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Optimal FDG PET/CT Volumetric Parameters for Risk Stratification in Patients with Locally Advanced Non-small Cell Lung Cancer: Results from the ACRIN 6668/RTOG 0235 Trial

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Abstract

Purpose—In recent years, multiple studies have demonstrated the value of volumetric FDG-PET/CT parameters as independent prognostic factors in patients with non-small cell lung cancer (NSCLC). We aimed to determine the optimal cut-off points of pretreatment volumetric FDG-PET/CT parameters in predicting overall survival (OS) in patients with locally advanced NSCLC, and to recommend imaging biomarkers appropriate for routine clinical applications.

Methods—Patients with inoperable stage IIB/III NSCLC enrolled in ACRIN 6668/RTOG 0235 were included. Pretreatment FDG-PET scans were quantified using semiautomatic adaptive contrast-oriented thresholding and local-background partial-volume-effect-correction algorithms. For each patient, the following indices were measured: metabolic tumor volume (MTV), total lesion glycolysis (TLG), SUVmax, SUVmean, partial-volume-corrected TLG (pvcTLG) and pvcSUVmean for the whole-body, primary tumor and regional lymph nodes. The association

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between each index and patient outcome was assessed using Cox proportional hazards regression. Optimal cut-off points were estimated using recursive binary partitioning in a conditional inference framework and used in Kaplan-Meier curves with log-rank testing. The discriminatory ability of each index was examined using time-dependent receiver operating characteristic (ROC) curves and corresponding area under the curve (AUC(t)).

Results—196 patients were included. Pretreatment whole-body and primary tumor MTV, TLG and pvcTLG were independently prognostic of OS. Optimal cut-off points were 175.0, 270.9, and 35.5 cm³ for whole-body TLG, pvcTLG, and MTV, and were 168.2, 239.8, and 17.4 cm³ for primary tumor TLG, pvcTLG, and MTV, respectively. In time-dependent ROC analysis, AUC(t) for MTV and TLG were uniformly higher than that of SUV measures over all time points. Primary tumor and whole-body parameters demonstrated similar patterns of separation for those patients above versus below the optimal cut-off points in Kaplan-Meier curves, and in time-dependent ROC analysis.

Conclusion—We demonstrated that pretreatment whole-body and primary tumor volumetric FDG-PET/CT parameters, including MTV, TLG, and pvcTLG, are strongly prognostic for OS in patients with locally advanced NSCLC, and have similar discriminatory ability. Therefore, we believe that, after validation in future trials, the derived optimal cut-off points for primary tumor volumetric FDG-PET/CT parameters, or their more refined versions, could be incorporated into routine clinical practice, and may provide more accurate prognostication and staging based on tumor metabolic features.

Introduction

Lung cancer is the leading cause of cancer-related deaths in the United States and worldwide [1, 2]. The management of lung cancer can consist of a combination of surgery, chemotherapy and radiation therapy, and depends on the accurate determination of tumor size, location, nodal involvement and distant disease extent based on imaging modalities and tissue sampling. ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has been recommended for initial evaluation of all non-small cell lung cancer (NSCLC) patients with no evidence of distant metastasis on conventional imaging [3]. It also has an integral role in radiotherapy treatment planning [4–7], prognostication and response monitoring of patients with NSCLC [8].

In recent years, multiple studies suggested a superior correlation of volumetric FDG-PET/CT parameters, including metabolic tumor volume (MTV) and total lesion glycolysis (TLG), with progression-free and overall survival (OS) of NSCLC patients compared with conventional anatomical parameters or maximum standardized uptake value (SUVmax) [9–11]. The majority of these studies were single-center retrospective investigations with small, heterogeneous patient populations with respect to disease stage and treatment [8]. Moreover, MTV and TLG were generally computed using a fixed SUVmax threshold, which has significant limitations, including underestimating MTV and TLG in lesions with high SUVmax and overestimating these parameters in lesions with SUVmax close to background [12]. Furthermore, few studies have attempted to translate the prognostic value of these parameters to practical measures for day-to-day clinical practice. Defining optimal cut-off points for volumetric FDG-PET/CT parameters would further facilitate these imaging

biomarkers being used in routine clinical practice, and may open new avenues for more accurate prognostication built upon the metabolic staging of cancer patients. Another commonly overlooked issue in clinical research is correction for partial volume effect in the calculation of FDG-PET/CT parameters. Several phantom and simulation studies have demonstrated the benefit of partial-volume-effect correction for accurate FDG-PET/CT quantification [13–15]. To date, however, partial volume effect correction has been investigated in a limited number of clinical studies [16, 17].

In this study, we aimed 1) to examine the discriminatory ability of volumetric FDG-PET/CT parameters to predict OS among patients with locally advanced NSCLC, and to determine the optimal cut-off points for these parameters, 2) to assess the correlation and agreement between partial-volume-effect-corrected FDG-PET/CT parameters and their non-corrected counterparts, and 3) to compare parameters with prognostic value and recommend imaging biomarkers most appropriate for routine clinical applications.

Methods

American College of Radiology Imaging Network (ACRIN, now ECOG-ACRIN) 6668/ Radiation Therapy Oncology Group (RTOG, now NRG Oncology) 0235 was the largest prospective, multi-institutional trial, to date, conducted to assess the prognostic value of pre- and post-treatment FDG-PET imaging for patients treated with definitive chemoradiotherapy for Stage III and medically inoperable stage IIB NSCLC ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00083083) identifier: NCT00083083). The study design has been described previously [18]. In brief, enrolled patients had locally advanced NSCLC with no evidence of distant metastatic disease by conventional imaging, Zubrod performance status of 0–1 and were candidates for definitive concurrent chemoradiotherapy. Treatment consisted of thoracic radiotherapy in 1.8–2.0 Gy daily fractions to a total dose of at least 60 Gy with concurrent platinum-based doublet chemotherapy. All patients underwent FDG-PET or FDG-PET/CT on a scanner qualified by the ACRIN Imaging Core Laboratory[19] prior to the initiation of chemoradiotherapy, and again at 12 to 16 weeks after completion of radiotherapy on the same scanner. Patients were observed for a minimum of 2 years (or until death) after completion of treatment in accordance with standard clinical practice. Patients consented to the original prospective study, which was approved by the local institutional review board of each participating institution. PET/CT images were collected centrally and transferred to our image-processing laboratory for this secondary analysis.

