

# Hemoglobin A1c level is a prognostic factor for locoregional recurrence in stage III non-small cell lung cancer patients treated with radiotherapy

Moonkyoo Kong  | Yu Jin Lim 

Department of Radiation Oncology, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, Republic of Korea

## Correspondence

Moonkyoo Kong, Division of Lung & Head and Neck Oncology, Department of Radiation Oncology, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, 23 Kyungheeda-gil, Dongdaemoon-gu, Seoul, 02447, Republic of Korea.  
Email: kongmoonkyoo@khu.ac.kr

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## Abstract

**Background:** The level of hemoglobin A1c (HbA1c) might be associated with the severity of tumor hypoxia in patients with cancer. Here, we evaluated the association between the level of HbA1c and survival outcome in stage III non-small cell lung cancer patients treated with radical radiotherapy.

**Methods:** We retrospectively analysed the clinical data of 104 patients with lung cancer treated with radiotherapy. The HbA1c levels of all patients were checked 1 week before the start of radiotherapy. Survival outcomes were analysed according to the HbA1c level.

**Results:** The 1-, 2-, and 3-year locoregional recurrence-free survival rates were 88.3%, 68.8%, and 63.0%, respectively, in the patient group with HbA1c levels  $\leq 6\%$  and 75.5%, 54.4%, and 41.8%, respectively, in the patient group with HbA1c levels  $>6\%$  ( $p = 0.015$ ). The HbA1c level remained a significant prognostic factor for locoregional recurrence-free survival on multivariable analysis (hazard ratio = 2.014, 95% confidence interval = 1.088–3.726,  $p = 0.026$ ).

**Conclusions:** Pretreatment HbA1c level is a significant prognostic factor for locoregional recurrence-free survival in patients with stage III non-small cell lung cancer treated with radical radiotherapy. Routine monitoring of pretreatment HbA1c levels and aggressive glycemic control may be considered to prevent the development of locoregional recurrence in these patients.

## KEYWORDS

hemoglobin A1c, locoregional recurrence, lung cancer, radiotherapy

## INTRODUCTION

In 1909, Schwarz reported that the radiation response of tumors was reduced when blood flow to the tumor decreased.<sup>1</sup> Now, it is well known that oxygen is a potent chemical modifier of radiosensitivity and that hypoxic tumors show poor local control after radiotherapy.<sup>2–4</sup>

In diabetes mellitus, a chronic hyperglycemic state causes inflammation, oxidative stress, and subsequent endothelial dysfunction, and microvascular/macrovascular occlusion. In addition, chronic hyperglycemia causes alterations in blood viscosity and hemodynamic balance, which contribute to microvascular occlusion and tissue ischemia.<sup>5–8</sup> These changes caused by chronic hyperglycemia can aggravate tumor hypoxia.

Since the vasculature of tumors is immature and unstable,<sup>9–11</sup> vascular occlusion and subsequent tissue hypoxia which caused by a chronic hyperglycemic state can be more serious in tumors.

Hemoglobin A1c (HbA1c) reflects the mean plasma glucose level for the previous approximately 3 months and has low intraindividual variability.<sup>12,13</sup> Several studies have reported that elevated HbA1c levels are an independent risk factor for vascular complication.<sup>14–16</sup> Therefore, we can assume that HbA1c levels may be associated with the severity of tumor hypoxia in patients with cancer. Given that hypoxic tumors are resistant to radiotherapy, we can also assume that HbA1c levels may be associated with the development of local recurrence in cancer patients who treated with radiotherapy.

In this study, we evaluated the association between HbA1c levels and survival outcomes in stage III non-small cell lung cancer (NSCLC) patients treated with radical radiotherapy.

## METHODS

The inclusion criteria were patients with histologically proven stage III non-small cell lung cancer, who received radical radiotherapy with or without chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ , no prior thoracic irradiation, no previous or concurrent illness that would compromise the completion of treatment, and available follow-up data. Patients who received postoperative or palliative radiotherapy were excluded from the study. Patients without evaluable pretreatment HbA1c levels were also excluded. From January 2011 to May 2019, 448 patients with pathologically-confirmed stage III NSCLC received radiotherapy at our institution. Of these patients, we excluded 79 who received postoperative radiotherapy, 72 who received palliative radiotherapy, 62 who had prior thoracic irradiation history, 42 who did not have available follow-up data, and 37 who had poor general condition (ECOG performance status  $\geq 3$ ). Fifty-two patients without evaluable pretreatment HbA1c levels were also excluded. Finally, 104 patients met the inclusion criteria and were included in the study. The hospital records, including results of imaging and laboratory studies of all study participants, were retrospectively reviewed. The Institutional Review Board of our institution approved this retrospective study (KHUH-2021-04-069) and waived the need for written informed consent because it was a retrospective observational study. The study was conducted in compliance with the principles of the Helsinki Declaration and was registered in the CRIS Registration System (KCT0006199).

