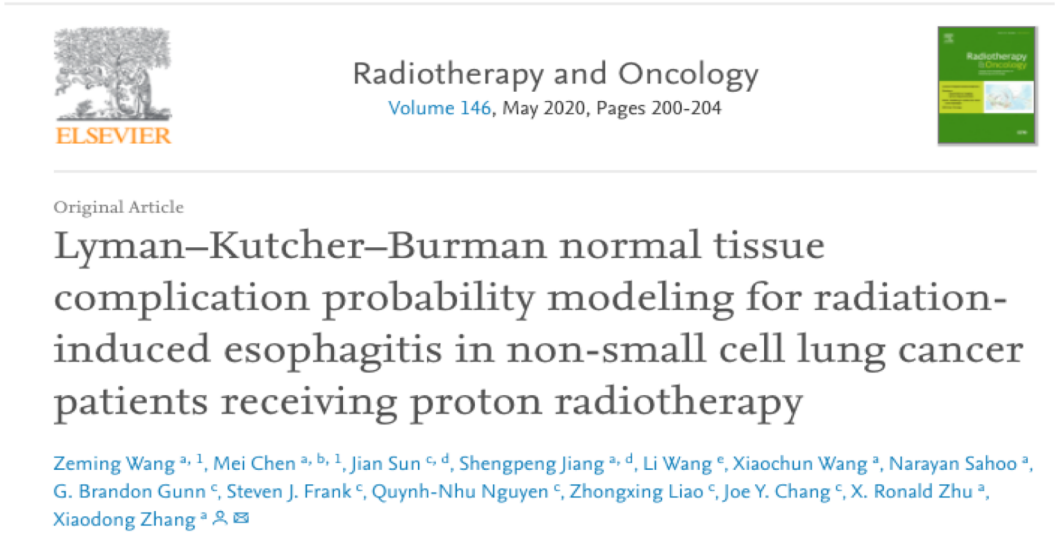
Development of NTCP Models for Proton Therapy

Mei Chen, Xiaodong Zhang

University of Texas, MD Anderson Cancer Center



ELSEVIER

Radiotherapy and Oncology

Volume 146, May 2020, Pages 200-204

Original Article

Lyman–Kutcher–Burman normal tissue complication probability modeling for radiation-induced esophagitis in non-small cell lung cancer patients receiving proton radiotherapy

Zeming Wang [a, 1], Mei Chen [a, b, 1], Jian Sun [c, d], Shengpeng Jiang [a, d], Li Wang [e], Xiaochun Wang [a], Narayan Sahoo [a], G. Brandon Gunn [c], Steven J. Frank [c], Quynh-Nhu Nguyen [c], Zhongxing Liao [c], Joe Y. Chang [c], X. Ronald Zhu [a], Xiaodong Zhang [a]

Outline

- Overview some proton NTCP model development works in MDACC based on the MDACC's proton outcome data
- Difference of photon and proton NTCP model: esophagitis modeling in NSCLC patients
- Importance of the "better" model for the model based treatment selection
- Role of advanced machine learning model in the model development
- Impact of variable RBE on the model development
- Summary

NTCP model development in MDACC

Radiation pneumonitis for both proton and photon patients

$$RMSD = D_{eff(n=0.5)} = \sqrt{\sum D_i^2 \times v_i}$$

Clinical Investigation

Validation of Effective Dose as a Better Predicto of Radiation Pneumonitis Risk Than Mean Lung Dose: Secondary Analysis of a Randomized Trial

Susan L. Tucker, PhD,* Ting Xu, MD, PhD,* Harald Paganetti, PhD,† Timo Deist, PhD,‡ Vivek Verma, MD,§ Noah Choi, MD,† Radhe Mohan, PhD,‖ and Zhongxing Liao, MD*

*Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Housto Texas; †Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical Schoo Boston, Massachusetts; ‡The D-Lab: Decision Support for Precision Medicine, GROW—School for Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands; §Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, Nebraska; an ‖Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas

Lyman modeling

In the standard Lyman model, the NTCP is modeled using a cumulative normal distribution:

$$NTCP = \frac{1}{2\pi} \int_{-\infty}^{t} e^{-u^2/2} du \qquad (1)$$

where t is given by:

$$t = \frac{D_{eff} - TD_{50}}{m \times TD_{50}} \qquad (2)$$

The parameter TD_{50} represents the dose corresponding to 50% probability of the given complication, m is proportional to the inverse slope of the dose-response curve, and D_{eff} is the effective dose to which the entire volume is exposed:

$$D_{eff} = \left(\sum D_i^{1/n} \times v_i \right)^n \qquad (3)$$

Table 1 Parameter estimates of the generalized Lyman model for grade ≥2 RP risk using the effective-dose with fitted n (left), mea lung dose (with n fixed at 1) (middle), or RMSD (with n fixed at 0.5) (right)

	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Parameter	Effective dose model		Mean lung dose model		RMSD model	
TD_{50} (Gy)	35.7	23.8-47.6	23.4	20.0-26.8	34.8	32.1-37.
m (1/Gy)	0.21	0.11-0.31	0.36	0.22-0.51	0.22	0.13-0.3
n	0.48	0.20-0.76	1	NA	0.5	NA
μ	1.38	1.20-1.56	1.38	1.20-1.56	1.38	1.20-1.5
σ	0.61	0.49-0.75	0.61	0.49-0.75	0.61	0.49-0.7

Abbreviations: CI = confidence interval; m = proportional to the inverse of the slope of the dose-response curve pertaining to the given complicatio n = parameter that affects relative weighting of different dose levels; NA = not applicable (n fixed in model fit); RMSD = root mean squared dos RP = radiation pneumonitis; TD_{50} = tolerance dose corresponding to 50% probability of the given complication (radiation pneumonitis μ, σ = parameters determining the shape of the time distribution (latency) over which RP occurs in the absence of censoring.

