Original Article
Middle East Journal of Cancer; July 2016; 7(3): 137-143

Predictive Factors of Radiation-Induced Lung Toxicity in Lung Cancer Patients: A Retrospective Study

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Abstract

Background: Radiation-induced lung toxicity is an important dose-limiting toxicity in lung cancer radiotherapy, for which there are no generally accepted predictive factors. This study seeks to identify risk factors associated with the development of severe radiation-induced lung 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 three dimensional-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 a treatment planning system. Lung dose–volume histograms and various dosimetric parameters were calculated. Univariate and multivariate logistic regression analyses were performed.

Results: The following grades of radiation-induced lung toxicity were observed in patients - grade 0: 17 (31.5%), grade 1: 5 (9.3%), grade 2: 13 (24.1%), grade 3: 15 (27.8%), and grade 5: 4 (7.4%). A total of 19 (35.2%) patients developed grade ≥3 and were considered to have an event. Univariate analysis showed that age, presence of chronic obstructive pulmonary disease and location of the primary tumor had significant associations with severe radiation-induced lung toxicity. Other dosimetric variables such as tumor side, histology, forced expiratory volume in 1 s, smoking, and gender showed no significant correlations with severe radiation-induced lung toxicity. Multivariate analysis showed that the presence of chronic obstructive pulmonary disease (P=0.001) and location of the primary tumor (P=0.010) were the only predictive factors for severe radiation-induced lung toxicity.

Conclusion: This study demonstrates that patients with chronic obstructive pulmonary disease and lower lung lobe tumors have a high risk of severe radiation-induced lung toxicity when treated with combined chemoradiotherapy. These easily obtained clinical factors should be considered when calculating the risk for radiation-induced lung toxicity.

Keywords: Dose–volume histogram, Lung cancer, Radiotherapy, Toxicity

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Middle East Journal of Cancer

Received: February 17, 2016; Accepted: April 12, 2016

Introduction

Radiation therapy for lung cancer is challenging because of the movement of the tumor with respiration and proximity of dose limiting critical organs such as the spinal cord, esophagus, and heart. In addition, most tumors are large and irregularly shaped. Despite the use of sophisticated radiotherapy techniques, irradiation of nearby normal tissues is unavoidable during radiotherapy treatments for lung cancer.[1]

One common, important dose-limiting toxicity in lung cancer irradiation is radiation-induced lung toxicity (RILT), which usually develops during or shortly within 6 months after radiotherapy.[1] Radiation-induced lung toxicity is a clinical diagnosis. Radiographic abnormalities without symptoms do not warrant intervention. Clinical symptoms range from mild shortness of breath to severe pulmonary dysfunction that requires oxygen therapy, hospitalization, and may be potentially fatal.[2] Thus, clinicians should be aware of its presentation; otherwise RILT can be easily confused with other lung diseases or tumor progression.

Despite several studies that suggested various dosimetric, clinical, and biological factors to be potential predictors of RILT, none has been shown to be superior.[3-11] Dosimetric parameters highly correlate to each other and may contribute more to providing a means of comparing treatment plans for their relative risks, rather than providing an absolute risk assessment.[3-8]

Clinical parameters such as performance status, age, sex, smoking history, and tumor site are associated with RILT.[12,13] Biological markers such as transforming growth factor-beta (TGF-β1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and IL-10 have been investigated. Currently no conclusive data exists for the predictive power of either clinical factors or biomarkers.[9,10]

This retrospective study attempted to identify risk factors associated with development of severe RILT in terms of clinical factors and dosimetric parameters in patients who presented to our tertiary center.

Materials and Methods

We reviewed medical and treatment records of 54 patients with histologically proven non-small cell lung cancer (NSCLC) who received 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 gray (Gy), complete follow-up for at least 6 months post-radiotherapy, and a retrievable treatment plan. The medical records of all patients were reviewed regarding history and physical examination, chest X-ray, chest computed tomography (CT) scan, and metastatic workup. Clinical parameters that included age, gender, smoking history, forced expiratory volume in 1 s (FEV1), and presence of chronic obstructive pulmonary disease (COPD), type of chemotherapy, RILT grade, RILT 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, and 14 (25.9%) received only radiotherapy. The gross tumor volume (GTV) was defined based on the CT scan of the primary lung lesion and involved lymph nodes. A margin of 8 mm was added 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 radiotherapy dose of 54 - 66 Gy in conventional fractionation.