The detailed methods of initial diagnosis and pretreatment evaluation have been described in our previous studies.<sup>17,18</sup> Briefly, 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, bone scan, and positron emission tomography (PET). The HbA1c levels of all patients were checked 1 week before the start of radiotherapy.

All patients received CT-planned radiotherapy. The detailed radiotherapy methods have been described in our previous study.<sup>17</sup> Briefly, the primary tumor and grossly involved lymph nodes were the targets of radiotherapy, and elective nodal irradiation was not performed. The implementation and regimen of chemotherapy were individualized based on each patient's performance status and compliance. Follow-up visits were scheduled 2 weeks after completion of radiotherapy and every 2–3 months thereafter. At the follow-up visit, basic

**TABLE 1** Patient and tumor characteristics

Characteristics	N (%)
Age (years)	
Median (range)	72 (45–85)
Gender	
Male/female	85 (81.7)/19 (18.3)
Diabetes mellitus	
Yes/no	25 (24.1)/79 (75.9)
Smoking status	
Current/former/never	56 (53.8)/28 (26.9)/20 (19.3)
ECOG performance status	
0/1/2	13 (12.5)/67 (64.4)/24 (23.1)
Histology	
SqCC/adeno/adenoSqCC	69 (67.3)/34 (31.7)/1 (1)
AJCC stage	
IIIA/IIIB	63 (60.6)/41 (39.4)
Location	
Right/left	46 (44.2)/58 (55.8)
Upper & middle/lower	67 (64.4)/37 (35.6)
RT technique	
IMRT/3D-CRT	34 (32.7)/70 (67.3)
Total dose (BED, Gy <sub>10</sub> )	
Median (range)	76.2 (70–84.4)
Daily dose (Gy)	
Median (range)	2 (1.8–2.5)
RT interruption	
Yes/no	22 (21.2)/82 (78.8)
RT duration (weeks)	
Median (range)	7 (5–9)
Chemotherapy	
Yes/no	59 (56.7)/45 (43.3)
Types of chemotherapy	
Concurrent/sequential	45 (76.2)/14 (23.8)
Hemoglobin A1c (%)	
Median (range)	6 (4.4–10.6)
Fasting glucose (mg/dl)	
Median (range)	121 (81–301)
Hemoglobin (g/dl)	
Median (range)	11.8 (7.6–15.5)

Abbreviations: Adeno, adenocarcinoma; AdenoSqCC, adenosquamous cell carcinoma; AJCC, American Joint Committee on Cancer; BED, biologically equivalent dose. ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiotherapy; RT, radiotherapy; SqCC, squamous cell carcinoma; 3D-CRT, three-dimensional conformal radiotherapy.

laboratory studies, chest radiographs, and chest CT scans were performed. PET was also performed as required.

The primary endpoint of this study was locoregional recurrence-free survival. The secondary endpoints were

**TABLE 2** Survival outcomes of the whole cohort

Endpoint	Survival rate (%)			Median survival time (months)
	1-year	2-year	3-year	
Overall survival	81.6	54.9	48.8	21.0
Locoregional recurrence-free survival	63.1	52.8	45.6	12.1
Distant metastasis-free survival	70.0	55.2	51.5	13.1

overall survival and distant metastasis-free survival. The locoregional recurrence and distant metastasis were defined in our previous study.<sup>17</sup> Actuarial survival rates were estimated using the Kaplan–Meier method, and comparisons between groups were performed using log-rank tests. Survival times were calculated from the date of lung cancer diagnosis to the date of the event or the final follow-up visit. Variables found to have a *p*-value <0.50 on univariable analysis were further analysed by multivariable analysis using Cox's proportional hazard regression test with the enter method. All tests were two-sided, and the threshold for statistical significance was set at *p* < 0.05. All analyses were performed using SPSS version 21.0 (IBM Corporation).

