

Diabetes mellitus is a predictive factor for radiation pneumonitis after thoracic radiotherapy in patients with lung cancer

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Purpose: We evaluated the effects of diabetes mellitus (DM) and DM-related serologic factors (HbA1c and fasting glucose) on the development of radiation pneumonitis in patients with lung cancer.

Methods: We retrospectively analyzed the clinical data of 123 patients with lung cancer treated with radiotherapy. Radiation pneumonitis was scored according to the toxicity criteria of the Radiation Therapy Oncology Group. We used binary logistic regression analysis to find significant predictive factors for the development of grade ≥ 3 radiation pneumonitis.

Results: On univariable analysis, V20, mean lung dose, DM, HbA1c, and fasting glucose level were significantly associated with the development of grade ≥ 3 radiation pneumonitis. On multivariable analysis, V20, mean lung dose, DM, HbA1c, and fasting glucose level remained significant predictive factors for grade ≥ 3 radiation pneumonitis. The incidence of grade ≥ 3 radiation pneumonitis was 44.4% in patients with DM and 20.7% in patients without DM. The incidence of grade ≥ 3 radiation pneumonitis was 12.7% for HbA1c level $\leq 6.15\%$ and 41.5% for HbA1c level $>6.15\%$. The incidence of grade ≥ 3 radiation pneumonitis was 17.2% for fasting glucose level ≤ 121 mg/dL and 35.5% for fasting glucose level >121 mg/dL.

Conclusion: DM, HbA1c, and fasting glucose level are significant predictive factors for the development of grade ≥ 3 radiation pneumonitis in patients with lung cancer. Patients with DM, patients who have HbA1c $>6.15\%$, and patients who have fasting glucose >121 mg/dL should be treated with greater caution.

Keywords: lung cancer, radiotherapy, radiation pneumonitis, diabetes mellitus

Introduction

Radiotherapy (RT) is a fundamental treatment modality in the management of lung cancer. Definitive RT with concurrent chemotherapy is the standard treatment for patients with unresectable locally advanced lung cancer. In addition, radiosurgery has been recently used in patients with resectable early-stage lung cancer.¹ Radiation pneumonitis is one of the most common toxicities following thoracic RT, and the incidence of symptomatic radiation pneumonitis is estimated to be in the range of 15–45%.^{2–5} Because radiation pneumonitis can significantly compromise the quality of life and can reduce the overall survival of patients with lung cancer who received RT,⁶ several studies have reported predictive factors for radiation pneumonitis.^{3,7–10}

Several investigators have reported diabetes mellitus (DM) as a significant predictive factor for radiation toxicities in several cancers. In prostate cancer patients, greater

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incidence of radiation-induced gastrointestinal and genitourinary toxicities was seen in patients with DM.^{11–15} In breast and colorectal cancer, studies have also reported that radiation toxicities were more common in patients with DM than patients without DM.^{16,17} However, studies investigating the correlations between DM and radiation toxicities in lung cancer patients are rare. One preliminary study, published only in abstract form, reported that DM can be associated with the development of radiation pneumonitis in lung cancer patients.¹⁸ In People's Republic of China, Zhou et al retrospectively analyzed the clinical data of 332 lung cancer patients and reported that the incidence of radiation pneumonitis was significantly higher in the DM group than in non-DM group.¹⁹ However, Zhou et al's paper is written in Chinese, so we were unable to analyze the full text. Yet, it remains unclear whether DM is associated with the development of radiation pneumonitis in patients with lung cancer.

In this study, we evaluated the effects of DM and DM-related serologic factors (HbA1c and fasting glucose) on the development of radiation pneumonitis in patients with lung cancer.

