

Primary Tumor Standardized Uptake Value (SUV_{max}) Measured on Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) is of Prognostic Value for Survival in Non-small Cell Lung Cancer (NSCLC)

A Systematic Review and Meta-Analysis (MA) by the European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project

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Hypothesis: The 2-[¹⁸F]-fluoro-2-deoxy-D-glucose positron emission tomography is an imaging tool for assessing clinical tumor, node, metastasis in non-small cell lung cancer (NSCLC). Primary tumor standardized uptake value (SUV) has been studied as a potential prognostic factor for survival. However, the sample sizes are limited leading to conduct a meta-analysis to improve the precision in estimating its effect.

Methods: We performed a systematic literature search. For each publication, we extracted an estimate of the hazard ratio (HR) for comparing patients with a low and a high SUV and we aggregated the individual HRs into a combined HR, using a random-effects model.

Results: We found 13 eligible studies dedicated to NSCLC. Most of them included patients with stages I to III/IV and used a SUV assessment corrected for body weight. Number of patients ranged from 38 to 315 (total: 1474); 11 studies identified a high SUV as a poor prognostic factor for survival although two studies found no

significant correlation between SUV and survival. SUV measurement and SUV threshold for defining high SUV were study dependent, eight studies looked for a so-called best cutoff (maximizing the logrank test statistic) without adjusting the *p* value for multiplicity. Overall, the combined HR for the 13 reports was 2.27 (95% confidence interval [CI]: 1.70–3.02); excluding the studies proposing a “best” cutoff, it was 2.08 (95% CI: 1.431–3.04).

Conclusion: Our meta-analysis suggests that the primary tumor SUV measurement has a prognostic value in NSCLC; these results should be confirmed in a meta-analysis on individual patients’ data.

Key Words: SUV, Meta-analysis, Non-small cell lung cancer, PET scan.

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With the exception of stage and performance status, no prognostic factors have been definitively established in lung cancer.^{1,2} Clinical features including gender, age, weight loss, and serum markers, such as lactate dehydrogenase, neuron-specific enolase, cytokeratin fragment 21-1 levels, or leukocytes or neutrophils counts, have been studied but are not sufficiently accurate for individual patient management.^{2,3} More accurate markers would be helpful to stratify patients for therapy and predict outcomes.

Cancer stage is currently the most important prognostic factor for survival, also having implications in the therapeutic strategy. The last, and 6th edition of the *TNM Classification of Malignant Tumors*, mainly based on surgical patients, was published in 1997.⁴ This staging system relied on conventional imaging (cases collected from 1975), but during the last decade, positron emission tomography (PET) with the glucose analogue 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (¹⁸F-

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FDG) has emerged as a useful tool for several malignancies. For lung cancer, two meta-analyses^{5,6} have established the superiority of ¹⁸F-FDG-PET over computed tomography (CT) and other imaging modalities for the diagnosis and staging of lung cancer.

Other retrospective studies have explored the survival prognostic significance of the standardized uptake value (SUV) value, a semiquantitative simplified measurement of tissue deoxyglucose metabolic rate, but most of these reports only include a small number of patients. Based on these considerations and in the context of the International Association for the Study of Lung Cancer (IASLC) Staging Project proposals for the forthcoming, 7th edition of the *TNM Classification for Malignant Tumors*, we performed a systematic review of the literature on ¹⁸F-FDG-PET scan and survival and a meta-analysis of the data to determine the prognostic value of primary tumor SUV in patients with lung cancer.

MATERIALS AND METHODS

To be eligible for the systematic review, a study had to fulfill the following criteria: limited to lung cancer (any stage or any histology), ¹⁸F-FDG-PET studies performed on a dedicated device (excluding gamma-camera), to assess the relationship between pretherapeutic SUV and survival at least in univariate analysis, and to have been published as a peer reviewed article in the English, Dutch, or French language. Abstracts were excluded as it cannot be expected to find enough details to assess methodology or survival information to perform meta-analysis. Reports using all modalities of care were included.

Studies were identified by an electronic search on Medline databank using the following keywords: "lung or lung cancer or lung carcinoma or nonsmall cell or non small cell or NSCLC or small cell or SCLC or lung neoplasms" and "positron emission tomography or PET or PET imaging tomography" and "FDG-F¹⁸ or FDG or ¹⁸F-fluorodeoxyglucose or ¹⁸F-FDG" and "SUV or standardized uptake value or uptake value" and "prognosis or prognostic factor or outcome," and "survival." The references reported in all the identified studies were used to complete this search which ended in June 2006. The final list of articles eligible for the review was analyzed to identify articles in which there might be overlap in the cohorts of patients used.

