

Clinical radiobiology

Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy

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Abstract

Background and purpose: To correlate acute esophageal toxicity with dosimetric and clinical parameters for non-small cell lung cancer (NSCLC) patients treated with radiotherapy (RT) alone or with chemo-radiotherapy (CRT).

Patients and methods: We analyzed the data of 156 patients with medically inoperable or locally advanced NSCLC. Seventy-four patients were irradiated with high dose RT only, 45 patients with sequential CRT (Gemcitabine/Cisplatin) and 37 patients with concurrent CRT (Cisplatin daily 6 mg/m²). The radiation dose delivered ranged from 49.5 to 94.5 Gy (2.25-2.75 Gy per fraction) with an overall treatment time of 5-6 weeks. For all patients the maximal acute esophageal toxicity (RTOG/EORTC criteria) was scored and related to dose-volume parameters, as well as to clinical and treatment-related parameters. All parameters were tested univariable and multivariable in a binary logistic regression model. The toxicity data of a homogeneous subgroup was fitted to the Lyman-Kutcher-Burman model.

Results: Grade 2 acute esophageal toxicity or higher occurred in 27% ($n=42$) of the patient population of which nine patients developed grade 3 toxicity and one patient grade 4. All 10 patients with grade ≥ 3 esophageal toxicity received concurrent CRT. At multivariable analysis, the most significant clinical parameter to predict acute esophageal toxicity was the concurrent use of CRT. The most significant dosimetric parameter was the esophagus volume that received at least 35 Gy. The data of the patients who did not receive concurrent CRT were well described by the Lyman-Kutcher-Burman normal tissue complication probability model. The optimal fit of the data of non-concurrent treated patients to this model was obtained using the following values for the parameters: $TD_{50}=47$ Gy (41-60 Gy), $n=0.69$ (0.18-6.3) and $m=0.36$ (0.25-0.55) where the numbers between brackets denote the 95% confidence interval. Acute esophageal toxicity was not significantly increased for patients treated with sequential CRT.

Conclusion: Both concurrent CRT and the volume that receives at least 35 Gy were predictors of acute esophageal toxicity.

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Keywords: Lung cancer; Conformal radiotherapy; Acute esophageal toxicity; Equivalent uniform dose; Dose-volume histogram

For patients with inoperable non-small cell lung cancer (NSCLC) with favorable prognostic features, the use of concurrent chemo-radiotherapy (CRT) treatment is superior to sequential CRT [5]. However the concurrent use of CRT is associated with increased esophageal toxicity [3,4,23,26]. More detailed knowledge of treatment-related risk factors for developing acute esophagitis is of great importance since esophagitis is becoming more and more a dose-limiting factor in the concurrent treatment of patients with NSCLC [8], especially when the tumor or mediastinal adenopathy is

located near the esophagus. If acute esophagitis leads to an interruption of the radiotherapy treatment, the advantage of concurrently given chemotherapy might disappear. Other risk factors than concurrent CRT, like length of the esophagus irradiated and dose-volume parameters, for developing acute esophagitis have been evaluated in several studies [2,20,23,26]. The results of these studies with regard to dosimetric factors are ambiguous.

The purpose of this study was to investigate the relation of acute esophageal toxicity with the 3D dose distribution in the esophagus and with clinical and treatment related factors such as the use of sequential or concurrent chemotherapy.

¹ Both authors have equally contributed to this paper.

Patients and methods

Between December 1998 and March 2003, 156 patients with good prognostic features were selected from a group of medically inoperable or locally advanced NSCLC patients. The good prognostic features were defined according to Eastern Cooperative Oncology Group (ECOG) ≤ 2 and weight loss $< 10\%$ in the last 3 months. A total of 142 patients had biopsy proven NSCLC. Fourteen patients had a growing tumor on chest X-ray examination or CT scan of the chest that was positive on an ^{18}F FDG PET scan (Table 1). The median age of all patients was 69 years (range: 31-88 years). About one third of the patients was medically inoperable (stage I and II disease). These patients were treated in a dose-escalation trial mostly with radiotherapy alone.