Materials and methods

Inclusion criteria were histologically proven primary lung cancer, receipt of RT with or without chemotherapy, receipt of a total RT dose ≥ 50 Gy, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3 , no prior thoracic irradiation, no previous or concurrent illness that would compromise the completion of RT, and follow-up period ≥ 6 months. Patients who underwent radiosurgery or pre-RT surgical resection were excluded from this study. Patients who did not have available data of pre-RT DM-related serologic factors (HbA1c and fasting glucose) were also excluded. From January 2011 to December 2017, 767 patients with pathologically confirmed primary lung cancer received RT at Kyung Hee University Medical Center or Kyung Hee University Hospital at Gangdong. Of those patients, 289 who underwent pre-RT surgical resection, 110 who received a total RT dose ≤ 50 Gy, 87 who had prior thoracic irradiation, 69 who underwent radiosurgery, and 35 who had poor general condition (ECOG performance status ≥ 4) were excluded. Fifty-four patients who did not have available follow-up data were also excluded. Finally, 123 patients met the inclusion criteria and were included in this study. The hospital records, results of imaging studies, and laboratory results of all study participants were retrospectively reviewed. The Institutional Review Boards of our institutions approved this study

(KMC IRB 1819–09) and all research was carried out in compliance with the Helsinki Declaration. Because this was retrospective observational study, the Institutional Review Boards of our institutions waived the need for written informed consent.

The initial diagnosis of lung cancer was pathologically confirmed in all patients based on either endoscopic bronchial or percutaneous needle biopsy. Pretreatment evaluation consisted of complete history and physical examination, basic laboratory studies, pulmonary function test, electrocardiogram, trans-thoracic echocardiogram, chest radiography, chest computed tomography (CT) scan, brain magnetic resonance imaging, and positron emission tomography (PET). The cancer stage was restaged according to the 8th edition of the American Joint Committee on Cancer staging system. We retrospectively reviewed hospital records and identified whether each patient had DM or not. All patients were checked HbA1c and fasting glucose level 1 week before the start of RT.

All patients received CT-planned RT. The gross tumor volume (GTV) encompassed the primary tumor and grossly involved lymph nodes visualized on chest CT and PET. The clinical target volume (CTV) included the GTV plus a 6–8 mm margin, and the planning target volume (PTV) was created by adding an 8–15 mm margin to the CTV. The patients, who cooperated well with the instructions of medical staff, underwent four-dimensional CT simulation to track the movement of the targets along the respiratory cycle. In the patients who underwent four-dimensional CT simulation, GTV was created using maximal intensity projection images and the CTV included the GTV plus a 6–8 mm margin. The PTV was created by adding a 3–5 mm margin to the CTV. Elective nodal irradiation was not performed in all patients. Prescription dose was determined by a radiation oncologist based on the size of the target lesions, the patient's general condition, and the probability of RT-induced toxicity. A daily dose of 1.8–4 Gy was delivered at five fractions per week, resulting in a total dose of 50–72 Gy. For standard comparison of different RT dose schedules, biologically equivalent doses were calculated using a linear quadratic model with an α/β ratio of 10. The sequence and regimen of chemotherapy were individualized based on patient performance status and compliance.

Patients were evaluated with weekly chest X-ray during RT. Follow-up visits were scheduled 2 weeks after completion of RT and every 1–2 months thereafter. Visits

were more frequent for those who experienced treatment-related toxicities. Complete history and physical examination, basic laboratory studies, and chest radiograph were conducted at each follow-up visit. Chest CT and PET were also performed as needed. Radiation pneumonitis was diagnosed by a treating radiation oncologist on the basis of clinical symptoms and characteristic imaging findings within the RT field, and scored according to the toxicity criteria of the Radiation Therapy Oncology Group. Patients presenting with severe symptoms unresponsive to antitussive agents with suspicious radiologic changes were treated with steroids and scored as grade 3 radiation pneumonitis.

