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Absence of a Relationship between Tumor ^{18}F-fluorodeoxyglucose Standardized Uptake Value and Survival in Patients Treated with Definitive Radiotherapy for Non–Small-Cell Lung Cancer

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Introduction: A recent meta-analysis suggested that patients with non–small-cell lung cancer (NSCLC) whose primary tumors have a higher standardized uptake value (SUV) derived from ^{18}F-fluorodeoxyglucose positron emission tomography (PET) have a worse prognosis in comparison with those with tumors with lower values. However, previous analyses have had methodological weaknesses. Furthermore, the prognostic significance over the full range of SUV values in patients treated nonsurgically remains unclear. The aim of this retrospective study was to investigate the relationship between survival and maximum SUV (SUV_{max}) analyzed as a continuous variable, in patients with NSCLC, staged using PET/computed tomography (CT) and treated with radiotherapy with or without chemotherapy.

Methods: Eligible patients had a histological diagnosis of NSCLC, were treated with radical radiotherapy with or without chemotherapy as their primary treatment, and had pretreatment PET/CT scans. SUV_{max}, defined as the maximum pixel SUV value retrieved from the primary tumor, was analyzed primarily as a continuous variable for overall survival.

Results: Eighty-eight patients met eligibility criteria: stage I, 19; stage II, 10; and stage III, 59. Median SUV_{max} was 15.0 (range, 2.5–56). Higher stage was associated with higher SUV_{max} values ($p = 0.048$). In univariate analysis, there was no evidence of a prognostic effect of SUV_{max} (hazard ratio per doubling = 0.83; 95% confidence interval, 0.62–1.11; $p = 0.22$). Analyzing SUV_{max} as a dichotomous variable (median cut point = 15.0), the hazard ratio (high: low) for risk of death was 0.71, with $p = 0.18$ (95% confidence interval, 0.44–1.15).

Conclusions: In this cohort of patients, increasing SUV_{max} derived from ^{18}F-fluorodeoxyglucose–PET/CT was associated with increasing tumor, node, metastasis (TNM) stage. We found no evidence of an association of increasing SUV_{max} with a shorter survival. Previous reports of an association between prognosis and SUV_{max} may partly be the result of methodological differences between this study and previous reports and an association between stage and SUV_{max}.

Key Words: Non–small-cell lung cancer, Positron emission tomography, Standardized uptake value, Prognosis.

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In patients with non–small-cell lung cancer (NSCLC), the most important tumor-related prognostic factor is the tumor, node, metastasis (TNM) stage.[1] The current noninvasive standard for tumor staging is hybrid positron emission tomography/computed tomography (PET/CT) using ^{18}F-fluorodeoxyglucose (FDG). PET/CT has been shown to provide more precise anatomical and functional interpretations than PET or CT imaging alone.[2]

In addition to its efficacy in assessing nodal and metastatic disease, FDG-PET/CT is thought to have a potential role as a prognostic factor. FDG uptake is commonly expressed as the standardized uptake value (SUV), a semiquantitative value defined as the tissue concentration of FDG in the region of interest divided by the injected dose normalized by body weight.

An update of the systematic review and meta-analysis of previous published studies, in which many patients were treated surgically and staged with FDG-PET,[3,4] has suggested that the maximum SUV (SUV_{max}) of the primary tumor derived from ^{18}F-FDG-PET scanning is potentially a prognostic indicator for outcome for patients with NSCLC. Nonetheless, this was not a consistent finding across all studies, which consisted mainly of patients with early-stage

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disease (stage IIB or less). Furthermore, most studies examined the effect of SUV_{max} as a dichotomous variable, using a cutoff value equal in most case to either the median or a so-called best cut point determined from the data, which will therefore vary from one study population to another.

Given the superiority of hybrid FDG-PET/CT in providing more accurate staging, in this study we assessed the survival outcomes of medically or surgically inoperable NSCLC patients treated with radical radiotherapy (RT) or chemoirradiation at our institution. The aim was to determine whether primary tumor SUV_{max}, derived from the initial pretreatment FDG-PET/CT and evaluated as a continuous variable, provides prognostic information for overall survival (OS) independently of tumor stage.

