Memorial Sloan Kettering Cancer Center

Review of NTCP models for Thoracic radiotherapy: where are we?

Maria Thor, *PhD*

Presentation outline

- Endpoints with the largest amount of published NTCP models
  - Acute esophagitis (AE)
  - Radiation Pneumonitis (RP)
- Recent, likely important endpoints
  - Cardiac toxicity
- How can I implement these models in my home clinic?
  - Model validation
  - AE and RP examples

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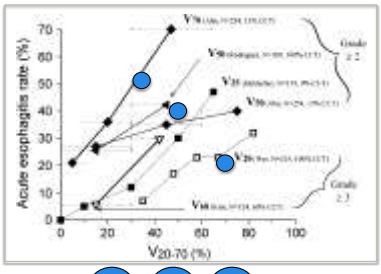
QUANTEC on AE: Dose/volume guidelines but no precise limit



V_{70} ≤20% V_{60} ≤40% V_{35} ≤50% → AE≤30%

Werner-Wasik M *IJROBP* 2010

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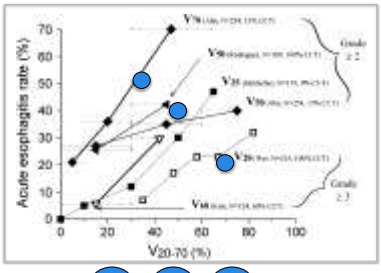

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Other predisposing factors? Age, Concurrent chemo, Dysphagia, Tumor vol

Werner-Wasik M *IJROBP* 2010

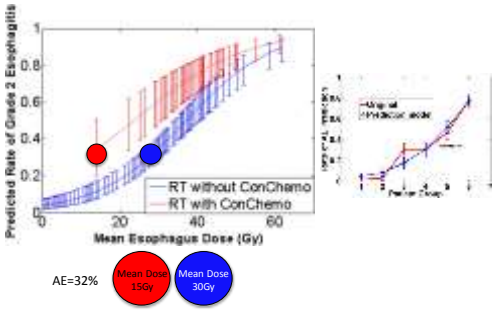
AE post-QUANTEC: Mean dose + Concurrent chemo

- N=374 (stage III: 62%), AE≥Grade 2=32%
- Stepwise cross-validated logistic regression ($N_{variables}$=50)

Huang EX *IJROBP* 2012

AE post-QUANTEC: Mean dose + Concurrent chemo

- (1.5ConChemo)+(0.07Mean Dose)-3.1
- Good performance (calibration: right; AUC=0.83)



Huang EX *IJROBP* 2012

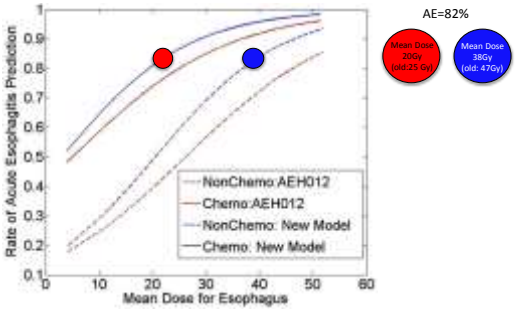
AE post-QUANTEC: Mean dose + Concurrent chemo

- N=115 (≥stage II: 75%), AE≥Grade 2=82%
- Validation of old model and generation of new model

Huang EX *Adv Radiat Oncol* 2016

AE post-QUANTEC: Mean dose + Concurrent chemo

- Old and new model similar (AUC=0.78, 0.78; p_{HL}=0.54, 0.66)
- New model: (1.8ConChemo)+(0.09Mean Dose)-1.8



Huang EX *Adv Radiat Oncol* 2016

AE post-QUANTEC: Mean dose + Concurrent chemo

- N=149 (stage II/III), AE≥Grade 2=36%
- Similar modeling approach as in the two Huang studies

Wijsman R *R&O* 2015

AE post-QUANTEC: Mean dose + Concurrent chemo

- (2.6ConChemo)+(0.12Mean Dose)+(1.2Female)+(0.99StageIII)-6.4
- Good performance (AUC=0.82; p_{HL}=0.13)

