Significance of ^{18}F-FDG PET Parameters According to Histologic Subtype in the Treatment Outcome of Stage III Non–small-cell Lung Cancer Undergoing Definitive Concurrent Chemoradiotherapy

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Abstract

We examined the prognostic role of positron emission tomography-computed tomography (PET-CT) parameters in patients with stage III non–small-cell lung cancer treated with definitive chemoradiotherapy according to histology. With lower PET-CT parameters, adenocarcinoma showed significantly worse distant metastasis-free survival. Our results validate and highlight the need for consideration of histologic subtypes as well as PET-CT parameters when predicting clinical outcomes.

Purpose: We analyzed positron emission tomography-computed tomography (PET-CT) in patients with stage III non–small-cell lung cancer (NSCLC) undergoing concurrent chemoradiotherapy (CRT) to examine the prognostic value of PET-CT parameters according to histologic subtypes (squamous cell carcinoma [SqCC] and adenocarcinoma [ADC]). **Methods:** A total of 130 patients with stage III NSCLC who underwent definitive CRT were identified. We obtained PET-CT parameters such as maximum (SUV_{max}) and mean (SUV_{mean}) standardized uptake value, total lesion glycolysis (TLG), metabolic tumor volume (MTV), and coefficient of variation (CV). Each parameter was bifurcated based on the optimal cutoff, and propensity score matching was performed between the SqCC and ADC groups. **Results:** There were 108 patients with SqCC or ADC, and 44 patients each were allocated to the SqCC and ADC groups via propensity score matching. SUV_{max}, SUV_{mean}, TLG, and MTV values were significantly higher in SqCC than in ADC ($P = .004$, $P = .006$, $P = .003$, and $P = .03$, respectively). In the SqCC group, PET-CT parameters were not associated with survival outcomes. However, in the ADC group, SUV_{max} and SUV_{mean} were related to locoregional progression-free survival ($P = .008$ and $P = .017$, respectively), and TLG and MTV were related to overall survival ($P = .044$ and $P < .001$, respectively). In addition, patients with ADC showed more frequent distant metastasis ($P = .011$) and worse distant metastasis-free survival compared with patients with SqCC ($P = .009$). **Conclusions:** PET-CT provided different prognostic implications between SqCC and ADC in patients with locally advanced NSCLC receiving radical CRT. This suggests that it is necessary to consider the histologic subtype and PET-CT parameters concurrently when predicting survival outcomes.

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Introduction

Non–small-cell lung cancer (NSCLC) is one of leading causes of cancer-related death in Korea.[1] The majority of locally advanced NSCLC cases are inoperable. Although concurrent chemoradiotherapy (CRT) is used as the standard of care, local control and treatment outcomes remain poor in unresectable NSCLC. Therefore, considerable effort has been made to find prognostic factors in order to predict treatment results and improve treatment outcomes.[2]

18-fluoro-deoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) is already well-established for staging NSCLC and is also an important tool for the management of cancer. In addition, PET-CT has been used to predict treatment response or prognosis. The standardized uptake value (SUV) from PET-CT is the most commonly used parameter for disease characterisation and is associated with prognosis.[3] The volumetric parameters, including metabolic tumor volume (MTV) and total lesion glycolysis (TLG), have also been reported as prognostic factors for survival.[4-6] More recent studies evaluate the potential value of intratumoral heterogeneity from CT and PET-CT scans of NSCLC.[7-10] Still, a systematic review study showed inconsistent results, meaning that the value of PET-CT parameters in NSCLC needs further investigation.[11]

NSCLC includes several histologic subtypes. Because chemotherapy efficacy and biological features are different among subtypes, distinguishing squamous cell carcinoma (SqCC) from adenocarcinoma (ADC) is important for patients with advanced-stage NSCLC.[12] Furthermore, previous studies demonstrated remarkable differences in the expression of hypoxia- and glycolysis-related markers and PET-CT parameters according to the histologic type of resected NSCLC.[13,14] However, they analyzed patients with various stages with different treatment strategies. To overcome the limitation of the previous studies, the current study evaluated the difference and clinical value of PET-CT parameters according to the histologic subtype in patients with locally advanced NSCLC with uniformly received definitive CRT.

Patients and Methods

Patients and Treatment

After institutional review board approval, we retrospectively reviewed the medical records of patients with stage III NSCLC who received definitive CRT between February 2006 and January 2013. We identified 130 patients who underwent chest CT, FDG PET-CT, brain magnetic resonance imaging, and pulmonary function testing before treatment. In our institution, the treatment strategy was determined by the multidisciplinary clinic. If CRT was recommended, patients were referred to radiation oncologists and medical oncologists. Target volume was delineated based on primary tumor and metastatic nodal regions. Elective nodal irradiation was not routinely performed. The planning target volume was set using an individualized margin from the clinical target volume by considering lung motion, tumor location, and size. The concurrent chemotherapy regimen was determined by each patient's performance status, age, and medical comorbidities, including renal function.

PET-CT

All patients underwent Biograph PET-CT scans (Siemens Medical Solutions). Patients fasted for at least 6 hours before each scan, and 5.18 MBq/kg of FDG was intravenously injected. Images were obtained from the skull base to the upper thigh 1 hour after the administration of FDG. PET images were reconstructed using the iterative reconstruction algorithm (3D row-action maximum-likelihood algorithm), and the region of interest was automatically drawn over the primary tumor mass in the axial, coronal, and sagittal images. Voxels representing more than 40% of the SUV_{max} in the region of interest were included to define the tumor. AMIDE software (Stanford University) was used to analyze PET images (Figure 1). The SUVs were calculated as follows: SUV = FDG activity concentration/(injected FDG dose/lean body weight). The maximal and average SUV of primary tumor and lymph nodes were presented as SUV_{max} and SUV_{mean}, respectively. MTV was determined as voxels presenting SUVs over threshold within the automatically contoured primary tumor volume, and TLG was the product of SUV_{mean} and MTV. To evaluate the intratumoral metabolic heterogeneity, we chose the coefficient of variation (CV), which was defined as the standard deviation of $SUVs/SUV_{mean}$.

