APPLICATIONS OF F18-FDG-PET IN ONCOLOGY AND STANDARDISATION FOR MULTI-CENTRE STUDIES

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0. Introduction

This Recommendation describes the Dutch F18-FDG-PET standard (NEDPAS) for quantitative whole body FDG PET multi-centre studies written by the HOVON imaging workgroup in collaboration with the Netherlands Society of Nuclear Medicine. This quideline has officially been approved by the Netherlands Society of Nuclear Medicine since 9 November 2007. The aim is to ensure that multi-center FDG-PET studies using SUV (standardised uptake value) measurements are conducted in a standardised manner.. The guidelines referred to below have been developed for this purpose. They also contain a description of essential calibration measurements that are needed so that individual SUVs can be compared. Section 14 *Addendum* is of particular relevance to these hospitals as it describes the various doses, reconstruction protocols, VOI measurements and quality assurance procedures that form part of these multi-centre studies.

The content of this document can also be used as a recommendation for hospitals that do perform F18-FDG-PET studies but do not take part in multi-centre trials.

1. Principle

FDG is a glucose analogue. Its use in oncology is based on the fact that most types of tumours need more glucose than most other types of normal tissue (see *Interpretation and pitfalls*). F18-FDG is absorbed into the cell via glucose transporters in the cell membrane (Glut) and, in contrast to glucose, most of it is then trapped in the cell after phosphorylation by hexokinase. The kinetics of F18-FDG are such that static imaging produces adequate images approximately 60 minutes after administration. Not all tumours are F18-FDG avid: for example, many broncho-alveolar carcinomas have no Glut transporter upregulation. Furthermore, not all patients with a particular type of tumour will have an F18-FDG-positive tumour: this applies to e.g. renal cell cancer, thyroid cancer and carcinoid cancer. The reason for this variability is not entirely clear.

2. Indications

PET is an 'evolving' field at both a national and international level, with sometimes striking differences between individual countries. The summary below is therefore subjective in nature and based on a combination of experience and literature (1-13).

a. primary presentation
- diagnosis: unknown primary malignancy, solitary pulmonary nodule (in the case of a discrepancy between the clinical and radiological estimates of the likelihood of cancer (2));
- staging on presentation: non-small-cell lung cancer (3), T3 oesophageal cancer (4), Hodgkin's disease (generally when it is unclear whether the disease has extended beyond the neck/armpits/mediastinum), locally advanced cervical cancer and perhaps also locally advanced breast cancer / ENT tumours with risk factors.

b. response evaluation: malignant lymphoma, GIST, at present other applications only in a research setting. Oesophageal cancer, lung cancer and breast cancer appear promising.

c. restaging in the event of (suspected) relapse (for tumours that are likely to accumulate F18-FDG)

- elevated serum markers (e.g. colorectal, thyroid, ovarian, cervix, melanoma, breast and germ-cell tumours)
- where local treatment has been carried out to treat a limited relapse that may be associated with high morbidity (e.g. liver/lung metastases, local relapse).

3. Data that should accompany the request for a PET study

a. Indication, reason for request of PET study (see 2. *Indications*)
b. Height and weight (these must be determined precisely in the case of SUV measurements, see below)
c. (If known) tumour type, tumour sites that have already been noted
d. (Oncological) prior history
e. Diabetes mellitus (medication)
f. Results of other imaging tests (especially CT/MRI).

4. Radiopharmaceutical

Product	:	F-18-fluorodeoxyglucose (F18-FDG)
Nuclide	:	Fluoro-18
Dosage	:	Dependent on the scanner used and the patient's weight. (See 7. *Performance*).
Administration	:	Intravenous

5. Preparing the patient

Patients are not allowed to consume any food or sugar for at least four hours prior to the start of the PET study. In practice, this means that patients scheduled to undergo the PET study in the morning should not eat after midnight and those scheduled for an afternoon PET study may have a light breakfast before 8.00 a.m. Medication can be taken as normal. Adequate pre-hydration (for example, one litre (!) of water in the two hours prior to injection; where necessary, take the volume of water in oral contrast medium for a diagnostic CT scan into account) is important to ensure a sufficiently low urine F18-FDG concentration (less chance of artefacts) and for radiation safety reasons. The infusion used to administer intravenous pre-hydration must not contain any glucose. Patients must avoid extreme exertion before the PET study (for example, they must not cycle to the hospital). The following rules apply to patients with diabetes mellitus:

type II diabetes mellitus (controlled by drugs)

- the PET study should preferably be performed in the late morning
- patients must comply with the fasting rules indicated above
- patients may continue to take oral substances to lower their blood sugar.

type I diabetes mellitus and insulin-dependent type II diabetes mellitus

- ideally, an attempt should be made to achieve normal glycaemic values prior to the PET study, in consultation with the patient and his/her attending MD
- the PET study should be scheduled for late morning
- the patient should eat a normal breakfast at 7.00 a.m. and inject the normal amount of insulin. Thereafter the patient should not consume any more food or fluids, apart from the prescribed amount of water.

In the case of patients on continuous insulin infusion, the PET study should if possible be scheduled early in the morning. The insulin pump is kept on the "night setting" until after the PET study. The patient can have breakfast after the PET study.

A bladder catheter is placed only if required, and this should preferably be done before F18-FDG is administered. Administration of a diuretic (furosemide) can be considered in the case of small pelvic tumours, but this should not be routine practice.

There is no reason for routine administration of sedatives (diazepam, temazepam). Sedatives can be considered in the case of tumours in the head and neck region to reduce muscle uptake. These should then be given about 60 minutes before administration of F18-FDG. Benzodiazepines are not helpful in avoiding or reducing the so-called brown fat phenomenon.

Blood glucose level must be measured prior to administering F18-FDG.
A Glucometer® or a similar device (capable of performing overall euglycaemia measurements) can be used for this purpose, but a blood glucose test must be performed in the hospital's own laboratory using a calibrated and validated method in the case plasma glucose level is used as correction of SUV measurements.

