Received: 7 June 2022 | Accepted: 21 July 2022

DOI: 10.1111/1759-7714.14601

ORIGINAL ARTICLE

WILEY

Chronic hyperglycemia is an adverse prognostic factor for locoregional recurrence-free survival in small cell lung cancer patients treated with radical 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 Kyungheedae-gil, Dongdaemoon-gu, Seoul, 02447, Republic of Korea.
Email: kongmoonkyoo@khu.ac.kr

Funding information
National Research Foundation, Grant/Award Number: 2022R1F1A1074912

Abstract

Background: Plasma glucose levels might be associated with the severity of tumor hypoxia in patients with cancer. In our previous study, we found that chronic hyperglycemia significantly increased the risk of locoregional recurrence in patients with non-small cell lung cancer treated with radical radiotherapy (RT). Here, we evaluated the association between plasma glucose levels in terms of hemoglobin A1c (HbA1c) and locoregional recurrence-free survival in patients with limited-stage small cell lung cancer treated with radical RT.

Methods: We retrospectively analyzed the clinical data of 59 patients with small cell lung cancer. HbA1c levels were measured 1 week before the start of RT. Survival outcomes were analyzed according to HbA1c levels. Multivariable analysis was conducted to identify whether HbA1c level was a significant prognostic factor for survival.

Results: The 1-, 2-, and 3-year locoregional recurrence-free survival rates were 90.9, 86.1, and 78.9%, respectively, in the low HbA1c group, and 45.1, 27.1, and 20.3%, respectively, in the high HbA1c group ($p < 0.001$). The 1-, 2-, and 3-year distant metastasis-free survival rates were 67.2, 57, and 57%, respectively, in the low HbA1c group, while it was 56.6, 24.9, and 24.9%, respectively, in the high HbA1c group ($p = 0.024$). HbA1c level remained a significant prognostic factor for locoregional recurrence-free survival in the multivariable analysis ($p = 0.010$).

Conclusions: Chronic hyperglycemia is a significant prognostic factor for locoregional recurrence-free survival in patients with limited-stage small cell lung cancer treated with radical RT. Routine monitoring of plasma glucose levels and aggressive glycemic control should be conducted to prevent locoregional recurrence.

KEYWORDS
hyperglycemia, locoregional recurrence, lung cancer, radiotherapy

INTRODUCTION

It is well known that a chronic hyperglycemic state causes vascular occlusion and alterations in blood viscosity, which contribute to micro−/macrovascular occlusion and tissue hypoxia.[1–4] Therefore, a chronic hyperglycemic state may be associated with tumor hypoxia in patients with cancer. Although this hypothesis is a matter of speculation, which should be confirmed in in vivo and in vitro experimental studies, it is a reasonable inference.

In our previous study, we evaluated the association between blood glucose levels and survival outcomes in patients with stage III non-small cell lung cancer who were treated with radical radiotherapy (RT). In that study, the patient group with hemoglobin A1c (HbA1c) >6% had a higher risk of locoregional recurrence than the group with

HbA1c ≤6%, with a relative risk of 2.014.[5] We assumed that we could obtain such results in our previous study because HbA1c reflects the mean plasma glucose level for the previous 3 months, and hypoxic tumors are resistant to RT.[6–8]

In this study, we evaluated the association between plasma glucose levels in terms of HbA1c and locoregional recurrence-free survival in patients with limited-stage small cell lung cancer treated with radical RT.

METHODS

The inclusion criteria were histologically proven limited-stage small cell lung cancer, radical RT with or without chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, no prior thoracic irradiation, no previous or concurrent illness that would compromise the completion of treatment, and available follow-up data. Patients without evaluable pre-RT HbA1c levels were excluded from the study. From March 2015 to March 2020, 156 patients with pathologically confirmed limited-stage small cell lung cancer received RT at our institution. Of these patients, we excluded 27 who received palliative RT, 26 who had an ECOG performance status ≥3, 11 who had prior thoracic irradiation, and 13 who did not have available follow-up data. Twenty patients without available pre-RT HbA1c data were also excluded. Finally, 59 patients met the inclusion criteria and were included in this study. Hospital records, including the results of imaging and laboratory studies of all patients, were retrospectively reviewed. The Institutional Review Board of our institution approved this retrospective study and waived the need for written informed consent because it was a retrospective observational study (KHUH-2022-01-017). The study was conducted in compliance with the principles of the Helsinki Declaration and registered in the Clinical Research Information Service (CRIS) Registration System (KCT0006995).