Image Analysis

Metabolic tumor volume (MTV), total lesion glycolysis (TLG), maximum, mean and peak standardized uptake values (SUV_{max}, SUV_{mean} and SUV_{peak}, respectively) as well as partial-volume-effect-corrected SUV_{mean} (pvcSUV_{mean}) and TLG (pvcTLG), of all FDG-avid lesions were quantified from pre-treatment FDG-PET/CT scans using semiautomatic adaptive-contrast-oriented thresholding and local background partial-volume-effect-correction algorithms, as implemented in a commercially available software package (ROVER software, ABX, Radeberg, Germany). The technical details, accuracy, and reproducibility of these algorithms have been described previously [20–23]. A single reader,

who is a board-certified nuclear medicine physician with 6 years of experience and who was blinded to all clinical outcomes, semi-automatically delineated all FDG-avid thoracic lesions, including the primary tumor and sites of nodal metastases. A second reader verified all measurements and compared lesion labeling to that from the primary study image analysis using SUVmax and SUVpeak records from the ACRIN Imaging Core Laboratory. For each patient, three sets of FDG-PET/CT parameters were defined: primary tumor, lymph node, and whole-body. For MTV and TLG, in the lymph node and whole-body regions, values were summed over all identified FDG-avid lesions. All parameters are described in detail in Appendix Table 1. Subjects with unavailable pre-treatment FDG-PET/CT scans, or with pre-treatment scans where poor image quality precluded measurement, were excluded from analysis.

Statistical Analysis

The goals of this secondary analysis were to examine the discriminatory ability of pre-treatment FDG-PET/CT parameters to predict OS, to assess agreement between partial-volume-effect-corrected parameters and their non-corrected counterparts, and to derive optimal cut-off points for parameters demonstrating prognostic value. In addition, we also evaluated the predictive ability of pre-treatment FDG-PET/CT parameters for a second patient outcome of locoregional control (LRC), which was defined as a failure within the irradiated primary lung tumor and/or the involved regional lymph node fields.

Summary statistics, including the mean, standard deviation, median and range were computed for all pre-treatment FDG-PET/CT parameters. Survival time was defined as the interval from study registration to either death or patient censoring. In examining time to local regional failure, patients who died prior to recording a local-regional failure were treated as censored.

In assessing the prognostic ability of each FDG-PET/CT parameter, we separately fit two Cox proportional hazards regression models: a univariable model (continuous variable), and a multivariable model (continuous variable) adjusting for sex, age, baseline performance status, and baseline clinical stage. Model diagnostics related to the Cox model were assessed using scaled Schoenfeld residuals. Based on our previous publication, baseline performance status was modeled via a time-dependent coefficient [24]. The discriminatory ability of whole-body and primary tumor FDG-PET/CT parameters was examined using time-dependent (cumulative sensitivity/dynamic specificity) receiver operating characteristic (ROC) curves, and the corresponding estimate of the area under curve (AUC(t)) at the 2-year time point. These estimates measure the ability of each FDG-PET/CT metric to discriminate between subjects who died on or prior to 2 years versus those who survived past 2 years. Differences in AUC(t) between partial-volume-effect-corrected parameters and their non-corrected counterparts, as well as between whole-body and primary tumor parameters, were also estimated. Corresponding 95% confidence intervals were calculated using the bootstrap technique with 2000 iterations. For prognostic FDG-PET/CT parameters, optimal cutoff points were estimated using recursive binary partitioning in a conditional inference framework. Kaplan-Meier curves with log-rank testing were generated to depict the association with OS, splitting at the derived optimal cut-off points.

The prognostic ability of each FDG-PET/CT parameter with respect to LRC was assessed using Cox proportional hazards regression models in the same manner as described above for OS. In addition, an exploratory analysis was conducted using the timing of locoregional failure to predict OS. This analysis was restricted to the subset of patients who experienced locoregional failure, and survival time was defined from the date of locoregional failure to either death or patient censoring.

All statistical tests were two-sided. Analyses were performed using R version 3.2.3 (R project, <http://www.r-project.org>).

Results

Patient Characteristics

Of the 250 patients enrolled in ACRIN 6668 / RTOG 0235, 16 subjects were ineligible. Of the remaining 234 subjects, 196 (84%) were included in the current analysis. Reasons for exclusion of the remaining patients were no pre-treatment FDG-PET (n=1), DICOM header data corruption preventing accurate quantification (n=17), poor image quality, which precluded measurement of FDG-PET/CT parameters (n=14), and missing imaging studies (n=6). Totals of 196, 192 and 151 patients were eligible for whole-body, primary tumor and lymph node-level analyses, respectively. Patient demographics and clinical characteristics of the subjects included in this analysis are summarized in Table 1.

FDG-PET parameters

The median SUV_{peak} and SUV_{max} in the primary tumor were 11.0 (interquartile range (IQR)=6.9 – 14.9) and 13.1 (IQR=8.6 – 18.0), respectively. Regarding total tumor burden, median whole-body MTV was 37.0 cm³ (IQR = 21.8 – 62.9 cm³), median whole-body TLG was 303.0 (IQR = 145.4 – 551.5), and median whole-body pvcTLG was 442.0 (IQR = 214.3 – 762.8). Summary statistics for all 7 measured FDG-PET/CT parameters, including partial volume effect corrected indices, are summarized by region in Table 2.

Overall survival

Among subjects in the analysis set, the median survival time from study registration was 20.2 months, with 144 subjects experiencing death (75.0%) at the time of analysis. Multivariable Cox proportional hazards regression showed that MTV, TLG, and pvcTLG of both the primary tumor and whole-body regions were independent predictors of OS with comparable hazard ratios (Table 3). No FDG-PET/CT parameters derived from the lymph node region were associated with OS. Detailed statistics on Cox proportional hazards regression, including lymph node level analysis, are summarized in Appendix Table 2.

Similarly, for both the primary tumor and whole-body regions, MTV, TLG and pvcTLG demonstrated the highest estimated area under the curve (AUC(t)) at the 2-year time point from time-dependent (cumulative sensitivity/dynamic specificity) receiver operating characteristic (ROC) curve analysis (Table 4; Appendix Table 3). Whole-body MTV, TLG and pvcTLG had slightly higher estimated AUC(t) at the 2-year time point in comparison to their primary tumor counterparts; however, 95% confidence intervals for the difference

overlapped with zero in each instance (Table 4; Appendix Table 3). The corresponding plot of time-dependent AUC(t) values for these parameters over the observed range of follow-up time is shown in Figure 1, which shows a similar pattern for primary tumor and whole-body parameters (Appendix Figure 1).

