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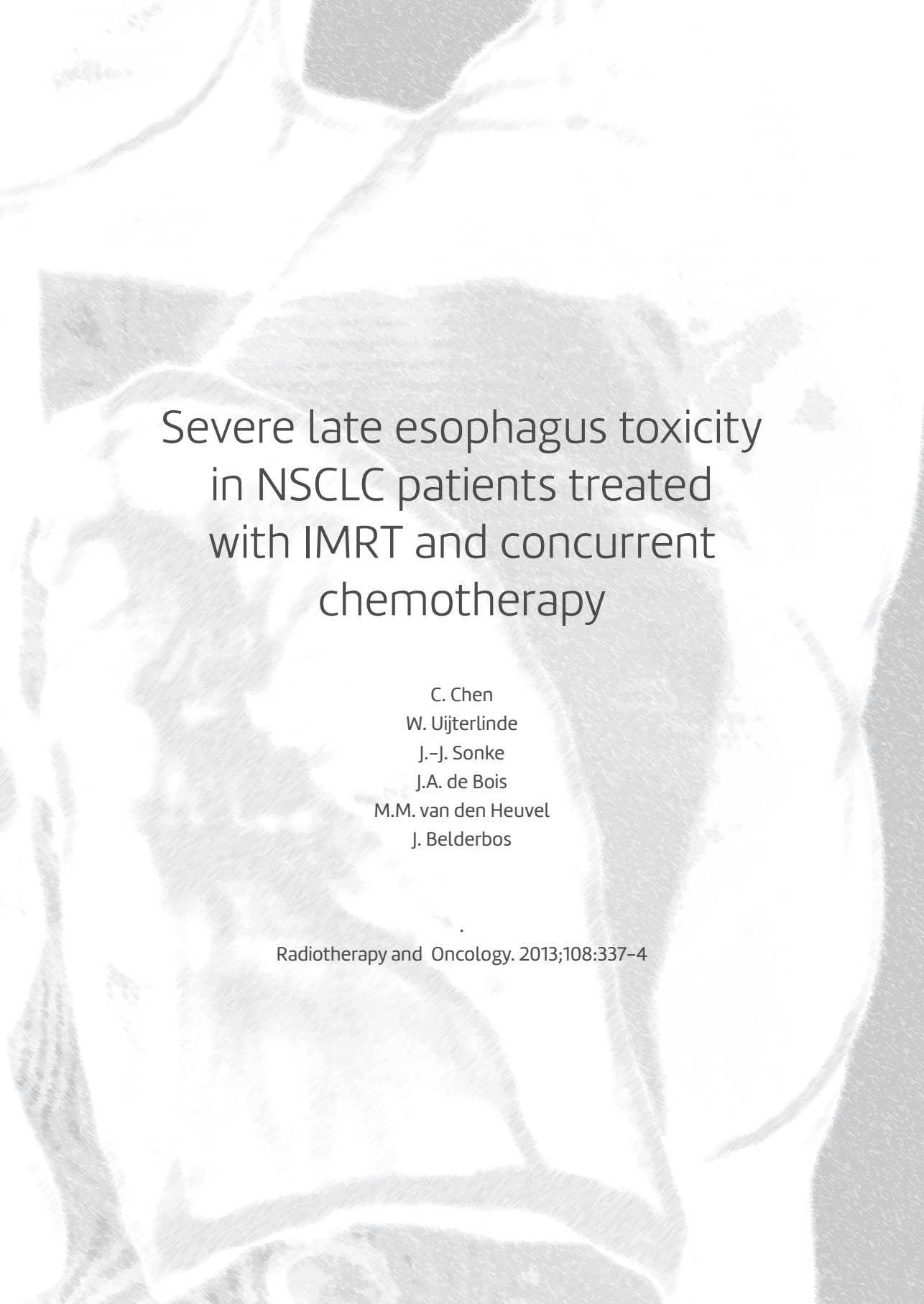
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Severe late esophagus toxicity in NSCLC patients treated with IMRT and concurrent chemotherapy

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Abstract

Background and Purpose: We reported the incidence of severe late esophagus toxicity (LET) in locally advanced NSCLC patients treated with intensity-modulated radiation therapy (IMRT) and concurrent chemotherapy. Acute esophagus toxicity (AET) and the dose to the esophagus were analyzed for their associations with severe LET.

Material and Methods: Two hundred and thirty one patients treated from 2008-2011 with hypofractionated IMRT (66Gy/24fx) and concurrent daily low dose cisplatin were included. The association between AET and severe LET (grade ≥ 3 RTOG/EORTC) was tested through Cox-proportional-hazards model. Equivalent uniform dose (EUD) to the esophagus and the volume percentage receiving more than x Gy (V_x) were applied by Lyman-Kutcher-Burman (LKB) model.

