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Predictors of Early Radiation Induced Esophageal Toxicity in Radiotherapy of Locally Advanced Non-small Cell Lung Cancer

Maher Soliman

Oncology Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Abstract

Background: Radiation induced esophageal toxicity is a primary cause of treatment interruptions in the radiotherapy of lung cancer, for which there are no clear predictive factors. This study attempts to identify risk factors associated with the development of severe radiation induced esophageal toxicity using clinical and dosimetric parameters.

Methods: We reviewed the medical records of 54 patients with histologically proven stage III non-small cell lung cancer treated with 3D-conformal radiotherapy at Alexandria Main University Hospital between January 2008 and December 2011. The original treatment plans for those patients were restored and imported to the treatment planning system. The external surface of esophagus was contoured for each patient. We calculated the esophagus dose–volume histograms and various dosimetric parameters. Univariate and multivariate logistic regression analyses were performed.

Results: Of the 54 patients, 6 (11.1%) had grade 3 radiation induced esophageal toxicity and 2 (3.7%) had grade 4. There was no grade 5 toxicity. The most statistically significant parameters for predicting RIET grade 3 or worse included esophageal volume that received ≥50 Gy (V50), esophageal volume that received ≥55 Gy (V55), and the use of concurrent chemotherapy according to univariate and multivariate logistic regression analyses.

Conclusion: This study demonstrates that the best predictive factors for severe early radiation induced esophageal toxicity are concurrent chemotherapy, and esophageal volumes ≥50 Gy and ≥55 Gy in non-small cell lung cancer treated with 3D-conformal radiotherapy.

Keywords: Dose–volume histogram, Lung cancer, Radiotherapy, Esophageal toxicity

♦Corresponding Author:
Maher Soliman, PhD, MD
Champollion Street, El-Khartoum Square, Azarita Medical Campus, Faculty of Medicine, Alexandria University, Alexandria 21526, Egypt
Tel: (+2) 03-4848280
Fax: (+2) 03-4848280
Email: maher.soliman@daad-alumni.de

Introduction

Worldwide, lung cancer is the leading cause of cancer death. In an attempt to improve radiotherapy outcome in locally advanced lung cancer, the combination of chemotherapy with radiotherapy has been investigated. The results revealed

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better local control and overall survival compared to radiotherapy alone.[1-3] However, this combination has resulted in more toxicity, which may lead to treatment interruptions and indirectly reduce the effect obtained by this combined modality.[1-3]

Early radiation induced esophageal toxicity (RIET) is one of the most common causes of treatment interruption during radiotherapy of lung cancer. Avoidance of esophageal irradiation during radiotherapy of lung cancer is impossible due to its long central course, as well as the large irregularly shaped and centrally located lung cancers and their frequent metastases to mediastinal lymph nodes.[4]

Several trials evaluated the impact of treatment interruption and overall treatment time on the outcome of radiation therapy for patients with non-small cell lung cancer (NSCLC) and found significantly poorer local control and survival with prolongation of overall treatment time.[5-7] Therefore, efforts should be exerted to define parameters that predict severe early RIET in advance to avoid treatment interruptions or breaks and improve local control and overall survival.

Multiple studies addressed a wide range of different dosimetric and clinical parameters to be correlated with early RIET in radiotherapy of NSCLC, with inconsistent results.[8-13] Therefore, we attempted, in this retrospective study, to identify risk factors associated with development of severe early RIET according to clinical and dosimetric parameters in NSCLC patients who presented to our tertiary center.

Materials and Methods

We retrospectively reviewed the records of 54 patients with histologically proven NSCLC treated with 3D-conformal radiotherapy (3D-CRT) at Alexandria Main University Hospital between January, 2008 and December, 2011. Inclusion criteria were: stage III disease, completed definitive treatment to doses ≥54 Gy, completed follow-ups for at least 6 months post-radiotherapy, and a retrievable treatment plan. The medical records of all patients were reviewed for history and physical examination, chest X-ray, chest computed tomography (CT) scan, and metastatic workup. Clinical parameters that included age, gender, WHO performance status, weight at presentation, weight loss over 6 months before diagnosis of lung cancer, chemotherapy received, RIET grade, RIET interval, last follow-up date, and status at last follow-up were recorded.

Patient treatment

A total of 33 (61.1%) patients received induction platinum-based chemotherapy, 7 (13%) received concurrent chemoradiotherapy (CRT), and 14 (25.9%) received only radiotherapy. The gross tumor volume (GTV) was defined based on the CT scan as the primary lung lesion and involved lymph nodes. We added a margin of 8 mm to generate the clinical target volume (CTV). Planning target volume (PTV) was created by the addition of 7 mm more to the CTV. All patients received a total dose of 54-66 Gy delivered in a conventionally fractionated regimen (1.8 –2.0 Gy/fraction/day).