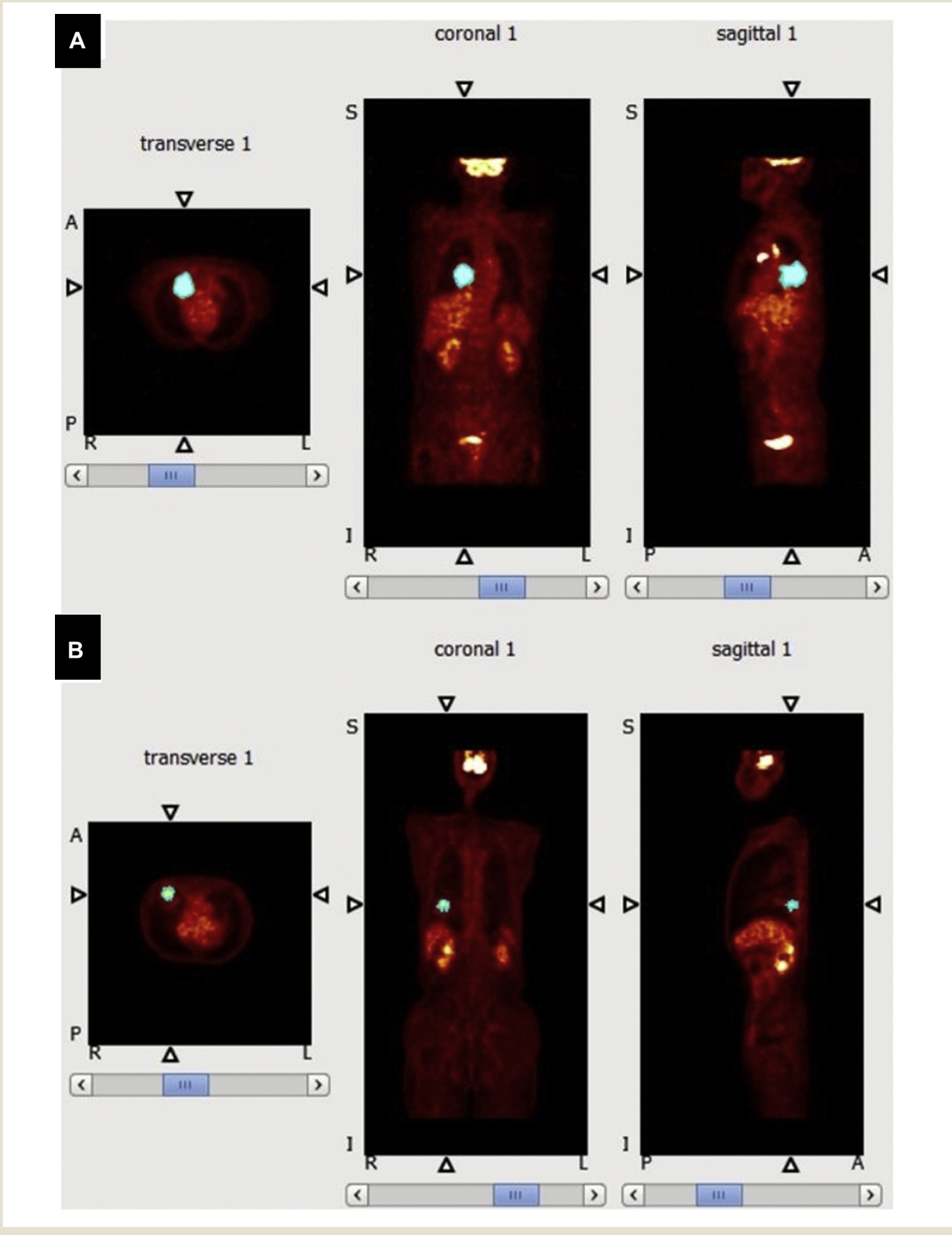
Statistical Analysis

In the current study, the date of the initial PET-CT was used as the date of diagnosis. Overall survival (OS) and progression-free survival (PFS) were calculated as the interval from the date of diagnosis to the date of the event. Locoregional progression-free survival (LRPFS) and distant metastasis-free survival (DMFS) were calculated as the time from the date of diagnosis to the date that locoregional progression was detected in the thorax and the date of distant metastasis detection, respectively. Survival was estimated using the Kaplan-Meier method. The log-rank test and the Cox proportional hazard model were used for univariate and multivariate analyses, respectively. Multivariate analysis was performed on variables with a P-value $< .1$ via univariate analysis. An optimal cutoff point that maximized the sum of sensitivity and specificity with OS was used to evaluate the prognostic significance of the PET-CT parameters. PET-CT parameters were analyzed using the Spearman correlation analysis, Student t test, and Pearson χ^2 test. Factors with a P-value $< .05$ were regarded as statistically significant. Propensity score matching was performed to minimize the bias between the SqCC and ADC groups. This propensity model consisted of the following covariates: gender, age, Eastern Cooperative Oncology Group (ECOG) performance status, smoking history, and clinical T and N stage. One-to-one matching was performed using the nearest-neighbor method. Statistical analyses were performed using PASW Statistics for Windows, Version 23.0 (SPSS Inc) and R version 3.4.0 (http://cran.rproject.org) with the MatchIt package for propensity score matching.

Results

The patient and tumor characteristics of the entire cohort are shown in Supplemental Table 1 (in the online version). There were 107 (82.3%) men and 23 (17.7%) women, with a median age of 63 years (range, 43-81 years). After histologic diagnosis, 64 were diagnosed with SqCC, 44 with ADC, 5 with poorly differentiated carcinoma, 1 with sarcomatoid carcinoma, 1 with large cell carcinoma, and 15 with non-specified NSCLC. Regarding clinical stage according to the TNM seventh edition, 72 patients (55.4%) were in stage IIIA, and 58

Figure 1 Example of PET-CT Images of a Patient With SqCC Exhibiting High SUV_{max} (21.5), MTV (29.8 cm^3), and TLG (367.1 cm^3) (A) and a Patient With ADC Exhibiting Low SUV_{max} (6.0), MTV (17.2 cm^3), and TLG (70.6 cm^3) (B)



Abbreviations: ADC = adenocarcinoma; MTV = metabolic tumor volume; PET-CT = positron emission tomography-computed tomography; SqCC = squamous cell carcinoma; SUV_{max} = maximum standardized uptake volume; TLG = total lesion glycolysis.