The radiation pneumonitis for both photon and proton model can be described by RMSD model

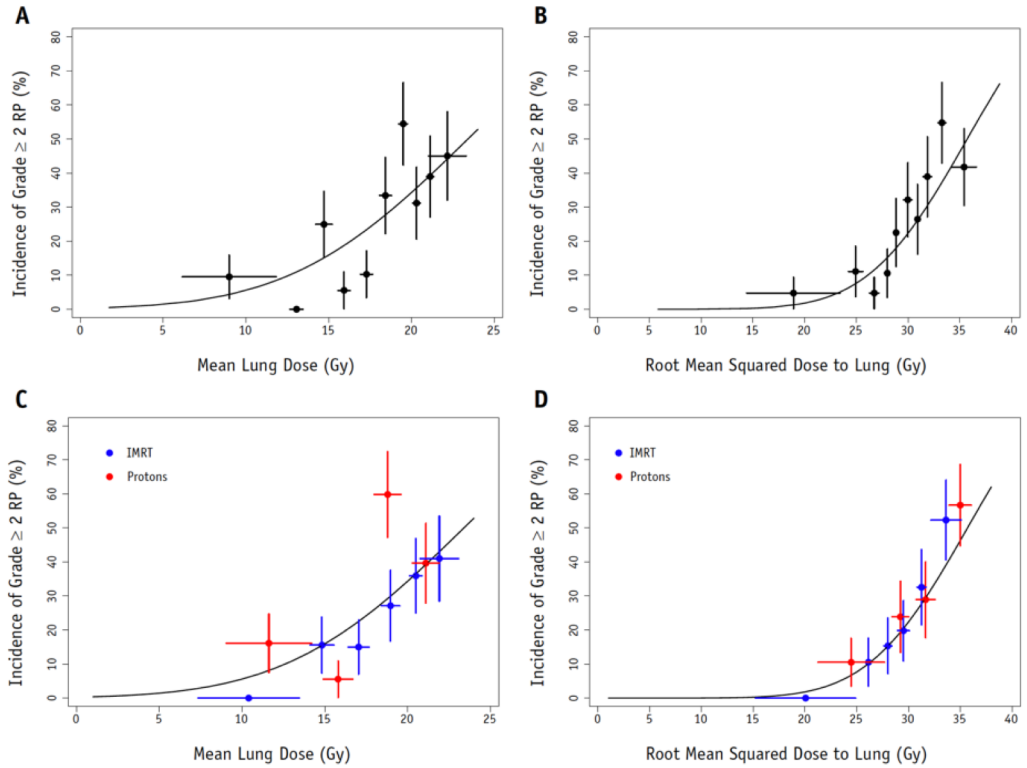


Fig. 2. Solid curves indicate predicted risk of grade ≥2 radiation pneumonitis from fits of the generalized Lyman model using mean lung dose ($n = 1$; A and C) or root mean squared dose ($n = 0.5$; B and D) as the dosimetric parameter. Plotted symbols represent groups of 20 to 21 patients each, with location on the abscissa indicating the average dosimetric value per group, ±1 standard deviation, and location on the ordinate indicating the Kaplan-Meier estimate, ±1 standard error, of grade ≥2 radiation pneumonitis at 12 months.

No separate model needed

Generalized LKB model

- A feature of the LKB model is that toxicity is regarded as a binary endpoint and scored as “yes” or “no” for each patient. This approach does not take into account the fact that some patients without toxicity might have experienced toxicity with longer follow-up. Moreover, the standard Lyman model does not incorporate **nondosimetric** risk factors such as comorbidities and other patient characteristics.
- A generalization of the Lyman model incorporating censored time-to-toxicity data and nondosimetric patient factors

Generalized Lyman model with covariates added

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

where t is equal to the following:

$$t = \frac{EUD*DMF1_1*\ldots*DMF_k - TD_{50}}{m*TD_{50}}, \text{ and}$$

$$EUD = (\sum_i v_i D_i^{\frac{1}{n}})^n,$$

The impact of the covariates such as SNPs, cTNT and other non-dosimetric factors are modeled by dose modifying factors $DMF_i, \ldots, DMF_k$. The dose modifying factors are calculated as $DMF_i = \exp(-\delta_i Y_i)$ where δ_i is the fitting parameters and Y_i represents the non-dosimetric factors. We will first model the non-dosimetric factors $Y_i$as the binary variable. For the continuous variables such as cTNT, we will first do the threshold analysis can convert them into binary variable.