Binary logistic regression analysis was used to identify significant predictive factors for the development of grade ≥ 3 radiation pneumonitis. Because of the close association among the RT dosimetric factors, we only included V20 and mean lung dose in the statistical analysis. V20 is the volume of lung to receive >20 Gy and volume of lung was defined as total lung volume minus PTV. Variables found to have a P -value <0.10 on univariable analysis were further analyzed by multivariable analysis using binary logistic regression analysis with a backward stepwise method. Because DM, HbA1c, and fasting glucose are closely associated with one another, we included them separately in multivariable analysis. To find the best cutoff values of HbA1c and fasting glucose level, we conducted receiver operating characteristic analysis. All tests were two-sided and a P -value <0.05 was considered statistically significant. All analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient and tumor characteristics are summarized in Table 1. All patients were followed for more than 12 months. During the follow-up period, 122 patients experienced radiation pneumonitis. Grade 1 radiation pneumonitis developed in 52 patients (42.3%), grade 2 in 36 patients (29.2%), and grade 3 in 34 patients (27.6%). Only one patient experienced grade 4 radiation pneumonitis. Cumulative incidence of grade ≥ 3 radiation pneumonitis is depicted in Figure 1. All patients with grade ≤ 3 radiation pneumonitis were successfully treated with conservative management and some of the patients with grade 3 radiation pneumonitis were treated with steroid agents. However, because the patient who experienced grade 4 radiation pneumonitis did not achieve symptomatic relief, the patient was intubated and placed on a ventilator. There was no radiation pneumonitis-related death during follow-up duration.

Predictive factors for grade ≥ 3 radiation pneumonitis were analyzed and are summarized in Tables 2 and 3. On univariable analysis, V20 (odds ratio=1.064, 95% CI=1.024–1.106, $P=0.001$), mean lung dose (odds ratio=1.121, 95% CI=1.038–1.210, $P=0.003$), DM (odds ratio=3.067, 95% CI=1.327–7.085, $P=0.009$), HbA1c (odds ratio=1.744, 95% CI=1.277–2.383, $P<0.001$), and fasting glucose level (odds ratio=1.014, 95% CI=1.005–1.022, $P=0.003$) were significantly associated with the development of grade ≥ 3 radiation pneumonitis. On multivariable analysis, V20 (odds ratio=1.055, 95% CI=1.008–1.104, $P=0.022$), mean lung dose (odds ratio=1.110, 95% CI=1.012–1.218, $P=0.027$), DM (odds ratio=2.710, 95% CI=1.048–7.004, $P=0.040$), HbA1c (odds ratio=1.510, 95% CI=1.067–2.137, $P=0.020$), and fasting glucose level (odds ratio=1.011, 95% CI=1.001–1.021, $P=0.031$) remained significant predictive factors for grade ≥ 3 radiation pneumonitis. Gender, ECOG performance status, RT technique (three-dimensional vs four-dimensional), and GTV were marginally significant on univariable analysis. However, not all of these remained significant predictive factors on multivariable analysis. The incidence of grade ≥ 3 radiation pneumonitis was 44.4% in patients with DM and 20.7% in patients without DM.

According to receiver operating characteristic analysis, the best cutoff values of HbA1c and fasting glucose level were 6.15% (sensitivity=75.9%, specificity=69.6%, $P<0.001$) and 121 mg/dL (sensitivity=69%, specificity=57%, $P=0.003$), respectively. The incidence of grade ≥ 3 radiation pneumonitis was 12.7% for HbA1c level $\leq 6.15\%$ and 41.5% for HbA1c level $>6.15\%$. The incidence of grade ≥ 3 radiation pneumonitis was 17.2% for fasting glucose level ≤ 121 mg/dL and 35.5% for fasting glucose level >121 mg/dL.

