Methodological issues and key results in the QUANTEC 2010 review of quantitative analysis of normal tissue effects in the clinic

(The QUANTEC steering committee:)
Soeren Bentzen, Sandy Constine, Joe Deasy, Avi Eisbruch, Andrew Jackson, Larry Marks, Randy Ten Haken, Ellen Yorke

Methodological issues
1. No consensus on best NTCP models (e.g., simple vs. large model)
2. Results not stated in comparable terms (e.g., NTCP model vs. DVH thresholds)
3. Sometimes the ‘target’ tissues aren’t known
4. Endpoint definitions can be questionable
5. Results depend on typical dose distributions, which are evolving
6. Implicit assumption of organ uniformity (ignoring stem cell rescue, etc.)
7. Assumption that spatial dose pattern doesn’t matter

A sample of key results
- Xerostomia and salivary parotid gland irradiation
- Late rectal bleeding
- Radiation pneumonitis and lung irradiation
- Erectile dysfunction and penile bulb irradiation

Avoiding xerostomia (‘dry-mouth syndrome’) in H&N patients
- Salivary function is stimulated or unstimulated
- Stimulated flow is dominated by parotid gland contributions
- Unstimulated consists of contributions from submandibular salivary glands and multiple smaller glands
**QUANTEC: ORGAN-SPECIFIC PAPER**

**RADIOTHERAPY DOSE-VOLUME EFFECTS ON SALIVARY GLAND FUNCTION**

Joseph O. Deasy, Ph.D., Vitali Motroenko, Ph.D., Lawrence Mark, M.D., K. S. Clifford Caoil, M.D., Hsin Nam, Ph.D., and Abraham Einhorn, M.D.

(A) - 6 mos. post-RT  
(B) - 12 mos. post-RT

(Bianco et al. IROBP 2005)

**Treatment planning constraints to avoid xerostomia in head and neck radiotherapy: an independent test of QUANTEC criteria using a prospectively collected dataset**

Vitali Motroenko, Ph.D., Jena Wu, M.D., Allan Howan, M.D., Zaid Solek, Ph.D., Aditya Apte, Ph.D., Joseph O. Deasy, Ph.D., Stephen Harrow, M.D., Caruna Rabuka, M.D., Adam Mugli, D.D.S., and Anna Thompson, M.D.

Departments of 1Medical Physics, 2Radiation Oncology, and 3Oncology, Vancouver Cancer Centre, British Columbia Cancer Agency, Vancouver, BC, Canada; 4Department of Medical Physics, Memorial Sloan Kettering Cancer Centre, New York, NY

(In press, IROBP)
XEROSTOMIA PATIENT REPORTED OUTCOMES ARE A LINEAR FUNCTION OF CONTRALATERAL PAROTID GLAND MEAN DOSE

Ziad H Saleh1, Wade Thorstad2, Aditya Apte1, and Joseph O. Deasy2
1- Memorial Sloan-Kettering Cancer Center (Department of Medical Physics), New York, USA
2- Washington University School of Medicine (Department of Radiation Oncology), St. Louis, USA
Induction + Concurrent ChemoRT
PROs scores correlation with the mean dose to Contralateral parotid gland

PROs response as a linear function is steeper compared to RT alone

\[ \text{Slope} = 2.04 \quad \text{Slope} = 0.66 \quad \text{Slope} = 2.07 \]

\%

Continued benefit to patient by reducing mean dose

Dose-volume limits for grade 2 rectal toxicity with LQ corrected doses (α/β = 3 Gy)

Yield: Results in different relative contributions to gEUD within the DVH:
Are IMRT rectal dose-volume limits a problem?

Typical 3DCRT plan (sagittal)  Typical IMRT plan (sagittal)

Rectal gEUD = 53 Gy (a= 10) Rectal gEUD = 24 Gy

Variation in rectal DVHs for daily Fx’s

Rectal and bladder motion during conformal radiotherapy after radical prostatectomy

(Claudio Fiorino, Franco Poppo, Puspa Pratap, Sari Brezzzi, Pietro Costantini, Michele Marsico, Riccardo Cantone, Giuseppe Sungiannolo)

(Rad Oncol 2005)
Purpose/background:
- Validating a predictive model for late rectal bleeding would enable safer treatments or dose escalation.
- We tested the normal tissue complication probability (NTCP) model recommended in the recent QUANTEC review (Michalski et al., IJROBP, 2010 (76) S123-9).