Pathological confirmation of the initial diagnosis was made in all patients using either a percutaneous needle or an endoscopic bronchial biopsy. The detailed methods of initial diagnosis and pretreatment evaluation have been described in our previous studies.[9,10] Briefly, chest and abdomen computed tomography (CT), brain magnetic resonance imaging (MRI), and positron emission tomography (PET) were checked in all patients. Patients were then evaluated to determine whether their tumor masses could safely be encompassed in a tolerable definitive RT plan. HbA1c and fasting glucose levels were measured 1 week before the start of RT in all patients. All patients underwent CT-planned RT. The detailed RT methods have been described in our previous studies.[10,11] Briefly, the gross tumor volume (GTV) encompassed the primary tumor and grossly involved lymph nodes. 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. In the patients who underwent four-dimensional CT simulation, the PTV was created by adding a 3–5 mm margin. The preferred chemotherapy regimen was etoposide plus carboplatin, and chemotherapy was conducted concurrently with RT, if possible. The prescription RT dose and chemotherapy regimen were individualized based on the patient's general condition and compliance. The most common RT fractionation schedule was 66 Gy with a daily 2.2 Gy, with 15 patients receiving this fractionation schedule. The second most common fractionation schedule was 54 Gy with a daily 1.8 Gy, with 12 patients receiving this fractionation schedule.

Follow-up visits were scheduled 2 weeks after the completion of RT and every 2–3 months thereafter. Visits were more frequent among patients who experienced treatment-related toxicities. During the follow-up visit, a complete history and physical examination, basic laboratory studies, chest radiographs, and chest CT scans were performed. PET was performed as required. Salvage treatment, such as

TABLE 1 Patient and tumor characteristics

Characteristics	N (%)
Age (years) Median (range)	65.1 (42–86.9)
Gender Male/female	51 (86.4)/8 (13.6)
Smoking status Current/former/never	40 (67.8)/13 (22)/6 (10.2)
ECOG performance status 0/1/2	22 (37.3)/30 (50.8)/7 (11.9)
Location Right/left Upper or middle/lower	33 (55.9)/26 (44.1) 38 (64.4)/21 (35.6)
RT technique 3D-CRT/IMRT	28 (47.5)/31 (52.5)
Total RT dose (BED, Gy_{10}) Median (range)	69.8 (53.1–84.9)
Daily RT dose (Gy) Median (range)	2 (1.8–3)
RT interruption Yes/No	10 (16.9)/49 (83.1)
RT duration (weeks) Median (range)	6 (3–8)
Chemotherapy Yes/No	54 (91.5)/5 (8.5)
Chemotherapy types Concurrent/sequential	35 (64.8)/19 (35.2)
Diabetes mellitus Yes/No	13 (22.1)/46 (77.9)
Hemoglobin A1c (%) Median (range)	5.9 (4.8–11.8)
Fasting glucose (mg/dl) Median (range)	118 (73–547)
Hemoglobin (g/dl) Median (range)	12.4 (7.3–14.9)

Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; BED, biologically equivalent dose; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiotherapy; RT, radiotherapy.

TABLE 2 Survival outcomes of the whole patients

Survival endpoint	Median survival time (months)	Survival rate (%)		
		1-year	2-year	3-year
Overall	24	79.7	66.1	56.1
Locoregional recurrence-free	15.6	71.6	60.6	57
Distant metastasis-free	15	61.2	43.3	43.3

