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Risk factors of radiation pneumonitis in patients with NSCLC treated with concomitant chemoradiotherapy—Are we underestimating diabetes?—Turkish oncology group (TOG)/Lung cancer study group

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Abstract

Introduction: To evaluate the clinical and dosimetric parameters that increase the risk of radiation pneumonitis (RP) in locally advanced non-small cell lung cancer (NSCLC) patients treated with concomitant chemoradiotherapy of nationwide multicentric data analysis.

Methods: All data of 268 patients who underwent definitive chemoradiotherapy were retrospectively collected from eight institutes participating in this study. Patient, tumor and treatment-related factors and dosimetric parameters were analyzed for grade ≥2 RP. The toxicity scoring system of The Radiation Therapy Oncology Group used for grading the severity of pneumonitis. A relationship with the risk of RP with potential predictive factors were evaluated by univariate and multivariate analyses. A recursive partition analysis (RPA) was applied to stratify patients according to the risk of developing RP.

Results: There were 90 (33.6%) patients who had grade ≥2 RP. The median time to pneumonitis after treatment was 4 months (range:1-6 months). In univariate analysis, diabetes mellitus (DM), use of cisplatin/etoposide, total and daily radiotherapy (RT)

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fraction dose, the planning target volume (PTV) size, mean lung dose, V5, V10 and RT technique were associated with the development of pneumonitis. In multivariate analysis, only DM ($P = 0.008$) was found to be independent risk factors for RP. According to RPA, the risk of developing RP was highest in patients with DM.

Conclusions: In our study, besides the known dosimetric factors, DM was found to be the most important risk factor causing RP development in multivariate analysis and RPA. The risk is tripled compared to patients without DM.

KEYWORDS

Diabetes Mellitus, dose-volume histogram, lung cancer, radiation pneumonitis, RT

1 | INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers and often occurs with locally advanced disease at the time of diagnosis.[1] Radiotherapy (RT) is one of the primary treatment modality in these patients.[2] It is also well known that the concurrent administration of chemotherapy (CT) with RT improves survival and local control in patients.[3] However, the lung is a highly radiosensitive organ and radiation-induced lung toxicity is one of the most important dose-limiting side effects of thoracic irradiation.[4] Radiation pneumonitis (RP) is defined as an acute inflammatory disease that occurs as damage caused by radiation in normal lung tissue. Usually, it is seen in the first 6 months after thoracic irradiation and the incidence is between 13% and 37%.[5,6]

Currently, radiation-related side effects have been successfully minimized by sophisticated RT techniques; however, we still encounter with RP.[7,8] After defining some specific dosimetric parameters with the common use of three-dimensional conformal radiotherapy (3D-CRT) planning systems, the risk of developing RP has become better predictable.[9-11] In many studies, the mean lung dose (MLD) and V20 (lung volume receiving ≥20 Gy) were demonstrated as predictive factors.[6,9-11] Also, it has been reported that several factors such as various chemotherapeutic agents and concomitant use of them with RT, treatment and patient-related factors increase the risk of RP.[12,13]

In the current study, it was aimed to investigate the predictive factors that are associated with the risk of grade ≥2 RP in patients with locally advanced NSCLC treated with concurrent chemoradiotherapy in our country, and to show whether it differs from the literature.

2 | MATERIALS AND METHODS

2.1 | Patient population and data collection

Between 2009 and 2015, a total of 268 patients with locally advanced non-small cell lung cancer (LA-NSCLC) who underwent definitive concurrent CT with RT at eight different oncology centers in our country were included in this study. The inclusion criteria were as follows: (a) All patients were diagnosed with histologically confirmed NSCLC; (b) they received concurrent platinum-based CT regimens with RT; (c) the RT was delivered with 3D-CRT or Intensity Modulated Radiation Therapy (IMRT) technique and (d) the patients had a Karnofsky performance status (KPS) score ≥70%. Patients with small cell lung cancer, patients with metastatic disease or patients who received postoperative RT were excluded from the study. The medical records and treatment data of all patients were obtained from archived files and evaluated retrospectively. Since this study was retrospective and multicentric, approvals of the institutional review boards of participating centers were obtained.