## RESULTS

Patient and tumor characteristics are summarized in Table 1. Forty-five patients received concurrent chemotherapy with a regimen of weekly paclitaxel plus carboplatin. Among them, three and six patients received additional induction chemotherapy and consolidation chemotherapy, respectively, in conjunction with concurrent chemotherapy. Fourteen patients received induction chemotherapy alone with a regimen of cisplatin plus etoposide. The remaining 45 patients underwent radical radiotherapy alone. Although 22 patients experienced temporary radiotherapy interruption due to treatment-related toxicities, all patients completed the planned treatment. The median follow-up duration of all patients was 21.0 months (range, 2.1–88.2).

The survival outcomes of all patients are summarized in Table 2. During the follow-up period, 54 patients remained alive. Almost all the deceased patients died due to cancer progression and cancer-related complications. However, two died of coronary heart disease, three died of chronic renal failure, two died of cerebral hemorrhage, and two died of liver cirrhosis. In addition, three patients died of acute renal failure, sepsis, and asphyxia caused by food aspiration, respectively. The 1-, 2-, and 3-year overall survival rates of all patients were 81.6%, 54.9%, and 48.8%, respectively.

During the follow-up period, 49 patients experienced locoregional recurrences and 41 patients experienced distant metastases. Among these patients, 27 experienced both locoregional recurrences and distant metastases. Among the 22 patients who only experienced locoregional recurrences without distant metastasis, eight received salvage

**TABLE 3** Patient and tumor characteristics of low and high HbA1c groups

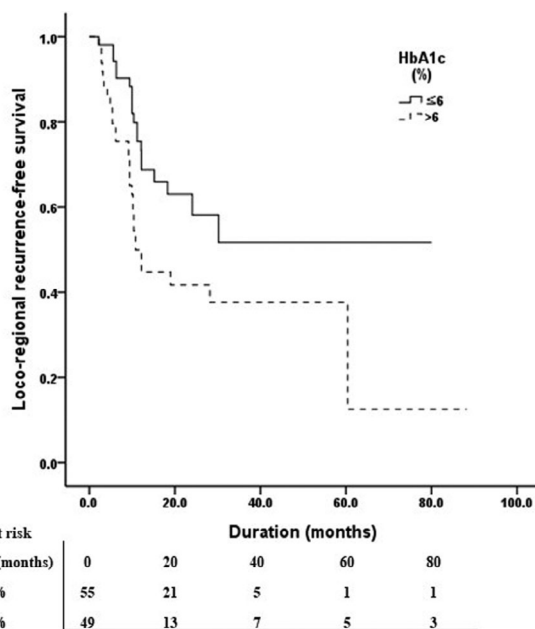
Characteristics	HbA1c (%)		<i>p</i> -value
	≤6 ( <i>n</i> = 55)	>6 ( <i>n</i> = 49)	
Age (years)			
Median (range)	71 (45–85)	73 (52–82)	0.542
Gender			
Male/female	47/8	38/11	0.298
Diabetes mellitus			
Yes/no	4/51	21/28	<0.001
Smoking status			
Current/former/never	26/18/11	30/10/9	0.296
ECOG performance status			
0/1/2	7/30/18	6/37/6	0.069
Histology			
SqCC/adeno/adenoSqCC	42/12/1	28/21	0.043
AJCC stage			
IIIA/IIIB	36/19	27/22	0.281
Location			
Right/left	24/31	22/27	0.863
Upper and middle/lower	39/16	28/21	0.285
RT technique			
IMRT/3D-CRT	22/45	12/25	0.571
Total dose (BED, Gy <sub>10</sub> )			
Median (range)	76.2 (70–84)	76.2 (70–84.4)	0.873
Daily dose (Gy)			
Median (range)	2 (1.8–2.5)	2 (1.8–2.4)	0.699
RT interruption			
Yes/no	12/43	10/39	0.794
RT duration (weeks)			
Median (range)	7 (5–9)	7 (5–9)	0.913
Chemotherapy			
Yes/no	30/25	29/20	0.375
Types of chemotherapy			
Concurrent/sequential	23/7	22/7	0.214
Fasting glucose (mg/dl)			
Median (range)	115 (81–236)	137 (81–301)	0.007
Hemoglobin (g/dl)			
Median (range)	11.7 (7.8–15.5)	12.1 (7.6–14.8)	0.897