TABLE 3 Characteristics of the low and high hemoglobin A1c groups

Characteristics	Hemoglobin A1c (%)		*p*-value
	≤6 ($n = 35$)	>6 ($n = 24$)	
Age (years) Median (range)	65.1 (49.6–86.9)	66 (42–83)	0.826
Gender Male/female	30/5	21/3	0.794
Smoking status Current/former/never	24/8/3	16/5/3	0.882
ECOG performance status 0/1/2	14/16/5	8/14/2	0.594
Location	18/17	15/9	0.400
Right/left	26/9	12/12	0.056
Upper or middle/lower			
RT technique 3D-CRT/IMRT	16/19	12/12	0.746
Total RT dose (BED, Gy_{10}) Median (range)	72 (53.1–84.9)	64.26 (53.1–84)	0.284
Daily RT dose (Gy) Median (range)	2 (1.8–3)	1.9 (1.8–3)	0.845
RT interruption Yes/No	8/27	2/22	0.144
RT duration (weeks) Median (range)	6 (3–8)	6 (3–7)	0.681
Chemotherapy Yes/No	31/4	24/0	0.053
Chemotherapy types Concurrent/sequential	23/8	13/11	0.121
Diabetes mellitus Yes/No	2/33	11/13	<0.001
Fasting glucose (mg/dl) Median (range)	109 (73–185)	159 (76–547)	0.001
Hemoglobin (g/dl) Median (range)	12.9 (7.3–14.9)	11.6 (7.7–14.2)	0.066

Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; BED, biologically equivalent dose; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiotherapy; RT, radiotherapy.

surgical resection, RT, or chemotherapy, was performed in patients with confirmed locoregional recurrence or distant metastasis, as required.

The primary endpoint of this study was locoregional recurrence-free survival. The secondary endpoints were overall and distant metastasis-free survival. Locoregional recurrence and distant metastasis were defined in our previous study.[11] Briefly, locoregional recurrence was defined as evidence of tumor recurrence in the ipsilateral thorax, ipsilateral and/or contralateral hilum, mediastinum, and supraclavicular lymph node regions. Distant metastasis was defined as evidence of tumor in any other area. Because no uniform method was available for defining the cutoff value of HbA1c, we defined the best cutoff value of HbA1c as 6%, referring to our previous results.[5] Using this cutoff value, patients were allocated to either the low or high HbA1c groups. Baseline characteristics between the groups were compared using the Wilcoxon rank-sum test for discrete variables and the Mann–Whitney U test for continuous variables. Actuarial survival rates of both groups were estimated using the Kaplan–Meier method and compared using log-rank tests to verify whether HbA1c level was a significant prognostic factor for survival. If confirmed significant, HbA1c was further analyzed by multivariable analysis including other variables which were found to have a *p*-value <0.50 on univariable analysis. As diabetes mellitus, HbA1c, and fasting glucose are closely associated with one another, we included them separately in the multivariable analysis. The detailed statistical methods have been described in our previous study.[5]

RESULTS

The patient and tumor characteristics are summarized in Table 1. A total of 35 patients underwent concurrent chemotherapy. Among them, 25 and seven patients received additional adjuvant and induction chemotherapy, respectively, in conjunction with concurrent chemotherapy. In addition, one patient received induction and adjuvant chemotherapy in conjunction with concurrent chemotherapy. Nineteen patients underwent sequential chemotherapy. Among them, 18 and one patient received induction and adjuvant chemotherapy, respectively. The most common chemotherapy regimen was etoposide plus cisplatin. Among the 54 patients who received chemotherapy, 52 received the etoposide plus cisplatin regimen. The remaining two patients received irinotecan plus carboplatin. The median follow-up duration for all patients was 24 months (range, 4–144).

The survival outcomes of all patients are summarized in Table 2. During the follow-up period, 28 patients died. Almost all deceased patients died because of small cell lung cancer progression. However, five died of pneumonia, while three died of leukemia, colon cancer, and coronary heart disease, respectively. The 1-, 2-, and 3-year overall survival rates of all patients were 79.7, 66.1, and 56.1%, respectively.

Twenty-six patients experienced locoregional recurrences, while 33 patients experienced distant metastases. Among these patients, 19 experienced both locoregional

TABLE 4 Survival outcomes according to pretreatment hemoglobin A1c level

Survival endpoint	HbA1c (%)	Median survival time (months)	Survival rate (%)			*p*-value
			1-year	2-year	3-year	
Overall	≤6	29	85.7	72.2	63.6	0.080
	>6	21.7	70.8	56.9	45.5	
Locoregional recurrence-free	≤6	24	90.9	86.1	78.9	<0.001
	>6	10.8	45.1	27.1	20.3	
Distant metastasis-free	≤6	20	67.2	57	57	0.024
	>6	14.1	56.6	24.9	24.9	

Abbreviations: HbA1c; hemoglobin A1c.