Results: A total of 171 patients were eligible for this study. Severe LET was observed in 6% patients. Both the maximum grade and the recovery rate of AET were significantly associated with severe LET. In the EUD_n -LKB model, the fitted values and 95% confidence intervals (CIs) were $TD_{50} = 76.1$ Gy (73.2~78.6), $m=0.03$ (0.02~0.06) and $n=0.03$ (0~0.08). In the V_x -LKB model, the fitted values and 95% CIs were $Tx_{50} = 23.5\%$ (16.4~46.6), $m=0.44$ (0.32~0.60) and $x=76.7$ Gy (74.7~77.5).

Conclusions: Severe AET, $EUD(n=0.03)$ and $V_{76.7}$ to the esophagus were significantly associated with severe LET. An independent validation study is required.

Introduction

The improved survival in locally advanced NSCLC patients treated with concurrent chemo-radiation (CCRT) comes at a price of acute esophagus toxicity (AET). Around 22% patients develop grade 3 AET toxicity after accelerated Intensity Modulated Radiotherapy (IMRT) and concurrent cisplatin [1]. A number of studies have investigated the dosimetric [1,2], clinical [3] and even biomarkers [4] in association with AET. Little is known, however, about late esophagus toxicity (LET), especially severe LET such as esophagus stenosis, perforation or trachea-esophageal fistula. Unlike AET, severe LET affects the long-term quality of life. Therefore, it is crucial to determine the dose-response relationship for severe LET.

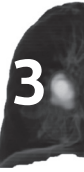
Long follow-up times and high survival rates are crucial for analyzing LET. For these reasons, only few studies have reported the incidence of LET in NSCLC patients [5,6,7,8,9]. Using 3D conformal radiotherapy (3D-CRT), the reported crude incidence of severe LET in concurrent chemo-radiation varies from 5% to 16%. Although without solid evidence, several implications can be drawn from previous studies: (1) Severe AET is associated with severe LET [10]; (2) Escalated dose with hyperfractionation induces more severe LET as compared to standard RT [7]; (3) RT dose or/and concurrent chemotherapy is associated with severe LET [6,7,10,8].

In this study we reported the incidence of severe LET in a cohort of NSCLC patients treated in a single institute with hypofractionated IMRT and concurrent chemotherapy. Furthermore, we investigated two hypotheses: severe AET is associated with severe LET and RT dose is associated with severe LET. Additionally, we conducted exploratory tests on clinical and treatment variables.

Methods and materials

Patient selection

From 2008 until 2011, a total of 231 patients with cytologically or histologically proven locally advanced NSCLC were treated with CCRT in the Netherlands Cancer Institute (NKI). Medical records and treatments of these patients were retrospectively reviewed. Patients were excluded from the study if they had



dysphagia or other esophagus problems prior to treatment, died or were, otherwise lost follow-up within 3 months after treatment, were adaptively re-planned during RT to account for anatomical changes, or had prior/subsequent RT to the thorax. A prior or subsequent RT to the thorax leads to a risk of developing LET that is not directly associated with the current RT. Thus patients who met this requirement were excluded.

Treatment

The treatment consisted of hypofractionated IMRT to 66 Gy (24×2.75Gy) and daily low dose cisplatin (6mg/m² with a maximum of 12 mg), intravenously administered as a bolus injection 1-2 hours before the irradiation. Some patients were included in a randomised trial with (26 patients) or without the addition of weekly cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor [11]. For radiotherapy planning, a four-dimensional CT scan (4DCT) was acquired in order to minimize the respiratory induced systematic errors and access the breathing amplitude of the primary tumor. 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), involved lymph nodes and organs at risk (OARs). All patients had a FDG-PET scan before the start of treatment. The GTV was expanded to a planning target volume (PTV) using margins of 12mm plus 1/4 of the primary tumour peak-to-peak amplitude in orthogonal directions as observed in the 4DCT. For the lymph nodes an isotropic PTV margin of 12mm was used. Heart, spinal cord, lung and esophagus were delineated according to departmental guidelines. The esophagus contour was delineated conform written protocolized instructions on the CT-scan by trained technicians. The cranial limit was the cricoid and the caudal limit was the gastro-esophageal junction. The contours were checked by the radiation oncologist. Dose distribution was calculated using inhomogeneity correction (Pinnacle version9.2). Dose constraints and objectives were defined in biologically equivalent dose in 2 Gy per fraction (EQD₂). For the esophagus a V₃₅<65% (α/β=10 Gy) was encouraged when optimizing the IMRT plan. Dose objectives for other OARs were: mean lung dose≤20 Gy (α/β=3 Gy), spinal cord≤52 Gy (α/β=2 Gy), total mean heart dose≤40 Gy, 2/3 heart≤50 Gy, and 1/3 heart≤66 Gys (α/β=4 Gy). Patients received repetitive cone-beam CT scans for an off-line setup correction protocol.

