SUV: Advancing Comparability and Accuracy

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1.0 Overview and Current Clinical Use

1.1 Clinical Driver for SUV

^{18}F-FDG PET imaging is a clinical tool used widely in oncology, cardiology and neurology. As an analogue of glucose, uptake of ^{18}F-FDG provides an indication of glucose metabolism throughout the body and enables clinicians to detect regions of hypermetabolism, that may indicate cancer, or regions of hypometabolism, that may indicate necrosis or be characteristic of certain forms of dementia.

While a qualitative assessment of oncological PET images is often sufficient for lesion detection and diagnosis, the assessment of treatment response, especially predicting response during treatment, requires a quantitative assessment of changes in ^{18}F-FDG uptake, as a surrogate for glucose metabolism; for example, as proposed in the PERCIST[14] framework.

Perhaps the most precise method for quantifying ^{18}F-FDG uptake is to use regression analysis (e.g., compartment modeling or Patlak-Gjedde analysis) of the data acquired during a dynamic acquisition. However, the logistical complexities and long duration of dynamic studies, including the need for invasive arterial sampling, mean that the majority of clinical ^{18}F-FDG scans are performed using a short static protocol.

The most widely used (semi-)quantitative index for evaluating static PET images is the Standardized Uptake Value (SUV). This value provides a normalized measure of radiotracer uptake that enables comparison across scans and between patients.

syngo® TrueD, Siemens's advanced application for hybrid imaging, provides comprehensive support for the clinical use of SUV in oncology for staging, restaging and therapy planning. Combined with the advanced hardware and reconstruction algorithms in HD-enabled scanners, including the new Biograph® mCT PET•CT scanner, Siemens is delivering practical tools to support improved accuracy and comparability of SUV in the clinic.

1.2 SUV in the Clinic

PET SUV has been widely used for lesion characterization, prognostic stratification and monitoring disease progression or treatment response. Fletcher[3] presents a comprehensive review on the use of ^{18}F-FDG in oncology across a wide range of malignancies, demonstrating the use of SUV in differentiating benign from malignant tumors and predicting survival. A review by Weber[13] provides an overview of the use of PET SUV in monitoring therapy and predicting outcome. PET SUV is also being evaluated by Siemens' clinical partners for its potential to guide delivery of radiation dose in intensity modulated radiotherapy.

2.0 Computing SUV

2.1 Derivation of SUV

When performing an ^{18}F-FDG scan, the physiological property of interest is the glucose utilization rate (Metabolic Rate of Glucose, or MR_{Glc}), which relates to the irreversible uptake rate of ^{18}F-FDG (Ki) by:

$$MR_{Glc} = \frac{[Glc]}{LC} \times K_i \qquad [1]$$

[Glc] is the plasma glucose concentration, and LC is a lumped constant used to account for uptake differences between ^{18}F-FDG and glucose. As outlined by Huang[5], Sokoloff[11] estimated Ki by:

$$K_i = \frac{C(T)}{\int_0^T P(T)\, dt} \qquad [2]$$

C(T) is the total radioactivity concentration in a given tissue, or volume of interest (VOI), at time T. To be accurate, T needs to be sufficiently large to result in negligible amount of free ^{18}F-FDG in the tissue or VOI. The denominator represents the area under the plasma time activity curve (TAC), and is the integral of the ^{18}F-FDG concentration available for tissue uptake up until time T.

C(T) can measured directly from a VOI drawn on a reconstructed PET image calibrated to Bq/ml. The integral in the denominator, however, cannot be measured from a static scan (a dynamic scan would be required). Instead, it is approximated as being proportional to the injected dose divided by the body weight of the patient to give:

$$K_i = \frac{C(T)}{Q \times D/BW} \qquad [3]$$

D is the dose injected (Bq), BW is the patient's body weight (g) and Q is a proportional constant. It should be noted that by replacing the time-dependent integral in the denominator with a time-independent measure, the SUV will not be time-independent (see Section 3.3 below).

