Large Decreases in Standardized Uptake Values After Definitive Radiation Are Associated with Better Survival of Patients with Locally Advanced Non–Small Cell Lung Cancer

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We evaluated potential associations between maximum standardized uptake value (SUV_{max}) on ^{18}F-FDG PET before and after radiation therapy (RT) and survival outcomes for patients with locally advanced non–small cell lung cancer. **Methods:** Patients with stage III non–small cell lung cancer ($n = 49$) who had undergone ^{18}F-FDG PET at the M.D. Anderson Cancer Center both before and up to 3.5 mo after undergoing radiochemotherapy were studied; exclusion criteria were patients with a history of thoracic surgery, RT, or other cancer or those who had received a total radiation dose less than 60 Gy. We assessed associations between overall survival (OS) or disease-free survival (DFS) and post-RT SUV_{max} and the extent of decrease in SUV_{max} in the primary tumor (PT) and regional lymph nodes (LNs). SUV_{max} was assessed as a continuous variable by Cox proportional hazards regression analysis. **Results:** Univariate and multivariate analyses showed that having a high post-RT SUV_{max} (either PT or LNs) was associated with a higher risk of death (univariate analyses: hazard ratio [HR] for PT SUV_{max}, 1.27, $P < 0.0001$; HR for LN SUV_{max}, 1.32, $P = 0.004$) and disease recurrence (univariate analyses: HR for PT SUV_{max}, 1.16, $P = 0.004$; HR for LN SUV_{max}, 1.32, $P = 0.001$). Moreover, after definitive RT, the greater the decrease in SUV_{max} in the lesion that had the highest SUV_{max} at diagnosis, the longer the OS (HR, 0.06; $P = 0.002$), DFS (HR, 0.03; $P = 0.001$), local–regional control (HR, 0.04; $P = 0.002$), and distant metastasis-free survival (HR, 0.07; $P = 0.028$). **Conclusion:** The post-RT SUV_{max} in both the PT and the LNs was a predictor of survival—specifically, the higher the residual SUV_{max} after RT, the poorer the OS and DFS; and the greater the decrease in SUV_{max} in the lesion with the highest SUV_{max} at diagnosis, the longer the OS and DFS. This information should help to identify patients who are at high risk of recurrence and for whom additional treatments can be designed accordingly.

The current standard of care for patients with unresectable clinical stage III non–small cell lung carcinoma (NSCLC) is combined chemoradiation therapy. The median survival time after such treatment is approximately 17 mo (*1*)—a significant improvement over historical treatment with radiation therapy (RT) or surgery alone but still quite poor. New treatment strategies for this disease are thus still urgently needed.

PET has had an increasing role in the initial staging and posttreatment evaluation of various types of cancer, including breast cancer, lymphoma, head and neck cancer, and NSCLC (*2–8*). The uptake of the glucose analog ^{18}F-FDG by NSCLC tumor cells has been found to be useful for restaging at recurrence and for delineating radiotherapeutic targets (*9–11*). The standardized uptake value (SUV) in ^{18}F-FDG PET before initial curative treatment has also been shown by some (*12,13*), but not all (*14*), to be a prognostic factor for survival outcomes. Therefore, the potential value of ^{18}F-FDG PET for predicting prognosis in advanced NSCLC before and after treatment still needs to be established.

A decline in ^{18}F-FDG uptake in the primary tumor or lymph nodes (LNs) after chemotherapy, RT, or both treatments for NSCLC is thought to reflect a reduction in the metabolic activity of the tumor and thus can be used to assess tumor response to therapy. The evaluation of the metabolic change after RT would be of considerable benefit given the difficulty of assessing whether the therapy worked with other imaging techniques (*15*). However, whether reductions in SUV in the primary tumor or LNs from before to after RT are linked with survival in patients with NSCLC

remains uncertain. Also unclear is whether reductions in SUV could be associated with the likelihood of either local relapse or distant metastasis in such patients.

Hence, we undertook this study to assess potential associations between survival outcomes and the maximum SUV (SUV_{max}) measured by ^{18}F-FDG PET before and after therapy as well as the percentage of change in SUV_{max} in the primary tumor, regional LN with the highest SUV_{max}, SUV_{max} sum of all regional LNs, target lesion (either primary tumor or LN) with the highest SUV_{max}, and SUV_{max} sum of the primary tumor and all regional LNs in patients with inoperable stage III NSCLC who were candidates for curative therapy.

MATERIALS AND METHODS

Patients

This retrospective analysis was approved by the institutional review board of The University of Texas M.D. Anderson Cancer Center. Subjects were identified by a database search of patients with lung cancer treated with definitive radiochemotherapy in the Department of Radiation Oncology at M.D. Anderson Cancer Center between January 2007 and December 2008. Patients who were included in this study were those who had undergone an ^{18}F-FDG PET study done at M.D. Anderson both before and up to 3.5 mo after completing RT, who had no history of thoracic surgery or radiation therapy, who had no prior other cancer, and who had received a total radiation dose of 60 Gy or more. Ultimately, 49 patients met the selection criteria for this study. Disease had been staged according to the 2002 edition of the American Joint Committee on Cancer staging system (16). CT or ^{18}F-FDG PET scans were obtained every 3 mo for the first 2 y after treatment, then every 6 mo for 5 y, and then annually thereafter to check for evidence of recurrence.