Table 1 Comparison of Baseline Characteristics Between Patients With SqCC and ADC

Variables	SqCC (n = 64)	ADC (n = 44)	*P* Value
Gender[a]			
Men	59 (92.2)	32 (72.7)	.006
Women	5 (7.8)	12 (27.3)	
Age, y[a]			
< 70	47 (70.8)	37 (44.1)	.191
≥ 70	17 (29.2)	7 (29.2)	
ECOG PS[a]			
0	8 (12.5)	9 (20.5)	.265
1, 2	56 (87.5)	35 (79.6)	
Smoking history[a]			
Ex-smoker/current	8 (12.5)	14 (31.8)	.039
Never	55 (85.9)	30 (68.2)	
TNM stage[a]			
IIIA	32 (50.0)	28 (63.7)	.161
IIIB	32 (50.0)	16 (36.4)	
T stage[a]			
T1-2	29 (45.3)	37 (84.1)	< .001
T3-4	35 (54.7)	7 (15.9)	
N stage[a]			
N0-1	6 (9.4)	1 (2.3)	.141
N2-3	58 (90.6)	43 (97.7)	
PET-CT parameters[b]			
SUV_{max}	16.45 ± 7.52	12.51 ± 5.93	.004
SUV_{mean}	9.83 ± 4.54	7.71 ± 3.54	.010
TLG, cm^3	431.77 ± 412.23	182.47 ± 205.22	< .001
MTV, cm^3	43.86 ± 41.80	22.54 ± 21.32	.002
CV	0.23 ± 0.03	0.23 ± 0.04	.282

Abbreviations: ADC = adenocarcinoma; CV = coefficient of variation; ECOG PS = Eastern Cooperative Oncology Group performance status; MTV = metabolic tumor volume; PET-CT = positron emission tomography-computed tomography; SqCC = squamous cell carcinoma; SUV_{max} = maximum standardized uptake value; SUV_{mean} = mean standardized uptake value; TLG = total lesion glycolysis.
[a]Values are presented as number (%).
[b]Values are presented as mean ± standard deviation.

patients (44.6%) were in stage IIIB. Regarding PET-CT parameters, median SUV_{max}, SUV_{mean}, TLG, MTV, and CV were 13.78 (range, 3.77-37.20), 8.41 (range, 2.14-22.64), 210.32 cm^3 (range, 9.97-1733.88 cm^3), 26.98 cm^3 (range, 1.19-218.97 cm^3), and 0.233 (range, 0.097-0.283), respectively. Regarding treatment, radiotherapy was performed with 3-dimensional conformal technique for all patients, and the median total radiotherapy dose was 66 Gy (range, 60-72 Gy) with a median daily dose of 2 Gy (range, 1.8-4 Gy). A weekly docetaxel (20 mg/m^2) and cisplatin (20 mg/m^2) regimen was used in 123 (94.6%) patients, and a carboplatin-based regimen was also used in 7 patients.

The median follow-up time for surviving patients was 51.3 months (range, 19.2-109.4 months). The median PFS and OS were 12.5 months and 35.5 months, respectively. Supplemental Tables 2 and 3 (in the online version) demonstrate the results of univariate and multivariate analyses of survival for the entire cohort.

After excluding 22 patients that could not be categorized into either SqCC or ADC, we compared the values of the PET-CT parameters in each SqCC and ADC group for 108 patients. Table 1 shows the clinicopathologic characteristics and PET-CT parameters of patients with SqCC and ADC. The proportion of women and patients with smoking history were higher in the ADC group ($P = .006$ and $P = .039$, respectively) and advanced T stage (T3-4) was higher in patients with SqCC ($P < .001$). Regarding the PET-CT parameters, SUV_{max}, SUV_{mean}, TLG, and MTV values were significantly higher in patients with SqCC than in patients with ADC ($P = .004$, $P = .01$, $P < .001$, and $P = .002$, respectively). However, there was no significant difference between CV in patients with SqCC and patients with ADC ($P = .282$). The receiver operating characteristics (ROC) analysis of patients with stage III NSCLC found the cutoff values of 14.0 for SUV_{max} (area under the ROC curve [AUC], 0.58; $P < .001$), 9.0 for SUV_{mean} (AUC, 0.58; $P < .001$), 360 cm^3 for TLG (AUC, 0.67; $P < .001$), 45 cm^3 for MTV (AUC, 0.71; $P < .001$), and 0.255 for CV (AUC, 0.62; $P = .034$).

To reduce the bias owing to confounding factors, we conducted propensity score matching (Table 2). Although patients with cN2 stage predominated in both groups, there was no significant

Table 2 Comparison of Baseline Characteristics Between Patients With SqCC and ADC After Propensity Score Matching

Variables	SqCC (n = 44)	ADC (n = 44)	*P* Value
Gender[a]			
Men	40 (90.9)	32 (72.7)	.051
Women	4 (9.1)	12 (27.3)	
Age, y[a]			
< 70	32 (72.7)	37 (84.1)	.195
≥ 70	12 (27.3)	7 (15.9)	
ECOG PS[a]			
0	6 (13.6)	9 (20.5)	.395
1, 2	38 (86.4)	35 (79.6)	
Smoking history[a]			
Ex-smoker/current	6 (13.6)	14 (31.8)	.073
Never	38 (86.4)	30 (68.2)	
TNM stage[a]			
IIIA	29 (65.9)	28 (63.6)	.823
IIIB	15 (34.1)	16 (36.4)	
T stage[a]			
T1-2	29 (65.9)	37 (84.1)	.084
T3-4	15 (34.1)	7 (15.9)	
N stage[a]			
N0-1	5 (11.4)	1 (2.3)	.091
N2-3	39 (88.6)	43 (97.7)	
No. of N2 stations[c]			
Single	10 (37.0)	9 (31.0)	.635
Multiple	17 (63.0)	20 (69.0)	
PET-CT parameters[b]			
SUV_{max}	16.98 ± 8.02	12.5 1 ± 5.93	.004
SUV_{mean}	10.24 ± 4.79	7.71 ± 3.53	.006
TLG, cm^3	367.30 ± 343.21	182.47 ± 205.22	.003
MTV, cm^3	34.81 ± 30.04	22.54 ± 21.32	.030
CV	0.226 ± 0.030	0.233 ± 0.035	.350

