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Chapter 3

Acute esophagus toxicity in lung cancer patients after Intensity Modulated Radiotherapy and concurrent chemotherapy

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Abstract

Purpose: The purpose of this study is to investigate the dose-effect-relation between acute esophageal toxicity (AET) and dose-volume-parameters of the esophagus after Intensity Modulated Radiotherapy (IMRT) and concurrent chemotherapy for Non-Small Cell Lung Cancer (NSCLC) patients.

Methods and materials: 139 inoperable NSCLC patients treated with IMRT and concurrent chemotherapy were prospectively analyzed. The fractionation scheme was 24 x 2.75 Gy. All patients received concurrent a daily dose Cisplatin (6 mg/m²). Maximum AET was scored according to CTC 3.0. Dose-volume-parameters V5 to V70, D_{mean} and D_{max} of the esophagus were calculated. A logistic regression analysis was performed to analyze the dose-effect relation between these parameters and grade ≥2 and grade ≥3 AET. The outcome was compared to the clinically used esophagus V35 prediction model for grade ≥2 after radical 3D conformal radiotherapy (3DCRT) treatment.

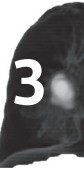
Results: In our patient group 9% did not develop AET, 31% developed grade 1, 38% grade 2 and 22% grade 3 AET. The incidence of grade 2 and 3 AET was not different compared to patients treated with CCRT using 3DCRT. The V50 turned out to be the most significant dosimetric predictor for grade ≥3 AET (p=0.012). The derived V50-model was shown to predict grade ≥2 significantly better compared to the clinical V35-model (p<0.001).

Conclusions: For NSCLC patients treated with IMRT and concurrent chemotherapy, the V50 was identified as most accurate predictor of grade ≥3 AET. There is no difference in the incidence of grade ≥2 AET between 3DCRT and IMRT in patients treated with concurrent chemoradiotherapy.

Introduction

Concurrent chemoradiotherapy (CCRT) has become the treatment of choice in locally advanced non-small cell lung cancer (NSCLC). A recent meta-analysis showed that for patients with NSCLC, treatment with CCRT significantly improved local control and survival compared to sequential chemoradiotherapy (SCRT) (1). However, this is at the cost of more side-effects; CCRT results in more acute esophagus toxicity (AET) than RT-only or SCRT (2-7). A part of the esophagus is often irradiated due to overlap with the planning target volume because of involvement of mediastinal lymph nodes or mediastinal tumor invasion. The mucosal layer of the esophagus is sensitive to irradiation induced damage (2-7). Patients with insufficient intake due to radiation esophagitis are at risk for premature discontinuation of therapy. Predicting the risk of AET makes it possible to take appropriate precautions, such as individualized patient information, dietary guidance, hydration or tube feeding. Identifying the low-risk patients of AET gives the opportunity to escalate the dose of radiotherapy to improve tumor control.

Intensity Modulated Radiotherapy (IMRT) facilitates a more conformal dose distribution leading to increased organ sparing compared to 3D-conformal-radiotherapy (3DCRT) (8-10). In a previous study, with mainly RT-only and SCRT treatments, we reported the V35 (relative volume of the esophagus receiving more than 35 Gy), as the best predictor of AET grade ≥ 2 after radical 3DCRT-treatment (2). The treatment-planning esophagus constraint for 3DCRT at that time was length of the esophagus ≤ 12 cm and elective nodal irradiation was given [2]. In this historical dataset the incidence of grade 2 (54%) and grade 3 (27%) AET was higher in a subset of 37 patients treated with CCRT (2). The derived V35 model was therefore scaled to cover the higher incidence of AET for CCRT, but due to the small sample size, evaluation of the best predictor for AET in CCRT was not feasible. Other studies revealed several dose-volume-parameters to predict AET (2-7). One specific dose-volume-parameter was not designated yet as most reliable predictor of AET. All studies were based on 3DCRT. However, with IMRT dose-distributions and dose-volume-parameters for the esophagus have changed, which might reveal other predictors for AET. The purpose of this study is to investigate the dose-effect-relation between acute esophagus toxicity and dose-volume-parameters of the esophagus after IMRT and concurrent chemoradiation for NSCLC patients.



