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FDG-PET Maximum Standardized Uptake Value is Prognostic for Recurrence and Survival after Stereotactic Body Radiotherapy for Non-Small Cell Lung Cancer

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Abstract

Objectives—Glucose metabolic activity measured by [¹⁸F]-fluoro-2-deoxy-glucose positron emission tomography (FDG-PET) has shown prognostic value in multiple malignancies, but results are often confounded by the inclusion of patients with various disease stages and undergoing various therapies. This study was designed to evaluate the prognostic value of tumor FDG uptake quantified by maximum standardized uptake value (SUV_{max}) in a large group of early-stage non-small cell lung cancer (NSCLC) patients treated with stereotactic body radiotherapy (SBRT) using consistent treatment techniques.

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Conflict of Interest Statement

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Materials and Methods—219 lesions in 211 patients treated with definitive SBRT for stage I NSCLC were analyzed after a median follow-up of 25.2 months. Cox regression was used to determine associations between SUV_{max} and overall survival (OS), disease-specific survival (DSS), and freedom from local recurrence (FFLR) or distant metastasis (FFDM).

Results— $SUV_{max} > 3.0$ was associated with worse OS ($p < 0.001$), FFLR ($p = 0.003$) and FFDM ($p = 0.003$). On multivariate analysis, OS was associated with SUV_{max} (HR 1.89, $p = 0.03$), gross tumor volume (GTV) (HR 1.94, $p = 0.005$) and Karnofsky performance status (KPS) (HR 0.51, $p = 0.008$). DSS was associated only with SUV_{max} (HR 2.58, $p = 0.04$). Both LR (HR 11.47, $p = 0.02$) and DM (HR 3.75, $p = 0.006$) were also associated with higher SUV_{max} .

Conclusion—In a large patient population, $SUV_{max} > 3.0$ was associated with worse survival and a greater propensity for local recurrence and distant metastasis after SBRT for NSCLC.

Keywords

stereotactic body radiation therapy; non-small cell lung cancer; PET

1. Introduction

Stereotactic body radiotherapy (SBRT) has emerged as a highly effective treatment modality for early-stage non-small cell lung cancer (NSCLC) and it is now widely used in medically inoperable patients or those patients who refuse surgery [1]. Although the rate of local recurrence after SBRT is low, disease-specific survival in this patient population remains suboptimal [2-4]. Identification of tumor or patient characteristics prognostic for tumor recurrence and patient survival could potentially inform clinical decisions.

[^{18}F]-fluoro-2-deoxy-glucose positron emission tomography (FDG-PET) is a commonly used imaging modality in the workup and staging of NSCLC. The maximum standardized uptake value (SUV_{max}) is the most frequently used parameter to quantify tumor FDG uptake. SUV_{max} is a measure of tumor glucose metabolism and is correlated with prognostic features such as proliferation index and differentiation status [5-7]. While tumor size alone has long been recognized as prognostic in the setting of early-stage NSCLC [8], SUV_{max} may be a more robust prognostic feature, as it incorporates information about metabolic activity and potentially the biology of the tumor. Indeed, SUV_{max} has emerged as a promising prognostic marker in NSCLC, with a meta-analysis of surgically treated NSCLC patients demonstrating SUV_{max} to be prognostic for overall survival [9, 10]. Several groups have attempted to characterize the importance of pre-treatment SUV_{max} in the setting of SBRT for NSCLC, yet most studies have been limited by a small number of events or have included patients treated with conventional radiotherapy, and the results regarding the prognostic value of SUV_{max} have been inconclusive.

Here we report a detailed characterization of the prognostic value of SUV_{max} before lung SBRT in the largest such study to date. We also analyzed the association of SUV_{max} with local or distant failures and determined an optimal SUV_{max} cutoff value that could be more broadly used to determine prognosis in the setting of SBRT.

2. Materials and Methods

2.1 Inclusion Criteria

All patients with newly diagnosed, biopsy-proven T1-T2N0M0 NSCLC who received lung SBRT from August 2006 to August 2012 at our institution were identified. Patients were excluded from the analysis if they were being treated for a tumor recurrence, had received chemotherapy within the last year, had an active non-lung cancer malignancy at the time of SBRT or had ever received prior thoracic radiotherapy. Lesions were only included if they had been assessed by PET imaging within 4 months before the initiation of SBRT and were treated with no more than 5 fractions to a definitive dose of at least 45 Gy in 5 fractions.