Radiation-induced lung toxicity (RILT)

Radiation-induced lung toxicity was assessed by review of the patients' radiotherapy charts and medical files. Most patients were seen weekly during radiotherapy, 4-6 weeks after completion of their course of radiation, and for additional follow-up visits at 3, 6, and 12 months thereafter, with a median follow-up duration of 8.4 months.

We graded RILT according to the Common Terminology Criteria for Adverse Events

(CTCAE) version 3.0 14 as follows: grade 1 asymptomatic RILT diagnosed by radiographic findings only; grade 2: symptomatic RILT that did not interfere with daily activities; grade 3: symptomatic RILT that interfered with daily activities or required administration of oxygen; Grade 4: required assisted ventilation; and grade 5: resulted in death. The pre-treatment (baseline) dyspnea score was compared to the post-therapy score. We defined clinical RILT as an increase of dyspnea grade of one or more after radiotherapy. The time of occurrence of RILT was considered as the date of the maximum dyspnea score during or up to 6 months after radiotherapy. Patients who experienced CTCAE grade ≥3 (symptomatic, interfering with activities of daily living) were considered to have an event.

Lung segmentations

The original treatment plan and the baseline CT scans for each patient were restored and imported to the treatment planning system (TPS). Segmentation of the ipsi- and contralateral lungs was automatically generated using the lung window, excluding the large bronchovascular structures and GTV. The entire lung volume was obtained by union of both the ipsilateral (without GTV) and contralateral lungs. For each patient, we calculated the lung dose volume histogram (DVH) directly from the physical dose distribution. From the lung DVH, the following parameters were extracted: maximum dose (D_max), mean dose (D_mean), V5, V10, V20, V30, V40, and V45. We defined V20 as the percentage of CT-defined lung volume that received ≥20 Gy; the other V parameters were calculated in the same manner.

Statistical analysis

Univariate binary logistic regression analyses were performed to evaluate the effect of each clinical and dosimetric variable on the occurrence of RILT (grade ≥3). Clinical parameters of sex (men vs. women), presence of COPD (no vs. yes), FEV1 (≥2 vs. <2 L), smoking (smoker vs. former smoker vs. non-smoker), histology [squamous cell carcinoma (SCC) vs. adenocarcinoma (AC) vs. other], primary tumor location (upper- vs. middle- vs. lower-lobe), side (left hemithorax vs. right hemithorax) and use of chemotherapy (neoadjuvant vs. concurrent vs. none) were considered as categorical variables using the first subset as an indicator. Age and dosimetric parameters of V5, V10, V20, V30, V40, V45, D_max, and D_mean were analyzed as continuous variables.

Multivariate binary logistic regression model analysis using the forward stepwise method was performed (including all variables that attained or

Table 1. Patients' characteristics.

Variable	N	%
Age (median)	60 y	(range: 40-84)
Gender		
Male	44	81.5
Female	10	18.5
Smoking status		
Non-smoker	4	7.4
Smoker	28	51.9
Former smoker	22	40.7
COPD		
Yes	18	33.3
No	36	66.7
FEV1		
<2 L	28	51.8
≥2 L	26	48.2
Clinical stage		
IIIA	18	33.3
IIIB	36	66.7
Histology		
SCC	29	53.7
AC	22	40.7
Other	3	5.6
Grade		
G1	2	3.7
G2	27	50
G3	19	35.2
Unknown	6	11.1
Side of tumor		
Left	18	33.3
Right	36	66.7
Lobe		
Upper	23	42.6
Middle	14	25.9
Lower	17	31.5
Chemotherapy		
Neoadjuvant	33	61.1
Concurrent	7	13
None	14	25.9

COPD: Chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in 1 s; SCC:Squamous cell carcinoma; AC: Adenocarcinoma.

Table 2. Univariate analysis of dosimetric and clinical parameters that affect radiation-induced lung toxicity (RILT).