Patients with stage III disease were treated within an EORTC study 08972-22973 randomizing patients for concurrent or sequential chemo-radiotherapy. For patients treated within this EORTC study, restrictions for the maximum length of the esophagus irradiated to specific doses were taken. Due to these restrictions patients with lower lobe tumors were often excluded so that upper lobe tumors are more frequently seen in this group of patients.

Within the study population, three treatment groups were distinguished: patients treated with radiotherapy only ($n=74$); patients receiving sequential CRT ($n=45$) and patients with concurrent CRT ($n=37$) (Table 2).

EORTC protocol

Sixty-eight patients (44%) were treated within or identical to a randomized phase III study (EORTC 08972-22973) comparing concurrent CRT or sequential CRT. In both treatment arms the patients received accelerated high dose conformal radiotherapy: 66 Gy in 24 fractions (2.75 Gy per fraction) in 32 days. The concurrent chemotherapy used consisted of daily low dose intravenous

Characteristic	No. of patients (N=156)	%
Gender		
Male	109	70
Female	47	30
Stage		
I	34	22
II	18	12
IIIA	42	27
IIIB	62	40
Tumor site		
Upper lobe	118	76
Middle/lower lobe	24	15
Mediastinum	3	2
Main bronchus	11	7
Histology/cytology		
Squamous	46	29
Adenocarcinoma	56	36
Large cell/not specified	40	26
Unknown	14	9

Table 2
Treatment characteristics

	Dose escalation study (N=88)	EORTC 08972- 22973 protocol (N=68)
Treatment group		
RT alone	73	1
Sequential CRT	15	30
Concurrent CRT	0	37
Dose (Gy)	49.5-94.5	66
Fraction size (Gy)	2.25	2.75
Overall RT treat- ment time (weeks)	6	5

6 mg/m² Cisplatin 1-2 h before each fraction. For patients receiving sequential CRT, two courses of Gemcitabine (1250 mg/m² on days 1 and 8) and Cisplatin (75 mg/m² on day 2) were given. The interval between the second chemotherapy course and the start of the irradiation was 4-5 weeks. Twenty-two patients refused the randomization and were treated with the standard treatment (concurrent CRT) with the exception of one patient who refused any chemotherapy and received radiotherapy alone (Table 2). In this EORTC protocol all patients were irradiated using a concomitant boost technique, consisting of elective nodal irradiation (ENI) to a dose of 40 Gy in 20 fractions and a concomitant boost of 15 Gy to the gross tumor volume (GTV). The daily dose to the GTV was 2.75 to a dose of 66 Gy. After 20 fractions resulting in a dose of 55 Gy to the GTV, a boost to the GTV was given of 4 fractions of 2.75 to a dose of 66 Gy.

For N0 disease, the homolateral hilum was taken into the elective nodal treatment fields. In case of N1 or N2 disease, the mediastinum (with the exception of the lower paroesophageal lymph nodes) were electively irradiated. For N2 disease the homolateral supraclavicular area was included as well. The ENI was given with two opposite anterior-posterior fields. The length of the esophagus irradiated in the elective fields (40 Gy) was restricted to 18 cm. The length of the esophagus in the boost fields (total dose 66 Gy) was restricted to 12 cm [24].

Dose escalation trial

Eighty-eight patients were treated within our phase I/II dose escalation trial [1]. Fifteen out of these eighty-eight patients received sequential chemotherapy prior to the irradiation (Table 2). Twelve patients had a combination of Gemcitabine and Cisplatin and three patients received a combination of Taxol or Taxotere and Cisplatin. For these patients the interval between the last course of chemotherapy and the start of the irradiation was at least 6 weeks.

Within the dose escalation trial the overall treatment time was restricted to 6 weeks and the fraction size was 2.25 Gy. When over 30 treatment fractions were prescribed, the patients were irradiated twice a day for the additional fractions with at least a six-hour interval. The dose delivered to the patients in this dose escalation trial ranged from 49.5 to 94.5 Gy with a median dose of 81.0 Gy. In this dose escalation protocol no ENI was prescribed. For the esophagus

an effective volume² (V_{eff}) constraint was used with a maximum of 30% at a reference dose of 80 Gy with $n=0.06$ [7]. Twelve out of 88 patients treated within this trial were entered at a lower dose level than prescribed because the esophagus constraint was reached (all had stage III disease).

