Testing the undescended testis

de Vries, A.

Citation for published version (APA):
Uptake of $^{18}$F-FDG in the healthy testes of young men as assessed by PET/CT; including the interobserver and intraobserver variation

Annebeth Meij–de Vries
Remco JJ Knol
Sergiy V Lazarenko
Robert W Meijer
Evelyn M van der Plas
Hugo A Heij

Submitted
ABSTRACT

Objective
Knowledge of the physiological testicular accumulation of $^{18}$F-FDG is essential in order to discriminate between normal and pathological findings. In this study, the $^{18}$F-FDG-uptake in healthy testes of young men was assessed using PET/CT-scans.

Methods
A total of 40 testes of 20 men with a mean age of $26.5 \pm 3.9$ years were evaluated. $^{18}$F-FDG-uptake was expressed as the standardized uptake value (SUV). Testicular volume was measured on CT and PET. All scans were assessed by three researchers, one of whom assessed every scan twice. Laterality indices and interobserver and intraobserver variation were evaluated. Correlation between the SUV$_{\text{max}}$ and SUV$_{\text{peak}}$, between SUV$_{\text{mean}}$ and SUV$_{\text{peak}}$ and between age and SUV$_{\text{peak}}$ was assessed.

Results
Testes showed an average SUV$_{\text{max}}$ of $3.42 \pm 0.61$, SUV$_{\text{peak}}$ of $3.06 \pm 0.54$ and SUV$_{\text{mean}}$ of $2.44 \pm 0.44$. The average testicular volume on CT was $23.0 \pm 6.4$ ml, whereas on PET it was $18.0 \pm 5.1$ ml. Laterality indices were calculated of $0.077 \pm 0.065$ (SUV$_{\text{max}}$), $0.074 \pm 0.066$ (SUV$_{\text{peak}}$), $0.072 \pm 0.063$ (SUV$_{\text{mean}}$), $0.245 \pm 0.259$ (CT) and $0.200 \pm 0.188$ (PET). Interobserver and intraobserver reliability were found to be perfect for the standardized uptake values (Intraclass Correlation Coefficient (ICC) $0.992 - 1.0$) but poor for testicular volumes (ICC $0.854 - 0.902$).

Conclusions
Testicular $^{18}$F-FDG uptake in young men can be measured accurately on PET/CT and shows high symmetry. Consequently, $^{18}$F-FDG PET/CT has the potential to become a useful instrument in the evaluation of the functioning of the individual testis.
INTRODUCTION

$^{18}$F-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) imaging in combination with computed tomography (CT) is mainly used to assess malignant lesions.\(^1\)

However, in normal tissue $^{18}$F-FDG also accumulates in various degrees.\(^2\) It is essential to know what this physiological uptake is, in order to discriminate between normal and pathological findings. Moreover, testicular $^{18}$F-FDG uptake correlates positively with the main sperm parameters and is likely to be a promising parameter for testis function.\(^3\)

In testicular tissue, normal $^{18}$F-FDG uptake has been studied in men over the age of 35 and in a pediatric study population.\(^4-6\) However, data on men between the ages of 18 and 32 years and on the reliability of the $^{18}$F-FDG uptake measurements are lacking. Therefore, the aim of this study is to measure the physiological testicular $^{18}$F-FDG uptake in young men and to assess the usability of these measurements by calculating the laterality indices and the interobserver and intraobserver variation.

MATERIAL AND METHODS

Study population

From January 2012 until April 2013, a total of 1555 men underwent a diagnostic whole body FDG-PET/CT scan in our hospital. In the age group of our interest (18 – 32 years), 20 scans (40 testes) were performed on men with a mean age of 26.5 ± 3.9 years (range 19.3 – 31.2 years). All PET/CT scans were carried out with the same type of scanner. Indications for the diagnostic whole body FDG-PET/CT scans included Hodgkin’s disease (8), suspicion of malignancy (4), colon carcinoma (3), sarcoidosis (2), tuberculosis (1), B-cell lymphoma (1) and a suspicion of endocarditis (1). None of the patients had a history of undescended testis or showed any abnormality of the testes on the PET/CT scan.

