Feasibility of an SUV normalization to 1 hour after the $^{18}$F-FDG injection

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Abstract
The aim of this work was to reduce the SUV variability related to the time delay between $^{18}$F-FDG injection and the static PET acquisition, by means of a normalization to a 1-h time delay. Two static PET acquisitions separated by approximately 1 h were performed on each of 14 cancer patients, with SUVs on 22 hypermetabolic lesions calculated for both scans. The pairs of SUVs were normalized to each other using the parameterized input function with one free parameter ($\alpha_3$). This optimized parameter was found by computing the value which yielded equal normalized SUV pairs, on average, over the whole series. Without normalization, SUVs measured at later scans were found to be significantly greater than the earlier ones: mean ($\pm$ SD) ratio of $0.84 (\pm 0.08$; range $0.69–0.97$). After normalization, with an $\alpha_3$ value of $0.0257 \text{ min}^{-1}$, as expected, the mean ($\pm$ SD) ratio was $1.00 (\pm 0.07$; range $0.88–1.10$).

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Résumé
Faisabilité d’une normalisation du SUV à 1 heure après injection du $^{18}$F-FDG. Une méthode de normalisation du SUV à 1 h après injection du $^{18}$F-FDG, afin de réduire sa dépendance par rapport au délai de temps entre injection et acquisition est présentée. Deux acquisitions statiques, séparées approximativement de 1 h, ont été acquises sur 14 patients atteints de cancers, et le SUV a été évalué pour 22 lésions apparaissant sur les deux acquisitions. Les paires de SUV ont été utilisées pour la normalisation, en introduisant une fonction d’entrée dont le paramètre $\alpha_3$ a été optimisé en recherchant la valeur qui aboutissait en moyenne sur toute la série à des SUV normalisés égaux. Sans normalisation, le SUV tardif s’est révélé significativement plus élevé que le précoce : rapport moyen ($\pm$ DS) de $0.84 (\pm 0.08 ; 0.69–0.97$). Après normalisation ($\alpha_3 = 0.0257 \text{ min}^{-1}$), le rapport moyen ($\pm$ DS) des SUV normalisés est de $1.00 (\pm 0.07 ; 0.88 ; 1.10$).

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Mots-clés : TEP ; Oncologie ; Correction du SUV ; Modèle cinétique

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1. Introduction

Patlak’s analysis and compartmental analysis are considered as gold-standards for assessing the 18F-FDG uptake rate constant in tumours, hence tumour glucose metabolism [1–4]. However, these methods are invasive and cumbersome, as they require a serial arterial blood sampling, and a dynamic data acquisition for about one hour after tracer injection. Alternative simplified kinetic analyses have been proposed to reduce invasiveness of blood sampling by using a single venous sample or by using data from left ventricle or aorta blood appearing in images [5,6]. In comparison with Patlak’s analysis and compartmental analysis [1–4], introducing exponential input function (IF), [5], Eq. (1) becomes:

\[ \lambda C_T(t) = K\lambda f(t) \]  

(2)

with

\[ f(t) = \sum_{i=1}^{3} H_i(e^{-\lambda t} - e^{-\alpha_i t})/ (\alpha_i - \lambda) \]

(3)

where \( H_i \) and \( \alpha_i \) are the coefficients of the tri-exponential IF [5]. Consequently, at \( t = 60 \) min the trapped tracer activity per tumour volume unit is:

\[ \lambda C_T(60) = K\lambda f(60) \]

(4)

Substituting \( K \) by its value in Eq. (2) and rearranging, yields the following expression for the trapped tracer activity at 1 h after injection:

\[ \lambda C_T(60) = \lambda C_T(t)f(60)/f(t) \]

(5)

where \( \lambda C_T(t) \) represents the trapped 18F-FDG activity per tumour volume unit at any time after tracer injection.