^{18}F-FDG PET Technique

Baseline (pretreatment) ^{18}F-FDG PET scans were obtained a median of 26 d before the start of RT. For patients who had received induction chemotherapy, we used the SUV_{max} and clinical disease stages that had been assigned at initial diagnosis for our analysis. The median lag time between the end of the RT and the time of the ^{18}F-FDG PET evaluation was 2.5 mo (range, 1–3.5 mo). For patients who had received adjuvant chemotherapy, the posttreatment scan was obtained after the chemotherapy. Scans were begun after a 6-h fast, with an intravenous injection of 370–555 MBq of ^{18}F-FDG, and emission and transmission scans were obtained 60 min afterward. All patients were required to have had a blood sugar level of 150 mg/dL or less before ^{18}F-FDG injection. Scans were obtained with a Discovery ST PET/CT scanner (GE Healthcare).

SUV Measurements

One experienced radiologist reviewed all ^{18}F-FDG PET images and obtained the SUV_{max} for all patients. The SUV_{max} in the gross primary tumor and in each LN was calculated and recorded from scans obtained before and after RT. Changes in SUV (ΔSUV) after treatment were calculated with the following equation: $\Delta SUV = ([SUVpre - SUVpost]/SUVpre) \times 100$, where SUVpre and SUVpost denote pre- and posttreatment SUV, respectively. The primary tumor and LNs were manually drawn on the transaxial images around the focal ^{18}F-FDG uptake zone by referring to CT images before and after RT. For those cases considered to represent complete metabolic response (i.e., areas with ^{18}F-FDG uptake $\leq$ that in the aortic arch) or complete radiologic response (i.e., LN having a short axis of <10 mm), the SUV_{max} of the anatomic area corresponding to the pretreatment lesion was taken (Fig. 1). The SUVs of the primary tumor and LNs were calculated as SUV = activity concentration (kBq [μCi]/mL)/(injected dose [MBq (mCi)]/body weight [kg]). We used the maximum SUV_{max} to avoid partial-volume effects (17). The SUV_{max} is defined as the SUV of a 1-pixel region of interest corresponding to the maximum value in the primary tumor or LN; thus, SUV_{max} represents the value least affected by the partial-volume effect.

Statistical Analysis

Data were analyzed using Stata/SE 11.1 software (Stata Corp LP). Our goal was to investigate associations between the SUV_{max} in the primary tumor or LNs and survival outcomes. For that purpose, we analyzed the SUV_{max} before and after RT and the percentage of the change after RT in the following categories: the primary tumor, regional LN with the highest SUV_{max}, SUV_{max} sum of all regional LNs, target lesion with the highest SUV_{max}, and SUV_{max} sum of primary tumor and all the regional LNs. Target lesions were defined as the primary tumor and any involved LNs. The Kaplan–Meier method was used to estimate the probability of overall survival (OS) and disease-free survival (DFS). Potential associations between the SUV_{max} and survival outcomes were assessed in univariate analyses using the Cox proportional hazards model, and SUV_{max} was evaluated as a continuous variable.
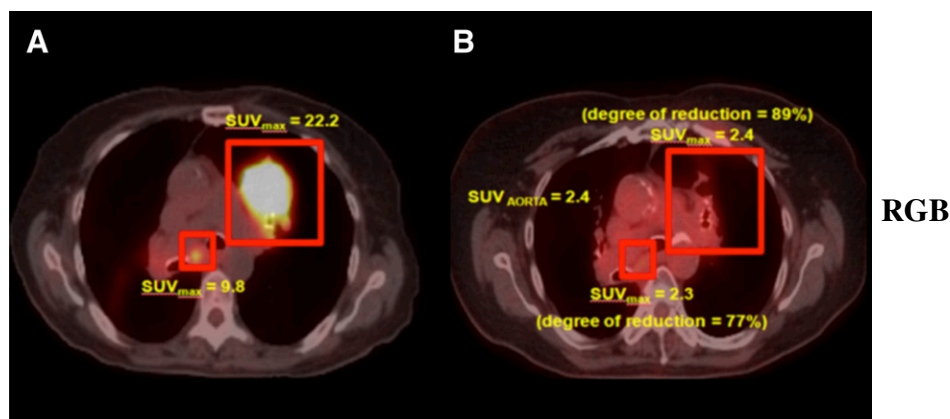
FIGURE 1. PET/CT scans of ^{18}F-FDG uptake by primary tumor and lymph nodes at diagnosis (A) and after radiation therapy (B). SUV_{aorta} = SUV in aorta.

