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### Prediction of toxicity in concurrent chemoradiation for non-small cell lung cancer

Uijterlinde, W.I.

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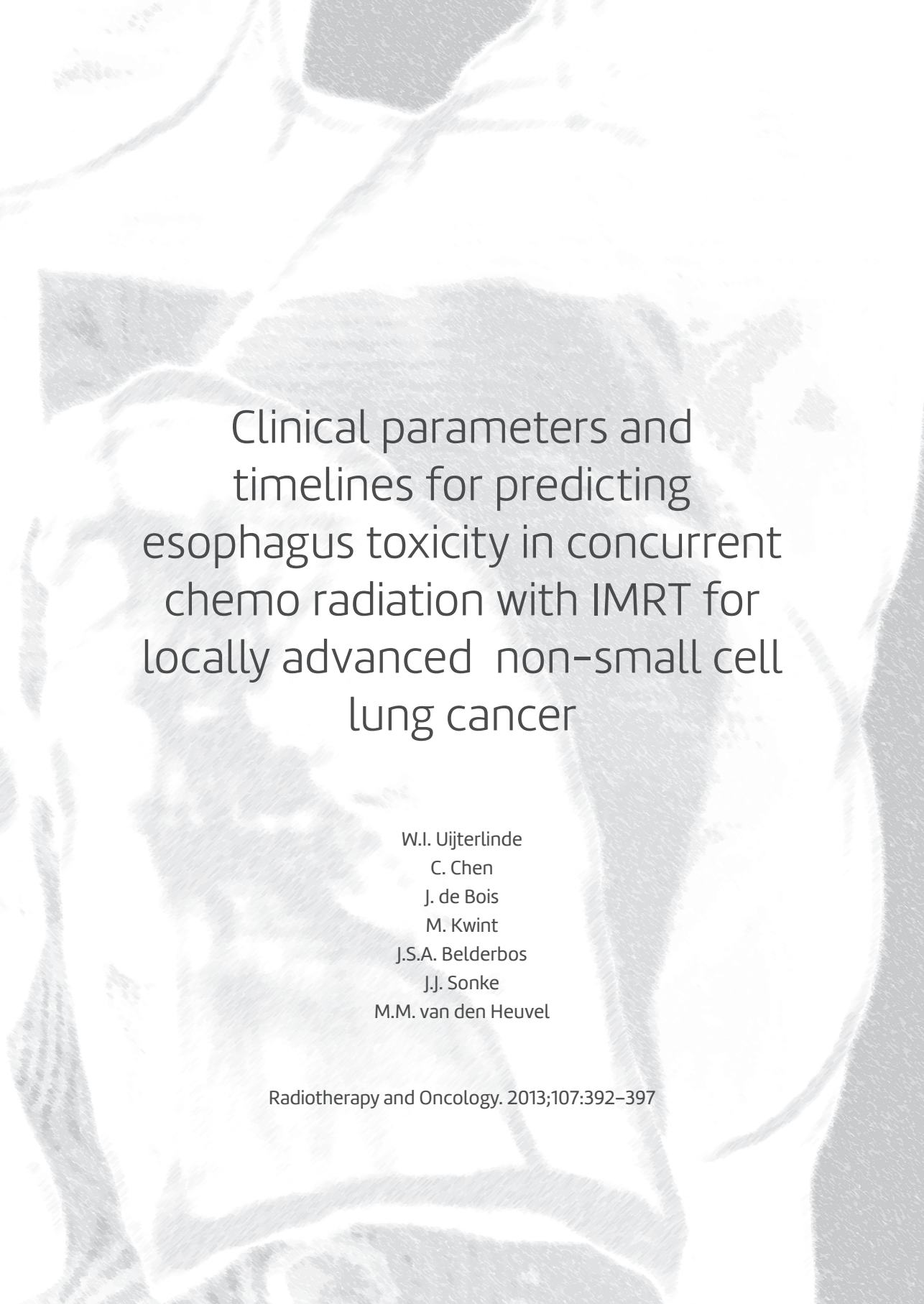
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Clinical parameters and  
timelines for predicting  
esophagus toxicity in concurrent  
chemo radiation with IMRT for  
locally advanced non-small cell  
lung cancer

W.I. Uijterlinde

C. Chen

J. de Bois

M. Kwint

J.S.A. Belderbos

J.J. Sonke

M.M. van den Heuvel

## Abstract

**Background and Purpose:** The aim of this study was to correlate clinical and dosimetric variables with acute esophageal toxicity (AET) following Intensity Modulated Radiotherapy (IMRT) with concurrent chemotherapy for locally advanced non-small cell lung cancer (NSCLC). In addition, timeline of AET was reported.

