Combined Chemoradiotherapy-induced Weight Loss Decreases Survival in Locally Advanced Non-small Cell Lung Cancer Patients

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Abstract. *Background/Aim:* The aim of the study was to investigate the prognostic impact and predictors of weight loss during definitive radiotherapy in non-small cell lung cancer (NSCLC) patients. *Patients and Methods:* A total of 125 NSCLC patients (2003-2016) who had received definitive radiotherapy were included in the study. Multivariate analyses were performed to estimate prognostic values. Predictors for weight loss were analyzed. *Results:* The median survival of patients with weight loss (>5%) during radiotherapy and for those without any significant weight loss was 15.6 and 33 months, respectively ($p=0.015$). Non-intensity modulated radiotherapy (IMRT) technique was the only factor associated with weight loss ($p=0.039$). Weight loss was a poor prognostic factor for overall survival (OS) (hazard ratio [HR] 2.072, $p=0.018$), and IMRT was a favorable prognostic factor (HR=0.192, $p=0.029$). *Conclusion:* During definitive radiotherapy, weight loss of >5% resulted in decreased OS rate in locally advanced NSCLC. IMRT might increase OS rate by minimizing weight loss.

Despite the availability of optimal treatments for patients with locally advanced non-small cell lung cancer (NSCLC), the median survival of patients is only 20-30 months (1).

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Thus, there is a critical need to develop various strategic approaches to improve prognosis in lung cancer patients.

In addition to the interaction between cancer cells and treatment protocols for cancer, host status is also an important determinant of the prognosis of cancer patients (2). To date, body weight and its change are emerging as significant prognostic factors in cancer patients.

In NSCLC patients, although several studies have also demonstrated that weight loss during chemo-radiotherapy is a prognostic factor, classical causes of weight loss, such as radiation esophagitis can be changed with the development of therapeutic methods (3, 4). In addition, none of the patients in these studies were treated with intensity-modulated radiotherapy (IMRT). Therefore, the major predictors of radiotherapy-related weight loss have not been well-defined for the NSCLC patients in the IMRT era.

In our study, the prognostic impact and the predictors of weight loss were evaluated for NSCLC patients receiving definitive radiotherapy including IMRT.

Patients and Methods

Patient selection. This study retrospectively reviewed a group of NSCLC patients who were treated with radiotherapy at a single institution during the years 2003-2016. Patients who fulfilled the following criteria were included in this study: ≥ 20 years of age, pathologically diagnosed, treated with definitive radiotherapy, and information about their body weight before (within one month) and after radiotherapy (within one month). Patients were excluded based on the following criteria: evidence of distant metastasis, surgery as the first course of treatment before or after radiotherapy, previously received radiotherapy for the same lesion, had double malignant tumors except cured cancers or early stage thyroid cancer.

The cancer stage was evaluated based on the guidelines of the American Joint Committee on Cancer-8th edition. Patients' comorbid conditions were scored by the Charlson Comorbidity Index (CCI). This study was approved by the Institutional Review Board of our institution.

Treatment options. All of our patients received definitive radiotherapy. Induction and/or concurrent chemotherapies were allowed as treatment options. Three-dimensional conformal radiotherapy (3D-CRT), or IMRT were used for treating our patients.

For 3D-CRT and IMRT, gross tumor volume (GTV) included the primary disease as well as involved regional lymph nodes. Clinical target volume (CTV) was 7 mm around the GTV. For planning target volume (PTV)-1 and PTV-2, 7 and 1.0 cm margin was added to the CTV and GTV, respectively. Total radiotherapy doses prescribed to the PTV-1 and PTV-2 were ≥ 44 Gy and ≥ 60 Gy, respectively. The simultaneously integrated boost (SIB) technique was generally used for IMRT. Elective nodal irradiation was not performed unless patients exhibited lymph node involvement.

Body weight changes. Body weight (kg) and BMI [weight (kg)/height² (m²)] were assessed within one month before and after radiotherapy. Following the classification used by a previous study, demonstrating that East Asians with a BMI between 22.6 and 27.5 show a low risk of death (5), our patients were classified into three groups based on BMI values (<22.6, 22.6-27.5, and >27.5).