The factors that are considered to be relevant to the risk of developing RP were examined in three different groups.

1. *Patient-related risk factors:* age, gender, performance status, smoking history and comorbid disease, such as chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM) and collagen vascular disease (CVD)
2. *Tumor-related risk factors:* stage, tumor localization, tumor size and histology
3. *Treatment-related risk factors:* CT scheme, total and fractionated RT doses, RT technique and dose volume histogram (DVH) parameters [clinical target volume (CTV), planning target volume (PTV) and, the percentage of total normal lung volume receiving 5, 10, 20 Gy and MLD].

2.2 | Radiotherapy and CT

Patients were immobilized in the supine position with their arms above their heads. The planning computed tomography (CT) scans were performed between 3 and 5 mm slice thicknesses covering the entire thorax in the treatment position.

Primary tumor and nodal involvement visualized on CT and/or PET/CT were identified as the gross tumor volume (GTV) and it was contoured by fusion with PET/CT in the

77% of patients. The clinical target volume was defined as GTV plus 6-8 mm. The PTV was generated by adding a 1-1.5 cm margin to the CTV, according to each center's planning protocol. Elective nodal irradiation was not performed in any patients. RT was delivered either with a 3D-CRT or with the IMRT technique and was administered once daily five times a week in the conventional fraction. The total irradiation dose (median: 61.2 Gy, ranged from 50 to 66.6 Gy) prescribed to 95% of the PTV.

None of the patients were treated by induction CT. All patients received platinum-based concurrent chemoradiotherapy. The CT regimen was selected according to each center's clinical protocol.

In the assessment of the dosimetric parameters, PTV, CTV volumes, MLD and the percentage of total normal lung volume receiving 5-10-20 Gy was obtained from each patient's lung DVH.

2.3 | Determination of RP

During chemoradiotherapy, patients were followed up weekly. Later, the first evaluation of the patient was performed 4-6 weeks after completion of RT and monitoring was continued every 3 months during the first 2 years. Follow-up evaluations were performed with physical examination and thorax CT or PET/CT and routine blood tests. Pneumonitis was diagnosed and graded according to the radiological findings and clinical symptoms in the first 6 months after treatment. If viral or bacterial pneumonia was suspected, pulmonology consultation was requested for differential diagnosis. Since the radiation oncologists in our country prefer to use the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) scoring system based on both clinical and radiological findings in the grading of RP, we used this grading system for evaluation.[14] Grade ≥2 pneumonitis was considered to be a significant event and the main outcome.

2.4 | Statistical analysis

The relationship between the development of RP and the potential clinical and dosimetric factors described above was tested with univariate and multivariate analyses. In addition, a recursive partition analysis (RPA), a statistical method that creates a decision tree according to predictive factors was used to establish risk groups. All the variables with a significance level ≤0.05 in the univariate analysis were included for the RPA. The time of RP appearance was estimated by the Kaplan-Meier method. The statistical analysis was performed using SPSS version 20 for Windows (IBM Corp.). A $P \leq 0.05$ was considered to be significant.

3 | RESULTS

3.1 | Patient, tumor and treatment characteristics

The median age was 60 years (range, 31-83 years) and 89% of the patients were male. All patients had at least 6 months of follow-up. Comorbid diseases were COPD in 75 (28%) patients, DM in 33 (12.3%), patients and CVD in 6 (2.2%) patients. The distribution of patients, according to the stage was as follows: 7 in stage IIA, 10 in IIB, 171in IIIA and 80 in IIIB.

Most of the patients (38.4%) received carboplatin (AUC2) and paclitaxel (40 mg/m^2)/weekly and 31.3% of the patients received cisplatin (50 mg/m^2 D1, D8) and etoposide (50 mg/m^2 D1-D5)/28 days. The RT dose was >60 Gy in 60% of patients. Median CTV and PTV volumes were 263 cc. (range, 22.4-1700 cc) and 532.5 cc. (range, 74.8-2275 cc), respectively. The median value of MLD was 16 Gy and median doses of the lungs V5-V10-V20 were 54.5%, 42% and 28%, respectively. Patient, tumor and treatment characteristics are shown in Table 1.