2.2 Imaging

PET imaging during the study period was performed with various PET/CT systems. All PET scans performed at our institution followed the same protocol. Patients were fasted for at least 6 hours prior to FDG injection. Uptake between injection and imaging was at least 60 minutes. Images were reconstructed with an iterative, ordered subset expectation maximization algorithm, as provided by the scanner manufacturer. Blood glucose levels were below 200mg/dl at the time of FDG injection in all patients.

2.3 Treatment

Patients were immobilized using an alpha cradle, and those patients simulated since 2008 were imaged using a 4D-CT scan to assess tumor motion during the respiratory cycle. The gross tumor volume (GTV) was contoured based on a free-breathing CT scan and an internal target volume (ITV) was created based on respiratory motion visualized on the 4D-CT. The ITV was expanded by a 2mm margin to generate the clinical target volume (CTV). This was further expanded by 5mm to create the planning target volume (PTV).

The prescription dose was administered to the 100% isodose line surrounding the PTV. Treatment was typically delivered using intensity-modulated radiation therapy and four to seven coplanar 6MV beams. Patients were treated on linear accelerators (Varian Medical Systems, Palo Alto, CA) equipped with on-board imaging capability. A cone-beam CT (CBCT) was performed prior to each treatment, and the GTV identified on the CBCT was registered with that on the planning scan, with adjustments made for setup errors of 2mm or greater in any direction. A risk-adapted dosing scheme was utilized, with typically 9 to 10 Gy $\times$ 5 fractions for central tumors, 12 Gy $\times$ 4 fractions for lesions within 1cm of the chest wall, and 18 to 20 Gy $\times$ 3 fractions for other peripheral tumors.

2.4 Statistical Analysis

Local recurrence (LR) was defined as recurrence within the PTV, while distant metastasis (DM) was defined as a malignant pleural effusion or recurrence outside the thorax. Freedom from local recurrence (FFLR) and freedom from distant metastasis (FFDM) were both defined as the time from completion of SBRT to the first evidence of disease recurrence on CT or PET imaging. Development of disease involving the contralateral lung was regarded as a new primary in the absence of spread to other adjacent or distant sites. Those recurrences not verified by biopsy were carefully reviewed separately by at least two authors

to verify the presence of imaging features characteristic of recurrent disease, such as increasing size and/or FDG avidity over time. Tumors that did not recur were censored at the time of last imaging. For patients who underwent SBRT to two synchronous lung tumors and subsequently developed a distant metastasis, each metastasis was attributed to a single index lesion based on tumor histology and timing of the recurrence. Overall survival (OS) was defined as the time from end of SBRT until the date of death or the date of last follow up. Disease-specific survival (DSS) was defined similarly to OS, with only NSCLC-related deaths regarded as events. For 9 patients treated with SBRT to 2 separate lesions, the lesion treated first was used for survival analyses.

To avoid inadvertent bias, an optimal cutoff value for SUV_{max} was determined by dividing the observed SUV_{max} values into deciles from 10% to 90%. Chi-square testing with adjustment was used to determine which values for SUV_{max} were significantly associated with OS. The SUV_{max} value with the lowest unadjusted p-value was selected, and its significance was confirmed using appropriate adjustment for multiple testing [11].

FFLR, FFDM and OS were estimated with the Kaplan-Meier method and compared using log-rank testing. Univariate Cox regression was utilized to assess for associations with patient and tumor characteristics including patient age, patient gender, Karnofsky performance status (KPS), histologic subtype, gross tumor volume (GTV), pre-treatment SUV_{max} and biologically equivalent prescribed dose using an alpha/beta of 10 (BED Gy₁₀). BED Gy₁₀ was dichotomized using the value of 100 Gy₁₀, which has previously been reported as the minimum dose required for optimal tumor control [12]. GTV was dichotomized based on the median value of 6.7cm³. The multivariate analysis (MVA) included all variables with a p-value of < 0.10 on univariate analysis (UVA). For DSS, a competing risks regression model was used, with death from other causes as a competing risk. A p-value of < 0.05 was regarded as significant for all analyses.