**Material and Methods:** 153 patients with locally advanced NSCLC treated with 66 Gy/2.75 Gy/24 fractions radiotherapy and concurrent daily low dose cisplatin were selected. Medical records and treatments of these patients were retrospectively reviewed. Maximum AET grade  $\geq 2$  and maximum grade 3 were the endpoints of this study. Dates for onset, maximum and recovery (to baseline) of AET were reported. Univariate and multivariate analysis were applied to correlate clinical, tumor, dosimetric and chemotherapy dose variables to AET grade  $\geq 2$  and grade 3.

**Results:** AET grade 2 occurred in 37% and grade 3 in 20% of the patients. The median onset of AET was around day 15 for all grades. The median onset of the maximum grade was day 30 for both grade 2 and 3. The median duration was 43 days for grade 1, 50 days for grade 2 and  $>80$  days for grade 3. Of the grade 3 AET patients, 48% recovered within 3 months. Esophagus V50, ethnic background, and the number of cisplatin administrations were significantly correlated with grade 3 AET.

**Conclusions:** For NSCLC patients treated with concurrent chemotherapy and IMRT, a higher number of cisplatin administrations, non-Caucasian background and higher V50oes were associated with grade 3 AET. The median onset of AET grade 3 is 15 days after start of treatment, maximized at day 30, with a median duration of  $>80$  days.

## Introduction

Concurrent chemoradiation (CCRT) is the treatment of choice for locally advanced non-small cell lung cancer (NSCLC). The increase in survival compared to sequential chemoradiation or radiotherapy alone (resp. 6% and 11% at 3 years) is due to the improved local tumor control (1,2,3). Concurrent cisplatin is added for its radio sensitizing effect; it shows a substantial preferential radio sensitization of hypoxic cells at low radiation doses (1-4 Gy) (4). For this reason, daily cisplatin (6 mg/m<sup>2</sup>) administered concurrently with accelerated high dose radiotherapy has become an accepted treatment option (1). Mediastinal tumor location and/or lymph nodes are common in locally advanced NSCLC patients, resulting in the involvement of the esophagus in the radiation field. Due to the sensitizing effect of Cisplatin, the incidence of acute esophageal toxicity (AET) is higher in CCRT compared to sequential chemoradiation or radiotherapy only (5,6). Mucosal inflammation (7) and edema of the esophagus causes functional impairment, and is clinically described as a blocking sensation or pain when swallowing. Severe AET usually leads to weight loss and malnutrition requiring intravenous hydration, tube feeding or even hospitalization. Early identification of patients at risk makes it possible to take precautions, such as individualized patient information, dietary guidance, adequate medication, hydration and/or tube feeding. So far, various dosimetric and clinical variables have been investigated for predicting grade  $\geq 2$  AET, such as Dmax, Dmean (7), V35 (6) gender, age, pre-treatment weight loss, performance status (PS) and nodal stage (8-15). However in these studies the treatment regimens were heterogeneous, ranging from concurrent/sequential chemoradiation to radiotherapy alone. Furthermore, the dose planning was based on 3D conformal radiotherapy (3DCRT) rather than IMRT. To update the predictors, Kwint et al. (16) recently investigated the relations between dosimetric variables and AET in the same patient cohort treated with CCRT using IMRT. They concluded that there was no difference in the incidence of AET grade  $\geq 2$  between 3DCRT and IMRT, and that V50 was identified as the most significant prognostic parameter for grade AET grade  $\geq 3$ . However, the development of AET over time, the effect of the number of Cisplatin administrations, and other clinical parameters were not studied. In this paper, we investigated both clinical and dosimetric prognostic parameters of AET and further investigated the timeline of AET.



## Material and Methods

### *Patient selection*

Between 2008 and 2010, 231 consecutive patients with cytologically or histologically proven inoperable locally advanced NSCLC were treated with CCRT in our Institute. Patients were excluded from this study if they participated in clinical trials with novel additive treatment that might influence toxicity, had a RT scheme different from the standard regimen, or had missing follow-up. No approval from the Medical Ethical committee was acquired.