Discussion

Hsia et al retrospectively analyzed the clinical data of 118 lung cancer patients and reported that DM itself was not associated with higher radiation pneumonitis risk.²⁰ Orton et al also evaluated the correlation between DM and radiation pneumonitis in 66 patients with lung cancer and reported that the rate of radiation pneumonitis in patients with DM was not significantly different from that in patients without DM, although the patients with DM showed higher incidence of radiation pneumonitis.¹⁸ In People's Republic of China, two retrospective studies evaluated the relationship between DM and the incidence of radiation pneumonitis in patients with lung cancer and

Table 1 Patient and tumor characteristics

Characteristics	N (%)
Age (years) Median (range)	68 (28–87)
Gender Male/female	99 (80.5)/24 (19.5)
ECOG performance status 0/1/2/3	15 (12.2)/63 (51.2)/42 (34.1)/3 (2.5)
AJCC stage I/II/III	15 (12.2)/17 (13.8)/91 (74.0)
Site Right/left	62 (50.4)/61 (49.6)
Smoking status Never/former/current	25 (20.4)/43 (34.9)/55 (44.7)
Underlying lung disease Yes/no	26 (21.1)/97 (78.9)
Histology SqCC/adenoca/SCLC/ NSCLC/NEC	51 (41.5)/28 (22.8)/34 (27.6)/7 (5.7)/3 (2.4)
Chemotherapy Yes/no	78 (63.4)/45 (36.6)
Chemotherapy Con/ind/adj/ind+con	60 (76.9)/13 (16.7)/2 (2.6)/3 (3.8)
RT technique 3D-CRT/IMRT	50 (40.7)/73 (59.3)
RT technique 3D simulation/4D simulation	74 (60.2)/49 (39.8)
Total dose (BED, Gy ₁₀) Median (range)	76.2 (60–86.4)
Daily dose (Gy) Median (range)	2 (1.8–4)
GTV (cc) Median (range)	107 (3.4–1188.2)
V20 (%) Median (range)	23.0 (5.0–52.1)
Mean lung dose (Gy) Median (range)	13.5 (5.8–30.2)
Diabetes mellitus Yes/no	36 (29.3)/87 (70.7)
HbA1c (%) Median (range)	6.1 (4.9–12.2)

(Continued)

Table 1 (Continued).

Characteristics	N (%)
Fasting glucose (mg/dL) Median (range)	122.5 (73.1–294.2)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; SqCC, squamous cell carcinoma; adenoca, adenocarcinoma; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; NEC, neuroendocrine carcinoma; con, concurrent; ind, induction; adj, adjuvant; RT, radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; 3D, three-dimensional; 4D, four-dimensional; BED, biologically equivalent dose; GTV, gross tumor volume; HbA1c, hemoglobin A1c.

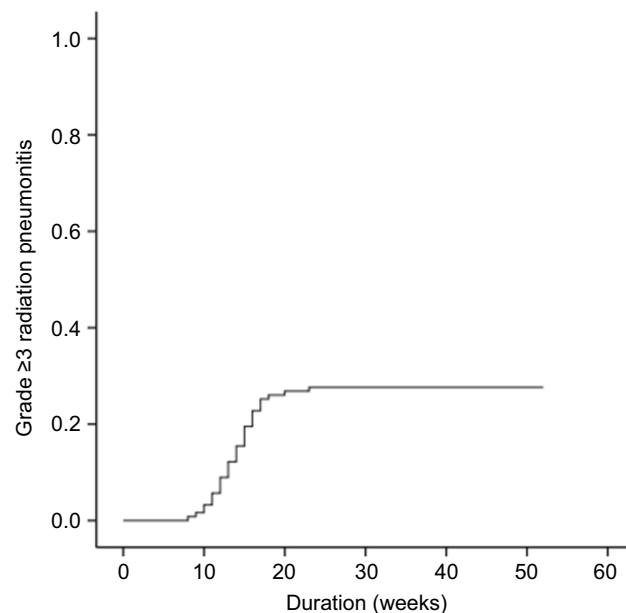


Figure 1 Cumulative incidence of grade ≥ 3 radiation pneumonitis among all patients. Grade 3 radiation pneumonitis developed in 34 patients (27.6%) and grade 4 developed in 1 patient.

reported that DM is a significant risk factor for radiation pneumonitis.^{19,21} However, the two studies conducted in People's Republic of China were published in Chinese, and Hsia et al's and Orton et al's studies were published only abstract form, so we were not able to review the full text. In our study of 123 patients, we evaluated the effects of DM and DM-related serologic factors (HbA1c and fasting glucose) on the development of radiation pneumonitis in patients with lung cancer. On uni- and multivariable analyses, DM, HbA1c, and fasting glucose level were significantly associated with the development of grade ≥ 3 radiation pneumonitis. This is one of the first studies to report the impacts of DM and DM-related serologic factors on the development of radiation pneumonitis.