Abbreviations: ADC = adenocarcinoma; CV = coefficient of variation; ECOG PS = Eastern Cooperative Oncology Group performance status; MTV = metabolic tumor volume; PET-CT = positron emission tomography-computed tomography; SqCC = squamous cell carcinoma; SUV_{max} = maximum standardized uptake value; SUV_{mean} = mean standardized uptake value; TLG = total lesion glycolysis.
[a]Values are presented as number (%).
[b]Values are presented as mean ± standard deviation.
[c]Patients with clinical N2 stage were only included.

difference in the involved number of N2 stations between matched cohorts ($P = .635$). Higher SUV_{max}, SUV_{mean}, TLG, and MTV values for SqCC than ADC were consistently shown after propensity score matching with statistical significance. We performed a Spearman correlation analysis evaluating the relationship between tumor size and PET-CT parameters. In both groups, tumor size was significantly correlated with TLG, MTV, and CV (all $P < .001$), but there was no significant correlation between size and SUV_{max} and SUV_{mean} (data not shown). Subsequently, we assessed the prognostic impact of PET-CT parameters according to the histologic type in matched patients (Tables 3 and 4). In SqCC, only ages higher than 70 were related to worse OS, and cN2 stage was related to worse PFS and LRPFS. PET-CT parameters were not related to OS, PFS, LRPFS, and DMFS. In ADC, however, PET-CT parameters were correlated with survival. $SUV_{max} \leq 14$ and $SUV_{mean} \leq 9$ were related to better LRPFS but not to PFS or OS (Figure 2). On the other hand, OS showed significant correlation with TLG and MTV for ADC (Figure 3).

Table 5 shows the patterns of failure after definite CRT in matched patients. Treatment response, locoregional progression, and in-field progression were not significantly different between SqCC and ADC, but distant metastasis was significantly more frequent in the ADC group. Survival differences between SqCC and ADC were also assessed (see Supplemental Tables 4 and 5 in the online version). Patients with ADC had worse DMFS than those with SqCC at a statistically significant level ($P = .009$).

Discussion

In this study, we analyzed the role of PET-CT parameters that could be easily obtained in patients with locally advanced NSCLC receiving definitive CRT and the prognostic significance of those parameters according to histologic subtype. SUV_{max}, SUV_{mean},

Table 3 Survival Analyses in Patients With SqCC After Propensity Score Matching

Variables	N	OS		PFS		LRPFS		DMFS	
		2-Y Rate, %	*P* Value	2-Y Rate, %	*P* Value	2-Y Rate, %	*P* Value	2-Y Rate, %	*P* Value
Gender									
Men	40	67.5	.984	44.3	.619	46.9	.679	89.3	.398
Women	4	50.0		50.0		50.0		100	
Age, y									
< 70	32	75.0	.023	45.2	.728	48.4	.612	96.6	.204
≥ 70	12	41.7		46.3		46.3		74.1	
ECOG PS									
0	6	68.4	.774	40.0	.662	40.0	.585	100	.745
1, 2	38	50.0		45.8		48.5		89.2	
Smoking history									
Ex-smoker/ current	6	50.0	.516	43.9	.919	46.7	.982	88.7	.994
Never	38	68.4		50.0		50.0		100	
T stage									
T1-2	29	69.0	.869	39.1	.198	42.7	.280	92.7	.446
T3-4	15	60.0		56.3		56.3		85.7	
Tumor size, cm									
≤ 4	18	73.1	.313	48.8	.554	48.8	.731	94.1	.455
> 4	26	55.6		42.3		46.2		87.8	
N stage									
N0-1	5	80.0	.174	80.0	.033	80.0	.041	100	.162
N2-3	39	64.1		40.0		42.7		89.0	
SUV_{max}									
≤ 14.0	20	75.0	.177	53.9	.618	58.0	.448	94.7	.361
> 14.0	24	55.0		32.6		32.6		87.1	
SUV_{mean}									
≤ 9.0	22	72.7	.528	52.0	.990	56.8	.786	90.4	.575
> 9.0	22	59.1		37.7		37.7		90.2	
TLG, cm^3									
≤ 360.0	28	64.3	.502	37.9	.650	41.8	.805	92.3	.596
> 360.0	16	68.8		56.3		56.3		87.1	
MTV, cm^3									
≤ 45.0	31	67.7	.133	44.4	.410	47.9	.313	93.2	.188
> 45.0	13	61.5		46.2		46.2		83.1	
CV									
≤ 0.255	40	65.0	.336	41.5	.178	44.2	.201	91.9	.884
> 0.255	4	75.0		75.0		75.0		75.0	

Abbreviations: CV = coefficient of variation; DMFS = distant metastasis-free survival; ECOG PS = Eastern Cooperative Oncology Group Performance Status; LRPFS = locoregional progression-free survival; MTV = metabolic tumor volume; OS = overall survival; PFS = progression-free survival; SqCC = squamous cell carcinoma; SUV_{max} = maximum standardized uptake value; SUV_{mean} = mean standardized uptake value; TLG = total lesion glycolysis.

TLG, and MTV were higher in patients with SqCC than patients with ADC. Additionally, we have demonstrated that PET-CT parameters were impactful as prognosticators for survival in ADC, but not in SqCC. These results demonstrate that there is a difference in metabolism according to histologic subtype and its relation to survival despite being in the same patients with locally advanced stage III NSCLC.

