RESEARCH ARTICLE

Dosimetric and Clinical Predictors of Acute Esophagitis in Lung Cancer Patients in Turkey Treated with Radiotherapy

Durmus Etiz[1]*, Evrim Bayman[1], Melek Akcay[1], Bilgehan Sahin[1], Cengiz Bal[2]

Abstract

Background: The purpose of this study was to determine the clinical and dosimetric factors associated with acute esophagitis (AE) in lung cancer patients treated with conformal radiotherapy (RT) in Turkey. Materials and Methods: In this retrospective review 104 lung cancer patients were examined. Esophagitis grades were verified weekly during treatment, and at 1 week, and 1 and 2 months afterwards. The clinical parameters included patient age, gender, tumor pathology, number of chemotherapy treatments before RT, concurrent chemotherapy, radiation dose, tumor response to RT, tumor localization, interruption of RT, weight loss, tumor and nodal stage and tumor volume. The following dosimetric parameters were analyzed for correlation of AE: The maximum (D_{max}) and mean (D_{mean}) doses delivered to the esophagus, the percentage of esophagus volume receiving ≥10 Gy (V_{10}), ≥20 Gy (V_{20}), ≥30 Gy (V_{30}), ≥35 Gy (V_{35}), ≥40 Gy (V_{40}), ≥45 Gy (V_{45}), ≥50 Gy (V_{50}) and ≥60 Gy (V_{60}). Results: Fifty-five patients (52.9%) developed AE. Maximum grades of AE were recorded: Grade 1 in 51 patients (49%), and Grade 2 in 4 patients (3.8%). Clinical factors had no statistically significant influence on the incidence of AE. In terms of dosimetric findings, correlation analyses demonstrated a significant association between AE and D_{max} (>5117 cGy), D_{mean} (>1487 cGy) and V_{10-60} (percentage of volume receiving >10 to 60 Gy). The most significant relationship between RT and esophagitis were in D_{max} (>5117 cGy) (p=0.002) and percentage of esophageal volume receiving >30 Gy (V_{30}>31%) (p=0.008) in the logistic regression analysis. Conclusions: The maximum dose esophagus greater than 5117 cGy and approximately one third (31%) of the esophageal volume receiving >30 Gy was the most statistically significant predictive factor associated with esophagitis due to RT.

Keywords: Acute esophagitis - lung cancer – radiotherapy - side effect

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Introduction

Radiotherapy (RT) is used in the treatment of 64% of cases with lung cancer (with a curative intent in 46%) (Tyldesley et al., 2001). Tumors close to the midline and mediastinal lymphadenopathies increase the dose of exposure of the esophagus. For this reason, acute esophagitis (AE) is a frequent adverse effect seen in patients receiving RT for lung cancer. Grade 3-4 AE has been reported in 20-30% in simultaneous chemoradiotherapy (CRT) administrations (De Ruysscher et al., 2012). Parameters predicting the AE in advance would prevent interruptions of treatment and would increase the success of treatment (local control and overall survival).

Administration of CRT, hyperfractioned RT, esophageal volume receiving a dose (%) more than 35 Gy (V_{35}), V_{45}, V_{50}, V_{60}, and mean esophageal dose (D_{mean}), and environmental and volumetric esophageal doses have been faulted for AE development in the literature (Maguire et al., 1999; Werner Wasik et al., 2000; Bradley et al., 2004; Patel et al., 2004; Rose et al., 2009). However, there is no generally accepted predictive factor for AE development. The aim of this study is to evaluate the association between the dose distribution, clinical factors, and AE development in the esophagus during the treatment of lung cancer.

