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FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging

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FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0

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Abstract The aim of this guideline is to provide a minimum standard for the acquisition and interpretation of PET and

PET/CT scans with [18F]-fluorodeoxyglucose (FDG). This guideline will therefore address general information about [18F]-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) and is provided to help the physician and physicist to assist to carrying out, interpret, and document quantitative FDG PET/CT examinations, but will concentrate on the optimisation of diagnostic quality and quantitative information.

This guideline is a joint project of the EANM Oncology Committee and the EANM Physics Committee. In addition, this guideline is based on the following three documents:

(1) DGN (Deutsche Gesellschaft für Nuklearmedizin) Leitlinie: "FDG-PET/CT in der Onkologie" by Krause BJ, Beyer T, Bockisch A, Delbeke D, Kotzerke J, Minkov V, Reiser M, Willich N, Arbeitsausschuss Positronenemissionstomographie der Deutschen Gesellschaft für Nuklearmedizin. 2007.

(2) SNM Guidelines: "Procedure Guidelines for tumour imaging with 18F-FDG PET/CT 1.0." by Delbeke D, Coleman RE, Guiberteau MF, Brown ML, Royal HD, Siegel BA, Townsend DW, Berland LL, Parker JA, Hubner K, Stabin MG, Zubal G, Kachelries M, Cronin V, Holbrook S. 2006.

(3) "Applications of F18-FDG-PET in Oncology and Standardisation for Multi-Centre Studies" by Boellaard R, Oyen WJG, Hoekstra CJ, Hoekstra OS, Visser EP, Willemsen AT, Arends AJ, Verzijlbergen JF, Paans AM, Comans EFI, Lugtenburg E, Stoker J, Schaefer-Prokop C, Zijlstra JM, Pruim J. HOVON Imaging workgroup and the Netherlands Society of Nuclear Medicine. 2007

Keywords Guideline · FDG · PET · PET/CT · Tumour · Oncology · Quantification · QC · QA

Introduction

The aim of this guideline is to provide a minimum standard for the acquisition and interpretation of PET

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and PET/CT scans with [^{18}F]-fluorodeoxyglucose (FDG). PET is a *quantitative* imaging technique and therefore requires a common quality control (QC)/quality assurance (QA) procedure to ensure that optimal images are acquired for our patients and that these images would be acceptable and interpretable by any clinician in another hospital. This is essential for the management of patients who have the right to have their health care provided in any hospital they chose. Common standards will help promote the use of PET/CT imaging and increase the value of publications and their contribution to evidence-based medicine and potentially enable the role of semi-quantitative and quantitative image interpretation since the numeric values should be consistent between platforms and institutes that acquire the data. FDG PET/CT is being used increasingly to evaluate tumour response in addition to diagnosis and staging of tumours. Increasingly, research is being performed in radiotherapy planning and it will be important that areas such as edge detection of tumours have a translatable measurement.

This guideline will therefore address general information about [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) and is provided to help the physician and physicist to assist in carrying out, interpret and document quantitative FDG PET/CT examinations, but will concentrate on the optimisation of diagnostic quality and quantitative information. Note, that in this guideline quantification of FDG PET and PET/CT is defined as quantification using standardised uptake values (SUV), as it represents the most commonly used (semi-)quantitative parameter for analysis of oncology FDG PET studies. However, other (full) quantitative measures, which require more complex data-collection procedures, are being used as well, but they are beyond the scope of the present guideline. In this guideline, areas of information will provide a minimum standard for FDG PET and PET/CT data acquisition, quality control, and quality assurance.

The Procedure Guidelines for Tumour Imaging with FDG PET/CT 1.0 of the Society of Nuclear Medicine

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(SNM)¹ [1], the German Guidelines for FDG-PET/CT in Oncology² [2], the quality control/assurance procedures used in the UK for lymphoma/head and neck cancer studies and the Netherlands protocol for standardisation of quantitative whole-body FDG PET/CT [3] studies have been integrated in the present guideline. An overview of other and previously published guidelines [1, 2, 4–14] or recommendations can be found in the supplement issue of the Journal of Nuclear Medicine 2009 [15].