Patients and methods

Patient selection

Between January 2008 and November 2010, patients with locally advanced NSCLC treated with CCRT in our institute were prospectively followed. Inclusion criteria for this study were treatment with CCRT, histology or cytology proven NSCLC, WHO \leq 2, adequate renal and hepatic functions and life expectancy >6 months. The clinical AET grades as well as the dose-volume-parameters of the esophagus were available for all patients. Former studies reported different dosimetric predictors for AET for SCRT and RT-only, compared to CCRT [6,7]. Therefore only patients were selected who received at least 50% of the planned chemotherapy dose and 100% of the radiotherapy dose.

All patients were treated with IMRT of 66 Gy in 24 fractions, once daily, 5 times per week. The concurrent chemotherapy regimen consisted of daily low dose Cisplatin intravenous (6 mg/m²) 1-2h before irradiation.

Radiotherapy preparation

For all patients a 3D-midventilation-CT (MidV-CT) was selected out of a respiration correlated 4DCT, in which the moving tumor was closest to its time-averaged mean position (11). The gross tumor volume (GTV) and all pathological lymph nodes were delineated on the MidV-CT which was also registered with a recent fludeoxyglucose-positron-emission-tomography-(FDG-PET)-scan. Delineations were discussed in a multidisciplinary meeting. The GTV was expanded to a planning target volume (PTV) using margins of 12 mm + $\frac{1}{4}$ of the 4DCT peak-to-peak tumor amplitude in orthogonal directions. For the lymph nodes a uniform PTV margin of 12 mm was used (12).

Critical organs were delineated according to a written protocol: heart, spinal cord, lungs and esophagus (from cricoid to gastro-esophageal-junction). The planning-constraints used for the organs at risk were; esophagus V35<65%, mean lung-dose \leq 20 Gy, spinal cord \leq 50 Gy, total heart \leq 40 Gy and $\frac{2}{3}$ of the heart \leq 50 Gy and $\frac{1}{3}$ of the heart \leq 66 Gy. Equally spaced, 7-field IMRT-plans were calculated using 10 or 6 MV photons and direct machine parameter optimization in the homo-lateral lung (Pinnacle version 9.0, Philips, Best, the Netherlands) (10). The prescription-dose was specified at a representative point in the PTV. The dose inhomogeneity within the PTV was >90% and <115%.

Scoring of acute esophagus toxicity

AET was scored using the Common Toxicity Criteria 3.0 from start of treatment, till 3 months after. Grade 2 was scored in case of symptomatic and altered eating and intravenous fluids indicated for a period shorter than 24 hrs. Grade 3 included symptomatic and severely altered eating/swallowing and intravenous fluids, tube feedings, or total parenteral nutrition indicated ≥ 24 hrs; and grade 4 included life-threatening consequences. The patients were examined and toxicity was scored at baseline and weekly during treatment, until 3 weeks after treatment by the treating physician. Thereafter the patients were followed with 2 months intervals or more frequently if indicated. All patients consulted a dietician at least twice during treatment.

Dosimetric analysis

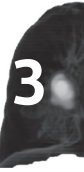
The physical RT-dose was converted to Normalized Total Dose (NTD) for 2 Gy per fraction with an α/β -ratio of 10 Gy for acute toxicity. With the NTD corrected dose, esophageal dose-volume-histograms (DVH) were computed and dose-volume-parameters were derived in steps of 5 Gy from V5 to V70, as well as the D_{mean} and D_{max} . For comparison with 3DCRT, DVH parameters of the current study using IMRT were compared to the data of 36 of the 37 patients treated with CCRT in the historical dataset (data for 1 patient was missing) (2).

Statistical analysis

To evaluate the introduction of IMRT in the CCRT-protocol, we compared the incidence of grade 2 and 3 AET with the historical patient data (2) using a chi-squared test.