TABLE 5 Prognostic factors for locoregional recurrence-free survival

Variables	2-year survival rate (%)	Univariable *p*-value	Multivariable[a]		
			Hazard ratio	95% confidence interval	*p*-value
Age (years) < 65 vs. ≥65	53.7 vs. 66.1	0.328	1.076	0.432–2.678	0.875
Gender Male vs. female	60.8 vs. 60	0.640			
Smoking status Current vs. former or never	57.5 vs. 66.9	0.287	0.825	0.298–2.284	0.711
ECOG performance status 0 vs. 1–2	66 vs. 56	0.780			
RT technique 3D-CRT vs. IMRT	60.4 vs. 61.1	0.879			
Total RT dose (BED, Gy_{10}) ≤ 70 vs. >70	57.8 vs. 64.7	0.569			
RT duration (weeks) ≤ 6 vs. >6	60.1 vs. 66.7	0.364	0.663	0.203–2.172	0.498
Chemotherapy Concurrent vs. sequential	63.7 vs. 47.2	0.212	1.326	0.433–4.056	0.612
Diabetes mellitus Yes/No	33.8 vs. 67.5	0.013	0.564	0.137–2.316	0.427
Hemoglobin A1c (%) ≤ 6 vs. >6	86.1 vs. 27.1	<0.001	3.959	1.385–11.315	0.010
Fasting glucose (mg/dl) ≤ 120 vs. >120	65.5 vs. 55.1	0.310	0.782	0.261–2.348	0.662
Hemoglobin (g/dl) ≤ 12.5 vs. >12.5	47 vs. 79.2	0.071	0.823	0.293–2.314	0.711

Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; BED, biologically equivalent dose; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiotherapy; RT, radiotherapy.
[a]The first group is the reference category for the calculation of the hazard ratio and 95% confidence interval.

recurrences and distant metastasis. Among the seven patients who only experienced locoregional recurrence without distant metastasis, three received salvage RT with concurrent chemotherapy, one received salvage RT, and three refused salvage treatment. The 1-, 2-, and 3-year locoregional recurrence-free survival rates of all patients were 71.6, 60.6, and 57%, respectively. Almost all 33 patients who experienced distant metastasis received palliative chemotherapy, except for three who refused palliative treatment. The 1-, 2-, and 3-year distant metastasis-free survival rates of all patients were 61.2, 43.3, and 43.3%, respectively.

Using cutoff values of 6%, 35 and 24 patients were allocated to the low and high HbA1c groups, respectively. The patient and tumor characteristics of both groups are summarized in Table 3. The number of patient with diabetes and the serum level of fasting glucose were significantly higher in the high HbA1c group. We analyzed the survival outcomes according to HbA1c levels, and the results are summarized in Table 4. HbA1c levels were significantly associated with locoregional recurrence-free and distant metastasis-free survival. The 1-, 2-, and 3-year locoregional recurrence-free survival rates were 90.9, 86.1, and 78.9%,

