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Original Article

NTCP model for postoperative complications and one-year mortality after trimodality treatment in oesophageal cancer

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ABSTRACT

Purpose/Objectives: To develop normal tissue complication probability (NTCP) models for postoperative pulmonary and cardiac complications and one-year mortality after preoperative chemoradiotherapy and surgery in oesophageal cancer patients.

Methods: 691 patients from two institutions (2002–2017) were included; 134 treated with protons. Multivariable logistic regression analyses on 601 patients studied the predictive value of clinical/treatment-related (gender, age, body mass index (BMI), smoking, cardiac comorbidity, chronic obstructive pulmonary disease, histology, cT/N) and dosimetric variables (absolute/relative lung/heart volumes receiving or spared from xGy, mean doses, planning target volume) for the presence of pulmonary complications, cardiac complications and one-year mortality. Model validation was performed using a non-random split-sample of 90 patients. Model performance was assessed by AUC and calibration plots.

Results: Respectively 144/601 (24.0%) and 165/601 (27.5%) patients developed a pulmonary or cardiac complication. For pulmonary complications, an NTCP model with optimism-corrected AUC of 0.75 (95%CI = 0.73–0.76) was obtained. The model contained mean lung dose (OR = 1.15, 95%CI = 1.09–1.22, $p < 0.001$), increasing age (OR = 1.03, 95%CI = 1.01–1.06, $p = 0.002$), BMI (OR = 1.04, 95%CI = 0.99–1.08, $p = 0.084$) and squamous cell carcinoma (OR = 3.22, 95%CI = 1.97–5.24, $p < 0.001$) as predictors. In validation, AUC of 0.79 was obtained (calibration slope 1.26). For cardiac complications, only age (OR = 1.06, 95%CI = 1.04–1.09, $p < 0.001$) with optimism-corrected AUC of 0.67 (95%CI = 0.65–0.68) was selected.

For one-year mortality, an NTCP model with optimism-corrected AUC of 0.63 (95%CI = 0.58–0.66) was obtained. Lung absolute V_{35} (OR = 1.0016, 95%CI = 1.0007–1.0026, $p = 0.001$), cN (OR = 2.45, 95%CI = 1.18–5.09, $p = 0.017$), cT4 (OR = 2.51, 95%CI = 1.10–5.74, $p = 0.029$) and cardiac comorbidity (OR = 2.91, 95%CI = 1.46–5.77, $p = 0.002$) were selected as predictors. At validation, AUC of 0.57 was obtained (calibration slope 0.75).

Conclusion: We were able to build and validate NTCP models for the presence of a postoperative pulmonary complication and for one-year mortality after trimodality treatment in oesophageal cancer.

Radical resection has long been the mainstay of treatment in patients with locoregionally advanced oesophageal cancer. However, outcome with this single modality treatment was poor with five-year survival rates ranging between 14% and 35% [1]. In a quest to improve outcome, several neoadjuvant and adjuvant strategies using chemotherapy or chemoradiotherapy have been investigated [2,3]. Currently, preoperative chemoradiotherapy (preCRT) followed by surgery is considered standard of care in the treatment of locally advanced oesophageal cancer [4,5].

While this multimodality approach has demonstrated an overall survival benefit, the combination of radiotherapy with cytotoxic drugs followed by extensive surgery is associated with considerable morbidity and mortality. Even in experienced centres, postoperative 30-day or in-hospital mortality rates up to 5% have been reported, and up to half of all surgically treated patients experience severe postoperative complications, mainly of pulmonary, gastrointestinal and cardiac origin [6,7]. Little is known on how preoperative treatment contributes to the risk of morbidity and mortality after extensive surgery. While a large meta-analysis suggests that preCRT does not significantly increase the risk of postoperative morbidity or mortality, other individual trials do report a higher

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incidence of lung complications and postoperative deaths after preCRT [8–11]. As for radiotherapy-related toxicity, the individual risk for postoperative morbidity and mortality depends on the complex interplay between clinical factors and the dose delivered to a certain volume of healthy tissue surrounding the tumour.

Because of this radiotherapy-related toxicity, improving the dose distribution is a key issue in the field of radiation oncology. The implementation of advanced radiotherapy techniques, such as proton therapy allows us to reduce the dose to the organs at risk while maintaining or even increasing the dose to the target volume; thus aiming to improve outcome with respect to both tumour control probability as normal tissue complication rate. In oesophageal cancer, there is evidence that supports the clinical benefit of proton therapy, in terms of reduced side effects [12–14].

To identify patients at high risk of treatment-induced complications in which the potential benefit of proton therapy can be investigated, multifactorial normal tissue complication probability (NTCP) models, based on clinical and treatment-related factors and dosimetric data, are needed. The rationale behind this model-based approach is that proton therapy may lead to improved clinical outcome due to less toxicity in patients, when three essential requirements are met: (1) bio-equivalent dose to the target volume can be delivered (similar local control); (2) normal tissue sparing can be obtained with proton therapy (different dose), and (3) different dose will result in clinically significant lower complication risk (or lower NTCP) [15].

In this study we aimed to build and validate an NTCP model for the presence of postoperative lung and cardiac complications and for one-year mortality after trimodality treatment in patients with advanced oesophageal cancer in a large multicentre dataset containing both photon and proton treatments.

Material and methods

The TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) recommendations for a type 2B study were followed [16]. The study was approved by the Institutional Ethical Review Board of the University Hospitals of Leuven (S59667).

Patients

Consecutive patients with a locally advanced oesophageal cancer treated with preCRT followed by surgery at the University Hospitals Leuven (Belgium) between 2002 and 2017 and the University of Texas MD Anderson Cancer Center (United States of America) between 2007 and 2017 were extracted from prospectively recorded databases. Exclusion criteria were histology other than squamous cell carcinoma (SCC) or adenocarcinoma (AC) and the presence of distant metastases.