Materials and Methods

Patient characteristics

One hundred and four patients who were planned to receive three-dimensional conformal RT in the Clinic of Radiation Oncology at Osmangazi University School of Medicine between July 2010 and January 2012 were evaluated. Cases with the histopathological diagnosis of non-small-cell lung carcinoma (NSCLC) or small-cell lung carcinoma (SCLC), with T3 or T4 tumors and/or mediastinal lymph node involvement, not operated on for medical reasons or according to the choice of the patient, and with a Karnofsky Performance Scale of 70 and above were included in the study. Cases with multiple primary diagnoses and/or distant metastasis were not included in the study. Cases that developed metastasis during the treatment were excluded from the study. Ninety-seven

*[1]Department of Radiation Oncology, [2]Department of Biostatistics, School of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey *For correspondence: detiz@ogu.edu.tr*

of the cases of this study group were males (93.3%) and 7 were females (6.7%). NSCLC/SCLC rate in the histopathological evaluation was 93/11. The median age was 61.5 years (39-79 years). The NSCLC group comprised of 50 cases with stage III B (48%), 27 cases with stage III A (26%), 18 cases with N0 (17.3%). The characteristics of the patients are presented in Table 1. Median tumor volume was 80 cm^3 (6-820 cm^3) and median lymph node volume was 2 cm^3 (0-46 cm^3).

Chemotherapy

Ninety-eight percent of the patients (95.2%) received chemotherapy before RT with median of three cycles (0-12). The most frequently used chemotherapy regimens were cisplatin (75 mg/m^2)-gemcitabine (1250 mg/m^2) and cisplatin (75-100 mg/m^2)-etoposide (100 mg/m^2). Forty-nine cases (47.1%) received simultaneous chemotherapy with RT. For radiosensitization, weekly cisplatin 40 mg/m^2 (a total of 6 times) was administered in patients with NSCLC, and cisplatin (80 mg/m^2, first day)-etoposide (100 mg/m^2, 1-3 days) (a total of two times) was given to patients with SCLC.

Intravenous hydration was provided with 1-2 L of infusion fluid given over 8-12 hours. The balance of adequate hydration and urinary output were followed during the 24 hours following the treatment. Patients receiving simultaneous chemotherapy or patients with a decreased oral intake were hydrated, given enteral nutritional support and analgesics with hospitalization.

Radiotherapy

Three-dimensional conformal radiotherapy was planned for all patients. Tomographic planning sections were obtained in 5 mm intervals in the supine position with arms immobilized over the head with a T-bar. Gross tumor volume (primary tumor and lymph nodes with short diameter greater than 1 cm) was contoured according to ICRU-62 using CT and PET-CT (ICRU Report 62, 1999). Clinical target volume (CTV) was calculated by adding 6 mm in squamous cell carcinoma, 8 mm in adenocarcinoma, 3 mm in the presence of pathological lymph nodes, and 8 mm in SCLC. Elective mediastinal nodal irradiation was only used in SCLC. PTV was obtained by adding 1-1.5 cm to the CTV. PTV received a minimum of 93% and a maximum of 107% of the planned dose. Heterogeneity correction was performed. The esophagus was contoured from cricoid cartilage to the gastroesophageal intersection in order to include its external wall. Dose volume histograms were evaluated in all patients. Critical organ dose tolerances were identified as V_5<50% (lung volume receiving more than 5 Gy was less than 50%), V_{20}<30% (lung volume receiving more than 20 Gy was less than 30%), mean lung dose <15 Gy, and maximum spinal cord dose <50 Gy and cardiac V_{30}<50% (cardiac volume receiving 30 Gy was less than 50%). Irradiation was performed with linear accelerator equipment (Precise-ELEKTA™) with 6 MV X-rays. Oblique fields following the anterior-posterior fields excluding the spinal cord outside the field were used in all patients. Fields were controlled by electronic portal imaging in the first treatment and followed at weekly intervals. The median dose of RT was 60 Gy (45-62 Gy). Fractions were applied as 1.8-2 Gy/day, 5 days a week. Mediastinal RT was administered in 86 cases (82.6%). Esophageal-tumor and lymph node volumes, and maximum-minimum-mean esophageal doses were recorded in dose volume histogram evaluations (XiO; Computerized Medical Systems™ , St. Louis, MO).

