR)

\[ X = b_0 + b_1 D + b_i Y_i \]

\[ p(X) = \frac{1}{1 + \exp(-X)} \]

\[ OR_i = e^{b_i Y_i} \]
Assume same dose representation for different risk groups

Treat dose metric and clinical factors as standard regression parameters

Logistic regression – direct relationship with odds ratios (OR)

\[ X = b_0 + b_1 D + b_i Y_i \]

\[ p(X) = \frac{1}{1 + \exp(-X)} \]

\[ OR_i = e^{b_i Y_i} \]

\[ D_{50}^{OR} = D_{50} \left( 1 - \frac{1}{4} \ln(OR) \right) \]

\[ \gamma_{50}^{OR} = \gamma_{50} - 0.25 \ln(OR) \]

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Appelt & Vogelius, Radiother Oncol, 2012
Example: Acute urinary toxicity for rectal cancer radiotherapy

- 345 rectal cancer patients treated with 50-66 Gy / 1.8-2 Gy per fraction, both IMRT and 3D-CRT
- Relationship between acute cystitis (CTCAE v 3.0) and dose to the bladder
- Best predictor: $V_{35\text{Gy}}$ to the bladder (relative volume)

OR_{\text{male}} = 1.82 (1.17–2.80), OR_{\text{brachy}} = 1.36 (1.02–1.80) each 5 Gy
Example: Rectal cancer tumour regression after CRT

- 222 rectal cancer patients treated with 50-66 Gy / 1.8-2 Gy per fraction
- Relationship between EQD2 and tumour regression grade on pathological specimen

Blue, solid: TRG1 (complete response)
Green, dashed: TRG1-2 (major response)

N-stage: OR=2.06 for N0 vs N1-2, p=0.039
Size: OR=0.65 for each 50 mL increase in size, p=0.040

Tumour size and N-stage – TRG 1&2 response

Appelt et al, IJROBP, 2013
Example: Smoking and risk of radiation pneumonitis


\[ \text{NTCP}(D, V) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t'} e^{-u^2/2} du \]

\[ t = \frac{D - TD_{50}/V^n}{m \cdot TD_{50}/V^n} \]

Introduce dose modifying factor (DMF):

\[ t = \frac{D_{\text{eff}} - TD_{50} \cdot \exp(\delta_1 \cdot Y_1) \cdot \ldots \cdot \exp(\delta_k \cdot Y_k)}{m \cdot TD_{50} \cdot \exp(\delta_1 \cdot Y_1) \cdot \ldots \cdot \exp(\delta_k \cdot Y_k)} \]

\[ \text{DMF} = \exp(\delta_i \cdot Y_i) \]

Corresponds to a multiplicative (interaction, second order) effect
Example: SNPs and risk of radiation pneumonitis


\[
\text{NTCP}(D, V) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\tau} e^{-u^2/2} du
\]

\[
t = \frac{D - TD_{50}/V^n}{m \cdot TD_{50}/V^n}
\]

Introduce dose modifying factor (DMF):

\[
t = \frac{D_{\text{eff}} - TD_{50} \cdot \exp(\delta_1 \cdot Y_1) \cdot ... \cdot \exp(\delta_k \cdot Y_k)}{m \cdot TD_{50} \cdot \exp(\delta_1 \cdot Y_1) \cdot ... \cdot \exp(\delta_k \cdot Y_k)}
\]

\[
\text{DMF} = \exp(\delta_i \cdot Y_i)
\]

Corresponds to a multiplicative (interaction, second order) effect
Example: Surgery and risk of incontinence after prostate RT

Peeters et al (IJROBP, 2006)
Modelling including clinical factors

EUD

$D_{\text{mean}}$

$V_x$
Modelling including clinical factors

Assume completely different dose dependence for different risk groups
- Fit separate models for each group
- Or specify a parametric dependence on clinical factors
Modelling including clinical factors

Advantage:
May help to understand underlying differences in pathophysiology

Limitations
• Potential lack of power
• Depends on discrete clinical groups (no continuous factors)

Good robustness check of models
Example: Hematological toxicity during pelvic IMRT


Pelvic bone marrow dose related to acute toxicity using LKB model

A

Mitomycin + 5FU

B

Cisplatin
Example: Radiation induced liver disease

Cheng et al. *Inclusion of biological factors in parallel-architecture normal-tissue complication probability model for radiation-induced liver disease.* *IJROBP*, 2005