### *Treatment*

Radiotherapy consisted of 66Gy (66 Gy/2.75 Gy/24 fx) with daily low dose cisplatin (6mg/m<sup>2</sup> with a maximum dose of 12mg), intravenously administered as a bolus injection 1-2 hours before the irradiation. Breathing-induced motion of the pulmonary tumor was evaluated using a four-dimensional CT scan (4DCT) in order to reduce the respiratory induced systematic errors. A mid-ventilation scan (MidV-scan) with the tumor closest to its time-averaged mean position was reconstructed from the 4DCT. This MidV-scan was used to delineate the gross tumor volume (GTV), lymph nodes and organs at risk (OARs). All patients had a recent fludeoxyglucose- (FDG) positron-emission-tomography (PET)-CT scan within 6 weeks of start of treatment. This FDG-PET-scan was registered to the MidV-scan. The GTV was expanded to a planning target volume (PTV) using margins of 12mm plus 1/4 of the 4DCT peak-to-peak tumor amplitude in orthogonal directions. For the lymph nodes a uniform PTV margin of 12mm was used. Heart, spinal cord, lung and esophagus, were delineated according to departmental guidelines. The esophagus was delineated from the cricoid to the gastro-esophageal-junction. Treatment plans were designed in Pinnacle version 9.2 (Philips, Best, The Netherlands) with direct machine parameter optimization and collapsed cone superposition convolution based dose calculation. The dose constraints were: esophagus V35Gy <65%, mean lung dose ≤20Gy, spinal cord ≤50Gy, total heart ≤40Gy, 2/3 heart ≤50Gy and 1/3 heart ≤66Gy, where the dose was converted into equivalent dose in 2Gy fractions (EQD<sub>2</sub>). Cisplatin administrations were discontinued if patients experienced serious gastro-intestinal, cardiac, renal or haematological toxicity. Patients were treated on a Synergy linac (Elekta Ltd, Crawley, UK) with integrated CBCT for patient position verification. Setup errors were corrected

based on the alignment of the vertebrae using an offline shrinking action level protocol (initial action level 9mm, 3 initial imaging fractions). Patient specific quality assurance was performed by in-vivo portal dosimetry (17-18).

### *Toxicity assessment*

AET was prospectively scored by the physician or clinical nurse specialist using the Common Toxicity Criteria *version 3.0* at baseline, twice weekly during treatment and every 2 weeks until 12 weeks after treatment. Thereafter, patients were followed at a 3-month interval. The items scored included: Nausea & Vomiting; Dysphagia; Anorexia; Weight loss; Constipation; Dyspnoea, Cough and Pain. The maximum AET grade  $\geq 2$  and maximum grade 3 were the endpoints of the study. Also, the dates when patients reported their start of the symptoms (onset), the maximum, and the recovery (to baseline) of AET were retrieved.

### *Assessed variables*

The physical RT dose was first converted to EQD<sub>2</sub> with  $\alpha/\beta$ -ratio of 10Gy. The dose volume histogram of the esophagus was then computed using the EQD<sub>2</sub> dose. In a previous study on the same patient population V50 was the most significant dosimetric prognostic parameter (16), thus V50 was included in our analysis. Summarized from the published literature (5-15), a number of clinical variables were evaluated, including age, gender, PS, ethnic background, nodal stage and pre-treatment weight loss ( $\geq 5\%$  within 6 months prior to treatment). Additionally, the sum of the GTV plus the positive lymph nodes and the number of cisplatin administrations were evaluated.

### *Statistical analysis*

Correlations between assessed variables were computed by Spearman coefficient or chi-square test. Univariate analyses were performed to determine the strength of association between the assessed variables and the occurrence of AET (grade  $\geq 2$  or grade 3). Fisher's exact test was used for discrete variables, while a logistic regression was used for continuous variables. Subsequently, a multivariate analysis was conducted on the full model including all the variables that were assessed in the univariate analysis. The adjusted odds ratio and p-values from the full model present the multicollinearity between the variables, allowing identifying potential confounding or interactions between



variables in the association with AET. Finally, we presented a reduced model through backward elimination using Akaike information criterion (AIC). The reduced model might be used for predicting AET, considering both the goodness-of-fit and model complexity. SPSS for windows release 18.0 was used for data entry and analysis.