Eleven physicians and one biostatistician reviewed all the publications to assess their methodological quality, to determine their eligibility for inclusion in the quantitative meta-analysis and to extract the most important information determining the clinical and PET characteristics. A methodological quality scale was designed for the purpose of this study using the variables available in the publications. This score assessed the clinical and PET reports. The clinical report included the distribution of the expected "prognostic factors" (age, gender, performance status, stage, histology, and weight loss), tumor stage description, staging characteristics (definition of the size of a pathologic mediastinal adenopathy, systematic use of a CT thorax for lung staging, systematic metastatic work-up, systematic use of a CT or

magnetic resonance imaging of brain, histologic confirmation of metastatic mediastinal adenopathy, and if the analysis of the relationship between SUV was performed without knowledge of survival results and conversely [double blind]), description of the results of survival analysis (number of patients, number of deaths, follow-up duration, number of patients lost to follow-up, univariate and multivariate analyses, description of statistical tests, survival definition, SUV cutoff definition). The PET report included patients characteristics (weight/height, glycaemia, histologic subtype), ¹⁸F-FDG-PET acquisition protocol characteristics (injected dose of ¹⁸F-FDG, delay between injection and data acquisition, fasting duration), and technical parameters (investigation area, delay between CT thorax and PET acquisition, SUV formula, type of PET engine, duration of emission time, duration of transmission time, attenuation and reconstruction parameters, type of SUV). The clinical and PET reports were respectively scored on 44 and 40 points. A value between 0 and 2 was attributed to each item. When an item was not applicable to a particular study, it was ruled out. The scores were expressed in percentage of the maximal theoretical value that can be obtained.

The following methodology, as we have already used in previous meta-analyses,^{7,8} was applied for aggregating the estimated effects of the ¹⁸F-FDG-PET SUV on survival. We measured the impact of SUV on survival by hazard ratio (HR) between the survival distributions of two groups. For each trial, this HR was estimated by a method depending on the results provided in the publication. The most accurate method consisted to retrieve the HR estimate and its variance from the reported results, or to calculate them directly using parameters given by the authors for the univariate analysis: the O-E statistic (difference between numbers of observed and expected events), the confidence interval (CI) for the HR, the logrank statistic, or its *p* value. If not available, we looked for the total number of events, the number of patients at risk in each group, and the logrank statistic or its *p* value, allowing calculation of an approximation of the HR estimate. Finally, if the only exploitable data were in the form of graphical representations of the survival distributions, we extracted from them survival rates at some specified times to reconstruct the HR estimate and its variance, with the assumption that the rate of patients censored was constant during the study follow-up.⁹ If authors report survival of three or more groups (for example, using several cutoff values for SUV), we pooled the results making a comparison between two groups feasible. The individual HR point estimates were combined after acceptance of the null hypothesis of the homogeneity of the treatment effect across the various trials, using the Peto method¹⁰ to obtain a global HR estimate of the treatment effect. By convention, a HR > 1 implied a survival benefit for lower primary tumor SUV. The HR was calculated using a fixed-effects method. In case of significant test for heterogeneity (*p* < 0.10), a random-effects method was applied. This impact of SUV on survival was considered as statistically significant if the 95% CI for the overall HR did not overlap 1. All reported *p* values were two-tailed.

RESULTS

Sixteen studies, published between 1998 and 2006 were potentially eligible for this review.^{11–26} Three studies included similar cohorts of patients^{15–17} and we took into account only the most complete one. One study was not assessable for meta-analysis because no quantitative threshold was evaluated (in this study a ¹⁸F-FDG-PET scan was interpreted as negative if the tumor uptake of ¹⁸F-FDG was less than or equal to mediastinal uptake).¹² In two other studies, patients without definite diagnosis of cancer were reported in the analysis without separated results between cancer patients and the others.^{13,14} To reduce the risk of error by including patients without cancer, we performed two meta-analyses one with and one without these two studies.