Secondary objectives were to (1) assess the effect of SUV_{max} on progression-free survival (PFS), (2) examine for any correlations between SUV variables and baseline patient and tumor variables, and assess whether there are any interactions between the above variables in their relationship to outcome. A further secondary objective was to examine the methodological validity of the "best cut point" method, using our data.

METHODS

Study Design

This was a retrospective cohort study of patients with NSCLC receiving radical RT at the Peter MacCallum Cancer Centre (Peter Mac) between January 2000 and December 2006.

Patient Selection

Before data collection, the study protocol was approved by the ethics committee of the Peter Mac. Eligible patients were identified via the Peter Mac PET Centre and RT databases if they met the following criteria: histological diagnosis of NSCLC, received radical RT (60 Gy in 30 fractions) with or without concurrent chemotherapy as their primary treatment, were at least 18 years or older at commencement of treatment, and had pretherapeutic imaging with an integrated PET/CT scanner (GE Discovery LS PET/CT scanner, Milwaukee, WI). Hence, patients who had stand-alone PET imaging instead of PET/CT scanning before treatment were excluded from this study. Other exclusion criteria were a history of other malignancies within the last 5 years (with the exception of in situ carcinoma and nonmelanoma skin cancer), prior treatment for NSCLC including surgery, and evidence of metastasis before treatment.

Data Collection

Patient demographics and potential prognostic factors were collected from the review of the hospital's electronic medical records. This included tumor histology and differentiation, NSCLC stage according to TNM classification of malignant tumors (6th edition), Eastern Cooperative Oncology Group (ECOG) performance status, weight loss over the 3 months before diagnosis, smoking status, lung function, and Simplified Co-morbidity Score.[5]

RT treatment details and chemotherapy regimen, if applicable, and relevant parameters from PET/CT scanning details were recorded.

FDG-PET/CT Imaging Technique and Interpretation

An integrated PET/CT scanner (GE Discovery LS PET/CT scanner) was used for all patients in this study. Patients were required to fast 4 to 6 hours before PET/CT imaging. FDG-PET/CT scans encompassing the lower neck to the proximal thighs were performed on the combined PET/CT scanner. Image acquisition started at approximately 1 hour after FDG injection. Contemporaneous noncontrast CT scans were performed for the purposes of attenuation correction and anatomical correlation.

SUV Methodology

SUV_{max} was derived using an SUV threshold isocontour based volume of interest around the primary tumor. The operator defined a volume manually around the entire tumor but excluding nearby benign structures with FDG avidity. The operator had discretion for selecting the SUV contour for the tumor, but usually a value of 4. In-house software (MARVN 2.16) was used to manually draw the region of interest placed over the entire primary lung tumor and to calculate SUV. An ellipsoid volume of interest was placed over a representative region of the liver from which the patient's mean liver SUV was recorded. This was used as a quality assurance parameter to ensure concordance of SUV_{max} measurements. The percentage of FDG uptake by the primary lung tumor (% dose) was also recorded.

Endpoint Definitions

Time-to-event endpoints

Patients were followed to the end of 2008, and dates of disease progression and death recorded. After 2008, follow-up was incomplete and so a close out date was used to minimize reporting bias.

The start date for all time-to-event outcomes was the date of commencement of RT. OS was defined as time to death from any cause. PFS was defined as time to progression or death. All times were censored at the end of 2008 and by the date of last follow-up in patients lost to follow-up.

Statistical Analysis

The primary aim was to assess whether SUV_{max} was related to OS after adjusting for T stage. Secondary aims were to assess the relationship between SUV_{max} and PFS.

Baseline patient and tumor characteristic distributions were tabulated and their association with SUV_{max} examined using Wilcoxon or Kruskal-Wallis tests for categorical variables and Spearman rank correlation coefficients for continuous variables. SUV_{max}, SUV_{mean}, and percentage dose were transformed to normalize their distribution using logarithms to base 2; this allows the interpretation of hazard ratios (HRs) in terms of doublings.

Survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. The median

potential follow-up time for the study was calculated using the reverse Kaplan–Meier method.[6]

The assessment of the relationship of baseline variables to OS and PFS was undertaken using Cox regression for continuous variables or when assessing multiple variables simultaneously. The log-rank test was used to assess the relationship of single categorical variables to outcome. A Cox regression model with an interaction term was used to assess whether the prognostic effect of SUV_{max} differed according to the level of another factor (T stage, ECOG performance status, and histology). The relationship of SUV_{max} to the relative hazard rate (mortality rate) as a continuous function was estimated graphically using a cubic spline fitted to martingale residuals from a Cox model.