3.2 | RP and predictive factors

The median occurrence time for pneumonitis after treatment was 4 months (range: 1-6 months). Ninety patients (33.6%) developed grade ≥2 RP. Of these, 68 were grade 2, 18 were grade 3, 1 was grade 4. Fatal pneumonitis (grade 5) was seen in three patients (%1.1). All of these three cases were treated with the IMRT technique, the total RT dose was >60 Gy and the irradiated volumes (PTV) were larger. MLD was >16 Gy in two patients. In addition, one of them had DM and two of them had COPD.

In univariate analysis, among the patient-related risk factors, only DM was associated with RP ($P < 0.001$). As treatment-related risk factors, use of cisplatin/etoposide as CT regimen ($P = 0.011$), the total radiation dose >60 Gy ($P < 0.001$), the daily fraction dose of 1.8 Gy ($P < 0.001$), the PTV volume >532 cc. ($P = 0.020$), MLD >16 Gy ($P = 0.020$) V5 >54.5% ($P = 0.039$) and V10 >42% ($P = 0.020$) were significantly correlated with the risk of RP. In addition, patients treated with 3D-CRT technique had an increased risk for RP compared with IMRT ($P = 0.039$). The results are shown in Table 2.

When we compared the mean values of the dosimetric factors between the groups with and without RP, there were significant differences for total radiation dose ($P = 0.020$), V5 ($P = 0.032$) and V10 ($P = 0.030$) values. Also, CTV and PTV volumes were found to be significantly larger in the group developing RP (Table 3).

Important predictive factors in univariate analysis were assessed by multivariate analysis. Only DM ($P = 0.008$) was found to be significant as a predictive factor. The risk of RP in diabetic patients was three times higher. In addition, a total radiation dose ($P = 0.07$), PTV volume ($P = 0.061$) and the

TABLE 1 Patient and tumor characteristics (n = 268)

Characteristics	n (%)
Sex	
Male	238 (88.8)
Female	30 (11.2)
Age (year)	
Median (range)	60 (31-83)
<60	122 (45.5)
≥60	146 (54.5)
Karnofsky performance status	
≥80	245 (91.4)
<80	23 (8.6)
Smoking	
Nonsmoker	32 (11.9)
Ex-smoker	206 (76.9)
Current smoker	30 (11.2)
Chronic obstructive pulmonary disease	
Yes	75 (28)
No	193 (72)
Diabetes mellitus	
Yes	33 (12.3)
No	235 (87.7)
Collagen vascular disease	
Yes	6 (2.2)
No	262 (97.8)
Histology	
Squamous cell carcinoma	179 (66.8)
Adenocarcinoma	80 (29.9)
Other	9 (3.4)
Stage	
IIA	7 (2.6)
IIB	10 (3.7)
IIIA	171 (63.8)
IIIB	80 (29.9)
Tumor size	
<5 cm	140 (52.2)
≥5 cm	128 (47.8)
Tumor location	
Right lung	167 (62.3)
Left lung	101 (37.7)
Tumor lobe location	
Upper	145 (54.1)
Middle	56 (20.9)
Lower	67 (25)
Chemotherapy agents	
Cisplatin (weekly)	64 (23.9)
Carboplatin/Paclitaxel	103 (38.4)
Cisplatin/Etoposide	84 (31.3)
Other	17 (6.3)
Radiotherapy technique	
3D-CRT	140 (52.2)
IMRT	128 (47.8)
Radiation dose (Gy)	
Median (range)	61.2 (45-73.8)
≤60 Gy	108 (40.3)
>60 Gy	160 (59.7)
Fractionation	
1.8 Gy	136 (50.7)
2 Gy	132 (49.3)
Clinical target volume (cc) median (range)	263 (22.4-1700)
Planning target volume (cc) median (range)	532.5 (74.8-2275)
Mean lung dose (Gy) Median (range)	16 (2.8-54)
Lung volume receiving ≥5 Gy (%) median (range)	54.5 (9-99)

Abbreviations: 3D-CRT, 3 dimensional conformal radiotherapy; IMRT, intensity modulated radiation therapy.