Optimal cut-off points, calculated using recursive binary partitioning, were 175.0 for whole-body TLG, 270.9 for whole-body pvcTLG, and 35.5 cm³ for whole-body MTV, and 168.2, 239.8 and 17.4 cm³ for primary tumor TLG, pvcTLG and MTV, respectively. Kaplan-Meier curves of overall survival, along with log-rank testing, using these derived optimal cut-off points are shown in Figure 2. Primary tumor and whole-body parameters demonstrated similar patterns of separation for those patients above versus below the optimal cut-off points (Figure 2).

Partial volume effect corrected parameters

Partial-volume-effect-corrected whole-body parameters showed strong correlation with their non-corrected counterparts; however, agreement was better between whole-body TLG and pvcTLG (concordance correlation coefficient (CCC)=0.93, 95% CI 0.92 – 0.94), than between whole-body SUVmean and pvcSUVmean (CCC=0.72, 95% CI 0.67–0.76) (Appendix Figure 2). In addition, as was expected, partial-volume-effect-corrected parameters were uniformly larger than their non-corrected counterparts. The partial volume effect, namely the percent difference between corrected and non-corrected measures, was inversely correlated with MTV (Appendix Figure 2). A similar pattern was observed with primary tumor parameters (data not shown). In this cohort, both partial volume effect corrected parameters and their non-corrected counterparts demonstrated similar prognostic and discriminatory ability. In particular, in Cox proportional hazards regression modelling, pvcTLG and TLG, as well as pvcSUVmean and SUVmean, had similar hazard ratios within each region (Table 3), and time-dependent (cumulative sensitivity/dynamic specificity) ROC curves demonstrated similar AUC(t) at the 2-year time point (Figure 3; Table 4).

Locoregional Control

Among subjects in the analysis set, the median locoregional control time from study registration was 14.7 months, with 69 subjects experiencing locoregional failure (40.1%). Whole-body MTV, TLG, and pvcTLG were each significantly associated with locoregional failure; however, the association diminished over time, no longer retaining statistical significance by 12 months. Detailed statistics on locoregional control are summarized in Appendix Table 4. In a subset analysis using local regional failure time to prognosticate overall survival, we observed that patients with earlier local regional failure had worse survival outcomes (Appendix Table 5).

Discussion

In the primary analysis of ACRIN 6668/RTOG 0235, Machtay et al. [18] found that neither pretreatment SUVpeak nor SUVmax was prognostic of clinical outcomes for patients with Stage III and inoperable stage IIB NSCLC. Although post treatment SUVpeak was associated with OS in these patients based on a continuous variable statistical model, the

pre-specified binary cut-off of 3.5 was not statistically significant, thus limiting the utility of this parameter in routine clinical decision-making [18]. Although measurement of SUV_{peak} and SUV_{max} are available on almost all commercial workstations, and different averaging methods of these parameters have been suggested by several investigators, these measures reflect the disease activity of only a single lesion with the highest uptake, and thus may overlook lesions with sub-dominant FDG avidity; moreover, these measures do not reflect total disease activity. Several studies have suggested that gross tumor volume (GTV), defined anatomically using CT, is an independent prognostic factor for inoperable NSCLC patients treated with chemoradiation [24–26]. However, CT-based tumor volume may not reveal real tumor burden because routine CT protocols do not have contrast resolution for soft-tissue structures and they have limited ability to distinguish nonviable or nonmalignant tissues, such as necrosis, fibrosis, and pleural effusion, from malignant tissue and primary tumor and lymph nodes, which usually have irregular shapes. As such, CT-based whole-body tumor burden calculations are cumbersome and suboptimal[27].

Several retrospective studies have suggested that MTV or TLG measured on FDG-PET are independent prognostic factors for patients with NSCLC[8]. However, to our knowledge, all such prior studies enrolled heterogeneous patient populations with stage I–IV NSCLC, and/or with varying treatment regimens of surgery, adjunct chemotherapy, definitive chemoradiation, or chemotherapy only, and there is currently no other study considering FDG-PET MTV or TLG in only stage III NSCLC patients. In a prior secondary analysis of ACRIN 6668/RTOG 0235, Ohri et al. [28] partly alleviated this shortcoming by examining whole-body MTV, although primary tumor and lymph node metrics were not reported. In another secondary analysis by Bazan[29], the authors used a fixed SUV threshold method to measure MTV, and did not compare primary tumor with whole body MTV or TLG or lymph node parameters. Moreover, none of these studies evaluated the role of partial-volume-effect correction.

In the current analysis, we aimed to conduct a comprehensive assessment of all parameters at different regions, and to estimate optimal cuff-off points in order to suggest clinically practical biomarkers. Therefore, we have examined primary tumor and lymph node regions separately, in addition to whole-body metrics. We found that lymph node level analysis did not associate with OS or locoregional control, and that the prognostic value of primary tumor volumetric parameters was similar to whole-body parameters. Furthermore, in time-dependent (cumulative sensitivity/dynamic specificity) receiver operating characteristic (ROC) analysis, our results seem to suggest that primary tumor volumetric parameters have similar discriminatory ability in predicting 2-year OS, compared to whole-body parameters. Considering that calculation of whole-body FDG-PET parameters is more time consuming and prone to inter-reader and intra-reader errors, we have identified and suggest that primary tumor MTV is a promising imaging-based biomarker for routine clinical practice. In the current analysis, we also defined optimal cut-off points for primary tumor MTV of 17.4 cm³ and for TLG of 168.2 based on recursive binary partitioning. We emphasize that these optimum cut-off points were obtained from PET studies performed according to standard clinical protocols at different institutions during five years. Therefore this patient population is similar to day-to-day practice cases, and these cut-off points could conceivably be used at other institutions. However, it is crucial to emphasize that the suggested cut-off points

require validation in future trials with more diverse clinical settings prior to implementation. .