In addition, esophageal doses were reported as esophageal volumes (%) of 10 Gy (V_{10}), 20 Gy (V_{20}), 30 Gy (V_{30}), 35 Gy (V_{35}), 40 Gy (V_{40}), 45 Gy (V_{45}), 50 Gy (V_{50}), and >60 Gy (V_{60}).

Toxicity scoring and follow-up

Age and gender of the patients, tumor pathology, type of treatment (only RT/concurrent CRT), number of chemotherapy cycles before RT, localization of the tumor, T and N stage, severity of AE according to RTOG criteria. RTOG scoring system is presented in Table 2. (At the beginning, and the first, second, third, fourth, fifth, and sixth week, and following the first week, and first and second month). Days of interruption of RT, total RT dose, and tumor response results in the second month were recorded in the "RT reporting and oncological follow-up

Table 1. Patient Characteristics

Patient Characteristics		No. of Cases	%
Median Age (year)		61.5 (39-79)	
Sex (F/M)		7-97	6.7/93.3
Pathology (NSCLC/SCLC)		93/11	89.4/10.6
Treatment (CRT/RT)		49/55	47.1/52.9
Stage	IB	2	1.9
	IIA	3	2.9
	IIB	11	10.6
	IIIA	27	26
	IIIB	50	48
	Limited SCLC	11	10.6
NSCLC	N0	18	17.3
	N1	9	8.7
	N2	57	54.7
	N3	9	8.7
RT dose	≤60 Gy	36	34.6
	≥60 Gy	68	65.4
Tumor localization	Upper right	44	42.3
	Middle right	6	5.8
	Lower right	15	14.4
	Upper left	25	24
	Lower left	14	13.5

*NSCLC: Non-small-cell lung cancer; SCLC: Small-cell lung cancer; CRT: Concurrent chemoradiotherapy; RT: Radiotherapy only

Table 2. Radiation Therapy Oncology Group (RTOG) Criteria for Acute Esophagitis

0	No change compared to beginning
1	Mild dysphagia or odynophagia necessitating topical anesthetics, nonnarcotic drugs or soft diet
2	Moderate dysphagia or odynophagia necessitating narcotic drugs or mashed/liquid diet
3	Severe dysphagia or odynophagia necessitating nasogastric feeding, IV fluids or hyperalimentation (Accompanying dehydration or >15% weight loss)
4	Complete obstruction, ulceration, perforation or fistula
5	Death

system" (IMPAC Medical Systems™ , Inc. 100 West Evelyn Avenue Mountain View, CA 94041).

All patients received sucralphate and nystatin suspension (4×5 ml/day) starting with the RT. Follow-up oncology visits were planned for every three months in the first two years, every six months between two and five years, and annually after five years.

Statistical analysis

Parameters that may be associated with AE development, such as age (Spearman correlation coefficient) and gender (Fisher's exact test) of the patients, simultaneous chemotherapy administration (Fisher's exact test), number of chemotherapy cycles before RT (Fisher's exact test), total RT dose (Fisher's exact test), tumor response to RT (Spearman correlation coefficient), pathological type of the tumor (Fisher's exact test), tumor localization (Fisher's exact test), T stage (Spearman correlation coefficient), N stage (Spearman correlation coefficient), tumor volume and esophageal volume (Spearman correlation coefficient), interruption of RT (Fisher's exact test), weight loss during RT (Spearman correlation coefficient) and administered doses and volumes (Spearman correlation coefficient, logistic regression analysis) were evaluated.

Statistical analysis was performed using the SPSS (Statistical Package for Social Science –Version 20.0- for Windows) program. A value of $p<0.05$ was accepted as statistically significant.