The principal characteristics of the 13 studies eligible for the meta-analysis are described in Table 1. The majority of the 1474 patients presented with nonmetastatic non-small cell lung cancer (NSCLC); there were only two small cell lung cancers and one carcinoid tumor.²⁰ Patients were generally staged according to the 1997 edition of the *TNM Classification of Malignant Tumors*. According to the threshold defined by the authors, high SUV was associated with poor prognosis in 11 studies whereas in two, the prognostic role of SUV for survival remained undetermined. The main SUV characteristics reported in the publication are described in Table 2. SUV_{max} was used in eight studies, normalized by body weight in seven (Appendix 1) and by lean body mass in one (Appendix 2). In three studies, the authors used SUV_{mean} normalized by body weight, with different percentages for defining the isocontours of the volume of interest around the tumor. In one study, SUV_{max} and SUV_{mean} normalized by body weight and by lean body mass were studied but only the SUV_{mean} normalized by body weight was used for the survival analysis. The choice of the SUV threshold between patients with high survival and low survival was based on eight cases on a so-called best cutoff, meaning that the authors chose as SUV threshold the value maximizing the

logrank test statistic among several survival comparisons. This method is known to lead to a high risk of false-positive result especially if no adjustment of *p* values for multiplicity is done. In the other publications, the threshold was arbitrarily chosen (*n* = 1), based on the median (*n* = 3) SUV values or was a choice done as validation of results from another author (*n* = 1).

The methodological quality of the studies was moderate. Overall, the median quality score was 57%, ranging from 27 to 68%. The respective median values for the clinical and PET reports were 61% (range 34–80%) and 53% (range 5–65%).

In a first meta-analysis, we excluded the two studies with patients without definite diagnosis of cancer.^{13,14} Eleven studies were thus included in the quantitative meta-analysis. The number of patients ranged from 38 to 162 per study, for a total of 1108. The results are detailed in Table 3 and Figure 1. The combined HR for the 11 studies was 2.07 (95% CI: 1.66–2.58) with a fixed-effects model, meaning that high primary tumor SUV was associated with reduced survival. We observed a significant heterogeneity (*p* = 0.05) essentially because of one study.²³ After exclusion of that publication, the test was no more statistically significant (*p* = 0.31). We performed the same analysis using a random-effects model. The HR was 2.13 (95% CI 1.54–2.95). If the two studies^{13,14} including patients without histologically proven diagnosis of lung cancer were included in the analysis, we obtained an overall HR of 2.22 (95% CI 1.83–2.70) (fixed effects) or 2.27 (95% CI 1.70–3.02) (random effects, test for heterogeneity *p* = 0.06).

We performed the same analysis excluding the studies proposing a so-called best cutoff. From the eight such studies, two were nevertheless included in the analysis because we were able to use median SUV values instead of the value proposed by the authors.^{16,20} The test for heterogeneity was statistically significant (*p* = 0.05). Using a random-effects model, the combined HR was 1.77 (95% CI 1.01–3.12)

TABLE 1. Principal Characteristics of the 13 Studies Included in the Meta-Analysis

Study	Publication Date	<i>n</i> Pts	ISS	Stage	Histology	High SUV as Prognostic Factor for Survival
Ahuja et al. ²⁶	1998	155	1997	I–IV	NSCLC	Unfavorable
Sugawara et al. ²³	1999	38	1986	I–IV	NSCLC	Undetermined
Vansteenkiste et al. ²²	1999	125	1997	I–IIIB	NSCLC	Unfavorable
Dhital et al. ²⁰	2000	77	1986	≤IIIA	All ^a	Unfavorable
Higashi et al. ¹⁶	2002	57	1997	I–IIIB	NSCLC	Unfavorable
Jeong et al. ¹⁸	2002	73	1997	I–IV	NSCLC	Unfavorable
Downey et al. ²⁵	2004	100	1997	<IV	NSCLC	Unfavorable
Port et al. ¹¹	2005	64	1997?	?	NSCLC	Undetermined
Sasaki et al. ²⁴	2005	162	1997	I–IIIB	NSCLC	Unfavorable
Prevost et al. ²¹	2006	120	1997	I–IV?	NSCLC	Unfavorable
Eschmann et al. ¹⁹	2006	137	1997?	III	NSCLC	Unfavorable
Borst et al. ¹⁴	2005	51	?	I–III	NSCLC	Unfavorable
Cerfolio et al. ¹³	2005	315	1997	I–IV	NSCLC	Unfavorable

n Pts, number of patients; ISS, date of International Staging System applied in the study; NSCLC, non-small cell lung cancer; SUV, standardized uptake value.