In the prior analysis by Ohri et al. [28], pretreatment volumetric PET measures of all thoracic lesions were found to be predictors of OS. The authors contoured the primary tumor and lymph nodes in the patients using a semiautomatic gradient-based contouring algorithm (as opposed to our iterative contrast-oriented algorithm) to measure the MTV and TLG along with traditional SUVmax. Primary tumor and lymph node FDG-PET parameters were combined to give a unique whole-body measure for each parameter. In the current analysis, in addition to separately analyzing primary tumor and lymph node measures, we also assessed the role of partial volume effect on pretreatment volumetric FDG-PET parameters by performing partial-volume-effect correction on the measurements. Previous studies have shown the feasibility and reproducibility of contrast-oriented thresholding algorithms and 3D lesion-based partial-volume-effect correction [20], which has been shown to increase PET values, and is presumed to enhance the quantification accuracy for lung malignancies, particularly in patients with small primary tumors. However, in the current analysis, for this cohort of patients, partial-volume-effect-corrected parameters and non-corrected counterparts had similar prognostic and discriminatory ability for OS.

Although it is difficult to provide a definitive explanation for these findings, several factors may contribute to this negative result. First, in this cohort, MTV demonstrated the highest prognostic value, which obviously is not affected by partial volume effect. However, even in the univariate Cox proportional hazard regression models (Appendix Table 2), corrected and non-corrected SUV did not significantly predict OS, and the hazard ratios and AUC(t) for TLG and pvcTLG were similar. Second, hypothetically, only large tumors were included in this study. To investigate this possibility, we performed a subgroup analysis on the primary tumors and lymph nodes with MTV less than the median. However, even in smaller lesions, partial-volume-effect correction did not enhance the prognostic value of different PET parameters (results not shown). Third, in the current study, post-treatment FDG-PET/CT images were not included. Consequently, the significance of partial-volume-effect correction in response monitoring was not determined—further studies are needed to investigate this potential application[15]. Algorithms for partial-volume-effect correction are not available in the majority of commercial image processing software. Further, MTV, which showed the highest prognostic value among all parameters, is not affected by partial volume averaging. Therefore, we believe that although correction for partial volume could theoretically increase the accuracy of FDG-PET/CT parameter quantification, it may not significantly improve the prognostic value of these parameters in the clinical setting.

Our current study has some limitations. First, at this time, recommending a single specific algorithm among the diverse variety of techniques for PET image segmentation and partial-volume-effect correction, which are mostly at the research software level and not commercialized, is premature. However, the most promising PET segmentation techniques seem to be based on adaptive thresholding, which consider background uptake in the delineation algorithms. Second, there are limitations in the quantification techniques currently used in the literature, including the techniques used in the current analysis, which are still not able to delineate lesions with high background uptake. Therefore, we were not

able to process some of the post-treatment images; as such, we necessarily limited this study to pretreatment images. Additional studies are needed to assess the role of volumetric FDG PET/CT parameters for response monitoring and the significance of partial-volume-effect correction in the context of comparing pre- and post-treatment measures. This may optimally be assessed in patients with stage IV disease receiving chemotherapy alone that would not have tissue around the primary tumor showing post radiation inflammatory changes and associated FDG uptake.

Conclusions

We demonstrated that pretreatment whole-body and primary tumor volumetric FDG-PET/CT parameters, including MTV, TLG and pvcTLG, are strongly prognostic for OS in patients with locally advanced NSCLC. These parameters have uniformly better discriminatory ability than corresponding SUV measures. The discriminatory ability of partial volume effect-corrected and non-corrected counterparts, and whole-body and primary tumor parameters were similar. We believe that after validation in future trials, the derived optimal cut-off points for primary tumor volumetric FDG-PET/CT parameters, or their more refined versions, could be incorporated into routine clinical practice, and may provide more accurate prognostication and staging based on tumor metabolic features.

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Appendix

Appendix Table 1

Description of pre-treatment FDG-PET/CT measures (SUV, MTV, TLG) for the whole-body, primary tumor and lymph node regions.

SUV _{max}	Maximum activity concentration in the lesion
SUV _{mean}	Mean concentration of FDG in the lesion
pvcSUV _{mean}	Partial volume effect corrected SUV _{mean}
SUV _{peak}	Mean concentration of FDG in a spherical region of 1.2 cm diameter (1 ml) automatically centered at the most active portion of the tumor
MTV	Metabolic tumor volume determined by semiautomatic lesion delineation software
TLG	Total lesion Glycolysis
pvcTLG	Partial volume effect corrected TLG
Whole-body	
SUV _{max}	Maximum SUV _{max} of all lesions in the whole body
ASUV _{max}	Average SUV _{max} of all lesions in the whole body
SUV _{mean}	WBTG/WBMTV
pvcSUV _{mean}	WBpvcTLG/WBMTV
SUV _{peak}	Maximum SUV _{peak} of all lesions in the whole body
TLG	Sum of TLG of all lesions in the whole body
pvcTLG	Sum of pvcTLG of all lesions in the whole body
MTV	Sum of MTV of all lesions in the whole body
Lymph node	
SUV _{max}	Maximum SUV _{max} of all lymph nodes
SUV _{mean}	TLG/LNMTV
pvcSUV _{mean}	LNpvcTLG/LNMTV
SUV _{peak}	Maximum SUV _{peak} of all lymph nodes
TLG	Sum of TLG of all lymph nodes
pvcTLG	Sum of pvcTLG of all lymph nodes
MTV	Sum of MTV of all lymph nodes
Primary tumor	
SUV _{max}	Maximum SUV _{max} of all primary tumors
SUV _{mean}	TTLG/TMTV

pvcSUV _{mean}	TpvcTLG/TMTV
SUV _{peak}	Maximum SUV _{peak} of all primary tumors
TLG	Sum of TLG of all primary tumors
pvcTLG	Sum of pvcTLG of all primary tumors
MTV	Sum of MTV of all primary tumors

Abbreviations:

MTV=Metabolic tumor volume

TLG=Total lesion glycolysis

SUV=Standardized uptake value

WB=Whole-body

LN=Lymph node

T=Primary tumor

PVC=Partial volume effect correction

Appendix Table 2

Univariable and multivariable Cox proportional hazard regression models for overall survival (OS) using continuous pre-treatment FDG-PET/CT measures (SUV, MTV, and TLG) from the whole body, primary tumor and lymph node regions. Partial volume effect corrected measures are italicized and denoted by the prefix pvc.