3. Results

3.1 Patient and treatment characteristics

We reviewed 381 lesions treated with SBRT for NSCLC at our institution from 2006 to 2012. A total of 219 lesions in 211 patients met the inclusion criteria and were analyzed. Median follow-up was 25.2 months (range 4.3 to 75.2 months). Patient, tumor and treatment characteristics are shown in Table 1. All lesions were biopsy-proven and treated with SBRT in 3 to 5 fractions, with over 80% receiving a BED of at least 100 Gy₁₀. The median time from pre-treatment PET to SBRT was 1.7 months (range 0.1 to 3.9 months). 115 lesions (52.5%) were assessed by PET scans performed at our institution, while the remaining 104 (47.5%) had pre-treatment PET scans at outside facilities. The median SUV_{max} was 4.6 (range 0.5 to 28.4), and there was no significant difference between the distributions of values when comparing outside PET scans to those performed at our institution (interquartile range 3.0 to 9.0 vs. 2.4 to 9.2, p=0.41). 21 LRs were observed during the follow up period, of which 10 (47.6%) were confirmed by biopsy. 38 patients developed DMs, and there were 93 patient deaths, of which 38 were attributed to NSCLC.

3.2 Determination of an Optimal SUV_{max} Cutpoint

The observed SUV_{max} values were divided into deciles, and nine potential cutpoints were created based on these values. Each cutpoint was then tested for association with the endpoint of OS (Table 2). While multiple cutoff values reached significance, the SUV_{max} representing the 30% decile (SUV_{max} = 3.08) was most significant (p=0.00075). This cutpoint retained significance after adjustment for multiple testing (p=0.019).

Based on this analysis, lesions were classified as having a “low” (< 3.0) or “high” (> 3.0) SUV_{max}. A comparison of tumor and patient characteristics between these two groups is shown in Table 3. Tumors within the low SUV_{max} group were significantly more likely to be of smaller size (p<0.0001) and adenocarcinoma histology (p=0.0007). 12 tumors were documented to be consistent with bronchioalveolar histology on pathologic analysis, 8 (67%) of which were within the low SUV_{max} group.

3.3 Outcomes

Patients with tumors characterized by a pre-treatment SUV_{max} ≤ 3.0 demonstrated a significantly better OS than patients with an SUV_{max} > 3.0 (Figure 1). The 2-year OS was 90.2% in the low SUV_{max} group, as compared to 64.5% in the high SUV_{max} group (p<0.0001). Tumors with an SUV_{max} ≤ 3.0 also demonstrated significantly improved FFLR (98.4% vs. 82.7%, p=0.003) and FFDM (91.5% vs. 77.3%, p=0.003), as compared to those with an SUV_{max} > 3.0.

On univariate Cox regression, KPS ≥ 80, GTV > the median value of 6.7cm³ and SUV_{max} > 3.0 were significantly associated with OS (Table 4). On multivariate analysis, KPS (HR 0.51, p=0.008), GTV (HR 1.94, p=0.005) and SUV_{max} (HR 1.89, p=0.03) retained significance. Given the high rate of competing risks in this patient population, we also analyzed the association of these variables with DSS (Table 5). SUV_{max} remained significantly associated with DSS (HR 2.58, p = 0.04).

SUV_{max} > 3.0 was also found to be significantly associated with LR (HR 11.47, p=0.02) (Table 5). BED ≥ 100 Gy (HR 0.32, p=0.01) and tumor GTV (HR 4.21, p=0.005) were also found to correlate with LR. Only SUV_{max} (HR 3.75, p=0.006) and male gender (HR 2.00, p=0.03) were significantly associated with DM. Due to a small number of events, multivariate analyses were not performed for LR or DM.

4. Discussion

PET imaging has become widely adopted in the evaluation of extent of disease in patients with newly diagnosed NSCLC. SUV_{max} is the most widely used PET parameter, and it has been shown to have potential prognostic value in patients undergoing surgical resection for NSCLC. Downey et al. reported that, in a combined cohort of early-stage and locally advanced NSCLC, pre-surgical SUV_{max} predicted overall survival after resection [13]. Additional data have emerged regarding the prognostic value of SUV_{max} in early-stage NSCLC patients undergoing surgery, with several retrospective studies linking pre-operative SUV_{max} to DSS [14-17] and OS [17-21]. In the setting of SBRT, however, the prognostic

value of pre-treatment SUV_{max} has not been consistently demonstrated, and the extent to which it predicts patterns of failure remains unclear.