Table 2 Univariable analysis to identify predictive factors for grade ≥ 3 radiation pneumonitis

Variable	Odds ratio	95% confidence interval	P-value
Age (years)	1.001	0.961–1.042	0.957
Gender			
Male	1		
Female	3.191	0.885–11.502	0.076
ECOG performance status			
0–1	1		
2–3	2.050	0.906–4.638	0.085
AJCC stage			
1–2	1		
3	1.926	0.713–5.199	0.196
Smoking status			
Never	1		
Former or current	1.267	0.458–3.503	0.649
Lung disease			
No	1		
Yes	1.525	0.603–3.854	0.373
Chemotherapy			
No	1		
Yes	1.293	0.560–2.982	0.547
V20 (%)	1.064	1.024–1.106	0.001
Mean lung dose (Gy)	1.121	1.038–1.210	0.003
RT technique			
3D-CRT	1		
IMRT	0.821	0.369–1.826	0.629
RT technique			
3D simulation	1		
4D simulation	2.105	0.944–4.695	0.069
Total RT dose (BED, Gy ₁₀)	0.976	0.924–1.030	0.371
Daily RT dose (Gy)	1.507	0.454–5.004	0.503
GTV (cc)	1.001	1.000–1.003	0.079
Diabetes mellitus			
No	1		
Yes	3.067	1.327–7.085	0.009
HbA1c (%)	1.744	1.277–2.383	<0.001
Fasting glucose (mg/dL)	1.014	1.005–1.022	0.003

Abbreviations: ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; RT, radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; 3D, three-dimensional; 4D, four-dimensional; BED, biologically equivalent dose; GTV, gross tumor volume; HbA1c, hemoglobin A1c.

The pathophysiologic process of radiation pneumonitis involves inflammation, epithelial degeneration, endothelial sloughing, disruption of microvasculature, induction of free radicals, and the accompanying oxidative stress.²² It is well known that chronic DM causes inflammation, oxidative stress, endothelial dysfunction, and microvascular

occlusive changes.^{23,24} Chronic DM also causes alterations in blood viscosity, which contributes to tissue ischemia.²⁵ All changes caused by DM are involved in the pathophysiologic process of radiation pneumonitis, and those changes aggravate the deleterious effects of RT and disturb the repair of damaged pulmonary tissues. It is possible that

Table 3 Multivariable analysis to identify predictive factors for grade ≥ 3 radiation pneumonitis

Variable	Odds ratio	95% confidence interval	P-value
Gender			
Male	1		
Female	2.267	0.562–9.144	0.250
ECOG performance status			
0–1	1		
2–3	1.575	0.604–4.104	0.353
V20 (%)	1.055	1.008–1.104	0.022
Mean lung dose (Gy)	1.110	1.012–1.218	0.027
RT technique			
3D simulation	1		
4D simulation	1.663	0.592–4.672	0.335
GTV (cc)	1.001	0.998–1.003	0.647
Diabetes mellitus			
No	1		
Yes	2.710	1.048–7.004	0.040
HbA1c (%)	1.510	1.067–2.137	0.020
Fasting glucose (mg/dL)	1.011	1.001–1.021	0.031

Abbreviations: ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; 3D, three-dimensional; 4D, four-dimensional; GTV, gross tumor volume; HbA1c, hemoglobin A1c.

these are the reasons why patients with DM in our study experienced higher incidence of grade ≥ 3 radiation pneumonitis than patients without DM (44.4% vs 20.7%, $P=0.009$). For the same reasons, patients who have higher HbA1c (41.5% vs 12.7, $P<0.001$) or fasting glucose (35.5% vs 17.2%, $P=0.003$) experienced higher grade ≥ 3 radiation pneumonitis in this study.