Let us now consider the SUV at time \( t \), which is defined as:

\[ \text{SUV}(t) = \lambda C_{\text{Tot}}(t)W/A_{\text{inj}} \]

(6)

where \( \lambda C_{\text{Tot}}(t) \) is the total tracer activity in the whole tumour volume (free 18F-FDG in blood and tissue, and trapped 18F-FDG), \( A_{\text{inj}} \) is the injected tracer activity, and \( W \) is the patient’s weight. At \( t = 60 \) min, since \( C_{\text{Tot}}(60) \) is a surrogate for \( C_T(60) \) [8,9], introducing Eq. (4) in Eq. (6), and rearranging, yields:

\[ \text{SUV}(60) = \text{SUV}(t)f(60)/f(t) \]

(7)

2. Methods

2.1. SUV normalization

Assuming 18F-FDG is trapped in an irreversible manner, a two-compartment model has recently allowed us to derive the time–activity curve (TAC) of trapped tracer in a tumour [10]:

\[ \lambda C_T(t) = K\lambda C_p(t=0)(e^{-\lambda t} - e^{-\alpha t})/(\alpha - \lambda) \]

(1)

where \( C_T(t) \) is the trapped 18F-FDG concentration in the tumour, \( \lambda = 0.693/110 \text{ min}^{-1} \) is the physical decrease constant of the tracer, (hence \( \lambda C_T(t) \) represents the trapped 18F-FDG activity per tumour volume unit which can be measured), \( K \) is the uptake rate constant, and \( C_p(t=0) \) represents the tracer concentration in the plasma at the blood tracer peak. Eq. (1) assumes that the 18F-FDG blood TAC decays with a mean constant ‘\( \alpha \)’. However, it has been shown that the 18F-FDG plasma clearance was multiexponential. Assuming a tri-exponential input function (IF), [5], Eq. (1) becomes:

\[ \lambda C_T(t) = K\lambda f(t) \]

(2)

with

\[ f(t) = \sum_{i=1}^{3} H_i(e^{-\lambda t} - e^{-\alpha_i t})/ (\alpha_i - \lambda) \]

(3)

where \( H_i \) and \( \alpha_i \) are the coefficients of the tri-exponential IF [5]. Consequently, at \( t = 60 \) min the trapped tracer activity per tumour volume unit is:

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\[ \text{SUV}(60) = \text{SUV}(t)f(60)/f(t) \]

(7)

2.2. Patients and data acquisition

The investigation conforms with the principles outlined in the Declaration of Helsinki. An institutional ethics committee has approved the study and informed consent was obtained, after the procedure has been explained, from all of the subjects. A total of 14 patients (three females, eleven males) were included in this study. Table 1 presents patients’ ages, weights, and heights. No patient suffered from known impaired renal or hepatic function. All patients presented primary or metastatic cancer: lung (6 primary, 5 metastatic), or metastatic cancer: lung (6 primary, 5 metastatic), head and neck (2 primary), colon (1 primary). After a 6 hour fasting, preinjection blood glucose levels averaged 96 mg/dl (±16; range 61–129 mg/dl; 129 mg/dl for patient 1 with type II diabetes). Approximately 340 MBq of 18F-FDG was injected intravenously over less than 1 min (Table 1).
All $^{18}$F-FDG PET examinations were acquired on a PET-scan discovery ST (General Electric Medical System) in 3D mode, without septa, producing 47 slices over an approximately 150-mm axial field of view, and a 3-min time of acquisition per step. The imaging acquisition parameters were in-plane and axial resolution of 3.91 and 3.27 mm FWHM, respectively, in plane field of view of 600 mm, 128 $\times$ 128 pixel matrix. An image matrix of 256 $\times$ 256 pixel was used for iterative reconstruction (FORE + OSEM; subsets: 32; iterations: 5; Gaussian filter: 5.14 mm FWHM). CT transmission scans were acquired previously to the PET scanner for attenuation correction: pitch of 1.675, slice thickness of 2.5 mm, in plane field of view of 500 mm, 512 $\times$ 512 pixel matrix.

Patients underwent a first PET static acquisition for diagnostic purposes, involving several steps to cover a large part of the body. A second PET static acquisition was achieved at 69 min, on average, after the first (range 46–99 min), with identical acquisition parameters, but involving only one step over hypermetabolic lesions which appeared in the first one. Injection-acquisition time delays for the first (time $t_1$) and the second static acquisition (time $t_2$) are given in Table 1. For the first acquisition, the time $t_1$ corresponds to the acquisition of the particular step involving hypermetabolic lesions which were studied, and does not correspond to the start of the whole of the scan.