Esophagus contouring

The original treatment plan and baseline CT scans for each patient were restored and imported to the treatment planning system (TPS). In each patient, the external surface of esophagus was contoured in each CT slice from the lower border of the cricoid cartilage to the gastro-esophageal junction by only one radiation oncologist (MS) for consistency, using the mediastinal windows (center: 30, width: 350 H.U.). We generated the dose-volume histograms (DVH) and recorded mean esophageal dose (Eso_mean), maximum esophageal dose (Eso_max), and esophageal volume (Vdose) that received doses of ≥20 Gy (V20), ≥30 Gy (V30), ≥40 Gy (V40), ≥50 Gy (V50), and ≥55 Gy (V55).

We determined the CT slices in which the total circumference received doses ≥20 Gy, ≥30 Gy, ≥40 Gy, ≥50 Gy, and ≥55 Gy. Then, by summing the slices through which the entire circumference received a certain dose together, we obtained the length of esophagus with the entire circumference that received pre-specified doses, namely EL20, EL30, EL40, EL50, and EL55. EL20 was the esophagus length through which the entire circumference received ≥20 Gy.

Radiation induced esophageal toxicity (RIET)

We assessed RIET by review of radiotherapy charts and medical files of the patients. Most were

seen weekly during radiotherapy, 4–6 weeks after completion of their course of irradiation, then 3, 6, and 12 months thereafter, with a median follow-up duration of 8.4 months. Radiation induced esophageal toxicity was scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0[14] as follows: grade 1 - symptomatic, but able to consume a regular diet; grade 2 - symptomatic with altered eating/swallowing (e.g., altered dietary habits, oral supplements) with IV fluids indicated <24 h; grade 3 - symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake), IV fluids, tube feedings, or total parenteral nutrition indicated ≥24 h; grade 4 - life-threatening consequences (e.g., obstruction, perforation); and grade 5 – fatal outcome. We defined RIET that occurred within 3 months from start of radiotherapy as early RIET and thereafter, late RIET. The maximum dysphagia score was taken into account as the total score in these multiple assessments. Patients who experienced early RIET grade ≥3 were considered to have an event.

Statistical analysis

Univariate binary logistic regression analyses were performed to evaluate the effect of each clinical and dosimetric variable on the occurrence of RIET (grade ≥3). Clinical parameters of sex (men vs. women), WHO performance status (0-1 vs. 2), weight loss over 6 months before the diagnosis (<5% vs. ≥5%), primary tumor location (upper- vs. middle- vs. lower-lobe), and use of chemotherapy (none vs. neoadjuvant vs. concurrent) were considered categorical variables using the first subset as an indicator. Continuous variables consisted of age, GTV and dosimetric parameters (V20, V30, V40, V50, V55, Eso_max, Eso_mean, EL20, EL30, EL40, EL50, and EL55).

Multivariate binary logistic regression model analysis using the forward step-wise method was performed to evaluate the association between clinical and dosimetric parameters to the development of severe RIET. As the dosimetric parameters correlate highly with each other, we have independently tested each dosimetric parameter with other clinical factors in multivariate analysis. All statistical tests were two-sided and performed using SPSS (v. 22) software (SPSS Inc., Chicago, IL, USA). A *P*-value of ≤0.05 was considered statistically significant.

Table 1. Patients' characteristics.

Variable	No.	%
Age (median)	60 years	(range: 40-84)
Gender		
Male	44	81.5
Female	10	18.5
GTV (median)	81.6	(range: 25.31-280.1)
Weight (median)	75	(range: 53-115)
WHO-PS		
0	8	14.8
1	31	57.4
2	15	27.8
Weight loss-6m		
<5%	39	72.2
≥5%	15	27.8
Clinical stage		
IIIA	18	33.3
IIIB	36	66.7
Histology		
SCC	29	53.7
AC	22	40.7
Other	3	5.6
Lobe		
Upper	23	42.6
Middle	14	25.9
Lower	17	31.5
Chemotherapy		
None	14	25.9
Neoadjuvant	33	61.1
Concurrent	7	13

GTV: Gross tumor volume; WHO-PS: WHO-performance status; Weight loss-6m: Weight loss over 6 months before diagnosis; SCC: Squamous cell carcinoma; AC: Adenocarcinoma

Results

Patients' characteristics

Table 1 summarizes the patients' characteristics. We treated 44 (81.5%) men and 10 (18.5%) women, with a median age of 60 years (range: 40–84). The median GTV was 81.57 cm^3 (range: 25.31-280.07). Patients had a median weight at presentation of 75 kg (range: 53-115), and approximately one-third had significant weight loss (5% or more) over 6 months before diagnosis. We noted that two-thirds of the patients had good performance status of 0-1 according to their WHO scores. The clinical stage was IIIA in 18 patients and IIIB in 36 patients. Approximately half had squamous cell carcinoma and 40.7% had adenocarcinoma. The primary tumor was located in

Table 2. Univariate analysis of dosimetric and clinical parameters that affected radiation induced esophageal toxicity (RIET).