Each patient gave written informed consent for the evaluation of their PET/CT data for scientific research.
**18F-FDG PET/CT scan**

Whole-body 18F-FDG PET/CT scanning was performed using a Biograph 16 TruePoint PET/CT scanner (Siemens Healthcare, Knoxville, USA).

All 20 patients had a blood glucose level below 10 mmol/l and received an intravenous injection of FDG. The average injected dose was 4.7 MBq/kg body weight (range 2.4 – 6.4 MBq/kg), and the average time between FDG administration and the start of the PET acquisition was 62 minutes (range 44 – 74 minutes).

In 10 patients, a low-dose CT scan was performed for localization and attenuation correction purposes. Scanning parameters included 50 ref.mAs and 130 kV with 4D Care Dose. No intravenous contrast was administered to these patients. A diagnostic CT total body with 110 ref.mAs and 110 or 130 kV with 4D Care Dose was acquired for the other 10 patients, and these patients were given intravenous contrast.

For PET scanning, a 3D emission scan was acquired with 6 or 7 bed position (195 and 225 transaxial images respectively), using 4 minutes per bed position. Images with CT-based attenuation correction were reconstructed, using OSEM3D reconstruction with 4 iterations, 8 subsets, a Gaussian post-smoothing filter of 5 mm, 168x168 matrix, pixel size 4.07 mm x 4.07 mm and slice thickness 5 mm.

**Image analysis and parameters**

Images (Figure 1) were interpreted on syngo.via VA20A equipped workstations, using the MM Oncology software package (version 1.0; Siemens Healthcare, Erlangen, Germany), which can display CT, PET and fused PET/CT images simultaneously.

In order to measure testicular volume by CT, the testes were selected semi-automatically using the generic segmentation tool in this software package. The resulting selected area was checked visually in all orthogonal planes (slice thickness 2 mm) and reshaped manually in case of obvious errors. Subsequently the testicular volumes were calculated automatically by summing the volume estimates from the selected areas in each slice.

Standardized uptake values (SUV) were calculated from the PET images as the ratio of the activity (kBq) in tissue per ml to the activity in the injected dose (MBq) per patient body weight in kg. Volume of Interest (VOI)s were selected on the PET images using the VOI isocontour tool in the oncology software package mentioned above, with a threshold of 50%. Spheres were placed manually around each testis on the 3D PET images and rotated to the correct orientation of the testis. Within the resulting isocontour, \( \text{SUV}_{\text{max}} \)
Normal testicular FDG-uptake

(SUV of single pixel with highest uptake in the VOI), $SUV_{\text{peak}}$ (mean SUV of 1 cm$^3$ with highest uptake in VOI), $SUV_{\text{mean}}$ (mean SUV in whole VOI) and the volume of the VOI were measured and recorded. All scans were assessed by three researchers (observer 1, 2, 3), one of them assessed every scan twice (observer 3a and 3b).

![Figure 1 Example of PET/CT images in a patient with symmetric testicular uptake of FDG, coronal (A) and axial (B).](image)

**Statistical analysis**

All data were managed and analyzed with SPSS, version 14.0. The laterality index was defined as $\frac{|L - R|}{(L + R) \times 2}$, where $L =$ left testicular SUV and $R =$ right testicular SUV. The intraclass correlation coefficient (ICC) was used to evaluate interobserver and intraobserver variability; the ICC is 1.0 if there is a perfect reliability. Furthermore, linear regression was used to calculate the exact correlation between the three different researchers (interobserver variation) and between the first and second assessment of one of the researchers (intraobserver variation). A correlation coefficient ($r$) $> 0.7$ was regarded as a good correlation. Linear regression was expressed as $Y = a + bx$, where the intercept ($a$) is 0 and the slope ($b$) 1 if there is a perfect correlation. The correlations between the $SUV_{\text{max}}$ and $SUV_{\text{peak}}$, between $SUV_{\text{mean}}$ and $SUV_{\text{peak}}$ and between age and $SUV_{\text{peak}}$ were assessed with linear regression and the Pearson’s correlation coefficient test. A p-value $< 0.05$ was regarded as statistically significant.
RESULTS

Table 1 shows the mean and laterality indices of the SUVmax, SUVpeak and SUVmean, testicular volume on CT and VOI of the 40 healthy testes in young men.