Importance of incorporating non-dosimetric factors into Model

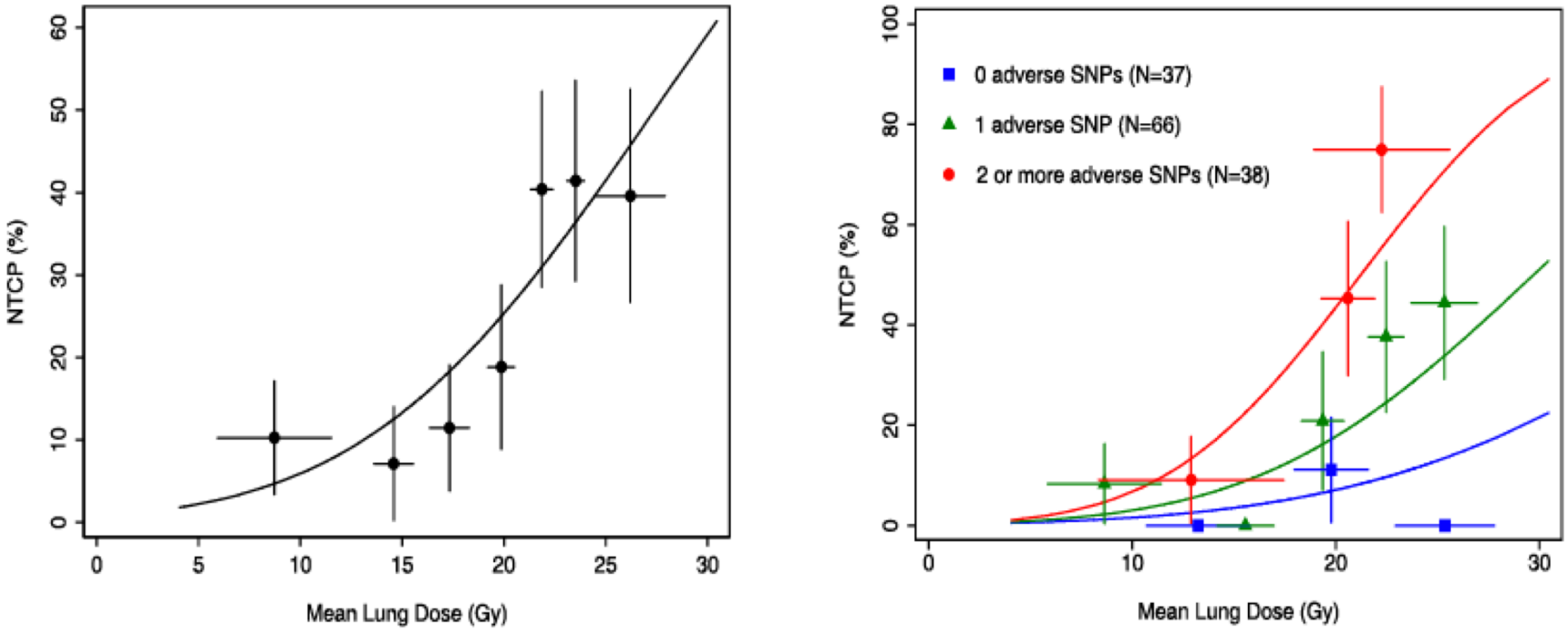
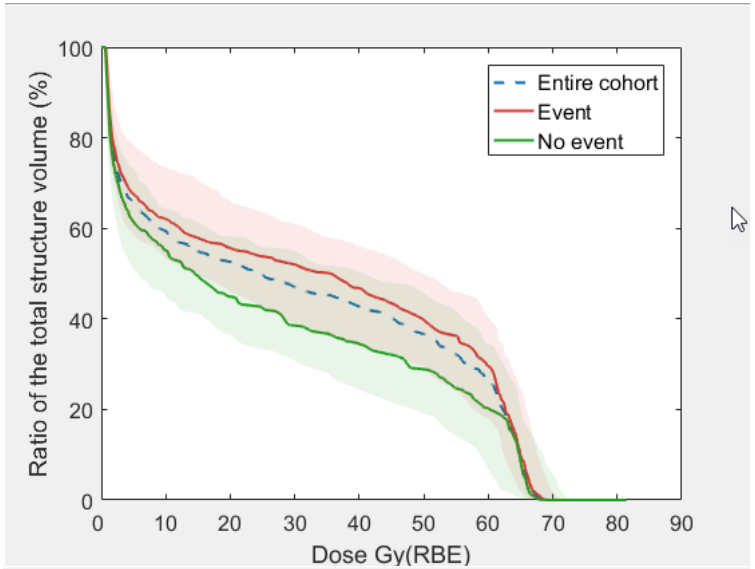


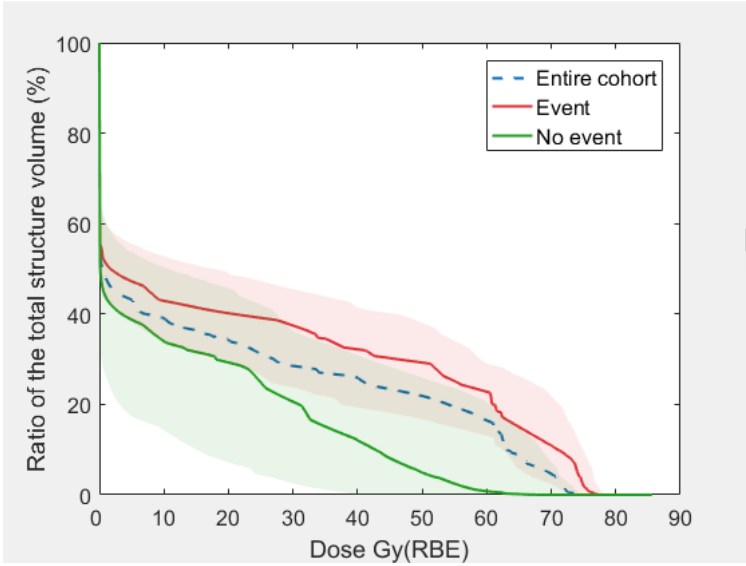
Figure 7. Incorporating SNP into NTCP model significantly improved predictive power for radiation pneumonitis. (left) MLD model, (right) number of risk SNP incorporated into the MLD model

Esophagitis in NSCLC patients receiving PSPT

- 328 patients PSPT alone or with concurrent chemotherapy
- 50-82.5 Gy (RBE)
- Physician evaluation CTCAE 3.0
- Endpoint of the study: grade ≥ 2 esophagitis within 6 months from the first treatment
- Grade 2-3 136 patients (41.5%)
- Grade 4-5 0 patients