Schuurbiers et al[13] showed that the mean TLG of SqCC was higher than that of ADC, but disease-free survival was longer for SqCC than ADC in patients with resectable early NSCLC. According to analyses of microvessel density and hypoxia- and glycolysis-related markers, it was suggested that hypoxia is more common in SqCC and may induce glucose transporter 1 expression, leading to high TLG values and tumor necrosis. Koh et al[14,15]

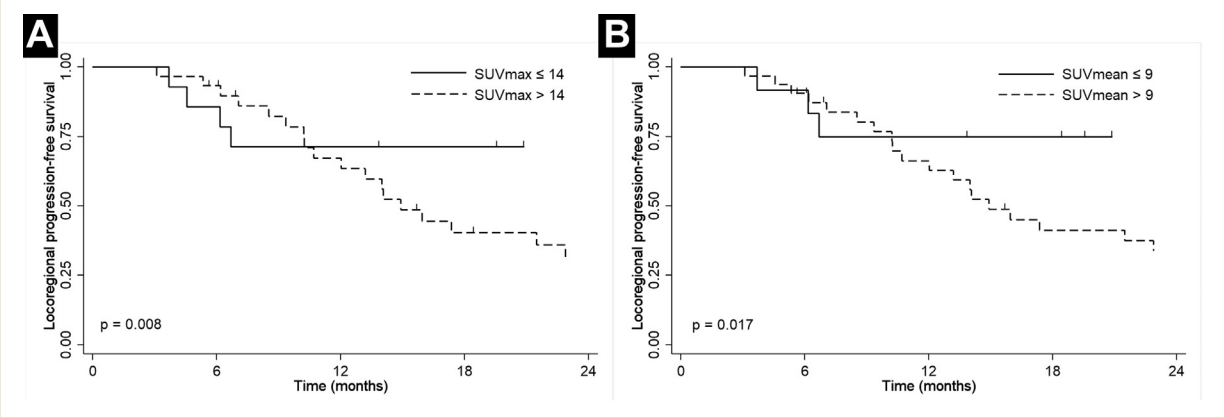
Table 4 Survival Analyses in Patients With ADC After Propensity Score Matching

Variables	N	OS		PFS		LRPFS		DMFS	
		2-Y Rate, %	*P* Value	2-Y Rate, %	*P* Value	2-Y Rate, %	*P* Value	2-Y Rate, %	*P* Value
Gender									
Men	32	62.5	.589	31.5	.482	51.1	.702	58.5	.267
Women	12	91.7		25.0		31.3		75.0	
Age, y									
< 70	37	73.0	.045	30.2	.896	43.2	.910	65.2	.588
≥ 70	7	57.1		21.4		47.6		51.4	
ECOG PS									
0	9	88.9	.385	33.3	.719	44.4	.795	66.7	.75
1, 2	35	65.7		27.9		44.2		62.1	
Smoking history									
Ex-smoker/ current	14	63.3	.954	21.4	.882	41.7	.604	62.8	.844
Never	30	85.7		33.7		46.8		64.3	
T stage									
T1-2	37	73.0	.706	29.9	.991	45.8	.936	59.5	.592
T3-4	7	57.1		28.6		42.9		85.7	
Tumor size, cm									
≤ 4	26	73.1	.183	28.3	.780	48.7	.653	56.4	.523
> 4	18	66.7		32.4		41.0		72.2	
N stage									
N0-1	1	-	.134	-	.298	-	.408	-	.517
N2-3	43	72.1		27.9		43.5		62.3	
SUV_{max}									
≤ 14.0	30	76.7	.919	42.9	.156	71.4	.008	64.6	.880
> 14.0	14	57.1		21.8		31.5		59.2	
SUV_{mean}									
≤ 9.0	32	78.1	.489	41.7	.354	75.0	.017	66.3	.470
> 9.0	12	50.0		24.8		33.8		55.6	
TLG, cm^3									
≤ 360.0	38	76.3	.044	29.0	.823	44.1	.957	65.2	.473
> 360.0	6	33.3		33.3		50.0		50.0	
MTV, cm^3									
≤ 45.0	39	76.9	< .001	30.9	.056	44.4	.714	66.2	.069
> 45.0	5	20.0		-		-		40.0	
CV									
≤ 0.255	33	66.7	.238	30.9	.382	46.2	.949	64.2	.502
> 0.255	11	81.8		27.3		42.4		61.4	

Abbreviations: ADC = adenocarcinoma; CV = coefficient of variation; DMFS = distant metastasis-free survival; ECOG PS = Eastern Cooperative Oncology Group Performance Status; LRPFS = locoregional progression-free survival; MTV = metabolic tumor volume; OS = overall survival; PFS = progression-free survival; SUV_{max} = maximum standardized uptake value; SUV_{mean} = mean standardized uptake value; TLG = total lesion glycolysis.

reported that volume-dependent PET parameters, MTV and TLG, differed according to the histologic subtype, and high glucose transporter 1 expression was associated with the poorer OS. They included patients at various pathologic stages (stage I, 51.2%; stage II, 26.7%; and stage III 22.1%) without matching, and adjuvant chemotherapy was performed in 28.6% and adjuvant radiotherapy in 33.5%. In contrast, the patients included in our study were relatively homogeneous, all of whom received CRT with stage III NSCLC, and we reported the clinical outcomes after propensity score matching. In addition, we demonstrated that SqCC also showed higher values of PET-CT parameters, such as SUV_{max}, SUV_{mean}, TLG, and MTV. Although we could not confirm the expression of glycolysis- and hypoxia-related molecules in unresectable NSCLC, it is suggested that glycolysis and hypoxia may differ depending on the histologic subtype based on the previous studies and our research results.