## Results

Of the 231 patients treated with IMRT and concurrent chemotherapy, 43 patients were excluded because they were treated in the context of a clinical trial with additive treatment; 6 patients were scheduled for non-standard radiotherapy schedules; 5 patients had irretrievable DVHs due to re-planning during treatment and 24 patients were lost to follow-up. As a result, 153 patients were eligible for this study. The median follow-up was 23 months. The median age was 63 years, 56% were male, 88% had TNM stage 3, 80% had nodal stage 2 or 3, 88% were Caucasian and 79% had a WHO Performance score of 0-1. Patient characteristics, clinical and dosimetric variables are summarized in Table 1. Three patients discontinued radiotherapy after 22 and 23 fractions due to refusal or fever but they were included in the study. The remaining 150 patients completed all 24 fractions of RT, in an overall treatment time of 32-35 days. A total of 51 patients (33%) failed to complete all 24 administrations of cisplatin, 22 (14%) due to renal impairment, 18 (12%) due to nausea and vomiting, 9 (6%) due to haematological toxicity and 2 (1%) due to cardiovascular events. Seventeen patients (11%) did not experience AET; 48 (32%) developed grade 1; 57 (37%) developed grade 2; 31 (20%) developed grade 3 AET; no grade 4 or 5 were observed. In the 136 patients with grade  $\geq 1$  AET, 103 patients had their complete timeline recorded (Table 2) and the following timeline statistics were based on these 103 patients. The median onset time was AET 15-16 days after the start of the treatment, irrespective of the maximum grade. This timeline corresponds with 12 administrations of cisplatin. The maximum toxicity for both grade 2 and 3 patients was reached at a median of day 30 with an equivalent of 22 cisplatin administrations. The severity of AET is significantly associated with the recovery rate (chi-square test,  $p < 0.001$ ): In 91% of patients with grade 1, complete recovery to baseline was observed within 3 months. For grade 2, the complete recovery rate was 86%, whereas only 48% of the

patients with grade 3 AET recovered completely within 3 months. The recovery rate over time was plotted in Figure 1. The median duration of AET was 43 (95% CI: 33-53) days for grade 1, 50 (95% CI: 40-60) days for grade 2 and >80 days for grade 3 (median duration for grade 3 could not be computed exactly due to the <50% recovery rate) (Table 2).

**Table 1.** Patient characteristics, clinical and dosimetric variables in NSCLC patients treated with CCRT (n=153).

Characteristic	N=153
Median age (y) (range)	63 (36~87)
Gender (%)	
Male	85 (55.6%)
Female	68 (44.4%)
Performance Status (%)	
WHO 0	7 (4.5%)
WHO 1	114 (74.5%)
WHO 2	32 (21.0%)
Ethnic background (%)	
Caucasian	134 (87.6%)
Non-Caucasian	19 (12.4%)
Tumor histology/cytology (%)	
Large cell carcinoma	63 (41.2%)
Squamous cell carcinoma	43 (28.1%)
Adeno carcinoma	27 (17.6%)
Other	6 (3.9%)
Missing	14 (9.2%)
Pre-treatment weight loss $\geq$ 5% (%)	
Yes	54 (35.3%)
No	99 (64.7%)
TNM Stage (7th edition of IASLC) (%)	
2a/2b	18 (11.8%)
3a	90 (58.8%)
3b	45 (29.4%)



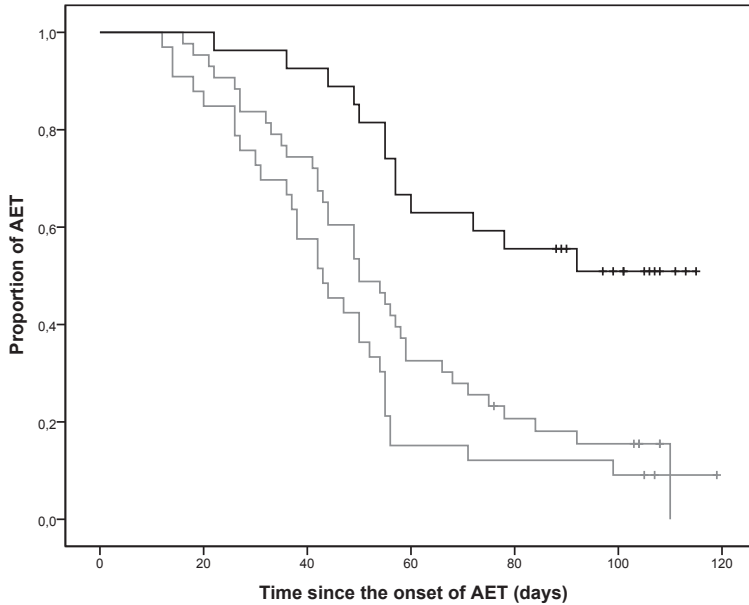
Characteristic	N=153
T (%)	
T0-T1	25 (16.4%)
T2	55 (35.9 %)
T3	27 (17.6%)
T4	46 (30.1%)
N (%)	
0	17 (11.1%)
1	14 (9.2 %)
2-3	122 (79.7%)
Number of cisplatin administrations (%)	
1~12	17 (11.1%)
13~20	24 (15.7%)
21~23	10 (6.5%)
24	102 (66.7%)
Median volume of GTV plus positive lymph nodes (cc) (range)	121.3 (4.9~1830.5)
Radiotherapy dose (%)	
66Gy (24 fractions)	150 (98.1%)
60.5Gy (22 fractions)	1 (0.6%)
55Gy (20 fractions)	2 (1.3%)
Median V50 (%) (range)	34.8 (0~94.8)