Treatment

Pretreatment evaluations included a complete medical history and physical examination; complete blood count and biochemical survey; computed tomography (CT) of the chest and abdomen or ^{18}-fluoro-2-deoxyglucose positron emission tomography (^{18}F-FDG-PET)-CT scan; oesophagogastroduodenoscopy with biopsy; endoscopic ultrasound of the oesophagus. The American Joint Committee on Cancer Manual for Staging of Cancer (AJCC)/Union for International Cancer Control (UICC) (edition at time of diagnosis) was used for tumour staging.

Treatment regimens were discussed at the multidisciplinary tumour board. Radiotherapy was delivered in fractions of 1.8 Gy or 2.0 Gy to a total dose of 36.0–56.0 Gy, except for six patients treated with a fraction size of 2.25 to 63.0 Gy, by three-dimensional conformal radiotherapy (3D-CRT; $n = 233$, 33.7%), intensity modulated radiotherapy (IMRT; $n = 256$, 37.0%), volumetric arc therapy (VMAT; $n = 68$, 9.8%) or proton therapy (passively scattered proton therapy or intensity modulated proton therapy; $n = 134$, 19.4%). Chemotherapy was given according to standard protocol. Patients received either cisplatin-based ($n = 252$, 36.5%), carboplatin-based ($n = 74$, 10.7%), oxaliplatin-based ($n = 147$, 21.3%) or taxane-based ($n = 209$, 30.2%) chemotherapy. In 9 patients (1.3%), the chemotherapy regimen was unknown. Three hundred and ninety seven (57.5%) received platinum-based (except two) induction chemotherapy. Surgery consisted of an open or minimally invasive transthoracic oesophagectomy, combined with either a 2-field or 3-field lymphadenectomy.

Outcome measures

The endpoints for analysis were the presence of a postoperative pulmonary complication and the presence of a cardiac complication during hospitalization or within 30 days after readmission. These were assessed by the surgeon and prospectively scored in the databases at the two centres. Pulmonary complications were defined as pneumonia, respiratory failure and acute respiratory distress syndrome (ARDS). Cardiac complications include cardiac arrest, acute myocardial infarction, ventricular or atrial dysrhythmia, heart failure and pericarditis. Only clinically relevant complications requiring treatment were considered, according to the Esophageal Complications Consensus Group (ECCG) and Comprehensive Complication Index (CCI), excluding a CCI less or equal to 300 (defined as any deviation from a normal postoperative course without the need for interventions or pharmacological treatment, except for drugs as analgetics, diuretics, antiemetics, antipyretics, electrolytes and physiotherapy) [17,18]. One-year mortality was assessed based on all-cause mortality one year after surgery, and determined using municipal registers and hospital records. For the endpoint of one-year mortality, patients with a follow-up of less than 12 months were excluded.

Statistical analysis

Summary statistics were presented as medians and interquartile range (IQR) for continuous variables and as frequencies and percentages for categorical variables.

Univariable logistic regression analyses were performed to study the predictive value of both lung and heart dosimetric variables for postoperative pulmonary complications, for postoperative cardiac complications and for one-year mortality: the absolute and relative lung and heart volumes receiving x Gy (Vx, per 5 Gy increment; from 5 Gy to 45 Gy), the absolute lung and heart volume spared from x Gy (per 5 Gy increment; from 5 Gy to 45 Gy), the mean lung and heart dose and the planning target volume (PTV). These dosimetric variables were first ranked based on their association (area under the curve (AUC) of the univariable logistic regression) with the endpoint. The best ranked variable was selected first. Subsequently, each next variable was excluded from the ranking if its Pearson's correlation was $r > 0.8$ with any previously selected variable. For the remaining variables, it was checked whether non-linear transformations (log, square root, inverse transformations, etc.) improved the association. Results were reported as odds ratios (OR) with 95% confidence intervals (95%CI) and p-value. Dose–volume metrics were assessed from each individual isodose distribution, if appropriate after summation of physical doses of multiple radiotherapy plans. The lungs and heart were delineated according to the delineation guidelines/atlases of the Radiation Therapy Oncology Group (RTOG) and the heart atlas from Feng et al. [19–21]. Considered clinical variables in model building were: gender, age, body mass index

(BMI), history of cardiac disease, smoking behaviour, chronic obstructive pulmonary disease (COPD), histology and clinical tumour (cT) and nodal (cN) stage. Single imputation was used for BMI (1 case (0.1%) unknown), COPD (53 cases (7.7%) unknown), smoking behaviour (9 cases (1.3%) unknown), cardiac history (5 cases (0.7%) unknown), cT (3 cases (0.4%) unknown) and cN (3 cases (0.4%) unknown), and the dosimetric variable PTV (13 cases (1.9%) unknown). The added value of dosimetry to the use of clinical information was verified in three steps. Initially, a multivariable prediction model was built with only the clinical variables using a forward stepwise procedure with $p = 0.05$ (deviance criterion) as critical p-value to stay in the model. Afterwards, the clinical prediction model was extended by a stepwise addition of dosimetric variables which were ranked in the univariable analysis. Finally, the obtained model was extended by adding the variable radiation modality (photon versus proton therapy). The discriminative ability of the prediction models was quantified using the AUC and compared between nested models using the likelihood ratio test. To obtain stable prediction models, all modelling steps were repeated in a 100 times repeated 5-fold cross-validation process. The most frequently obtained models were selected. Final model coefficients were determined by fitting these selected models on the complete development dataset. Correction for optimism was performed using 500 bootstrap samples.