The *best cut point method* in the context of these data determines the cutoff value for dichotomizing SUV_{max} as that value for which the p value comparing high and low SUV_{max} groups with respect to OS is a minimum. We examined all possible cut point values between the 10th and 90th percentiles of SUV_{max} to allow sufficient numbers of events in each group. We used two methods to obtain an adjusted p value to correct for the method by which the nominal p value was obtained: a formula given by Altman et al.[6] and a permutation test. The Altman formula in our case is given by:

$$p_{corr} \approx -1.63 p_{min} \left(1 + 2.351 \log(p_{min})\right)$$

where p_{min} is the minimum p value obtained (the *nominal p value*) and p_{corr} is the true (adjusted) p value. All analyses were undertaken using the R Statistical Package.

RESULTS

There were 88 patients who met eligibility criteria for analysis. Table 1 summarizes baseline characteristics and their relationship to SUV_{max} for the 88 PET/CT patients. The range of SUV_{max} was from 2.5 to 56; median = 15.0. Higher T stage was correlated with higher SUV_{max} ($p = 0.048$). There was a trend of higher nodal status and clinical stage to higher SUV_{max} ($p = 0.52$ and $p = 0.3$, respectively). Median SUV_{max} values were 10.7 (T1), 14.0 (T2), 15.6 (T3), and 16.0 (T4). Squamous cell carcinoma histology was associated with higher values of SUV_{max} ($p = 0.002$): median values of SUV_{max} were squamous cell carcinoma 16.4, adenocarcinoma 11.1, and other histologies 12.6.

Analyses of Outcomes

Of the 88 patients, there were 69 deaths (53 cancer-related), and 58 patients had documented disease progression (30 locoregionally and 45 in metastatic sites). Seventy-two patients had either progressive disease or died (or both). Only one patient was lost to follow-up (after 3 months). The median potential follow-up time was 53 months and ranged from 26 to 81 months in the 87 patients not lost to follow-up.

There was no statistically significant relationship between log (SUV_{max}) and OS ($p = 0.21$; HR = 0.83; Table 2). A similar result was obtained when assessing SUV_{max} adjusting for T stage ($p = 0.12$; HR [per doubling of SUV_{max}] = 0.78; Table 2). Figure 2 shows the risk of death as a continuous function across the range of SUV_{max} values observed, with no indication of worsening outcome (in fact observed risk of dying decreases).

When comparing high and low SUV_{max} dichotomized at the median (15.0), HR (high: low) = 0.72; 95% confidence interval = 0.44 to 1.14; $p = 0.18$ (Fig. 1*A*). A HR of 1.14 represents less than 5% difference in OS rates at the overall median survival time, indicating that there is no prognostic effect of increasing SUV_{max} resulting in an adverse outcome. SUV_{max} grouped using quartile cut points (10.5, 15.0, 19.0) indicated relative hazard rates of 1.15, 1.21, 0.87, and 0.82 for increasing SUV_{max} groups, respectively ($p_{trend} = 0.21$; Fig. 1*B*).

Tests for interaction indicated no evidence for a prognostic effect of SUV_{max} differing by subgroup of T stage ($p = 0.79$), ECOG performance status ($p = 0.66$), or histology ($p = 0.39$). Analyses of other continuous SUV variables (mean, percentage dose uptake in tumor) on OS and PFS produced very similar results (Table 2).

Best Cut Point Method

The data were analyzed according to the "best cut point method" for the analysis of OS by SUV_{max}. Figure 3 shows the nominal p value and HR at each examined cut point plotted against the cut point value. The smallest p value (0.020) occurred at 12.6 (39th percentile of SUV_{max}), corresponding to a HR of 0.58. Using the formula given by Altman et al.[6] to obtain a corrected p value gave $p_{Altman} = 0.28$. The alternative permutation test method gave $p_{perm.} = 0.23$ (SE = 0.004).