Variable	Analysis Type ¹	Hazard Ratio ²	99% CI lower bound	99% CI upper bound	P-value
Primary tumor					
SUV _{peak}	Univariable	1.01	0.97	1.04	0.65
	Multivariable	1.00	0.97	1.04	0.78
SUV _{max}	Univariable	1.01	0.98	1.04	0.43
	Multivariable	1.01	0.98	1.03	0.53
SUV _{mean}	Univariable	1.01	0.96	1.06	0.63
	Multivariable	1.00	0.96	1.05	0.79
<i>pvcSUV_{mean}</i>	Univariable	1.01	0.98	1.04	0.56
	Multivariable	1.01	0.97	1.04	0.68
TLG	Univariable	1.18	1.02	1.36	0.003
	Multivariable	1.17	1.02	1.36	0.004
<i>pvcTLG</i>	Univariable	1.20	1.03	1.40	0.002
	Multivariable	1.20	1.03	1.39	0.003
MTV	Univariable	1.27	1.07	1.52	<0.001
	Multivariable	1.28	1.07	1.55	<0.001
Lymph node					
SUV _{peak}	Univariable	0.99	0.94	1.04	0.64
	Multivariable	0.98	0.94	1.03	0.40
SUV _{max}	Univariable	0.99	0.95	1.03	0.60
	Multivariable	0.99	0.95	1.03	0.41
SUV _{mean}	Univariable	1.00	0.94	1.07	0.99

Variable	Analysis Type ¹	Hazard Ratio ²	99% CI lower bound	99% CI upper bound	P-value
	Multivariable	0.99	0.93	1.06	0.83
<i>pvcSUV_{mean}</i>	Univariable	1.00	0.96	1.04	0.90
	Multivariable	1.00	0.96	1.04	0.95
TLG	Univariable	1.05	0.85	1.29	0.57
	Multivariable	1.01	0.82	1.25	0.87
<i>pvcTLG</i>	Univariable	1.06	0.85	1.32	0.48
	Multivariable	1.02	0.82	1.27	0.78
MTV	Univariable	1.05	0.82	1.34	0.64
	Multivariable	1.01	0.78	1.30	0.92
Whole-body					
SUV _{peak}	Univariable	1.00	0.97	1.04	0.74
	Multivariable	1.00	0.97	1.04	0.97
SUV _{max}	Univariable	1.01	0.98	1.04	0.48
	Multivariable	1.01	0.98	1.03	0.65
ASUV _{max}	Univariable	1.00	0.97	1.03	0.94
	Multivariable	1.00	0.96	1.03	0.86
SUV _{mean}	Univariable	1.01	0.96	1.06	0.75
	Multivariable	1.00	0.95	1.05	0.99
<i>pvcSUV_{mean}</i>	Univariable	1.01	0.97	1.04	0.56
	Multivariable	1.00	0.97	1.04	0.79
TLG	Univariable	1.27	1.04	1.55	0.002
	Multivariable	1.24	1.01	1.53	0.007
<i>pvcTLG</i>	Univariable	1.31	1.06	1.62	<0.001
	Multivariable	1.27	1.03	1.58	0.004
MTV	Univariable	1.43	1.11	1.84	<0.001
	Multivariable	1.42	1.08	1.85	<0.001

¹The multivariable model adjusted for age, sex, baseline clinical stage (IIB/IIIA vs. IIIB), and baseline performance status (included as a time-dependent coefficient via an appropriate interaction with time).

²For all SUV measures, the hazard ratio is interpreted per 1-unit increase in SUV. For all MTV measures, the hazard ratio is interpreted per log increase in MTV. Finally, for all TLG measures, the hazard ratio is interpreted per log increase in TLG.

Abbreviations:

MTV=Metabolic tumor volume

TLG=Total lesion glycolysis

SUV=Standardized uptake value

Appendix Table 3

Estimated area under the time-dependent (cumulative sensitivity/dynamic specificity) receiver operating characteristic curve (AUC), along with 95% confidence interval, corresponding to 2-year overall survival (OS) for whole body and primary tumor FDG-PET/CT measures, along with corresponding differences. Partial volume effect corrected measures are italicized and denoted by the prefix pvc. 95% confidence intervals were derived from the bootstrap technique (n=2000).

Variable	AUC	95% CI
Whole-body		
MTV	0.635	(0.547, 0.714)
<i>pvcTLG</i>	0.632	(0.547, 0.710)
TLG	0.625	(0.543, 0.709)
SUV _{mean}	0.527	(0.441, 0.610)
<i>pvcSUV_{mean}</i>	0.526	(0.441, 0.606)
SUV _{max}	0.525	(0.444, 0.610)
SUV _{peak}	0.511	(0.431, 0.595)
ASUV _{max}	0.509	(0.424, 0.589)
MTV – ASUV _{max}	0.126	(0.022, 0.231)
MTV – SUV _{peak}	0.124	(0.021, 0.225)
<i>pvcTLG – ASUV_{max}</i>	0.123	(0.048, 0.193)
<i>pvcTLG – SUV_{peak}</i>	0.121	(0.051, 0.193)
TLG – ASUV _{max}	0.116	(0.038, 0.187)
TLG – SUV _{peak}	0.114	(0.037, 0.184)
MTV – SUV _{max}	0.11	(0.008, 0.217)
MTV – <i>pvcSUV_{mean}</i>	0.109	(-0.008, 0.220)
MTV – SUV _{mean}	0.108	(0.000, 0.216)
<i>pvcTLG – SUV_{max}</i>	0.107	(0.031, 0.183)
<i>pvcTLG – pvcSUV_{mean}</i>	0.106	(0.027, 0.186)
<i>pvcTLG – SUV_{mean}</i>	0.105	(0.034, 0.177)
TLG – SUV _{max}	0.101	(0.019, 0.174)
TLG – <i>pvcSUV_{mean}</i>	0.099	(0.016, 0.178)
TLG – SUV _{mean}	0.098	(0.021, 0.175)
<i>pvcTLG – TLG</i>	0.007	(-0.002, 0.017)
<i>pvcSUV_{mean} – SUV_{mean}</i>	-0.001	(-0.020, 0.018)
Primary Tumor		
MTV	0.619	(0.534, 0.699)
<i>pvcTLG</i>	0.614	(0.532, 0.697)
TLG	0.609	(0.524, 0.689)
SUV _{max}	0.534	(0.450, 0.615)
SUV _{mean}	0.526	(0.439, 0.611)