WHO: world health organization; TNM: tumor/nodes/metastasis; GTV: gross tumor volume; Gy: Gray; V50: 50% of the esophagus receiving xGy

**Table 2.** The onset, maximum grade day and recovery rate of AET. Of the 153 patients, 136 experienced AET, for whom timeline data was available from.

	<b>maxGrade 1 n=33</b>	<b>maxGrade 2 n=43</b>	<b>maxGrade 3 n=27</b>	<b>Total N=103</b>
Onset (days): median (range)	16 (2-28)	15 (6-47)	16 (2-33)	15 (2-47)
Onset max grade (days): median (range)	16 (2-28)	30 (15-60)	30 (15-58)	23 (2-60)
Recovery rate within 3 months after CCRT (%)	30 (90.9%)	37 (86.0%)	13 (48.1%)	80 (77.7%)

AET: acute esophagus toxicity; CCRT: concurrent chemoradiation



**Figure 1.** Cumulative probability of AET recovery (to baseline) for 103 NSCLC patients with grade  $\geq 1$  AET: grade 3 in black ( $n=33$ ), grade 2 in gray-solid ( $n=43$ ) and grade 1 in gray-dot ( $n=27$ ). Time to event was defined as the time from the onset of AET until recovery to baseline. Patients who did not recover within 3 months were classified as not recovered. The median duration was 43 days for grade 1, 50 days for grade 2 and  $>80$  days for grade 3. (Median duration for grade 3 could not be computed exactly due to less than 50% recovery rate). The number of patients at risk are included on the x-axis

Among assessed variables, a higher PS score was correlated with non-Caucasian (chi-square test,  $p=0.005$ ); nodal stage was correlated with a higher V50 (Spearman's  $Rho=0.426$ ); age was negatively correlated with the number of cisplatin administrations (Spearman's  $Rho=-0.272$ ). In the univariate analysis, PS, amount of cisplatin administrations, ethnic background, nodal stage and V50 were significantly ( $p<0.05$ ) associated with AET grade  $\geq 2$ . V50, ethnic background and number of cisplatin administrations were associated with AET grade 3, while age and PS were borderline significant (Table 3).

All the variables were included in the full model multivariate analysis. For grade  $\geq 2$  AET, ethnic background and the number of cisplatin administrations remained statistically significant, while age, PS and V50 obtained borderline  $p$ -values (Table 4). In the reduced model using AIC, tumor volume and pre-treatment weight loss were excluded.

The prognostic value of ethnic background, the number of cisplatin administrations and V50 for grade 3 AET remained statistically significant in the full model and they were also included in the reduced model.

**Table 3.** Univariate and multivariate logistic regression models for predicting grade  $\geq 2$  AET in 153 NSCLC patients.