Figure 2 Locoregional Progression-Free Survival by SUV_{max} (A) and SUV_{mean} (B) in ADC in Patients With Stage III NSCLC

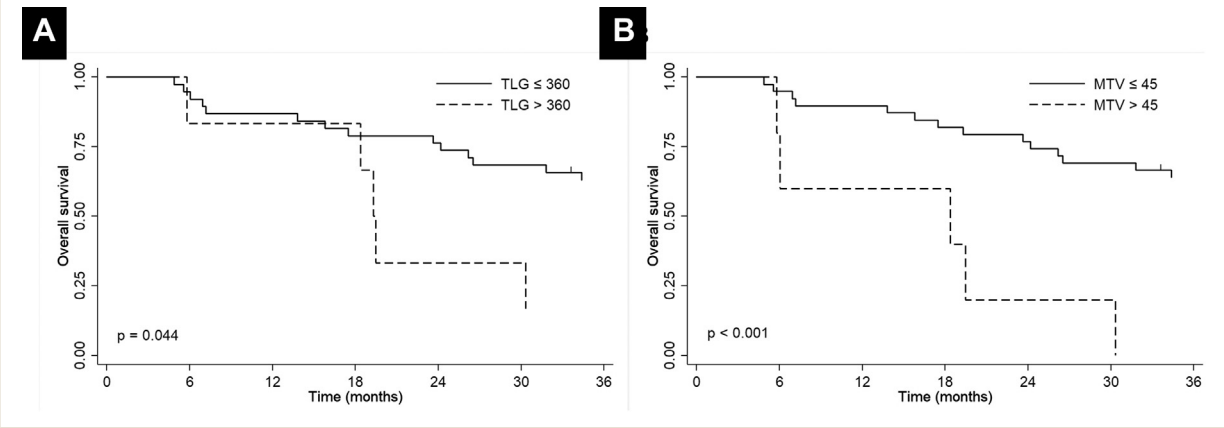


Abbreviations: ADC = adenocarcinoma; NSCLC = non–small-cell lung cancer; SUV_{max} = maximum standardized uptake volume; SUV_{mean} = mean standardized uptake volume.

The current study showed the difference in the importance of PET-CT parameters according to the histologic type in patients with stage III NSCLC who underwent CRT. PET-CT parameters were highly related to ADC NSCLC, but there was no significant association in SqCC. Higher SUV_{max} and SUV_{mean} were associated with poorer LRPFS at a statistically significant level in ADC, but these did not lead to inferior PFS or OS. We assumed that this may be related to the higher distant metastasis potential of ADC, as shown by lower DMFS and more frequent distant metastasis events in ADC than SqCC after propensity score matching. Though the prognostic impact of the histologic type of NSCLC is still controversial, there are several studies that have shown poorer DMFS in patients with ADC NSCLC. Using data from 4 RTOG (Radiation Therapy Oncology Group) studies, Cox et al[16] analyzed the failure patterns of NSCLC according to the histologic subtype and reported that ADC was more likely to metastasize than SqCC when treated with chemotherapy in addition to radiotherapy. Hung et al[17] reported that non-squamous cell histology predicted a higher risk of distant metastasis in resected stage I NSCLC. In another study, patients with stage I NSCLC who were not fit for surgery received radiotherapy, and results showed that 5-year DMFS was significantly better in SqCC than that of ADC.[18] Although ADC has shown a higher incidence of distant metastases relative to SqCC, the current treatment strategies for NSCLC are essentially the same, irrespective of histologic subtype. Given our present results, intensified systemic therapy may be necessary depending on the histologic subtype.

Several PET-CT parameters have been used to measure metabolic activity in PET-CT and provide clinical significance in NSCLC.[4,19-21] However, what constitutes the best predictor of clinical outcomes is still controversial. One of the most commonly used indicators is SUV_{max}; because it is the highest value of a single voxel in the tumor, it has the disadvantage of being likely to cause random error.[21] To overcome this, volume-based parameters,

Figure 3 Overall Survival by TLG (A) and MTV (B) in ADC in Patients With Stage III NSCLC



Abbreviations: ADC = adenocarcinoma; MTV = metabolic tumor volume; NSCLC = non–small-cell lung cancer; TLG = total lesion glycolysis.

Table 5 Treatment Outcomes of Patients With SqCC and ADC After Propensity Score Matching

Variables	SqCC (n = 44), n (%)	ADC (n = 44), n (%)	*P* Value
Treatment response			
No	9 (20.5)	10 (22.7)	.796
Yes	35 (79.5)	34 (77.3)	
Locoregional progression			
No	17 (38.6)	17 (38.6)	1.000
Yes	27 (61.4)	27 (61.4)	
In-field progression			
No	25 (56.8)	32 (72.7)	.118
Yes	19 (43.2)	12 (27.3)	
Distant metastasis			
No	36 (81.8)	25 (56.8)	.011
Yes	8 (18.2)	19 (43.2)	

Abbreviations: ADC = adenocarcinoma; SqCC = squamous cell carcinoma.

including MTV and TLG, have been analyzed.[4] MTV suggests a metabolically active tumor burden. Previous studies have shown prognostic values of MTV that were better than SUV_{max} and SUV_{mean}.[20] In the current study, the PET-CT parameters that were related to LRPFS and OS in ADC NSCLC were different. Values related to the maximum voxel, such as SUV_{max} and SUV_{mean}, were related to LRPFS, and those related to metabolic tumor burden, such as MTV and TLG, were related to OS. The previous study evaluated the association between PET parameters and OS in resected patients with ADC, and only MTV and TLG among the conventional parameters were significantly associated with OS, which is consistent with our result.[15] Therefore, it may be speculated that patients that have ADC NSCLC with higher SUV_{max} and SUV_{mean} would have poor locoregional control after CRT, and eventually, those with a higher metabolic tumor burden would have a poorer prognosis.

In addition to conventional PET parameters, heterogeneity has been described recently through the radiomics approach, which analyses textural features together. Several studies have indicated that various heterogeneity indices are useful in cancer, especially for NSCLC. Cook et al[22] reported that texture characteristics, such as coarseness, contrast, and busyness, help to predict response after CRT. In 53 patients with NSCLC treated with CRT, they found that responders showed significantly lower coarseness and higher contrast and busyness, and coarseness was an independent risk factor of OS. They also reported that heterogeneity helps to predict response and disease progression after erlotinib. Changes in entropy were associated with survival and therapy response in patients with stage IIIB-IV NSCLC.[23] Kang et al[8] assessed PET-CT parameters to predict tumor progression in patients with inoperable NSCLC, similarly to our study. For their parameters, they used SUV_{max}, MTV, and the area under the curve of the cumulative SUV-volume histograms, which has been known to represent the tumor heterogeneity. After multivariate analyses, PFS was significantly associated with area under the curve of the cumulative SUV-volume histograms and SUV_{max}. The recent study reported the prognostic value of textural features in patients with ADC, and the lower complexity was independently related with poor OS.[15] In the current study, however, CV representing tumor heterogeneity was not shown to be a prognostic factor for survival in both SqCC and ADC NSCLC. Although there is an advantage that CV is relatively easy to obtain for physicians, our results may mean that the prognostic value of CV was lower than that of the other heterogeneity indexes. Because we did not analyze the other heterogeneity indexes in the current study, further research is needed to elucidate the role of CV.