Variable	AUC	95% CI
SUV_{peak}	0.518	(0.434, 0.605)
<i>pvcSUV_{mean}</i>	0.515	(0.432, 0.599)
$MTV - pvcSUV_{mean}$	0.104	(-0.004, 0.205)
$MTV - SUV_{peak}$	0.101	(0.018, 0.183)
<i>pvcTLG - pvcSUV_{mean}</i>	0.098	(0.015, 0.181)
<i>pvcTLG - SUV_{peak}</i>	0.095	(0.036, 0.158)
$MTV - SUV_{mean}$	0.094	(0.003, 0.176)
$TLG - pvcSUV_{mean}$	0.094	(0.015, 0.176)
$TLG - SUV_{peak}$	0.091	(0.031, 0.154)
<i>pvcTLG - SUV_{mean}</i>	0.088	(0.020, 0.151)
$MTV - SUV_{max}$	0.086	(0.003, 0.174)
$TLG - SUV_{mean}$	0.084	(0.014, 0.151)
<i>pvcTLG - SUV_{max}</i>	0.08	(0.013, 0.143)
$TLG - SUV_{max}$	0.076	(0.008, 0.144)
<i>pvcTLG - TLG</i>	0.004	(-0.004, 0.012)
<i>pvcSUV_{mean} - SUV_{mean}</i>	-0.01	(-0.037, 0.015)
Difference in AUC (Whole-body – Primary Tumor)		
WB MTV – PT MTV	0.016	(-0.046, 0.077)
WB <i>pvcTLG</i> – PT <i>pvcTLG</i>	0.019	(-0.036, 0.074)
WB TLG – PT TLG	0.016	(-0.038, 0.069)

Abbreviations:

MTV=Metabolic tumor volume

TLG=Total lesion glycolysis

SUV=Standardized uptake value

WB=Whole-body

PT=Primary tumor

Appendix Table 4

Univariable and Multivariable Cox proportional hazard regression models for local-regional control (LRC) using continuous pre-treatment FDG-PET/CT measures (SUV, MTV, and TLG) from the whole body, primary tumor and lymph node regions. Partial volume effect corrected measures are italicized and denoted by the prefix pvc. In analyzing time to locoregional failure, some of the FDG-PET/CT parameters demonstrated extreme departures from the proportional hazards assumption, which is integral to the Cox model. To remedy this, for the affected features, models with time-dependent coefficients were fit through an appropriate interaction with time.

Variable	Analysis Type ¹	Hazard Ratio ²	99% CI lower bound	99% CI upper bound	P-value
Primary tumor					
SUV_{peak}	Univariable	1.01	0.97	1.05	0.61
	Multivariable	1.01	0.97	1.06	0.46

Variable	Analysis Type ¹	Hazard Ratio ²	99% CI lower bound	99% CI upper bound	P-value
SUV _{max}	Univariable	1.01	0.97	1.05	0.50
	Multivariable	1.01	0.98	1.05	0.36
SUV _{mean}	Univariable	1.01	0.95	1.08	0.65
	Multivariable	1.02	0.95	1.09	0.55
<i>pvcSUV_{mean}</i>	Univariable	1.01	0.97	1.06	0.44
	Multivariable	1.01	0.97	1.06	0.42
TLG	Univariable	_ .3	_ .3	_ .3	_ .3
	Baseline	1.53	1.03	2.26	0.005
	6 months	1.34	1.02	1.75	0.006
	12 months	1.17	0.95	1.43	0.05
	Multivariable	_ .3	_ .3	_ .3	_ .3
	Baseline	1.46	0.97	2.20	0.016
	6 months	1.32	1.00	1.75	0.010
	12 months	1.19	0.96	1.47	0.03
<i>pvcTLG</i>	Univariable	_ .3	_ .3	_ .3	_ .3
	Baseline	1.58	1.04	2.39	0.004
	6 months	1.37	1.03	1.83	0.005
	12 months	1.19	0.96	1.48	0.04
	Multivariable	_ .3	_ .3	_ .3	_ .3
	Baseline	1.52	0.98	2.34	0.014
	6 months	1.36	1.01	1.83	0.008
	12 months	1.21	0.97	1.52	0.03
MTV	Univariable	_ .3	_ .3	_ .3	_ .3
	Baseline	1.76	1.09	2.84	0.003
	6 months	1.47	1.06	2.06	0.003
	12 months	1.23	0.96	1.59	0.03
	Multivariable	_ .3	_ .3	_ .3	_ .3
	Baseline	1.69	1.02	2.78	0.007
	6 months	1.48	1.05	2.09	0.004
	12 months	1.30	0.99	1.70	0.013
Whole body					
SUV _{peak}	Univariable	1.01	0.97	1.06	0.51
	Multivariable	1.01	0.97	1.07	0.45
SUV _{max}	Univariable	1.01	0.97	1.05	0.41
	Multivariable	1.02	0.98	1.06	0.33
ASUV _{max}	Univariable	1.01	0.97	1.06	0.52
	Multivariable	1.02	0.97	1.07	0.36
SUV _{mean}	Univariable	1.02	0.95	1.09	0.48

Variable	Analysis Type ¹	Hazard Ratio ²	99% CI lower bound	99% CI upper bound	P-value
	Multivariable	1.03	0.95	1.11	0.37
<i>pvcSUVmean</i>	Univariable	1.02	0.97	1.07	0.25
	Multivariable	1.03	0.98	1.08	0.18
TLG	Univariable	_ .3	_ .3	_ .3	_ .3
	Baseline	2.26	1.33	3.84	<0.001
	6 months	1.68	1.15	2.46	<0.001
	12 months	1.25	0.94	1.66	0.04
	Multivariable	_ .3	_ .3	_ .3	_ .3
	Baseline	2.50	1.39	4.49	<0.001
	6 months	1.76	1.17	2.64	<0.001
	12 months	1.24	0.92	1.65	0.06
<i>pvcTLG</i>	Univariable	_ .3	_ .3	_ .3	_ .3
	Baseline	2.39	1.37	4.14	<0.001
	6 months	1.76	1.18	2.62	<0.001
	12 months	1.29	0.96	1.74	0.03
	Multivariable	_ .3	_ .3	_ .3	_ .3
	Baseline	2.70	1.45	5.02	<0.001
	6 months	1.86	1.21	2.85	<0.001
	12 months	1.28	0.94	1.74	0.04
MTV	Univariable	_ .3	_ .3	_ .3	_ .3
	Baseline	2.78	1.44	5.35	<0.001
	6 months	1.89	1.19	3.00	<0.001
	12 months	1.29	0.91	1.82	0.06
	Multivariable	_ .3	_ .3	_ .3	_ .3
	Baseline	3.07	1.52	6.18	<0.001
	6 months	1.98	1.22	3.24	<0.001
	12 months	1.28	0.88	1.86	0.08

¹The multivariable model adjusted for age, sex, baseline clinical stage (IIB/IIIA vs. IIIB), and baseline performance status (included as a time-dependent coefficient via an appropriate interaction with time).