Because of the possible confounding effect of clinical factors on survival, associations found to be significant in the univariate analysis were adjusted by patient factors (age, sex, race, Karnofsky performance status, weight loss, and smoking habits), tumor factors (histology, stage), and treatment factors (type of chemotherapy, RT technique, and dose). Multivariate analyses were performed using a logistic regression model, with a stepwise backward elimination procedure. A *P* value of 0.05 or less was considered statistically significant. Survival time was measured from the end of RT to the first occurrence of the considered event (death, local–regional recurrence [inside the radiation field, or both inside and outside the radiation field], or distant metastasis).

RESULTS

Patients, Treatments, and Follow-up

[Table 1]   Patient characteristics are listed in Table 1. The median follow-up time for all patients was 25.5 mo (range, 3.9–49.4 mo). All patients had good performance status (Karnofsky performance score $\geq$ 70) and underwent RT 5 d a week to a total dose of 63–74 Gy (median, 66 Gy) over 6–7 wk at 1.8–2.0 Gy per day. Forty-eight patients received platinum and taxane-based chemotherapy, 47 concurrent with RT and 1 sequentially. Of the 22 local–regional relapses, 16 occurred inside the radiation field; of the 18 distant metastases, 5 were in the brain.

Survival Analyses

SUV$_{max}$ for Primary Tumor. In 8 patients, distinguishing the ^{18}F-FDG accumulation of the primary tumor from that of the LNs was difficult because the primary tumor extended to the hilar or subcarinal station. In those cases, the ^{18}F-FDG accumulation was regarded as the SUV for
[Table 2] the primary tumor. We observed that the higher the SUV$_{max}$
[Fig. 2] was after RT (Table 2), the shorter was the OS time ($P <$
[Fig. 3] 0.0001; Fig. 2) and DFS time ($P =$ 0.004; Fig. 3). Figures 4
[Fig. 4] and 5 illustrate the effect of SUV$_{max}$ on OS and DFS, re-
[Fig. 5] spectively, with the cut-off point of the SUV$_{max}$ after RT set at 3.7 (the 50th percentile for primary tumors); patients with an SUV$_{max}$ less than 3.7 had better OS and DFS than did those with an SUV$_{max}$ of 3.7 or greater (OS, $P =$ 0.0008; DFS, $P =$ 0.0112). We then investigated whether the interval between the end of RT and the PET scan had any influence on tumor response. For that purpose, we compared the SUV$_{max}$ after RT in those patients who underwent PET 2.5 mo or less after RT (the median time between RT end date and PET scan date) and those who had the evaluation more than 2.5 mo after RT. We found no significant difference in the SUV$_{max}$ after RT between both subgroups ($P =$ 0.201). However, we did find that for the subgroup with the PET scan more than 2.5 mo after RT, the SUV$_{max}$ after RT was associated with OS time ($P =$ 0.021). To clarify the patterns of relapse, we evaluated local–regional control (LRC) and distant metastasis-free survival (DMFS) rates in terms of SUV$_{max}$ and found that the higher the SUV$_{max}$ was after RT, the higher was the risk of local–regional recurrence inside ($P =$ 0.002) and both inside and outside ($P =$ 0.002) the radiation field. However, no

significant associations with DMFS were found. All results that were statistically significant in the univariate analysis retained significance in the multivariate analysis (Table 3). Finally, for the primary tumor, the SUV$_{max}$ at [Table 3] diagnosis was not associated with any of the outcomes that were assessed.

SUV$_{max}$ for Regional LNs. Because some patients had more than one positive LN, we considered the single regional LN with the highest SUV$_{max}$ and the SUV$_{max}$ sum of all PET-positive LNs separately for these analyses. No significant difference was found in the extent of SUV$_{max}$

TABLE 1
Patient Characteristics

Characteristic	Value
Age (y)	
Median	66
Range	37–87
Sex (*n*)	
Male	26 (53.06)
Female	23 (46.94)
Race (*n*)	
White	45 (91.84)
Other*	4 (8.16)
Karnofsky performance status (*n*)	
<80	8 (16.33)
80	19 (38.78)
>80	22 (44.90)
Weight loss (*n*)	
<5%	8 (16.33)
≥5%	41 (83.67)
Smoking history (*n*)	
Current smoker	11 (22.45)
Quit smoking	35 (71.43)
Never smoked	3 (6.12)
Histology (*n*)	
Adenocarcinoma	19 (38.78)
Squamous	19 (38.78)
NSCLC, not otherwise specified	11 (22.45)
Clinical stage (*n*)	
IIIA	17 (34.69)
IIIB	32 (65.31)
Induction chemotherapy (*n*)	
Yes	10 (20.41)
No	39 (79.59)
Concurrent chemotherapy (*n*)	
Yes	47 (95.92)
No	2 (4.08)
Adjuvant chemotherapy (*n*)	
Yes	17 (34.69)
No	32 (65.31)
Radiation technique (*n*)	
Intensity-modulated radiation therapy	42 (85.71)
Proton-beam therapy	7 (14.29)
Radiation dose (*n*)	
Median	66
Range	63–74

*Other includes African Americans and Asians.
Data in parentheses are percentages.