The statistical analysis of AET predictability was performed in two steps. First, the V5-V70, D_{mean} and D_{max} were analyzed for correlation with the AET grade using Spearman's rank correlation coefficients. In the second step, the best dosimetric predictors for grade ≥ 2 and ≥ 3 AET were estimated, using a stepwise logistic regression method. The stepwise regression was done in a forward selection fashion, which involves starting with all candidate variables and testing them one by one for statistical significance, deleting variables that were least significant until the best predictor remained. The resulting logistic function is expressed as:

$$\text{AET Grade probability} = \frac{1}{1 + \exp-(b_0 + b_1Vx)}$$



Where β_0 and β_1 are the estimated coefficients and V_x is the most significant dosimetric parameter. The new model was then compared with the currently used constraint of the V35 (2) using chi-square distribution with 3 degrees of freedom (β_0, β_1, V_x). The dose-volume-parameters of the current IMRT-patients were compared to the historical 3DCRT-data using a 2-sided student t-test. The data was analyzed by SPSS for Windows software, release 15.0 and graphs were generated by Matlab for Windows software, release R2009a.

Results

Patients

Between January 2008 and November 2010, 139 consecutive NSCLC patients treated with IMRT and concurrent chemotherapy were selected (Table 1). Median age was 63 years (range 38-85 years). A total of 109 (78%) patients received all 24 doses of chemotherapy. Due to decreasing renal function (N=20), gastro-intestinal (N=6), hematological (N=2) or cardiovascular (N=2) side effects, the Cisplatin stopped early after 13 up to 23 administrations (mean 19) in 22% of the patients.

From the 139 patients the incidences of AET were, 12 (9%), 43 (31%), 53 (38%) and 31 (22%) for grade 0, 1, 2 and 3 AET respectively. No grade 4 and 5 AET was observed. In analogy to the historical data, current AET was increased compared to the historical data for RT-only and SCRT [2] ($p < 0.0002$). The current incidences using IMRT were not significantly different from the historical CCRT data with 3DCRT-treatment ($p = 0.4832$ for AET grade ≥ 2 and $p = 0.5457$ for AET grade ≥ 3).

Table 1: Patients Characteristics

Characteristic	No. of patients (N=139)	%
Gender		
Male	84	60.4
Female	55	39.6
Stage		
IB	1	0.7
IIA	4	2.9
IIB	6	4.3
IIIA	82	59.0
IIIB	36	25.9
Recurrent NSCLC	10	7.2
Histology		
Squamous	47	33.8
Adenocarcinoma	29	20.9
Large cell/not specified	63	45.3
WHO		
0	14	10.1
1	101	72.7
2	24	17.3
Smoking during treatment		
Yes	87	62.6
No	52	37.4
Weight loss $\geq 5\%$ last 6 months		
Yes	50	36.0
No	89	64.0

WHO= world health organization

Dosimetric variables

With the use of IMRT the relative volume of the esophagus receiving dose levels ranging from 5–40 Gy were significantly lower compared to 3DCRT, while the volume receiving 70 Gy was significantly increased (Figure 1).

The esophageal V65 turns out to have the highest correlation with AET with a correlation coefficient of 0.300 ($p < 0.001$), although V25-V70, D_{max} and D_{mean} all significantly correlated with AET (Table 2). Additionally, correlations between dosimetric variables (e.g. with V50 shown in Table 2) indicate high mutual correlation with each other. This indicates that a wide range of dose-volume-parameters are predictive of AET. For this reason, in building the logistic model, we only selected the most significant parameter to predict grade ≥ 2 and ≥ 3 AET, as can be achieved with the forward conditional selection logistic regression method. For prediction of grade 3 AET, the V50 was shown to be the most significant ($p = 0.013$) parameter with a β_0 of -2.486 and a β_1 of 0.032.

For grade 2 AET, the D_{\max} was the remaining parameter after forward selection. However, we expect that using D_{\max} in the plan optimization will not sufficiently influence the dose distributions. Since grade 3 AET is clinically more relevant, and also for practical reasons, we also estimated the binary logistic regression parameters for grade 2 AET using the V_{50} , which was also shown to be highly significant ($p=0.012$). Doing so, we establish one single parameter which can be used to predict the probability of both grade ≥ 2 AET and grade ≥ 3 AET. The probability of developing acute esophagitis grade ≥ 3 can now be estimated using:

$$\text{AET grade 3 probability} = \frac{1}{1 + \exp(-(-2.486 + 0.032V_{50}))}$$

and for grade 2 AET:

$$\text{AET grade } \geq 2 \text{ probability} = \frac{1}{1 + \exp(-(-0.515 + 0.027V_{50}))}$$

The sigmoid shaped relationship between AET grade ≥ 2 and ≥ 3 and the V_{50} is plotted in Figure 2, together with the actual incidences of AET.