Follow-up examination. All patients were examined at least once a week during radiotherapy. After completion of radiotherapy, the follow-up examination with chest computed tomography (CT) scan was performed at one month, and then every three months for the next three years followed by every six months for at least five years. Tumor response (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) was assessed during every follow-up examination of the patient. In cases of suspected metastasis, additional tests, such as positron emission tomography (PET)-CT scan, were performed. Treatment-related toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Statistical analysis. Loco-regional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), and OS were defined as the interval between the first date of treatment (radiotherapy and/or chemotherapy) and the date of loco-regional recurrence, distant metastasis, and death from any cause, respectively, or the date of last follow-up.

For univariate analysis, the Kaplan–Meier survival estimate was compared using a log-rank test. Statistically significant variables (with a p -value<0.2) were identified as candidate prognostic factors and incorporated in a multivariate Cox regression analysis. The Pearson's chi-square test was performed to compare the characteristics of patients who experienced weight loss with those who did not. SPSS version 25.0 for Windows was used for all analyses. Plots were generated using the R software (R Project, version R-3.5.1; R Foundation for Statistical Computing, Vienna, Austria) (packages: 'survival', 'survminer', and 'ggplot2').

Results

Comparison of patient characteristics according to weight loss. The median time interval from the last day of radiotherapy to the day of weight measurement was 0.3 months (range=0-1 months). During radiotherapy, 20.8% of patients experienced a weight loss of >5%. A weight loss of >5% was observed at a significantly high frequency in patients not treated with IMRT ($p=0.039$). Radiotherapy-

induced esophagitis and pneumonitis were not significantly associated with weight loss of >5% ($p=0.506$ and $p=0.121$, respectively) (Table I).

Univariate analyses. For our patient population, the median survival was 32.5 months [95% confidence interval (CI)=25.8-39.1]. The median survival of patients who experienced a weight loss of >5% during radiotherapy was 15.6 months (95%CI=1.8-29.4), while the median survival of the remaining patients was 33 months (95%CI=19.4-46.6, $p=0.015$) (Table II).

The most favorable median survival was observed for the patients who had a BMI in the range of 22.6 to 27.5 compared to the other patient groups (33.0 months, 95%CI=16.0-50.0). For patients with BMI <22.6 and >27.5, the median survival times were 29.6 months (95% CI=16.3-42.9) and 21.0 months (6.5-35.4), respectively. Patients who were treated with IMRT ($p=0.033$) and those who received a total dose of ≥ 66 Gy ($p=0.124$) showed increased OS.

Multivariate analyses. Multivariate analysis demonstrated that a weight loss of > 5% was associated with a significantly poor OS rate [hazard ratio (HR)=2.702, 95% confidence interval (CI)=1.131-3.794, $p=0.018$] (Figure 1c). Patients who received radiotherapy [a total dose of ≥ 66 Gy (HR=0.340, 95%CI= 0.168-0.687, $p=0.003$)] in combination with IMRT (HR=0.192, 95%CI=0.044-0.844, $p=0.029$) showed better OS rates than those who received a radiation dose of <66 Gy and were treated with 3D-CRT.

LRRFS and DMFS rates for patients with or without weight loss of >5%. Multivariate analyses, incorporating the same variables that were used in the multivariate analysis for determining the OS rate, were also performed for estimating LRRFS and DMFS rates. The results showed that during radiotherapy, a weight loss of >5% did not decrease the LRRFS rate (HR=0.932, 95%CI=0.419-2.073, $p=0.863$) but did reduce the DMFS rate (HR 2.299, 95%CI=1.183-4.470, $p=0.014$) (Figure 1a and b).

Treatment-related toxicities. Radiotherapy-induced esophagitis was observed in 22 of 125 patients. The number of patients with grades 1, 2, and 3 esophagitis was 10, 10, and 2, respectively. Median time to develop esophagitis was found to be 3 weeks (range=1.5 weeks-3 months) following initiation of radiotherapy. Both patients with grade 3 esophagitis had to be hospitalized due to their condition. One of them showed weight gain of <5% and the other weight loss of $\leq 5\%$ during the course of radiotherapy.