TABLE 2
Univariate Analyses of SUVs and Survival

| Variable	Median	Interquartile range	OS Hazard ratio	OS P	DFS Hazard ratio	DFS P	LRC inside field Hazard ratio	LRC inside field P	LRC inside + outside field Hazard ratio	LRC inside + outside field P	Distant metastasis-free survival Hazard ratio	Distant metastasis-free survival P
Primary tumor												
SUV$_{max}$ at diagnosis	14	10.6–16.9	1.03	0.368	0.99	0.769	1.01	0.837	1.01	0.838	0.93	0.191
SUV$_{max}$ after RT	3.7	2.7–5.5	1.27	<0.0001	1.16	0.004	1.19	0.002	1.17	0.002	1.16	0.066
Reduction (%) in SUV$_{max}$	70	44–80	0.53	0.158	0.62	0.229	0.52	0.159	0.60	0.257	0.52	0.242
Regional LN*												
SUV$_{max}$ at diagnosis	11	6.4–15.4	0.99	0.826	1.01	0.842	1.02	0.582	1.01	0.692	0.94	0.266
SUV$_{max}$ after RT	3.1	2.4–4.1	1.32	0.004	1.32	0.001	1.26	0.011	1.29	0.002	1.11	0.533
Reduction in SUV$_{max}$	64	32–80	0.19	0.070	0.48	0.330	0.65	0.681	0.55	0.481	0.26	0.213
SUV$_{max}$ sum												
All LNs at diagnosis	17.2	10.4–30.6	0.98	0.365	0.99	0.903	0.98	0.632	1.01	0.468	0.98	0.374
All LNs after RT	6.3	3.3–9.5	1.01	0.776	1.09	0.065	1.05	0.374	1.29	0.007	0.99	0.950
Reduction (%) in all LNs	60	43–80	0.20	0.098	0.45	0.321	0.41	0.408	0.55	0.332	0.32	0.337
Target lesion† SUV$_{max}$												
At diagnosis	15.4	11.1–17.9	1.04	0.264	1.01	0.802	1.00	0.982	0.99	0.938	0.97	0.645
After RT	3.8	2.7–5.2	1.27	<0.0001	1.17	0.003	1.19	0.004	1.17	0.004	1.17	0.044
Reduction (%)	72	55–80	0.06	0.002	0.03	0.001	0.06	0.007	0.04	0.002	0.07	0.028
Sum of primary tumor + LNs SUV$_{max}$												
At diagnosis	24.4	15.1–38.3	0.98	0.422	1.00	0.678	0.99	0.524	1.01	0.622	0.99	0.745
After RT	7.9	5.9–13.9	1.06	0.083	1.13	0.001	1.06	0.091	1.13	0.001	1.08	0.115
Reduction (%)	65	45–74	0.04	0.004	0.06	0.033	0.06	0.020	0.07	0.021	0.11	0.163

*Regional LN with the highest SUV$_{max}$.
†Target lesion (either primary tumor or LN) with the highest SUV$_{max}$.
Values shown are hazard ratios.

reduction between the primary tumor (median, 70%) and the regional LN with the highest SUV$_{max}$ after RT (median, 64%; $P = 0.384$). We found that, after RT, the higher the uptake was in the single LN with the highest post-RT SUV$_{max}$, the shorter were the OS time ($P = 0.004$; Fig. 2), the LRC inside the radiation field ($P = 0.001$), the LRC both inside and outside the radiation field ($P = 0.002$), and the DFS time ($P = 0.001$; Fig. 4). Figures 4 and 5 illustrate the effect of SUV$_{max}$ on OS and DFS, respectively, with the cut-off point of the SUV$_{max}$ after RT set at 3.1 (the 50th percentile for LNs); patients with an SUV$_{max}$ of less than 3.1 also had better OS and DFS than did those with an SUV$_{max}$ of 3.1 or more (OS, $P = 0.0143$; DFS, $P = 0.0028$). For the summed SUV$_{max}$ of all PET-positive LNs, only the uptake after RT was significantly associated with LRC inside and outside the radiation field ($P = 0.007$). The results also indicated that the higher the summed SUV$_{max}$ was after RT, the shorter was the LRC. These associations all retained significance in multivariate analysis (Table 3). Again, the SUV$_{max}$ at diagnosis did not correlate with any of the measured outcomes.