Variable	SE	*P*-value	OR	95% CI
Age	0.036	0.031	1.082	1.007 - 1.162
Sex	0.758	0.704	0.750	0.170 - 3.313
COPD	0.691	0.000	13.000	3.358 - 50.325
Middle lobe	0.858	0.680	1.425	0.265 - 7.657
Lower lobe	0.748	0.004	8.708	2.008 - 37.760
Side	0.599	0.687	1.273	0.393 - 4.117
Former smoker	1.091	0.314	0.333	0.039 - 2.829
Non-smoker	1.088	0.867	0.833	0.099 - 7.027
Adenocarcinoma	0.613	0.426	0.614	0.185 - 2.040
Other histology	1.465	0.737	1.636	0.093 - 28.904
FEV1	0.586	0.857	0.900	0.286 - 2.837
V5	0.016	0.397	1.014	0.982 - 1.047
V10	0.023	0.647	1.011	0.965 - 1.058
V20	0.041	0.555	1.024	0.946 - 1.109
V30	0.050	0.948	1.003	0.910 - 1.106
V40	0.060	0.901	0.993	0.883 - 1.116
V45	0.064	0.974	1.002	0.884 - 1.136
D_mean	0.072	0.605	1.038	0.902 - 1.194
D_max	0.167	0.076	1.345	0.970 - 1.865

SE: Standard error; OR: Odds ratio; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in 1 s; Vd: Percentage of lung volume that received ≥ the radiation dose in gray (Gy); D_mean: Mean dose; D_max: Maximum dose.

had a trend towards significance in univariate analyses) to evaluate the association between clinical and dosimetric parameters to the development of severe RILT. 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 to be statistically significant.

Results

Patients' characteristics

Patients' characteristics are summarized in Table 1. There were 44 (81.5%) men and 10 (18.5%) women who underwent treatment, with a median age of 60 years (range: 40–84). There were 4 (7.4%) non-smokers, 28 (51.9%) smokers, and 22 (40.7%) former smokers. Only 18 patients had documented COPD. The median baseline FEV1 was 2 L (range: 1–3.7). The clinical stage was IIIA in 18 patients and IIIB in 36 patients. Approximately half of the patients had SCC and 40.7% had AC. There were 36 patients that had a tumor in the right hemithorax and 18 with a tumor in the left hemithorax at presentation. The primary tumor was located in the upper lobe in 23 (42.6%) patients, in the middle lobe in 14 (25.9%), and in the lower lobe in 17 (31.5%).

There was no RILT (grade 0) reported in 17 (31.5%) patients, whereas 5 (9.3%) had grade 1, 13 (24.1%) had grade 2, 15 (27.8%) had grade 3, and 4 (7.4%) patients had grade 5 RILT. A total of 19 (35.2%) patients developed grade ≥3 and were considered to have an event.

Only age, presence of COPD and location of the primary tumor showed significant associations with severe RILT and D_max tended to be significant in univariate logistic regression analysis (Table 2). However, dosimetric variables, tumor side, histology, FEV1, smoking, and gender did not have significant correlations to severe RILT.

Multivariate logistic regression analysis showed that the presence of COPD (*P*=0.001) and location of the primary tumor (*P*=0.010) were the only predictive factors for severe RILT (Table 3).

Discussion

The incidence of clinically significant RILT occurred in approximately 5%–50% of patients irradiated for cancers of the lungs.[15] There were discrepancies in the reported incidences of RILT because of inconsistencies in the criteria used to define RILT using different scoring systems,

Table 3. Multivariate analysis of dosimetric and clinical parameters that affected radiation-induced lung toxicity (RILT).

Variable	SE	*P*-value	OR	95% CI
D_max	0.220	0.597	1.123	0.730 - 1.728
Age	0.055	0.981	1.001	0.899 - 1.115
COPD	0.905	0.001	19.317	3.277 - 113.858
Middle lobe	1.041	0.837	0.807	0.105 - 6.209
Lower lobe	0.953	0.010	11.611	1.794 - 75.159
Constant	0.816	0.001	0.068	

SE: Standard error; OR: Odds ratio; CI: Confidence interval; D_max: Maximum dose; COPD: Chronic obstructive pulmonary disease.

different end-points, heterogeneity in patient populations, and differences in treatment regimens and radiotherapy techniques.[16] In the present study, 35.2% of patients developed grade ≥3 RILT.