Abbreviations: Adeno, adenocarcinoma; AdenoSqCC, adenosquamous cell carcinoma; AJCC, American Joint Committee on Cancer; BED, biologically equivalent dose; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiotherapy; RT, radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy.

concurrent chemoradiotherapy, five received salvage surgical resection, two received salvage radiotherapy alone, while seven refused salvage treatment. The 1-, 2-, and 3-year locoregional recurrence-free survival rates of all patients were 63.1%, 52.8%, and 45.6%, respectively. Almost all 41 patients who experienced distant metastases received palliative chemotherapy, except for six patients who refused

**TABLE 4** Analysis of survival according to pretreatment hemoglobin A1c level

Endpoint	HbA1c (%)	Survival rate (%)			<i>p</i> -value
		1-year	2-year	3-year	
Locoregional recurrence-free survival	≤6	88.3	68.8	63	0.015
	>6	75.5	54.4	41.8	
Overall survival	≤6	81.5	69.1	52.9	0.749
	>6	81.6	65.6	47.9	
Distant metastasis-free survival	≤6	82.9	67.9	65.1	0.128
	>6	80.5	58	49.2	

**FIGURE 1** Locoregional recurrence-free survival curve according to HbA1c levels. The 1-, 2-, and 3-year locoregional recurrence-free survival rates were 88.3%, 68.8%, and 63%, respectively, in the patient group with low HbA1c levels and 75.5%, 54.4%, and 41.8%, respectively, in the patient group with high HbA1c levels ( $p = 0.015$ )

palliative treatment. The 1-, 2-, and 3-year distant metastasis-free survival rates of all patients were 70.0%, 55.2%, and 51.5%, respectively.

According to receiver operating characteristic analysis, the best cutoff value of pretreatment HbA1c was 6.0% (sensitivity = 73.5%, specificity = 65.5%,  $p = 0.002$ ). Using this cutoff value, 55 patients were allocated to the low HbA1c group and 49 patients were allocated to the high HbA1c group. Patient and tumor characteristics of both groups are summarized in Table 3. We analysed survival outcomes according to pretreatment HbA1c levels, and the results are summarized in Table 4. Pretreatment HbA1c levels were significantly associated with locoregional recurrence-free survival. The 1-, 2-, and 3-year locoregional recurrence-free survival rates were 88.3%, 68.8%, and 63.0%, respectively, in the patient group with low HbA1c levels, and 75.5%, 54.4%,

and 41.8%, respectively, in the patient group with high HbA1c levels ( $p = 0.015$ ) (Figure 1). Univariable and multivariable analysis, including other variables, were conducted to identify whether pretreatment HbA1c level is a significant prognostic factor for locoregional recurrence-free survival in stage III NSCLC patients treated with radical radiotherapy (Table 5). On univariable analysis, age ( $p = 0.032$ ) and HbA1c level ( $p = 0.015$ ) were significantly associated with locoregional recurrence-free survival. HbA1c level remained a significant prognostic factor for locoregional recurrence-free survival on multivariable analysis (hazard ratio = 2.014, 95% confidence interval = 1.088–3.726,  $p = 0.026$ ).

## DISCUSSION

This retrospective study evaluated the association between pretreatment HbA1c levels and survival outcomes in 104 patients with stage III NSCLC and found that the HbA1c level, which was checked 1 week before the start of radiotherapy, is a significant prognostic factor for locoregional recurrence-free survival in patients with stage III NSCLC who were treated with radical radiotherapy. The patient group with HbA1c >6% had a higher risk of developing locoregional recurrence than the group with HbA1c ≤6%, with a relative risk was 2.014. To the best of our knowledge, this is the first study to report the impact of HbA1c on the development of locoregional recurrence in patients with lung cancer treated with radiotherapy. Although this is a retrospective study with inherent biases, HbA1c can be combined with existing prognostic factors to allow personalized treatment for patients with lung cancer. We hope that further studies are conducted to confirm our results and the efficacy of personalized treatment combining HbA1c and existing prognostic factors in patients with lung cancer treated with radiotherapy.