Radiotherapy preparation

For all patients, a treatment planning CT scan was made with 5-mm slice thickness of the entire thorax with the patient breathing freely. The gross tumor volume (GTV) was defined as the primary tumor and the pathological lymph nodes detected with mediastinoscopy, CT scan and/or ¹⁸F¹⁸FDG PET scan. In case the patient received chemotherapy prior to irradiation, the GTV was delineated on the post chemotherapy CT scan. In case the primary tumor or a pathologic lymph node station reached a complete response after chemotherapy, this site was still incorporated in the GTV. The external contour of the esophagus was delineated every cm. The cranial limit to draw the esophagus on the CT scan was 2 cm above the jugulum. The lowest CT slice to contour the esophagus was at the level of the gastro-esophageal junction.

For all 156 patients a conformal treatment plan was designed with multiple 8 MV photon beams, each shaped with the multi-leaf collimator. CT-based dose calculations were performed using a 3D treatment planning system (U-MPlan, University of Michigan) applying an equivalent path length inhomogeneity correction.

The radiation dose was calculated in the isocenter. The required dose homogeneity within the PTV was -5 to $+7\%$ according to the ICRU guidelines [11]. Electronic portal imaging (EPI) was used in a patient set-up verification procedure to verify and correct the set-up of the patient, using large orthogonal fields (18 cm \times 18 cm) with 18 monitor units. These fields for EPI were incorporated in the 3D dose distribution planning procedure [17].

Esophagitis scoring

The patients were seen once a week by the radiation oncologist during their radiation treatment. At baseline and during the irradiation treatment the patient's weight was measured weekly. All patients consulted a dietician at least once during the first weeks of the irradiation period. Acute esophageal toxicity was graded by one radiation oncologist according to the RTOG/EORTC criteria. Grade 2 esophagitis is scored in case of moderate dysphagia requiring narcotic agents or puree/liquid diet. Grade 3 esophagitis in case of severe dysphagia with dehydration or weight loss $> 15\%$ from pre-treatment baseline, requiring nasogastric feeding tube, I.V. fluids, or hyperalimentation. Grade 4 esophagitis was scored in case of complete obstruction, ulceration, perforation or fistula. The charts of all patients were reviewed and the maximum esophagitis grade was noted. After completion of treatment the patients were followed at 2 months intervals or more frequently if necessary.

² V_{eff} is derived from a dose-volume histogram (DVH) by requiring that uniform irradiation of this volume to the reference dose gives the same complication risk as the original DVH (using a power-law volume effect) [12].

Dosimetric analysis

The treatment plans of the total study population, including the CT scan, contours, beam data, and dose distributions, were transferred from the treatment planning system to a dosimetric and volumetric database [10]. The database was especially developed to perform extensive analyses of dose-volume-effect relationships of large radiotherapy studies.

For some patients the treatment field border was above the cranial limit of the drawn esophagus contour (2 cm above the jugulum). Therefore, in the database the delineation of the esophagus was extended in the cranial direction to the lower limit of the cricoid for all patients. Furthermore, the contouring was checked by one observer on consistency, amongst others to ensure that the caudal limit was at the level of the gastro-esophageal junction.

The Dose-Volume Histograms (DVHs) were re-computed by the database-analysis package. In the computation process, air was removed automatically by leaving out the CT voxels with Hounsfield units lower than 500. To correct for differences in the dose per fraction, the physical dose was converted into the Normalized Total Dose (NTD) [14] with an α/β ratio of 10 Gy. This value was chosen because it corresponds to acute reacting tissue. We evaluated only relative DVHs.

We determined the length over which the complete circumference of the esophagus was irradiated to at least 40 and 66 Gy, because these parameters were found to be significant predictors in several studies [20,24]. This parameter was calculated by virtual unfolding of the esophagus followed by a projection of the dose onto a 2D map, a so-called dose map [9]. We integrated the length over which the full width of the dose map, i.e. the esophageal circumference, was irradiated to at least 40 and 66 Gy. Subsequently we evaluated relative length parameters.