Variable	SE	*P*-value	OR	95% CI
V20	0.030	0.237	1.037	0.977 - 1.100
V30	0.033	0.083	1.059	0.993 - 1.131
V40	0.030	0.055	1.059	0.999 - 1.123
V50	0.025	0.027	1.056	1.006 - 1.109
V55	0.024	0.024	1.057	1.007 - 1.108
EL20	0.136	0.374	1.129	0.864 - 1.475
EL30	0.168	0.642	1.082	0.777 - 1.505
EL40	0.129	0.703	1.050	0.816 - 1.353
EL50	0.102	0.961	1.005	0.823 - 1.227
EL55	0.121	0.666	1.054	0.831 - 1.337
Eso_Max	0.044	0.937	0.997	0.915 -1.085
Eso_Mean	0.045	0.120	1.073	0.982 - 1.173
Age	0.042	0.771	1.012	0.933 - 1.098
Sex	1.132	0.638	0.587	0.064 - 5.398
WHO-PS	0.926	0.389	0.450	0.073 - 2.766
Weight loss _5%	0.880	0.849	0.846	0.151 - 4.745
Neoadjuvant CTx	0.793	0.151	3.125	0.660 - 14.792
Concurrent CTx	0.926	0.024	8.062	1.314 - 49.462
Middle lobe	0.986	0.286	2.864	0.415 - 19.772
Lower lobe	0.976	0.406	2.250	0.332 - 15.236
GTV	0.007	0.258	0.992	0.978 - 1.006

SE: Standard error; OR: Odds ratio; CI: Confidence interval; V20: Percentage of esophageal volume (Vdose) that received ≥20 Gy; EL20: Esophagus length through which the entire circumference received ≥20 Gy; Eso_max: Maximum esophageal dose; Eso_mean: Mean esophageal dose; WHO-PS: WHO-performance status; Weight loss_ 5%: Weight loss over 6 months before diagnosis ≥5%; CTx: Chemotherapy; GTV: Gross tumor volume.

the upper lobe in 23 (42.6%), the middle lobe in 14 (25.9%), and lower lobe in 17 (31.5%) patients.

Radiation induced esophageal toxicity (RIET) events

Only 3 (5.6%) patients did not develop RIET. We observed grade 1 RIET in 21 (38.9%), grade 2 in 22 (40.7%), grade 3 in 6 (11.1%), and grade 4 in 2 (3.7%) patients. A total of 8 (14.8%) patients developed RIET grade 3 or higher and were considered to have an event.

Tables 2 and 3 summarize the results of univariate and multivariate analyses to evaluate the association between clinical and dosimetric parameters and occurrence of early RIET grade 3 or higher.

In univariate analyses, there was a significant association between the use of concurrent chemotherapy (*P*=0.024), V50 (*P*=0.027), and V55 (*P*=0.024) with early RIET grade 3 or higher. V30 and V40 tended to be significant. However, all other dosimetric and clinical variables showed no significant correlation with severe RIET.

Using multivariate logistic regression analysis, the same parameters - concurrent CRT (*P*=0.040), V50 (*P*=0.043), and V55 (*P*=0.032) were found to be the only predictive factors for severe RIET.

Discussion

Early RIET appears to be the primary cause of treatment interruptions in radiotherapy for NSCLC. The incidence of early RIET grade ≥3 following radiotherapy alone or combined CRT ranges from 5% to 53%.[15] It is difficult to compare the incidence, severity, and predictors of RIET between publications because of differences in scoring systems for RIET, endpoint definitions, radiotherapy techniques, doses and fractionation schemes, in addition to heterogeneous patient populations. In our study, we have observed that the incidence rate of early RIET grade 3 or worse was 14.8%, which supported the results of previous studies.[8,10,16]

Currently, there is no clear universal dosimetric parameter in the literature considered to be the fiducial cutoff value for severe early RIET. The commonly used DVH does not reflect spatial information on the dose distribution in a tubular structure such as the esophagus. Therefore, we have analyzed our data according to dose-volume, dose-length, and clinical

Table 3. Multivariate analysis of dosimetric and clinical parameters that affected radiation induced esophageal toxicity (RIET).