Variable	Univariate		Multivariate full model		Multivariate reduced model	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (per decade)	1.01 (0.82~1.50)	0.512	1.42 (0.98~2.05)	0.062	1.43 (1.00~2.06)	0.051
Gender (male vs. female)†	1.01 (0.53~1.93)	0.971	0.53 (0.23~1.19)	0.121	0.53 (0.24~1.16)	0.114
PS (WHO $\geq 2$ vs. WHO $\leq 1$ )†	2.67 (1.11~6.42)	0.028	2.44 (0.91~6.52)	0.075	2.35 (0.90~6.14)	0.080
Ethnic background (non-Caucasian vs. Caucasian)†	4.59 (1.28~16.50)	0.019	5.29 (1.27~22.03)	0.022	5.32 (1.29~21.96)	0.021
Nodal stage (N $\geq 1$ vs. N0)†	3.76 (1.25~11.28)	0.018	2.63 (0.71~9.72)	0.146	2.63 (0.72~9.62)	0.144
Vol (per 100cc)	0.97 (0.81~1.15)	0.688	0.95 (0.76~1.19)	0.667	--	--
Pre-treatment weight loss $\geq 5\%$ (yes vs. not)	1.81 (0.91~3.60)	0.092	1.41 (0.64~3.11)	0.394	--	--
Cisplatin (per 5 administrations)	1.41 (1.05~1.89)	0.021	1.48 (1.06~2.06)	0.021	1.51 (1.09~2.09)	0.013
V50 (per 5 Gy)	1.14 (1.03~1.26)	0.012	1.11 (0.99~1.25)	0.083	1.12 (1.00~1.26)	0.054

†: Reference category

OR: Odds ratio

CI: Confidence interval

The quantitative effect from radiotherapy and chemotherapy are further presented in Figure 2 (a&b), showing the risk of developing AET grade  $\geq 2$  and grade 3 using V50 and cisplatin as univariate variables. Figure 2(a) indicates that when V50 is zero, there is still a risk of grade  $\geq 2$  AET. This risk may be caused by chemotherapy, or some dosimetric factors which were not captured by V50. Similarly, Figure 2(b) indicates that even without cisplatin (zero administrations), a non-zero risk already exists of developing AET grade 2. This might be the result of radiotherapy and is in accordance with 21% grade  $\geq 2$  AET which was observed in patients treated with RT alone (12). Note that without sufficient data on such range, the implications on zero V50 and zero cisplatin

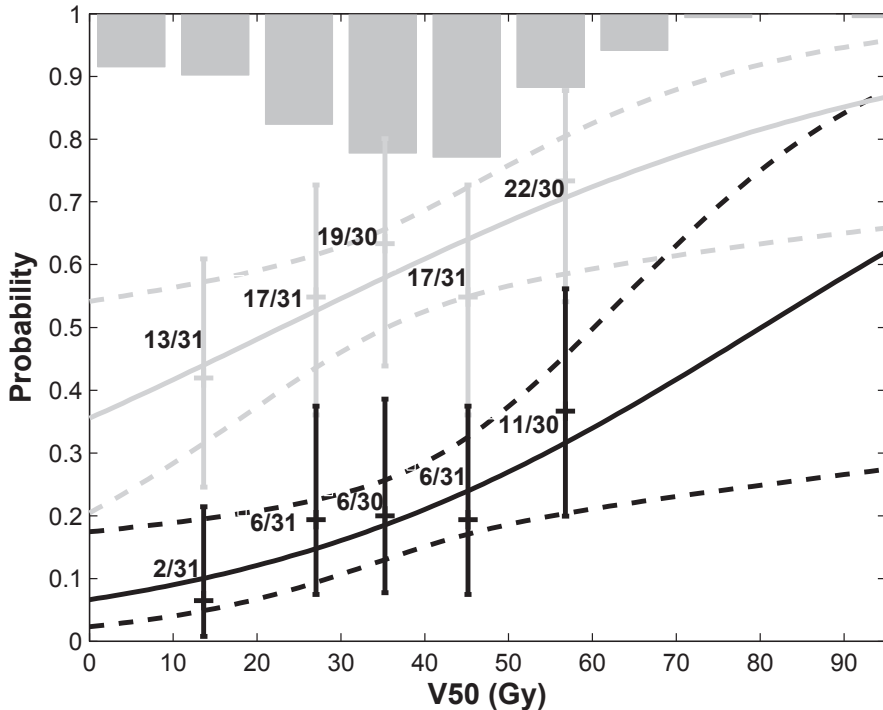
**Table 4.** Univariate and multivariate logistic regression models for predicting grade 3 AET in 153 NSCLC patients.

Variable	Univariate		Multivariate full model		Multivariate reduced model	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (per decade)	1.01 (0.82~1.50)	0.512	1.42 (0.98~2.05)	0.062	1.43 (1.00~2.06)	0.051
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†: Reference category

OR: Odds ratio CI: Confidence interval

were drawn on the extrapolated curve. These results need to be confirmed in an independent data set. The curve for grade 3 AET appears to have a big slope around 20 cisplatin administrations: 30 AET grade 3 patients (out of 112 total patients) received more than 20 cisplatin administrations, whilst only 1 AET grade 3 patient received exactly 20 cisplatin administrations. Patients with more than 20 cisplatin administrations had a significantly higher risk of developing grade 3 AET ( $p < 0.001$ , Fisher's exact test).