To illustrate the need to replace our current V_{35} -model for grade ≥ 2 AET, we have plotted the actual V_{35} data of the current study with respect to the model (Figure 3). The log-likelihood difference between the V_{35} data estimated with the old model and the V_{50} data estimated with the new model corresponded to a significant difference with a p-value of 0.011 (chi-square distribution with 3 degrees of freedom), indicating superiority of the V_{50} model.

Using the Mann-Whitney test, patients experiencing grade 3 AET and receiving all planned doses of Cisplatin (26%) were compared to patients that stopped Cisplatin early (10%). This incidence was not significant different ($p=0.083$).

Figure 1: Average esophageal dose-volume-histogram for the historical patients planned with conformal radiotherapy, and the current IMRT-dataset. The error bars denote the 95% standard error. Both groups were compared for each dose level using a 2-sided students T-test (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$)

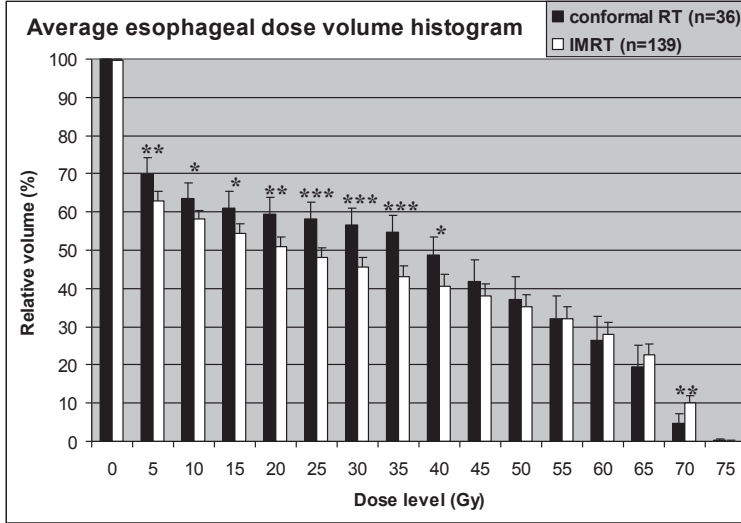
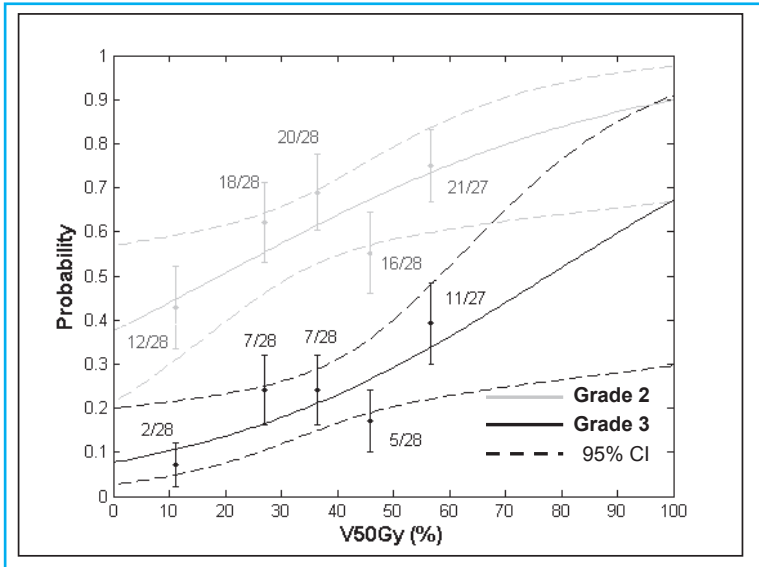


Figure 2: Probability of developing AET grade 2 (grey line) and grade 3 (black line) using the logistic model based on V50. The 95% confidence intervals are plotted in dash-dotted lines. The actual incidences, together with its 95% confidence intervals, are plotted in the vertical lines.