Model validation was performed using a nonrandom split-sample (TRIPOD type 2B study) of 90 patients selected based on treatment date (last 30 patients of each institution treated with photons and last 30 patients treated with proton therapy). Discrimination was assessed and calibration plots were analysed for their intercept (ideally 0) and slope (values below and above 1 indicating model over- and underfitting, respectively) [22]. The appropriate model updating technique was chosen using a closed testing procedure, i.e. adjusting only the intercept as a baseline risk correction was compared to a slope adjustment and to a re-estimation of all model coefficients [23].

All analyses were performed using Statistica version 13 (Dell Inc., Tulsa, OK) and MATLAB R2015b (The Mathworks Inc., Natick, MA).

Results

In total, 691 patients were included in the study (Table 1). Respectively 281 and 410 patients were treated at the University

Table 1
Patient and tumour characteristics in the development and validation set.

Variable	Statistic	All ($n = 691$)	Development set ($n = 601$)	Validation set ($n = 90$)	p-Value
Age	Median (IQR)	63 (56; 69)	63 (57; 70)	61 (54; 68)	0.14
Gender					0.98
Male	n (%)	561 (81.2)	488 (81.2)	73 (81.1)	
Female	n (%)	130 (18.8)	113 (18.8)	17 (18.9)	
BMI	Median (IQR)	25 (22; 29)	25 (22; 29)	27 (24; 30)	<0.001
Smoking					0.005
No smoking	n (%)	184 (26.6)	149 (24.8)	35 (38.9)	
Smoking	n (%)	498 (72.1)	443 (73.7)	55 (61.1)	
Unknown	n (%)	9 (1.3)	9 (1.5)	0 (0.0)	
Cardiac history					0.28
No	n (%)	616 (89.1)	543 (90.3)	73 (81.1)	
Yes	n (%)	70 (10.1)	58 (9.7)	12 (13.3)	
Unknown	n (%)	5 (0.7)	0 (0.0)	5 (5.6)	
COPD					0.003
No	n (%)	586 (84.8)	499 (83.0)	87 (96.7)	
Yes	n (%)	53 (7.7)	53 (8.8)	0 (0.0)	
Unknown	n (%)	52 (7.5)	49 (8.2)	3 (3.3)	
Histology					0.65
AC	n (%)	556 (80.5)	482 (80.2)	74 (82.2)	
SCC	n (%)	135 (19.5)	119 (19.8)	16 (17.8)	
Tumour stage					0.54
cT1	n (%)	7 (1.0)	6 (1.0)	1 (1.1)	
cT2	n (%)	63 (9.1)	55 (9.2)	8 (8.9)	
cT3	n (%)	586 (84.8)	508 (84.5)	78 (86.7)	
cT4	n (%)	33 (4.8)	31 (5.2)	2 (2.2)	
Unknown	n (%)	2 (0.3)	1 (0.2)	1 (1.1)	
Nodal stage					0.12
cN0	n (%)	169 (24.5)	141 (23.5)	28 (31.1)	
cN+	n (%)	519 (75.1)	458 (76.2)	61 (67.8)	
Unknown	n (%)	3 (0.4)	2 (0.3)	1 (1.1)	
Radiotherapy					
Radiation technique					<0.001
Photon treatment	n (%)	557 (80.6)	497 (82.7)	60 (66.7)	
Proton treatment	n (%)	134 (19.4)	104 (17.3)	30 (33.3)	
Total radiation dose (Gy)					0.02
<45.0 Gy	n (%)	69 (10.0)	68 (11.3)	1 (1.1)	
45.0–50.4 Gy	n (%)	615 (89.0)	527 (87.7)	88 (97.8)	
>50.4 Gy	n (%)	7 (1.0)	6 (1.0)	1 (1.1)	
Surgery					<0.001
Open	n (%)	595 (86.1)	535 (89.0)	60 (66.7)	
Minimally invasive	n (%)	88 (12.7)	58 (9.7)	30 (33.3)	
Transhiatal	n (%)	5 (0.7)	5 (0.8)	0 (0.0)	
Unknown	n (%)	3 (0.4)	3 (0.5)	0 (0.0)	

IQR = interquartile range; n = number; BMI = body mass index; COPD = chronic obstructive pulmonary disease; AC = adenocarcinoma; SCC = squamous cell carcinoma. p-Value: Mann-Whitney U test.

Hospitals Leuven and the University of Texas MD Anderson Cancer Center. The majority of patients was male (n = 561, 81.2%) and the median age was 63 years (IQR 56–69). Most patients had a history of smoking or were active smokers (n = 498, 72.1%) and had no history of cardiac disease (n = 616, 89.1%) nor COPD (n = 586, 84.8%). The predominant histologic tumour type was AC (n = 556, 80.5%) and cT3 was the most common tumour stage (n = 586, 84.8%). Most patients had positive lymph nodes upon clinical staging (n = 519, 75.1%).

Respectively 144 of 601 (24.0%) and 13 of 90 (14.4%) patients in the development and validation set developed a pulmonary complication (Table 2).

The top-ranked dosimetric parameters significantly associated with the development of a postoperative pulmonary complication were mean lung dose (MLD; OR = 1.21, 95%CI = 1.14–1.27, $p < 0.001$), heart relative V_{30} (OR = 1.03, 95%CI1.02–1.04, $p < 0.001$) and lung absolute V_{30} (OR = 1.0020, 95%CI = 1.0014–1.0027, $p < 0.001$) (Appendix Table A1).

Table 2
Incidence of postoperative pulmonary and cardiac complications in the development and validation set. Absolute numbers and percentage of patients.