^a Only 2 small cell lung cancers and 1 carcinoid tumor among 77 patients.

TABLE 2. Main SUV Characteristics Reported in the 13 Publications Assessable for Meta-Analysis

Study	Type of SUV	Correction of SUV	SUV Threshold Definition	SUV Threshold
Ahuja et al. ²⁶	SUV mean (SUR)	Weight	Best cut-off	10
Sugawara et al. ³	SUV max	Lean body mass	Median	8.7
Vansteenkiste et al. ²²	SUV max	Weight	Best cut-off	7
Dhital et al. ²⁰	SUV max	Weight	Best cut-off	15 or 20
Higashi et al. ¹⁶	SUV mean	Weight	Best cut-off	5
Jeong et al. ¹⁸	SUV max	Weight	Best cut-off	7
Downey et al. ²⁵	SUV max	Weight	Median	9
Port et al. ¹¹	Unspecified SUV	—	Arbitrary	2.5
Sasaki et al. ²⁴	SUV max	Weight	Best cut-off	5
Prevost et al. ²¹	SUV mean SUV max	Weight Lean body mass	Literature value	10
Eschmann et al. ¹⁹	SUV mean	Weight	Best cut-off	12
Borst et al. ¹⁴	SUV max	Weight	Best cut-off	15
Cerfolio et al. ¹³	SUV max	Weight	Median	10

Best cut-off, author maximized the logrank test statistic to determine the best cut-off; SUV, standardized uptake value; SUR, standardized uptake ratio.

TABLE 3. Meta-Analysis of Primary Tumor SUV Prognostic Impact on Survival in Lung Cancer (all Studies)

References	Publication Date	n Pts	HR	95% CI
Ahuja et al. ²⁶	1998	155	2.05	1.24–3.37
Dhital et al. ²⁰	2000	77	1.30	0.70–2.60
Downey et al. ²⁵	2004	100	2.60	1.02–6.64
Eschmann et al. ¹⁹	2006	137	1.71	1.00–2.93
Higashi et al. ¹⁶	2002	57	6.20	1.34–28.75
Jeong et al. ¹⁸	2002	73	4.33	1.80–10.45
Port et al. ¹¹	2005	64	2.36	0.24–22.88
Prevost et al. ²¹	2005	120	2.36	1.34–4.15
Sasaki et al. ²⁴	2005	162	7.66	1.41–41.50
Sugawara et al. ²³	1999	38	0.56	0.21–1.44
Vansteenkiste et al. ²²	1999	125	2.72	1.50–4.94
Borst et al. ¹⁴	2005	51	3.15	1.59–6.22
Cerfolio et al. ¹³	2005	315	2.65	1.63–4.31

Meta-analysis including only pathologically proven lung cancer (n = 11 studies)

Fixed effects	1108	2.07	1.66–2.58
Random effects	1108	2.13	1.54–2.95

Meta-analysis including patients without pathologically proven lung cancer (n = 13 studies)

Fixed effects	1474	2.22	1.83–2.70
Random effects	1474	2.27	1.70–3.02

HR, hazard ratio; CI, confidence interval; SUV, standardized uptake value; n Pts, number of patients.

(Table 4). If the two studies without histologically proven lung cancer^{13,14} were included, the combined HR were 2.13, 95% CI: 1.65–2.76 (fixed effects) or 2.08, 95% CI: 1.43–3.04 (random effects). Last, we looked at the role of SUV in nonmetastatic lung cancer, excluding studies incorporating stage IV diseases. Six publications were available, including 658 patients (Table 5). As the test for heterogeneity was not significant ($p = 0.16$), we used a fixed-effects model. The combined HR was 2.09 (95% CI 1.54–2.83). When adding a study without histologically proven lung cancer,¹⁴ the HR was 2.23 (95% CI 1.69–2.95).