AE=36%

Wijsman R *R&O* 2015

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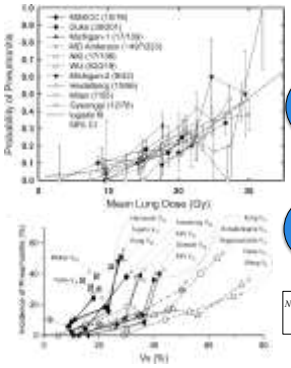
QUANTEC on RP: Recommended dose/volume limits



MLD ≤20-23Gy

V_{20} ≤30-35%

RP≤20%

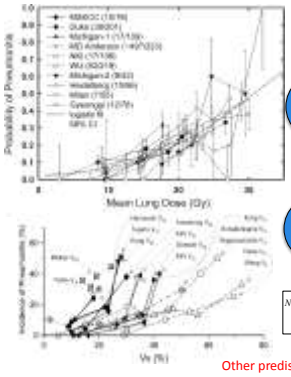
$$NTCP = \frac{1}{1+\exp\left(4\gamma_{50}\left(1-\frac{MLD}{D_{50}}\right)\right)}$$

D_{50}=30.8Gy

γ_{50}=0.97

Marks LB *IJROBP* 2010

QUANTEC on RP: Recommended dose/volume limits



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D_{50}=30.8Gy

γ_{50}=0.97

Other predisposing factors?

Marks LB *IJROBP* 2010

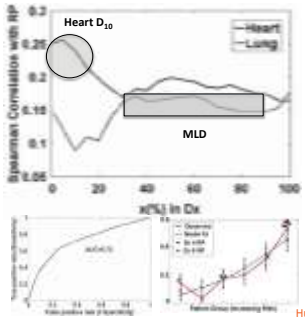
RP post-QUANTEC: Lung and heart dose interaction

- N=209, RP≥Grade 2=23%
- Stepwise cross-validated logistic regression ($N_{variables}$>100)

Huang EX *Acta Oncol* 2011

RP post-QUANTEC: Lung and heart dose interaction

- $(0.02\text{HeartD}_{10})+(0.06\text{MLD})-3.5$
- Good performance (calibration: lower right; AUC=0.72)



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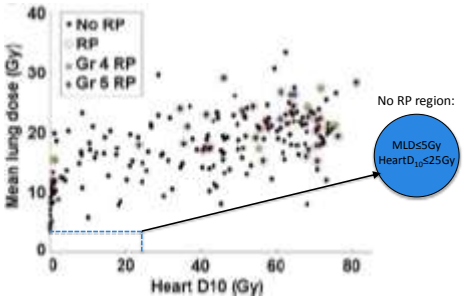


Huang EX *Acta Oncol* 2011

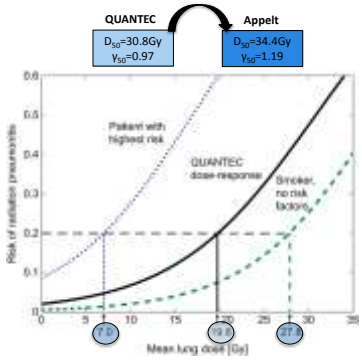
RP post-QUANTEC: Lung dose and predisposing factors

- QUANTEC's MLD response adjusted for predisposing factors
- ORs from meta-analysis
  - Mid/inferior tumor location: OR=1.87
  - Old age (63y): OR=1.66
  - Pulmonary comorbidity : OR=2.27
  - Sequential chemotherapy: OR=1.60
  - Smoking: OR=0.62, 0.69 (Current, Former)

Vogelius I *Acta Oncol* 2012

Appelt AL *Acta Oncol* 2014

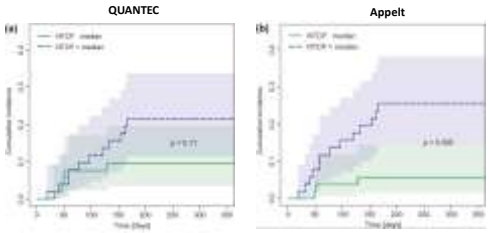
RP post-QUANTEC: Lung dose and predisposing factors



Appelt AL *Acta Oncol* 2014

RP post-QUANTEC: Lung dose and predisposing factors

- Validation (N=103, RP≥Grade 2=35%)
- Generalizable with respect to risk groups (QUANTEC was not)