Postoperative complication	Development set (n = 601)	Validation set (n = 90)	p-Value
Pulmonary	**144 (24.0)**	**13 (14.4)**	**0.045**
Pneumonia	124 (20.6)	8 (8.9)	0.008
Respiratory failure	62 (10.3)	5 (5.6)	0.15
ARDS	22 (3.7)	2 (2.2)	0.49
Cardiac	**165 (27.5)**	**18 (20.0)**	**0.14**
Cardiac arrest	4 (0.7)	1 (1.1)	0.64
Acute myocardial infarction	26 (4.3)	1 (1.1)	0.14
Atrial dysrhythmia	125 (20.8)	13 (14.4)	0.16
Ventricular dysrhythmia	12 (2.0)	4 (4.4)	0.15
Heart failure	3 (0.5)	0 (0.0)	0.50
Pericarditis	4 (0.7)	0 (0.0)	0.44

One patient could have more than one complication.
ARDS = acute respiratory distress syndrome; n = number.
p-Value: Chi-squared test.

In the 500 clinical models obtained in cross-validation, histology (100.0%), age (99.8%) BMI (58.2%) and gender (40.2%) were selected most often. The most frequently obtained model combined the covariates age (OR = 1.04, 95%CI = 1.02–1.07, $p < 0.001$), BMI (OR = 1.05, 95%CI = 1.00–1.09, $p = 0.028$) and squamous cell carcinoma histology (OR = 4.60, 95%CI = 2.89–7.32, $p < 0.001$). The discriminative ability of this clinical prediction model equals 0.71 (95%CI 0.66–0.76). A model with one dosimetric variable was selected in 58.2% of the cases. MLD was thus included in our final model (OR = 1.15, 95%CI = 1.09–1.22, $p < 0.001$) (Table 3). When adding the MLD information to the clinical prediction model, the AUC increased from 0.71 to 0.75 (95%CI = 0.70–0.80, $p < 0.001$). Finally, the radiation modality variable did not improve the model fit significantly. Fig. 1A shows a graphical representation of the optimal multivariable logistic regression model. At internal validation, an optimism-corrected AUC of 0.75 (95%CI = 0.73–0.76) was obtained.

In the validation set, the model had an AUC of 0.79 (95%CI = 0.64–0.88) and a calibration intercept of −0.41 and slope of 1.26 (Fig. 2A). According to the closed testing procedure, there was no evidence in the validation data to update the model.

Respectively 165 of 601 (27.5%) and 18 of 90 (20.0%) patients in the development and validation set developed a cardiac complication (Table 2).

The top-ranked dosimetric variables were the heart absolute V_{30} (OR = 1.0010, 95%CI = 1.0002–1.0017, $p = 0.011$), heart absolute V_5 (OR = 1.0009, 95%CI = 1.0001–1.0017, $p = 0.020$), and lung relative V_{10} (OR = 1.01, 95%CI = 1.00–1.03, $p = 0.008$) (Appendix A).

In the 500 clinical models obtained in cross-validation, age (100.0%) and cardiac comorbidity (48.2%) were selected most often. The most frequently obtained model selected age (OR = 1.06, 95%CI = 1.04–1.09, $p < 0.001$) (Table 3). The discriminative ability of this clinical prediction model equals 0.67 (95% CI = 0.62–0.71). A model without a dosimetric variable was selected in 58.0% of the cases and there was no significant improvement by adding dosimetric variables. At internal validation, an optimism-corrected AUC of 0.67 (95%CI = 0.65–0.68) was obtained.

Table 3
The optimal multivariable logistic regression model for the development of a postoperative pulmonary or cardiac complication and for one-year mortality.

		Odds ratio (95%CI)	p-value	Model coefficients	Clinical AUC (95%CI)	AUC adding dosimetry (95%CI)
Pulmonary complications						
Intercept				−6.227		
Age (year)		1.03 (1.01–1.06)	0.002	0.034	0.71	0.75
Histology	Adenocarcinoma	Reference			(0.66–0.76)	(0.70–0.80)
	Squamous cell carcinoma	3.22 (1.97–5.24)	<0.001	1.168	*0.71	*0.75
BMI		1.04 (0.99–1.08)	0.084	0.038	(0.67–0.73)	(0.73–0.76)
MLD (Gy)		1.15 (1.09–1.22)	<0.001	0.144		
Validation: AUC of 0.79 (0.64–0.88), slope 1.26, intercept −0.41						
Cardiac complications						
Intercept				−4.921		
Age (year)		1.06 (1.04–1.09)	<0.001	0.063	0.67	
					(0.62–0.71)	
					*0.67	
					(0.65–0.68)	
Validation: AUC of 0.63 (0.47–0.77), slope 0.87, intercept −0.33						
One-year mortality						
Intercept				−3.175		
cN		2.45 (1.18–5.09)	0.017	0.895	0.63	0.69
cT4		2.51 (1.10–5.74)	0.029	0.921	(0.58–0.68)	(0.63–0.75)
Cardiac comorbidity		2.91 (1.46–5.77)	0.002	1.067	*0.63	*0.63
					(0.54–0.66)	(0.58–0.66)
Lung absolute V_{35} (cm^3)		1.0016 (1.0007–1.0026)	0.001	0.002		
Validation: AUC of 0.57 (0.39–0.74), slope 0.75, intercept 0.40						

*Optimism-corrected AUC.
95%CI = 95% confidence interval; AUC = area under curve; MLD = mean lung dose; BMI = body mass index; cN = clinical nodal stage; cT = clinical tumour stage; absolute V_{35} = absolute volume receiving 35 Gy.