²For all SUV measures, the hazard ratio is interpreted per 1-unit increase in SUV. For all MTV measures, the hazard ratio is interpreted per log increase in MTV. Finally, for all TLG measures, the hazard ratio is interpreted per log increase in TLG.

³A single hazard ratio is not reported, as the specified variable is time varying, indicating that the hazard ratio varies over time.

Abbreviations:

MTV=Metabolic tumor volume

TLG=Total lesion glycolysis

SUV=Standardized uptake value

Appendix Table 5

Univariable Cox proportional hazards regression models using timing of locoregional failure (LRF) from baseline (how soon from registration the patient experienced LRF) to predict overall survival (OS) among the subset of patients who experienced LRF (n=69). Survival time was defined from the date of LRF to either death or patient censoring. The median survival time of this subset was 9.0 months.

Variable	Level	Estimate (SE)	Hazard ratio (95% CI)	p-value
Timing of LRF (continuous)	-	-0.05 (0.02)	0.96 (0.91, 0.998) ^I	0.04
Timing of LRF (categorical)	6 mos	Ref	Ref	-
	6 mos < LRF 12 mos	-0.76 (0.35)	0.47 (0.24, 0.93)	0.03
	LRF > 12 mos	-0.76 (0.34)	0.47 (0.24, 0.91)	0.03

^I The hazard ratio is interpreted per 1-month increase.

Appendix Figure 1.

Area under the time-dependent (cumulative sensitivity/dynamic specificity) receiver operating characteristic curve (AUC(t)) corresponding to overall survival (OS) over the range of observed follow-up time, demonstrating the discriminatory abilities of whole-body (A) and primary tumor parameters (B).

Appendix Figure 2.

(A) Scatterplot of whole-body SUVmean versus pvcSUVmean (B) Plot of percentage of difference between whole-body SUVmean and pvcSUVmean by tumor size (C) Scatterplot of whole-body TLG versus pvcTLG (D) Plot of percentage of difference between whole-body TLG and pvcTLG by tumor size.

Figure 1.

Area under the time-dependent (cumulative sensitivity/dynamic specificity) receiver operating characteristic curves (AUC(t)) corresponding to overall survival (OS) over the range of observed follow-up time for whole-body and primary tumor MTV, TLG and pvcTLG. Appendix Figure 1 shows the AUC(t) for all parameters.

Figure 2. Kaplan-Meier (KM) curves corresponding to overall survival (OS) for prognostic whole-body and primary tumor FDG-PET/CT parameters (MTV, TLG, pvcTLG), dichotomized by their respective derived optimal cut-off points.

Figure 3.

Area under the time-dependent (cumulative sensitivity/dynamic specificity) receiver operating characteristic curves (AUC(t)) corresponding to overall survival (OS) over the range of observed follow-up time, comparing TLG to pvcTLG and SUVmean to PVC SUVmean of both primary and whole-body parameters. Appendix Figure 1 shows the AUC(t) for all parameters.

Table 1

Demographic and clinical characteristics for all eligible patients and for the subset of analyzable patients.

	Eligible Patients (N=234)	Analyzable Patients (N=196)
Age (years)		
Median	65	65
Range	36–85	36–85
Race ¹	N (%)	N (%)
Asian	31 (13.25)	29 (14.80)
Black or African American	27 (11.54)	17 (8.67)
Native Hawaiian/Pacific Islander	1 (0.43)	1 (0.51)
White	171 (73.08)	145 (73.98)
Unknown	8 (3.42)	8 (4.08)
Ethnicity		
Hispanic or Latino	7 (2.99)	6(3.06)
Not Hispanic or Latino	217 (92.74)	182(92.86)
Unknown	10 (4.27)	8(4.08)
Sex		
Male	150 (64.10)	127 (64.80)
Female	84 (35.90)	69 (35.20)
Baseline clinical stage		
IIB/IIIA	127 (54.27)	104 (53.06)
IIIB	107 (45.73)	92 (46.94)
Baseline performance status		
0 (fully active)	102 (43.59)	87 (44.39)
1 (ambulatory, capable of light work)	132 (56.41)	109 (55.61)
Chemotherapy regimen		
Carboplatin/Paclitaxel	95 (40.60)	77 (39.29)
Cisplatin/Etoposide	35 (14.96)	26 (13.27)
Other	89 (38.03)	80 (40.82)

	Eligible Patients (N=234)	Analyzable Patients (N=196)
Data not available	15 (6.41)	13 (6.63)
Radiation dose		
<50 Gy	9 (3.85)	8 (4.08)
50–60 Gy	11 (4.70)	9 (4.59)
60–70 Gy	146 (62.39)	122 (62.24)
70 Gy	52 (22.22)	44 (22.45)
Data not available	16 (6.84)	13 (6.63)

¹ Multiple races may be endorsed by a single participant, so that percentage totals may exceed 100%.

Table 2

Distributional summaries of pre-treatment FDG-PET/CT measures (SUV, MTV, TLG) for the whole-body, primary tumor and lymph node regions. Partial volume effect corrected measures are italicized and denoted by the prefix pvc.

