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Original article

Multivariable normal-tissue complication modeling of acute esophageal toxicity in advanced stage non-small cell lung cancer patients treated with intensity-modulated (chemo-)radiotherapy

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ABSTRACT

Background and purpose: The majority of normal-tissue complication probability (NTCP) models for acute esophageal toxicity (AET) in advanced stage non-small cell lung cancer (AS-NSCLC) patients treated with (chemo-)radiotherapy are based on three-dimensional conformal radiotherapy (3D-CRT). Due to distinct dosimetric characteristics of intensity-modulated radiation therapy (IMRT), 3D-CRT based models need revision. We established a multivariable NTCP model for AET in 149 AS-NSCLC patients undergoing IMRT.
Materials and methods: An established model selection procedure was used to develop an NTCP model for Grade $\geqslant$2 AET (53 patients) including clinical and esophageal dose–volume histogram parameters.
Results: The NTCP model predicted an increased risk of Grade $\geqslant$2 AET in case of: concurrent chemoradiotherapy (CCR) [adjusted odds ratio (OR) 14.08, 95% confidence interval (CI) 4.70–42.19; $p < 0.001$], increasing mean esophageal dose [D_{mean}; OR 1.12 per Gy increase, 95% CI 1.06–1.19; $p < 0.001$], female patients (OR 3.33, 95% CI 1.36–8.17; $p = 0.008$), and $\geqslant$cT3 (OR 2.7, 95% CI 1.12–6.50; $p = 0.026$). The AUC was 0.82 and the model showed good calibration.
Conclusions: A multivariable NTCP model including CCR, D_{mean}, clinical tumor stage and gender predicts Grade $\geqslant$2 AET after IMRT for AS-NSCLC. Prior to clinical introduction, the model needs validation in an independent patient cohort.
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The introduction of intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) for advanced stage non-small cell lung cancer (NSCLC) patients allows for the delivery of highly conformal dose distributions enabling treatment of larger target volumes or the delivery of increased prescription doses [1,2]. Nevertheless, patients may still suffer from acute esophageal toxicity (AET) during and shortly after radiotherapy for advanced stage disease, because large high-dose volumes of centrally located tumors or involved mediastinal lymph nodes often border the esophagus [3,4].

Furthermore, AET is enhanced with concurrent chemoradiotherapy (CCR) [5]. Although CCR improves survival, the increased AET has a negative impact on the overall quality of life and may lead to hospitalization and treatment interruptions jeopardizing treatment outcome. Hence, predicting AET may be helpful in anticipating (chemo-)radiotherapy induced esophageal toxicity.

Several studies have assessed the prevalence of AET in (non-small cell) lung cancer patients in relation to the dose delivered to the esophagus and other tumor and patient related characteristics [4,6–17]. Heterogeneous outcomes have been reported, particularly for the dosimetric variables predicting for AET [4,9,10,18,19]. Up till now, there is no consensus on the single best dose–volume histogram (DVH) parameter to predict AET with high accuracy and precision. Furthermore, most studies are based on patients treated with three-dimensional conformal radiotherapy (3D-CRT), while the vast majority of patients is being treated with IMRT or VMAT these days. These techniques can deliver more conformal dose distributions than 3D-CRT, however, often at the cost of increased target dose heterogeneity and larger proportions of surrounding healthy tissues receiving low doses [2,20]. As a consequence, the dosimetric differences between 3D-CRT and IMRT/VMAT may

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possibly influence the risk of AET and thus new predictive models for AET after IMRT/VMAT are needed.

In this study we systematically investigated the relationship between DVH and clinical parameters to establish a predictive model for Grade $\geqslant 2$ AET in advanced stage NSCLC patients treated with step-and-shoot IMRT or VMAT.

Materials and methods

Patients and treatment characteristics

In this retrospective study, we assessed a cohort of 149 consecutive patients that had undergone (chemo-)radiotherapy for histopathologically confirmed advanced stage or inoperable NSCLC between March 2008 and June 2013. The study has been carried out in accordance with the national applicable rules concerning the review of research ethics committees and informed consent.

For staging purposes, every patient underwent a diagnostic ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan combined with a low-dose computed tomography (CT) scan, and magnetic resonance imaging of the brain. CCR was only delivered to patients in good clinical condition; all others underwent sequential treatment or radiotherapy alone.

For radiation treatment planning, an intravenous contrast-enhanced CT scan (Big Bore Brilliance CT scanner; Philips Medical Systems, Best, The Netherlands) of the thorax (3 mm slice thickness), directly followed by a slow-CT scan of the primary tumor, were acquired while the patient was in treatment position. Both CT data sets were transferred to the Pinnacle^3 (Version 8.0–9.2; Philips Radiation Oncology Systems, Fitchburg, WI) treatment planning system (TPS). The primary tumor and suspicious lymph nodes (confirmed by histopathology after endobronchial/endoesophageal ultrasonography, enlarged or with malignant features on CT scan, and/or FDG-PET positive) were considered the gross tumor volume (GTV). Clinical target volumes (CTV) enclosed the GTV of the primary tumor and lymph nodes with 10 mm and 5 mm margins, respectively. Planning target volumes (PTVs) were created by an isotropic 5 mm expansion of the CTVs. Delineation of the organs at risk (OAR) such as lungs, heart and spinal cord (i.e., inner margin entire bony thoracic spinal canal) was automatically performed by the TPS and was adjusted manually if necessary. Because of the retrospective nature of this analysis and the importance of accurate DVH data concerning the esophagus, the outer rim of the esophageal wall (from the lower border of the cricoid cartilage to the gastro-esophageal junction) was re-contoured by one single physician (RW).