RT technique ($P = 0.088$) showed a tendency toward statistical significance (Table 4).

3.3 | RPA for RP risk

To identify patients who are more likely to have a significant risk of developing RP, we used the decision tree (RPA). All patients were classified into five risk groups according to RPA (Figure 1)

. Group 1 consisted of patients with DM and had the highest risk for the development of pneumonitis (60.6%). Group 2 consisted of nondiabetic patients who received >60 Gy with 3D-CRT technique and the risk of developing RP was 46.1% in this group. Groups 3 and 4 were intermediate risk groups. They consisted of nondiabetic patients who received ≤60 Gy and MLD ≥ 16 Gy or received >60 Gy with IMRT and the risk of RP is 27.5% and 26.3%, respectively. Group 5 had nondiabetic patients who received <60 Gy and MLD <16 Gy and had a low risk of RP (7.1%) (Table 5).

4 | DISCUSSION

RP is one of the most frequently encountered acute side effects after thoracic radiation, even today; despite the widespread use of modern RT techniques.[7,8] Generally, grade

TABLE 2 Univariate analysis of clinical and dosimetric factors that are considered to increase the risk of RP development[a]

Variable	RP < grade 2 (n = 178) n (%)	RP ≥ grade 2 (n = 90) n (%)	*P* value
Diabetes mellitus			
Yes	13 (39.4)	20 (60.6)	<0.001
No	165 (70.2)	70 (29.8)	
Tumor location			
Left	74 (73.3)	27 (26.7)	0.065
Right	104 (62.3)	63 (37.7)	
Chemotherapy agents			
Cisplatin (weekly)	45 (70.3)	19 (29.7)	
Carboplatin/ Paclitaxel	76 (73.8)	27 (26.2)	0.011
Cisplatin/ Etoposide	44 (52.4)	40 (47.6)	
Others	13 (76.5)	4 (23.5)	
Radiotherapy technique			
3D-CRT	85 (46.2)	55 (39.3)	0.039
IMRT	93 (53.8)	35 (27.3)	
Total radiation dose			
≤60 Gy	85 (78.7)	23 (21.3)	<0.001
>60 Gy	93 (58.1)	67 (41.9)	
Fractionation			
1.8 Gy	77 (56.6)	59 (43.4)	<0.001
2 Gy	101 (76.5)	31 (23.5)	
Planning target volume (cc)			
<532	98 (73.1)	36 (26.9)	0.020
≥532	80 (59.7)	54 (40.3)	
Mean lung dose			
<16 Gy	96 (73.3)	35 (26.7)	0.020
≥16 Gy	82 (59.9)	55 (40.1)	
V5, (%)			
<54.5%	97 (72.4)	37 (27.6)	0.039
≥54.5%	81 (60.4)	53 (39.6)	
V10, (%)			
<42%	96 (73.3)	33 (26.7)	0.020
≥42%	82 (59.9)	55 (40.1)	

Abbreviations: 3D-CRT, 3 dimensional conformal radiotherapy; IMRT, intensity modulated radiation therapy; RP, radiation pneumonitis.

[a]Only values that are statistically significant or have tendency toward significance are shown.

1-2 RP is more common, but in severe cases, the patient's quality of life may be deteriorated and sometimes it can even be fatal. The current study showed that the frequency of severe RP in our patients was 33.6% and the mortality rate was 1.1%.