Since knowledge of a value linearly proportional to MR_{Glc} is generally sufficient for clinical purposes, the conversion to MRGlc is generally omitted: instead, the SUV normalized by body weight is reported.

$$SUV_{BW} = \frac{C(T)}{D/BW} \qquad [4]$$

However, this formulation excludes the plasma glucose term [Glc], which can impact the validity of any comparisons made between scans of patients with significantly different blood glucose concentrations (see Section 3.1). However, patient preparation in most clinics imposes verification that the glucose level is within acceptable range for interpretation: this is usually achieved by requesting fasting for at least four hours before the injection.

Lastly, since one gram of tissue can be approximated as having a volume of 1 ml, SUV_{BW} is a unitless quantity.

2.2 Variations on SUV

While SUV_{BW} correlates well with MRGlc for many types of tumor[5], it has also been shown to correlate with the body weight of the patient. This is due to the relatively higher proportion of fat in heavier patients and the low uptake of ^{18}F-FDG in fat in the fasting state compared to non-fatty tissue. This results in underestimation of the area under the plasma TAC for heavier patients[12].

Given this correlation with body weight, TrueD supports two alternative normalization factors for SUV, namely lean body mass (LBM), and body surface area (BSA)[12]. SUVLBM is calculated as follows:

$$SUV_{LBM} = \frac{C(T)}{D/LBM} \qquad [5]$$

LBM* is computed for males as:

$$LBM_{MALE} = 1.10 \times BW - 120 \times \left(\frac{BW}{H}\right)^2 \qquad [6]$$

It is calculated for females as:

$$LBM_{FEMALE} = 1.07 \times BW - 148 \times \left(\frac{BW}{H}\right)^2 \qquad [7]$$

BW is patient body weight (in kg) and H is patient height (in cm).

SUV_{BSA} is calculated by:

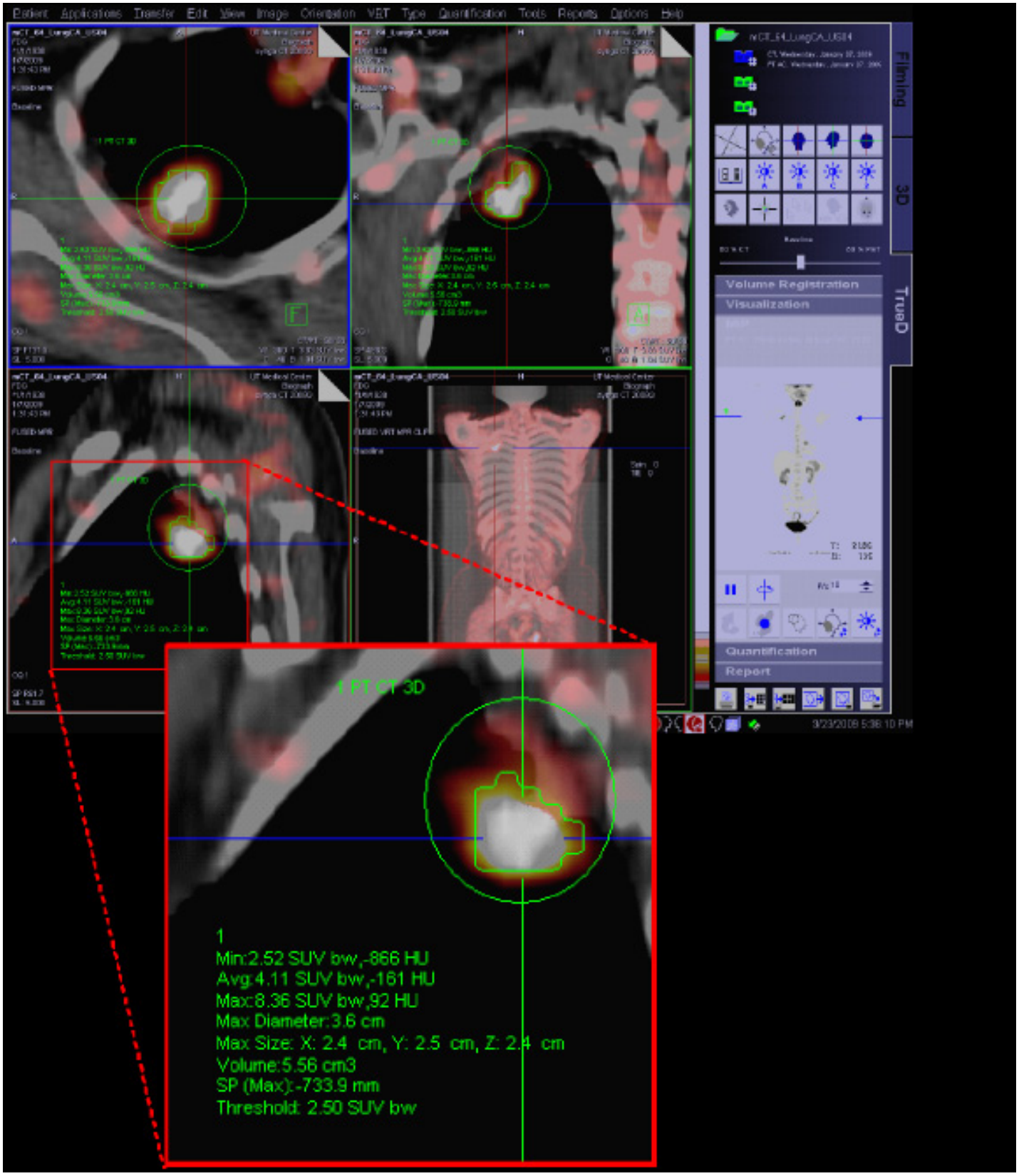
$$SUV_{BSA} = \frac{C(T)}{D/BSA} \qquad [8]$$