Toxicity assessment

Esophagus toxicity was scored by the physician or clinical nurse specialist at baseline, twice weekly from start till end of treatment, one week and three weeks after treatment. Thereafter, patients were followed every 3-6 months until 3 years, or more frequently if necessary, e.g. toxicity or suspicion of tumor progression. AET was scored within 3 months after RT using the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) (Table 4). If AET recovered to baseline within 3 months, the recovery dates was recorded. Esophagus toxicity symptoms persisting or occurring >3 months after treatment were scored as LET using the Radiation Therapy Oncology Group criteria (RTOG/EORTC) (Appendix, table 4). The reason of changing from CTCAE to RTOG/EORTC for LET was due to the more clarified radiotherapy-specific late toxicity criteria. The maximum grade of both AET and LET were recorded. Patients with stenosis, perforation or fistula (grade 3 or worse) were categorized as severe LET. An esophageal endoscopy was performed for these patients and a biopsy was conducted in case of suspicion for tumor progression. Stenosis or fistula caused by tumor progression (proven) was then not scored as LET. (Although there is a finite possibility that the stenosis or fistula were caused by both radiotherapy dose and tumor progression, this small probability was ignored in this study). The date of the diagnosis was recorded as the onset. Since all the data were retrospectively acquired, missing data were unavoidable, due to random loss of records or loss to follow-up. To minimize the possible bias of such a retrospective analysis, we choose severe LET as an endpoint that can be scored with high sensitivity and reliability.

Assessed variables

We first analyzed two hypotheses: (1) The severity of AET, i.e. the maximum grade and the recovery rate, is associated with severe LET; (2) Radiation dose to the esophagus is associated with severe LET. To compute dosimetric variables, the physical RT dose to the esophagus was first converted to EQD₂ voxel-by-voxel using LQ-model. An α/β of 3 Gy was used to model late effects, which was different to the $\alpha/\beta=10$ Gy used for the esophagus constraint during treatment plan optimization tailored to AET. For clarification, all doses mentioned in the remaining article are EQD₂ dose. Two variables were computed from the esophagus EQD₂ dose volume histogram (DVH): 1) the equivalent uniform dose EUD [12]; 2) V_x: the percentage of volume that was prescribed with $\geq x$



Gy. Furthermore, we conducted exploratory tests on several clinical variables: age, gender, performance status (PS), weight loss within 6 months before RT, thoracotomy after CCRT, the additional use of cetuximab and the number of cisplatin administrations.

Statistical analysis

Firstly, the actuarial incidence of severe LET was presented by Kaplan-Meier method, adjusting for lost to follow-up. Secondly, univariate analysis was conducted on AET, dosimetric variables, and other exploratory variables. Cox proportional hazards regression was applied to non-dosimetric variables including AET. For dosimetric variables (EUD and V_x), patients with severe LET and/or with more than 1 year follow-up were selected and the Lyman-Kutcher-Burman model (LKB) [13] was applied (Appendix). Furthermore, possible associations were evaluated using Spearman correlation coefficients or chi-square test. Note that the exploratory tests were conducted only to explore possible associations, the p-value and hazard ratios were not intended to draw conclusions. The data were analyzed by SPSS (18.0 for windows) and R (version 2.14.1).

Results

Among the 231 patients evaluated, none had dysphagia or other esophagus problems prior to treatment, 7 died, 24 were otherwise lost to follow-up within 3 months after treatment, 13 were adaptively re-planned and 16 had a previous/subsequent RT to the thorax. As a result, 171 patients were eligible for this study. Table 1 summarizes the patient characteristics and treatment. The median age was 63 year; 59% were male; 83% had WHO 0-1; 11% had a thoracotomy after CCRT; 15% received additional cetuximab. Cisplatin was administered for all 24 fractions in 72% of patients while none of the patients stopped due to esophagus toxicity. The median of the maximum and mean EQD₂ to the esophagus was 78.0 Gy and 31.6 Gy, respectively. The median overall treatment time was 31 (range 29~36) days.

A total of 11/171 patients (6%) developed severe LET at a median follow-up of 33 months (95% CI 29~37) with a median overall survival of 24 months (95% CI

16~32). Figure 1 depicts the actuarial incidence of severe LET together with the overall survival. Descriptions of the 11 severe LET patients are given in Table 2. The median onset time of severe LET was 5 months (range 3~12), i.e., all 11 patients expressed LET within 1 year. Eight patients developed stenosis (grade 3), which could be treated by dilatation. Three patients developed a fistula, which were treated with intraluminal stent. All 3 patients with fistula died from respiration insufficiency caused by pneumonia: 2 died within 1 week and one died at 3 months after the stent was placed. Three other patients had fistula (28, 31, 31 months) due to pathologically proven tumor progression and were not scored as LET.