Results

Patients' visits accounted for total of 1040 for 104 patients. The mean number of days of interruption was two days (range 0-10 days), and a median weight of

Table 3. Frequency of Acute Esophagitis According to Week

	Grade 0	Grade 1	Grade 2	Grade 3-5
Beginning of RT*	103	1	-	-
1st week	98	6	-	-
2nd week	86	18	-	-
3rd week	66	36	2	-
4th week	49	51	4	-
5th week	50	53	1	-
6th week	80	24	-	-
1 week after RT	94	10	-	-
1 month after RT	104	-	-	-
2 months after RT	104	-	-	-

*RT: Radiotherapy

Table 4. Associations between Clinical Factors and Acute Esophagitis

Variable	Correlation Coefficient (r*)	p value
Age	-0.36	0.311
Sex (M/F)	-	0.933
Tumor pathology (NSCLC/SCLC)	-	0.582
Number of chemotherapy cycles before RT (3 chemotherapy cycles/4 or more chemotherapy cycles)	-	0.615
Concurrent CRT (present/none)	-	0.09
Tumor localization (upper/middle/lower)	-	0.711
Tumor volume	0	0.911
Esophageal volume	0	0.953
T stage	-0.21	0.842
N stage	-0.03	0.732
RT dose (≤60/>60 Gy)	-	0.536
Response to RT (regression/stable/progression)	-0.05	0.610
Days of interruption of RT (3 days/4 or more days)	-	0.516
Weight Loss	0.1	0.295

*r: Spearman Correlation coefficient; RT: Radiotherapy, NSCLC: Non-small-cell lung cancer; SCLC: Small-cell lung cancer

Table 5. Association of Dosimetric Parameters with Acute Esophagitis

Variable	RT Start (r-p value)	1st wk** (r-p value)	2nd wk (r-p value)	3rd wk (r-p value)	4th wk (r-p value)	5th wk (r-p value)	6th wk (r-p value)	1 wk after RT (r-p value)
$D_{maximum}$ (5117cGy)	0.14-0.149	0.04-0.637	0.16-0.1066	**0.33-0.001***	**0.32-0.001***	**0.38-0.000***	**0.32-0.001***	**0.23-0.018***
$D_{minimum}$ (13cGy)	0.14-0.139	**0.19-0.047***	0.15-0.119	0.17-0.075	0.14-0.152	0.13-0.186	**0.22-0.026**	0.13-0.182
D_{mean} (1487cGy)	0.14-0.140	0.12-0.221	**0.22-0.022***	**0.4-0.000***	**0.47-0.000***	**0.49-0.000***	**0.44-0.000***	**0.21-0.031***
V_{10} (%)	0.14-0.154	0.10-0.313	**0.19-0.044***	**0.34-0.000***	**0.45-0.000***	**0.47-0.000***	**0.38-0.000***	0.13-0.188
V_{20} (%)	0.13-0.180	0.11-0.242	0.17-0.076	**0.34-0.000***	**0.44-0.000***	**0.45-0.000***	**0.37-0.000***	0.14-0.154
V_{30} (%)	0.13-0.174	0.13-0.183	0.18-0.062	**0.38-0.000***	**0.48-0.000***	**0.48-0.000***	**0.39-0.000***	0.18-0.059
V_{35} (%)	0.12-0.214	0.13-0.188	**0.20-0.036***	**0.37-0.000***	**0.43-0.000***	**0.44-0.000***	**0.40-0.000***	**0.21-0.029***
V_{40} (%)	0.13-0.192	0.04-0.638	**0.20-0.042***	**0.40-0.000***	**0.45-0.000***	**0.44-0.000***	**0.41-0.000***	**0.28-0.004***
V_{45} (%)	0.13-0.191	-0.02-0.812	0.13-0.178	**0.34-0.000***	**0.37-0.000***	**0.44-0.000***	**0.44-0.000***	**0.31-0.001***
V_{50} (%)	0.13-0.175	0.008-0.934	0.13-0.179	**0.24-0.015***	**0.25-0.009***	**0.33-0.001***	**0.41-0.000***	**0.23-0.016***
V_{60} (%)	-0.02-0.789	0.11-0.248	0.08-0.418	**0.20-0.041***	0.17-0.071	**0.26-0.008***	**0.39-0.000***	**0.30-0.002***

*Statistically significant correlation present. **week. r: Spearman Correlation coefficient. V_{10-60}: Esophageal volume higher than 10-60 Gy (%)

-1kg of weight loss (range -8kg to +4 kg) was identified. Maximum esophageal dose was median 5117 cGy (range: 20-6501 cGy), minimum esophageal dose was median 13 cGy (range: 0-1017 cGy), and mean esophageal dose was 1487 cGy (range: 5-3607 cGy).