Tissue oxygenation is critically dependent on capillary blood flow, which is determined by the arteriovenous pressure difference and vascular architecture.<sup>11</sup> In tumors, mechanical stress generated by proliferating tumor cells, imbalance between pro- and antiangiogenic molecules, and incomplete vascular differentiation causes tortuous vessels, sluggish blood flow, blood shunting, temporary occlusion, and hyperpermeability of vessels.<sup>10,11,19,20</sup> As a result, overall perfusion rates in tumors are lower than those in normal tissues, and this contributes to both acute and chronic hypoxia in tumors. The mechanism by which diabetes contributes to vascular complications is not clear, but it has been reported that chronic hyperglycemia is an important and initiating insult.<sup>21</sup> A long-standing hyperglycemic state triggers an increase in oxidative stress and inflammatory response, alteration in cellular redox potential, accumulation of advanced glycosylation end products in the subendothelial space, and the development of endothelial dysfunction and hypercoagulability.<sup>5,6,22,23</sup> All these changes can cause large and small vessel obstructions. In summary, unstable and tortuous vessels of the tumor can be easily obstructed, therefore tumor hypoxia becomes worse in a chronic hyperglycemic state. These may be the reasons why patients with higher pretreatment HbA1c levels showed worse

TABLE 5 Prognostic factors for locoregional recurrence-free survival

Variables	2-year survival rate (%)	Univariable	Multivariable <sup>a</sup>		
		<i>p</i> -value	Hazard ratio	95% confidence interval	<i>p</i> -value
Age (years)					
<72 vs. ≥72	36.7 vs. 68	0.032	0.514	0.263–1.005	0.052
Gender					
Male vs. female	49.8 vs. 67.3	0.258	0.464	0.155–1.388	0.169
Diabetes mellitus					
Yes vs. no	54.4 vs. 51.8	0.875			
Smoking status					
Current vs. former or never	49.2 vs. 57.9	0.724			
ECOG performance status					
0–1 vs. 2	51.4 vs. 65.5	0.785			
Histology					
SqCC vs. adeno	53.8 vs. 49.3	0.349	1.652	0.806–3.385	0.170
AJCC stage					
IIIA/IIIB	54 vs. 50.5	0.297	0.986	0.501–1.939	0.967
RT technique					
IMRT/3D-CRT	51.6 vs. 53.6	0.880			
Total dose (BED, Gy <sub>10</sub> )					
≤76 vs. >76	52.1 vs. 52.6	0.738			
Daily dose (Gy)					
≤2 vs. >2	56.9 vs. 48.9	0.660			
RT duration (weeks)					
<7 vs. ≥7	48.4 vs. 57.2	0.418	0.845	0.459–1.554	0.588
Chemotherapy					
Yes vs. no	47.6 vs. 58.3	0.120	0.883	0.420–1.851	0.740
Hemoglobin A1c (%)					
≤6 vs. >6	63 vs. 41.8	0.015	2.014	1.088–3.726	0.026
Fasting glucose (mg/dl)					
≤120 vs. >120	57.1 vs. 48.6	0.150	1.217	0.639–2.316	0.550
Hemoglobin (g/dl)					
≤11.8 vs. >11.8	58.4 vs. 47	0.585			

Abbreviations: Adeno, adenocarcinoma; AJCC, American Joint Committee on Cancer; BED, biologically equivalent dose; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiotherapy; RT, radiotherapy; SqCC, squamous cell carcinoma; 3D-CRT, three-dimensional conformal radiotherapy.

<sup>a</sup>First group was reference category for calculation of hazard ratio and 95% confidence interval.

locoregional recurrence-free survival than patients with lower HbA1c levels in our study. However, the proposed reasons are still a matter of speculation, and in-vivo and in-vitro experimental studies are required to confirm whether tumor hypoxia is aggravated in a chronic hyperglycemic state.

Some studies have reported that tumor hypoxia itself is correlated with aggressiveness. Hockel et al. reported that the oncological outcome of patients with cervical cancer treated with surgical resection only is also correlated with tumor hypoxia.<sup>24</sup> In addition, Graeber et al. reported that hypoxia provides a growth advantage for cells with mutated p53 and can select for more aggressive tumors.<sup>25</sup> Therefore, caution is required when interpreting our results. We previously reported that poor locoregional recurrence-free survival in patients with higher HbA1c levels was caused by decrease in the radiation

response of hypoxic tumors which was aggravated in the chronic hyperglycemic state. However, the aggressiveness of tumor hypoxia itself could be the reason for the poor survival outcome. At present, we do not know the exact mechanism underlying our results. However, because the HbA1c level was significantly associated with only locoregional recurrence-free survival and not with distant metastasis-free survival (Table 4), we believe that the radiation resistance of hypoxic tumors, which aggravated in long-standing hyperglycemic state, was a more powerful reason for the poor survival outcome of patients with higher HbA1c levels in our study. Regardless of the reasons, the fact that the HbA1c level is a significant prognostic factor for patients with lung cancer remains unchanged.