Severe LET occurred in 4/61 patients (7%) with grade 2 AET and 7/37 patients (19%) with grade 3 AET (Table 2). The maximum grade of AET was significantly ($p=0.002$) associated with severe LET (Table 3). Among 171 patients, we recorded in 141 patients whether AET was recovered (13 grade 0 AET, 47 grade 1, 49 grade 2 and 32 grade 3 AET). Severe LET occurred in 9/34 patients who did not recover to baseline within 3 months (Table 2). Patients with un-recovered AET had a significantly ($p<0.001$) higher risk of developing severe LET, compared to patients without AET or with a recovered AET (Table 3). Higher grade of AET was also associated with a lower recovery rate (chi-square test, $p<0.001$): Complete recovery was 40/47 (85%), 40/49 (82%), and 14/32 (44%) in patients with grade 1, 2 and 3 AET.

All patients with severe LET expressed this toxicity within 1 year after RT. Therefore, 113 patients with severe LET and/or with more than 1 year follow-up were selected to analyse the dose-response relationship for severe LET. The estimated parameter values are listed in Table 5 (appendix). The estimated n of 0.03 and x of 76.7 Gy consistently suggest that severe LET was induced by the high dose. Additionally, the boxplot of dose distributions between the non-LET and severe LET patients are illustrated in Figure 2. Clear separation of the DVH's occurs for doses higher than 75 Gy. The optimized NTCP curves are shown in Appendix, Figure 3. The exploratory tests on several clinical and treatment variables are shown in Table 3. No significant associations or large hazard ratios were found in the exploratory variables.

Results of the multivariate analysis are presented in Appendix Table 5. Including AET (grade ≥ 3) did not significantly improve the performance of EUD_n-LKB ($p=0.087$), while AET obtained marginal improvement in the V_x -LKB model ($p=0.050$). AET was associated with EUD ($n=0.03$) and V76.6 (Spearman $\rho=0.43$ and 0.41 , respectively) (14).



Table 1. Clinical, treatment and dosimetric characteristics of the locally advanced NSCLC patients treated with concurrent chemo-radiation in this study (N=171).

Characteristic	
median age (y) (range)	63 (36-85)
Gender (%)	
Male	101 (59.1%)
Female	70 (40.9%)
Performance status (%)	
WHO 0-1	141 (82.5%)
WHO 2	30 (17.5%)
Pre-treatment weight loss \geq 5% (%)	
Yes	63 (36.8%)
No	108(63.2%)
TNM Stage (7th edition of IASLC) (%)	
II0a/IIb	17 (10.0%)
IIIa	102 (59.6 %)
IIIb	52 (30.4%)
Tumor Stage (%)	
T0~T1	28 (16.4%)
T2	61 (35.6 %)
T3	34 (19.9%)
T4	48 (28.1%)
Nodal Stage (%)	
0	21(12.3%)
1	17 (9.9 %)
2~3	133 (77.8%)
Thoracotomy after CCRT (%)	
No	152 (88.9%)
Yes	19 (11.1%)
Additional Cetuximab (%)	
Yes	26 (15.2%)
No	145 (84.8%)
Median maximum dose (Gy) (range)	78.0 (17.5~90.2)
Median mean dose (Gy) (range)	31.6 (3.6~66.4)
Number of cisplatin administrations (%)	
1~12	14 (8.2%)
13~23	34 (19.9%)
24	123 (71.9%)
Median overall treatment time (day) (range)	31 (29~36)

WHO: world health organization; TNM: tumor/nodules/metastasis

Figure 1. Kaplan-Meier estimates of the actuarial incidence of severe late esophagus toxicity (LET) and the overall survival with 95% CI (Greenwood formula) for NSCLC patients (N=171). When computing the actuarial incidence of severe LET, patients with tumor progression induced fistula (N=3) were categorized as without severe LET until being censored at the date of tumor progression.

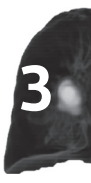
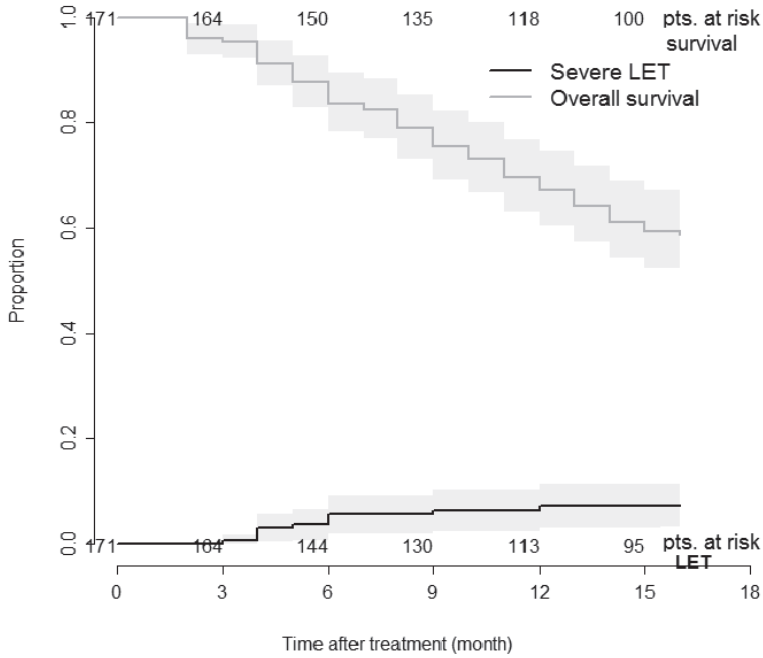


Table 2. Descriptions of the NSCLC patients with severe late esophagus toxicity (N=11).