- if glucose is < 11 mmol/l the FDG PET study can be performed
- if glucose is ≥11 mmol/l the FDG PET study must be rescheduled

N.B.: insulin must not be given to reduce glucose levels (this leads to greater muscle uptake of FDG) unless the interval between administration of insulin and administration of FDG is more than four hours.

The ambient temperature in the administration room / the room in which the patient is left to recover must be comfortable (it may be necessary to provide extra blankets) in order to avoid uptake in brown fat (see 11. *Interpretation and pitfalls*).

6. Essential data/aspects and required materials for the FDG PET study

a. Patient's height and weight (to be measured for SUV).
b. When did the patient last receive chemotherapy, G(m)-CSF and/or other growth factors? The protocol requires the minimum interval between administration of such substances and the PET study to be defined. In the case of patients undergoing regular treatment, the minimum period between the last dose and the PET study should be 10 days if possible.
c. (Ideally) a triple-channel system for administering the tracer and flushing with physiological saline; bedside glucose meter (for checking overall serum glucose especially in patients susceptible to hyperglycaemia (diabetics, patients taking corticosteroids)). N.B.: these bedside methods are not suitable for normalising/correcting SUV.

7. Performing the PET study

a. An indwelling intravenous device (e.g. Venflon) is used to administer the F18-FDG intravenously once the patient's blood glucose has been determined and blood samples for laboratory testing have been taken if necessary. Make sure that if there is a needle on the syringe it is free from FDG.
b. Flush and rinse out the administration syringe with at least 10 cc of normal saline using the three-way valve.
c. The venflon can be removed after intravenous administration (unless CT contrast agent is to be administered subsequently by intravenous injection).
d. The waiting room must be relaxed and warm. Give the patient extra blankets if necessary.
e. Tell patients to lie or sit as calmly as they can, and not to talk unnecessarily. They may go to the toilet while waiting.

f. During the waiting period patients will be asked to drink another half a litre of water, or this amount can be given in the form of physiological saline administered by infusion or catheter.
g. Ask the patient to urinate a few minutes before the start of the PET study.
h. The interval between FDG administration and the start of acquisition is 60 minutes. When repeating a scan on the same patient, try to apply the same interval (tolerance ±5 minutes).
i. A 'whole-body' uptake normally covers the part of the body from the mid-femora to the external auditory meatus (in that direction, as bladder activity increases during the scan). A longer scanning trajectory may be used if appropriate.
j. Scan acquisition depends on various factors, including the scanner type (PET, PET-CT) and the acquisition mode (2D, 3D). For CT settings in the case of PET-CT, CT whole body or low-dose CT, see 9. *Camera and computer*. Follow the supplier's recommendations (see table 2 for an example). Transmission scanning time for each bed position: depends on whether the scan is a CT scan or a transmission scan with Ge-68/Ga-68 source.
k. In the case of PET-CT, the patient is usually in supine position with the arms raised.
l. In general, PET-CT is carried out using a protocol comprising a scanogram/scout scan/topogram and a low-dose CT for attenuation correction (CT-AC) and anatomical correlation. IV contrast agent must not be administered during the low-dose CT because of its influence on SUV calculation.
m. In the case of dual-slice CT, artefacts are created in the diaphragm area when the patient breathes. The patient must therefore hold his/her breath for a few seconds on the technician's instructions during CT-AC acquisitions. No such instructions need be given in the case of PET-CT scanners with more than two slices. The CT-AC scan can then be carried out while the patient continues to breathe shallowly.
n. There is as yet no generally accepted oral contrast method for PET-CT scans. In the case of SUV measurements of intra-abdominal lesions it should be borne in mind that (oral) contrast agents affect the SUV outcome (10-12): intestinal preparation (with diluted 'positive' oral intestinal contrast agent) can produce quantitative inaccuracy of up to 20% (10, 11), and is therefore not recommended at present. Artefacts that can impair visual assessment have also been described (12). There is as yet insufficient experience with the use of negative oral contrast agents (13). These substances are therefore not (yet) the preferred choice.
o. A standard diagnostic CT scan with (i.v.) contrast agent may if appropriate be carried out according to standard radiological methods after the low-dose CT and PET acquisition.
p. F18-FDG dosage assuming a fixed scan duration of 5 min per bed position and a bed overlap of less than 25%:
In the case of 2D scans: ca. 5 MBq/kg body weight (± 10 %).
In the case of 3D scans: ca. 2.5 MBq/kg body weight (± 10 %).
q. In section 8 permitted alterations of the protocol are given.
r. Specifications of transmission scans based on a Ge-68 line source: > 3 minutes per bed position. Practitioners are advised to use the scanner manufacturer's settings for CT-based attenuation correction.

8. Protocol alterations permitted in the case of multi-centre studies

a. When using scanners with a high count rate capability (LSO, LYSO and GSO-based cameras with or without ToF), the dosage and scan duration for each bed position must be adjusted so that the product of the dose and scan duration +10% (see 8.5) is equal to or greater than the specifications set out below. Therefore, one may decide to apply a higher dosage and reduce the duration of the scan.

b. The figures for scanners with bed overlap of < 25% (Siemens and GE) are:
- Product of MBq/kg x min/bed > 27.5 for 2D scans
- Product of MBq/kg x min/bed > 13.8 for 3D scans

The dosage is then calculated as follows:

- Dose for 2D scans = 27.5 x weight / (min/bed)
- Dose for 3D scans = 13.8 x weight / (min/bed)
- Minimum scan duration = 3 minutes

c. And for scanners with a bed overlap of 50% (Philips):
   - Product of MBq/kg x min/bed > 6.9 (3D only)
   - Dose = 6.9 x weight / (min/bed)
   - Minimum scan duration = 2 minutes

d. The dose may be increased (to save on scanning time) only if the higher dose leads to count rates that are well within the scanner's count rate capacity. Dose elevation must not cause quantification problems. This is a matter for which each centre is individually responsible. They must demonstrate that the dose and scanning times are acceptable by means of phantom tests or published data relating to the scanner in question (where appropriate, on the basis of scanner specifications measured by the participating institution).