Materials/Methods:
- 161 prostate cancer patients were treated with 3D conformal radiotherapy for prostate cancer at the British Columbia Cancer Agency in a prospective protocol.
- Total prescription dose for all patients was 74 Gy, delivered in 2 Gy/fraction.
- Rectal dose volume histograms were extracted and fitted to a Lyman-Kutcher-Burman NTCP model. Two treatment plans could not be extracted.
- Late rectal bleeding (>=grade 2) was observed in 12/159 patients (7.5%).
**Results:** On this dataset, both models had only modest ability to predict complications:

- the best-fit model had a Spearman’s rank correlation coefficient of rs=0.099 (p=0.11) and AUC of 0.62;
- the QUANTEC model had rs=0.096 (p=0.11) and a corresponding AUC of 0.61.
- Although the QUANTEC model consistently predicted higher NTCP values, it could not be rejected according to the chi-square test (p=0.44).
Identifying the most influential tissues
Which tissues are most influential?

Correlation map shows hotspot just outside of contoured muscles – surprise!

(Ziad Saleh et al., poster this meeting)
Pneumonitis, mean dose response - whole lung

Mean dose (Gy)

Probability of pneumonitis

WUSTL RP dataset

- 228 patients with non-small cell lung cancer (NSCLC) treated definitively with radiation +/- chemotherapy between 1991-2001
- 48 cases of RP (steroids or more intensive intervention)
- 3D treatment plan archives available
  - Non-heterogeneity corrected dose distributions
- Minimum six months follow-up post-treatment unless patient developed pneumonitis < 6 mos.

Tumor location is associated with risk of pneumonitis

WUSTL and RTOG 93-11 datasets (Bradley et al. IJROBP 2007)

- Chosen from many candidate models; logistic function of:

  \[-1.5 + 0.11 \text{Mean Lung Dose} - 2.8 \times \text{Pos Sup Inf} \]

- Spearman’s rank correlation coefficient 0.3 (on cross validation data)
Heart irradiation as a risk factor for radiation pneumonitis

ELLEN X. HUANG, ANDREW J. HOPE, PATRICIA E. LINDSAY, MARCO TROVO, ISSAM EL NOQA, JOSEPH O. DEASY & JEFFREY D. BRADLEY

1. Department of Radiation Oncology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri, USA; Princess Margaret Hospital, Toronto, ON, Canada; and 2. National Cancer Institute, Aviano, Italy.

Dataset

- Heart volumes of WUSTL archived plans were re-contoured within CERR by a single physician (n = 209, with 48 RP events).
- Heart and normal lung (lung minus gross tumor volume) dose-volume parameters were extracted for further modeling using CERR.
- Evaluated factors included:
  - clinical factors (age, gender, race, performance status, weight loss, smoking, histology)
  - dosimetric parameters for heart and normal lungs (D5-D100, V10-V80, mean dose, maximum dose, and minimum dose)
  - treatment factors (chemotherapy, treatment time, fraction size)
  - location parameters (heart center-of-dose, sup-inf within the heart; and center-of-target mass within the normal lungs.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spearman Corr.</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>D5_Heart</td>
<td>0.256</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>D10_Heart</td>
<td>0.24</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td>V70_heart</td>
<td>0.239</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td>gEUD_Heart (a=10)</td>
<td>0.249</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximum Heart Dose</td>
<td>0.227</td>
<td>&lt;0.0006</td>
</tr>
<tr>
<td>Superior-Inferior position of GTV</td>
<td>0.219</td>
<td>&lt;0.0008</td>
</tr>
</tbody>
</table>

Highest univariate correlations
Are simple NTCP models sophisticated enough?
Features Selected by an Average 5/5 Model