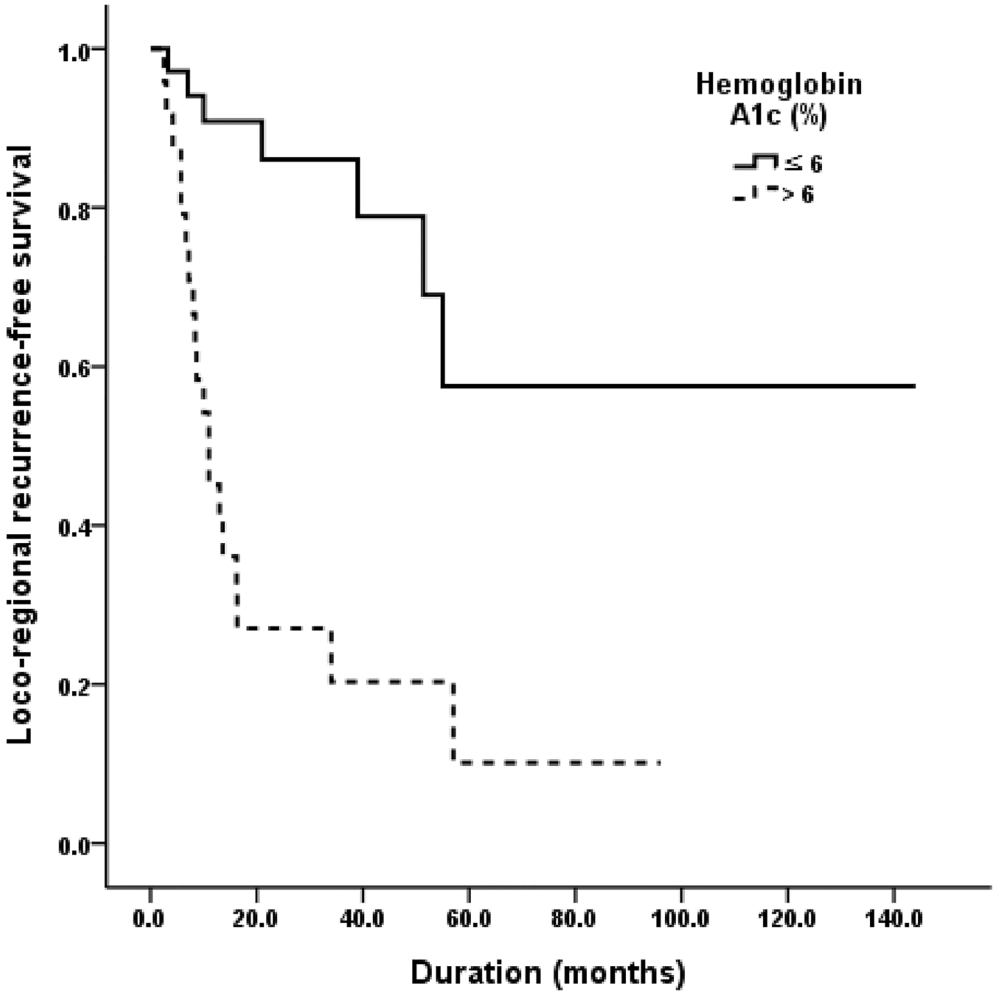

FIGURE 1 Locoregional recurrence-free survival curve according to hemoglobin A1c levels. The 1-, 2-, and 3-year locoregional recurrence-free survival rates were 90.9, 86.1, and 86.1%, respectively, in the patient group with low hemoglobin A1c levels and 54.2, 27.1, and 20.3%, respectively, in the patient group with high hemoglobin A1c levels ($p < 0.001$ in univariate and $p = 0.010$ in multivariate analysis)

respectively, in the low HbA1c group, and 45.1, 27.1, and 20.3%, respectively, in the high HbA1c group ($p < 0.001$). The 1-, 2-, and 3-year distant metastasis-free survival rates were 67.2, 57, and 57%, respectively, in the low HbA1c group, and 56.6, 24.9, and 24.9%, respectively, in the high HbA1c group ($p = 0.024$).

Univariable and multivariable analyses, including other variables, were conducted to identify whether HbA1c level was a significant prognostic factor for locoregional recurrence-free survival, with the results summarized in Table 5. In univariable analysis, diabetes mellitus ($p = 0.013$) and HbA1c ($p < 0.001$) were significantly associated with locoregional recurrence-free survival. Patients with diabetes mellitus or high HbA1c levels (>6%) had poor locoregional recurrence-free survival. HbA1c level remained a significant prognostic factor for locoregional recurrence-free survival in the multivariable analysis (hazard ratio = 3.959, 95% confidence interval = 1.385–11.315, $p = 0.010$) (Figure 1).