DISCUSSION

This study has demonstrated that in patients treated with radical RT for inoperable NSCLC, higher SUV_{max} derived from a staging FDG-PET/CT scan does not significantly correlate with poorer survival. Our data did demonstrate that increasing SUV_{max} was associated with increasing stage and squamous histology. After adjusting for these factors, there was still no clear and consistent adverse prognostic effect of higher SUV.

To our knowledge, this is the only published study investigating the prognostic potential of SUV_{max} using integrated PET/CT (rather than PET only) before commencing treatment in a cohort of patients with NSCLC treated non-surgically, either with radical RT or chemoradiation. Due to technical factors, including superior attenuation correction, PET/CT provides a more accurate value for SUV than stand-alone PET.[7] The aim of this study was to assess whether SUV_{max} had independent prognostic value after adjusting for tumor stage in this group of patients. We analyzed the effect of SUV_{max} as both a dichotomous and a continuous variable because if an effect exists it cannot be assumed that the effect is consistent across the full range of values.

This study therefore does not support the result of the meta-analysis.[4] There are several reasons that could contribute to these findings.

FDG uptake is a surrogate for increased glucose metabolism, which has been thought to represent tumor cell activity.[8,9] However, the exact mechanism of FDG activity and distribution within malignant tumors is not fully understood. FDG is not only taken up in malignant tumor cells but may reflect other metabolic processes within the heterogeneous

TABLE 1. Clinicopathological Characteristics of Study Cohort

Variable	Level	n	%	SUV_{max} Median (range)	*p*
Sex	Male	58	66	15.4 (2.5–56.1)	0.33
	Female	30	34	12.4 (2.9–45.6)	
Age	≤70	44	50	14.2 (2.5–56.1)	0.14
	>70	44	50	15.5 (2.9–45.6)	
ECOG PS[a]	0	21	25	14.8 (2.5–33.4)	0.98[b]
	1	52	62	15.7 (2.9–56.1)	
	2	11	13	14.4 (5.4–21)	
SCS	≤8	35	40	14.8 (6.8–45.6)	0.56
	>8	53	60	15.1 (2.5–56.1)	
Weight loss	None	46	53	15.0 (2.5–45.6)	0.44[b]
	<10%	30	35	15.1 (5.4–23.9)	
	>10%	10	12	12.2 (2.9–56.1)	
T stage	1	9	10	10.7 (2.5–45.6)	0.054[b]
	2	43	49	14.0 (2.9–33.8)	
	3	15	17	15.6 (9.8–36.3)	
	4	21	24	16.0 (7.3–56.1)	
N stage	0	27	31	14.2 (2.5–45.6)	0.52[b]
	1	12	14	16.5 (9.7–33.8)	
	2	43	49	14.6 (4.2–56.1)	
	3	6	7	15.7 (10.7–19.7)	
Clinical stage	1	19	22	14.2 (2.5–45.6)	0.3[b]
	2	10	11	14.8 (9.7–36.3)	
	3	59	67	15.1 (4.2–56.1)	
Histology	Adenocarcinoma	25	28	11.1 (2.5–45.6)	0.002[c]
	SCC	44	50	16.4 (5.4–51.7)	
	Other	19	22	12.6 (6.7–56.1)	
Differentiation	Well	4	6	12.9 (4.2–25.9)	0.74[b]
	Moderate	12	18	15.1 (2.9–33.8)	
	Poor, undifferentiated	49	75	14.6 (5.4–56.1)	
Chemotherapy	No	20	23	12.0 (2.5–36.3)	0.073
	Yes	67	77	15.3 (2.9–56.1)	
Smoking	≤40	45	52	14.4 (2.5–51.7)	0.86
	>40	42	48	15.1 (5.4–56.1)	

p values (*p*) test for association between the variable and SUV_{max}.
[a]ECOG PS.
[b]*p* value for trend.
[c]*p* value for any group differences.
SUV_{max}, standardized uptake value maximum; ECOG PS, Eastern Cooperative Oncology Group performance status; SCS, Simplified Co-morbidity Score; SCC, squamous cell carcinoma.

cellular components of the tumor, such as tumor hypoxia, inflammation, or necrosis, which are unrelated to tumor aggressiveness.[10]

Furthermore, the conclusions drawn from the results of the meta-analysis should be treated with caution, as the patient groups included in the studies included in the meta-analysis were highly selected both by stage and by treatment. Studies in patients with more advanced disease or those treated by nonsurgical means alone were underrepresented. The small proportion of patients with locoregionally advanced disease could have influenced the results. For example, in the study by Hoang et al.[11] of patients with more advanced disease (some treated with RT), FDG SUV_{max} was found not to have a significant relationship with survival.