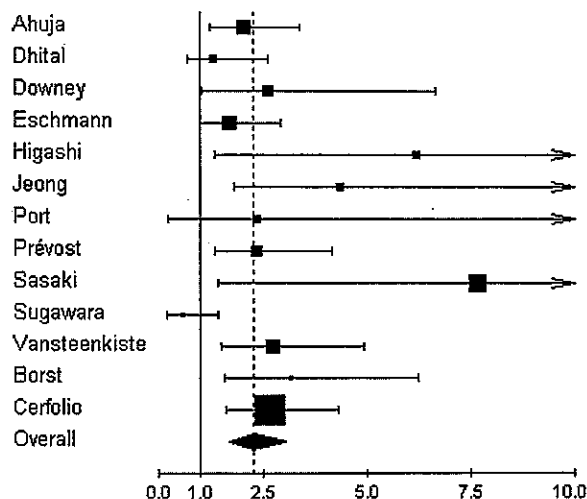


FIGURE 1. Graphical representation of the prognostic role of primary tumor SUV on survival in lung cancer. HR and 95% confidence interval (CI) for survival comparison in studies evaluating primary tumor SUV in lung cancer. HR >1 implied a survival benefit for reduced primary tumor SUVmax. The square size is proportional to the number of patients included in the study. The center of the diamond-shaped lozenge at the bottom of the figure gives the combined HR of the meta-analysis and its extremities the 95% CI HR = 2.27; 95% CI 1.70–3.02 (random-effect model). Total number of patients: 1474. SUV = standardized uptake value.

DISCUSSION

During the last decade, ¹⁸F-FDG-PET has become an important tool used to stage patients with NSCLC. The specific goal of this study was to evaluate its potential as a prognostic marker. The current meta-analysis confirmed that increased SUV of the primary tumor is a poor prognostic factor in patients with NSCLC. It remains unclear, however, if SUV is an independent prognostic feature as compared with stage and performance status.

TABLE 4. Meta-Analysis of Primary Tumor SUV Prognostic Impact on Survival in Lung Cancer (Excluding Studies Proposing a So-Called Best Cutoff)

References	Publication Date	n Pts	HR	95% CI
Port et al. ¹¹	2005	64	2.36	0.24–22.88
Dhital et al. ²⁰	2000	77	1.30	0.70–2.60
Downey et al. ²⁵	2004	100	2.60	1.02–6.64
Higashi et al. ¹⁶	2002	57	6.20	1.34–28.75
Prevost et al. ²¹	2005	120	2.36	1.34–4.15
Sugawara et al. ²³	1999	38	0.56	0.21–1.44
Fixed effects		456	1.74	1.23–2.44
Random effects		456	1.77	1.01–3.12

HR, hazard ratio; CI, confidence interval; SUV, standardized uptake value; n Pts, number of patients.

TABLE 5. Meta-Analysis of Primary Tumor SUV Prognostic Impact on Survival in Lung Cancer (Excluding Studies with Stage IV Diseases)

References	Publication Date	n Pts	HR	95% CI
Dhital et al. ²⁰	2000	77	1.30	0.70–2.60
Eschmann et al. ¹⁹	2006	137	1.71	1.00–2.93
Higashi et al. ¹⁶	2002	57	6.20	1.34–28.75
Sasaki et al. ²⁴	2005	162	7.66	1.41–41.51
Vansteenkiste et al. ²²	1999	125	2.72	1.50–4.94
Downey et al. ²⁵	2004	100	2.60	1.02–6.64
Fixed effects		658	2.09	1.54–2.83
Random effects		658	2.27	1.45–3.54

HR, hazard ratio; CI, confidence interval; SUV, standardized uptake value; n Pts, number of patients.

Overall, the prognosis of patients with NSCLC is poor, with less than 15% surviving beyond 5 years.⁴ Stage, currently determined by the 1997 International Staging System classification, is the most important prognostic factor in NSCLC patients having direct implications in the choice of therapeutic options. As pointed by different authors,^{27,28} this staging system still needs to be improved. The IASLC developed a task force to propose revisions for the 7th edition of the *TNM Classification of Malignant Tumors* concerning lung cancer. In this setting, a working group is assessing the potential usefulness of new prognostic factors.

Recently, attention has focused on new biologic factors, and the methodological group of the European Lung Cancer Working Party and others have evaluated the most relevant variables and found that some features could be of interest.^{8,29–36} Unfortunately, there are currently no data to support that any of these markers, including genomic profiles, can accurately predict outcomes in NSCLC. The observed HR in these studies was usually smaller in magnitude than those found in the present meta-analysis for primary tumor SUV.