<table>
<thead>
<tr>
<th>Best estimate of parameter (95% confidence interval)</th>
<th>$v_{50}$</th>
<th>$\alpha$</th>
<th>$D_{50}$</th>
<th>$k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group (151 patients)</td>
<td>0.54 (0.51–0.58)</td>
<td>0.14 (0.11–0.16)</td>
<td>50 Gy (24–110)</td>
<td>0.18 (0.11–0.27)</td>
</tr>
<tr>
<td>HBV carriers (76 patients)</td>
<td>0.53 (0.51–0.55)</td>
<td>0.073 (0.05–0.15)</td>
<td>50 Gy (0–100)</td>
<td>$4.56 \times 10^{-7}$ ($&lt;0.06$)</td>
</tr>
<tr>
<td>Non-HBV carriers (75 patients)</td>
<td>0.59 (0.52–0.63)</td>
<td>0.12 (0.08–0.13)</td>
<td>25 Gy (21–29)</td>
<td>59.8 (1–100)</td>
</tr>
</tbody>
</table>
Modelling including clinical factors

\[ EUD = \sum_{x} V_{x} D_{\text{mean}} \]
Modelling including clinical factors

p(D_{x1})
p(D_{x2})
p(D_{x3})
p(D_{x3})

Local dose-response function
=> Determine spatial distribution of dose-dependence

Local
• Dose

Patient-level
• Response / outcome
• Clinical factors


Dose map without symptoms
Dose map with symptoms
Significance map with multivariate modelling

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Modelling including clinical factors

Local dose-response function
=> Determine spatial distribution of dose-dependence

Local
• Dose
• Response

Patient-level
• Clinical factors

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Modelling including clinical factors

Local dose-response function => Determine spatial distribution of dose-dependence

Local
- Dose
- Response
- “Clinical factor”

Patient-level
- Clinical factors

Functional imaging

Modelling including clinical factors

\[ p(D_{x1}) \quad p(D_{x2}) \quad p(D_{x3}) \quad p(D_{x3}) \]

Local dose-response function
\[ \Rightarrow \text{Determine spatial distribution of dose-dependence} \]

Significant challenges surrounding within- and between patient variation & multiple testing

- WE-AB-KDBRC-6: Variogram-Weighted Generalized Least Squares Regression to Predict Spatially Variant Tumor Voxel Response On Longitudinal FDG-PET/CT Imaging of FLARE-RT Protocol Patients
- Chen et al. Multiple comparisons permutation test for image based data mining in radiotherapy. Radiat Oncol 2013
How do we handle larger numbers of risk factors?

EUD

$D_{\text{mean}}$

$V_x$
Estimating the effect of multiple risk factors on dose-response relationships

Example: Radiation pneumonitis

Acta Oncologica, 2012; 51: 975–983

REVIEW ARTICLE

A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis

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2Department of Oncology, Væl Sygehus, Væle, Denmark, and 3Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

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Estimating the effect of multiple risk factors on dose-response relationships

- Multivariate analysis of both dose and risk factors in full patient data sets
  - LARGE number of patients

- Alternative:
  Meta-analysis of already existing studies
  - Combine dose-response relationships with clinical risk factors as found in meta-analysis
Adjusting radiation dose–response relationships for clinical risk factors

Assume a fraction $s$ of the patients had a risk factor with odds ratio $OR$. 

$$NTCP_{\text{adjusted}}(D) = \frac{1}{1 + \exp\left(4y_0\left(1 - \frac{D}{D_0}\right)^\alpha\right)}$$

Adjusting radiation dose–response relationships for clinical risk factors

"Baseline" dose-response relationship, for patients without any of the risk factors

Assuming:
No correlation between risk factors

Estimate dose-response for patients without risk factor:

Adjusting radiation dose–response relationships for clinical risk factors

Assume a fraction \( s \) of the patients had a risk factor with odds ratio OR. Estimate dose-response for patients without risk factor:

\[
\begin{align*}
\gamma_{50} &= \frac{sP(1-P)}{s - (2P-1)^2} \left( \ln \left( \frac{P}{1-P} \right) + 4\gamma_{50} \right) \\
D_{50}^{a} &= 1 + \frac{1}{4\gamma_{50}} \ln \left( \frac{P}{1-P} \right) \\
P &= \frac{1}{2} \left( 1 + s \frac{OR - 1}{OR + 1} \right)
\end{align*}
\]