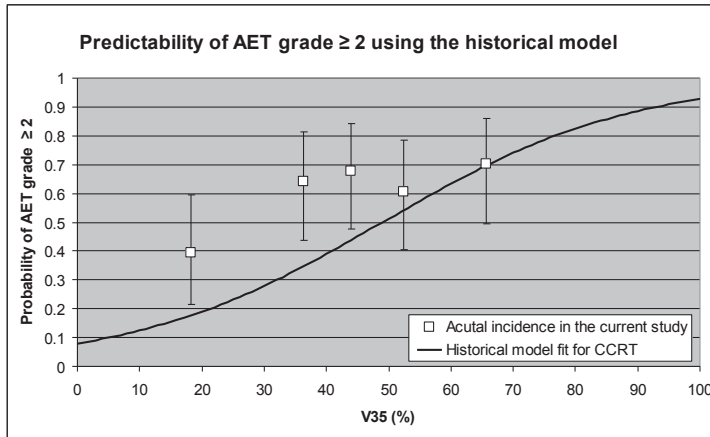


Figure 3: Probability of developing grade ≥ 2 AET using the current clinical model based on V35 (solid line). The datapoints illustrate the actual incidence of AET based on the V35, and their 95% confidence intervals.

Table 2: Spearman's rank correlation coefficients of dose volume parameters and acute esophagus toxicity (AET). * $p < 0.05$; ** $p < 0.01$

Variable	Correlation with AET	Correlation with V50
D _{max}	0.237 **	0.536 **
D _{mean}	0.220 **	0.960 **
V5	0.104	0.665 **
V10	0.135	0.727 **
V15	0.149	0.764 **
V20	0.161	0.833 **
V25	0.174 *	0.876 **
V30	0.193 *	0.909 **
V35	0.222 **	0.944 **
V40	0.231 **	0.970 **
V45	0.250 **	0.991 **
V50	0.250 **	--
V55	0.265 **	0.989 **
V60	0.284 **	0.938 **
V65	0.300 **	0.856 **
V70	0.247 **	0.708 **

Dmax= maximum dose; Dmean= mean dose; V=volume (of the esophagus) receiving xGy

Table 3. Results of the backward stepwise regression analysis; Volume of the esophagus receiving ≥ 50 Gy (V50) to predict Acute Esophagus Toxicity grade 2 and 3

Acute Esophagus Toxicity	Variable	Coefficient	Standard deviation of the coefficient	p -value	Odds ratio
Grade 2	V50	0.027	0.011	0.012	1.027
	Constant	-0.515	0.405	0.204	0.598
Grade 3	V50	0.032	0.013	0.012	1.033
	Constant	-2.486	0.561	<0.001	0.083

Discussion

To the best of our knowledge, this is the first analysis of dosimetric predictors of AET performed within a large patient group treated with IMRT and the same concurrent chemotherapy-regimen. Several studies have shown that treatment with CCRT gives an increased risk of AET (2,3,5-7), as was also confirmed in the current study. We showed that in the setting of CCRT, the incidence of AET was not significantly changed by the introduction of IMRT compared to 3DCRT. Our current clinical AET prediction model, using V35, resulted in inadequate prediction of AET grade ≥ 2 when treating with CCRT. With increasing incidence of grade 3 AET, prediction of grade 3 is deemed to be clinically more relevant, and we therefore propose to use the V50.

With the introduction of IMRT the volume of the esophagus receiving 5 to 40 Gy was significantly reduced, and simultaneously, the volume receiving 70 Gy was significantly increased (Figure 1). Using the historic prediction model based on V35 (2), one would expect that the incidence of grade ≥ 2 AET would have been reduced with IMRT, which was actually not the case. The inability of predicting AET using the V35 model in CCRT was indicated by the discrepancies between the actual incidence and the V35 prediction model (Figure 3). With use of CCRT, there were a substantial proportion of patients with more severe grade 3 AET, independent of use of IMRT, which was not addressed in the old V35 model. An update of the prediction model was therefore needed.

For grade 3 AET, the V50 was shown to be the best predictor, and for grade 2 AET the V50 also showed to perform significantly better than the current V35 model. With no significant change in AET incidence compared to patients treated with 3DCRT, it is also logical to find the best predictor at a dosimetric level at which the volume of esophagus was not different between 3DCRT and IMRT (between V45 and V65, Figure 1).