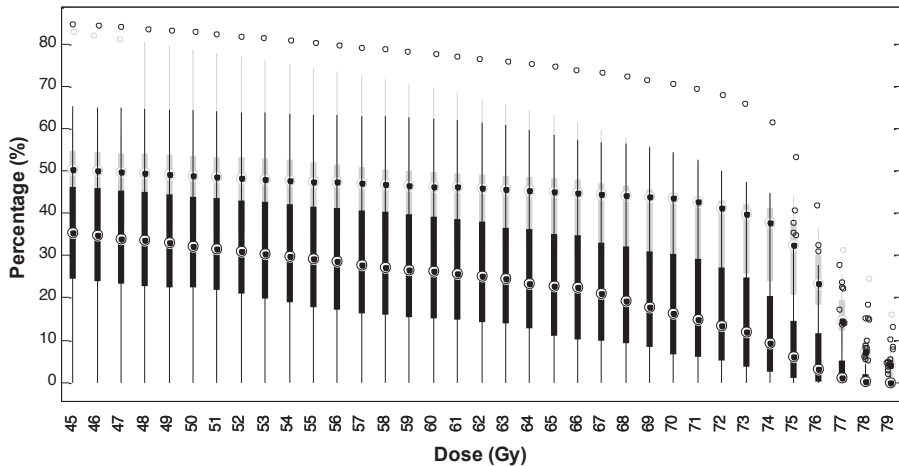
Patient	Onset stenosis (month)	Onset fistula (month)	Medication	LET grade (cause of death)	AET grade	Persist from AET
1	--	4	stent	5 (insufficient respiration)	2	No
2	3	--	dilatation	3	3	Yes
3	5	--	--	3	2	Yes
4	6	--	--	3	3	Yes
5	6	10	stent	5 (insufficient respiration)	2	No
6	4	--	--	3	3	Yes
7	6	--	dilatation	3	2	Yes
8	4	14	dilatation & stent	5 (insufficient respiration)	3	Yes
9	12	--	dilatation	3	3	Yes
10	9	--	--	3	3	Yes
11	4	--	dilatation	3	3	Yes

Table 3. Univariate analysis using Cox proportional hazards regression. Tested variables include the maximum grade (N=171) and the recovery rate of acute esophagus toxicity (AET) (N=141). Additionally, exploratory tests were conducted on clinical/treatment variables (N=171). Post-hoc power analysis was performed based on the Wald-statistic.

Variable	Hazard ratio (95% CI)	p-value	Post-hoc power
Max grade AET (grade 3 vs <grade 3†)	4.70 (1.74-12.74)	0.002	0.86
Recovered AET (No vs. Yes†)	15.54 (3.36~71.97)	<0.001	0.94
Age (per decade)	1.32 (0.71~2.45)	0.388	0.14
Gender (male vs. female†)	1.92 (0.51~7.24)	0.336	0.16
PS (WHO \geq 2 vs, WHO \leq 1†)	0.49 (0.06~3.82)	0.495	0.11
Pre-treatment weight loss \geq 5% (yes vs. not)	2.14 (0.65~7.03)	0.208	0.25
Thoracotomy after CCRT (yes vs. not)	0.63 (0.08~4.87)	0.653	0.07
Cetuximab (yes vs. not)	2.07 (0.55~7.82)	0.281	0.19
Cisplatin (per 5 doses)	3.06 (0.39~23.86)	0.286	0.19

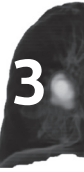
†:Reference category
 CI: Confidence interval

Figure 2. Boxplot of dose distributions between non-severe LET in black (N=102) and severe LET in gray (N=11) patients.