AE developed in 55 cases (52.8%). The most severe AE occurred in the fourth week of RT in 51 cases as grade 1 (49%) and in 4 cases as grade 2 (3.8%). Ten cases (9.6%) continued to have grade 1 at the first week after RT; while no signs of AE were identified on the first and second month follow-up visits. Grade 3 and above severe acute toxicity were not seen in any cases as presented in Table 3.

AE was detected in 35 of 52 patients (67.3%) with ages older than 61.5 years (median) and in 20 out of 52 patients (38.5%) with ages less than 61.5 years in the fourth week, which is the most frequent time of occurrence of mucositis (r=-0.36, p=0.311). AE was seen in 28 of 55 cases (51%) with only RT administration, while 27 of 49 cases (55%) with CRT had AE (p=0.090).

No associations were found between AE and gender (M/F) (p=0.933), tumor pathology (NSCLC/SCLC) (p=0.582), number of chemotherapy cycles received before RT (1-3 chemotherapy cycles/4 chemotherapy cycles or more) (p=0.615), esophageal volume (r=0.00, p=0.953), tumor volume (r=0.00, p=0.911), T stage (r=-0.21, p=0.842), N stage (r=-0.03, p=0.732), dose of RT (≤60 Gy/≥60 Gy) (p=0.536), tumor localization (p=0.711), response rate to RT (regression/stable/progression) (r=-0.05, p=0.610), interruption days for RT (p=0.516), and weight loss (r=0.10, p=0.295) (Table 4).

Table 6. Logistic Regression Analysis for Predictors of Acute Esophagitis

	B	S.E.	Sig.	Exp(B)	95% C.I. for EXP(B)	
	Lower	Upper	Lower	Upper	Lower	Upper
Maximal esophageal dose (>5117cGy)						
	0	0	**0.002**	1	0.999	1,000
Esophageal volume (>31%) higher than 30 Gy						
	0.135	0.051	**0.008**	1.114	1.036	1.264

Table 7. Dosimetric Factors Affecting Acute Esophagitis in the Literature

Reference	RT Dose (Gy)	Dosimetric and Clinical Factor
Bradley et al.	60-74 Gy (1.8-2Gy/day)	CRT, A_{55}, V_{60}
Werner-Wasik et al.	45-69.6 Gy*	CRT, HF
Singh et al.	60-74Gy (2 Gy/ day)	D_{max} (≥58 Gy)
Hirota et al.	50-60 Gy (2 Gy/ day)	$LETT_{45}$, V_{45}
Maguire et al.	64.2-85.6 Gy**	HF, pre RT dysphagia
Ahn et al.	30-86.4 Gy***	HF, pre RT dysphagia, D_{max}, age_{64}
Caglar et al.	46-70 Gy (2 Gy/day)	V_{55}
Takeda et al .	50-67 Gy (1.8-2 Gy/day)	V_{35}>30%
Present Study	45-62 Gy (1.8-2 Gy/day)	D_{max} (≥51Gy), V_{30}>31%

*98 cases with conventional RT, 7 cases with hyperfractioned RT. **58 cases with (64%) hyperfractioned RT. ***98 cases with (39%) hyperfractioned RT. CRT: Concurrent chemoradiotherapy. HF: Hyperfractionation. $LETT_{45}$: Esophageal length receiving more than 45 Gy. A_{55}: Esophageal surface area receiving equal or more than 55 Gy (cm^2). V_{30}: Esophageal volume receiving equal or more than 30 Gy (%). V_{35}: Esophageal volume receiving equal or more than 35 Gy (%). V_{45}: Esophageal volume receiving equal or more than 45 Gy (%). V_{55}: Esophageal volume receiving equal or more than 55 Gy (%). V_{60}: Esophageal volume receiving equal or more than 60 Gy (%)

Beginning in the 3th week, 4th week, 5th week and 6th week of RT, D_{max} values greater than 5117 cGy, D_{mean}. values greater than 1487, and V_{10-60} was found to be correlated with the development of AE (Table 5). A logistic regression analysis demonstrated that D_{max}. (p=0.002) and V_{30}>31% (p=0.008) were significant risk factors effecting AE development (Table 6).