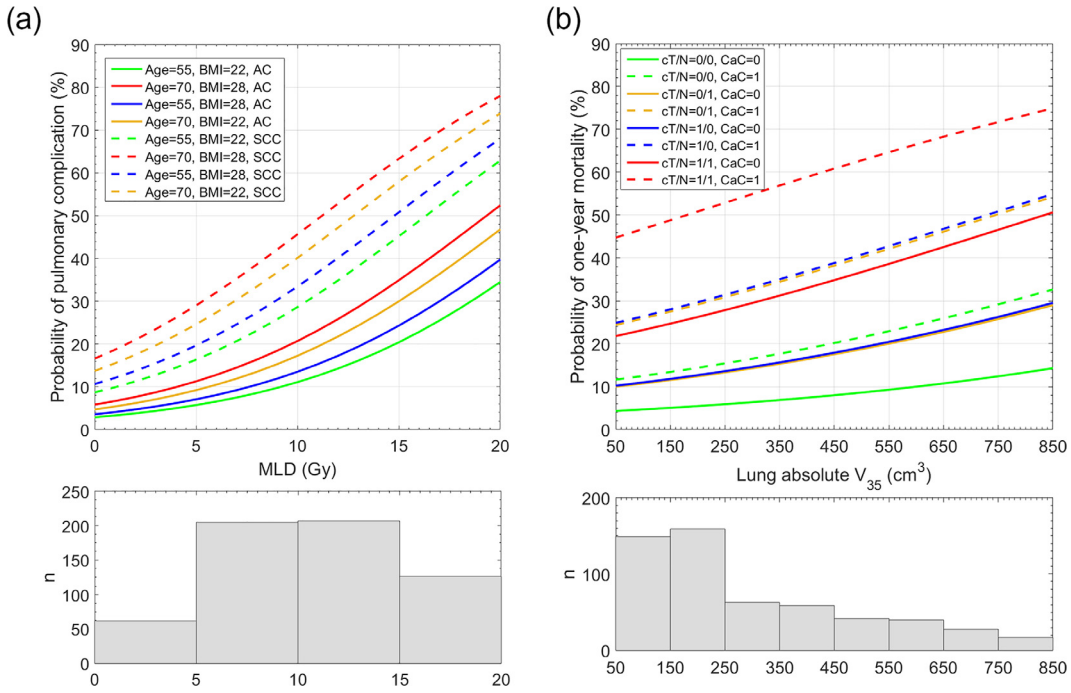

Fig. 1. Graphical representation of the optimal multivariable logistic regression model for the development of a postoperative pulmonary complication (A) and for one-year mortality (B). The distribution of MLD (A) and lung absolute V_{35} (B) values in the development dataset is shown at the bottom of the graphs. MLD = mean lung dose; BMI = body mass index; AC = adenocarcinoma; SCC = squamous cell carcinoma; cT = clinical tumour stage (cT4; 1 = present); cN = clinical nodal stage (cN+; 1 = present); CaC = cardiac comorbidity (1 = present); *n* = absolute number of patients in the development set.

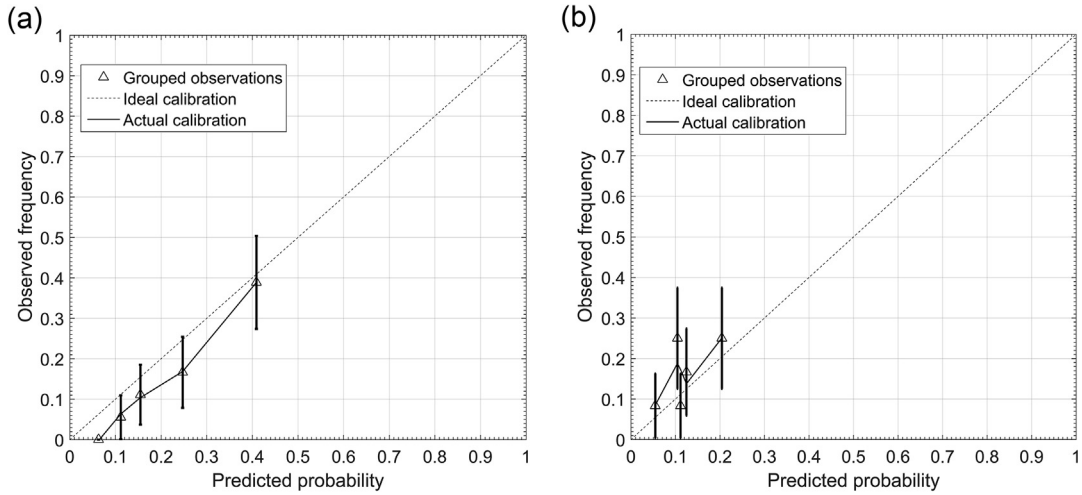

Fig. 2. Calibration curve of validation of the model for the development of a postoperative pulmonary complication (A) and for one-year mortality (B). The 'Actual calibration' curve is a 3rd order polynomial fit to the 'Grouped observations' data points. Predictions were divided into 5 equally sized bins of 18 patients (A) and 12 patients (B).

In the validation set, the model had an AUC of 0.63 (95% CI = 0.47–0.77) and a calibration intercept of −0.33 and slope of 0.87. There was no evidence for updating the model.

The one-year mortality in the development and validation set was 15.8% (89 of 564 patients) and 16.7% (10 of 60 patients). Top-ranked significant and uncorrelated dosimetric variables were the lung absolute V_{35} (OR = 1.0021, 95%CI = 1.0012–1.0030, $p < 0.001$), PTV (OR = 1.0009, 95%CI = 1.0004–1.0014, $p < 0.001$) and lung relative V_{20} (OR = 1.06, 95%CI = 1.03–1.10, $p < 0.001$) (Appendix A).