In our own study of 219 biopsy proven early-stage lung cancers – the largest such study to date – we found pre-treatment SUV_{max} to be significantly associated with OS. While it stands to reason that SUV_{max} would have similar prognostic value in the setting of surgery and an ablative treatment such as SBRT, multiple reports have not found a correlation between SUV_{max} and OS after SBRT [22-26]. Fundamental differences between surgical and SBRT patient populations may partially account for such contradictory findings. For instance, SBRT patients frequently have multiple comorbidities, making death from competing causes much more likely than in surgical series. We found SUV_{max} to be even more strongly associated with DSS, supporting the premise that competing risks can mask the prognostic value of SUV_{max} with respect to OS unless a sufficient number of events are included. It has also been hypothesized that radiobiologic effects could limit the prognostic utility of PET prior to radiotherapy, as tumors with lower FDG uptake could be less responsive to radiation, thus offsetting the biologic features associated with improved prognosis. Most probable, however, is that this lack of correlation between SUV_{max} and outcomes after SBRT is a function of the relatively small number of patients in most SBRT series. In keeping with the hypothesis that low sample size is the driving factor for these inconsistent results, 3 of the 4 studies demonstrating a correlation between SUV_{max} and OS in the setting of SBRT have been among the largest series reported [27-29].

We also found pre-treatment SUV_{max} to be strongly associated with LR. While our findings are consistent with the conclusions of a recent meta-analysis that included patients undergoing any form of lung radiotherapy,[30] a definitive association between pre-treatment SUV_{max} and LR specifically in patients undergoing SBRT, a radiotherapy technique with a low rate of LR, has not yet been demonstrated. Several prior studies limited to SBRT patients have not found an association between SUV_{max} and LR [24-26, 28, 31]. Other small retrospective studies have provided some evidence for an association between SUV_{max} and LR, yet interpretability has been limited by a low number of LR events. In an analysis of 26 lesions, Hamamoto et al. demonstrated that 5 LRs occurred in the high SUV_{max} group, compared to one in the low SUV_{max} group [32]. Two other reports have demonstrated an association between LR and higher SUV_{max} , but fewer than 10 LR events were observed in each study [23, 33]. Our large patient cohort allowed for a more robust analysis of the prognostic variables associated with LR, providing important evidence for an association between SUV_{max} and LR after SBRT. In addition to SUV_{max} , larger GTV was also significantly associated with LR in our analysis. We chose to assess tumor size by GTV because it is a robust measure that has been demonstrated to better correlate with patient outcomes after SBRT than cross-sectional measurements [8]. Other studies using less prognostic size measures, such as greatest tumor diameter or T stage, have the potential to overestimate the prognostic importance of SUV_{max} .

While both tumor volume and SUV_{max} were associated with LR, only SUV_{max} was associated with DM. This may indicate that, independent of its association with tumor size, higher SUV_{max} is reflective of a more aggressive tumor biology with a greater propensity for metastasis. As with LR, no consensus exists regarding the association between pre-SBRT

SUV_{max} and DM. Multiple prior reports have failed to link SUV_{max} to a higher risk of DM in the setting of SBRT for early-stage NSCLC [22, 26, 28, 31, 34]. Other studies have reported such an association, but differences in study design have limited their interpretation. Nair et al. demonstrated a strong association between SUV_{max} and DM in the largest prior such analysis of patients treated with radiotherapy. Unfortunately, over one-third of the 180 lesions included in their analysis received conventionally fractionated radiotherapy [25], which is associated with different failure patterns than SBRT. Similarly, studies by Clarke et al. and Takeda et al. included a substantial number of patients without biopsy-proven carcinoma [23, 27]. Our analysis of biopsy-proven NSCLC treated exclusively with SBRT provide important data detailing the prognostic value of SUV_{max} in the risk of DM in SBRT patients.

In studying SUV_{max}, we utilized an unbiased analysis to define an optimal cutpoint. After analyzing 9 potential cutpoints for SUV_{max}, multiple of these were found to be prognostic for OS (Table 2), suggesting that the risk associated with higher SUV_{max} is a continuum. Despite this observation, we sought to identify a single best SUV_{max} cutpoint that could potentially be utilized as a simple and practical cutpoint in future prospective trials of SBRT. We selected a cutpoint of 3.0 because it was most strongly associated with OS in our patient population. A cutpoint of 3.0 has previously been demonstrated to be prognostic in early-stage lung cancer patients treated with surgery [35]. Although this cutpoint may not be ideal in the setting of more advanced stage tumors, our findings suggest this to be a reasonable cutpoint to stratify patients with early stage disease into high and lower risk groups.