Statistical analysis

We used a binary logistic regression model to express the risk of developing acute grade ≥ 2 esophageal toxicity as a function of independent variables (risk factors). The link function used was the logit function, which results in a sigmoid shaped relationship between the estimated complication probability and the risk factors included in the model. The maximum likelihood method is used for the estimation of the regression coefficients and its standard errors. All parameters were tested univariable and multivariable. Analyses were performed using the logistic procedure in ©SPSS for Windows software, release 10.0 (SPSS, Inc., Chicago, IL) and SAS, release 8.1 (SAS, Carry, NC).

The following potential clinical and treatment related risk factors were tested in this study: treatment group (concurrent CRT, sequential CRT, radiotherapy only), gender, age, upper versus middle and lower lobe tumors, tumor stage, N 0/1 versus N 2/3, volume of the esophagus and the length of the esophagus.

The dosimetric factors tested in the model were: % volume of the esophagus receiving at least 5-60 Gy with dose steps of 5 Gy and the relative length of esophagus receiving 40 and 66 Gy or more over the complete circumference.

In addition, we fitted the acute esophagitis data to the Normal Tissue Complication Probability (NTCP) model that was proposed by Lyman [15]. In this model the dose-effect is described by the integral of a normal distribution:

$$\text{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-x^2/2} dx.$$

The integration limit t is given by

$$t = \frac{\text{EUD} - \text{TD}_{50}}{m \times \text{TD}_{50}},$$

where EUD is the Equivalent Uniform Dose, TD_{50} is the EUD at which the risk of complications is 50% and m is a parameter that is a measure of the slope of the sigmoid curve. The EUD is the dose that, when given as a uniform dose to the entire organ, would produce the same normal tissue complication probability as the original dose distribution.

The EUD is obtained by reducing a DVH to a single dose value using a power-law relationship

$$\text{EUD} = \left[\frac{1}{V} \sum_{i=1}^N D_i^{1/m} V_i \right]^n,$$

where V is the volume of the organ, V_i is the volume that receives a dose of D_i and N is the number of dose bins in the DVH [13,18,19]. The optimum values of the parameter n , m , and TD_{50} were determined by maximizing the likelihood of the observations. The uncertainty in the fitted parameters was assessed by the profile likelihood method. We varied each parameter separately around its most optimum value and determined the lower and upper bound value of the parameter at which the natural log of the likelihood function dropped by 3.84/2. The parameter value was varied while the likelihood function was maximized with the two other parameters. The value of 3.84 corresponds to a confidence level of 95% with 1 degree of freedom for a χ^2 distribution.

To construct a confidence region around the fitted NTCP curve we calculated on a 2D grid the variation of the natural log of the likelihood function as a function of the parameter m and TD_{50} . The parameter n was kept at its most optimum value. We determined the iso-likelihood contour that corresponded to a drop of the natural log of the likelihood by a factor of 2. This contour encloses the region in which a confidence level of 95% is expected. A bundle of NTCP curves was calculated using the parameter values on the contour. The envelope of this bundle confined the 95% confidence region [6,22,25]. The fit described above was applied for the patient group receiving sequential CRT or radiotherapy only.

Results

General patient characteristics are summarized in Table 1. With regard to the specified treatment groups, it was noted that age was not evenly distributed over the groups. An average of 73 years for the radiotherapy only group against 60 years for the other two treatment groups. This is due to the fact that medically inoperable patients (often the elderly with small tumor volumes) were treated with radiotherapy alone.

For the same reason, tumor stage was not evenly distributed over the treatment groups: the radiotherapy only group had 54% of stage I/IIA tumors against none in the other two groups who consisted mainly of stage III tumors.