In the 500 clinical models obtained in cross-validation, cN (100.0%), cardiac comorbidity (85.6%) and cT (79.6%) were selected most often. The most frequently obtained model combined the covariates cN (OR = 3.11, 95%CI = 1.53–6.32, $p = 0.002$), cT4 (OR = 3.36, 95%CI = 1.52–7.41, $p = 0.003$) and cardiac comorbidity (OR = 2.82, 95%CI = 1.44–5.52, $p = 0.003$). The discriminative ability of this clinical prediction model equals 0.63 (95%CI = 0.58–0.68). A model with one dosimetric variable was selected in 94.8% of the cases. Lung absolute V_{35} was thus included in our final model (OR = 1.0016, 95%CI = 1.0007–1.0026, $p = 0.001$) (Table 3). When adding the lung absolute V_{35} information to the clinical prediction model, the AUC increased from 0.63 to 0.69 (95%CI = 0.63–0.75, $p = 0.001$). Finally, the radiation modality variable did not improve the model fit significantly. Fig. 1B shows a graphical representation

of the optimal multivariable logistic regression model. At internal validation, an optimism-corrected AUC of 0.63 (95%CI 0.58–0.66) was obtained.

In the validation set, the model had an AUC of 0.57 (95% CI = 0.39–0.74) and a calibration intercept of 0.40 and slope of 0.70 (Fig. 2B). According to the closed testing procedure, there was no evidence in the validation data to update the model.

Discussion

In the current study, we developed and validated NTCP models for the presence of a postoperative pulmonary complication and for one-year mortality after preCRT followed by surgery in locally advanced oesophageal cancer.

In the literature, several studies revealed a correlation between the radiation dose to the lungs and the incidence of pulmonary complications [24–27]. After analysis of 110 patients, Wang et al. [25] stated that the volume of lung spared from doses $\geq$5 Gy was the strongest independent factor for the occurrence of postoperative pneumonia or ARDS. Also other dosimetric parameters, including MLD and the absolute volume of the lung receiving <5 Gy have been described [26,27]. Published data on the association of dose to the heart and radiation-induced lung or heart injury in patients receiving concurrent chemoradiation are scarce. One study of Hatakenaka et al. [28] found an impairment of the left ventricle function after preCRT for oesophageal cancer, measured by cine magnetic resonance imaging, which was more prominent in patients with a higher left ventricle dose. Previous studies are based on smaller patients cohorts and none of them investigated the relationship between the dose to the lungs and the incidence of postoperative cardiac complications, nor between dose to the heart and the incidence of pulmonary or cardiac complications. In our study, we studied both lung and heart dosimetric parameters in view of postoperative pulmonary and cardiac complications. To include the baseline pulmonary and cardiac function of the patients, we considered the following clinical variables in the model building: history of cardiac disease, smoking behaviour and COPD. Since we focused on postoperative complications, we assume that these were not present prior to the surgery. For pulmonary complications, we were able to build an NTCP model for the incidence of pneumonia, respiratory failure or ARDS. We focused on this subgroup of clinically relevant complications which are most likely correlated with the preoperative radiotherapy. In most of the patients experiencing a complication, more than one pulmonary and/or cardiac complication was present due to their mutual interactions. SCC was associated with more pulmonary complications, possible due to the more challenging surgery and the anatomic location of the primary tumour typically between aorta and pars membranacea. A separate model building for both histology subgroups could not reliably be built due to the low number of patients in the SCC cohort. However, the validation of the reported NTCP model was good showing that all model covariates describe well the associations to the outcome in the validation dataset, both for AC and SCC patients. Because a high correlation between histology and location of the tumour is expected, we only included the variable histology in the analysis. A lower BMI before the preCRT was protective for the development of a pulmonary complication. This seems logical since overweight suggests a reduction in lung volume and capacity. However, in literature, the impact of BMI on postoperative complications showed conflicting results and most studies were done in the setting of primary surgery [29–31]. As expected, increasing age had a negative influence on the development of a pulmonary complication. MLD significantly improved the clinical prediction model. This dosimetric parameter was described in prior studies and is frequently used in the radiotherapy treatment planning optimisation in oesophageal cancer [26,27]. In contrast to previous studies, a low dose lung volume was not retained as a predictor for postoperative pulmonary complications [25,26]. However, these volumes were significant in univariable analysis (e.g. lung relative V_5; $p < 0.001$), and were only excluded based on correlations with MLD. The heart relative V_{30} was ranked as second dosimetric variable significantly associated with the development of a postoperative pulmonary complication, but not retained in the final model. For cardiac complications, the lung relative V_{10} was associated in univariable analysis. This emphasizes the physiological interaction of the lungs and heart in thoracic irradiation, as described previously [32]. Unfortunately, we were not able to build an NTCP model for postoperative cardiac complications. Perhaps, radiation induced cardiac toxicity is more pronounced on the long-term [33].

Besides postoperative complications, we investigated a survival endpoint, which has several advantages. It is precise and easy to measure. Moreover, investigator bias and subjective interpretation are not possible. In our study, we focused on one-year mortality for several reasons. In a previous study in lung cancer patients, already after six months, an influence of the heart dose on overall survival was seen [34]. Additionally, the follow-up period in our validation cohort was rather short. For one-year mortality, we found an association with the lung absolute V_{35} in multivariable analysis. The discriminative ability of the prediction model is moderate. Its large 95%CI could be explained by the low number of patients and events in the validation set. However, the AUC is in line with previous prediction models for overall survival in other tumours [35]. Additionally, the slope of the calibration curve in the validation set was good (around 1). In contrast to the nomogram for overall survival based on oesophageal cancer patients in the CROSS trial, cardiac comorbidity was considered as a clinical variable in our study and turned out to be important for mortality in our model. Moreover, only pretreatment variables were included, since the assumption was to predict mortality before the start of the preCRT.