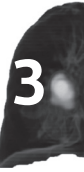
Discussion

We reported 6% severe LET at a 33 months median follow-up for locally advanced NSCLC patients after high dose hypofractionated IMRT and concurrent daily low dose chemotherapy. The most predictive dosimetric variables corresponded to high esophagus dose: $n=0.03$ for EUD and $x=76.7$ for V_x , respectively. Additionally, AET maximum grade and recovery rate were significantly associated with severe LET. Due to the clinical relevance as well as high sensitivity and reliability in scoring, severe LET as a whole was chosen as the endpoint in this study. In further studies, other target structures could be of interest as well, such as esophageal wall soft tissue, esophageal mucosal area. This is the first study that analyzed the incidence of severe LET in patients treated with IMRT. So far, several studies have reported the incidence of severe LET using 3D-CRT (Table 6). The crude incidence varies from 2% to 16%, depending on the chemotherapeutic and RT strategies, survival rate and follow-up time. Thus, actuarial incidence needs to be reported (Figure 1), rather than the crude incidence. The concurrent chemoradiation regimen using low dose cisplatin is one of the active regimens that are currently used. This hypofractionated regime of 66 Gy in 24 fractions was used in the randomized phase III EORTC study 08972-22973 [5]. Decreasing the overall treatment time is a method to improve the radiobiological effect. Especially for lung tumors the overall treatment time is an important factor for treatment outcome. The increased dose per fraction is expected to have more negative impact on LET than on AET. Contrarily, compared to the several studies using an escalated dose with hyperfractionation (Table 6), our regimen yields a comparable incidence rate of severe LET, given even a longer follow-up time and higher survival. Such benefits might come from the use of IMRT and the shortened overall treatment time. Additionally, a crude incidence of 5% was reported from our previous study [8] where the same treatment regimen was used. However the RT technique has evolved from 3D-CRT to IMRT while simultaneously allowing an increased inhomogeneity of 90%~115% within the PTV, as opposed to 95%~107%. In 3D-CRT, elective nodal irradiation (40 Gy/ 20fx) was used, while in this study only involved lymph node were irradiation. Additionally, using collapsed cone convolution superposition algorithm instead of the pencil beam algorithm, dose calculation becomes more accurate now than in the previous study. Given these variations, it is difficult to justify the incidence rate,



although they are comparable in both studies. Interestingly, a recent published study [9] using 3D-CRT 51~69 Gy (1.5 Gy BID till 45 Gy plus 2 Gy once daily and full dose chemotherapy) showed a comparable incidence to our study (7% vs. 6%), while both studies have also similar survival and follow-up time. In our study, all 11 severe LETs were observed within 1 year after RT. Therefore, we selected patients who had more than 1 year follow-up for dosimetric analysis. The estimated $n=0.03$ and $x=76.7$ suggest that severe LET was caused by the high dose region. In the EUD_n -LKB model, observing all 11 severe LET patients had >70 Gy implies that an $EUD \leq 70$ Gy could be a dose limit for preventing severe LET, giving a 100% sensitivity, but only a modest specificity of 37%. Knowing that the high dose region is usually small and sensitive to esophagus motion during the treatment, the delivered dose might be different from the planned dose. This might explain the low specificity. Emami et al. [15] estimated the 5% risk at 5 year for stenosis or perforation to be 60 Gy, 58 Gy and 55 Gy when 1/3, 2/3 and the whole esophagus was irradiated. In our study, $V76.7$ (converted with $\alpha/\beta=3$ Gy), corresponding to a physical dose of 66 Gy, was the most significant predictor for severe LET. In a previous study in the same patient cohort [1], $V50$ ($\alpha/\beta=10$ Gy) with a physical dose of 50 Gy turned out to be the most significant predictor for AET grade 3. These results imply that severe LET is caused by a higher dose than AET. However, a limitation for our analysis was that α/β -ratio of 3 Gy and 10 Gy were postulated without solid evidence. It is interesting to test whether AET contributes to LET, independent of RT dose. The biological mechanism is the consequential late effect (CLE). Pathogenesis of CLE shows that in tissues like gut, urinary bladder and oral mucosa, a superficial barrier protects against mechanical and/or chemical stress. The breakdown of the barrier by radiation displays as the acute reaction which allows for additional, mechanical or chemical trauma, or other secondary damage by changes to the target cells and structures involved in the late response [16]. In the multivariate analysis incorporating both dose and AET, AET showed borderline significance. However, due to the low power (Table 5), we were not able to make solid conclusions. More thorough studies are required to explore the biological mechanism between AET and LET, if any. In clinical practice, grade 3 AET was thought to be acceptable since this toxicity is often temporary and manageable. However, the high rate of 19% (7/37) grade 3 AET persisting into severe LET and the possibility of CLE require more intensive supportive care or even avoiding grade 3 AET in order to minimize severe LET. Exploratory