Our patient cohort was limited to those treated with SBRT at our institution, but we did not exclude patients based of the location of their pre-treatment FDG-PET scan. We found no significant difference in the distributions of SUV_{max} values between outside FDG-PET scans and those performed at our institution. We therefore believe that the inclusion of patients undergoing FDG-PET scans at outside institutions does not significantly alter our results and makes our study generalizable to a broader patient population, including those undergoing FDG-PET scans outside large academic centers.

5. Conclusions

As FDG-PET has become more prevalent in the workup for NSCLC, interest has grown in characterizing the extent of its prognostic value. Several investigators have previously attempted to characterize the significance of SUV_{max} prior to SBRT, but these studies have reached inconsistent conclusions. Our study is the largest series to date to investigate the role of SUV_{max} in the setting of SBRT, and it is further strengthened by the exclusion of non-biopsy proven NSCLC and lesions not treated with definitive doses of SBRT. Our study demonstrates that a pre-treatment SUV_{max} of > 3.0 on pre-treatment FDG-PET is prognostic in the setting of SBRT for early-stage NSCLC, associating with worse patient survival and a greater propensity for local recurrence and distant metastasis.

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Highlights

- The prognostic value of SUVmax before SBRT has not been consistently demonstrated
- An SUVmax cutpoint of 3.0 is optimal for stratifying SBRT patients by survival
- Pre-treatment SUVmax >3.0 is associated with worse survival in SBRT patients
- Higher SUVmax was also associated with both local and distant failure after SBRT

Figure 1.

Kaplan-Meier estimates of (A) overall survival, (B) freedom from local recurrence, and (C) freedom from distant metastasis after SBRT, stratified by pre-treatment SUV_{max} of ≤ 3.0 or > 3.0 .

Table 1

Patient, tumor and treatment characteristics.

Patient characteristics	
Age (years), median (range)	77 (51 - 95)
KPS (%), median (range)	80 (40 - 100)
Gender	
Female	119 (56.4%)
Male	92 (43.6%)
Tumor characteristics	
GTV (cm ³), median (range)	6.7 (0.2 – 125)
T stage	
T1a	114 (52.0%)
T1b	63 (28.8%)
T2a	40 (18.3%)
T2b	2 (0.9%)
Histology	
Adenocarcinoma	156 (71.2%)
Squamous cell carcinoma	60 (27.4%)
Unspecified	3 (1.4%)
PET characteristics	
PET to SBRT time (months), median (range)	1.7 (0.1 – 3.9)
SUV _{max} , median (range)	4.6 (0.5 – 28.4)
PET location	
Memorial Sloan Kettering Cancer Center	115 (52.5%)
Outside institution	104 (47.5%)
Treatment characteristics	
Prescription Dose (Gy)	
9 – 10 Gy × 5	42 (19.2%)
11 – 12 Gy × 4	87 (39.7%)
18 – 20 Gy × 3	88 (40.2%)
13 Gy × 3	2 (0.9%)
BED (Gy ₁₀)	
< 100	42 (19.2%)
100	177 (80.8%)

KPS = Karnofsky performance status, GTV = gross tumor volume. BED = biologically effective dose.

Table 2

Determination of the optimal SUV_{max} cutpoint to stratify patients by overall survival.

SUV _{max}		Hazard Ratio (95% CI)	p-value
Percentile	Value		
10	1.40	7.51 (1.85 – 30.6)	0.005 **
20	2.20	2.28 (1.22 – 4.29)	0.010 *
30	3.08	2.53 (1.48 – 4.34)	0.00075
40	3.80	2.17 (1.38 – 3.41)	0.00078
50	4.70	1.70 (1.12 – 2.58)	0.012 *
60	6.10	1.87 (1.23 – 2.81)	0.003 **
70	7.92	1.82 (1.20 – 2.78)	0.005 **
80	10.20	1.79 (1.12 – 2.85)	0.015 *
90	13.08	1.77 (0.94 – 3.33)	0.078

SUV_{max} values within the study population were divided into 10 percentile increments, from the 10th to 90th percentile. Each of these values for SUV_{max} were used as a cutpoint, and chi-square with adjustment was used to determine the association of each value with overall survival. The SUV_{max} with the lowest p-value is highlighted. The significance of corresponding p-values is indicated as follows:

*** <0.001.

* <0.05

** <0.01

Table 3

Comparison of patient, tumor and treatment characteristics between lesions with pre-treatment SUV_{max} 3.0 and > 3.0.