There has been a recent study investigating the role of SUV values obtained following therapy in patients with NSCLC treated with chemoradiation,[12] and initial findings are suggestive of an association between higher post-treatment SUV values and worse survival. Interestingly, as part of their exploratory analysis of pretreatment SUV values, no association with survival was found.

Although there have been previous studies[4,13] with patients managed surgically that have shown reduced OS and disease-free survival in patients with higher SUV_{max} values,

TABLE 2. Univariable and Multivariable Cox Regression Analyses of the Relationship of SUV as a Continuous Variable on OS and PFS

Outcome	Factor	HR	CI	*p*
OS	$\log_2(SUV_{max})$	0.83	0.62–1.11	0.21
OS (multivariable analysis)	$\log_2(SUV_{max})$	0.78	0.57–1.06	0.12
	T stage	0.15	0.93–1.58	0.15
PFS	$\log_2(SUV_{max})$	0.88	0.67–1.16	0.36
PFS (multivariable analysis)	$\log_2(SUV_{max})$	0.83	0.62–1.11	0.22
	T stage	1.19	0.92–1.53	0.18

Of the 88 patients, 69 had died and 72 had progressed or died (or both). Multivariable analyses assess $\log_2(SUV_{max})$ adjusting for T stage.
SUV_{max}, standardized uptake value maximum; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

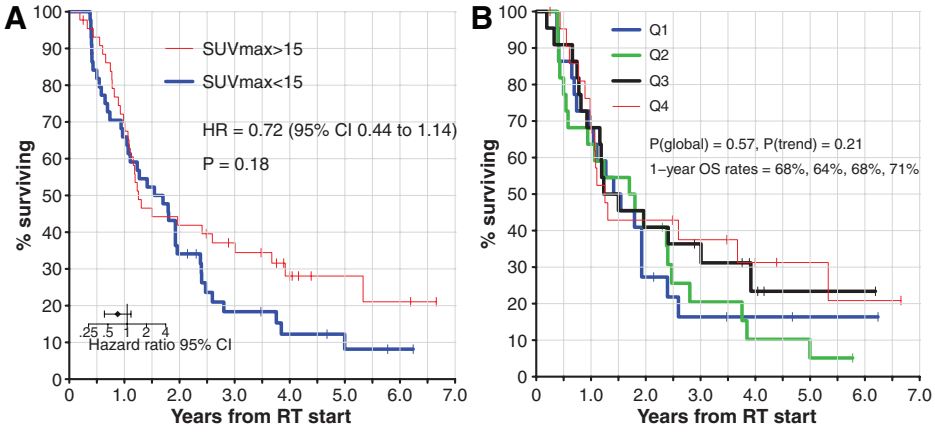

FIGURE 1. Kaplan–Meier survival curves by SUV_{max}. *A*, Dichotomized according to median cut point = 15.0. *B*, Using quartile cut points. Q1, smallest 25% of SUV_{max}; Q2, second smallest; Q3, third smallest; Q4, top 25% of SUV_{max}. SUV_{max}, standardized uptake value maximum; HR, hazard ratio; CI, confidence interval; RT, radiotherapy.

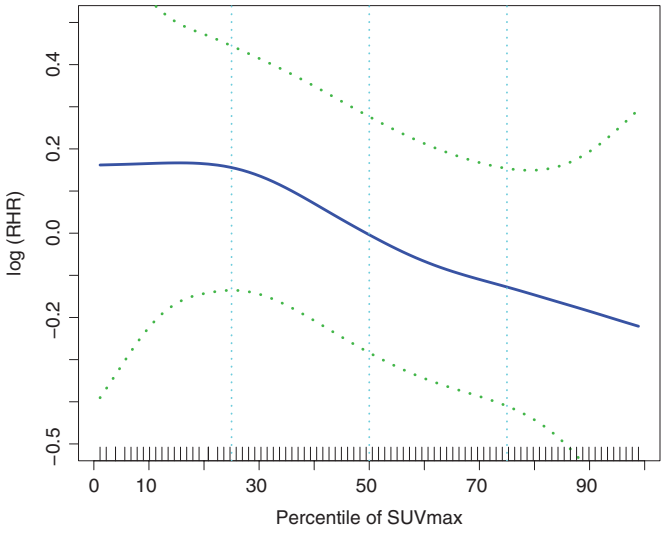

FIGURE 2. Smoothed relationship between SUV_{max} (ranked) and relative risk of progression or death. SUV_{max}, standardized uptake value maximum.