### 2.3. Evaluation of the SUV optimization

Maximal SUV normalized to patient’s body weight was assessed over a total of 22 hypermetabolic lesions which appeared in the two static acquisitions (Xeleris station). For each hypermetabolic lesion, this SUV was assessed over a total of 22 hypermetabolic lesions which were studied, and does not correspond to the start of the whole of the scan.

### Table 1

Patients 4 and 6: head and neck cancer; patient 13: colon cancer; others: lung cancer; (preinjection) glycaemia; $^{18}$F-FDG injected activity ($A_{inj}$); time delay between injection and first PET acquisition ($t_1$), and second PET acquisition ($t_2$); time delay between the two acquisitions ($t_2 - t_1$); $\alpha_3$ value independently optimized for each hypermetabolic lesion by targeting the $SUV_{N1}/SUV_{N2}$ ratio to a value of 1, respectively (see text).

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. of lesion</th>
<th>Age (year)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Glycaemia (mg/dl)</th>
<th>$A_{inj}$ (MBq)</th>
<th>$t_1$ (min)</th>
<th>$t_2$ (min)</th>
<th>$t_2 - t_1$ (min)</th>
<th>SUV$_1$/SUV$_2$</th>
<th>SUV$<em>{N1}$/SUV$</em>{N2}$</th>
<th>$\alpha_3$ (min$^{-1}$)</th>
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<td>69</td>
<td>67</td>
<td>169</td>
<td>129</td>
<td>320</td>
<td>105</td>
<td>172</td>
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<td>92</td>
<td>165</td>
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<td>90</td>
<td>298</td>
<td>94</td>
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<td>162</td>
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<td>128</td>
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<td>165</td>
<td>101</td>
<td>300</td>
<td>67</td>
<td>116</td>
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<td>4</td>
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<td>116</td>
<td>46</td>
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<td></td>
<td>0.88</td>
<td>1.04</td>
<td></td>
<td>0.0299</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean: 62 $\pm$ 196; SD: 10 $\pm$ 12; 7 $\pm$ 16; 60 $\pm$ 16; 20 $\pm$ 17; 0.08 $\pm$ 0.07; 0.0066.
and (3) in order to get $S_{UVN1}$ and $S_{UVN2}$ for each lesion in each acquisition, respectively. The computation of these latter values was achieved on a Microsoft Excel sheet, and required to introduce a tri-exponential IF (Eq. (3)) [5]. The respective contribution of each IF monoexponential function (IF1, IF2, IF3) to the whole blood $^{18}$F-FDG amount which is available for the tumour, should be compared. Each available amount is given by the area under the corresponding curve, and then is equal to $H_i \times \{1 - \exp(-\alpha_i t)\}/\alpha_i$, at any time $t$ after injection, respectively. From Hunter’s results [5], after a bolus injection, for an injection-acquisition time delay of 55 min, the order of magnitude of the averaged relative contribution of IF1, IF2, and IF3 are 2%, 9%, and 89%, respectively. In other words, the SUV mainly depends on the third exponential function ($H_3 - \alpha_3$). Consequently, four coefficients of the triexponential IF, namely $H_1 - \alpha_1$ and $H_2 - \alpha_2$, were set according to Hunter’s results for a tracer bolus injection, i.e. 5943 − 9.33 and 851 − 0.289, respectively. Then, the Excel solver program was used to target the $S_{UVN1}/S_{UVN2}$ ratio to a value of 1, by optimizing $H_3 - \alpha_3$ from Hunter’s values of 725 − 0.0125, respectively [5]. First, in order to validate the method, this procedure was carried out over the first 7 patients (9 hypermetabolic lesions), and then the optimized values of $H_3 - \alpha_3$ were arbitrarily applied in each of the remaining 7 patients (13 hypermetabolic lesions). Second, further optimized values of $H_3$ and $\alpha_3$ were computed by targeting the $S_{UVN1}/S_{UVN2}$ ratio to a value of 1 over the whole lesion series. Finally, the same procedure was also independently used for each hypermetabolic lesion, to obtain optimized values of $H_3$ and $\alpha_3$ by targeting the $S_{UVN1}/S_{UVN2}$ ratio of each hypermetabolic lesion to a value of 1, respectively.