SUV$_{max}$ for Target Lesion (Either Primary Tumor or Regional LNs). The target lesion with the highest SUV$_{max}$ at diagnosis was the primary tumor in 67% of cases and the LNs in 33%. Similar results were observed after RT, when the highest SUV$_{max}$ was the primary tumor in 63% of cases

and the LNs in 37% of cases. The higher the post-RT SUV$_{max}$ of the single target lesion with the highest post-RT SUV$_{max}$ was, the shorter were the OS ($P < 0.0001$), DFS ($P = 0.003$), LRC inside the radiation field ($P = 0.004$), LRC both inside and outside the radiation field ($P = 0.004$), and DMFS ($P = 0.044$; Table 2). Findings were similar for the extent of SUV$_{max}$ reduction after RT; specifically, the greater the SUV$_{max}$ reduction was after RT in the single target lesion with the highest SUV$_{max}$ at diagnosis, the longer were the OS ($P = 0.002$; Fig. 2), DFS ($P = 0.001$; Fig. 3), LRC inside the radiation field ($P = 0.007$), LRC both inside and outside the radiation field ($P = 0.002$), and DMFS ($P = 0.028$; Table 2). Figures 4 and 5 illustrate the effect of the post-RT SUV$_{max}$ of the single target lesion with the highest post-RT SUV$_{max}$ and the extent of SUV$_{max}$ reduction after RT on OS and DFS when dichotomized according to the 50th percentile of the corresponding variable. Patients with a post-RT SUV$_{max}$ of less than 3.8 or an SUV$_{max}$ reduction of 72% or more had better OS and DFS than did those with a post-RT SUV$_{max}$ of 3.1 or more (OS, $P = 0.0006$; DFS, $P = 0.0045$) or an SUV$_{max}$ reduction of less than 72% (OS, $P = 0.0074$; DFS, $P = 0.0603$). However, the pretreatment SUV$_{max}$ was not associated with any survival outcome. When analyzing the summed SUV$_{max}$ of the primary tumor plus all PET-positive LNs, we observed that the higher the values were after
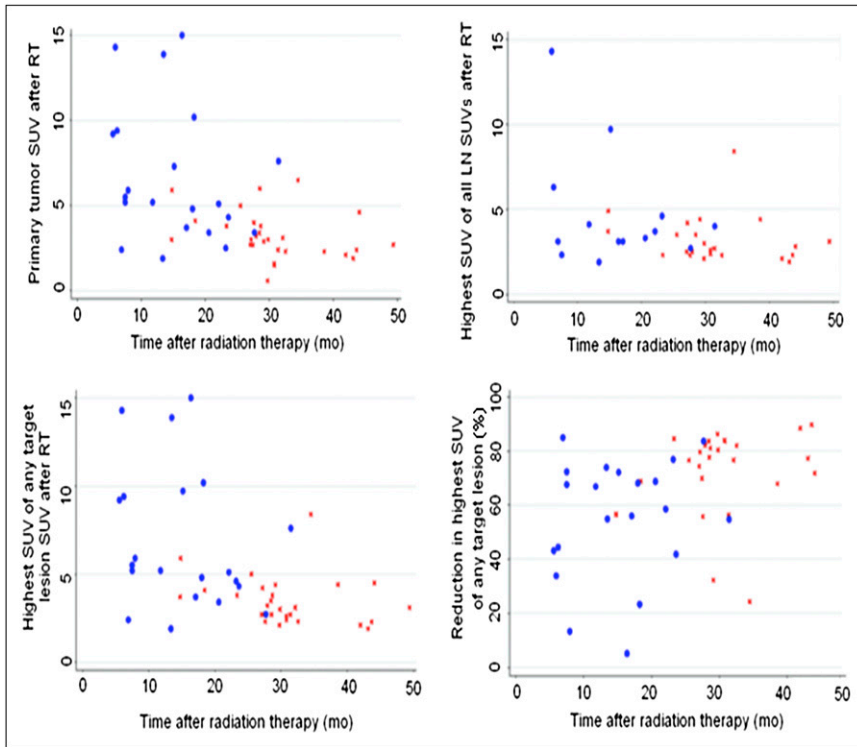
FIGURE 2. Scatterplot of OS time (*x*-axis) vs. SUV_{max} after radiotherapy for patients alive (red symbols) and or dead (blue symbols).

RT, the shorter were the LRC both inside and outside the radiation field ($P = 0.001$) and the DFS ($P = 0.001$). Finally, we found that the greater the reduction was in the summed SUV_{max} of the primary tumor plus all PET-positive LNs, the longer were the OS ($P = 0.004$), LRC inside and outside the field ($P = 0.021$), and DFS ($P = 0.033$; Table 2). All of these results, except for the association between the reduction in the summed SUV_{max} of the primary tumor plus all PET-positive LNs and OS, retained significance in multivariate analyses (Table 3).