To identify whether HbA1c level is a significant prognostic factor for distant metastasis-free survival, univariable and multivariable analyses were conducted, with the results summarized in Table 6. Univariable analysis showed that the type of chemotherapy ($p = 0.027$), HbA1c ($p = 0.024$), and Hb ($p = 0.011$) were significantly associated with distant metastasis-free survival. Patients who received sequential chemotherapy showed poor distant metastasis-free survival compared to those who received concurrent chemotherapy. Patients with high HbA1c levels (>6%) or low Hb levels (≤12.5 g/dl) also showed poor distant metastasis-free survival. In the multivariable analysis, only the Hb level remained a significant prognostic factor for distant metastasis-free survival (hazard ratio = 0.378, 95% confidence interval = 0.143–1.000, $p = 0.049$) (Figure 2).

DISCUSSION

This retrospective study evaluated the association between plasma glucose levels and survival outcomes in 59 patients with limited-stage small cell lung cancer treated with radical RT, and found that a chronic hyperglycemic status, which is represented by the HbA1c level, is a significant prognostic factor for locoregional recurrence-free survival. Patients with chronic hyperglycemia (HbA1c > 6%) had a higher risk of locoregional recurrence, with a relative risk of 3.959. In our previous study, we found that chronic hyperglycemia significantly increased the risk of developing locoregional

TABLE 6 Prognostic factors for distant metastasis-free survival

Variables	2-year survival rate (%)	Univariable *p*-value	Multivariable[a]		
			Hazard ratio	95% confidence interval	*p*-value
Age (years) < 65 vs. ≥65	40.9 vs. 45.8	0.443	0.879	0.397–1.946	0.750
Gender Male vs. female	46.9 vs. 25	0.500			
Smoking status Current vs. former or never	42.2 vs. 45.9	0.515			
ECOG performance status 0 vs. 1–2	58.5 vs. 34.5	0.074	1.538	0.677–3.494	0.304
RT technique 3D-CRT vs. IMRT	45.5 vs. 41.3	0.885			
Total RT dose (BED, Gy_{10}) ≤ 70 vs. >70	35.9 vs. 51	0.125	1.025	0.416–2.526	0.957
RT duration (weeks) ≤ 6 vs. >6	42.3 vs. 50	0.311	0.510	0.169–1.536	0.231
Chemotherapy Concurrent vs. sequential	54 vs. 26.3	0.027	1.288	0.496–3.346	0.603
Diabetes mellitus Yes/No	27.7 vs. 47	0.157	0.572	0.165–1.988	0.380
Hemoglobin A1c (%) ≤ 6 vs. >6	57 vs. 24.9	0.024	1.272	0.513–3.152	0.603
Fasting glucose (mg/dl) ≤ 120 vs. >120	51.5 vs. 33.8	0.133	1.285	0.541–3.054	0.570
Hemoglobin (g/dl) ≤ 12.5 vs. >12.5	30.4 vs. 63.6	0.011	0.378	0.143–1.000	0.049

Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; BED, biologically equivalent dose; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiotherapy; RT, radiotherapy.

[a]The first group is the reference category for the calculation of the hazard ratio and 95% confidence interval.

recurrence, with a relative risk of 2.014 in patients with stage III non-small cell lung cancer treated with radical RT.[5] This and our previous studies provide valuable information regarding the interaction between plasma glucose levels and the efficacy of RT in patients with cancer. Plasma glucose and HbA1c levels are easily derived and cost-effective blood parameters. If our results are confirmed by large-scale prospective studies, various convenient and cost-effective predictive models can be developed to predict treatment outcomes and individualize treatment strategies for high-risk patients.

It has been reported that DM and DM-related serological factors, such as HbA1c and fasting glucose levels, are significantly associated with the development of RT-induced toxicities in several studies.[12–16] We also evaluated the effects of pre-existing DM and DM-related serological factors on the development of radiation pneumonitis, and found that pre-existing DM, HbA1c, and fasting glucose levels were significant predictive factors for the development of grade ≥3 radiation pneumonitis.[10] However, no studies have evaluated the association between DM-related serological factors and RT response. The current and our previous studies[5] are the first to report the impact of chronic hyperglycemia on survival outcomes in patients with cancer treated with radical RT.