Table 1  Mean ± SD and range of SUV\textsubscript{max}, SUV\textsubscript{peak}, SUV\textsubscript{mean}, testicular volume (TV) on CT and VOI and their laterality indices measured by three researchers on 20 \textsuperscript{18}FDG-PET/CT scans of young men with 40 healthy testes.

<table>
<thead>
<tr>
<th></th>
<th>mean ± SD</th>
<th>range</th>
<th>laterality index</th>
<th>mean ± SD</th>
<th>range</th>
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<tbody>
<tr>
<td>SUV\textsubscript{max}</td>
<td>3.42 ± 0.61</td>
<td>2.07 – 4.82</td>
<td>0.077 ± 0.065</td>
<td>0 – 0.192</td>
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<tr>
<td>SUV\textsubscript{peak}</td>
<td>3.06 ± 0.54</td>
<td>1.81 – 4.14</td>
<td>0.074 ± 0.066</td>
<td>0 – 0.228</td>
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<td>SUV\textsubscript{mean}</td>
<td>2.44 ± 0.44</td>
<td>1.40 – 3.37</td>
<td>0.072 ± 0.063</td>
<td>0 – 0.248</td>
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<tr>
<td>TV\textsubscript{CT}</td>
<td>23.0 ± 6.4</td>
<td>10.2 – 42.8</td>
<td>0.245 ± 0.259</td>
<td>0 – 1.054</td>
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<tr>
<td>VOI</td>
<td>18.0 ± 5.1</td>
<td>9.0 – 33.8</td>
<td>0.200 ± 0.188</td>
<td>0 – 0.791</td>
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</table>

SUV = standardized uptake value
TV\textsubscript{CT} = testicular volume measured by CT (ml)
VOI = volume of interest (ml)

Interobserver and intraobserver reliability

The interobserver ICCs (+ 95% Confidence Interval) of the SUV\textsubscript{max}, SUV\textsubscript{peak}, SUV\textsubscript{mean}, testicular volume on CT, and VOI are shown in Table 2. The interobserver ICC for the testicular volumes on CT with contrast (n = 10) was 0.890 (0.768 – 0.953) and for the CT scans without contrast (n = 10) 0.805 (0.589 – 0.917).

Also shown in Table 2 are the intraobserver ICCs (+ 95% Confidence Interval) of the SUV\textsubscript{max}, SUV\textsubscript{peak}, SUV\textsubscript{mean}, testicular volume on CT, and VOI. The intraobserver ICC for the testicular volumes on CT with contrast (n = 10) was 0.893 (0.729 – 0.958) and for the CT scans without contrast (n = 10) 0.934 (0.832 – 0.974).
Table 2  Interobserver and intraobserver variability of $SUV_{\text{max}}$, $SUV_{\text{peak}}$, $SUV_{\text{mean}}$, testicular volume (TV) on CT and VOI measured on 20 $^{18}$FDG-PET/CT scans of young men with 40 normal testes, expressed as intraclass correlation coefficient (ICC).

<table>
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<tr>
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<th>Intraobserver variability</th>
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<tr>
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<td>ICC (95% CI)</td>
<td>ICC (95% CI)</td>
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<tr>
<td>$SUV_{\text{max}}$</td>
<td>0.997 (0.996 – 0.999)</td>
<td>1.0 (1.0 – 1.0)</td>
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<tr>
<td>$SUV_{\text{peak}}$</td>
<td>1.0 (1.0 – 1.0)</td>
<td>0.999 (0.999 – 1.0)</td>
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<tr>
<td>$SUV_{\text{mean}}$</td>
<td>0.997 (0.995 – 0.998)</td>
<td>0.992 (0.985 – 0.996)</td>
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<tr>
<td>$TV_{\text{CT}}$</td>
<td>0.854 (0.753 – 0.918)</td>
<td>0.916 (0.841 – 0.955)</td>
</tr>
<tr>
<td>VOI</td>
<td>0.883 (0.803 – 0.934)</td>
<td>0.902 (0.815 – 0.948)</td>
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</table>