DISCUSSION

PET/CT images provide functional information about cancer by assessing the uptake of a radioactive glucose
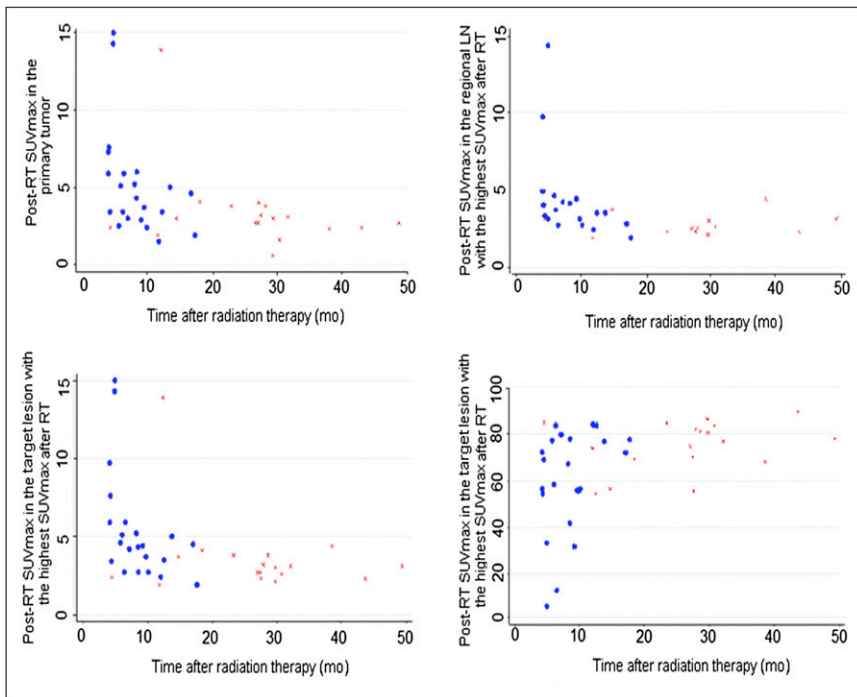
FIGURE 3. Scatterplot of DFS time (*x*-axis) vs. SUV_{max} after radiotherapy for patients with (red symbols) and without (blue symbols) recurrent disease.

CHANGE IN SUV AND OUTCOME IN LUNG CANCER • Lopez Guerra et al. **5**

FIGURE 4. OS according to 50th percentile of SUV_{max} after radiotherapy. *Total number of patients differs from other figures because 4 patients were stage N0 disease, and in 8 N-positive stage cases, it was difficult to distinguish each primary tumor accumulation of ^{18}F-FDG from its LN accumulation. Thus, ^{18}F-FDG accumulation was regarded as SUV_{max} for primary tumor.
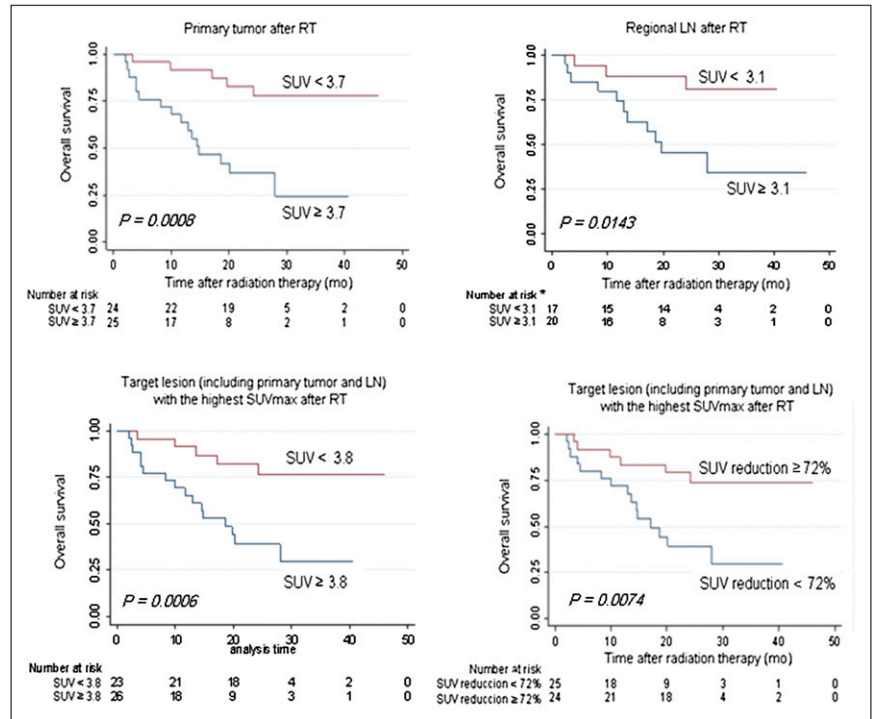
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analog by a tumor—a process that most likely reflects the biologic behavior of a particular case of cancer in terms of proliferation, metastatic potential, sensitivity to therapy, and more (*18,19*). The key findings of the current study were that the regional LN with the highest SUV_{max} after RT was sig-

nificantly associated with OS: the lower the post-RT SUV_{max} was, the longer the OS was. Our results also showed that the extent of reduction in SUV_{max} was associated with disease control after curative RT for locally advanced NSCLC: the greater the decrease in SUV_{max} was in the