Discussion

The esophagus is exposed to high dose radiation in situations of centrally localized tumors and/or the presence of mediastinal lymph nodes. It is desirable that the esophagus receive lower doses because of its proximity to the spinal cord and heart. There is a relative lack of knowledge about clinical and dosimetric markers effecting the development of AE during RT in the literature. Increased rates of different concurrent chemotherapy protocols further complicate the evaluation of toxic doses for the esophagus. In addition, the efficiency of treatment and adverse effects may vary according to different societies (Lara et al., 2010; Soo et al., 2012).

Emami et al. (1991) reported the TD 5/5 rates (5% stricture and perforation rate in 5 years) for the 1/3, 2/3, and whole esophagus as 60 Gy, 55 Gy, and 50 Gy, respectively. However, these findings are from the pre-three-dimensional RT planning and simultaneous chemotherapy applications period.

Various dosimetric and clinical factors have been reported to affect AE (Table 7) (Maguire et al., 1999; Werner Wasik et al., 2000; Singh et al., 2003; Bradley et al., 2004; Ahn et al., 2005; Court et al., 2012). Bradley et al. (2004) administered cisplatin, etoposide, gemcitabine, paclitaxel, and carboplatin-based CRT in their study performed in 166 cases with stages I-III NSCLC (25% patients). They identified that simultaneous chemotherapy doubled the risk of AE (p=0.001). Others reported this rate as a 12-fold increase (Werner Wasik et al., 1999; Qiao et al., 2005; Caglar et al., 2010). In a series of 105 lung cancers, grade 3 AE was not seen in patients who received only RT; while the rate of grade 3 AE was reported to be 18% in the CRT group (p=0.001) (Werner Wasik et al., 2000). Nevertheless, there are studies reporting no effects of CRT on the development of AE. In a series of 254 cases by Ahn et al. (2005) no differences were found in the rate of development of AE between the etoposide, gemcitabine, paclitaxel, carboplatin, and cisplatin-based CRT arm (32 cases) and no CRT arm (p=0.30). Takeda, confirmed the fact that CRT administration alone is not associated with the development of AE in his series of 35 cases (Takeda et al., 2005). In the present study, CRT was not a factor increasing the rate of AE, either. All patients receiving CRT were hospitalized and followed-up by daily patient visits, preventive drugs (sucralphate and nystatin) were administered under the control of the nurses, IV hydration was performed before chemotherapy, and enteral nutritional support was applied when necessary. These factors together may have prevented the progression of the symptoms of AE in this group. In addition, total RT dose (median 64 Gy) is higher than the present study (median 60 Gy) in the studies reporting an enhancing

role of CRT on the rate of development of AE (Table 7) (Werner Wasik et al., 2000; Bradley et al., 2004; Caglar et al., 2010).

The clinical symptoms of AE in the present study were followed-up on. The answer to whether it is clear that there is no organ injury when the individual has no complaint of AE is found in a study of 82 lung cancer patients from Japan. Fields of grade 3 ulcers were seen in the endoscopic evaluation of cases with no AE symptoms or with mild symptoms (RTOG grade 0-1) who received CRT. On the contrary, grade 3 AE symptoms were reported in only 8.5% of the cases who had endoscopic grade 3 ulcers and thus, it was stressed that the esophagus, contradictory to the previous knowledge, was a "quiet" organ in terms of symptoms (Hirota et al., 2001). In our study, the presence of clinical grade 1-2 symptoms do not imply that the real damage is limited to this level. In addition, not only severe AE, but also intermediate and mild AE could be the reason of the late adverse effects according to Dorr et al. this feature (superficial barrier function against mechanical and/or chemical stresses) also is valid for the intestines, oral mucosa, and urinary bladder (Dorr et al., 2001). Treatment of mild mucositis would prevent possible late adverse effects (Rodriguez et al., 2009). For this reason, such cases should be followed-up on for late adverse effects even if they are asymptomatic in terms of AE.