$SUV$ = standardized uptake value  
$TV_{\text{CT}}$ = testicular volume measured by CT (ml)  
VOI = volume of interest (ml)

The exact interobserver and intraobserver correlation as measured by linear regression for all parameters is presented in Table 3.
Table 3  Interobserver (A) and intraobserver (B) variability of SUV\textsubscript{max}, SUV\textsubscript{peak}, SUV\textsubscript{mean}, testicular volume (TV) on CT and VOI measured on 20 \textsuperscript{18}FDG-PET/CT scans of young men with 40 normal testes, calculated by linear regression and expressed as correlation coefficient (r), intercept (a) and slope (b).

<table>
<thead>
<tr>
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<tr>
<td><strong>SUV\textsubscript{max}</strong></td>
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<td>Obs1 vs Obs3</td>
<td>0.991</td>
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<td>Obs2 vs Obs3</td>
<td>0.998</td>
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<td>0.993</td>
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<tr>
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<td>0.999</td>
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<td>Obs2 vs Obs3</td>
<td>0.989</td>
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<tr>
<td>Obs1 vs Obs2</td>
<td>0.588</td>
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<td>Obs1 vs Obs3</td>
<td>0.744</td>
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<td>Obs2 vs Obs3</td>
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<td><strong>VOI</strong></td>
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<tr>
<td>Obs1 vs Obs2</td>
<td>0.810</td>
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<td>Obs1 vs Obs3</td>
<td>0.611</td>
<td>4.517</td>
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<tr>
<td>Obs2 vs Obs3</td>
<td>0.724</td>
<td>2.133</td>
<td>0.694</td>
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<tr>
<td><strong>SUV\textsubscript{max}</strong></td>
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<tr>
<td>Obs3a vs Obs3b</td>
<td>1.0</td>
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<tr>
<td><strong>SUV\textsubscript{peak}</strong></td>
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<tr>
<td>Obs3a vs Obs3b</td>
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<td><strong>SUV\textsubscript{mean}</strong></td>
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<td>Obs3a vs Obs3b</td>
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<td>Obs3a vs Obs3b</td>
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<td><strong>VOI</strong></td>
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<tr>
<td>Obs3a vs Obs3b</td>
<td>0.827</td>
<td>2.993</td>
<td>0.930</td>
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</table>

SUV = standardized uptake value  
Obs = observer  
TV\textsubscript{CT} = testicular volume measured by CT (ml)  
VOI = volume of interest (ml)
Correlation between SUV\textsubscript{max} and SUV\textsubscript{peak}
There was a significant, strong positive correlation between the SUV\textsubscript{max} and SUV\textsubscript{peak}: $r = 0.973; Y = 0.07 + 0.97x$, $p < 0.0001$ (Figure 2).

![Figure 2](image_url)  
**Figure 2** Strong positive correlation between the SUV\textsubscript{max} and SUV\textsubscript{peak} of the $^{18}$FDG-PET/CT imaging of young men with 40 normal testes and four measurements. $r = 0.973; Y = 0.07 + 0.97x; p < 0.0001$. 
Correlation between SUV\textsubscript{mean} and SUV\textsubscript{peak}

There was a significant, strong positive correlation between the SUV\textsubscript{mean} and SUV\textsubscript{peak}; \( r = 0.984; Y = 0.1 + 0.98x, p < 0.0001 \) (Figure 3).