Appelt AL *Acta Oncol* 2014

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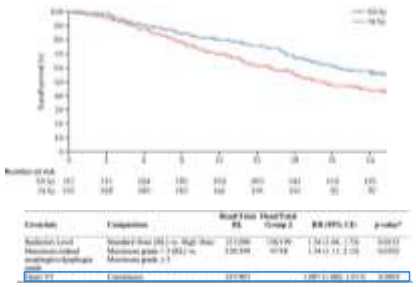
Heart dose predicts survival

- First indications: RTOG 0617

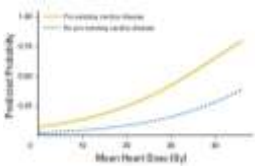


MVA: Heart V_5

Bradley JD *Lancet Oncol* 2015

Heart dose and cardiac toxicity

- N=125, ≥Grade 3 cardiac toxicity: 15%
  - Mean heart dose
  - Baseline cardiac disease



Dess RT *J Clin Oncol* 2017

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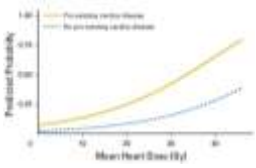
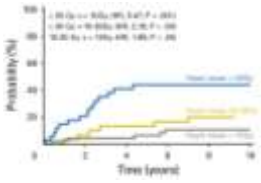


- N=112, ≥Symptomatic cardiac events: 23%
  - Mean heart dose
  - Baseline coronary artery disease



Dess RT *J Clin Oncol* 2017
Wang K *J Clin Oncol* 2017

Heart substructure dose and cardiac toxicity

- N=112, Arrhythmic/Ischemic/Pericardial: 11%/6%/8%
- Chambers, Heart, Pericardium (Mean dose, V_5, V_{30}, V_{60})
  - Arrhythmic: Heart (V_5), RA (V_{60})
  - Ischemic: Heart (V_5, V_{30}), LV (Mean, V_5, V_{30})
  - Pericardial: Heart (all), LA (all), RA (all)

Wang K *R&O* 2017

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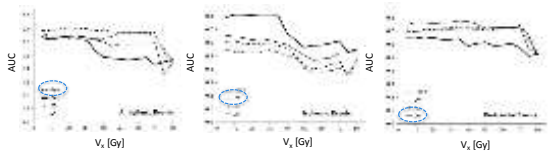

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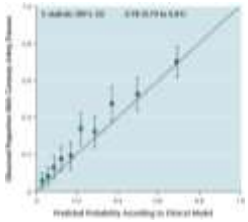
Model validation: Calibration + Discrimination =

- Detailed guidelines given in the TRIPOD statement
- Requirements: Published model equation, coefficients
- Calibration: How closely do predictions agree with observations
  - Calibration plot (ideal: data on identity line), X^2-test, Hosmer-Lemeshow test



Moons KGM *Ann Intern Med* 2015

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- Calibration: How closely do predictions agree with observations
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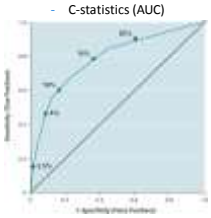
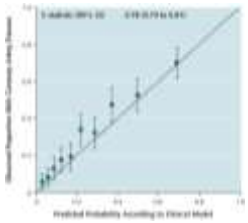
- Discrimination: Prediction's ability to differentiate between event and non-event
  - C-statistics (AUC)





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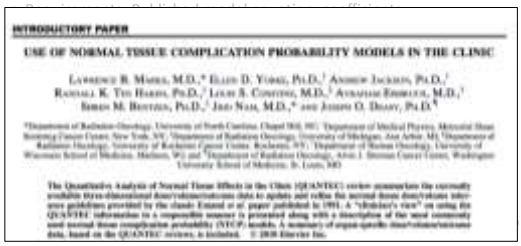

INTRODUCTORY PAPER

USE OF NORMAL TISSUE COMPLICATION PROBABILITY MODELS IN THE CLINIC

- Do NOT use a model for other purposes than for which it was developed!