"Baseline" dose-response relationship, for patients without any of the risk factors

Assuming:
No correlation between risk factors

Adjusting radiation dose–response relationships for clinical risk factors

Dose-response for patient with specific set of risk factors

\[ D_{50}^{\text{risk}} = D_{50}^0 \left( 1 - \frac{1}{4 \gamma_{50}^0 \ln OR_{\text{combined}}} \right) \]

\[ \gamma_{50}^{\text{risk}} = \gamma_{50}^0 - \frac{1}{4 \ln OR_{\text{combined}}} \]

\[ OR_{\text{combined}} = OR_{\text{risk factor 1}} \times OR_{\text{risk factor 2}} \times \ldots \]

Adjusting radiation dose–response relationships for clinical risk factors

• To use this method, we need
  • A dose-response relationship for an organ at risk
  • A set of risk factors + estimated ORs
  • The prevalence of the risk factors in the patient population that provided the dose-response relationship
Dose-response for radiation pneumonitis

\[ D_{50} = 30.8 \text{ Gy (95\% CI: 28.7, 33.9)} \]
\[ \gamma_{50} = 0.97 \text{ (95\% CI: 0.83, 1.12)} \]
<table>
<thead>
<tr>
<th>Clinical risk factor</th>
<th>Prevalence in QUANTEC studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing pulmonary co-morbidity</td>
<td>0.258</td>
</tr>
<tr>
<td>Mid or inferior tumour location</td>
<td>0.444</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.283</td>
</tr>
<tr>
<td>Former smoker</td>
<td>0.663</td>
</tr>
<tr>
<td>Old age</td>
<td>0.5</td>
</tr>
<tr>
<td>Sequential chemotherapy</td>
<td>0.258</td>
</tr>
</tbody>
</table>
"Baseline" dose-response for radiation pneumonitis

- No pulmonary co-morbidities
- Tumour in the upper lobe
- No history of smoking or current smoking habit
- <63 years old
- Not treated with sequential chemotherapy

\[ D_{50} = 34.4 \text{ Gy} (95\% \text{ CI: } 30.7, 38.9) \]
\[ \gamma_{50} = 1.19 \text{ (95\% CI: } 1.00, 1.43) \]
Individualized dose-response for radiation pneumonitis (iQUANTEC)

Smoker, no risk factors

Patient with highest risk:
- Pulmonary co-morbidities
- Tumour in the middle/lower
- No history of smoking or current smoking habit
- >63 years old
- Sequential chemotherapy

Corresponding individualised dose constraints

Appelt et al. Acta Oncol 2014
Using the iQUANTEC model to design clinical proton therapy trials

- Estimate (distribution of) predicted benefit of new technology in representative patient cohort
- Design phase III trial using this estimate - rather than a single effect estimate for all patients
- Use phase III trial to test & validate the NTCP model
  - Misspecified model can be detected
- Feed phase III result into estimate of benefit for future individual patients

- Exemplar:
  Randomised phase III trial of proton vs photon treatment for locally advanced NSCLC
  - Simulate output of large number of trials
  - Reduction in sample size of at least 20%
  - Trial result will allow for estimate of individual patient benefit

Rydhög, Appelt, et al. Submitted for publication
Individualised NTCP to assess benefit from new technology

• “Development of an isotoxic decision support system integrating genetic markers of toxicity for the implantation of a rectum spacer” van Milk et al. Acta Oncol 2018

• Combine
  • QUANTEC model for late rectal toxicity
  • Genetic markers (SNPs) for radiosensitivity identified in meta analysis

• Use image deformation to simulate rectal spacer implantation, and assess individual benefit in treatment planning
Summary

- Clinical factors can be taken into account on several levels when conducting bioeffect (TCP/NTCP) modelling
- Most common approach: Inclusion alongside dose metrics
  - In this case, standard GLM regression framework can be used
  - Note challenges of estimating CIs / significance levels if also optimising dose metric representation
  - Additive factors (OR in logistic regression):
    - First order factors
  - Multiplicative factors (“dose modifying factors”):
    - Second order factors / interaction effects
- Increasing number of publications examining local dose effects, including clinical factors, but methodology is not standardized
- Consider meta analysis approaches
- Planning prospective studies
  - Consider integrating TCP/NTCP model to be prospectively validated