SUV is a semiquantitative index that characterizes the tracer uptake, hence approximating the glucose metabolic rate (Appendix 1). However, SUV estimates suffer from poor reproducibility between centers because of the lack of standardization of the acquisition and processing protocols lead-

ing to its assessment (Appendix 2). In our study, this poor reproducibility was evidenced by the broad range of threshold values that have been used in the literature to distinguish between patients with low and high survival (thresholds varying from 2.5 to 20). Despite this variability, we were able to show that SUV was correlated with patient survival. Indeed, our study design calculated an HR for each study center, based on the SUV threshold used in that study, which somehow cancelled the threshold factor. By doing so, we could demonstrate that SUV was certainly worth considering as a prognostic factor, especially as, unlike immunohistochemistry, it can be estimated even when no surgical specimen is present.

To be a practical prognostic factor in routine practice, a single SUV threshold allowing distinguishing between long and short survival patients should be agreed on, or the methodology to be used to determine the optimal threshold for each center should be established. To set a consistent threshold, most sources of variability impacting the SUV estimates (Appendix 2) should be removed or at least controlled, for example, by phantom calibration.³⁷ Reducing the large variability currently affecting SUV estimates would probably enhance the prognostic value of SUV. In our meta-analysis, we could not take into account the variable conditions in which the SUV were obtained given the poor quality scores of the PET reports. A meta-analysis considering the individual patient data (IPD) will be needed to try to compensate for the large heterogeneity of the reported SUV.

Some biases might have occurred in our analysis. Indeed, some studies were not included in our meta-analysis because, e.g., separate data for lung cancer patients were not available. We did not look at trials presented only on their abstract form or at unpublished studies. Thus, some studies might have not been taken into account. We limited this problem by discussing with experts in the field during regular meetings of the IASLC International Staging Committee. We carefully looked at the possibility of patients' duplication by reporting the same cohorts in different publications. This led us to suppress two articles,^{15,17} although no reference to such duplicates was reported by the authors. Some difficulties could happen when analyzing and comparing the results of the individual trials. The stage and treatment case mix were somewhat different through the studies; in particular few treatment results were reported by the authors.

To avoid some biases of a literature-based meta-analysis, we aim to confirm our results in a meta-analysis of IPD. Literature-based meta-analyses has the advantage of including published trials immediately available for analysis and which results can be checked by everyone. Although we found in previous publications similar results with literature-based as with IPD meta-analyses,^{38,39} IPD add some interest like incorporating unpublished trials, updating results (allowing to have longer survival follow-up), and particularly allowing for multivariate analyses, adjusting for other variables, and subgroup analyses.

In conclusion, metabolic activity of primary tumor, reflected by SUV measurement with ¹⁸F-FDG-PET scan is a prognostic factor in patients with NSCLC. It still needs to be

compared with stage and performance status in a formal analysis to determine if this adds prognostic value. We are currently planning a meta-analysis based on IPD that will allow multivariate analysis and potentially reduce biases related to literature-based meta-analyses. These results may be of particular importance in the view of the forthcoming, 7th edition of the *TNM Classification for Lung Cancer*.

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APPENDIX 1: DEFINITIONS OF SUV_{MAX} AND SUV_{MEAN}

The standardized uptake value (SUV) is usually defined as the tracer uptake in the tumor divided by the injected dose normalized by the patient weight:

$$Suv = \text{Tumor Uptake (kBq/mL)} / [\text{injected Dose (kBq)/Patient Weight (g)}] \quad (1)$$

Assuming the patient has a density of 1 (1 ml = 1 g), the SUV is a dimensionless index. If the tracer was uniformly distributed throughout the body, the SUV would be 1 in any organ. As tumors usually have an enhanced metabolic rate, most tumors show an elevated SUV in ^{18}F -FDG PET (SUV > 1). However, SUV is only an approximate indicator of the glucose metabolic rate, and is by no means an accurate measurement of this rate.⁴⁰

Although SUV is a widely accepted index for assessing tumor uptake in ^{18}F -FDG PET, there is no consensus regarding how to estimate it. The major differences between the estimation methods come from the way tumor uptake is measured.⁴¹ Two classic measurement methods are:

Considering the tumor uptake is given by the maximum pixel value in the tumor, which yields SUV_{max} :

$$Suv_{max} = \text{Max Pixel Value In The Tumor (kBq/mL)} / [\text{injected Dose (kBq)/Patient Weight (g)}] \quad (2)$$