Moons KGM *Ann Intern Med* 2015
Marks LB *IJROBP* 2010

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Validation of AE and RP models

- AE Models
  - (1.5ConChemo)+(0.07Mean Dose)-3.1 — Huang EX *IJROBP* 2012
  - (1.8ConChemo)+(0.09Mean Dose)-1.8 — Huang EX *Acta Oncol* 2011
  - (2.6ConChemo)+(0.12Mean Dose)+(1.2Female) +(0.99StageIII)-6.4 — Wijsman R *R&O* 2015
- RP models
  - $NTCP = \frac{1}{1+\exp\left(4\gamma_{50}\left(1-\frac{MLD}{D_{50}}\right)\right)}$ $\gamma_{50} = 0.97$ $D_{50} = 30.8Gy$ — Marks LB *IJROBP* 2010
  - (0.02HeartD$_{10}$)+(0.06MLD)-3.5 — Huang EX *Acta Oncol* 2011
  - $NTCP = \frac{1}{1+\exp\left(4\gamma_{50,new}\left(1-\frac{MLD}{D_{50,new}}\right)\right)}$ $\gamma_{50,new} = 1.19^{\circ} - \frac{1}{4}\ln OR$ $D_{50,new} = 34.4D_{50}^{\frac{1}{\gamma_{50}}}\left(1-\frac{1}{4\gamma_{50}}\ln OR\right)$ — Appelt AL *Acta Oncol* 2014

Thor M 2018 (unpublished data)

Validation of AE and RP models: Data and implementation

- 241 stage III NSCLC patients
  - IMRT to 64Gy (50-80Gy) 2004-2014
  - AE, RP rates: 50%, 12%
  - Concurrent/sequential chemotherapy

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  - AE, RP rates: 50%, 12%
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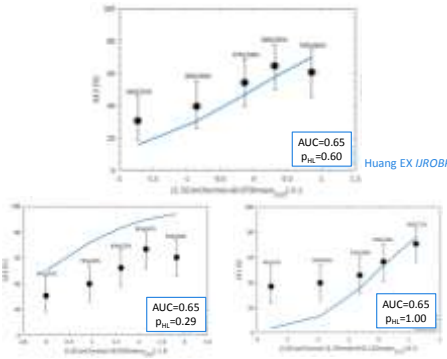
- Model validation
  - Fractionation-corrected doses (AE/RP: α/β=10Gy/3Gy)
  - Equations and coefficients from published models
  - Calibration and discrimination (p_{HL}, and AUC) over 1000 Bootstrap samples
  - Best model: Highest AUC with p_{HL}~0.50

Thor M 2018 (unpublished data)

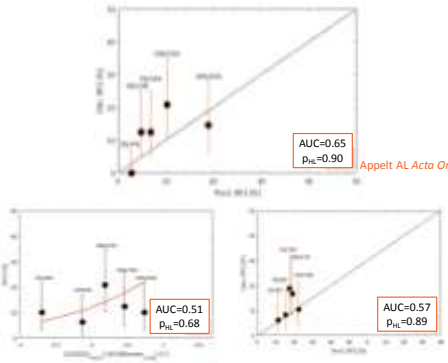
Validation of published AE and RP models: AE



Huang EX *IJROBP* 2012

Thor M 2018 (unpublished data)

Validation of published AE and RP models: RP



Appelt AL *Acta Oncol* 2014

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    - Heart dose + Baseline heart function
    - Potentially intra-heart sensitivity
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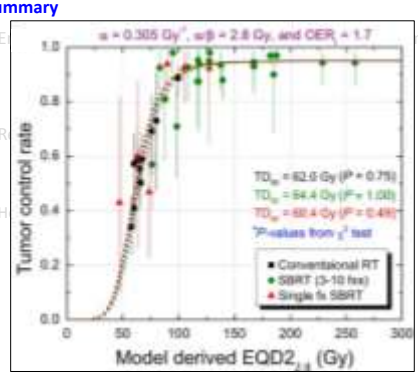
AE: Concurrent chemotherapy + Mean esophageal dose
RP: Mean lung dose + Individual characteristics

Summary

- E… …models
- R…
- H…



Jeong J *Clin Cancer Res* 2017

Thank you!

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Memorial Sloan Kettering Cancer Center

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