IMRT



PSPT

Esophagitis in NSCLC patients receiving PSPT

- Lyman-Kutcher-Burman (LKB) modeling

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

$$t = \frac{\mathrm{EUD} - TD_{50}}{m * TD_{50}},$$

$$\mathrm{EUD} = \left(\sum_i v_i D_i^{\frac{1}{n}} \right)^n$$

- 3 Parameters ***n, m, TD_{50}***
- Using maximum likelihood estimates

$$\mathrm{LL}(\mathrm{n}, \mathrm{m}, \mathrm{TD50}) = \sum_{p=1} \ln\left(\mathrm{NTCP}(\mathrm{n}, \mathrm{m}, \mathrm{TD}_{50})\right) + \sum_{p=0} \ln(1 - \mathrm{NTCP}(\mathrm{n}, \mathrm{m}, \mathrm{TD}_{50}))$$

n=0.24 Smaller volume effect

	PSPT	**3DCRT[1]**	**IMRT[2]**
n	0.24	0.44	1.04
m	0.51	0.32	0.65
TD_{50}	44.83	51	32.84

MDACC own IMRT data

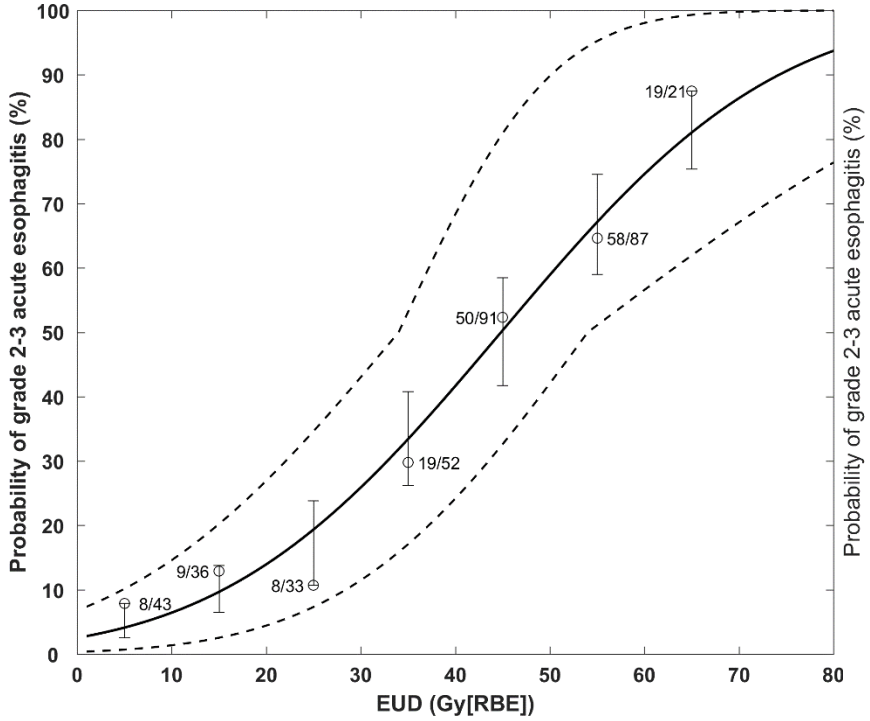
	n	m	TD50
IMRT	0.69	0.93	27.56

1. Chapet, O. *et al. Radiother. Oncol.* **77,** 176-181 (2005).
2. Wijsman, R. *et al. Radiother. Oncol.* **117,** 49-54 (2015).

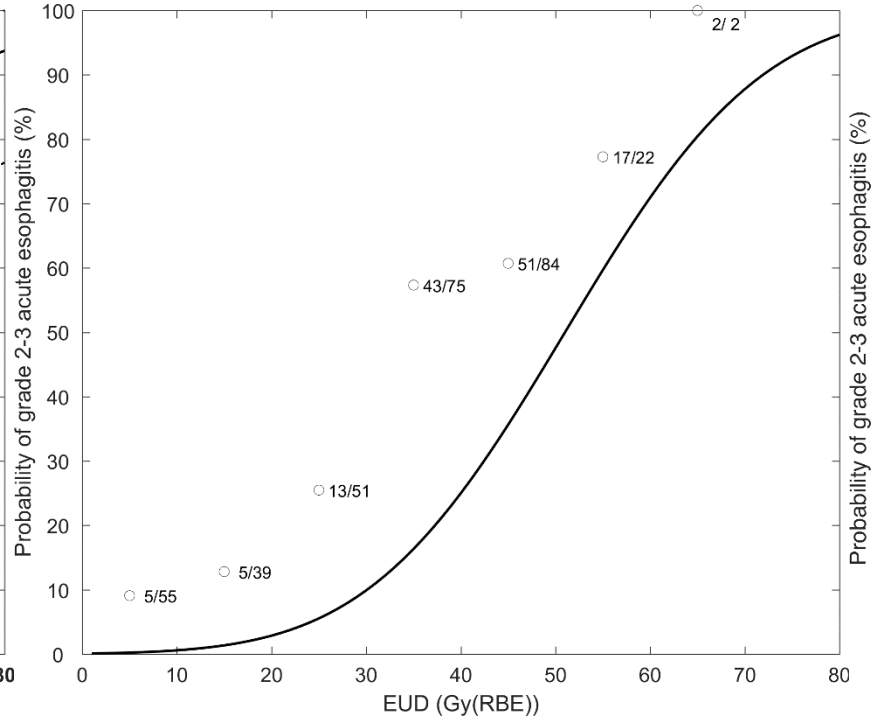
Esophagitis in NSCLC patients receiving PSPT

Predicted probability versus observed outcome
Photon-based models underestimated the NTCP