\textbf{Figure 3} Strong positive correlation between the SUV\textsubscript{mean} and SUV\textsubscript{peak} of the \textsuperscript{18}FDG-PET/CT imaging of young men with 40 normal testes and four measurements. \( r = 0.984; Y = 0.1 + 0.98x; p < 0.0001 \).
Correlation between age and SUV\textsubscript{peak}  
There was a significant, weak positive correlation between age and the SUV\textsubscript{peak}:
\[ r = 0.349; Y = 1.7 + 0.35x, \text{p} < 0.0001 \text{ (Figure 4).} \]

**Figure 4** Weak positive correlation between the age and SUV\textsubscript{peak} of the \textsuperscript{18}FDG-PET/CT imaging of young men with 40 normal testes and four measurements. \[ r = 0.349; Y = 1.75 + 0.35x; \text{p} < 0.0001. \]

**DISCUSSION**

In this study on testicular \textsuperscript{18}F-FDG uptake on PET/CT in a population of young men, we found a high interobserver and intraobserver reliability in assessing the SUV\textsubscript{max}, as well as the SUV\textsubscript{peak} and the SUV\textsubscript{mean}. Further, these SUV values had low laterality indices and correlated well with each other. Furthermore, the correlation between the SUV\textsubscript{peak} and age was weak.

Kosuda et al found a testicular SUV ranging from 1.90 to 3.34 (average; 2.44 ± 0.53), Kitajima et al reported a mean SUV\textsubscript{max} of 2.81 ± 0.43 in the age group of 30-39, and
the highest mean SUV\textsubscript{mean} Goethals et al found in a pediatric population was 1.4.\textsuperscript{4-6} Absolute uptake values such as SUVs are known to be affected by many technical and physiological factors. Therefore, measurements from different studies cannot reliably be compared.\textsuperscript{9-11} Nevertheless, the positive correlation ($r = 0.406$, $p = 0.005$) between age and the SUV\textsubscript{mean} described by Goethals et al has been interpreted as not in line with the negative correlation ($r = -0.284$, $p < 0.0001$) between age and SUV\textsubscript{max} that Kitajima et al described from the age of 36. In our study, we interpreted the positive correlation between age and SUV\textsubscript{peak} ($r = 0.349$; $Y = 1.7 + 0.35x$; $p < 0.0001$) as significant, but weak.

Although Goethals et al interpreted their results as not in line with the results of Kitajima et al, the reverse correlation may be a consequence of the maturation of testes in child- and adulthood and on the other hand, the aging of the testes with deterioration of the Leydig cells during the second part of a man’s life.\textsuperscript{12,13} Our finding of a significant but weak correlation between age (19.3 – 32.2 years) and SUV\textsubscript{peak} supports this theory since in our age group testicles are mature but do not alter yet.

Furthermore, in this study we found that the laterality of testicular $^{18}$F-FDG uptake is low: the laterality indices for SUV\textsubscript{max}, SUV\textsubscript{peak}, SUV\textsubscript{mean} were $0.077 \pm 0.065$, $0.074 \pm 0.066$ and $0.072 \pm 0.063$, respectively. These findings are comparable with the laterality indices of the SUV\textsubscript{max} reported by Kitajima et al ($0.066 \pm 0.067$).\textsuperscript{4} This implies that the SUVs are comparable for bilateral testes; there is a high symmetry in healthy testes and that a higher laterality index (for instance $> 0.15$) may be an indication for a pathologic process.