Incidence of esophagitis

The majority of patients developed mild esophagitis; for 66 patients (42%) grade 1 complaints occurred. A total of 42 patients (27%) developed moderate or severe dysphagia (\geq grade 2 acute esophagitis). Thirty-two patients experienced grade 2, nine grade 3 and 1 patient experienced grade 4 esophagitis. An incidence of 12% \geq grade 2 acute esophagitis was scored in the group treated with radiotherapy only. A higher incidence of 29% was seen for patients treated with sequential CRT. The patients treated with concurrent CRT had the highest probability to develop moderate to severe esophageal toxicity: 48%. Severe acute esophageal toxicity (grade \geq 3) was only seen in patients irradiated with concurrent CRT (10 patients).

All patients except six finished their radiotherapy treatment within the planned time schedule (patients in the dose escalation trial finished radiotherapy treatment within 6 weeks and EORTC study patients within 5 weeks). Out of the six patients exceeding the overall treatment time, four were due to holidays and/or equipment problems. For two patients treated with concurrent CRT, severe esophagus toxicity led to RT treatment interruptions of 1 and 2 days.

Dose-volume data

For the total study population the average mean dose in the esophagus was 25.1 Gy. Within the three treatment groups, the mean dose received by the esophagus was on average 16.8 Gy for patients treated with radiotherapy only, 32.4 Gy for patients treated with sequential CRT and 32.6 Gy for patients treated with concurrent CRT. For the three groups together the mean volume of the esophagus receiving at least 20, 40 and 60 Gy was 42.9, 30.7 and 17.3%, respectively. The length of the esophagus receiving at least 40 Gy varied between 0 and 18.5 cm with a mean of 7.1 cm. The mean length of the esophagus receiving at least 40 Gy was 12 cm in the concurrent CRT group, 10 cm in the sequential CRT group and 1 cm in the RT only group. For 66 Gy, the dose-length parameter varied between 0 and 8.7 cm, with a mean of 1.5 cm. The mean length of the esophagus receiving 66 Gy was 3 cm in the concurrent CRT group, 2 cm in the sequential CRT group and 1 cm in the RT only group.

Univariable analysis

The results of univariable (UV) and multivariable (MV) binary logistic regression analysis are shown in Table 3. A strong correlation was found between several tested dose-volume parameters and the risk to develop acute esophagitis \geq grade 2. For the volume receiving a certain dose or more, all tested dose levels between 20 and 60 Gy were significant ($P < 0.01$). The most significant volume effect was found for the relative esophagus volume receiving 35 Gy (V35) or more ($P < 0.001$ UV). The most significant length parameter was the % esophagus length receiving 40 Gy or more over the full circumference.

Table 3
Results of univariable (UV) and multivariable (MV) binary logistic regression with grade ≥ 2 esophagitis as endpoint

Variables (n=156)	UV P-value	MV P-value	OR (MV)
V35: % volume at least 35 Gy	<0.001	<0.001	1.06
% length 40 Gy full circumference	<0.001	0.8	-
% length 66 Gy full circumference	0.009	0.9	-
Volume esophagus	0.8	0.5	-
Length esophagus	0.3	0.5	-
Treatment group overall	<0.001	0.1	-
RT alone vs. sequential CRT	0.03	0.6	-
RT alone vs. concurrent CRT	<0.001	0.2	-
Concurrent CRT vs. sequential CRT	0.02	0.04	2.1
Concurrent CRT yes vs. no	<0.001	0.04	2.5
Age	0.01	0.7	-
Gender (male vs. female)	0.9	0.8	-
Upper vs. lower/middle lobe	0.4	0.1	-
N stage: N0N1 vs. N2N3	0.001	0.8	-
Stage	<0.001	0.6	-

Odds ratio's (OR) are given for variables with $P < 0.1$ at MV analysis.

With regard to the treatment groups, patients treated with concurrent CRT had a significant higher incidence of grade ≥ 2 esophagitis than the sequential CRT patient group ($P = 0.02$ UV) as well as with regard to the RT only patient group ($P < 0.001$ UV). Furthermore, sequential CRT had a higher incidence than RT only ($P = 0.03$ UV). Tumor stage, N stage, and age had a significant influence on the probability to develop acute esophagitis at univariable analysis ($P < 0.05$).