A comparison of the parameters predicting the development of AE reported in the literature is difficult in many aspects. Variables such as different scoring systems for esophagitis (RTOG and Common Terminology Criteria for Adverse Events CTCAE), different techniques of RT (three-dimensional RT, intensity modulated RT, X-ray, proton treatment), different dose and fraction schemes (conventional and hyperfractionation), different dose-volume histogram parameters (esophageal volume or esophageal surface area), different esophageal contouring protocols (whole organ or external esophageal contour only), differences in the numbers of schemes and cycles of chemotherapy applied simultaneously or before the RT, radioprotector use (amifostine) and different ethnic origins of the patients [Western society (America and Europe) and Far Eastern society (China and Japan)] effect the results.

Another reason for different results originates from the anatomical location of the esophagus. A conversion to the oblique fields of the spinal cord prevention after the first field of lung RT is completed occurs around the fourth week in which AE is maximal. Due to the inclusion of a part of the esophagus immediately in front of the spinal cord in the field, and the exclusion of part of it results in dose-volume histograms with different dosimetric features in this period. In addition, the fractioned dose of the esophagus changes in the oblique boost period since it remains in the partial field, while it receives a 1.8-2 Gy daily dose during the first part of RT. This makes the unit of mean (D_{mean}) esophageal dose meaningless since it has the same continued fraction and weekly same dose accumulation (Huang et al., 2012). No association was identified in the present study between the D_{mean} esophageal dose and AE in the regression analysis.

Some other factors that trigger AE are present, apart from RT and chemotherapy. These are esophageal infections (candida and herpes simplex esophagitis), the presence of gastroesophageal reflux disease (reflux complaints are confused with AE and are reported as a complaint of higher grade) and exposure of the stomach to RT (accompanying gastritis symptoms due to the inclusion of the stomach in the field in lower lobe tumors) (Werner Wasik et al., 2010). These additional factors render the identification of the association between RT and AE more difficult. Considering the serial structure of the spinal cord, and esophagus, it is expected to demonstrate findings of toxicity in exceeding doses of the maximal target value, such as the spinal cord.

In the present study, a maximal esophageal dose of greater than 51 Gy is found to increase the frequency of AE. This value is reported as 55 Gy by Singh et al. (2003) in their series of 207 cases from a Western society and 60 Gy by Qiao et al. (2005) in their series of 208 cases comprising a Far Eastern society.

In conclusions, maximal esophageal doses higher than 51 Gy and/or esophageal volumes approximately more than 1/3 receiving a 30 Gy dose are found to be risk factors for AE development in a series of 104 cases with lung cancer receiving RT administration.

References

Ahn SJ, Kahn D, Zhou S, et al (2005). Dosimetric and clinical predictors for radiation-induced esophageal injury. *Int J Radiat Oncol Biol Phys*, **61**, 335-47.

Bradley J, Deasy JO, Bentzen S, Naqa IE (2004). Dosimetric correlates for acute esophagitis in patients treated with radiotherapy for lung carcinoma. *Int J Radiat Oncol Biol Phys*, **58**, 1106-13.

Caglar HB, Othus M, Allen AM (2010). Esophagus in- field: a new predictor for esophagitis. *Radiother Oncol*, **97**, 48-53.

Court L, Wang J, Lin S (2012). SU-E-T-250:Dose-Response curves for the esophagus. *Med Phys*, **39**, 3761.

De Ruysscher D, Van Meerbeeck J, Vandecasteele K, et al (2012). Radiation-induced oesophagitis in lung cancer Patients : Is susceptibility for neutropenia a risk factor? *Strahlenther Onkol*, **188**, 564-7.