Variable	N	Min	Q1	Median	Mean	Q3	Max	Std Dev
Primary tumor								
SUV _{peak}	192	2.0	6.9	11.0	11.7	14.9	39.6	6.6
SUV _{max}	192	2.5	8.6	13.1	14.2	18.0	53.2	7.9
SUV _{mean}	192	1.5	5.5	8.1	8.8	11.5	28.3	4.7
<i>pvcSUV_{mean}</i>	192	1.6	8.0	12.1	13.1	17.2	45.0	6.8
TLG	192	2.6	45.1	156.9	375.0	393.7	5621.0	661.5
<i>pvcTLG</i>	192	4.8	71.0	221.4	510.8	559.7	7311.0	853.5
MTV	192	1.1	7.4	17.6	37.3	44.4	459.0	58.7
Lymph node								
SUV _{peak}	151	2.3	5.2	7.8	9.0	11.1	30.0	5.3
SUV _{max}	151	3.0	6.6	10.1	11.4	13.6	37.5	6.5
SUV _{mean}	151	1.7	3.8	5.2	6.1	7.4	24.3	3.6
<i>pvcSUV_{mean}</i>	151	1.9	5.6	8.5	9.7	12.6	38.7	6.0
TLG	151	2.7	35.0	76.8	147.3	189.6	1537.0	192.2
<i>pvcTLG</i>	151	5.6	53.9	113.5	216.7	280.8	2201.0	276.9
MTV	151	0.8	7.2	15.5	22.5	27.3	239.5	26.5
Whole-body								
SUV _{peak}	196	2.4	8.6	11.9	12.9	15.9	39.6	6.4
SUV _{max}	196	2.8	10.1	14.0	15.5	19.2	53.2	7.7
ASUV _{max}	196	2.8	8.6	12.1	13.2	16.7	38.6	6.5
SUV _{mean}	196	1.9	5.4	7.6	8.4	10.9	24.7	4.2
<i>pvcSUV_{mean}</i>	196	2.7	7.6	11.3	12.3	15.4	34.5	6.2
TLG	196	3.2	145.4	303.0	480.8	551.5	5621.0	662.0
<i>pvcTLG</i>	196	5.5	214.3	442.0	667.3	762.8	7311.0	863.1
MTV	196	1.6	21.8	37.0	53.8	62.9	483.5	61.4

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Abbreviations:
MTV=Metabolic tumor volume
TLG= Total lesion glycolysis
SUV=Standardized uptake value
Q1=25th percentile
Q3=75th percentile
Std Dev=Standard Deviation

Table 3

Multivariable Cox proportional hazard regression models for overall survival (OS) using continuous pre-treatment FDG-PET measures (SUV, MTV, and TLG) from both the primary tumor and whole-body. Partial-volume-effect-corrected measures are italicized and denoted by the prefix pvc.

Variable	Adjusted Hazard Ratio ^{1,2}	95% CI lower bound	95% CI upper bound	P-value
Whole-body				
SUV _{peak}	1.00	0.97	1.03	0.97
SUV _{max}	1.01	0.98	1.03	0.65
ASUV _{max}	1.00	0.97	1.02	0.86
SUV _{mean}	1.00	0.96	1.04	0.99
<i>pvcSUV_{mean}</i>	1.00	0.98	1.03	0.79
TLG	1.24	1.06	1.44	0.007
<i>pvcTLG</i>	1.27	1.08	1.50	0.004
MTV	1.42	1.15	1.74	<0.001
Primary tumor				
SUV _{peak}	1.00	0.98	1.03	0.78
SUV _{max}	1.01	0.99	1.03	0.53
SUV _{mean}	1.00	0.97	1.04	0.79
<i>pvcSUV_{mean}</i>	1.01	0.98	1.03	0.68
TLG	1.17	1.05	1.31	0.004
<i>pvcTLG</i>	1.20	1.06	1.34	0.003
MTV	1.28	1.07	1.52	<0.001

¹The multivariable model adjusted for age, sex, baseline clinical stage (IIB/IIIA vs. IIIB), and baseline performance status (included as a time-dependent coefficient via an appropriate interaction with time).

²For all SUV measures, the hazard ratio is interpreted per 1-unit increase in SUV. For all MTV measures, the hazard ratio is interpreted per log increase in MTV. Finally, for all TLG measures, the hazard ratio is interpreted per log increase in TLG.

Abbreviations:

MTV=Metabolic tumor volume

TLG=Total lesion glycolysis

SUV=Standardized uptake value

Table 4

Estimated area under the time-dependent (cumulative sensitivity/dynamic specificity) receiver operator characteristic curve (AUC(t)), along with 95% confidence interval, corresponding to 2-year overall survival (OS) for whole-body and primary tumor FDG-PET/CT measures, along with corresponding differences. Partial-volume-effect-corrected measures are italicized and denoted by the prefix pvc. 95% confidence intervals were derived from the bootstrap technique (n=2000). (Complete comparisons between all parameters are summarized in Appendix Table 3.)

Variable	AUC(t)	95% CI
Whole-body		
MTV	0.635	(0.547, 0.714)
<i>pvcTLG</i>	0.632	(0.547, 0.710)
TLG	0.625	(0.543, 0.709)
SUV _{mean}	0.527	(0.441, 0.610)
<i>pvcSUV_{mean}</i>	0.526	(0.441, 0.606)
SUV _{max}	0.525	(0.444, 0.610)
SUV _{peak}	0.511	(0.431, 0.595)
ASUV _{max}	0.509	(0.424, 0.589)
<i>pvcTLG</i> – TLG	0.007	(–0.002, 0.017)
<i>pvcSUV_{mean}</i> – SUV _{mean}	–0.001	(–0.020, 0.018)
Primary Tumor		
MTV	0.619	(0.534, 0.699)
<i>pvcTLG</i>	0.614	(0.532, 0.697)
TLG	0.609	(0.524, 0.689)
SUV _{max}	0.534	(0.450, 0.615)
SUV _{mean}	0.526	(0.439, 0.611)
SUV _{peak}	0.518	(0.434, 0.605)
<i>pvcSUV_{mean}</i>	0.515	(0.432, 0.599)
<i>pvcTLG</i> – TLG	0.004	(–0.004, 0.012)
<i>pvcSUV_{mean}</i> – SUV _{mean}	–0.01	(–0.037, 0.015)
Difference in AUC(t) (Whole-body – Primary Tumor)		
WB MTV – PT MTV	0.016	(–0.046, 0.077)
WB <i>pvcTLG</i> – PT <i>pvcTLG</i>	0.019	(–0.036, 0.074)
WB TLG – PT TLG	0.016	(–0.038, 0.069)

Abbreviations:

MTV=Metabolic tumor volume

TLG=Total lesion glycolysis

SUV=Standardized uptake value

WB=Whole-body

PT=Primary tumor