Multivariable analysis

At univariable analysis, the relative esophagus volume receiving 35 Gy (V35) appeared to be the strongest parameter associated with the probability of developing acute esophagus toxicity \geq grade 2. At multivariable testing, V35 remained the strongest predictor and other dose-volume and dose length parameters did not reach significance when they were tested in a multivariable model with V35 (Table 3). The estimated odds ratio for V35 is 1.06 (Table 3) indicating a higher risk for larger volumes irradiated to at least 35 Gy. With regard to the clinical parameters, none of them remained significant at MV analysis.

With regard to the treatment group, the overall test was not significant (MV $P = 0.1$) but we did find a significant result between two of the three treatment groups. Comparing the group receiving RT only with the group

receiving sequential CRT or with the concurrent CRT group, there is no significant difference (MV $P = 0.6$ and 0.2 , respectively). There is however a significant difference between the concurrent and the sequential CRT group ($P = 0.04$ -MV). Further, exploration of this phenomenon, revealed that the presence or absence of concurrent CRT was a significant factor ($P = 0.04$) when controlling for V35: the presence of concurrent CRT involves a significant higher risk to develop moderate to severe dysphagia. The corresponding odds ratio for the presence or absence of concurrent CRT is 2.5 (Table 3).

As a result of the MV logistic regression analysis, the probability of developing acute esophagus toxicity \geq grade 2 can now be formulated as follows for patients treated with RT or sequential CRT:

$$\text{Probability} = \frac{1}{1 + \exp - (-3.37 + 0.05 \times V35)}$$

For patients treated with concurrent CRT:

$$\text{Probability} = \frac{1}{1 + \exp - (-3.37 + 0.05 \times V35 + 0.92)}$$

The P -value of this model describing the probability of developing acute esophagitis \geq grade 2 as a function of V35 (in percentages) and the presence or absence of concurrent CRT, is less than 0.0001. This dose effect relationship between the esophagus volume receiving 35 Gy or more and the corresponding probability of developing acute esophagus toxicity \geq grade 2 is plotted in Fig. 1. In Fig. 1A, the patients who received RT only or sequential CRT are plotted, and in Fig. 1B, patients who received concurrent CRT are plotted. The actual incidences as present in our data set, are also plotted, together with 95% confidence limits.

As shown in Fig. 1, the observed incidence of esophagitis increases with increasing volumes irradiated to 35 Gy or more. Also the incidence within the treatment group receiving concurrent CRT is in our dataset clearly higher

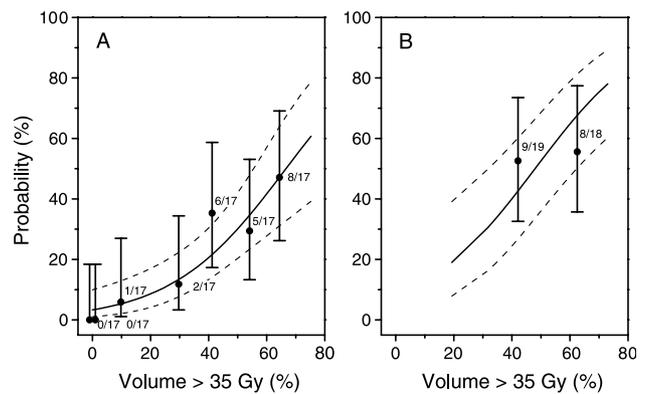


Fig. 1. In both figures the probability of acute esophagus toxicity \geq grade 2 is plotted as a function of the esophagus volume receiving 35 Gy or more (solid lines with corresponding 95% confidence intervals in dotted lines). On the left (A) the group of patients treated with sequential CRT or RT only. On the right (B) the group of patients treated with concurrent CRT. In both graphs the corresponding actual incidence of \geq grade 2 is plotted in solid circles with corresponding error bars (95% confidence interval), for dose bins of about 17 patients each.

compared to the patient group not receiving concurrent CRT. However, the fitted line in Fig. 1B where the dose-volume effect is plotted for the concurrent CRT group, does not seem to fit the data as nice as it does in Fig. 1A. For both fits, the steepness of the line is identical because they are the result of the same fit. In order to test whether the steepness of the dose-volume effect is significantly different within the concurrent CRT group, we tested whether there was a significant interaction between the variables concurrent CRT and V35. This interaction parameter appeared to be not significant ($P=0.1$) and, therefore, the fit of the dose-volume effect was not adjusted for this patient group.