e. It must be shown that the use of a higher dose (combined with a shorter scanning time) does not impair image quality as a higher dose usually leads to lower 'noise equivalent count rates' (NECR). This aspect is also covered by the requirement to increase the product of dosage and scanning time by 10%. A higher dose causes a disproportionate increase in the randoms contribution, which in turn leads to a lower NECR and therefore potentially poorer image quality.

f. In the case of BGO scanners, the specified dose as indicated under 7p must not be increased.

g. If the scanning duration for each bed position can be set separately, then the scanning duration per bed position may be further reduced by up to 50% for bed positions outside the thorax and abdomen (i.e. at the level of the head, neck and legs, as attenuation is less). The dose must still be calculated assuming the scanning duration per bed position as used for bed positions at the level of the thorax and the abdomen.

The specifications indicate that heavier patients receive a higher dose. A short scanning duration per bed position should also be offset by a higher dose. Two model calculations are given below to clarify the situation.

Calculation of dose to be administered, example 1:

- 3D scanner with a bed overlap of less than 25% (e.g. Siemens and GE cameras).
- Patient weighing 70 kg
- Scanning duration per bed position: 3 minutes per bed

  The dose to be administered is therefore:

  13.8 (MBq/kg per min/bed) x 70 (kg) / 3 (min/bed) = 13.8 x 70 /3 = 322 MBq.

Calculation of dose to be administered, example 2:

- 3D scanner with 50% bed overlap (e.g. Philips cameras).
- Patient weighing 70 kg
- Scanning duration per bed position: 3 minutes per bed

  The dose to be administered is therefore:

  6.9 (MBq/kg per min/bed) x 70 (kg) / 3 (min/bed) = 6.9 x 70 /3 = 161 MBq.

Table 1 presents the specifications set out in section 7 and the section above. The dose to be administered is given in MBq.

Table 1.

Mode	2D	3D	3D	3D	3D	3D	3D	3D	3D
Time/bed	5	5	4	3	2	5	4	3	2
Bed overlap	< 25%	< 25%	< 25%	< 25%	< 25%	50%	50%	50%	50%
Scanner	HR+,2D Discovery, 2D	HR+,3D Discovery	HR+,3D Biograph	HR+,3D Biograph	HR+,3D Biograph	Gemini GeminiToF	Gemini GeminiToF	Gemini GeminiToF	Gemini GeminiT
Patient weight (kg)		Biograph							
30-39	170	80	120	160	240	40	60	80	120
40-49	220	110	150	200	310	60	70	100	150
50-59	270	130	180	250	370	70	90	120	180
60-69	320	160	220	290	440	80	110	140	220
70-79	370	180	250	340	510	100	120	170	250
80-89	420	210	290	390	580	110	140	190	290
90-99	470	230	320	430	650	130	160	210	320
100-109	520	260	360	480	720	140	180	240	360
110-119	570	280	390	520	790	150	190	260	390
120-129	620	310	430	570	860	170	210	280	430
130-139	670	330	460	620	930	180	230	310	460
140-150	720	360	500	660	1000	200	250	330	500

N.B.: the scanners mentioned are given as examples. The key factors in determining the dose are the mode of acquisition (2D or 3D), the time per bed position (time/bed) and the degree of bed overlap.

9. Camera and computer

Other acquisition parameters

Emission scans must be conducted using the following additional settings:

- online randoms correction based on ‘delayed coincidence time window’ technique
- indication of the correct isotope, the patient's height and weight, and the dose administered
- decay correction must be 'on' (see any reconstruction settings) to allow for working back to the start of the scanning time, T = 0.

A 'dedicated' CT scan for attenuation (the 'CT-AC') must be carried out in accordance with the scanner manufacturer's recommendations (default settings).. The following additional provisions also apply:

- no contrast agent may be used before or during the CT-AC scan as it will cause artefacts in the PET scans. If a diagnostic (i.v.) contrast-enhanced CT is performed to complete the procedure, this must be done after the CT-AC and the PET studies have been finished.
- ensure that the patient is lying within the CT-AC field of view (FOV).

Pitfalls

1. In some PET-CT scanners, the FOV of the CT and CT-AC is smaller than that of the PET. Truncating the CT (and CT-AC) causes reconstruction artefacts and therefore inaccurate quantification of the PET scan.
2. When using Ge-68 transmission sources, they must be replaced on time (i.e.: at least once every eighteen months).
3. The dosage must never exceed the maximum dose as recommended by the supplier. If this is not specified, then the dose applied must not lead to the camera's maximum count rate being exceeded (dead time).

Table 2. Example of CT acquisition settings for a Siemens Biograph (see manufacturer's instructions for each scanner)

	mA	30
	kV	130
	Tube position	AP
	Length (mm)	1024
	Scan direction	Cranial -> Caudal
	Eff. mAs	40 (> 100 kg: 50, > 120 kg: 60)
	kV	130
	Care dose (on/off)	Off
	Rotation time (sec)	0.8
	Slice width (mm)	6.0
	Slice collimation (mm)	5.0
	Feed/Rotation (mm)	15.0
	Scan direction	Caudal -> Cranial
	Delay (s)	3
	Breathing instructions	Hold breath when instructed (only for dual-slice-CT)
	Arms	Raised
	FOV (mm)	500
	Slice width (mm)	6.0
	Recon increment (mm)	3.0
	Image order	Cranial -> Caudal
	Window	400/40 abdomen
	Kernel	B30s medium smooth

Reconstruction parameters (NEDPAS)

Standardisation of reconstruction settings is necessary in order to obtain comparable resolutions and recoveries and make SUVs interchangeable. Reconstructions must incorporate all the corrections needed for quantitative analysis, such as corrections for decay, dead time, attenuation, scatter and normalisation (correction for detector efficiencies). The following indicative settings also apply to different scanner types:

1. Siemens/CTI scanners:
   - (FORE+)2D OSEM with 4 iterations and 12 up to 16 subsets,
   - 5 mm FWHM Gaussian reconstruction filter in all directions
   - model-based scatter correction (default)
   - attenuation correction (CT or transmission source)
   - normalisation correction
   - matrix size of 128x128 up to 256x256
   - zoom =1.0

2. GE scanners:
   - Default reconstruction setting (OSEM with 2 iterations and 30 subsets (2D scans) or FORE + 2D OSEM 5 iterations with 32 subsets (3D scans)
   - 5 mm FWHM Gaussian filter in all directions
   - model-based scatter correction

- attenuation correction (CT or transmission source)
- normalisation correction
- matrix size 128x128 up to 256x256

3. Philips scanners (Gemini, Gemini ToF):

- There are two options:
  (1) Gemini TF: LOR-TF-RAMLA ("Blob-OS-TF") with 'normal' smoothing setting.
  (2) Gemini (non ToF): LOR-RAMLA using default settings (as of mid-2006).
- Further default settings for options 1 and 2 (where these are adjustable):
  - attenuation correction (CT or transmission source)
  - model-based scatter correction
  - normalisation correction
  - matrix size of 144x144

Exceptions/special features

Various new types of cameras are coming onto the market. It is not yet possible to specify rational dosage, acquisition and reconstruction specifications for them. Moreover, default reconstruction settings may change over time. Therefore, institutions may deviate from the recommended/prescribed dosage and acquisition protocol if it can be demonstrated that the alternative protocol provides equivalent data. This must be demonstrated by means of SNR at the level of the image, not in terms of NEC or NECR. The resolution must also match the study protocol specifications. Compliance with these requirements must be demonstrated by means of the tests described under Quality Control and inter-institution cross-calibration in addenda B to D. Calibration and activity recovery coefficients may not deviate from multi-centre standard specifications or the average results for the institutions taking part by more than 5%. These specifications are given in the addendum (chapter 14). In other words any (combination of) acquisition and reconstruction protocol and/or settings, which meet the multi-center QC specifications given in chapter 14, and especially those for the (absolute) recovery coefficients, are allowed

At present, some Philips Allegro scanners do not have a correct/accurate random scatter correction algorithm. Institutions are advised not to use these scanners for the time being if absolute SUV quantification is required (unless the reconstruction software of the scanner has been adjusted). The current scatter correction algorithm of the Philips Allegro has a less significant impact on the quality of visual assessment and applications in longitudinal studies examining tumour response on the basis of SUV ratios. Therefore, participation in multi-centre response monitoring studies is not excluded.

10. Reporting

The reconstructed images are assessed from a computer screen. The presence or absence of abnormal FDG accumulations, especially focal accumulations, in combination with their size and intensity are evaluated. Absence of such accumulations is particularly significant if other tests have revealed findings such as anatomical abnormalities. Where necessary (see 11. *Interpretation and pitfalls*) the report correlates these findings to other diagnostic tests and interprets them in that context (in consultation with a radiologist where necessary) and considers them in relation to the clinical data.

Both uncorrected and attenuation-corrected images need to be assessed in order to identify any artefacts caused by contrast agents, metal implants and/or patient motion.

Criteria for visual analysis must be defined for each study protocol.

Standard uptake values are used in multi-centre studies in addition to visual assessments. SUV is a measurement of the uptake in a tumour normalised on the basis of a distribution volume.
It is calculated as follows:

$$SUV = \frac{Act_{voi}\,(kBq/ml)}{Act_{administered}\,(MBq)/BW(kg)}$$

The following calculation is applied in the case of plasma glucose correction

$$SUV = \frac{Act_{voi}\,(kBq/ml)}{Act_{administered}\,(MBq)/BW(kg)} \times \frac{5.0}{Gluc_{plasma}}$$

In these calculations, Act_{voi} is the activity measured in the volume of interest (see 14.*Addendum A*), $Act_{administered}$ is the administered activity corrected for the physical decay of F18-FDG to the start of acquisition, and BW is body weight. Any alternative SUV normalisation processes (LBM, BSA) can easily be added afterwards if the patient's height, weight and gender are known (1). N.B.: the measured glucose content ($Gluc_{plasma}$) is normalised for an overall population average of 5.0 so that the SUVs with and without correction of glucose content are numerically practically identical (on average).

11. Interpretation and pitfalls

An FDG-PET scan of a fasting patient will show physiological FDG uptake mainly in the brain, urinary tract and to varying degrees in the myocardium and the colon. A high level of uptake in all skeletal muscles suggests that the patient was not fasting (obviously, this cannot be deduced from a normal serum glucose level). Detection limits naturally depend on the degree of contrast between the tumour and its immediate surroundings. It has been clearly shown that the sensitivity of FDG-PET is much lower in diabetic patients (5), though only for pancreatic cancer. There is no single detection limit for FDG-PET as it depends on many factors. The most significant of these are: histology (FDG avidity of the type of tumour), the volume of vital tumour cells, movement during acquisition (e.g. blurred signals in the case of pulmonary foci), and physiological uptake in the adjacent background. Though it is impossible to describe universal rules for detection limits, it has been demonstrated that even in the case of tumours that take up FDG in large amounts, such

as melanoma, the sensitivity of FDG-PET declines very rapidly when the diameter of the tumour is less than 6 mm (6). Aspecific, non-physiological uptake is based on inflammatory processes or uptake in brown fat (neck, upper mediastinum, paravertebral region) (7). In patients who have undergone surgery, uptake therefore depends on the extent of surgery and how far the wound has healed: for example, there are few visible signs of a mediastinoscopy after ten days but a sternotomoy will remain visible for months. The pattern for bone fractures is more or less the same as has been established for skeletal scintigraphy.