TABLE 3 Comparing the mean values of the dosimetric factors between the groups with and without RP

Factors	Mean (SEM) RP	Mean (SEM) No RP	*P* value
Dose (Gy)	62.64 (0.41)	61.62 (0.22)	0.020
CTV volume (cm^3)	383.14 (29.57)	302.83 (29.57)	0.020
PTV volume (cm^3)	652.00 (41.99)	560.08 (23.74)	0.041
V5 (%)	56.2 (1.9)	51.1 (1.3)	0.032
V10 (%)	45.2 (1.72)	40.8 (1.16)	0.030
V20 (%)	29.9 (1.06)	27.7 (0.84)	0.129
Mean lung dose (Gy)	17.2 (0.6)	15.8 (0.47)	0.088

Abbreviations: RP, radiation pneumonitis; SEM, standard error mean.

TABLE 4 Multivariate analysis of clinical and dosimetric risk factors-associated grade ≥2 RP

Variable	*P* value	HR (95% CI)
Diabetes mellitus	0.008	3.097 (1.352-7.093)
Chemotherapy agent	0.582	—
Radiotherapy technique	0.088	0.579 (0.309-1.085)
Total radiation dose	0.070	1.918 (0.948-3.880)
Fractionation	0.337	1.424 (0.692-2.929)
Planning target volume (cc)	0.061	1.748 (0.976-3.131)
Mean lung dose	0.316	1.530 (0.666-3.514)
V5 (lung volume receiving ≥5 Gy)	0.942	1.031 (0.452-2.351)
V10 (lung volume receiving ≥10 Gy)	0.251	1.694 (0.689-4.167)

Abbreviation: RP, radiation pneumonitis.

4.1 | Patient and tumor-related factors

Until now, many studies have been conducted to investigate the factors that increase the risk of RP.[9-11,13,15,16] In general, it has been reported that clinical factors such as age, gender, tumor location, stage, performance status, smoking, pretreatment poor pulmonary function affected RP development.[12,13] However, none of these were found to be associated with RP in our study. Only the presence of DM, which was one of the clinical parameters, significantly affected the risk of developing RP. In several studies conducted to date have reported DM as an important predictive factor for the development of radiation-induced toxicity in several cancers. Some studies demonstrated that the incidence of radiation-induced genitourinary and gastrointestinal toxicities was higher in patients with diabetes after prostate cancerRT. Besides, studies on breast and colorectal cancer patients reported that radiation-related toxicities were more common in diabetic patients.[17-21] However, few