Equivalent uniform dose

We determined the dose-effect relationship for the estimated probability to develop acute esophageal toxicity grade ≥ 2 , using the NTCP model that was proposed by Lyman. The dose-effect relationship was determined for the patients who received RT only or sequential CRT. We found the following values by maximizing the log likelihood function: $n=0.69$ (0.18-6.3), $m=0.36$ (0.25-0.55), and $TD_{50}=47$ Gy (41-60 Gy). The figures between the brackets indicate the 95% confidence interval. The relatively high value of the volume component n indicates that the probability of developing acute esophagitis does not depend only on the high dose region in the DVH. The fitted NTCP curve together with the actual incidence of acute esophagitis is shown in Fig. 2.

Discussion

Acute esophagitis in patients treated for lung cancer influences the quality of life of the patient and may result in

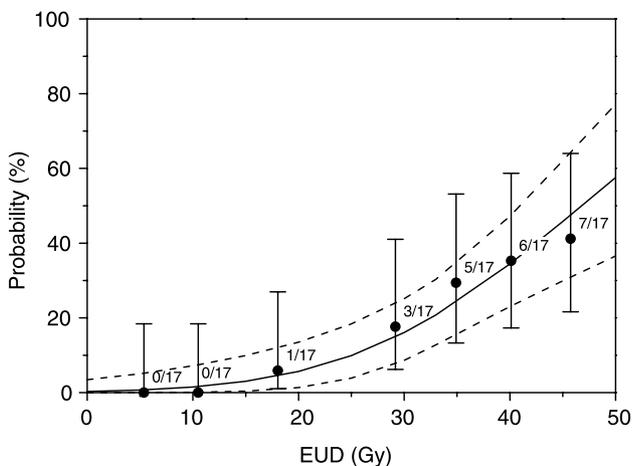


Fig. 2. The probability of acute esophagus toxicity \geq grade 2 versus EUD for the patients treated with sequential CRT and RT only. The data was binned in groups of 17 patients. The bins show the actual measured incidence of acute esophagus toxicity grade 2 or higher. The solid circles locate the mean EUD within each bin. The error bars represent the 95% confidence intervals of the data in the bins. The solid line represents the probability according to the NTCP model with the optimized parameters $n=0.69$, $m=0.36$, and $TD_{50}=47$ Gy. The dashed lines limit the 95% confidence region of the NTCP model.

a radiotherapy treatment interruption. An interruption of the radiotherapy treatment will negatively influence the treatment outcome and the advantage of concurrently given chemotherapy might disappear. Reports focusing on dosimetric or volumetric parameters as predictors for radiation esophagitis are scarce. We found the use of concurrent CRT to be a major factor in predicting acute esophagitis, which is in agreement with previous studies [3,4,23,26]. We also found several highly significant ($P<0.001$) dosimetric factors. At univariable analysis the length of the esophagus irradiated was found to be significant in our study. This result is consistent with several other studies reporting associations between dosimetric factors and acute dysphagia [2,20,23]. However in multivariable analysis the length of the esophagus irradiated was not a significant parameter.

Several other studies reported no significant relationship between dose parameters and maximum score of acute dysphagia [16,26]. In the study of Werner-Wasik et al. [26] both the use of concurrent CRT and hyperfractionated RT were important in the development and duration of acute esophagitis. No dose-volume parameter was predictive for acute esophagitis. The length of the esophagus irradiated was however measured on digitally reconstructed radio-graphs only. Maguire et al. reported an analysis based on dose-volume histograms and dose-surface histograms of the esophagus in NSCLC patients but none of the parameters studied were significant predictors of acute esophagitis [16]. Singh et al. found a relationship between concurrent CRT, the maximal dose to the esophagus ≥ 58 Gy and grade 3-5 esophagitis [23]. However, they did not report separate results for the UV and MV analysis of acute esophagitis.