Variable	SUV_{max} 3.0	SUV_{max} > 3.0	p-value
KPS (%)			
< 80	18 (26.9%)	51 (33.6%)	0.61
80	23 (34.3%)	47 (30.9%)	
> 80	26 (38.8%)	54 (35.5%)	
Age (years)			
> 77	31 (46.3%)	75 (49.3%)	0.77
77	36 (53.7%)	77 (50.7%)	
Gender			
Male	23 (34.3%)	70 (46.1%)	0.14
Female	44 (65.7%)	82 (53.9%)	
GTV (cm ³)			
> 6.7	15 (22.4%)	94 (61.8%)	< 0.0001 ***
6.7	52 (77.6%)	58 (38.2%)	
Histology			
Adenocarcinoma	58 (86.6%)	98 (64.5%)	0.0007 ***
Squamous cell/unspecified	9 (13.4%)	54 (35.5%)	
BED (Gy ₁₀)			
100	57 (85.1%)	120 (78.9%)	0.35
< 100	10 (14.9%)	32 (21.1%)	
PET - SBRT interval (months)			
> 1.7	37 (55.2%)	77 (50.7%)	0.56
1.7	30 (44.8%)	75 (49.3%)	

The significance of corresponding p-values is indicated as follows:

<0.001.

Table 4

Univariate and multivariate analysis demonstrating factors prognostic for overall survival (OS).

Variable	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
<u>KPS (%)</u>				
< 80	reference	N/A	reference	N/A
80	0.55 (0.33 – 0.91)	0.02 *	0.52 (0.31 – 0.87)	0.013 *
> 80	0.56 (0.35 – 0.91)	0.02 *	0.51 (0.31 – 0.84)	0.008 **
<u>Age (years)</u>				
> 77	1.22 (0.81 – 1.83)	0.35		
77				
<u>Gender</u>				
Male	1.46 (0.97 – 2.19)	0.07	1.32 (0.86 – 2.03)	0.21
Female				
<u>GTV (cm³)</u>				
> 6.7	2.42 (1.57 – 3.74)	<0.0001***	1.94 (1.22 – 3.09)	0.005 **
6.7				
<u>SUV_{max}</u>				
> 3.0	2.53 (1.48 – 4.34)	0.0007***	1.89 (1.06 – 3.36)	0.03 *
3.0				
<u>Histology</u>				
Adenocarcinoma	0.68 (0.44 – 1.04)	0.08	0.90 (0.56 – 1.44)	0.65
Squamous cell/unspecified				
<u>BED (Gy₁₀)</u>				
100	0.85 (0.51 – 1.43)	0.54		
< 100				
<u>PET - SBRT interval (months)</u>				
> 1.7	0.85 (0.56 – 1.29)	0.47		
1.7				

Only those variables reaching a significance of $p < 0.10$ on univariate analysis are shown and were included in the multivariate analysis. The significance of corresponding p-values is indicated as follows:

* < 0.05

** < 0.01 .

Table 5

Univariate analysis demonstrating factors prognostic for the endpoints of disease specific survival (DSS), local recurrence (LR) and distant metastasis (DM).

Endpoint	Variable	Hazard Ratio (95% CI)	p-value
DSS	SUV _{max}	2.58 (1.03 – 6.45)	0.04 *
LR	BED (Gy ₁₀)	0.32 (0.14 – 0.77)	0.01 *
	GTV (cm ³)	4.21 (1.54 – 11.52)	0.005 **
	SUV _{max}	11.47 (1.54 – 85.53)	0.02 *
DM	Gender (male)	2.00 (1.06 – 3.80)	0.03 *
	SUV _{max}	3.75 (1.46 – 9.61)	0.006 **

The significance of corresponding p-values is indicated as follows:

*
<0.05

**
<0.01.