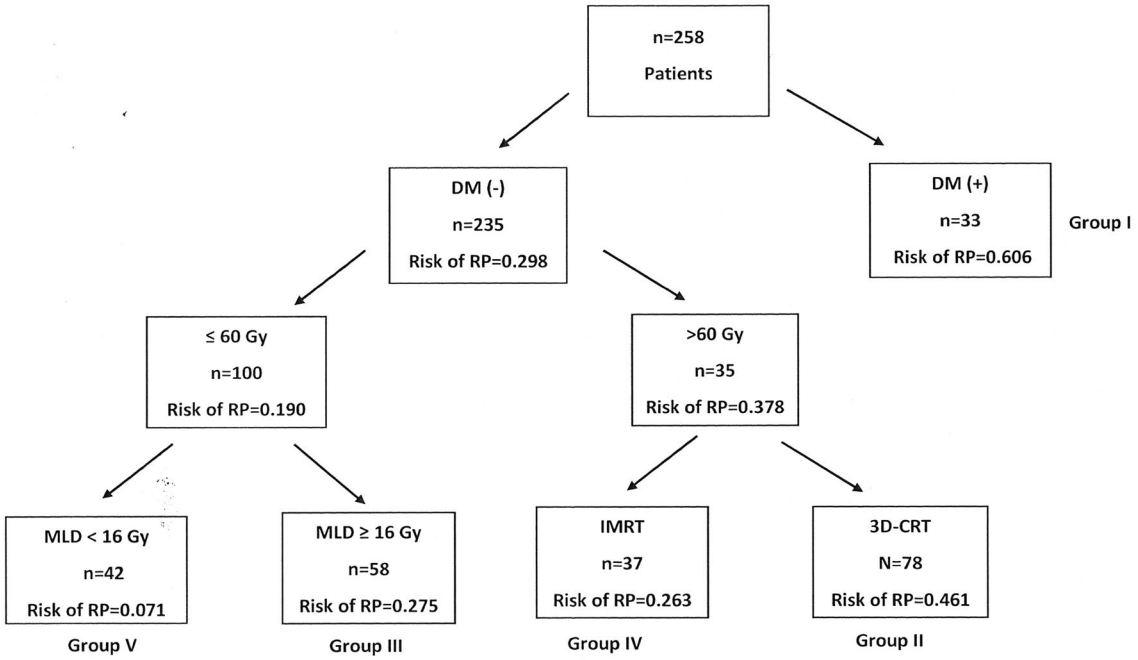

FIGURE 1 Recursive partitioning analysis (RPA) trees for the 268 patients. Patient and treatment characteristics were evaluated as potential split points. The risk of developing radiation pneumonitis (RP) was used as the endpoint and five prognostic groups were defined from eight terminal nodes. DM, diabetes mellitus; MLD, mean lung dose; IMRT, intensity modulated radiation therapy; 3D-CRT, 3 dimensional conformal radiotherapy

TABLE 5 Risk group splits according to the results of recursive partitioning analysis

Risk group	Number of patients	Risk of RP (%)
Group I		
DM (+)	33	60.6
Group II		
DM (−), dose >60 Gy, 3D CRT	78	46.1
Group III		
DM (−), dose ≤60 Gy, MLD ≥ 16 Gy	58	27.5
Group IV		
DM (−), dose >60 Gy, IMRT	37	26.3
Group V		
DM (−), dose ≤60 Gy, MLD < 16 Gy	42	7.1

Abbreviations: 3D-CRT, 3 dimensional conformal radiotherapy; DM, diabetes mellitus; IMRT, intensity modulated radiation therapy; RP, radiation pneumonitis.

studies in the literature show the association between the risk of developing RP and DM. In recently published three studies have been reported that DM increased the risk of RP by 2-fold in lung cancer patients treated with both conventional and stereotacticRT.[22-24] In the latest study, the relationship between DM, HbA1c and fasting glucose level and RP was shown for the first time and the incidence of grade ≥3 RP was reported to be 2-fold higher in diabetic patients than in nondiabetic patients.[25] In our cohort, it was observed that the RP risk increased 3-fold in diabetic patients. In addition, according to RPA analysis, the risk of RP development in patients with DM increased significantly, regardless of the dosimetric factors.

Today, DM is a common chronic endocrine disease that affects the entire body and is associated with high morbidity and mortality worldwide. Prolonged diabetes causes microvascular and macrovascular bed damage, leading to major complications such as nephropathy, retinopathy, neuropathy and cardiovascular disease.[17,26] Recently, lung tissue has also been identified as one of the target organs for diabetes in several studies.[26,27] Diabetes-induced tissue damage and RP development have a similar pathophysiological process. Inflammation, endothelial deterioration, oxidative stress and disruption of microvascularity play a major role in the development of both. After RT, successful repair of damage to normal tissues largely depends on the vascularity of the irradiated organ. However, diabetes-related microvascular obstructive disorders, capillary hyalinization, arteriolar obliteration and atherosclerosis can reduce perfusion in tissues. Chronic hyperglycemia also contributes to tissue ischemia by altering the viscosity of the blood. Furthermore, glycosylated hemoglobin exhibits greater affinity for oxygen thereby further reducing oxygen delivery rates in the compromised tissues.[26,27] As a result, these changes delay or inhibit the repair of radiation damage in pulmonary tissues and exacerbate the harmful effects of RT.

4.2 | Treatment-related factors

Among the dosimetric parameters that increase the risk of developing RP, MLD and V20 are the most well-known. Both Tsujino et al and Graham et al reported that the V20 value was the most significant risk factor associated with grade ≥2 RP in univariate and multivariate analyses.[9,10] Similarly, Kwa et al and Seppenwoolde et al have shown that MLD was associated with RP.[28,29] In our series, we found that MLD, V5 and V10 values were significantly correlated with grade ≥2 RP development in univariate analysis.