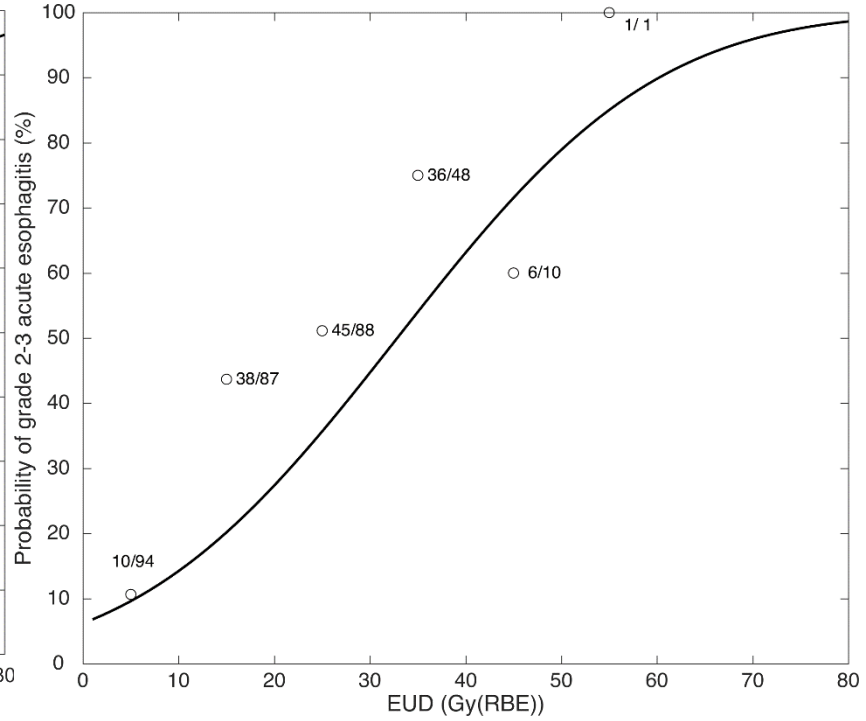
PSPT



3DCRT



IMRT



Selection of patients benefit from proton therapy based on the NTCP model

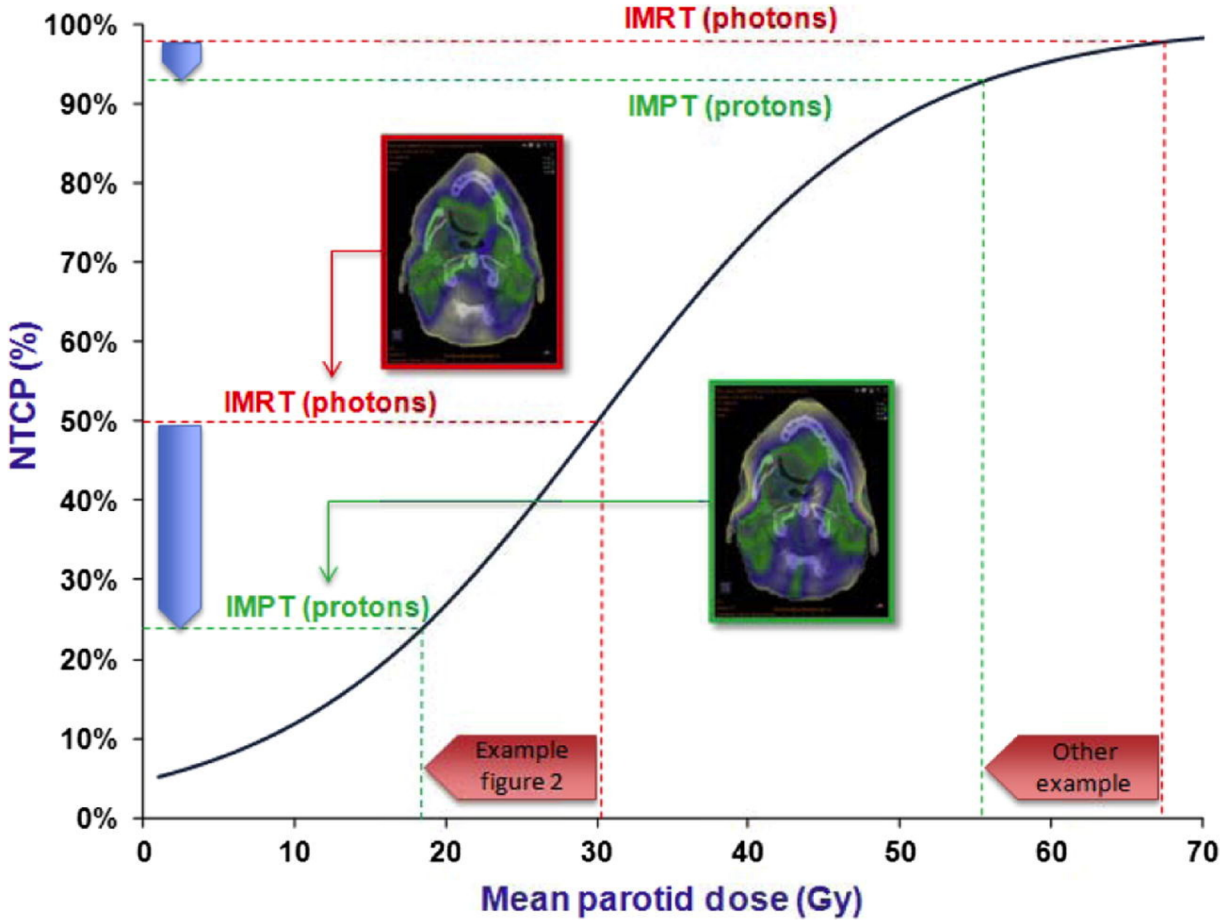
ELSEVIER

Radiotherapy and Oncology
Volume 107, Issue 3, June 2013, Pages 267-273

Proton radiotherapy

Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model-based approach

Johannes A. Langendijk [a], Philippe Lambin [b], Dirk De Ruysscher [c], Joachim Widder [a], Mike Bos [d], Marcel Verheij [e]



Virtual patient selection study based on the lung randomized trials

- 53 out of 57 patients treated with PSPT from lung IMRT/Proton randomized trials was selected for study
- 37 out of 53 patients developed greater than grade 2 esophagitis. (70%)
- Each patient has two optimized plans: PSPT plan and IMRT plan
- If using the NTCP model developed based on IMRT data (Wijsman, R. *et al. Radiother. Oncol.* **117,** 49-54 (2015)., if criterion of selection patient for proton treatment is that proton plan improves NTCP by 1%, 2%, 5%, 32, 30, 20 patients will be selected for proton treatment, however the rates of esophagitis are 69%, 70% and 75%
- If using NTCP model developed using proton data for proton plan and NTCP model developed using IMRT data for IMRT plan, if criterion of selection patient for proton treatment is that proton plan improves NTCP by 1%, 2%, 5%, 7, 5, 4 patients will be selected for proton treatment, the rates of esophagitis are 43%, 40% and 25%