The influence of the radiation modality was tested in the last step of model building. There was no significant improvement of the predictive ability in none of our models. Thus, it could be concluded that our prediction models can make a reliable outcome assessment of both photon and proton treatment plans. Subdivision of the photon irradiation into 3D-CRT, IMRT and VMAT was not appropriate since only a low number of patients were treated with VMAT in the training set and only the earliest cohort of patients received 3D-CRT. To account for the extent of the irradiated volume, we studied the predictive value of PTV, which was in univariable analysis associated with pulmonary complications ($p < 0.001$) and one-year mortality ($p < 0.001$). For the pulmonary complication endpoint, PTV was selected in none of the multivariable prediction models obtained during cross validation. This underlines the importance of the lung dose as a predictor for pulmonary complications, and the appropriateness of this NTCP model for selection of high-risk patients. For the one-year mortality endpoint, PTV was selected instead of a dosimetric feature into the prediction model in nearly one third of the cross validation folds, and the NTCP model accuracy was subject to a considerable correction for optimism. Future studies should therefore confirm the independent impact of lung dose on mortality.

The validated NTCP models of pulmonary complications and one-year mortality contain a lung dose parameter. Therefore, these models will help us to create an enriched cohort of patients who are most likely to benefit from proton therapy, based on clinical variables and dosimetric parameters (normal tissue sparing) [36]. This paves the way for intelligently designed prospective studies aiming at testing innovative radiation technologies and allows for more personalised and cost-effective implementation of new technologies.

To the best of our knowledge, this is the first NTCP model for postoperative pulmonary complications and one-year mortality in oesophageal cancer after trimodality treatment including a relatively large number of patients treated with proton therapy. Other strengths include that this is a large multi-centre study based on high-quality prospectively collected data with high uniformity between the centres, i.e. the endpoints. Furthermore, cross-validation and model validation using a nonrandom split-sample was performed. Moreover, a full lung and heart dose volume histogram analysis per 5 Gy increment was performed. A limitation of the study is the retrospective nature, although the clinical and treatment-related variables and endpoints were prospectively scored in the existing databases. In addition, we acknowledge that different treatment approaches (i.e. chemotherapy regimen, surgery) can affect our endpoints. However, as a result, our models are applicable to a more general cohort of patients treated with a variety of treatment modalities in different centres. Finally, several issues still need to be addressed regarding NTCP models. First, dose–volume models need to be continuously updated and adapted to new treatment conditions, preferentially based on prospective multicentre databases, to improve the prediction accuracy. This could potentially lead to dosimetric parameters that are specific to proton therapy dose distributions. Second, the question of which threshold NTCP we should use, remains unresolved.

For model building, we chose a two-step approach, i.e. building a clinical prediction model and extending this with dosimetric variables. This approach ensures that the selected dosimetric variables have an independent impact on the endpoint and that they are not just a surrogate of a clinical parameter. However, a one-step modelling approach (combining all clinical and a selection of univariately significant dosimetric parameters) had limited impact on the models built from our dataset. The only difference observed was for pulmonary complications, with one clinical factor (BMI) not included in the model. Our two-step approach might thus in this case be more conservative in terms of the outcome variability explained by the dosimetric factor MLD.

In conclusion, based on this patients cohort of 691 patients, we were able to build and validate an NTCP model for the presence of a postoperative pulmonary complication and for one-year mortality. These NTCP models can be used to select high-risk patients who might benefit from the lower normal lung doses achievable with proton therapy. No accurate prediction model for the presence of a cardiac complication was obtained.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.09.015.

References

[1] Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol 2009;27:5062–7. https://doi.org/10.1200/JCO.2009.22.2083.

[2] Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12:681–92. https://doi.org/10.1016/S1470-2045(11)70142-5.

[3] van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BPL, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074–84. https://doi.org/10.1056/NEJMoa1112088.

[4] Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v50–7. https://doi.org/10.1093/ANNONC/MDW329.

[5] National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology, NCCN Guidelines Version 1.2019: Esophageal and Esophagogastric Junction Cancers 2019.

[6] Seely AJE, Ivanovic J, Threader J, Al-Hussaini A, Al-Shehab D, Ramsay T, et al. Systematic classification of morbidity and mortality after thoracic surgery. Ann Thorac Surg 2010;90:936–42. https://doi.org/10.1016/j.athoracsur.2010.05.014.

[7] Bailey SH, Bull DA, Harpole DH, Rentz JJ, Neumayer LA, Pappas TN, et al. Outcomes after esophagectomy: a ten-year prospective cohort. Ann Thorac Surg 2003;75:217–22. discussion 222.

[8] Kumagai K, Rouvelas I, Tsai JA, Mariosa D, Klevebro F, Lindblad M, et al. Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. Br J Surg 2014;101:321–38. https://doi.org/10.1002/bjs.9418.

[9] Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997;337:161–7.

[10] Bosch DJ, Muijs CT, Mul VEM, Beukema JC, Hospers GAP, Burgerhof JGM, et al. Impact of neoadjuvant chemoradiotherapy on postoperative course after curative-intent transthoracic esophagectomy in esophageal cancer patients. Ann Surg Oncol 2014;21:605–11. https://doi.org/10.1245/s10434-013-3316-8.

[11] Reynolds JV, Ravi N, Hollywood D, Kennedy MJ, Rowley S, Ryan A, et al. Neoadjuvant chemoradiation may increase the risk of respiratory complications and sepsis after transthoracic esophagectomy. J Thorac Cardiovasc Surg 2006;132:549–55. https://doi.org/10.1016/j.jtcvs.2006.05.015.

[12] Lin SH, Komaki R, Liao Z, Wei C, Myles B, Guo X, et al. Proton beam therapy and concurrent chemotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys 2012;83:e345–51. https://doi.org/10.1016/j.ijrobp.2012.01.003.

[13] Wang J, Wei C, Tucker SL, Myles B, Palmer M, Hofstetter WL, et al. Predictors of postoperative complications after trimodality therapy for esophageal cancer. Int J Radiat Oncol Biol Phys 2013;86:885–91. https://doi.org/10.1016/j.ijrobp.2013.04.006.

[14] Lin SH, Merrell KW, Shen J, Verma V, Correa AM, Wang L, et al. Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer. Radiother Oncol 2017;123:376–81. https://doi.org/10.1016/j.radonc.2017.04.013.