BSA is computed as:

$$BSA = BW^{0.425} \times H^{0.725} \times 71.84 \qquad [9]$$

** N.B. The original formula for computing LBM for males was 1.1 x BW – 128 x (BW/H)² [James 1976]. However, this was reprinted by Morgan et al. [1994] as 1.1 x BW – 120 x (BW/H)², and consequently adopted by the PET community [Sugawara et al. 1999].*

Figure 2.1 *SUV measurement with TrueD using the 3D ellipsoid isocontouring VOI tool with a 2.50 SUV_{BW} absolute threshold. Data courtesy of University of Tennessee Medical Center, Knoxville, TN.*



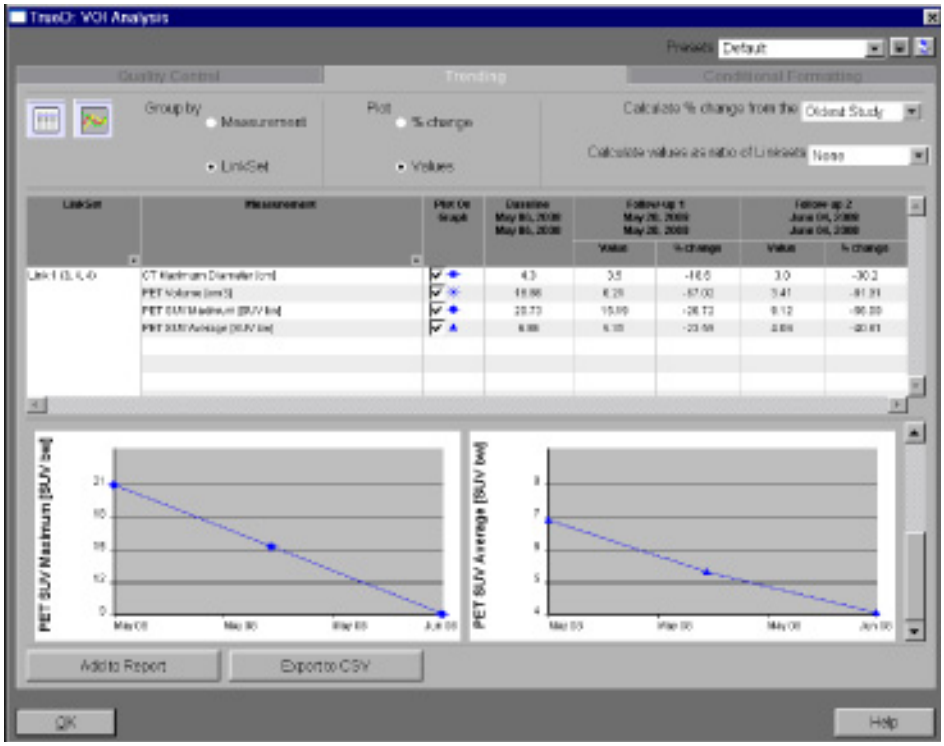


Figure 2.2. *Three-time point tumor trending with TrueD enables analysis of changes in SUV across time points. Data courtesy of University of Tennessee Medical Center, Knoxville, TN.*