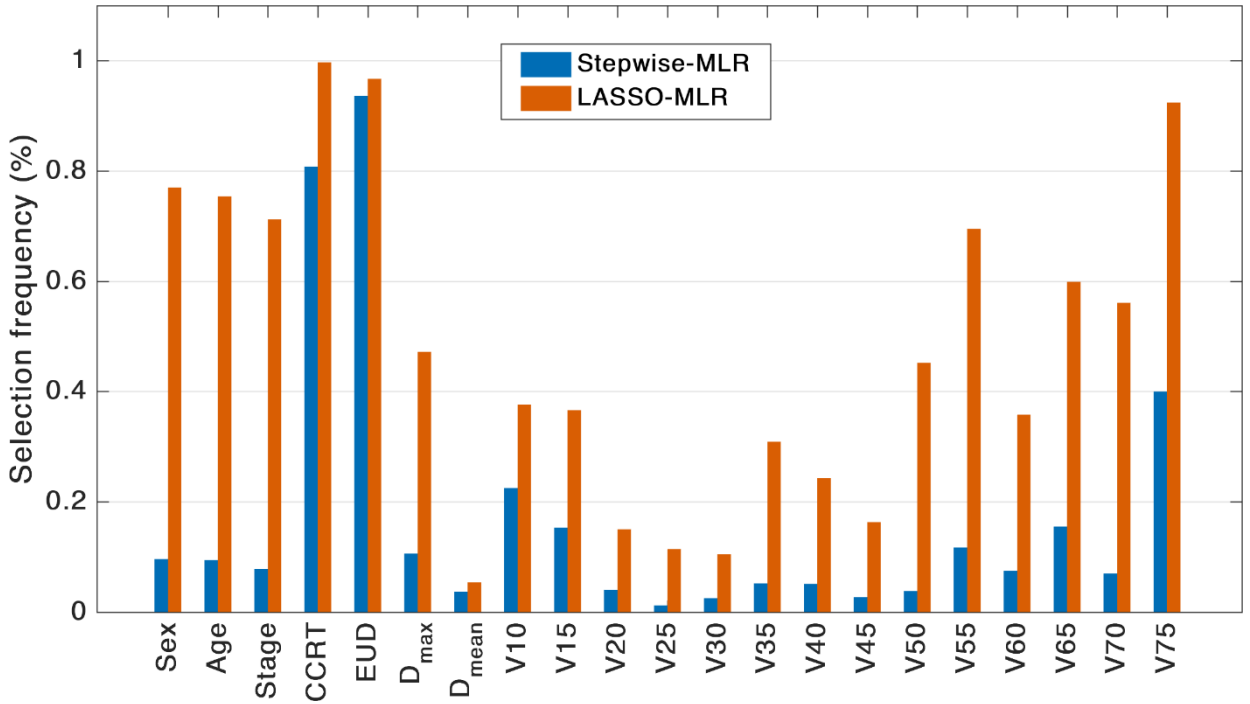
Using a not accurate model dose not help for the patient selection

Will advanced modeling technique help?

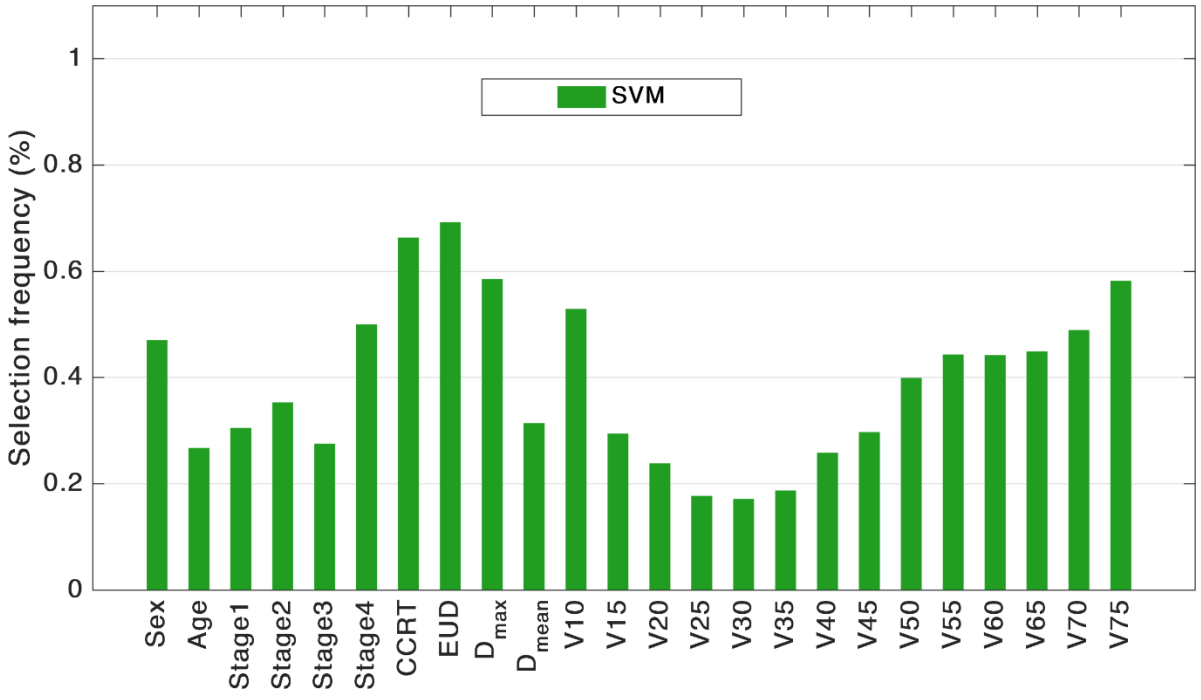
- Generalized LKB model accounting for the clinical factor (with or without Chemotherapy)
- Multivariable logistic regression model(Stepwise, LASSO feature selection)
- Machine learning-SVM