Although four-dimensional CT moving images may increase the certainty of the targets and lead to a reduction in unnecessary PTV margins, the patients who received four-dimensional RT showed a higher incidence of grade ≥ 3 radiation pneumonitis compared with patients who underwent three-dimensional RT in this study (36.7% vs 21.6%, odds ratio=2.105, 95% CI=0.944–4.695, $P=0.069$). We added PTV margins of 8–15 mm in patients who underwent three-dimensional RT, while we added 3–5 mm margins in patients who underwent four-dimensional RT. However, to include all images of 10 respiratory phases, we created GTV using maximal intensity projection images. Because the GTVs created by maximal intensity projection images were bigger than the GTVs created by three-dimensional CT images, the PTVs of four-dimensional RT were bigger than those of three-dimensional RT despite of lesser margins (median 215 cc vs 183 cc, $P=0.049$). These reasons may be why the patients who

received four-dimensional RT showed a higher incidence of grade ≥ 3 radiation pneumonitis compared with patients who received three-dimensional RT in this study.

There are several studies reporting correlations between RT dosimetric factors and development of radiation pneumonitis. However, all dosimetric parameters are found to be highly correlated with one another and differences in predictive value among different dosimetric parameters tend to be small.^{4,10,26} Because most studies reported that V20 and mean lung dose were the most important predictive factors for radiation pneumonitis, we included only V20 and mean lung dose in the statistical analysis to minimize potential confounding factors.

DM is one of the most common endocrine diseases worldwide, with a prevalence of 11% in Koreans over the age of 30 years.²⁷ In our study, 29.3% of the overall patient population was diagnosed with DM. Other studies reported DM in 14–33.3% of their patient groups.^{18–21} Because several studies showed a higher prevalence of DM in lung cancer patients compared with the general population, greater caution is warranted in implementation of RT and posttreatment monitoring for lung cancer patients. In addition, it is critical that the interactions between DM and potential DM-associated RT toxicities in this patient group should be further characterized. Our

study provides valuable information regarding the interactions between DM and RT toxicities in patients with lung cancer. Large-scale randomized prospective studies should be conducted to confirm our results.

Recently, personalized medicine has become a hot topic due to the lower cost of genetic testing and abundant research findings.²⁸ Several studies have conducted to find lung biomarkers predicting the development of radiation pneumonitis, and IL-6, TGF- β , and surfactant apoprotein are known to be novel biomarkers predicting radiation pneumonitis.^{29–31} It may be useful to combine well-known dosimetric parameters such as V20 and mean lung dose with various lung biomarkers to define a subgroup of patients with higher risk for radiation pneumonitis. In addition, DM, HbA1c, and fasting glucose level can be also combined with dosimetric parameters and lung biomarkers to further allow personalized thoracic RT. We hope further studies are conducted to confirm the efficacy of personalized thoracic RT combining dosimetric parameters, novel lung biomarkers, and DM-related factors in the near future.

There were several limitations in this study. First, this study was retrospective and may therefore have inherent biases. For example, diagnosis of DM was decided retrospectively by reviewing the patients' clinical data. Therefore, we were unable to control for the possibility that patients can develop DM after treatment, which could affect the development of late-onset radiation pneumonitis. In addition, we did not analyze some potential predictive factors for radiation pneumonitis, such as DM medication history. These biases may make it difficult to interpret the results obtained. Second, the sample size was relatively small. Third, the patient and tumor characteristics were heterogeneous. Despite these limitations, we believe our study addresses some unresolved issues regarding the relationship between DM and radiation pneumonitis.

Conclusion

DM, HbA1c, and fasting glucose level are significant predictive factors for the development of grade ≥ 3 radiation pneumonitis in patients with lung cancer. Patients with DM, patients who have HbA1c $>6.15\%$, and patients who have fasting glucose >121 mg/dL should be treated with greater caution.

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Disclosure

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