### 3. Results

The validation of the method, with two sub-series of patients, is presented in Table 2: the mean $S_{UVN1}/S_{UVN2}$ ratio (±95% reliability domain; Student’s $t$ distribution) for each group was 1.00 ± 0.05 (optimized $H_3 - \alpha_3$ over the first subseries was 725 − 0.0276; $H_3$ did not change in comparison with Hunter’s value) and 0.96 ± 0.04 ($H_3 - \alpha_3$ arbitrarily taken equal to 725 − 0.0276 for each lesion), respectively, showing no significant difference between the two groups.

The normalization procedure over the whole series provided further optimized values of $H_3$ and $\alpha_3$, which were found to be 725 ($H_3$ did not change in comparison with Hunter’s value) and 0.0257 min$^{-1}$, respectively (Table 1). As expected, the related mean $S_{UVN1}/S_{UVN2}$ ratio (±95% reliability domain; Student’s $t$ distribution) was 1.00 ± 0.03 (range 0.88–1.10; SD: 0.07), whereas, without normalization, the mean $S_{UV1}/S_{UV2}$ ratio (±95% reliability domain; Student’s $t$ distribution) was 0.84 ± 0.03 (range 0.69–0.97; SD: 0.08), indicating that the late (decay-corrected) SUV was significantly greater than the earlier one ($p < 0.05$). After optimization over the whole lesion series, no significant correla-

### Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. of lesion</th>
<th>$S_{UV1}/S_{UV2}$</th>
<th>$S_{UVN1}/S_{UVN3}$</th>
<th>$S_{UV1}/S_{UV2}$</th>
<th>$S_{UVN1}/S_{UVN3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>0.87</td>
<td>0.94</td>
<td>1</td>
<td>0.94</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
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<td>0.93</td>
<td>2</td>
<td>0.72</td>
</tr>
<tr>
<td>3</td>
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<td>13</td>
<td>0.86</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
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<td>1.00</td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>0.08</td>
<td>0.07</td>
<td></td>
<td>0.07</td>
</tr>
</tbody>
</table>

The late (decay-corrected) SUV was significantly greater than the earlier one ($p < 0.05$). After optimization over the whole lesion series, no significant correla-
tion was found between the individual SUV$_{N1}$/SUV$_{N2}$ ratios and any of the following parameters: injected activity, patient’s age, weight, height, pre-injection blood glucose level, time delay between injection and first PET acquisition, time delay between injection and second PET acquisition, time delay between the two acquisitions. It should be noted that we additionally checked that no optimization of $H_1 - \alpha_1$ and $H_2 - \alpha_2$ was possible (with $H_3 - \alpha_3$ fixed and the other 4 parameters left free and the system optimized again).

When the optimization procedure was independently performed for each hypermetabolic lesion, different optimized values of $\alpha_3$ were found (Table 1). The mean value (±SD) over the $\alpha_3$ series was 0.0268 min$^{-1}$ (±0.0066), which is slightly different from that found from the whole series. (The $H_3$ value for each lesion was again equal to 725.) A significant correlation was found between the SUV$_{N1}$/SUV$_{N2}$ ratio for each hypermetabolic lesion (penultimate column in Table 1), which was obtained with the optimized average $\alpha_3$ value of 0.0257 min$^{-1}$ (see above). This measurement uncertainty has been estimated to be 1.5% on average (range 0.5–3.0%).

The range of the SUV$_{N1}$/SUV$_{N2}$ ratio indicates that the normalization is efficient with a 7% SD and a 12% maximal relative measurement uncertainty (Table 1). Assuming that the measurement uncertainty of the time delay between injection and the first static acquisition (t$_{1}$), computed for each lesion (by computing on the Excel sheet), with an optimized average $\alpha_3$ value of 0.0257 min$^{-1}$, Equation of the linear fit is $y = -0.033x + 4.182$ ($r = 0.91$).

4. Discussion

This work shows that a non invasive SUV normalization to 1 h after $^{18}$F-FDG injection is feasible, in order to significantly reduce changes in the SUV related to the injection-acquisition time-delay. Although the principle of the method would allow us to normalize the SUV to any arbitrary time ($t = 120$ min, for example), the 1-h-normalization was chosen in order to keep usual landmarks of clinical practice. Before normalization, the late SUV was always found to be greater than the early one, up to 31%, i.e. the SUV$_1$/SUV$_2$ ratio was significantly lower than 1. As expected after normalization, with an optimized $\alpha_3$ value of 0.0257 min$^{-1}$, the mean SUV$_{N1}$/SUV$_{N2}$ ratio was 1, with a standard deviation and a maximal relative measurement uncertainty equal to 7 and 12%, respectively.