The current study has several limitations. First, this is a retrospective study with a limited number of patients, and it is not free from intrinsic biases. Second, as for most of other PET-CT parameter-related studies, regions of interest for analysis were subtracted semi-automatically. Although we have manually reviewed regions of interest if the heart or FDG-avid lesions, such as inflammation and atelectasis, are close by, error may be present. However, the present study revealed that there might be differences in the implication of PET-CT parameters for patients with SqCC and ADC stage III NSCLC who all received CRT, and to enhance our analysis, we used propensity score matching. Because our outcomes could not be repeated in other cohorts owing to this strength of our study, a validation study should be performed in future.

Conclusions

The current study confirmed that PET-CT parameters were higher in SqCC than ADC NSCLC, which may be associated with biological nature, and there were differences in the impact of PET-CT parameters affecting survival according to the histologic type. Additionally, we have demonstrated that the characteristics of PET-CT parameters that were prognostic factors of LRPFS differed from those related to OS in patients with stage III ADC NSCLC who received definitive CRT, which may be caused by the high metastatic potential of ADC NSCLC. The differential glucose metabolism and distant failure rate suggest the presence of biological features of NSCLC by histologic subtype. Therefore, this study suggests that not only PET-CT parameters but also histologic subtype need to be considered when predicting treatment response and survival in patients with stage III NSCLC treated with CRT.

Clinical Practice Points

- Compared with ADC, higher PET-CT parameters were observed in SqCC receiving definitive CRT in patients with stage III NSCLC.
- PET-CT parameter was significant prognostic factor only in ADC NSCLC patients, and higher MTV was associated with poor OS, but not with LRPFS.
- Different glucose metabolism and distant failure rates suggest the distinct biological characteristics of NSCLC by histologic subtype.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2018.08.018.

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Supplemental Data

Supplemental Table 1 Patient and Tumor Characteristics in the Entire Cohort (n = 130)

Variables	N (%)
Median age, y (range)	63 (43-81)
Gender	
Men	107 (82.3)
Women	23 (17.7)
ECOG PS	
0	22 (16.9)
1	104 (80.0)
2	4 (3.1)
Smoking history	
Ex-smoker/current	101 (77.7)
Never	28 (21.5)
T stage	
T1	24 (18.5)
T2	57 (43.8)
T3	21 (16.2)
T4	28 (21.5)
N stage	
N0	5 (3.8)
N1	3(2.3)
N2	81 (62.3)
N3	41 (31.5)
Overall stage	
IIIA	72 (55.4)
IIIB	58 (44.6)
Histology	
Squamous cell carcinoma	64 (49.2)
Adenocarcinoma	44 (33.8)
Others	22 (16.9)
Radiotherapy	
Median total dose, Gy (range)	66 (60-72)
Median daily dose, Gy (range)	2 (1.8-4)
Treatment response	
Complete remission	4 (3.1)
Partial remission	100 (76.9)
Stable disease	21 (16.2)
Progressive disease	5 (3.8)
EGFR mutation	
Wild	56 (43.1)
Mutation	29 (22.3)
No information	45 (43.1)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor.

Supplemental Table 2 Univariate and Multivariate Analyses of Overall Survival and Progression-free Survival in the Entire Cohort (n = 130)

Variables	N	Overall Survival			Progression-free Survival		
		3-Y Rate, %	*P* Value (Uni)	*P* Value (Multi)	3-Y Rate, %	*P* Value (Uni)	*P* Value (Multi)
Gender							
Men	107	46.6	.560		25.1	.647	
Women	23	59.7			17.4		
Age, y							
< 70	103	52.0	.016	.142	23.6	.528	
≥ 70	27	37.0			19.4		
ECOG PS							
0	22	59.1	.474		33.3	.817	
1, 2	108	46.9			21.8		
Smoking history							
Ex-smoker/ current	101	46.4	.183		26.9	.436	
Never	28	59.6			14.3		
Histology							
SqCC	64	44.7	.486		30.5	.112	
ADC, others	66	53.0			17.4		
T stage							
T1-2	81	51.8	.238		23.1	.645	
T3-4	49	44.1			24.7		
N stage							
N0-1	8	75.0	.113		75.0	.005	.006
N2	122	47.2			20.3		
SUV_{max}							
≤ 14.0	78	54.7	.534		19.7	.519	
> 14.0	52	40.4			26.9		
SUV_{mean}							
≤ 9.0	75	56.9	.265		19.7	.976	
> 9.0	55	38.2			26.6		
TLG, cm^3							
≤ 360.0	90	57.4	.015	.332	17.2	.913	
> 360.0	40	30.0			24.4		
MTV, cm^3							
≤ 45.0	94	58.2	.001	.036	23.9	.093	.097
> 45.0	36	25.0			19.5		
CV							
≤ 0.255	109	44.6	.058	.236	20.6	.071	.070
> 0.255	21	71.1			32.7		

Abbreviations: ADC = adenocarcinoma; CV = coefficient of variation; ECOG PS = Eastern Cooperative Oncology Group performance status; MTV = metabolic tumor volume; SqCC = squamous cell carcinoma; SUV_{max} = maximum standardized uptake value; SUV_{mean} = mean standardized uptake value; TLG = total lesion glycolysis.