2.3 SUV in TrueD

In TrueD, the Siemens advanced cancer management tool for hybrid imaging, SUV_{BW}, SUV_{LBM}, and SUV_{BSA} can all be computed with ease. Following the creation of an VOI, either in 2D or 3D, drawn freehand or thresholded, the user-preferred variant of SUV can be displayed by mean, max., min. and standard deviation (Figure 2.1). The preferred variant of SUV is selected via the configuration menu for TrueD.

In addition, with three-time point tumor trending, TrueD enables VOI propagation through automatically-registered follow-up scans, and analysis of changes in SUV across time points (Figure 2.2). The Quality Control tab also facilitates the review of those imaging parameters (e.g., post-injection imaging interval and reconstruction settings) which may affect the SUVs measured (see Section 3).

3.0 Sources of Variation

The relationship of SUV to glucose metabolism (MR_{Glc}) is complicated by a range of factors (Table 1). Physiological factors influence the relationship between glucose metabolism and cellular uptake of ^{18}F-FDG, while physical factors influence the relationship between cellular uptake of ^{18}F-FDG and the SUV measured in a PET image. Furthermore, procedural differences can also influence the measured SUV.

3.1 Physiological Factors

Body Composition – As discussed in Section 2.2, normalizing SUV by body weight tends to over estimate the volume of distribution for obese patients, and artificially inflate the computed SUV values. This is due to the reduced distribution of ^{18}F-FDG in fatty tissue compared to the other parts of the body, whereas the SUV formula assumes uniform distribution through the entire body mass. Alternative normalization metrics such as body surface area, or lean body mass are available in TrueD and can been used to reduce this bias[12].

Blood Glucose Concentration – Since ^{18}F-FDG and glucose effectively compete for transport into the cell and phosphorylation, higher blood glucose concentrations (BGC), as is often seen with diabetic patients, reduces cellular uptake of ^{18}F-FDG. While SUV corrections for blood glucose concentration are available, they are not widely used[1]. However, patients are asked to fast for at least four hours prior to the scan and have their BGC measured prior to scanning to ensure it is below a suitable threshold (e.g., 120 mg/dL[10]). If the glucose level cannot be controlled to remain within comparable limits between two PET exams, great care must be taken when reviewing two scans. For instance, consider a patient with a blood glucose concentration of 1.0 g/l, and a first scan of the patient showing a lesion with maximum SUV of 5.0. Consider then a second scan of that same patient some weeks later, this time with a blood glucose concentration of 0.7 g/l and the lesion maximum SUV climbing up to 6.0: the apparent increased uptake of SUV may be misleading as the blood glucose concentration decreased at an even higher proportion between the two scans. It may be, therefore, argued that the uptake of the lesion has actually decreased rather than increased.

Kidney Function – Differences in kidney function can also influence uptake of ^{18}F-FDG[13]. For example, impaired kidney function, as can result from some chemotherapy regimens, will result in slower clearance of ^{18}F-FDG from the plasma, thereby increasing total ^{18}F-FDG uptake in hypermetabolic cells. Despite this effect, kidney function is rarely assessed prior to a clinical PET scan.

3.2 Physical Factors

Partial Volume Effect – A consequence of both limited spatial resolution and discretisation, partial volume effect (PVE) results in the underestimation of ^{18}F-FDG uptake for lesions smaller than about three times the spatial resolution of the scanner device. This has significant implications for the quantitative accuracy of measuring uptake in small lesions, or lesions with a considerable nectrotic component.