Dorr W, Hendry JH (2001). Consequential late effects in normal tissues. *Radiother Oncol*, **61**, 223-31.

Emami B, Lyman J, Brown A et al (1991). Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*, **21**, 109-22.

Hirota S, Tsujino K, Hishikawa Y, et al (2001). Endoscopic findings of radiation esophagitis in concurrent chemoradiotherapy for intrathoracic malignancies. *Radiother Oncol*, **58**, 273-8.

Huang EX, Bradley JD, Naga IE, et al (2012). Modeling the risk of radiation-Induced acute esophagitis for combined Washington University and RTOG Trial 93-11 lung cancer patients. *Int J Radiat Oncol Biol Phys*, **82**, 1674-9.

ICRU Report 62 (1999). International Commision on Radiation Units and Measurements:Prescribing, recording and reporting photon beam therapy, Bethesda.

Lara PN Jr, Chansky K, Shibata T, et al (2010). Common arm comparative outcomes analysis of phase 3 trials of cisplatin+irinotecan versus cisplatin+etoposide in extensive stage small cell lung cancer: final patient-level results from Japan Clinical Oncology Group 9511 and Southwest Oncology Group 0124. *Cancer*, **116**, 5710-5.

Maguire P, Sibley G, Zhou SM, et al (1999). Clinical and dosimetric predictors of radiation-Induced esophageal

toxicity. *Int J Radiat Oncol Biol Phys*, **45**, 97-103.
Patel AB, Edelman MJ, Kwok Y, Krasna MJ, Suntharalingam M (2004). Predictors of acute esophagitis in patients with non small cell lung carcinoma treated with concurrent chemotherapy and hyperfractionated radiotherapy followed by surgery. *Int J Radiat Oncol Biol Phys*, **60**, 1106-12.
Qiao WB, Zhao YH, Zhao YB, Wang RZ (2005) Clinical and dosimetric factors of radiation-induced esophageal injury: radiation-induced esophageal toxicity. *World J Gastroenterol*, **11**, 2626-9.
Rodriguez N, Algara M, Foro P, et al (2009). Predictors of acute esophagitis in lung cancer patients treated with concurrent three-dimensional conformal radiotherapy and chemotherapy. *Int J Radiat Oncol Biol Phys*, **73**, 810-7.
Rose J, Rodrigues G, Yaremko B, Lock M, D'Souza D (2009). Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. *Radiother Oncol*, **91**, 282-7.
Singh AK, Lockett MA, Bradley JD (2003). Predictors of radiation-induced esophageal toxicity in patients with non-small-cell lung cancer treated with three dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys*, **55**, 337-41.
Soo RA, Kawaguchi T, Loh M, et al (2012). Differences in outcome and toxicity between Asian and caucasian patients with lung cancer treated with systemic therapy. *Future Oncol*, **8**, 451-62.
Takeda K, Nemoto K, Saito H, et al (2005). Dosimetric correlations of acute esophagitis in lung cancer patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys*, **62**, 626-9.
Werner-Wasik M, Scott C, Graham ML, et al (1999). Interfraction interval does not affect survival of patients with non-small cell lung cancer treated with chemotherapy and/or hyperfractionated radiotherapy: a multivariate analysis of 1076 RTOG patients. *Int J Radiat Oncol Biol Phys*, **44**, 327-31.
Werner-Wasik M, Pequignot E, Leeper D, Hauck W, Curan W (2000). Predictors of severe esophagitis include use of concurrent chemotherapy, but not the length of irradiated esophagus: a multivariate analysis of patients with lung cancer treated with nonoperative therapy. *Int J Radiat Oncol Biol Phys*, **48**, 689-96.
Werner-Wasik M, Yorke E, Deasy J, Nam J, Marks LB (2010). Radiation dose-volume effects in the esophagus. *Int J Radiat Oncol Biol Phys* ,**76**, 86.