Radiotherapy-induced pneumonitis was observed in 40 patients, and the median time for the development of radiotherapy-induced pneumonitis was 4.7 months (range=0.9-16.3 months) after initiating the therapy. Grades 3 or higher pneumonitis was not observed in our patient group.

Table I. Characteristics of patients with weight loss of 5% or more.

Characteristics	Weight loss of >5%				<i>p</i> -Value [†]
	No		Yes		
	No.	(%)	No.	(%)	
All	99	(100.0)	26	(100.0)	
Age					
<65	38	(38.4)	12	(46.2)	0.472
≥65	61	(61.6)	14	(53.8)	
Gender					
Male	83	(83.8)	22	(84.6)	0.923
Female	16	(16.2)	4	(15.4)	
ECOG performance status					
0-1	84	(84.8)	21	(80.8)	0.614
2	15	(15.2)	5	(19.2)	
CCI					
2-4	42	(42.4)	11	(42.3)	0.991
≥5	57	(57.6)	15	(57.7)	
Prior smoking history					
No	16	(16.2)	6	(23.1)	0.410
Yes	83	(83.8)	20	(76.9)	
Histology					
Adenocarcinoma	32	(32.3)	10	(38.5)	0.211
Squamous cell carcinoma	58	(58.6)	11	(42.3)	
NSCLC, NOS	9	(9.1)	5	(19.2)	
T stage					
T1	22	(22.2)	8	(30.8)	0.745
T2	32	(32.3)	9	(34.6)	
T3	29	(29.3)	6	(23.1)	
T4	16	(16.2)	3	(11.5)	
N stage					
N0	11	(11.1)	3	(11.5)	0.553
N1	6	(6.1)	1	(3.8)	
N2	47	(47.5)	9	(34.6)	
N3	35	(35.4)	13	(50.0)	
Induction chemotherapy					
No	35	(35.4)	12	(46.2)	0.312
Yes	64	(64.6)	14	(53.8)	
Concurrent chemotherapy					
No	20	(20.2)	5	(19.2)	0.912
Yes	79	(79.8)	21	(80.8)	

Characteristics	Weight loss of >5%				<i>p</i> -Value [†]
	No		Yes		
	No.	(%)	No.	(%)	
RT total dose					
<66 Gy	25	(25.3)	2	(7.7)	0.053
≥66 Gy	74	(74.7)	24	(92.3)	
RT modality					
3D-CRT	78	(78.8)	25	(96.2)	0.039
IMRT	21	(21.2)	1	(3.8)	
RT response					
CR	4	(4.0)	0	(0.0)	0.777
PR	80	(80.8)	22	(84.6)	
SD	8	(8.1)	2	(7.7)	
PD	7	(7.1)	2	(7.7)	
BMI before RT					
<22.6	43	(43.4)	12	(46.2)	0.923
22.6-27.5	46	(46.5)	12	(46.2)	
>27.5	10	(10.1)	2	(7.7)	
BMI after RT					
<22.6	43	(43.4)	20	(76.9)	0.006
22.6-27.5	44	(44.4)	6	(23.1)	
>27.5	12	(12.1)	0	(0.0)	
RT induced esophagitis					
No	79	(79.8)	24	(92.3)	0.506
Grade 1	9	(9.1)	1	(3.8)	
Grade 2	9	(9.1)	1	(3.8)	
Grade 3	2	(2.0)	0	(0.0)	
RT induced pneumonitis					
No	63	(63.6)	22	(84.6)	0.121
Grade 1	35	(35.4)	4	(15.4)	
Grade 2	1	(1.0)	0	(0.0)	

ECOG: Eastern Cooperative Oncology Group; CCI: the Charlson comorbidity index; NSCLC: non-small cell lung cancer; NOS: not otherwise specified; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; RT: radiotherapy; 3D-CRT: 3-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; BMI: body mass index. [†]Pearson's Chi-square test.