Variable	SE	*P*-value	OR	95% CI
V55	0.030	0.032	1.066	1.005 - 1.129
V50	0.030	0.043	1.062	1.002 - 1.126
V40	0.039	0.088	1.069	0.990 - 1.153
Age	0.064	0.861	0.989	0.872 - 1.121
Sex	1.380	0.379	0.297	0.020 - 4.435
Concurrent CTx	0.898	0.040	6.300	1.083 - 36.650
WHO-PS	1.196	0.920	1.128	0.108 - 11.764
Weight loss 5%	1.276	0.637	1.828	0.150 - 22.291
GTV	0.007	0.185	0.990	0.976 - 1.005

SE: Standard error; OR: Odds ratio; CI: Confidence interval; V20: Percentage of esophageal volume (Vdose) that received ≥20 Gy; CTx: Chemotherapy; WHO-PS: WHO-performance status; Weight loss_ 5%: Weight loss over 6 months before diagnosis ≥5%; GTV: Gross tumor volume.

parameters to investigate this issue.

In the present study, we found that V50 and V55 significantly predicted early RIET grade 3 or higher in multivariate forward step-wise logistic regression analysis. Consistent with our results, Kwint et al.[17] concluded that V50 was the most accurate predictor of grade ≥3 RIET for NSCLC patients treated with concurrent CRT. Zhu et al.[18] also reported that V50 significantly predicted RIET in multivariate analysis. Topkan et al.[19] retrospectively investigated data from 41 patients with stage III lung cancer treated with conventional fractionated irradiation and found only the V55 dosimetric parameter correlated with severe RIET. Zhang et al.[20] reported that V55 was the only dosimetric parameter that significantly predicted RIET in multivariate analysis. Hirota et al.[21] listed both V50 and V55 among factors that showed statistical correlations with RIET. Recently, Yu et al.[22] performed a systematic review of 28 publications that addressed radiation esophagitis in the treatment of lung cancer published between January 2009 and May 2015. The authors included V50 and V55 among the valuable parameters that predicted the occurrence of radiation esophagitis. Our data have supported this evidence. These two parameters are the most significant predictors of severe RIET.

In the current study, we found a significant association between the use of concurrent chemotherapy and the development of early RIET grade 3 or higher in multivariate analysis. This result agreed with several other studies that reported an association between concurrent chemotherapy and RIET.[16, 23-25] Kim et al.[16] retrospectively evaluated RIET grade 3 or higher in 124 patients treated curatively with 3D-CRT and reported an association between concurrent chemotherapy with the development of severe RIET. Singh et al.[23] found a significant relationship between concurrent chemotherapy and severe RIET. Bradley et al.[24] reported that concurrent CRT significantly correlated with RIET. In a study by Werner-Wasik et al.,[25] both the use of concurrent CRT and hyperfractionated radiotherapy were predictive factors for the development of RIET. In contrast to our findings, Maguire et al.[10] found no association between concurrent CRT and RIET on both univariate and multivariate analyses.

Unlike the intuitive expectation that the longer the length of the esophagus that receives irradiation, the higher the probability of RIET, in the current study, we have found no association between the esophageal length to dose amount and early RIET grade 3 or higher. Our results supported those by Maguire et al.[10] who evaluated the association between esophageal length and early RIET in 91 patients with NSCLC treated definitively with high-dose conformal radiation therapy at Duke University Medical Center. The authors reported that none of the dosimetric parameters analyzed significantly predicted grade 3 early RIET on univariate or multivariate analyses. Ahn et al.[9] showed an association between the length of the esophagus with 100% circumference that received ≥50-60 Gy and early RIET Grade 3 or higher according to univariate analysis, however this significance disappeared in multivariate analysis.

On the other hand, our results disagreed with Rosenman et al.[26] who found that early RIET could be predicted by the length of esophagus that received

40 or 60 Gy. Belderbos et al.[27] also reported that the most significant length parameter was the percentage of esophageal length that received 40Gy or more over full circumference on univariate analysis. Emami et al.[28] suggested that the tolerance dose for the probability of 5% complication within 5 years of treatment (TD5/5) for a volume of one-third was 60 Gy, whereas for two-thirds, it was 55 Gy, and 50 Gy for whole-organ irradiation.

To the best of our knowledge, this is the first study to evaluate clinical and dosimetric factors to predict the risk for development of RIET in locally advanced NSCLC patients treated with combined CRT in the Egyptian population. In conclusion, our report demonstrates that the best predictive factors for severe early RIET are concurrent CRT, V50, and V55 in NSCLC treated with 3D-CRT.

Conflict of Interest

No conflict of interest is declared.

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