**Figure 2a.** The risk of developing grade  $\geq 2$  (grey curve) and 3 (black curve) using V50 (a) and cisplatin (b) as univariate parameters. Dashed curves are the 95% confident intervals (CI). The actuarial incidences with the 95% CI (Clopper-Pearson interval) are also plotted. The histogram of V50 (per 10Gy) and cisplatin (per 5 doses) are illustrated on top.

## Discussion

In this study we described the timelines of AET development after IMRT and concurrent chemotherapy and its relation with clinical and dosimetric parameters. The number of cisplatin administrations and ethnic background were associated with grade  $\geq 2$  AET. The number of cisplatin administrations, V50 and ethnic background were significantly associated with both grade  $\geq 2$  and grade 3 AET.

The timeline of AET is rarely reported in literature. Wei et al. (15) reported that the maximum grade mostly occurred during week 3. Werner-Wasik et al. (19) described the median time of the start and the maximum grade, and the duration as 19, 22 and 29 days respectively for all AET grades. In our study, the median day of onset of AET was day 15, irrespective of the maximum grade. The median day of the maximum toxicity for grade 2 and 3 was day 30, later than that of grade 1.

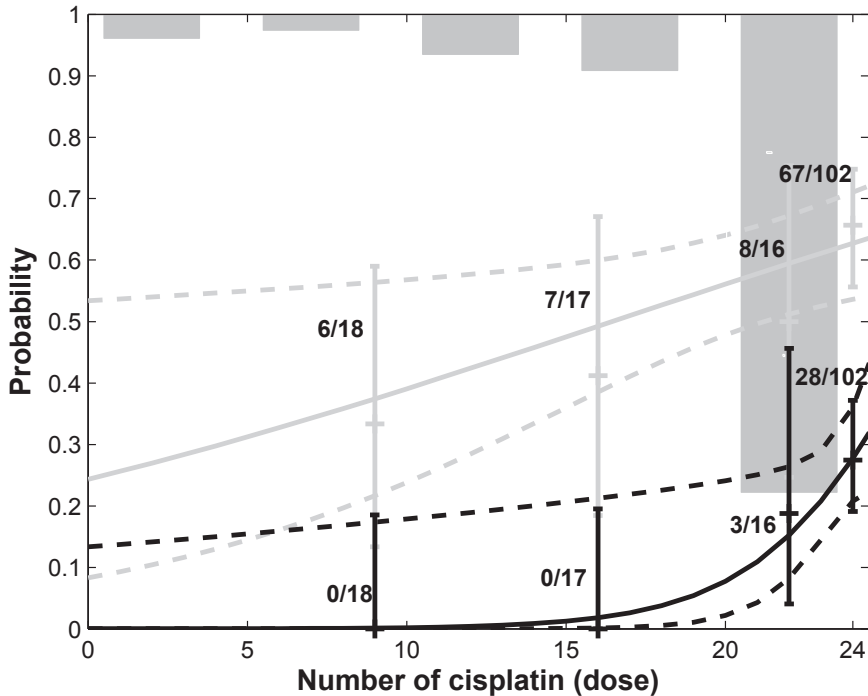


Figure 2b.

As CCRT is associated with a favourable overall survival of 35% at 3 years, a certain risk on grade 3 AET is deemed acceptable since the toxicity is often temporary and manageable. However in our study, grade 3 patients had a low recovery rate (48%) within 3 months and a long median duration (>80days). It means that 52% of grade 3 patients are subjective to a risk of developing late esophagus toxicity, which in the severe cases (e.g. stenosis and fistula) could deteriorate the long-term quality of life, or even compromise survival. Increased knowledge on the timeline of esophagus toxicity may lead to more clinical awareness and adequate supportive care interventions. Also, this information gives us the opportunity to inform the patient in detail and identify patients at risk. Additionally, we are currently acquiring more follow-up data in order to analyze the late esophagus toxicity.