At present, there is no generally accepted means to accurately predict the individual patient's risk of developing RILT. Three-dimensional (3D)-treatment planning has provided investigators with easy tools like DVH, from which several dosimetric parameters can be calculated. Several studies suggested that different dosimetric parameters can predict RILT such as V20, V30, and mean lung dose.[3-6] Another group have reported that the volume of lung exposed to relatively low doses of radiotherapy (e.g., 5 Gy) might be more predictive for RILT than the V20-30.[17] We have included all these dosimetric variables in our analysis and found that none had any significant association to RILT in either univariate or multivariate analysis, except for D_max which has shown a trend towards significance only in univariate analysis. These dosimetric parameters do not consider regional dose distribution in the lung and regional differences in lung function, which may arise from diseases such as COPD. In addition, there is an extremely high correlation between the different parameters. Thus, the determination of the optimal dosimetric parameter for clinical use is difficult.[3-7]

In our cohort, we have identified COPD as a significant risk factor for severe RILT in multivariate analysis and determined that patients with COPD were 19.3 (95% CI: 3.3 – 113.9) times more likely to have severe RILT. This finding is intuitively logical. Patients with COPD with a lower pulmonary reserve are less likely to tolerate further pulmonary insults compared to those with healthy baseline pulmonary function.[18] Very few publications have addressed the association between pretreatment COPD and the development of clinical RILT in patients with lung cancer. Our results have supported those reported by Rancati et al.[5] who found in multivariate analysis that the presence of COPD (P=0.026) was a significant predictive factor for RILT. Shi et al.[19] analyzed 94 locally advanced NSCLC patients treated with concurrent chemoradiotherapy and reported an association between COPD and RILT (P<0.05).

Of note, in the current study, we have found that patients with primary tumors located in the lower lobes were 11.6 (95% CI 1.8 - 75.2) times more likely to have severe RILT compared to patients with upper lung lobe tumors. The mechanism for lower lung sensitivity is unknown. Possible factors include lung physiology, such as motion and volume differences in the lower lobes.[13] It has been found that some regions of the lungs have greater functional importance. In patients with healthy lungs, the ventilation perfusion ratio reveals that gas exchange is better at the bases of the lungs compared to the apices. For lung cancer patients with COPD, emphysema preferentially affects the apical lungs; therefore the lung bases may be even more important for respiration. In addition, the lower lung demonstrates more motion than the upper lung, which may not be accurately accounted for in the treatment planning DVHs.[13] Three-dimensional-treatment planning information parameters provide some information regarding the distribution of this damage but do not take into account the physiologic distribution of functional lung tissue.[13] A radiotherapy portal treats a mobile

tumor with a margin of normal lung tissue. As tumor motion increases, port margins are increased to account for this movement and subsequently increasing the treated amounts of lung tissue near the GTV.[20] Increased quantities of functional lung treated at a higher dose increases damage and may result in additional nonfunctioning gas-exchange units.[21]

Consistent with the current study results, Yamada et al.[22] found an association between lower lung field and a 70% incidence of RILT compared with 20% for other sites ($P<0.01$). Multivariate analysis revealed a significant relationship between radiation site and the risk of RILT. Graham et al.[3] conducted univariate analysis and found a significant association between the primary tumor location and the development of RILT. Bradley et al.[12] found that the best derived model to predict RILT was a two-parameter model that consisted of mean lung dose and tumor location. Similar to our results, Hope et al.[13] reported that lower lobe tumor location was the most highly correlated parameter with RILT on univariate analysis (rho = 0.24). This finding agreed with Yorke et al.[23] who observed a significant correlation with lower lung dosimetric parameters as predictive of RILT compared to upper lung dosimetric parameters.

In this study, there was no correlation between chemotherapy and RILT. This could be due to the small number of patients that received concurrent chemoradiotherapy in our series. Consistent with the current study results, Inoue et al.[24] retrospectively evaluated 191 patients and reported that chemotherapy variables (chemotherapy use, radiotherapy timing, and use of mitomycin) did not correlate with the incidence of severe RILT, even in univariate analysis.

To the best of our knowledge, this is the first study to evaluate clinical and dosimetric factors to predict the risk for RILT development in locally advanced NSCLC patients treated with combined chemoradiotherapy in an Egyptian population. In conclusion, our report demonstrates that patients with COPD and lower lung lobe tumors have a high risk of severe RILT when treated with combined chemoradiotherapy. These easily obtained clinical factors should be considered when calculating the risk of RILT.

Conflict of Interest

No conflict of interest is declared.

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