[15] Widder J, Van Der Schaaf A, Lambin P, Marijnen CAM, Pignol JP, Rasch CR, et al. The quest for evidence for proton therapy: model-based approach and precision medicine. Int J Radiat Oncol Biol Phys 2016;95:30–6. https://doi.org/10.1016/j.ijrobp.2015.10.004.

[16] Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD Statement. Eur Urol 2015;67:1142–51. https://doi.org/10.1016/j.eururo.2014.11.025.

[17] Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'Journo XB, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg 2015;262:286–94. https://doi.org/10.1097/SLA.0000000000001098.

[18] Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien P-A. The Comprehensive Complication Index. Ann Surg 2013;258:1–7. https://doi.org/10.1097/SLA.0b013e318296c732.

[19] Jabbour SK, Hashem SA, Bosch W, Kim TK, Finkelstein SE, Anderson BM, et al. Upper abdominal normal organ contouring guidelines RTOG: consensus panel 2013. https://www.rtog.org/LinkClick.aspx?fileticket=dgwtfz553_g=&tabid=387.

[20] Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys 2011;79:10–8. https://doi.org/10.1016/j.ijrobp.2009.10.058.

[21] Kong FM, Quint L, Machtay M, Bradley J. Atlases for organs at risk (OARs) in thoracic radiation therapy 2013. http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx%5Cnpapers3://publication/uuid/3E06737D-3F53-49F8-9133-339E3AABA706.

[22] Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21:128–38. https://doi.org/10.1097/EDE.0b013e3181c30fb2.

[23] Vergouwe Y, Nieboer D, Oostenbrink R, Debray TPA, Murray GD, Kattan MW, et al. A closed testing procedure to select an appropriate method for updating

prediction models. Stat Med 2017;36:4529–39. https://doi.org/10.1002/sim.7179.
[24] Lee HK, Vaporciyan AA, Cox JD, Tucker SL, Putnam JB, Ajani JA, et al. Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose–volume histogram parameters. Int J Radiat Oncol Biol Phys 2003;57:1317–22. https://doi.org/10.1016/S0360-3016(03)01373-7.
[25] Wang SL, Liao Z, Vaporciyan AA, Tucker SL, Liu H, Wei X, et al. Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys 2006;64:692–9. https://doi.org/10.1016/j.ijrobp.2005.08.002.
[26] Tucker SL, Liu HH, Wang S, Wei X, Liao Z, Komaki R, et al. Dose-volume modeling of the risk of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys 2006;66:754–61. https://doi.org/10.1016/j.ijrobp.2006.06.002.
[27] Cho WK, Oh D, Kim HK, Ahn YC, Noh JM, Shim YM, et al. Dosimetric predictors for postoperative pulmonary complications in esophageal cancer following neoadjuvant chemoradiotherapy and surgery. Radiother Oncol 2019;133:87–92. https://doi.org/10.1016/j.radonc.2019.01.005.
[28] Hatakenaka M, Yonezawa M, Nonoshita T, Nakamura K, Yabuuchi H, Shioyama Y, et al. Acute cardiac impairment associated with concurrent chemoradiotherapy for esophageal cancer: magnetic resonance evaluation. Int J Radiat Oncol Biol Phys 2012;83:e67–73. https://doi.org/10.1016/j.ijrobp.2011.12.018.
[29] Blom RLGM, Lagarde SM, Klinkenbijl JHG, Busch ORC, Van Berge Henegouwen MI. A high body mass index in esophageal cancer patients does not influence postoperative outcome or long-term survival. Ann Surg Oncol 2012;19:766–71. https://doi.org/10.1245/s10434-011-2103-7.
[30] Gao H, Feng HM, Li B, Lin JP, Yang JB, Zhu DJ, et al. Impact of high body mass index on surgical outcomes and long-term survival among patients undergoing esophagectomy: a meta-analysis. Medicine (Baltimore) 2018;97:. https://doi.org/10.1097/MD.0000000000011091e11091.
[31] Shridhar R, Hayman T, Hoffe SE, Weber J, Almhanna K, Chuong M, et al. Body mass index and survival in esophageal adenocarcinoma treated with chemoradiotherapy followed by esophagectomy. J Gastrointest Surg 2012;16:1296–302. https://doi.org/10.1007/s11605-012-1843-4.
[32] Ghobadi G, Van Der Veen S, Bartelds B, De Boer RA, Dickinson MG, De Jong JR, et al. Physiological interaction of heart and lung in thoracic irradiation. Int J Radiat Oncol Biol Phys 2012;84:e639–46. https://doi.org/10.1016/j.ijrobp.2012.07.2362.
[33] Beukema JC, van Luijk P, Widder J, Langendijk JA, Muijs CT. Is cardiac toxicity a relevant issue in the radiation treatment of esophageal cancer?. Radiother Oncol 2015;114:85–90. https://doi.org/10.1016/j.radonc.2014.11.037.
[34] Speirs CK, DeWees TA, Rehman S, Molotievschi A, Velez MA, Mullen D, et al. Heart dose is an independent dosimetric predictor of overall survival in locally advanced non-small cell lung cancer. J Thorac Oncol 2017;12:293–301. https://doi.org/10.1016/j.jtho.2016.09.134.
[35] Oberije C, De Ruysscher D, Houben R, van de Heuvel M, Uyterlinde W, Deasy JO, et al. A validated prediction model for overall survival from stage III non-small cell lung cancer: toward survival prediction for individual patients. Int J Radiat Oncol Biol Phys 2015;92:935–44. https://doi.org/10.1016/j.ijrobp.2015.02.048.
[36] Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model-based approach. Radiother Oncol 2013;107:267–73. https://doi.org/10.1016/j.radonc.2013.05.007.