Results from a phase I/II trial for NSCLC patients treated with induction chemotherapy followed by concurrent CRT, were published by Rosenman and colleagues [20]. They reported a correlation between grade 3 and 4 esophagitis and the length of the esophagus receiving at least 40 and 60 Gy [20]. The incidence of severe esophagitis in this intensively treated group of patients was only 8%. In our patient material we had only a small subgroup of 37 patients receiving concurrent CRT. In this subgroup we found no significant dose-volume effect or dose-length effect.

Recently Bradley and colleagues [2] analyzed the acute esophageal toxicity in a group of NSCLC patients treated with RT only, concurrent CRT and sequential CRT similar to our patient group. Their drawing of the esophagus (from the bottom of the cricoid to the gastroesophageal junction) was identical to our delineation of the esophagus. Bradley et al. used oral contrast to delineate the esophagus. In their study, they concluded that the statistically most significant dosimetric predictive factors were the surface area of the esophagus receiving 55 Gy or more and the dose-volume receiving 60 Gy or more. They found concurrent CRT to be a strong predictive factor [2]. Although the chemotherapy scheme given concurrently (mostly Cisplatin and Etoposide) is quite different from our daily low dose Cisplatin, their conclusions are supported by our data.

The reported incidence of grade ≥ 3 acute toxicity for concurrent CRT with platinum containing chemotherapy is in between 5 and 34% [24]. The incidence of grade ≥ 3 acute toxicity for patients receiving daily low dose Cisplatin in

the phase I/II study performed prior to the phase III EORTC 08972 study was only 5%. The incidence of 27% grade ≥ 3 acute esophageal toxicity in our concurrent CRT group is much higher than we would expect based on the phase I/II study. This severe esophageal toxicity did cause short treatment interruptions in two out of the 37 patients treated with concurrent CRT.

In the patient group treated with radiotherapy only an effective volume constraint V_{eff} (with $n=0.06$) of maximal 30% at a reference dose of 80 Gy for the esophagus was used. Using this constraint we did not see any severe acute esophagus toxicity in this group of patients. Because our study, as well as several other large studies, has shown that sequential CRT does not significantly increase acute esophageal toxicity, [21] we are confident that this constraint is safe for patients treated with radiotherapy only or with sequential CRT.

A continuously rising risk of esophagitis was seen with increasing volumes, for several dose levels (20-60 Gy). The most significant dose level appeared to be V35 (the relative volume receiving 35 Gy or more). Since all significant dose levels showed high mutual correlations, this result should be interpreted with caution. It indicates that probably intermediate dose levels are more relevant, or at least as relevant, as higher dose levels.

From our results we can derive an estimated probability to develop grade 2 or higher acute esophagitis in patients irradiated with concurrent CRT or with sequential CRT or RT only, based on the volume of the esophagus receiving at least 35 Gy. New constraints could be formulated to keep this toxicity below an acceptable level. If we would accept, for example, a 30% probability to develop grade ≥ 2 acute esophagitis in patients treated with sequential CRT or RT only, then the maximum volume of the esophagus that may receive 35 Gy or more can be 50% of the esophagus volume, with a 95% confidence interval of 40-63% (Fig. 1). If we would accept the same complication probability for the concurrent CRT treatment, only a maximum of 31% volume (95% confidence interval 10-45%) would be acceptable. Since the confidence limits for the latter group are quite large, a more reliable constraint should be formulated when data of a larger group of patients becomes available.

Conclusion

Both concurrent chemo-radiotherapy and the esophagus volume that receives 35 Gy or more are predictors of acute esophageal toxicity. For patients treated with sequential CRT the risk to develop acute esophageal toxicity is not significantly increased compared to patients treated with radiotherapy only.

Acknowledgements

The authors wish to thank H. Bartelink, M. Van Herk and B.J. Mijnheer for critically reading the manuscript. This study was supported by the Dutch Cancer Society (Grant 98-1830 and Grant 99-2043).

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Received 11 November 2004; received in revised form 12 February 2005; accepted 1 March 2005; available online 10 May 2005

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