Though there are no conclusive data on the optimum interval between chemotherapy and PET, an interval of at least two weeks is generally considered between the last treatment and PET. This is because of any possible effects on tumour metabolism (such as macrophage impairment) and systemic effects (such as bone marrow activation following bone marrow depression, which may or may not be caused by growth factors). The effects of growth factors (Gm-CSF) or FDG biodistribution (bone marrow!) do not last for more than two weeks after the final administration. It is assumed that the effects of radiotherapy are somewhat longer-lasting; investigation of cases of laryngeal carcinoma treated by radiation has shown that it is best to wait for about four months after the end of treatment before conducting FDG-PET. This timing fits well into this clinical context as these patients rarely develop clinical problems in the first four months after treatment.

FDG-PET is generally assessed using visual criteria (in the context of oncology, looking for a focally increased uptake that may be compatible with malignancy in the clinical context (8)). It is unclear how far semi-quantitative measurements such as SUV can contribute to the assessment, partly because of the considerable variability in the methodology used (1, 9).This Recommendation is an attempt to increase uniformity of FDG PET investigations in multi-centre studies. It is therefore also essential that the equipment used is comparable. This can be achieved by means of calibration and cross-calibration, as described in 14. *Addenda B and C*.

12. Relationship with other diagnostic methods

Deviations on a PET scan must be correlated with the CT scan (MRI where appropriate). These kinds of test will in many cases already be available (and of course this is always the case with PET-CT scans). The aim of this correlation is to find an anatomical substrate (especially of the clinically significant PET findings), mainly in order to minimise false-positive results. In a direct sense this is the case where the CT scan provides a clear benign explanation for the FDG-positive focus. But if the corresponding deviation is suspect on the CT, the referring physician can be given clear information as to the biopsy site. If no substrate can be found on an adequate CT or MRI (technically adequate, suitable for the area being assessed and carried out not too long ago), then that deviation may be regarded as a false-positive. This ensures that patients presenting at the primary stage are never unjustly deprived of treatment with a curative aim.

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14 Addendum

A. Volume of interest (VOI)

Definition:

The following 3D-volumes (volumes of interest, VOI) may be determined:

1. 3D isocontour at 41% of the maximum pixel value with background correction (VOI_{41BG})
2. 3D isocontour at 50% of the maximum pixel value (VOI_{50})
3. 3D isocontour at 50% with background correction (VOI_{50BG})
4. 3D isocontour at 70% of the maximum pixel value (VOI_{70})
5. 3D isocontour at 70% with background correction (VOI_{70BG})
   and
6. Maximum pixel value (Max)

- The isocontour described in point 1 (VOI_{41BG}) generally corresponds best with the actual dimensions of the tumour (1), but only for higher tumour-to-background values and homogenous backgrounds. In practice, however, this VOI seldom results in useful tumour definition because of noise, inhomogenities in tumour and background, and sometimes low tumour-to-background ratios (low contrast between tumour and background). In this case, the VOI based on a higher isocontour value should be chosen. N.B. Other tumour segmentation methods have been described for tumour volumetry in literature. These, however, are not (yet) routinely used for determining SUVs and have to be further evaluated.
- The VOIs described in (1) to (6) form a series of increasing isocontour values, which result in smaller VOIs. In longitudinal studies (response monitoring), the VOI should be chosen that results in useful tumour definitions in all PET scans. This is based on the fact that largest VOI are most precise and thus most suitable (most reproducible) for measuring response [2-4, 6]. A reasonable alternative in multi-centre trials is therefore to always opt for a 70% isocontour VOI and/or the maximum pixel value.

Procedure:

VOIs can be created semi-automatically using the "NEDPAS" software (VUmc, available on request, r.boellaard@vumc.nl). The program has I/O for ECAT7 format files and DICOM provided this complies with Siemens/GE/Philips conformance statements. Other formats and/or DICOM dialects are not accepted and/or cannot be read. The program generates a report which gives the SUV for all VOIs. If it is not possible to create a useful/realistic VOI using the automatic method due to the presence of high background near to the lesion, the region of interest should be drawn manually (3D, using standard scanner software) with reporting of the maximum SUV value only. Local (institution's own) software may be used of course, provided it is compatible with the VOI method required for multi-centre study. Always check automatically generated VOIs visually. SUVs are calculated with and without correction for plasma glucose.

Pitfalls:

VOIs are generated semi-automatically, but it is often not possible to generate a reliable VOI if there is a high background or an area of high uptake (bladder, heart) close to/adjacent to the lesion, or if there is low uptake in the lesion. Semi-automatically generated VOIs must therefore be checked visually. If the VOIs are not reliable and/or do not correspond visually with the lesion, only the maximum SUV based on a manually generated VOI should be used for reporting.

B. Quality Control and Inter-institution Cross-Calibration

Introduction

Both physiological and physical factors influence the accuracy and reproducibility of 'standard uptake values' (SUV) in oncological FDG-PET studies. [6]. Variations in PET camera calibration, image reconstruction and data analysis and/or settings can have more than a 50% effect on the measured SUV [2-4]. The use of SUV in multi-centre oncological PET studies therefore requires an inter-institution calibration procedure in order to facilitate the interchangeability of SUVs between institutions. It is also important that all participating institutions use methodology which is as similar as possible. In order to ensure the interchangeability of SUVs, a minimum set of quality control procedures must be carried out, such as:

1. daily quality control
2. calibration/cross-calibration of PET or PET-CT camera with the institution's own or against another dose calibrator which is generally used to determine patient specific FDG doses.
3. inter-institution cross-calibration and determining 'activity recovery coefficients'.

Brief summary of the quality control procedures:

1 Daily quality control (Daily QC)

The aim of daily quality control is to determine whether the PET or PET-CT camera is functioning well; in other words to establish detector failure and/or electronic drift. Most commercial systems are equipped with an automatic or semi-automatic procedure for performing daily quality controls. For some scanners, the daily quality control includes tuning of hardware and/or settings. Thus both the procedure and its name may be different between various scanners. In all cases all daily quality control measures and/or daily setup/tuning measurements should be performed according the manufacturer's specifications. Users should check whether the daily quality control meets the specifications or passed the test correctly.