The impact of PVE can be minimized by reducing the uncertainty in determining the site of photon emission. This is achieved by improvements in both scanner hardware (i.e. Lutetium Oxyorthosilicate (LSO) crystal technology and fast electronics) and reconstruction techniques (i.e., ultraHD•PET with time-of-flight and point-spread function reconstruction). These technologies combine to significantly reduce the impact of PVE on the images produced.

The impact of PVE, and image quality in general, is typically assessed using the Image Quality, Accuracy of Attenuation, and Scatter Corrections protocol[9]. To facilitate this assessment, Siemens provides the workflow-driven NEMA 2007:IQ application with fully-automated VOI positioning.

Motion – The uncertainty in determining the site of photon emission is further complicated by patient motion (e.g., respiratory motion). This also leads to underestimation of ^{18}F-FDG uptake. However, technologies such as gated acquisition, help to minimize this effect.

3.3 Procedural Factors

Dose Preparation and Administration – All flavors of SUV require knowledge of the precise dose injected. Any residual activity remaining in the syringe that is not accounted for, or paravenous administration, will result in underestimation of SUV. Furthermore, the dose calibrator and PET scanner must be cross-calibrated, and clocks synchronized, to avoid systematic error in SUV computation. The cross-calibration phantom and workflow provided by Siemens facilitate this essential procedure.

Post-Injection Imaging interval – Uptake of ^{18}F-FDG often continues to increase as late as 90-minute post-injection in tumors. As such, the interval between ^{18}F-FDG administration and image acquisition will affect the SUV calculated, with longer intervals often resulting in higher SUVs. It is essential to minimise any variation in post-injection interval to facilitate comparison between patient studies. The Quality Control tab in TrueD allows the reviewing clinician to quickly identify variations in this interval.

Reconstruction & Smoothing – A range of reconstruction algorithms are available for generating the clinical image (e.g., Filtered Back Projection (FBP), Ordered Subsets Expectation Maximization (OSEM), ultraHD•PET, etc.), with different algorithms producing images with different statistical properties, and potentially different SUVs. For example, HD and ultraHD•PET will typically produce higher SUVs, closer to the true underlying uptake for a given lesion, than OSEM[2] (Figure 3.1). This is due to a combination of reduced uncertainty in determining the sight of photon emission, and the improved signal-to-noise properties that reduce the need for noise-suppression techniques which generally increase the impact of PVE.

The higher SUVs typically produced by HD and ultraHD•PET reconstructions will require a re-evaluation of the SUV thresholds used for lesion classification[7]. In fact, the SUV threshold of 2.5 recommended for staging mediastinal lymph nodes[4] was determined from studies on PET scanners which are now already more than 10 years old.

Iterative reconstruction algorithms, such as OSEM, are typically terminated prior to convergence to suppress noise. However, the number of iterations performed can significantly affect the SUV measured[7], with measured SUVs increasing with number of iterations.

Smoothing an image post reconstruction, e.g. with a Gaussian filter, will also influence the SUVs measured. The application of such a filter will increase the PVE and lead to an under estimation of SUV.

Given the impact of reconstruction on measured SUVs, consistency is important when the intention is to compare SUVs across scans, either intra-patient for disease monitoring, or inter-patient for lesion characterization and patient stratification. The Quality Control tab in TrueD allows the reviewing clinician to quickly identify differences in reconstruction parameters between studies.

VOI Definition – The method for defining the VOI will also affect the computed SUV. For example, PVE will result in a lower mean SUV when a larger VOI is defined for a lesion. Once an VOI is defined, both the SUV mean or the SUV max can be computed. The former is an average of all voxels within the VOI, while the latter is the value of the voxel with the highest SUV. The SUV mean is more sensitive to the method used to define the VOI and more susceptible to PVE than the SUV max; however, it is less sensitive to the noise in the image.

When using SUV mean to monitor treatment response, a consistent approach to VOI delineation is essential. Variations in manual delineation can have a considerable impact on the SUV mean. TrueD provides a variety of semi-automatic tools for delineation that can reduce inter- and intra-operator variability and improve consistency.