Several studies have reported that lower Hb levels are correlated with detrimental tumor oxygenation status. Vaupel et al. proved that tumor hypoxia is more frequent in anemic animals than in nonanemic animals in their experimental study.[17] Rudat et al. found significantly larger hypoxic fractions of tumors in patients with low Hb levels (≤11 g/dl) than in those with high Hb levels (>11 g/dl).[18] Clavo et al. also reported that tumor hypoxic fractions were higher in anemic patients than in nonanemic patients in their clinical study.[19] However, no study has evaluated the association between plasma glucose levels and tumor oxygenation status. Although we do not know the exact relationship between chronic hyperglycemia and tumor oxygenation status at this point, we suggested possible reasons why patients with chronic hyperglycemia showed poor locoregional recurrence-free survival after RT in our previous study.[5] Briefly, overall perfusion rates in tumors are lower than those in normal tissues, which increases the risk of both acute and chronic hypoxia in tumors.[20–22] Long-standing hyperglycemia causes an increase in inflammation and oxidative stress, accumulation of advanced glycosylation end products in the subendothelial space, endothelial dysfunction, and hypercoagulability.[1,2,23] As a result, tumor hypoxia worsens in chronically hyperglycemic state. Preclinical and clinical studies are required to confirm our

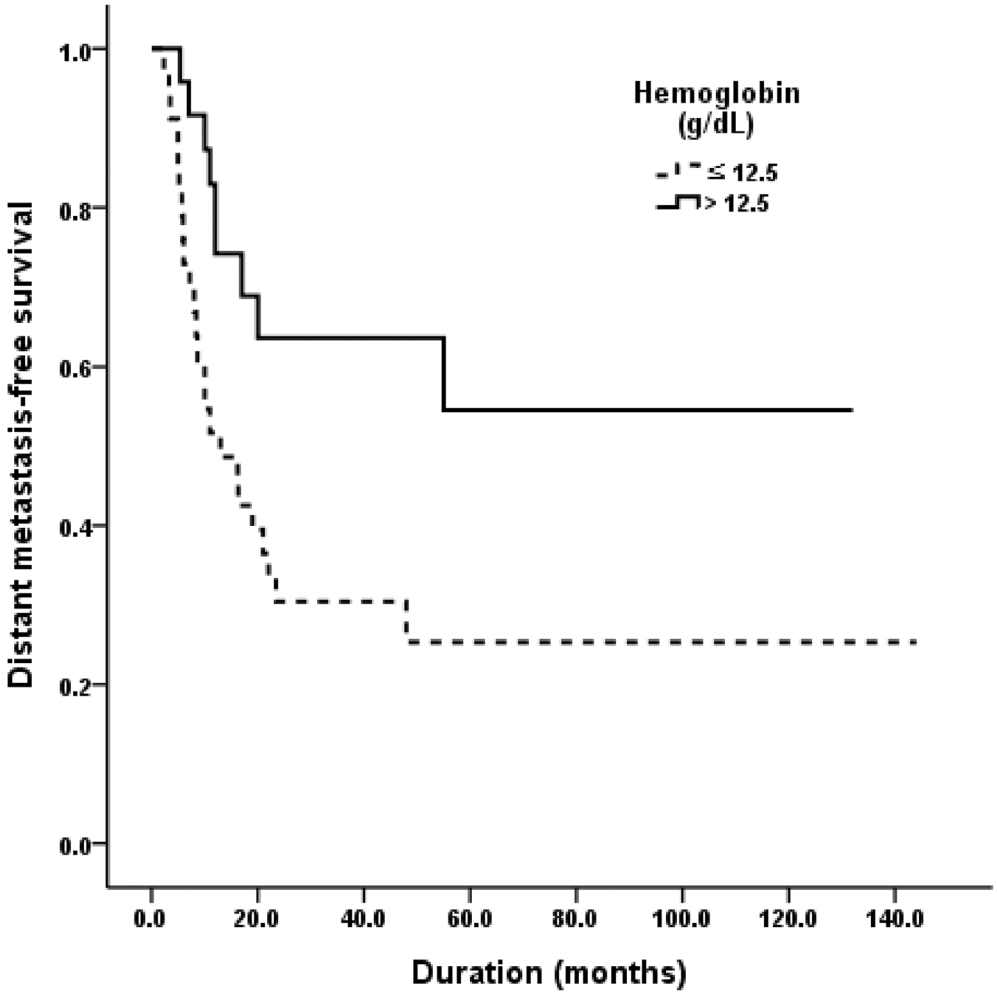

FIGURE 2 Distant metastasis-free survival curve according to hemoglobin levels. The 1-, 2-, and 3-year distant metastasis-free survival rates were 51.7, 30.4, and 30.4%, respectively, in the patient group with low hemoglobin levels and 82.9, 63.6 and 63.6%, respectively, in the patient group with high hemoglobin levels ($p = 0.011$ in univariate and $p = 0.049$ in multivariate analysis)

hypothesis and the relationship between plasma glucose levels and tumor oxygenation status.