Werner-Wasik et al. (7) described in their review that a higher dose, even on a small part of the esophagus, might be a risk factor for AET. They described several dosimetric parameters to be predictive in univariate analysis for grade 2 and 3 AET: V20 till V80. But most at risk for AET were esophagus volume doses receiving >40 -50 Gy. This data is consistent with our analysis, were V15 till V70 and D_{mean} and D_{max} of the esophagus were all significantly correlated with AET. The systematic review of Rose et al. (6) demonstrated that the D_{mean} , V20, V30, V40, V45 and V50 were the most studied dosimetric predictors, showing high



levels of association with AET. The dosimetric predictors of AET in Rose's review are consistent with the most significant predictor we found, the V50.

Caglar et al. published an analysis based on 3DCRT and concurrent chemotherapy with 109 patients (4). These patients were treated with or without induction chemotherapy followed by CCRT with different chemotherapy regimens. Radiotherapy dose varied between 50-68 Gy in 2 Gy fractions. V45 till V60 were indicated as most predictive dose-volume-parameters for AET. Besides the dose on the entire esophagus, Caglar et al. studied the region of the esophagus exposed to a high dose (esophagus infield). The V55 of the entire esophagus and esophagus infield was the most significant parameter to predict AET in multivariate analysis. They showed that when the D_{mean} of the esophagus infield was below 50 Gy, no grade 3 occurred. In our analysis we did not specify between entire esophagus dose and esophagus infield, but the dose of 50 Gy is in agreement with our V50 for predicting grade 3 AET.

In the current study RT was given with 2.75 Gy fractions. Despite the increased fraction dose, the incidence of grade 3 AET was not higher compared to Caglar et al. (4) (25%), where conventional 2 Gy fractions were used. The radiotherapy dose of our study was converted into NTD equivalent to fraction doses of 2 Gy with $\alpha/\beta=10$, for which the derived results may also be applied to other fractionation schemes providing the same α/β is used. Uitterhoeve et al. reported in a phase I/II EORTC trial that this fractionation-scheme was safe using 3DCRT and an EORTC phase III multicenter trial confirmed this (13,14). In 2005 the NKI-AVL introduced IMRT for all lung cancer patients treated with radical intent and to our clinical experience the safety of this treatment is well established. Uijterlinde et al. analyzed that our CCRT regimen with IMRT is well tolerated in cohort of 188 patients (15).

For the treatment of stage III NSCLC patients, a certain risk of grade 3 AET is deemed acceptable because the toxicity is often temporary and manageable. Late esophagus toxicity (LET) like a fistula or stricture of the esophagus may however cause life-threatening problems for the patient. For LET, proposed predictive parameters are D_{mean} and V50 (6), and V45 to V60 (4), but most studies analyzing LET were done in patient groups treated with heterogeneous radiotherapy and chemotherapy schedules. Belderbos et al. reported from the randomized trial comparing sequential (N=78) and concurrent (N=80) chemoradiation that a higher incidence of AET in the CCRT-arm did not result in a higher incidence of severe late toxicity (4 vs. 5 %). Follow-up of the patients included in the current study is ongoing to report LET in the future.

Limitations of the study

Limitations in general were the difficulties encountered with the scoring of AET in patients treated with CCRT. Although we scored prospectively, sometimes it is difficult to differentiate between AET and side effects of chemotherapy (e.g. anorexia).

The dose-volume-parameters were all based on the position of the esophagus during the midV-scan and were not corrected for movements of the esophagus during treatment. Motion analysis of the esophagus, and also the influence of length and circumference of the irradiated esophagus on AET is currently being investigated to further increase our knowledge on AET.

Our CCRT treatment consists of daily low dose Cisplatin but different chemotherapy-regimens are frequently used. Currently this radiotherapy scheme and full-dose concurrent chemotherapy is being tested in a randomized phase II trial (study identification-number NCT-01024829).



Conclusions

For NSCLC patients treated with concurrent chemoradiotherapy and IMRT, the V50 was identified as most accurate predictor of grade ≥ 3 AET. We advise to introduce the V50 model in clinical practice in order to reduce the risk of AET, and have a better prediction of severe acute esophageal toxicity. There is no difference in the incidence of grade ≥ 2 AET between 3DCRT and IMRT in patients treated with concurrent chemoradiotherapy.

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