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

Other predisposing factors?

AE post-QUANTEC: Mean dose + Concurrent chemo
- N=374 (stage III: 62%), AE≥Grade 2=32%
- Stepwise cross-validated logistic regression (N_{variables}=50)
AE post-QUANTEC: Mean dose + Concurrent chemo

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

AE=32%

Huang EX IJROBP 2012

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AE post-QUANTEC: Mean dose + Concurrent chemo

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

Huang EX Adv Radiat Oncol 2016

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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: \( (1.8 \text{ConChemo}) + (0.09 \text{Mean Dose}) - 1.8 \)

AE=82%

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

\[(2.6 \text{ConChemo}) + (0.12 \text{Mean Dose}) + (1.2 \text{Female}) + (0.99 \text{Stage III}) - 6.4\]

- Good performance (AUC=0.82; \(p_{HL}=0.13\))

AE=36%

- All risk factors
- Two risk factors
- One risk factor
- No risk factors

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QUANTEC on RP: Recommended dose/volume limits

\[ NTCP = \frac{1}{1 + \exp\left(\frac{4g_{50}}{D_{50}}\right)\times (1 - MLD)} \]

Other predisposing factors?

RP post-QUANTEC: Lung and heart dose interaction
- N=209, RP≥Grade 2=23%
- Stepwise cross-validated logistic regression (N_{variables}>100)
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)

Good performance (calibration: lower right; AUC=0.72)

No RP region:

MLD ≤ 5 Gy
HeartD_{10} ≤ 25 Gy

No RP region: MLD ≤ 5 Gy, HeartD_{10} ≤ 25 Gy

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 (65y): OR=1.66
  - Pulmonary comorbidity: OR=2.27
  - Sequential chemotherapy: OR=1.60
  - Smoking: OR=0.62, 0.69 (Current, Former)

Appelt AL Acta Oncol 2014

Appelt AL Acta Oncol 2014

Huang EX Acta Oncol 2011
Huang EX Acta Oncol 2011

Vogelius I Acta Oncol 2012
RP post-QUANTEC: Lung dose and predisposing factors

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

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Heart dose predicts survival

- First indications: RTOG 0617

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 / Clin Oncol 2017

Heart dose and cardiac toxicity

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

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

Dess RT / Clin Oncol 2017
Wang K / 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 ($V_{30}$)
  - Ischemic: Heart ($V_5$, $V_{30}$), LV (Mean, $V_5$, $V_{30}$)
  - Pericardial: Heart (all), LA (all), RA (all)

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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), $\chi^2$-test, Hosmer-Lemeshow test
- Discrimination: Prediction’s ability to differentiate between event and non-event
  - C-statistics (AUC)

Do NOT use a model for other purposes than for which it was developed!
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Validation of AE and RP models

AE Models
- (1.5ConChemo)+(0.07Mean Dose)\cdot 3.1
- (1.8ConChemo)+(0.09Mean Dose)\cdot 1.8
- (2.6ConChemo)+(0.12Mean Dose)+(1.2Female)+0.99StageIII\cdot 6.4

RP models
- 0.02HeartD\cdot 0.06MLD\cdot 3.5
- 0.2HeartD\cdot 0.06MLD\cdot 3.5
- (1.190 - 1.4lnOR)\cdot 34.4D50

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
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

- 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

Validation of published AE and RP models: AE

- AUC=0.65
  - AUC=0.65
  - p_HL=0.90

- AUC=0.65
  - AUC=0.51
  - p_HL=0.68

- AUC=0.57
  - AUC=0.57
  - p_HL=0.89

Validation of published AE and RP models: RP

- AUC=0.65
  - AUC=0.65
  - p_HL=0.90

- AUC=0.51
  - AUC=0.57
  - p_HL=0.89
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Summary

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Calibration + Discrimination =

- Heart dose + Baseline heart function
- Potentially intra-heart sensitivity

AE: Concurrent chemotherapy + Mean esophageal dose
RP: Mean lung dose + Individual characteristics
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