The prescribed dose to the PTV was 66 Gy in 33 (once-daily) fractions using IMRT (step and shoot until June 2011 or VMAT from April 2011 onwards). In 4 (2.7%) patients the prescribed dose could not be achieved without violating the normal-tissue dose constraints, and hence the number of fractions was reduced to 30 fractions. According to the ICRU 50/62 guidelines the −5% and +7% dose heterogeneity criteria for the PTV were aimed for [21,22]. A standard beam set-up (six co-planar 10 MV photon beams for IMRT and one 10 MV photon arc for VMAT) was used avoiding the contralateral uninvolved lung. Step-and-shoot IMRT was planned with a minimum of 10 monitor units per segment and a maximum of 60 segments. Gantry angular spacing between control points was 4° for the VMAT arc. Predicted dose deposition was calculated using a 3D collapsed-cone convolution superposition algorithm. Routine position verification prior to irradiation consisted of an off-line set-up and correction protocol.

The standard sequential chemotherapy regimen typically consisted of 3 (3-weekly) courses of gemcitabine (1250 mg/m^2; on day 1 and 8) and cisplatinum (80 mg/m^2; on day 1), whereas all patients undergoing CCR received 2 (3-weekly) courses of etoposide (100 mg/m^2; on day 1–3) and cisplatinum (50 mg/m^2; on day 1 and 8). Due to local policy, some patients from a referring hospital received one additional course of gemcitabine/cisplatinum 3 weeks before start of CCR.

Toxicity scoring

The standard follow-up protocol consisted of weekly assessment of acute toxicity by the treating radiation oncologist, even though this may have varied according to the patients' perceived well-being. In general, follow-up continued after the end of treatment until acute toxicity resolved. The Radiation Therapy Oncology Group acute radiation morbidity scoring criteria have been used by the treating radiation oncologist to evaluate esophageal toxicity [23].

Data collection and statistical analysis

All medical records were retrospectively reviewed. Anonymous patient and tumor characteristics together with the (maximum) AET scores (at any time point) were collected in a secured and audit trail-equipped database (OpenClinica, version 3.4, Waltham, MA). Full DVH data of the esophagus (solid organ including lumen) were retrieved from the TPS to extract the parameters: mean and maximum esophageal dose (D_{mean} and D_{max}, respectively), and the relative volume receiving $\geqslant 5$ Gy to $\geqslant 70$ Gy (V_{5Gy}–V_{70Gy}) in 5 Gy increments. To correct for spatial fractionation effects, these parameters were extracted from the DVHs after conversion from physical dose to 2 Gy per fraction equi-effective (EQD2) dose assuming $\alpha/\beta = 10$ Gy for acute toxicity.

Relevant clinical parameters and the abovementioned EQD2-corrected DVH parameters were evaluated for Grade $\geqslant 2$ AET using univariate logistic regression analysis. The resulting significant parameters were tested for between-group (Grade $\geqslant 2$ *vs* Grade $\leqslant 1$ AET) differences using the Mann–Whitney-*U* or Chi-square test, where appropriate. A p-value of <0.05 was considered statistically significant.

Data exploration and predictive modeling

In accordance with the method of El Naqa et al. [24], a Spearman cross-correlation matrix of the DVH parameters was first calculated to assess the degree of multicollinearity between variables. In case of high inter-variable correlations (correlation coefficient $\geqslant 0.8$), a surrogate variable was selected before actual modeling was performed. Furthermore, the Lyman–Kutcher–Burman (LKB) normal-tissue complication probability (NTCP) model was fitted to the Grade $\geqslant 2$ AET data using the EQD2-corrected DVHs to assess the volume effect [25]. After these data exploration steps, automated multivariable logistic regression model selection was performed using the MATLAB-based (version R2013b; The MathWorks, Natick, MA) Dose Response Explorer System (DREES; version 1.0 beta) [26]. First, the optimal model order was estimated by leave-one-out cross validation (2000 samples); i.e. the number of model parameters with the highest correlation coefficient for Grade $\geqslant 2$ AET was selected as the optimal number of parameters. The second step comprised the estimation of the model parameters by logistic regression analysis with forward selection on 2000 bootstrap samples. From these bootstrap samples, the most frequently selected model was chosen as the optimal model. Odds ratios (OR) and the accompanying 95% confidence intervals (CI) were calculated for these parameters using SPSS software (version 20.0; Chicago, IL).

The multivariable NTCP model for Grade $\geqslant 2$ AET with k prognostic variables ($\underline{x}$) is expressed by the multivariable logistic regression formula:

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