ECOG: Eastern Cooperative Oncology Group; CCI: the Charlson comorbidity index; NSCLC: non-small cell lung cancer; NOS: not otherwise specified; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; RT: radiotherapy; 3D-CRT: 3-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; BMI: body mass index. [†]Pearson's Chi-square test.

These toxicities (radiotherapy-induced esophagitis and pneumonitis) and the severities of these conditions did not significantly decrease the OS rate in univariate analyses. None of the two patients with grade 3 esophagitis died during their follow-up period. The inclusion of these factors in multivariate analysis did not affect the prognostic variables that showed significant associations in the analysis, and radiotherapy-induced toxicity was not a poor prognostic factor for the OS rate.

Discussion

In locally advanced NSCLC patients, a weight loss of >5% during definitive radiotherapy resulted in a decrease in OS

rate. Additionally, the non-IMRT technique was found to be a significant predictor of weight loss of >5%.

There may be several possible explanations for the treatment-related weight loss in lung cancer patients. The first possible consideration could be weight loss owing to cancer progression. In our study, however, there were only two patients who experienced both >5% weight loss and progression of disease after radiotherapy. Therefore, it may be unreasonable to simply explain the link between patients' weight loss during treatment and their survival decrease as an inverse causality.

A second possible reason for weight loss could be the insufficient food intake by the patients. Treatment-related

Table II. Univariate and multivariate analyses.

Characteristics	UVA			MVA		
	Median	95%CI	p-Value [†]	HR	95%CI	p-Value [‡]
All	32.5	(25.8-39.1)				
Age						
<65	33.0	(20.6-45.5)				
≥65	32.5	(23.9-41.1)	0.426	NA		
Gender						
Male	29.6	(20.8-38.4)		Reference		
Female	54.1	NA	0.016	0.492	(0.175-1.382)	0.178
ECOG performance status						
0-1	32.5	(25.7-39.2)				
2	20.7	(0.0-43.0)	0.387	NA		
CCI						
2-4	36.5	(25.9-47.1)		Reference		
≥ 5	31.1	(19.7-42.5)	0.138	1.422	(0.814-2.485)	0.216
Prior smoking history						
No	51.4	(40.1-62.7)		Reference		
Yes	29.6	(18.9-40.4)	0.037	3.137	(1.203-8.179)	0.019
Histology						
Adenocarcinoma	46.7	(20.4-73.1)				
Squamous cell carcinoma	32.5	(30.4-34.5)	0.370	NA		
NSCLC, NOS	20.7	(13.9-27.4)				
T stage						
T1	29.6	(10.1-49.1)				
T2	26.1	(14.9-37.2)	0.701	NA		
T3	32.5	(18.4-46.6)				
T4	54.1	(7.0-101.1)				
N stage						
N0	46.6	(0.0-95.2)				
N1	50.9	NA	0.966	NA		
N2	26.1	(5.9-46.2)				
N3	32.1	(28.1-36.2)				
Induction chemotherapy						
No	23.6	(14.5-32.7)		Reference		
Yes	37.9	(20.6-55.1)	0.001	0.337	(0.186-0.609)	<0.001
Concurrent chemotherapy						
No	26.1	(14.2-38.0)				
Yes	32.6	(26.8-38.3)	0.589	NA		
RT total dose						
<66 Gy	21.0	(14.8-27.1)		Reference		
≥66 Gy	32.6	(26.7-38.4)	0.124	0.340	(0.168-0.687)	0.003
RT modality						
3D-CRT	31.1	(23.9-38.4)		Reference		
IMRT	Not reached	NA	0.033	0.192	(0.044-0.844)	0.029
RT response						
CR	67.0	(0.0-136.4)		Reference		
PR	32.6	(27.5-37.7)	0.005	2.093	(0.455-9.620)	0.343
SD	46.7	(0.0-99.6)		1.557	(0.287-8.437)	0.608
PD	16.8	(2.8-30.8)		4.552	(0.835-24.815)	0.080
BMI before RT						
22.6-27.5	33.0	(16.0-50.0)		Reference		
<22.6 or >27.5	29.6	(15.7-43.5)	0.198	2.092	(1.202-3.642)	0.009
BMI after RT						
22.6-27.5	32.6	(19.8-45.3)				
<22.6 or >27.5	31.1	(23.4-38.8)	0.448	NA		
Weight (%) loss during RT						
≤5%	33.0	(19.4-46.6)		Reference		
>5%	15.6	(1.8-29.4)	0.015	2.072	(1.131-3.794)	0.018