FIGURE 5. DFS according to 50th percentile of SUV_{max} after radiotherapy. *Total number of patients differs from other figures because 4 patients were stage N0 disease, and in 8 N-positive stage cases, it was difficult to distinguish each primary tumor accumulation of ^{18}F-FDG from its LN accumulation. Thus, ^{18}F-FDG accumulation was regarded as SUV_{max} for primary tumor.
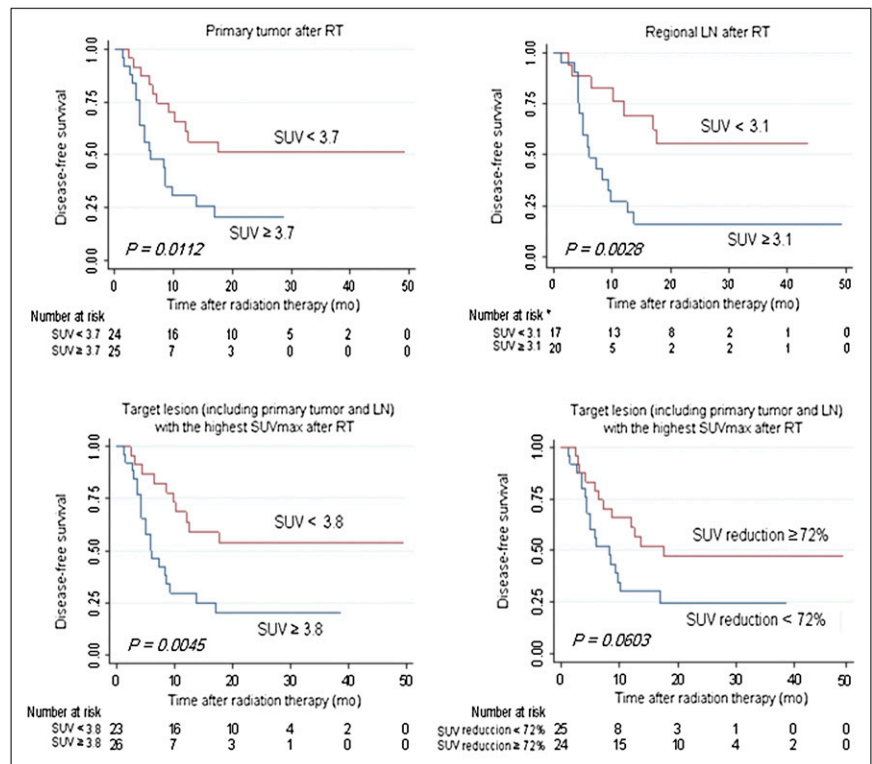
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TABLE 3
Multivariate Analyses of SUVs and Survival

Variable	OS		DFS		LRC inside field		LRC inside + outside field		Distant metastasis-free survival	
	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P
Primary tumor SUV$_{max}$ after RT	1.31	<0.0001	1.30	<0.0001	1.19	0.002*	1.35	<0.0001		—
Regional LN[†] SUV$_{max}$ after RT	1.63	<0.0001	1.32	0.001*	1.58	0.003	1.55	<0.0001		—
SUV$_{max}$ sum of all LNs after RT		—		—		—	1.43	<0.0001		—
Target lesion[‡] SUV$_{max}$ after RT	1.40	<0.0001	1.33	<0.0001	1.19	0.004*	1.38	<0.0001	1.17	0.044*
Reduction (%) in target lesion[‡] SUV$_{max}$	0.07	0.013	0.03	0.001*	0.06	0.007*	NA		0.07	0.028*
Sum of primary tumor + LNs SUV$_{max}$ after RT		—	1.15	<0.0001		—	1.19	<0.0001		—
Reduction (%) in sum of primary tumor + LNs SUV$_{max}$	0.10	0.053	0.06	0.033*	0.06	0.020*	NA			—

Variables shown are those that had statistical significance on univariate analysis.

*After stepwise backward elimination procedure, only this variable showed significance. Therefore, no other covariables could be included in final model for adjustment.

[†]Regional LN with highest SUV$_{max}$.

[‡]Target lesion (either primary tumor or LN) with highest SUV$_{max}$.

lesion (primary tumor or LN) that had the highest SUV$_{max}$ at diagnosis, the longer was the OS. We further found that the lower the post-RT SUV$_{max}$ was in the primary tumor or the regional LN with the highest SUV$_{max}$ after RT, the longer were the DFS and LRC times. Finally, the greater the decline in SUV$_{max}$ was after RT of the lesion with the highest SUV$_{max}$ at diagnosis, the longer was the DMFS time.