Supplemental Table 3 Univariate and Multivariate Analyses of Locoregional Progression-free Survival and Distant Metastasis-free Survival in the Entire Cohort (n = 130)

Variables	N	Locoregional Progression-free Survival			Distant Metastasis-free Survival		
		3-Y Rate, %	*P* Value (Uni)	*P* Value (Multi)	3-Y Rate, %	*P* Value (Uni)	*P* Value (Multi)
Gender							
Men	107	33.4	.232		58.1	.855	
Women	23	20.3			66.7		
Age, y							
< 70	103	32.0	.231		58.1	.910	
≥ 70	27	19.8			68.1		
ECOG PS							
0	22	40.8	.963		52.5	.306	
1, 2	108	28.9			60.6		
Smoking history							
Ex-smoker/ current	101	34.8	.232		59.0	.697	
Never	28	19.8			61.5		
Histology							
SqCC	64	32.0	.941		72.3	.004	.006
ADC, others	66	29.8			47.2		
T stage							
T1-2	81	32.0	.992		58.7	.240	
T3-4	49	29.2			60.1		
N stage							
N0-1	8	75.0	.019	.015	100	.012	1.000
N2	122	27.8			56.2		
SUV_{max}							
≤ 14.0	78	37.9	.203		61.8	.803	
> 14.0	52	24.7			55.9		
SUV_{mean}							
≤ 9.0	75	37.1	.576		62.0	.347	
> 9.0	55	24.9			55.9		
TLG, cm^3							
≤ 360.0	90	29.5	.487		58.5	.638	
> 360.0	40	30.4			61.7		
MTV, cm^3							
≤ 45.0	94	32.2	.078	.086	60.7	.608	
> 45.0	36	22.5			54.8		
CV							
≤ 0.255	109	27.6	.087	.104	60.1	.953	
> 0.255	21	40.4			55.7		

Abbreviations: ADC = adenocarcinoma; CV = coefficient of variation; ECOG PS = Eastern Cooperative Oncology Group performance status; MTV = metabolic tumor volume; SqCC = squamous cell carcinoma; SUV_{max} = maximum standardized uptake value; SUV_{mean} = mean standardized uptake value; TLG = total lesion glycolysis.

Supplemental Table 4 Univariate and Multivariate Analyses of Overall Survival and Progression-free Survival in the Matched Cohort (n = 88)

Variables	N	Overall Survival			Progression-free Survival		
		3-Y Rate, %	*P* Value (Uni)	*P* Value (Multi)	3-Y Rate, %	*P* Value (Uni)	*P* Value (Multi)
Gender							
Men	72	51.2	.512		27.7	.671	
Women	16	68.8			25.0		
Age, y							
< 70	69	59.4	.002	.012	27.3	.846	
≥ 70	19	36.8			29.0		
ECOG PS							
0	15	60.0	.505		17.9	.746	
1, 2	73	53.4			27.5		
Smoking history							
Ex-smoker/ current	20	51.3	.591		20.0	.667	
Never	68	65.0			29.7		
Histology							
SqCC	44	52.2	.585		39.2	.087	
ADC	44	56.7			15.5		
T stage							
T1-2	66	54.5	.566		22.8	.156	
T3-4	22	54.6			40.7		
N stage							
N0-1	32	66.7	.483		83.3	.010	.035
N2	56	53.6			23.1		
SUV_{max}							
≤ 14.0	50	55.9	.548		41.1	.089	.011
> 14.0	38	52.6			15.2		
SUV_{mean}							
≤ 9.0	54	59.2	.885		37.0	.353	
> 9.0	34	47.1			20.9		
TLG, cm^3							
≤ 360.0	66	60.6	.087	.534	22.1	.440	
> 360.0	22	36.4			43.8		
MTV, cm^3							
≤ 45.0	70	61.4	.003	.072	26.4	.368	
> 45.0	18	27.8			31.1		
CV							
≤ 0.255	73	50.6	.128		26.2	.330	
> 0.255	15	73.3			32.0		

Abbreviations: ADC = adenocarcinoma; CV = coefficient of variation; ECOG PS = Eastern Cooperative Oncology Group performance status; MTV = metabolic tumor volume; SqCC = squamous cell carcinoma; SUV_{max} = maximum standardized uptake value; SUV_{mean} = mean standardized uptake value; TLG = total lesion glycolysis.

Supplemental Table 5 Univariate and Multivariate Analyses of Locoregional Progression-free Survival and Distant Metastasis-free Survival in the Matched Cohort (n = 88)

Variables	N	Locoregional Progression-free Survival			Distant Metastasis-free Survival		
		3-Y Rate, %	*P* Value (Uni)	*P* Value (Multi)	3-Y Rate, %	*P* Value (Uni)	*P* Value (Multi)
Gender							
Men	72	36.5	.920		66.3	.558	
Women	16	29.2			80.4		
Age, y							
< 70	69	36.4	.643		70.2	.393	
≥ 70	19	29.3			66.2		
ECOG PS							
0	15	28.6	.812		64.1	.844	
1, 2	73	35.5			69.6		
Smoking history							
Ex-smoker/ current	20	27.8	.664		74.4	.626	
Never	68	37.8			67.5		
Histology							
SqCC	44	41.5	.739		82.6	.009	.049
ADC	44	27.6			55.5		
T stage							
T1-2	66	31.8	.365		66.2	.124	
T3-4	22	44.4			76.9		
N stage							
N0-1	32	83.3	.028	.059	100.0	.048	1.000
N2	56	31.2			66.3		
SUV_{max}							
≤ 14.0	50	56.0	.017	.148	68.2	.821	
> 14.0	38	18.3			69.7		
SUV_{mean}							
≤ 9.0	54	54.3	.070	.596	69.6	.967	
> 9.0	34	23.9			68.1		
TLG, cm^3							
≤ 360.0	66	30.9	.796		68.9	.831	
> 360.0	22	47.7			68.1		
MTV, cm^3							
≤ 45.0	70	34.5	.371		71.1	.376	
> 45.0	18	38.3			58.5		
CV							
≤ 0.255	73	35.1	.513		69.3	.934	
> 0.255	15	35.6			65.5		

Abbreviations: ADC = adenocarcinoma; CV = coefficient of variation; ECOG PS = Eastern Cooperative Oncology Group performance status; MTV = metabolic tumor volume; SqCC = squamous cell carcinoma; SUV_{max} = maximum standardized uptake value; SUV_{mean} = mean standardized uptake value; TLG = total lesion glycolysis.