In addition, interobserver and intraobserver variability were evaluated. There was a weak interobserver and intraobserver reliability in the testicular volumes measured on CT (with or without contrast) as well as in the VOI on the PET/CT. Moreover, the correlation between both parameters was moderate ($r = 0.513$; $Y = 11.5 + 0.5x$; $p < 0.0001$). This leads to the conclusion that testicular volume is an unreliable parameter to evaluate using a PET/CT scan. However, all standard uptake values (max, peak and mean) showed a very good interobserver and intraobserver repeatability. SUV\textsubscript{max} corresponds with the single pixel with the highest $^{18}$F-FDG uptake in the VOI and is of particular value in PET/CT images of high statistical quality.\textsuperscript{14} SUV\textsubscript{peak}, which represents the mean SUV of the 1 cm$^3$ with the highest $^{18}$F-FDG uptake in the VOI, provides a slightly more robust alternative. The ICCs of interobserver and intraobserver variability are 1.0 and 0.999, respectively; therefore, the SUV\textsubscript{peak} seems a perfectly reliable
Normal testicular FDG-uptake parameter. This parameter has an average ± SD of 3.06 ± 0.54, a laterality index of 0.074 ± 0.066 and good correlations with $SUV_{max}$ ($r = 0.973; Y = 0.07 + 0.97x; p < 0.0001$) and $SUV_{mean}$ ($r = 0.984; Y = 0.1 + 0.98x; p < 0.0001$); as a result, the $SUV_{peak}$ appears to be an ideal parameter for the evaluation of testicular $^{18}$F-FDG uptake.

The limitations of this study need to be addressed. First, the number of scans (20) and testes (40) is relatively small. Since January 2012 a new scanner has been in use and as the scanner might influence the SUVs, it was decided to include only the PET/CT scans made on this new scanner. Besides, scans were included only of men in the age group of our interest (18 - 32 years). These two inclusion criteria limited the number of scans to 20, with 40 testes.

Second, this was a retrospective study. Testes were not placed in a proper position and in some cases both testes were in contact with each other which hampered the automatic detection of the testis with the generic segmentation tool on CT. Further, although the scans were performed on the same scanner, there were some differences in the scanning protocol. For example, intravenous contrast agent was used in half the scans, whereas in the other half no contrast agent was administered. Analysis showed a significantly higher $SUV_{max}$ in the group with contrast agent compared to the group without contrast agent ($3.57 \pm 0.6$ vs $3.27 \pm 0.58$; $p = 0.034$), but no significant differences were found between both groups for the $SUV_{peak}$ ($3.17 \pm 0.55$ vs $2.95 \pm 0.51$; $p = 0.1$) and $SUV_{mean}$ ($2.53 \pm 0.44$ vs $2.34 \pm 0.42$; $p = 0.07$). The retrospective character of the present study may have caused some inaccuracy in the results and can be improved in a future prospective study with a proper positioning of both testes and one single scanning protocol.

Third, our study population contained a group of men with a variety of diseases with corresponding (chemo)therapies. Because an excess of FDG is given before scanning, cancerous or otherwise pathologic tissue does not compromise the FDG uptake of normal tissue, i.e. testicles. The influence of chemotherapy on testicular FDG uptake has been studied by Burger et al. They found no absolute or relative change in testicular FDG uptake after starting or during systemic chemotherapy for Hodgkin’s lymphoma. Furthermore, no involvement of the testes in the pathology of our study population had been diagnosed. Also, no other testicular abnormalities were seen on the PET/CT scans. Overall, we believe that there was no influence of the diseases with the corresponding therapies in our study population on the measured SUV values.

In short, SUV measurements with PET/CT of testicular $^{18}$F-FDG uptake seem reliable.
with a low interobserver and intraobserver variability and a high symmetry in young men with normal testes. SUV_{peak} seems to be the best parameter to use in the evaluation of this uptake. Consequently, the PET/CT seems a promising new method to evaluate testicular function, and this conclusion is supported by recently published data on the positive correlation between the rate of testicular $^{18}$F-FDG uptake and sperm parameters.\textsuperscript{3} The PET/CT scan will enable us to discriminate between the functioning of both bilateral testes. Therefore, it will overcome an important limitation of the main fertility parameters used previously, such as semen analysis or paternity.\textsuperscript{16} For example, the testicular $^{18}$F-FDG uptake measured on PET/CT might become an important parameter in the evaluation of the functioning of previously unilateral orchidopexied testes.

**CONCLUSION**

Testicular $^{18}$F-FDG uptake in young men can be measured accurately using PET/CT, with a low interobserver and intraobserver variability and shows a high symmetry. $^{18}$F-FDG PET/CT has the potential to become a useful instrument in the evaluation of the functioning of the individual testis.
Normal testicular FDG-uptake

References