It is well established that patients with inoperable NSCLC showing residual metabolic activity within the primary tumor after radiochemotherapy have worse OS than patients without such residual activity (18). Our results are consistent with data published by others. Several investigators have explored the usefulness of pretreatment ^{18}F-FDG PET for predicting outcome for patients with NSCLC, and several cut-off SUV levels have been proposed (13,19,20). However, other recent studies (14,21) have shown that pretreatment ^{18}F-FDG uptake of the primary tumor in patients with newly diagnosed advanced-stage NSCLC was not related to survival. For instance, Ikushima et al. (21) evaluated the relationship between the SUV$_{max}$ and clinical tumor features in 149 patients with NSCLC who underwent pretreatment PET ($n = 67$) or PET/CT ($n = 82$) and definitive RT. A high SUV$_{max}$ was a negative factor for LRC, DMFS, and OS on univariate analysis in the PET group, but the significance decreased when tumor size was included in the analysis. In addition, a high SUV$_{max}$ was not a negative factor for LRC, DMFS, or OS in the PET/CT group, suggesting that the evidence was not sufficient to conclude that pretreatment ^{18}F-FDG uptake in a primary NSCLC tumor provides prognostic information. Consistent with these findings, we did not observe a significant relationship between SUV$_{max}$ before RT and survival.

Therefore, the post-RT SUV$_{max}$ or the extent of reduction in ^{18}F-FDG PET SUV$_{max}$ after treatment may be a better method of predicting survival than the pretreatment values. This supposition is supported by several recent reports (22,23). For instance, Aerts et al. (22) found that patients with residual metabolically active areas within the primary tumor after RT had significantly worse survival than did individuals whose tumors showed a complete metabolic response. In our study, we found that higher post-RT SUV$_{max}$ not only in the primary tumor but also in the regional LN with the highest residual SUV$_{max}$ after RT were strong negative prognostic factors for survival. This finding in the regional LN was a novel discovery. In addition, the association found between the post-RT SUV$_{max}$ and OS noted for patients who had PET scans more than 2.5 mo after the end of RT (but not for those who had earlier PET scans) suggests that scans done sooner than 2.5 mo after RT may not reflect much of the effect of the RT.

The utility of the SUV for disease staging or its role after neoadjuvant chemotherapy for NSCLC has been described before (3,24–27). However, the usefulness of the extent of reduction in SUV after definitive RT, particularly in LNs, for assessing prognosis remains uncertain. In our analysis, neither the reduction in SUV$_{max}$ in the primary tumor nor the reduction in the LNs was associated with any survival outcome assessed. However, when evaluating the percentage of SUV$_{max}$ reduction after RT in the target lesion (either primary tumor or LN) with the highest SUV$_{max}$ at diagnosis, we found a significant association with OS. This result highlights the role of the most ^{18}F-FDG–avid lesion, regardless of whether that lesion is the primary tumor or the LNs, in predicting outcome after treatment of locally advanced NSCLC.

Greene et al. (16) proposed that a complete response after high-dose RT or concurrent chemoradiotherapy is defined as the complete disappearance of all evidence of ma-

lignant disease or residual radiographic abnormalities at 3 and 6 mo after completion of RT that then remains stable for an additional 6 mo or more. A recent Dutch study (18) confirmed the validity of metabolic response assessment up to 6 mo after RT as a surrogate of survival. To predict survival and obtain this information to help identify patients who are at high risk of recurrence and to design additional salvage treatment early, we decided to evaluate the first PET scan done after RT, which usually took place 1–3 mo after treatment, and found that we could indeed obtain this information as early as 3 mo after RT. Whether patients with residual ^{18}F-FDG uptake after RT should be offered additional treatment is still uncertain, and this question should be prospectively evaluated in protocols to evaluate further management strategies such as new targeted therapies or adjuvant chemotherapy for such patients. Currently, the American College of Radiology Imaging Network 6668/RTOG 0235 trial is prospectively evaluating whether the primary tumor ^{18}F-FDG SUV$_{max}$ shortly after definitive chemoradiation can predict long-term survival in inoperable stage II or III NSCLC. This multiinstitutional study will clarify whether our findings are also observed in a larger sample.

On the basis of our findings and others (13,18,23), we could speculate that tumor glucose metabolism is related to the metastatic potential of the tumor. Increased ^{18}F-FDG uptake on PET images may correlate with conventional tissue markers of tumor aggressiveness, markers of hypoxia or angiogenesis, or molecular markers of proliferation, such as Ki-67 (28,29). The overexpression of various molecular markers of tumor biology in common solid tumors such as NSCLC may be associated with PET findings, clinical outcome, or both, which would provide a new avenue for targeted therapies (30).

CONCLUSION

We found that the post-RT SUV$_{max}$ for the primary tumor and LNs, as well as the extent of reduction after RT in the target lesion that had the highest SUV$_{max}$ at diagnosis, were associated with OS and DFS in patients with NSCLC. These findings indicate that the post-RT SUV$_{max}$ and the extent of reduction may become a routinely used, quantifiable, and analytic indicator of disease activity and treatment efficacy.

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