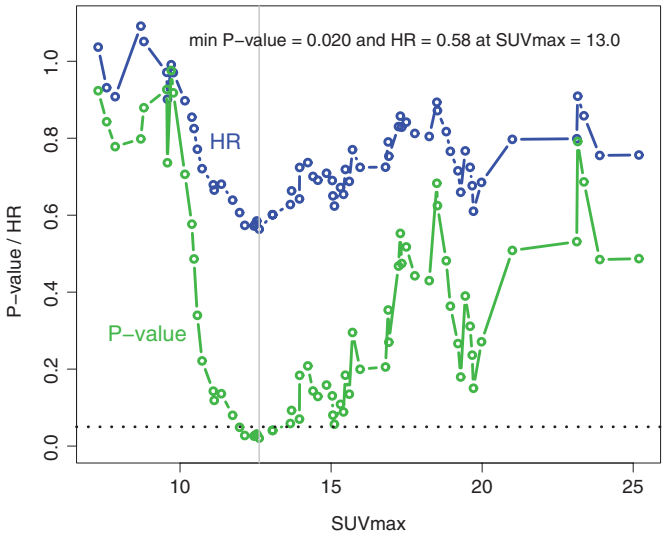

FIGURE 3. Obtaining the *best cut point* for analysis for overall survival of a dichotomized SUV_{max}. HR, hazard ratio; SUV_{max}, standardized uptake value maximum.

these values were derived from pretreatment stand-alone PET scans (as opposed to PET/CT) scans. More recently, Cistaro et al.[14] reported worse 2-year outcomes with presurgical SUV_{max} values above the calculated best cutoff value using PET/CT scanners. These studies had small sample sizes, and most were limited to patients with early-stage, resectable disease.

Some published reports suggest that there is a potential difference between absolute SUVs measured using PET and PET/CT.[15,16] To ensure homogeneity in our study cohort, patients who had surgical management as part of their therapy or were staged with PET only were excluded from the study.

Our primary analysis used SUV_{max} as a continuous variable. This is generally to be preferred to dichotomizing the variable as it is more powerful (information is not discarded) and is not subject to the arbitrariness of choice of cut point. This latter point is demonstrated in the example provided from our own data, where a cut point of SUV_{max} = 12.6 divided patients into groups, which were (nominally) statistically significantly different, but the median SUV_{max} of 15.0 was not.

In many previous publications that report a poor outcome with higher SUV values, the prognostic value of SUV was assessed by dichotomizing patients according to the "best cut point" method. As this method involves multiple tests based on a large number of potential cut points and choosing the one with smallest *p* value, the approach is associated with a large type I error rate—an inbuilt tendency to produce significance where no difference exists. A correction has to be made to the *p* value to make this a valid analysis, a practice that is commonly ignored. The analysis of our data using the best cut point method gave a "significant" nominal *p* value of 0.020, which after correction was reduced to a modest $p = 0.23$, consistent with the continuous variable analysis. The type I error rate using the uncorrected best cut point method in a study of the size of ours can be approximately 40%.

We acknowledge that there are limitations in our study, including the fact that this is a single institution retrospective study with relatively small numbers. It has been hypothesized that the impact of SUV_{max} on prognosis may be stage dependent—that in patients with more advanced stages, the metabolic activity measured by SUV_{max} on the primary tumor has lower prognostic value as it has been subsumed by the anatomic extent of the tumor.[4] We did not observe evidence for such a dependency in our data for T stage (or for ECOG performance status or histology).

Alternatively, it is possible that the relationship between primary tumor FDG uptake and survival, if present, could be a biphasic rather than linear relationship, with a limited role on prognosis in more advanced stage disease. It is clear from our data that further prospective, methodologically sound studies with larger sample sizes are required before it is possible to draw sound conclusions about the prognostic significance of SUV_{max} in NSCLC.

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