2 Calibration QC and cross-calibration of PET and/or PET-CT cameras

The aim of calibration and cross-calibration is to determine the correct and direct calibration of a PET or PET-CT camera with the institution's own or against another dose calibrator which is used to determine patient-specific FDG doses (5). If these doses are ordered directly from and supplied by a pharmaceutical company, cross-calibration of the PET camera should be carried out using a calibration sample supplied by that company (i.e. the customer should order an FDG dose of about 70 MBq, see below, as if it concerns a patient dose). Remember that cross-calibration must not be confused with normal calibration. Cross-calibration is a direct, relative calibration between the used (or institution's own) calibrator and the PET camera, and therefore provides information about possible calibration discrepancies between the PET camera and the dose calibrator, which is more essential for correct SUV quantification than the individual calibrations themselves. There may still be differences (of up to 15%) in the cross-calibration between PET camera and dose calibrator due to the fact that individual calibrations of the dose calibrator and the PET camera (usually carried out by the manufacturer) are performed using different calibration sources and procedures, and by different companies and/or persons. This explains the importance of a direct cross-calibration between the dose calibrator used and the PET camera used.

In short, the procedure is as follows: A syringe is filled with approximately 70 ± 10 MBq of F18-FDG solution and is re-measured in a calibrated dose calibrator (or the syringe is ordered from the pharmaceutical company). The F18-FDG is then introduced into a calibration phantom filled with an exact volume (< 1 %) of water, which results in a solution containing

an exactly known activity concentration (Bq/cc). Homogenisation of the F18-FDG in the phantom should be achieved by leaving an air bubble of approximately 10-20 ml within the phantom and subsequently shaking/mixing the phantom for a short period of time (10 minutes or more). If the institution has a calibrated well counter, three samples of approximately 0.5 ml should be taken from the calibration phantom solution using a pipette. The exact weight/volume of the samples should be determined before placing the samples in the well counter. Emission scans of the calibration phantom are performed with the PET or PET-CT camera using the recommended whole body acquisition protocol/procedure (including multibed acquisitions, see appendix). Once the activity has decayed (after an interval of 10 hours or more), a transmission scan is performed without moving the phantom from its position in the scanner. For PET-CT cameras on which attenuation correction is performed using a low dose CT-scan (CT-AC), the CT-AC scan can be carried out either directly before or after the emission scan.

Emission scans are reconstructed in accordance with the recommended reconstruction parameters as described in paragraph 9, *Camera and computer*. VOI analysis is performed in order to determine the average volumetric concentration of activity within the phantom as measured by the PET camera. Cross-calibration factors between the PET or PET-CT camera and dose calibrator and well counters can then be derived directly. Once the cross-calibration procedure has been completed, conversion factors will be known with which the counts/measurements for different equipment can be synchronised. N.B.: The cross-calibration factor between the PET camera and dose calibrator should be equal to 1.0 (< 5%). A 'standard operating procedure' (SOP) is described in 14. *Addendum C*. Software and/or processing programs, provided by the Vumc, may be used (on request available, r.boellaard@vumc.nl).

3 Image quality and recovery coefficients (IQRC)

Although a correct cross-calibration is guaranteed using the quality control procedure described above, differences in SUV quantification may still occur in multi-centre trials as a result of differences in the reconstruction and data analysis methodology used by participating institutions. In particular, differences in the final image reconstruction (i.e. following reconstruction, including all effects due to filters and pixel size settings etc.) have, depending on the shape of the tumour, a significant effect on the SUV result for smaller (< 5 cm diameter) tumours. It is therefore important to determine the accuracy of the SUV using a standardised 'anthropomorphic' phantom containing spheres (tumours) of varying sizes. Phantoms such as these enable us to verify SUV quantification under clinically relevant conditions. The aim of the IQRC quality control procedure is:

1. to determine/check the correctness of a calibration and quantification using a non-standard (calibration) phantom
2. to measure 'activity concentration recovery coefficients' as a function of sphere (tumour) size.

The IQRC quality control procedure is carried out in accordance with the 'image quality, accuracy of attenuation and scatter corrections' procedure described in the NEMA Standards Publication NU 2-2001, "Performance measurements of positron emission tomographs". VOIs are defined manually according to this procedure. However, it is known that automatic definition of 3D volumes of interest (VOI) based on isocontours using fixed percentages results in a higher SUV accuracy and precision than those determined using manually defined ROIs or VOIs (2,3,6). Therefore, 3D-VOIs are also determined using an automatic VOI method such as described in paragraph 14, *Addendum A*:

(1) 3D isocontour at 41% with background correction (VOI_{41BG})
(2) 3D isocontour at 50% of the maximum pixel value (VOI_{50})
(3) 3D isocontour at 50% with background correction (VOI_{50BG})
(4) 3D isocontour at 70% of the maximum pixel value (VOI_{70})
(5) D isocontour at 70% with background correction (VOI_{70BG}), and
(6) Maximum pixel value (Max)

The procedure for making this VOI is as follows: Firstly, the location of the pixel with the maximum SUV in the tumour must be determined (manually or semi-automatically). Secondly, a 3D-VOI is generated automatically based on the maximum SUV/pixel value and its location with a 3D 'region growing' algorithm in which all pixels/voxels above the defined threshold limit are included (mentioned in points 1-6). In order to implement/apply this procedure, the VUmc will provide software with which this VOI can be automatically generated, and this phantom test can be analysed. (Software is freely available on request through r.boellaard@vumc.nl). Once a VOI has been generated for each sphere, the average concentration of activity (or SUV) for the sphere can also be determined. The average VOI activity concentration value measured is then normalised with the actual concentration of activity in the spheres, which indicates the 'activity concentration recovery coefficient' per sphere (i.e., the ratio of the measured and actual concentration of activity as a function of sphere size). The 'recovery coefficient' is finally defined as a function of sphere size and VOI definition. A standard operating procedure is presented in 14. *Addendum D*.