UVA: Univariate analysis; MVA: multivariate analysis; CI: confidence interval; HR: hazard ratio; NA: not applicable; ECOG: the Eastern Cooperative Oncology Group; CCI: the Charlson comorbidity index; NSCLC: non-small cell lung cancer; NOS: not otherwise specified; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; RT: radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; BMI: body mass index. [†]Kaplan–Meier survival estimate compared by a log rank test. [‡]Cox’s proportional hazards model.

Figure 1. Based on weight change during definitive radiotherapy, adjusted LRRFS, DMFS, and OS curves were prepared using the Cox model with a 5% cutoff. *p-Values: Multivariate analysis using the Cox proportional hazards model.

symptoms, such as nausea, vomiting, and esophagitis can induce a restriction of food intake (6). Therefore, identification of patients with a high risk of weight loss and intensive weight management during treatment would be helpful in improving survival outcomes (7).

Our study showed that radiotherapy-induced esophagitis or pneumonitis was not correlated with weight loss; this is likely due to grade 3 or higher toxicities observed in only three patients. However, radiation toxicity can be easily underestimated, and even mild loss of appetite or fatigue during radiotherapy may reduce food intake. Koom *et al.* demonstrated that approximately 40% of patients experienced malnutrition during radiotherapy, and anorexia was one of the major risk factors for malnourishment (8). Notably, among our patients who received IMRT, radiotherapy-related weight loss (>5%) occurred in only one patient. This observation suggests that IMRT may decrease the risk of weight loss by reducing the radiation dose to digestive organs and the radiation dose that causes weight loss may be lower than the dose causing radiation-induced toxicities.

The mechanism by which weight loss reduces the survival rate is not clear; however, it is strongly suggested that nutritional modulation is related to body's resilience and immunity (9). In our study, weight loss of >5% was significantly correlated with distant metastasis, implying an association between the body weight and immune system of the entire body. Thus, to prevent weight loss in patients who undergo definitive treatments, active nutritional support may be helpful to optimize and enhance the treatment effects (10-12).

Overweight status did not improve survival prognosis in our study. The patients who showed the most favorable prognosis were those who had a normal BMI (range=22.6-27.5) before radiotherapy. Unlike other studies that demonstrated the "obesity paradox" (13), this study lacked a sufficient number of obese patients. Therefore, further studies are needed to determine the significance of weight gain beyond normal weight in the affected patients.

Induction chemotherapy showed a good prognosis in our study. In previous studies, induction chemotherapy prior to radiotherapy did not improve survival outcomes (14). Being a retrospective study, it is likely that our patients who responded poorly to induction chemotherapy or those who showed a poor performance status after induction chemotherapy were less likely to receive additional radiotherapy.

Multivariate analysis revealed that the survival rates were significantly increased by IMRT and high dose radiotherapy (total dose of ≥ 66 Gy) relative to the conventional radiotherapy techniques and a low radiation dose (total dose of <66 Gy). It remains unclear whether an increase in radiation dose (>60 Gy) improves the survival rate of NSCLC patients (15). Nevertheless, high radiotherapy dose using SIB-IMRT technique has shown favorable results and thus may be considered as a promising treatment option for NSCLC patients.

One of the limitations of this study was the lack of food intake information of the patients. Although dietary information is considered to be one of the most important factors responsible for modulating weight change, it was difficult to obtain quantitative food intake information in a retrospective setting. Therefore, prospective studies are warranted to collect data regarding the periodic measurement of food intake and body weight during radiotherapy, and further tailor appropriate intervention strategies to prevent weight loss.

Authors' Contributions

JSK and CH conceived and designed the study. YJK collected the data and performed the analysis. CH and YJK wrote the paper. JSK, KYE, and IAK revised the manuscript. All Authors gave final approval of the version to be submitted and the revised version.

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