tests conducted on our patient sample do not show any extreme hazard ratios for which the available patient cohort was underpowered (Table 3). Therefore, the results are presented for reference in further studies. Additionally, the type of cytotoxic agent or pre-existing dysphagia may also be associated with severe LET. However, in our patient cohort, we do not have enough variation to conduct these tests. Another limitation of the study is that the dosimetric variables were derived from the planned dose, which differs from the delivered dose, due to esophageal motions during the RT. Such discrepancies might become influential (especially if the higher dose is of interest). Therefore, sensitivity analysis needs to be conducted on the uncertainty of esophagus motion. Furthermore, the α/β used in the LQ model was postulated as 3. Further studies are required to validate this. Last but not least, this is a retrospective and single institution single regimen study, which is susceptible to selection-bias; Due to the small number of events in our study, we were not able to draw solid conclusions on whether AET contributes to LET independently from dose. For these reasons, we suggest the readers to interpret the findings in this study with caution. An independent validation study, provided with more events or even multicentre and prospective, is planned to warrant the findings. At a median follow-up of 33 months, 6% of the locally advanced NSCLC patients developed severe LET after accelerated IMRT and concurrent chemotherapy. Severe AET and recovery rate were significantly associated with severe LET. The most predictive dosimetric variables were esophagus EUD ($n=0.03$) and V76.7. An independent validation study is planned.



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Appendix

NTCP models

For dosimetric variables EUD and V_x , the Lyman-Kutcher-Burman model was applied [10]. Expressions for EUD_n-LKB model are:

$$EUD = \left[\frac{1}{V} \sum_{i=1}^N EQD_{2i}^{1/n} V_i \right]^n \quad (1),$$

$$t = \frac{EUD - TD_{50}}{m \cdot TD_{50}} \quad (2),$$

$$NTCP = \frac{1}{2p} \cdot \int_{-\infty}^t e^{-u^2/2} du \quad (3),$$

where V_i represents the volume receiving EQD_{2i} in the i^{th} bin, V the total volume, n the volume effect, TD_{50} the EUD with a complication risk of 50% and m the slope of the curve. For V_x -LKB model:

$$t = \frac{V_x - Tx_{50}}{m \cdot Tx_{50}} \quad (4),$$

where Tx_{50} represents the percentage volume receiving x Gy EQD_2 for a complication risk of 50%.

Multivariate analyses including both dosimetric and clinical variables were conducted using a modified LKB model. Suppose the clinical variable is C , for EUD_n-LKB model, t is modified as:

$$t = \frac{EUD - TD_{50} + eff_c \cdot C}{m \cdot TD_{50}} \quad (5),$$

Similarly, t in the V_x -LKB model becomes:

$$t = \frac{V_x - Tx_{50} + eff_c \cdot C}{m \cdot Tx_{50}} \quad (6).$$

The extra parameter eff_c transforms the effect of the clinical variable into either a positive or a negative dose quantity, thus modifying the TD_{50} or



Tx_{50} . Incorporating parameter eff_c in this model is virtually equivalent to a multivariate logistic model [15]. Values of the parameters were estimated through maximum likelihood estimation (MLE) and 95% CIs were computed using profile likelihood method [19].

LKB model is a classical dose-response model that has been widely accepted by radiotherapy community. Its parameters TD_{50} and m are easily interpretable. However, LKB model was not developed for categorical/clinical variables such as AET and the interpretation of a univariate LKB-like model for categorical variables is not trivial. On the other hand, it is easy to interpret the relation between a categorical variable and LET using Cox model. Therefore, we decided to use the two different models on dosimetric and non-dosimetric variables. In the multivariate analysis, we tried to combined both variables using a modified LKB model, where AET functions as an offset of TD_{50} , although there are other possible forms of combinations for the multivariate model.

Table 4: CTCAE3.0 and RTOG/ EORTC criteria for acute and late esophagus toxicity

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE 3.0 acute	Symptomatic, able to eat regular diet	Symptomatic and altered eating/ swallowing (e.g. altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/ swallowing (e.g. inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥ 24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	death
RTOG/ EORTC late	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semisolid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilatation required	Necrosis / perforation fistula	death

Table 5. Optimized parameter values with the 95% CIs and the maximum log-likelihood (MaxLLH) for univariate and multivariate models EUD_n-LKB and V_x-LKB in predicting severe late esophagus toxicity (LET) for NSCLC patients (N=113).

LKB Model	Parameters (95% CI)				p-value	Post-hoc power
	TD ₅₀	m	n	eff _ε		
EUD	76.1 (73.2~78.6)	0.03 (0.02~0.06)	0.03 (0~0.08)	--	<0.001	1.00
EUD+AET (grade 3)	76.6 (73.2~81.0)	0.03 (0.02~0.06)	0.04 (0~0.04)	1.8 (-0.2~6.7)	0.087	0.40
	Tx ₅₀	m	x	eff _ε		
V _x	23.5 (16.4~46.6)	0.44 (0.32~0.60)	76.7 (75.2~77.6)	--	0.01	0.99
V _x +AET (grade 3)	29.2 (18.2~58.2)	0.37 (0.26~0.52)	76.6 (74.7~77.5)	9.2 (0.0~27.6)	0.050	0.50