Another important factor that increases RP risk is the selected CT regimen. Currently, concurrent treatment is the standard management for the locally advanced disease but there are many agents used concurrently with RT in the treatment of lung cancer. The meta-analysis by Palma et al was showed that there was a significant relationship between the selected concurrent CT regimen and RP. They reported that the risk of grade ≥2 RP was increased by 3.3-fold in patients receiving concurrent carboplatin and paclitaxel with RT compared to the use of cisplatin and etoposide with RT.[12] In another study, it was reported that patients treated with concurrent docetaxel and cisplatin regimens have a higher rate grade ≥3 RP (18.4%) than concurrent cisplatin-vinorelbine regimens (9.5%).[30] In our study, it was observed that the risk of developing RP was significantly higher in patients treated with 4 weekly cisplatin-etoposide and RT. There might be several reasons; first, the dose of cisplatin-etoposide was higher than the weekly administration, second the total RT dose was >60 Gy in 83% patients and third, CTV and PTV volumes were larger in this group of patients. Therefore, there might be a complex interaction between them.

RT technique used during the treatment was another risk factor for RP. The 3D-CRT technique has increased the risk of grade ≥2 RP compared to IMRT in our study. Nowadays, IMRT is a more preferred technique, because of its high conformity index and its ability to protect normal tissues more than 3D-CRT. Shi et al and Yom et al reported that the incidence of severe RP was significantly lower in patients treated with concurrent CT and IMRT.[8,16] However, in our study RPA analysis showed that for nondiabetic patients even if the IMRT technique was used, 26.3% of the patients developed RP, if the RT dose was >60 Gy.

There are some limitations to be mentioned in our study. First, this is a retrospective study; second since it is a multicentric study, the data are heterogeneous concerning the patient characteristics, CT regimen, RT technique and dose, etc. [Correction added on 6 July 2020, after first online publication: the preceding sentence has been corrected.] Particularly the contouring of the volumes and the planning of the treatment were made by different physicians/physicists and there was no central revision. However, each participating center was well experienced in the treatment of lung cancer. Data on pretreatment pulmonary function tests were not available. Additionally, investigating a large number of variables may have increased the risk of type I statistical error. Despite all these, we believe that there were enough patients in our study, reflecting the validity of our findings in our population.

5 | CONCLUSION

In our study, similar to the literature, several significant factors for development of RP are defined including concurrently ciplatin/etoposide use, planning technique (3D-CRT or IMRT), PTV volume, total radiation dose, fraction size and some dosimetric parameters. In addition, the presence of DM was found to be the most important risk factor increasing RP development both in multivariate analysis and risk classification system. The risk of RP in diabetic patients was 3-fold higher than in those without diabetes. Besides well-known dosimetric factors, DM has recently been described as an important risk factor affecting the development of radiation-induced toxicity in many publications. Prospective studies with more patients are needed in this topic. Nevertheless, in patients with diabetes who will undergo concurrent chemoradiotherapy for lung cancer should be more careful and closely monitored during planning and treatment.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

AUTHOR CONTRIBUTIONS

This study was carried out by Turkish Oncology Group/Lung Cancer Study Group. Designed the study: Dincbas FO, Ergen SA, Kılıc D, Collected data:Yucel B, Kıraklı EK, Akyurek S, Altınok P, Ulger S, Etiz D, Yılmaz U, Ergen SA, Analyzed data: Ergen SA, Dincbas FO, Interpreted results: Dincbas FO, Ergen SA, Akyurek S, Drafted article: Ergen SA, Dincbas FO, Akyurek S, Bozcuk H. All authors have revised and approved this work.

ETHICS

Since retrospective studies were not included within "the regulations of ethics committee of non-invasive clinical researches" of the year 2016; each participating center has been taken approval from its own institutional review boards for using archive data.

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