This is the first study that investigated the cumulative effect of a concurrent chemotherapy regimen on AET. Results indicate that both V50 and the number of cisplatin administrations were associated with AET grade  $\geq 2$  or 3, suggesting that higher grade toxicity is the consequence of the accumulative effect of

both chemotherapy and radiotherapy. Chemotherapy and radiotherapy destroy rapidly dividing cells, such as those in the basal epithelial cell layer. Cisplatin hampers the repair of DNA damage caused by the irradiation. Cell death decreases the renewal rate of the basal epithelium, causing mucosal atrophy, ulceration, and initiation of the inflammatory response (20). Therefore, V50 could be used as a constraint in treatment planning. On the other hand, the number of cisplatin administrations that a patient can have is unknown before treatment, thus it is not feasible as a prognostic factor, although a causal relationship may exist. However, the risk curve of cisplatin (Figure 2b) agrees with the timeline results that around the 12<sup>th</sup> cisplatin administration (day 15), the risk of grade 3 AET starts and becomes severe after the 22<sup>nd</sup> administration (day 30).

Werner-Wasik (18) reported an association between Caucasians and grade >3 AET. Contrarily, we found an association between non-Caucasian background and AET (grade  $\geq 2$  and 3), although the odds ratio has a large confidence interval, probably due to the limited number of non-Caucasians. This association might be explained by the cross cultural differences in pain and discomfort tolerability and attitude (21) as well as communication and language difficulties. This may also explain the correlation between higher PS and non-Caucasian background in our patient group. An alternative explanation is the biological mechanism determined by the genetic susceptibility to AET (7), which leads to racial differences in the inflammatory process. Novel techniques like the analysis of single-nucleotide polymorphism (SNP) can be used to differentiate toxicity in these groups.

Increased nodal stage has been identified as a predictor in several studies, either in univariate or multivariate analysis (5, 12, 13, 22). Werner-Wasik et al. (23) pointed out that it is most likely a surrogate for larger tumors. In our study, nodal stage is correlated with V50, but not with the volume of the GTV (including nodes). Thus we further hypothesize that nodal stage is a surrogate for the involved mediastinal nodes, which is correlated to V50.

Age as a predictor of AET has been published in several studies (5, 14). Belderbos et al (5) and Ahn et al (13) did not mention whether this was a positive or negative correlation, while Dehing-Oberije et al (14) reported a negative correlation. In our study, a controversial effect on age was found: Age was borderline positively associated with AET grade  $\geq 2$  in the multivariate model, while age became negatively associated with AET grade 3 in the univariate model. Since age was negatively correlated to the number of cisplatin

administrations, suggesting that younger patients have a higher tolerance of cisplatin doses, subsequently leading to a higher risk of AET. This negative age-cisplatin association was particularly strong between patients who received fewer and patients who received more than 20 cisplatin administrations (Mann-Whitney test,  $p=0.003$ ). Therefore, the considerable increase of risk for grade 3 AET around 20 administrations (Figure 2b) possibly excludes age as a negative association in the full multivariate model. Another possible explanation for this finding might be the less vulnerable mucosa of the elderly because of morphological and biochemical changes (23).

There are some limitations to our study. The regimen of 66Gy in 24 fractions of 2, 75 Gy was used in the phase III EORTC study 08972-22973 and is our routine regimen. However, in this study the dose was recalculated to EQD2 to correct this high dose per fraction. We therefore expect that the results of this study are applicable to other fractionating schemes.

Secondly, although prospectively scored, all assessed variables were retrospectively reported which includes a risk of misinterpretation.

Apart from the total dose and cisplatin, it would be interesting to correlate the actual given RT dose and cisplatin at the time point to AET, and this might facilitate to find the underlying causes of AET. However, in this study, we focused on whether these variables can be prognostic for AET during the early stage of treatment. Although the V50oes was known before the start of treatment, the compliance to 24 Cisplatin administrations was not known yet and therefore this parameter cannot be used as a prognosticator. Also, patient reported outcome (PRO) was not assessed which may have contributed to the toxicity analysis (25). Furthermore, different concurrent chemotherapy regimens are more commonly used and therefore, our model needs to be adapted and validated externally with other concurrent chemotherapy regimens. Although the radiotherapy induced oesophagus toxicity is considerable, there is always a risk of overfitting and confirmatory trials are needed.

For NSCLC patients treated with concurrent chemotherapy and IMRT, number of cisplatin administrations, non-Caucasian ethnicity and V50oes are associated with AET grade 3. The median onset of AET is 15 days after starting treatment, maximized at day 30, corresponding with the accumulative effect of cisplatin and radiotherapy, and has a median duration of >80 days. This information is of clinical relevance as it can be used for patient education and to effectively manage esophageal toxicity.



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