The measured activity concentration recovery coefficients must meet certain specifications which are given below. These specifications are based on recovery coefficients measured according this procotol on various PET and PET/CT scanners (Siemens, Philips, GE).

NEDPAS specifications for activity concentration recovery coefficients (RC) measured according the Image Quality QC procedure (addendum 14A,D). Specifications are given for recovery coefficients obtained using VOI_{50BG} and the maximum pixel value only.

RC specification for VOI_{50BG}

Sphere volume (ml)	Expected RC	Maximal RC	Minimal RC
26.52	0.77	0.83	0.71
11.49	0.73	0.79	0.67
5.57	0.66	0.73	0.59
2.57	0.60	0.68	0.53
1.15	0.45	0.52	0.38
0.52	0.30	0.35	0.25

RC specifications for maximum pixel value

Sphere volume (ml)	Expected RC	Maximal RC	Minimal RC
26.52	0.98	1.08	0.88
11.49	0.95	1.05	0.85
5.57	0.89	1.01	0.77
2.57	0.84	0.94	0.75
1.15	0.63	0.74	0.51
0.52	0.38	0.46	0.29

Minimum frequency of quality control procedures:

Procedure:	**Frequency:**
Daily QC	Daily
Cross-calibration	At least 1x per 3 months and always immediately following software and hardware revisions/upgrades and immediately following new setups/normalisations.
IQRC	Once per institution participating in a multi-centre trial and always following reconstruction/scanner software adjustments (especially adjustments to the reconstruction and/or data analysis (region of interest) software/hardware).

All relevant data, including reconstructed images and fully completed SOPs, should be made available to the central data reviewing centre. Data must be delivered in ECAT7 or DICOM format. DICOM files must comply with the scanner manufacturer's 'conformance statement' on DICOM specifications. Each institution is responsible for ensuring these specifications are met.

References:

1. Dalen JA van, Hoffmann AL, Dicken V, et al. A novel iterative method for lesion delineation and volumetric quantification with FDG PET. Nucl Med Commun. 2007; 28:485-93.
2. Boellaard R., Krak N. C., Hoekstra O. S., and Lammertsma A. A. Effects of noise, image resolution, and VOI definition on the accuracy of standard uptake values: a simulation study. *J Nucl Med* 2004; 45:, 1519-1527.
3. Krak N. C., Boellaard R., Hoekstra O. S., et al. A. Effects of VOI definition and reconstruction method on quantitative outcome and applicability in a response monitoring trial. *Eur J Nucl Med Mol Imaging 2005;32: 294- 301*.
4. Krak N. C., Hoekstra O. S., and Lammertsma A. A. Measuring response to chemotherapy in locally advanced breast cancer: methodological considerations. *Eur J Nucl Med Mol Imaging* 2004; 31: Suppl 1, S103-S111.
5. Greuter H. N., Boellaard R., van Lingen A., Franssen E. J., and Lammertsma A. A. Measurement of 18F-FDG concentrations in blood samples: comparison of direct calibration and standard solution methods. *J Nucl Med Technol* 2003; 31**:** 206-209.
6. Thie J. A. Understanding the standardized uptake value, its methods, and implications for usage. *J Nucl Med* 2004; 45: 1431-1434.

C. Calibration QC of PET and information required for CRF and Standard Operating Procedure for multi-centre studies

1. Requirements

- Approximately 70 MBq F18-FDG
- Calibration phantom (cylindrical) with exact known volume
- Date
- Location/hospital
- Performed by
- Scanner (manufacturer/type)
- Volume of calibration phantom (ml)

2. Preparation

- Draw up approximately 70 MBq of 18F and fill up to 4.5-5.5 cc with water, then measure the activity using the dose calibrator. N.B.: The activity required depends on the time that PET scanner measurements are to start. The dose must therefore be adjusted if necessary so that the phantom contains approximately 50-70 MBq at the time of the calibration measurement. Alternatively, this syringe can be ordered according specifications of this SOP from a pharmaceutical company.
- Activity in syringe = ... MBq at (time) ..... hrs.
- A dose calibration measurement label may be attached below (if available).

- Remove approximately 10 ml water from the calibration phantom (which has been completely filled with water) and then introduce the F18-FDG from the syringe. Flush the syringe thoroughly. An air bubble of approximately 5 cc will therefore be left in the phantom for homogenisation purposes!
- Shake the calibration phantom well.

3. Well counter (optional; only if specified in study)

If the department has a well counter that is calibrated for F18-FDG:

- Take 3x 0.5 ml samples from the phantom using a pipette. Before taking the sample, place the counting tube on the scales and set these to 0. Then take 0.5 ml of the phantom solution using a pipette and weigh the counting tube containing the 0.5 ml sample.

- Record the net weight of the samples in the space below:

  Sample 1: ..... gr

  Sample 2: ..... gr

  Sample 3: ..... gr

- Count the activity in the samples using the well counter(s) (30 or 60 seconds counting time is sufficient). Record the number of CPM (corrected for dead time) measured by the channel calibrated for F18. Make a note of the start time for counting.

  CPM sample 1: ..... cpm

  CPM sample 2: ..... cpm

  CPM sample 3: ..... cpm

  Start time for counting (hh:mm:ss)=

4. PET scans

- Place the phantom in the scanner. Perform an emission scan using the acquisition parameters described in paragraphs 7, 8 and 9 (note that the emission scan will now take a minimum of 10 min for PET/CT scanners and 30 min for PET only scanners) A transmission scan of at least 10 minutes will be made after a 10-hour interval, or a CT-AC using standard settings can be performed immediately before or after emission scanning. Emission scans should be performed in both 2D and 3D (if this is possible).
- Record start times for scans, please read from console and later check in file header (if possible):

  Acquisition time of 2D scan =

  Acquisition time of 3D scan =

5. Reconstructions

'Quantitative' reconstruction parameters must be used as specified in paragraph 9; this applies for all scanners.