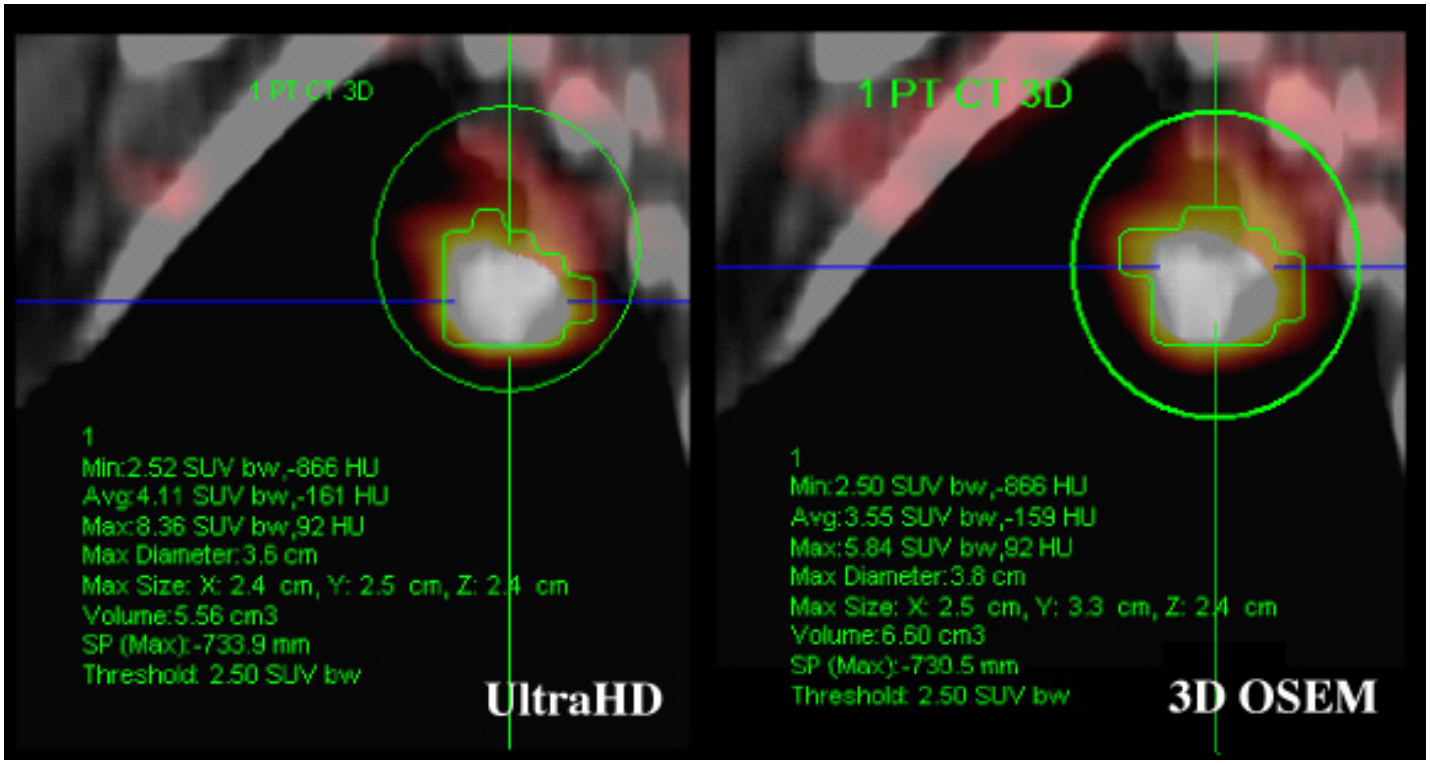


Figure 3.1. *Comparison of SUVs measured for the same lesion when reconstructed with ultraHD•PET (3it12s 0mm filter; on the left) or 3D OSEM (2it24s 5mm filter; on the right). Both VOIs were generated using the 3D ellipsoid isocontour tool with an absolute threshold of 2.50 SUV_{BW}. The maximum and average SUVs are higher for the ultraHD•PET reconstruction and volume of the VOI is smaller. This is due to the reduced partial volume error associated with ultraHD•PET reconstruction. Data courtesy of University of Tennessee Medical Center, Knoxville, TN.*