Feature selection

Multivariable logistic regression



SVM



Parameters and coefficients

Models	Parameters/Features	Coefficients/Formula
sLKB	n, m, TD_{50}	n = 0.24, m = 0.51, TD_{50} = 44.83 Gy (RBE)
gLKB	n, m, TD_{50y}, TD_{50n}	n = 0.23, m = 0.54, TD_{50y} = 42.17 Gy (RBE) TD_{50n} = 57.84 Gy (RBE)
Stepwise-MLR	CCRT, EUD	$\log\left(\frac{p}{1-p}\right) = -3.5845+0.8505*CCRT+0.0664*EUD$
LASSO-MLR	CCRT, EUD, V75	$\log\left(\frac{p}{1-p}\right) = -3.2766+0.7913*CCRT+0.0573*EUD+0.0438*V75$
SVM	CCRT, EUD	$C=2^{15}$, $\delta=2^{-13}$

Will advanced modeling technique help?

Models	AUC	LL	ΔAIC
sLKB	0.785 (0.783)*	-178.55	--
gLKB	0.799 (0.796)*	-174.46	6.18
Stepwise-MLR	0.800 (0.797)*	-174.20	10.70
LASSO-MLR	0.803 (0.799)*	-172.48	12.14
SVM	0.799 (0.784)*	-174.45	9.59

* Apparent performance(optimism-corrected performance

Biological uncertainty

- $S = \exp(-\alpha d - \beta d^2)$
- $S = \exp(-\alpha d)$
- $\alpha = \alpha_0(1 + cLET)$ LET<30kev/um
- BD = -log(S)/α_0 = (1+cLET)d
- cLET*d: additional biological dose due to LET effect
- c = 0.04

10-cm range 5-cm SOBP LET=2.5 kev/um RBE=1.1

Bragg peak LET=7.5 kev/um RBE=1.3

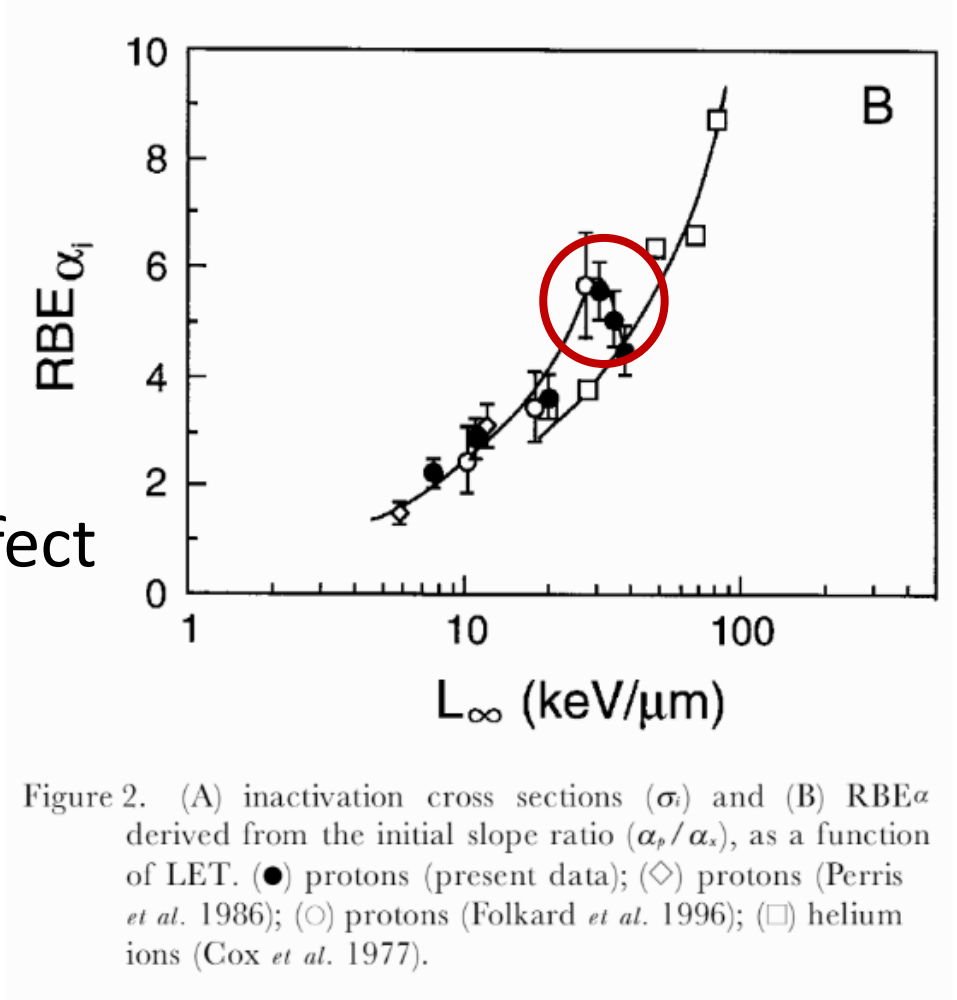


Figure 2. (A) inactivation cross sections (σ_i) and (B) RBE$^\alpha$ derived from the initial slope ratio (α_p/α_x), as a function of LET. (●) protons (present data); (◇) protons (Perris *et al.* 1986); (○) protons (Folkard *et al.* 1996); (□) helium ions (Cox *et al.* 1977).