6. Archiving for multi-centre studies and analysis

According to the relevant study protocol. Please note: The reconstructed images must be supplied in DICOM format. DICOM files must comply with the relevant scanner manufacturer's 'DICOM conformance statement'.

7. Pitfalls

- Ensure that clocks are synchronised in all working areas (in other words, scanner area, on the PET or PET/CT camera itself, on the PET or PET/CT camera computers, in the hot lab or analysis lab and on/nearby/around the dose calibrator being used and/or on the dose calibrator's computer). Non-synchronised clocks and incorrectly reported times will result directly in calibration errors! A 15-minute mismatch, for example, results in an avoidable calibration error of 10%.
- Not flushing the syringe adequately when introducing the activity into the phantom means that not all the activity in the syringe is transferred to the phantom and will result in incorrect interpretation of the results.
- Check whether the activity in the syringe has been measured with or without a clean needle. Particularly where small volumes are concerned, a large proportion of the activity can be present in the needle during the dose measurement. If the needle is subsequently exchanged for a 'clean' needle, the dose measurement will no longer

correspond with the actual net activity in the syringe.

Some types of scanners require the correct phantom weight (= net volume), the dose and the time to be filled in when the scan protocols are applied. If this information is omitted, the reconstruction software will not implement correction factors for quantification. Unfortunately, this may also apply to human studies!. Be aware that dose is specified at dose calibration time, which is in practice not necessarily equal to injection time or start of the PET/CT study. Apply necessary corrections for decay, if needed or use dose calibration time.

D CRF/SOP Image Quality and Activity Concentration Recovery Coefficient PET (for multi-center studies)

1. Requirements

- F18 activity (volume not important) in 2 ml syringes
- 1x 10 MBq, 1x 20 MBq (record the volume and clearly record the time of calibration)
- 1 measuring cup of exactly 500 ml
- Felt-tip pen
- NEMA NU2-2001 (section 7) Image Quality phantom with exact dimensions/volumes.

2. Preparation

Stock solution for the spheres:

- Fill the measuring cup with exactly 500 ml
- Add the 10 MBq F18-FDG, record the exact dose below, plus the time of calibration and volume in the syringe:
  Activity = ... MBq at ..... (hh:mm:ss)
  Volume (of solution of activity in syringe) = ... (ml)
- Stick the dose calibration measurement label (if available) in the space below

- Homogenise the solution thus made
- Fill <u>all</u> the spheres from the NEMA NU2-2002 image quality phantom with stock solution. Note that this deviates from NEMA NU 2-2001 (section 7) procedures!

Filling the Image Quality Phantom

- Introduce the spheres into the NEMA NU 2-2001 phantom (if not fixed within the phantom)
- Fill the background compartment of the phantom completely with water
- Remove 20-30 cc water from the phantom
- Empty the syringe containing the 20 MBq into the background (flush well so that all the activity is introduced into the phantom)
- Homogenise the phantom

3. Scans

- Make standard quantitative whole body scans (2 bed positions) of the phantom according to the specifications in paragraphs 7 to 9; emission scans of at least 10 mins/bed position, however, are required for this test.
- Record the scan times: ..... mins emission (3 mins transmission, if no CT-AC).
- Record T = 0 (start time of the scans)

4. Reconstructions

In accordance with specifications given in paragraph 9.

5. Analysis

The following data can be determined using the "Image Quality QA" program:

- The average concentration of background activity in the reconstructed PET images using several VOIs. The accuracy of the PET scanner cross-calibration for the image quality phantom can be derived from this.
- The average pixel size in the 'scatter' insert, to check the scatter correction.
- The average concentration of activity in the spheres based on isocontours (described in the protocol) and the resulting activity recovery coefficients as a function of sphere size.
- The accuracy of the calibration and activity recovery coefficients as a function of sphere size are used for reporting and should meet the specification given previously.
- Explanatory note: Dose calibrations are performed at the study centre itself or at the FDG supplier's site. N.B.: Supplies of FDG may have smaller volumes.

6. Archiving/multi-centre analysis

In accordance with study protocol. Please note:

- Relevant data (completed CRF and reconstructed images) must be made available to the central data analysis centre for multi-centre quantification monitoring.
- The reconstructed images must be supplied in ECAT7 or DICOM format.
- DICOM files must comply with the relevant scanner manufacturer's 'DICOM conformance statement'. Each institution is responsible for ensuring this requirement is met.

Non-conformance to the specified data format makes quantification of the study impossible, resulting in the institution being excluded from any further participation in the study. In mutual consultation, it may be possible to find an alternative solution.

7. Pitfalls

- Ensure that clocks are synchronised in all working areas (in other words, scanner area, on the PET camera itself, on the PET camera computers, in the hot lab or analysis lab and on/nearby/around the dose calibrator being used and/or on the dose calibrator's computer). Non-synchronised clocks and incorrectly reported times result directly in calibration errors!
- Not flushing the syringe adequately when introducing the activity into the phantom means that not all the activity in the syringe is transferred to the phantom and will result in incorrect interpretation of the results.

- Check whether the activity in the syringe has been measured with or without a clean needle. Particularly where small volumes are concerned, a large proportion of the activity can be left behind in the needle during the dose measurement. If the needle is subsequently exchanged for a 'clean' needle, the dose measurement will no longer correspond with the actual net activity in the syringe.
- Some types of scanners require the correct phantom weight (= volume), the dose and the time to be filled in while the scan protocols are being applied. If this information is omitted, the reconstruction software will not implement correction factors for quantification. Unfortunately, this also applies to human studies!

8. Other recommendations

If the department has a calibrated well counter available (see calibration procedure), this is the tool of preference with which to determine/verify the exact concentration of activity in the spheres and in the background of the phantom.