Specifically:

- 3D freeform isocontouring with absolute or relative thresholding
- 2D freeform isocontouring with absolute or relative thresholding
- 3D ellipsoid isocontouring with absolute of relative thresholding
- 2D ellipsoid isocontouring with absolute of relative thresholding

The relative impact of each of the factors discussed above on a measured SUV is study dependent and will vary according to the physiological state of the patient, the scanner technology used, and the protocols used to perform and analyze the scan. For example, the SUV for a lung lesion imaged on an old scanner will suffer more from PVE due to motion and scanner resolution than for a head and neck tumor imaged on a modern scanner. All these factors hinder the clinical acceptance of the SUV in some disciplines of oncology (particularly, therapy planning). The table below summarizes these sources of variation and lists the approaches available on the system or clinical side to mitigate their effects:

Table 1. *Sources of variation and approaches to minimizing their impact on SUV.*

Source of variation		Mitigation	
Physiological	Body composition	TrueD	TrueD enables LBM / BSA normalizations in order to reduce dependency of SUV on patient weight
	Blood glucose concentration	Clinical	Patient fasting and monitoring of the Blood Glucose Concentration pre-scan reduces variation in SUV due to blood glucose
	Kidney function	Clinical	Assessment of kidney function in relevant populations is needed to understand dependency of glucose uptake, leading to changes in preparation protocol if needed (post-injection time, etc.)
Physical	Partial volume effect	Biograph	HD and ultraHD•PET reconstruction reduces uncertainty in determining the site of photon emission and incorporates scanner geometry in the reconstruction process to minimize the dependency on hardware geometry.
		syngo	**syngo's* NEMA Image Quality application provides an automated method for assessing PVE and image quality.
	Respiratory Motion	Biograph	Gated acquisition and display reduce the impact of motion on SUV measurement
		TrueD	Review of the amplitude and shape of VOI motion during respiration helps refine SUV measurements
Procedural	Dose preparation & administration	Clinical	Cross-calibration of PET scanner and dose calibrator as well as measurement of residual activity in syringe aids accuracy in assessing injected dose.
		syngo	*Phantom and workflow provided by Siemens support cross calibration.
	Post-injection imaging interval	TrueD & Clinical	Consistent interval between ^{18}F-FDG injection and image acquisition reduces impact of SUV time-dependency. Differences in interval between studies can be identified in TrueD's 'Quality Control' tab.
	Reconstruction & Smoothing	TrueD & Clinical	Consistency in reconstruction parameters reduces source of SUV variability. Differences in reconstruction parameters can be identified in TrueD's 'Quality Control' tab.
	VOI definition	TrueD & Clinical	Consistency in VOI delineation method reduces source of SUV variability. Semi-automatic delineation tools in TrueD reduce inter- and intra-operator variability

** syngo in this instance represents the syngo Acquisition Workplace for PET (or ICS) software that ships standard with any Siemens PET or PET•CT scanner*

4.0 Conclusion

^{18}F-FDG SUV is a semi-quantitative metric and is widely-used in oncology as a regional measure of glucose metabolism. Its efficacy in lesion characterization, prognostic stratification and monitoring disease progression/treatment response has been demonstrated.

There are a number of factors, physiological, physical and procedural, that can have considerable impact on the computed SUV (Table 1). Siemens provides solutions for reducing the impact of a number of these factors at both the hardware level, with the Biograph HD and ultraHD•PET systems, and the software level, with TrueD and *syngo* Acquisition Workplace for PET (or ICS) software. For example, ultraHD•PET reconstruction combined with advanced LSO crystal technology and ultrafast electronics reduce PVE. A range of SUV normalizations including LBM and BSA reduce the impact of body composition on the SUVs calculated. Furthermore, semi-automatic tools for VOI delineation reduce inter-operator variation and improve consistency in the analysis.

Other factors including dose administration, post-injection imaging interval, body composition, blood glucose concentration and kidney function, must be monitored and controlled as part of a consistent imaging protocol, especially where comparisons are made between scans.

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