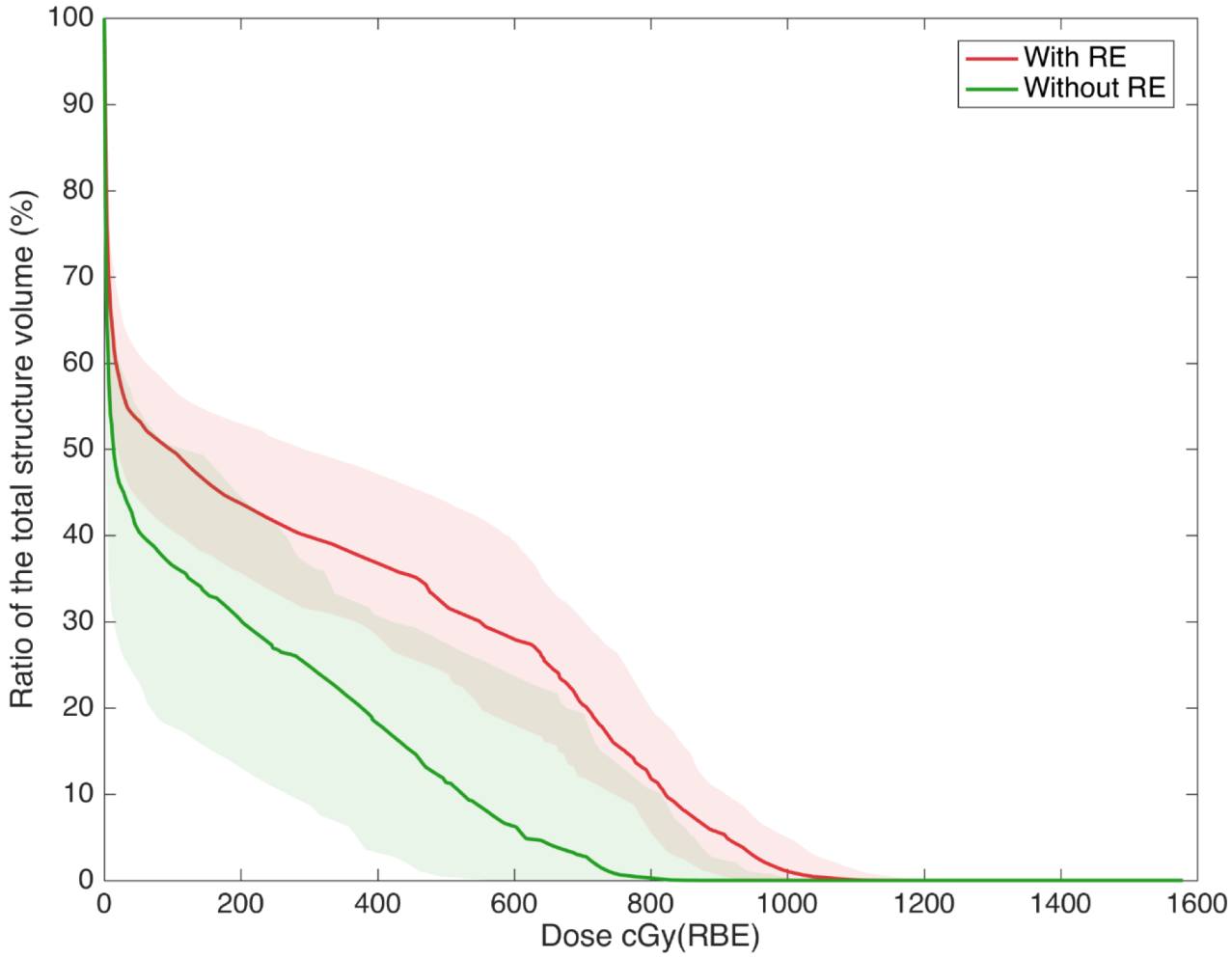
BELLI F. CERA R. CHERUBINI M. DALLA VECCHIA AMI HAQUE F. IANZINI G. MOSCHINI O. SAPORA G. SIMONE MA TABOCCHINI P. TIVERON, M. (1998). RBE-LET relationships for cell inactivation and mutation induced by low energy protons in V79 cells: further results at the LNL facility. *International Journal of Radiation Biology*, *74*(4), 501-509.

Have we underestimated NTCP using RBE=1.1 ?

- 114 patients
- One treatment course
- Prescription 60-87.5 Gy (RBE)
- Plan recalculated by Monte-Carlo-like fast dose calculator
- Biological uncertainty: $0.04LET_d*D$

Have we underestimated NTCP using RBE=1.1 ?

	Grade 0-1	Grade 2-3	P Value
DLmax	8.71 ± 3.94	11.33 ± 2.28	<0.001
DLmean	1.87 ± 1.44	3.07 ± 1.06	<0.001
DL1cc	6.47 ± 3.54	9.24 ± 1.94	<0.001
DL2cc	5.77 ± 3.46	8.74 ± 1.90	<0.001
DL5cc	4.43 ± 3.25	7.62 ±1.92	<0.001



Have we underestimated NTCP using RBE=1.1 ?

Multivariable logistic regression models with or without DL

Dose	**DL**	**AUC**	**LL**	**Log likelihood ratio test *p* value**
D2cc, V75		0.846	-54.34	--
D2cc, V75	DLmax	0.841	-54.33	0.89
D2cc, V75	DLmean	0.850	-53.65	0.24
D2cc, V75	DL1cc	0.839	-54.33	0.89
D2cc, V75	DL2cc	0.838	-54.34	1
D2cc, V75	DL5cc	0.842	-54.25	0.68

Summary

- Proton dose distribution pattern and photon dose distribution pattern are different. This required us to develop proton specific NTCP model
- It should be cautious to use NTCP model developed using photon data to perform the model based patient selection for proton treatment
- LKB model and generalized LKB model is not worse than the current most up to date machine learning approach
  - Data is not large enough
- It is time for the proton therapy community to work together to share the data and develop proton “QUANTEC”