Diabetes mellitus and diabetes-related serological factors such as HbA1c and fasting glucose are highly correlated

with one another. In our previous study, we evaluated the effects of preexisting diabetes and diabetes-related serological factors on the development of radiation pneumonitis.<sup>26</sup> We retrospectively analysed the clinical data of 123 lung cancer patients treated with radiotherapy and found that pre-existing diabetes, HbA1c, and fasting glucose level were significant predictive factor for the development of grade  $\geq 3$  radiation pneumonitis. However, only HbA1c was significantly associated with locoregional recurrence-free survival in current study. If properly treated, diabetic patients can maintain good glycemic control. Because of requirement for an overnight fast, checking of fasting glucose level is inconvenient and fasting glucose has high variability.<sup>27</sup> On the other hand, HbA1c reflect the long-term mean plasma glucose level and has stability after collection, low variability, and no requirement for an overnight fast. Therefore, the American Diabetes Association have advocated measurement of HbA1c as the preferred approach to the diagnosis and management of hyperglycemia.<sup>28</sup> Moreover, although preexisting diabetes, fasting glucose, and HbA1c levels were significantly associated with development of radiation pneumonitis, HbA1c was most powerful factor among them in our previous study.<sup>26</sup> Therefore, we believe that HbA1c level may reflect chronic tumor hypoxia better than pre-existing diabetes and fasting glucose level. Researchers who plan to conduct additional studies should keep this in mind.

There were some limitations to this study. First, this study was retrospective, so may have inherent biases. For example, we excluded patients without evaluable pretreatment HbA1c levels, which may introduce an unintended selection bias. In addition, we could not include a medication history of diabetes in our analysis because of incomplete medical records. These biases may make it difficult to interpret the results obtained. Second, the sample size was small, so minor differences might not have been detected during statistical analysis. Third, the treatment characteristics were heterogeneous. Radiotherapy fractionation schedules and chemotherapy regimens were decided by the attending physicians rather than using a predetermined protocol. Finally, the duration of the follow-up period was not long.

Despite these limitations, we firstly found an association between HbA1c levels and locoregional recurrence in patients with lung cancer treated with radiotherapy. Although large-scale randomized prospective studies should be conducted to confirm our results, HbA1c could serve as a helpful prognostic factor, and routine evaluation of pretreatment HbA1c levels should be considered in patients with stage III NSCLC treated with radical radiotherapy. And, additional studies are required to determine whether aggressive glycemic control can increase radiotherapy response and locoregional recurrence-free survival in patients with lung cancer. Recent two prospective randomized clinical trials (the NRG-LU001 and the OCOG-ALMERA trials) reported that the addition of metformin to concurrent chemoradiotherapy did not improve progression-free survival in nondiabetic patients with stage III NSCLC,<sup>29,30</sup> although several preclinical and retrospective studies have reported antineoplastic effect of metformin. The retrospective

data may have biases, being drawn from a population with diabetes. Therefore, favorable survival outcomes of retrospective studies could be originated from glycemic control effect of metformin rather than direct antineoplastic effect. We plan to conduct additional studies to identify whether the differences between pre- (1 week before the start) and post-treatment (3 months after the completion) HbA1c level are associated with radiotherapy response in patients with lung cancer. In a similar way, the differences between pre- (1 week before the start) and post-treatment (1 month after the completion) glycoalbumin level can be evaluated to identify its relevance to oncologic outcomes in lung cancer patients treated with radical radiotherapy. Through these studies, we hope to find the answer to question whether better glycemic control increase radiotherapy response or not. In addition, it will be necessary to conduct further studies evaluating the efficacy of HbA1c levels in several cancers other than lung cancer.

In conclusion, the pretreatment HbA1c level is a significant prognostic factor for locoregional recurrence-free survival in patients with stage III NSCLC treated with radical radiotherapy. Routine monitoring of pretreatment HbA1c levels and aggressive glycemic control may be considered to prevent the occurrence of locoregional recurrence in these patients.

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#### CONFLICT OF INTEREST

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#### ORCID

Moonkyoo Kong  <https://orcid.org/0000-0003-3703-0417>

Yu Jin Lim  <https://orcid.org/0000-0003-2243-8989>

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