<table>
<thead>
<tr>
<th>Rank</th>
<th>Feature Description</th>
<th>Mean AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>COS Heart Z (.5815)</td>
<td>0.681</td>
</tr>
<tr>
<td></td>
<td>Performance Status (.2597)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$D_{60}$ Lung MC (.1705)</td>
<td>0.772</td>
</tr>
<tr>
<td></td>
<td>COMLAT (.0726)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$MOH_{60}$ Lung MC (.4783)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COMSI (.2465)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Performance Status (.2815)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$MOH_{30}$ Lung MC (.1588)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$D_{35}$ Lung MC (.1456)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Performance Status (.1906)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>$MOH_{30}$ Heart MC (.3935)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$D_{75}$ Lung MC (.3549)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Performance Status (.1906)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$D_{45}$ Lung MC (.3476)</td>
<td>0.802</td>
</tr>
<tr>
<td></td>
<td>$MOH_{2}$ Heart MC (.2728)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

- Heart irradiation may be an important risk factor for radiation pneumonitis, as previously seen in animal studies (Luijk et al., IJROBP 2007).
- In this single-institution dataset, RP is better associated with high-dose heart irradiation factors than previously reported lung dosimetry factors.
- The lung 'location effect' was not selected in multivariate modeling when heart factors were included.
- Obviously, these observations need to be tested on independent datasets.

Another validation study: acute esophagitis (dysphagia)
Radiation-induced dysphagia: multivariate analysis

Table 1. Odds ratio’s for developing dysphagia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.03</td>
<td>0.97</td>
<td>0.95 - 0.99</td>
<td>0.003</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>male</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>0.50</td>
<td>1.65</td>
<td>1.12 - 2.43</td>
<td>0.012</td>
</tr>
<tr>
<td>WHO-PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>0.57</td>
<td>1.76</td>
<td>1.13 - 2.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no/sequential</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>concurrent</td>
<td>0.93</td>
<td>2.53</td>
<td>1.64 - 3.91</td>
<td></td>
</tr>
<tr>
<td>MED</td>
<td>0.06</td>
<td>1.06</td>
<td>1.04 - 1.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAXED</td>
<td>0.03</td>
<td>1.03</td>
<td>1.01 - 1.05</td>
<td>0.0002</td>
</tr>
<tr>
<td>OTT</td>
<td>-0.06</td>
<td>0.94</td>
<td>0.92 - 0.96</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

As shown in Table 1, the multivariate analysis reveals several factors associated with the development of dysphagia. Age, gender, WHO performance status (PS), chemotherapy regimen, and medical status (MED) were found to be significant predictors. The odds ratios and confidence intervals indicate the relative risk of developing dysphagia associated with each variable. For instance, a one-year increase in age is associated with a decrease in the odds of developing dysphagia by approximately 3%. Male gender is associated with a higher risk of dysphagia compared to female gender. Patients with a WHO-PS ≥ 2 have a higher risk of dysphagia compared to those with a WHO-PS 0-1. Concurrent chemotherapy is associated with a higher risk of dysphagia compared to sequential chemotherapy. MED is also a significant predictor, with patients having high MED more likely to develop dysphagia. OTT was found to have a negative association with dysphagia, indicating that a longer time from treatment to assessment is associated with a lower risk of developing dysphagia.

The C-statistic for this model is 0.77 (bootstrap), indicating good discriminatory power.

Nomogram to predict dysphagia

The nomogram visually represents the predictive model, allowing clinicians to estimate the probability of developing dysphagia based on patient characteristics. By assigning points for each variable, one can sum these points and locate the predicted probability on the nomogram.

External validation

Washington University/Mallinckrodt data (n=216)

The external validation study confirms the model’s predictive accuracy on a new dataset. The AUC for ≥ Grade 3 dysphagia is 0.77, and for ≥ Grade 2 dysphagia is 0.75, indicating good discrimination.

C. Oberije et al, Radiotherapy and Oncology, 2010

Courtesy of J. Deasy, J. Bradley, I. El Naqa, E. Huang
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