In our previous study, chronic hyperglycemia was significantly associated with locoregional recurrence-free survival, but not with distant metastasis-free survival.[5] The results of the current study were similar to those of our previous study ($p = 0.010$ for locoregional recurrence-free survival and $p = 0.603$ for distant metastasis-free survival in multivariable analysis). Because tumor hypoxia, which is aggravated in a chronic hyperglycemic state, exerts an adverse effect on radiation response, locoregional recurrence-free survival might be mainly influenced by chronic hyperglycemia rather than distant metastasis-free survival. However, several studies have reported that tumor hypoxia promotes gene mutation, tumor angiogenesis, and can increase the development of distant metastasis.[24–26] In the current study, the patient group with chronic hyperglycemia (HbA1c > 6%) showed significantly worse distant metastasis-free survival in the univariable analysis, although the significance was lost in the multivariable analysis. Additional studies with larger sample sizes are required to identify the relationship between chronic hyperglycemia and the development of distant metastasis.

This study has several limitations. First, it was a retrospective study; therefore, it may have had inherent biases. For example, we excluded patients without evaluable pre-RT HbA1c levels, which may have introduced an unintended selection bias. Second, the sample size was small because the patients in this study were from a single center. Therefore, minor differences may not have been detected in the statistical analyses. Third, treatment characteristics were heterogeneous. RT fractionation schedules and chemotherapy regimens were decided based on the patient's general condition and compliance rather than using a predetermined protocol. Fourth, the follow-up period was not long. Finally, the role of chemotherapy remains unclear. We focused our discussion on the relationship between chronic hyperglycemia and RT response in this study. However, because the majority of patients received additional chemotherapy in conjunction with radical RT, further studies should be conducted to explore the relationship between chronic hyperglycemia and chemotherapy response. These limitations may have made it difficult to interpret the results. However, despite these limitations, we firstly found an association between plasma glucose levels and the efficacy of RT in patients with small cell lung cancer. In our previous study, we reported the impact of plasma glucose levels on the efficacy of RT in patients with non-small cell lung cancer.[5] Although prospective studies with large sample sizes should be conducted to confirm

our results, we believe that plasma glucose levels can be effectively used to predict treatment outcomes in patients with cancer treated with RT. In addition, we hope to conduct further studies to evaluate the prognostic effect of plasma glucose levels in several cancers other than those of the lung.

In conclusion, the plasma glucose level is a significant prognostic factor for locoregional recurrence-free survival in patients with limited-stage small cell lung cancer treated with radical RT. Routine monitoring of plasma glucose levels and aggressive glycemic control should be conducted to prevent locoregional recurrence in these patients.

ACKNOWLEDGMENTS

The authors would like to thank to Uin Kong for writing assistance and Editage (www.editage.co.kr) for the English language editing. This study was supported by the National Research Foundation (NRF) grant funded by the Korea government (Ministry of Science & ICT) (2022R1F1A1074912).

CONFLICT OF INTEREST

Authors have no conflict of interest.

CLINICAL TRIAL REGISTRATION

This study was registered in the Clinical Research Information Service (CRIS) Registration System (KCT0006995).

ORCID

Moonkyoo Kong https://orcid.org/0000-0003-3703-0417
Yu Jin Lim https://orcid.org/0000-0003-2243-8989

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How to cite this article: Kong M, Lim YJ. Chronic hyperglycemia is an adverse prognostic factor for locoregional recurrence-free survival in small cell lung cancer patients treated with radical radiotherapy. Thorac Cancer. 2022. https://doi.org/10.1111/1759-7714.14601