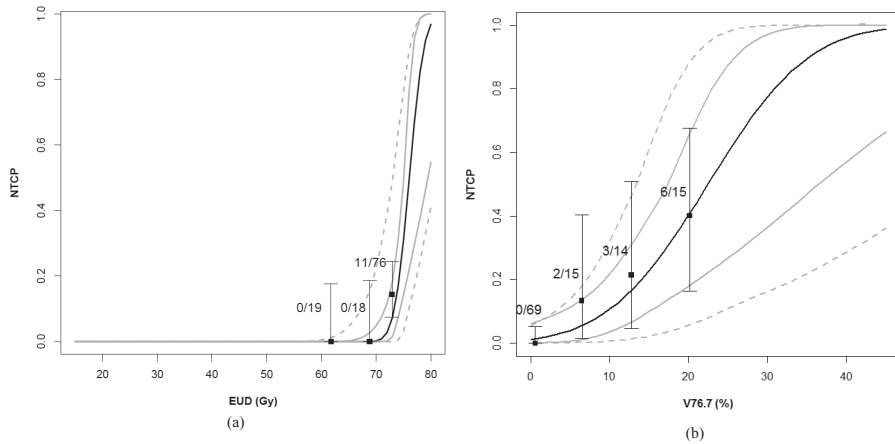


Figure 3. Optimized NTCP models of (a) EUD-LKB model (n=0.03) and (b) V_x-LKB model (x=76.6) for NSCLC patients (N=113). Gray curves are the 95% CIs of NTCP at the optimized n and x values (profile likelihood method). The actuarial incidences with the 95% CI (Clopper-Pearson method) are also plotted. For figure (a), all 11 LET patients are first included in one bin, then the rest of the patients were categorized into 2 bins according to the median. For figure (b), all patients without LET are included in one bin. The rest of the patients were then categorized according to percentile. CIs of the NTCP (obtained from all three parameters) projected on EUD or V_x are also plotted in dashed lines. EUD ranges from 14.0~77.8 Gy. V76.7 ranges from 0~42.1%.

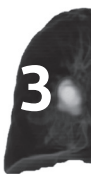


Table 6. Crude incidence of severe LET in NSCLC patients treated with chemo-radiation. QD: once-a-day; BID: twice-a-day; Hypo: hypofractionation.

Study	Patients	Radiotherapy	Chemotherapy	Criteria	Median FU (months)	Median OS (months)	Crude incidence LET
Byhardt et al. [2], 1998	Stage II, IIIA/B N=136	3D-CRT 60 Gy/6wk(QD)	Sequential	RTOG	--	13.6	2% ≥G3 LET
Maguire et al. [16], 1999	N =82	3D-CRT 63 Gy/6.5wk	Sequential /Concurrent	RTOG	--	16.3	4% ≥G3 LET
	N =170	3D-CRT 69.6 Gy/6wk (BID)	Concurrent	RTOG	--	15.8	8% ≥G3 LET
	Stage I~IIIA/B N =66	3D-CRT 64.2~85.6 Gy (QD/BID)	None/Sequential/ Concurrent	RTOG	--	--	3% ≥G3 LET
	T1~T4, N0~N2 N =40	3D-CRT 60.5~66 Gy/30~32 d (Hypo)	Concurrent	RTOG	21	13.5	5% ≥G3 LET
Rosenman et al. [17], 2002	Stage IIIA/B N =62	3D-CRT 60~74 Gy(QD)	Sequential +Concurrent	RTOG	43	24	6% ≥G3 LET
Komaki et al. [6], 2002	Stage II, IIIA/B N =81	3D-CRT 63 Gy/7wk (QD)	Sequential +Concurrent	RTOG	--	16.4	4% ≥G3 LET
Singh et al. [7], 2003	N =82	3D-CRT 69.6 Gy/6wk (BID)	Concurrent	RTOG	--	15.5	16% ≥G3 LET
	N2/N3, T3/T4 N =207	3D-CRT 60~74 Gy (QD)	None/Sequential/ Concurrent	RTOG	24	--	6% ≥G3 LET
Bradley et al. [17], 2004	Stage I~IIIA/B N =166	3D-CRT 60~74 Gy (QD)	None/Sequential/ Concurrent	RTOG	--	--	3% ≥G3 LET
Belderbos et al. [5], 2007	Stage I~IIIA/B N =76	3D-CRT 66 Gy/30~32 d (Hypo)	Sequential	RTOG	39	16.2	4% ≥G3 LET
Van Baardwijk et al. [6], 2012	N =66	3D-CRT 66 Gy/30~32 d	Concurrent	RTOG	39	16.5	5% ≥G3 LET
	Stage III N =137	3D-CRT 51~69 Gy (BID+QD)	Concurrent	CTCAE	30.9	25.0	7.3% ≥G3 LET
Our study, 2012	Stage II~IIIA/B N =171	IMRT 66 Gy/30~32 d (Hypo)	Concurrent	RTOG/EORTC	33	24	6% ≥G3 LET