The main part of the measurement uncertainty of the 1-h-normalized SUV is very likely related to known phenomena which influence the quantification of lesion activity [11]. Among these phenomena, in the present
experiment design, it is suggested that scattered radiations, attenuation correction (in particular for lower lung lesions due to respiratory motion), and partial volume effect are responsible for the main part of the measurement uncertainty. However, the measurement uncertainty of the proposed normalization procedure is also partly related to the $t_1$ measurement uncertainty. A 3-min $t_1$ uncertainty leads to averaged and maximal changes in the ratio of 1.5 and 3%, respectively. Moreover, Fig. 2 clearly indicates that the earlier the first static acquisition, i.e. the shorter the time $t_1$, the greater the measurement uncertainty in the 1-h-normalized SUV. Considering that the proposed normalization does allow us to assess the 1-h-normalized SUV from an acquisition achieved beyond 1 h after injection, it is then possible to partly lower the measurement uncertainty. In addition, it should be noted that the later the acquisition, the lower the part of the contribution of IF1 and IF2 to the whole blood $^{18}$F-FDG amount which is available for the tumour, and the more reliable is the only IF3 optimization of the proposed normalization. A third origin of the measurement uncertainty of the 1-h-normalized SUV is likely related to the variability of the time constant $\alpha_3$ for the decay of the slowest blood component of the input function. This constant plays a major role in $^{18}$F-FDG uptake, which is both supported by Hunter’s results [5] and the present ones. However, there is a discrepancy between Hunter’s average value of $\alpha_3$ and that of the present results, 0.0125 and 0.0257 min$^{-1}$, respectively. Firstly, it should be noted that, to the very best of our knowledge, the $^{18}$F-FDG plasma clearance far beyond 1 h after injection has not been extensively studied. Secondly, Hunter’s paper does not clearly state whether the $^{18}$F-FDG blood TACs have been corrected for the physical decay of the tracer before performing the tri-exponential fit: therefore, adding 0.0063 (= ln 2/110) to 0.0125 min$^{-1}$ would lead to a value of 0.0188 min$^{-1}$, which would get closer to that of the present results. Thirdly, Fig. 3 shows a comparison between two theoretical tumour TACs obtained with a tri-exponential IF involving the $\alpha_3$ value by Hunter et al. and that of the present results (Eq. (3)), respectively. Simulation from Hunter’s IF shows that the maximal activity in the tumour occurs at about 105 min after the tracer injection (70 min for that of the present results), that is not realistic. Finally, it should be noted that the proposed $\alpha_3$ optimization affects the SUV, which involves all the tissue activity, from both trapped tracer and free tracer in blood and interstitial volumes [10] (Eq. (6)). This feature may also explain an overestimated $\alpha_3$ value in comparison with that of Hunter et al., since the amount of free tracer in blood and interstitial volumes is greater at early imaging than at late imaging. Nevertheless, the major role of $\alpha_3$ in $^{18}$F-FDG uptake is highlighted in the present experiments by the significant correlation (Fig. 1; $r = 0.94$) between the SUV$_{N1}$/SUV$_{N2}$ ratios for each hypermetabolic lesion, which were obtained with an optimized average $\alpha_3$ value of 0.0257 min$^{-1}$ over the whole lesion series, and the $\alpha_3$ values which were independently optimized for each hypermetabolic lesion. As a consequence, this correlation shows that the proposed non-invasive normalization procedure unavoidably involves a measurement uncertainty related to a $\alpha_3$ variability.

In conclusion, a non invasive SUV normalization to 1 h after $^{18}$F-FDG injection is feasible, which could allow the physician to plan PET examinations with more flexibility about the injection-acquisition time delay. Although a larger number of cancer patients is required to assess more precisely the measurement uncertainty of the 1-h-normalized SUV, the presented preliminary results indicate that it is very likely reasonable (7% SD for the present series of 14 cancer patients), and that it could be partly lowered when the acquisition is achieved beyond one hour after injection.

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References