Measuring the tumor uptake as the mean pixel value in a volume of interest (VOI) around the tumor, which yields SUV_{mean} :

$$Suv_{max} = \text{Mean Pixel Value In A Tumor Voi (kBq/mL)} / [\text{injected Dose (kBq)/Patient Weight (g)}] \quad (3)$$

Unlike SUV_{max} , SUV_{mean} depends on the way the VOI around the tumor is drawn. To avoid manual drawing that makes the result dependent on the operator, an isocontour, defined as a percentage of the maximum pixel value in the tumor (typically between 50 and 80%) is often used. However, there is no consensus on the percentage that should be used, so even the way SUV_{mean} is calculated can greatly

vary among centers. In addition, there are some other ways to define the VOI, such as using a fixed sized region regardless of the tumor size.

APPENDIX 2: FACTORS INFLUENCING THE RESULTS OF THE SUV CALCULATION

The most important sources of variability in SUV estimates are listed below:

- The method of tumor uptake estimate (Appendix 1): it greatly impacts the SUV, which can vary by a factor of about 2 depending on the VOI considered to measure the tumor uptake.⁴¹⁻⁴³
- The spatial resolution in the reconstructed images (depending itself on the image reconstruction algorithm and of its parameters), which directly affects the blurring of the tumor in the images, hence the tumor pixel values. The same tumor with two PET imaging systems with different spatial resolutions will appear to have different uptakes through the partial volume effect.^{41,42} This is especially true for SUV_{max} , which can vary by more than 10% depending on the spatial resolution in the reconstructed images.
- The way the PET images have been compensated for physical biases such as attenuation. For instance, CT-based attenuation correction tends to yield higher SUV (from 10 to 50%) than attenuation correction based on a conventional PET transmission device.
- The normalization factor used to estimate the FDG made available to the tumor (denominator of Eq. 1). Most often, the injected activity is normalized by the patient weight (Eq. 1), but other normalizations, such as using the lean body mass or the body surface area⁴⁴ have been proposed to account for the fact that body fat does not have the same FDG uptake as lean tissues.
- The plasma glucose level of the patient, as the FDG competes with the plasma glucose; lower SUV are observed in fed patients compared with patients under fasting conditions.⁴⁵ Normalization to account for the plasma glucose level has been proposed.
- The delay between the injection time and the imaging time: the longer this delay, the higher the SUV, as equilibrium is usually not reached at 45 to 60 minutes postinjection.⁴⁶ Changes in SUV between 45 minutes and 90 minutes postinjection scans can be of about 20%.

As new corrections become available, SUV will also depend on:

- Whether the PET images are compensated for respiratory motion, e.g., using respiratory gating, as respiratory motion introduces blur in the images, hence contributes to lowering the pixel values in the tumor.
- Whether the PET images are compensated for partial volume effects.

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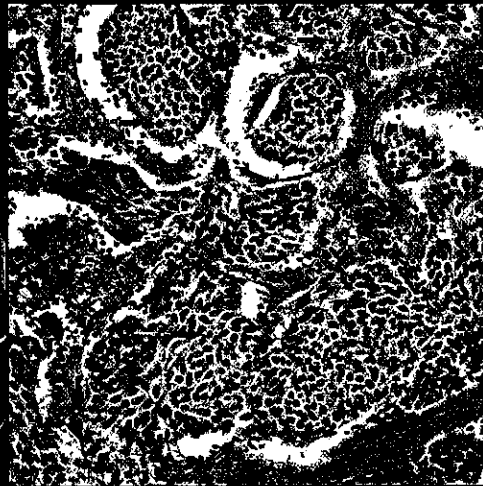
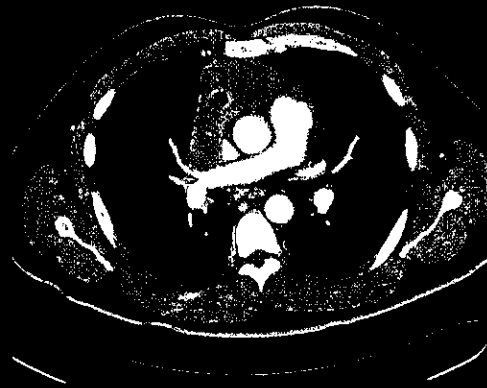
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