Principle

Positron emission tomography (PET) is a tomographic technique that computes the three-dimensional distribution of radioactivity based on the annihilation photons that are emitted by positron emitter labelled radiotracers. PET allows non-invasive quantitative assessment of biochemical and functional processes. The most commonly used tracer at present is the glucose analogue FDG. FDG accumulation in tissue is proportional to the amount of glucose utilisation. Increased consumption of glucose is a characteristic of most cancers and is in part related to over-expression of the GLUT-1 glucose transporters and increased hexokinase activity. Given the kinetics of FDG adequate static images are most frequently acquired approximately 60 min after administration. It is recognized, however, that the uptake period is highly variable, FDG concentration not reaching a plateau for up to 4–6 h in some tumours [16]. Moreover, not all cancers are FDG avid. Variable uptake is likely related to biological features of individual cancers, as is observed in bronchoalveolar carcinomas, renal, thyroid cancers, several subtypes of malignant lymphoma, carcinoids but also most prostate carcinomas. The reason and prognostic relevance of this biological heterogeneity is not always clear. However, in the majority of cases, FDG PET is a sensitive imaging modality for the detection, staging, re-staging as well as for assessment of therapy response in oncology [6, 17–25].

In contrast to PET, computed tomography (CT) uses an x-ray beam to generate tomographic images. CT allows the

visualisation of morphological and anatomic structures with a high anatomical resolution. Anatomical and morphological information derived from CT can be used to increase the precision of localisation, extent, and characterisation of lesions detected by FDG PET.

FDG PET and CT are established imaging modalities that have been extensively validated in routine clinical practice. Integrated PET/CT combines PET and CT in a single imaging device and allows morphological and functional imaging to be carried out in a single imaging procedure. Integrated PET/CT has been shown to be more accurate for lesion localisation and characterisation than PET and CT alone or the results obtained from PET and CT separately and interpreted side by side or following software based fusion of the PET and CT datasets. PET/CT gains more and more importance in oncology imaging. At the same time, there is greater awareness that the quantitative features of PET may have a major impact in oncology trials and clinical practice. Therefore this guideline focuses on the use of FDG PET/CT in oncology.

Definitions

- An integrated PET/CT system is a combination of a PET and a CT scanner with a single patient table.
- PET/CT allows a sequential acquisition of corresponding PET and CT portions of the examination without having to move the patient. Both data sets are intrinsically co-registered given that the patient does not move during or in between the acquisitions.
- The PET+CT fusion is the mechanical and data related fusion of PET and CT volume data sets in a combined data set. The software fusion of separate PET and CT data sets is referred to as PET+CT.
- A fused PET+CT data set allows the combined visualisation of the fused PET and CT datasets.
- A PET/CT examination can include the whole body or a portion of the body.
- Total body imaging: from the top of the head through the feet (only in a minority of the cases).
- Whole-body imaging: Base of the skull-base to mid-thigh imaging (covers most of the relevant portions of the body in oncology imaging).
- Limited-area tumour imaging (for the evaluation of tumour-related changes in a limited portion of the body).
- In PET/CT attenuation and scatter correction is carried out using the CT-transmission data.
- Low-dose CT or anatomical CT: CT that is only performed in order to carry out an attenuation correction (CT-AC) or used for anatomical co-localisation of PET-findings (with reduced voltage and current of the x-ray

¹ Sections of this document were adapted and reprinted with permission of the Society of Nuclear Medicine, Procedure Guidelines for Tumour Imaging with 18F-FDG PET/CT: Delbeke D (chair), Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA, Townsend DW, Berland LL, Parker JA, Hubner K, Stabin MJ, Zubal G, Kachelreiss M, Cronin V, Hoolbrook S. J Nucl Med 2006; 47: 885–895

² Sections of this document were translated and reprinted with permission of the DGN (Deutsche Gesellschaft für Nuklearmedizin): Krause BJ, Beyer T, Bockisch A, Delbeke D, Kotzerke J, Minkov V, Reiser M, Willich N und der Arbeitsausschuss Positronen-Emissions-Tomographie der Deutschen Gessellschaft für Nuklearmedizin. FDG-PET/CT in oncology. German Guideline. Nuklearmedizin 2007; 46: 291–301

beam), i.e. a low-dose CT is NOT intended for radiological diagnosis.

- If clinically indicated, a proper ‘diagnostic’ CT scan with intravenous and/or oral contrast media and deep inspiration breath hold can typically be combined with the PET/low-dose CT acquisition.

Indications

PET is a rapidly ‘evolving’ field at both the 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 expert experience and scientific literature [6, 17, 18, 20–26]. An excellent overview is given in [6], but these indications are constantly changing and require updating with time.

- *Primary presentation:* diagnosis: unknown primary malignancy, differentiation of benign and malignant lesions of e.g. a solitary lung nodule, especially in case of discrepant clinical and radiological estimates of the likelihood of cancer);
- *Staging on presentation:* non-small-cell lung cancer, T3 oesophageal cancer, Hodgkin’s disease, non-Hodgkin’s lymphoma, locally advanced cervical cancer, ENT tumours with risk factors and locally advanced breast cancer.
- *Response evaluation:* malignant lymphoma, GIST, at present other applications only in a research setting. Application for oesophageal, colorectal, lung and breast cancer appear promising.
- *Restaging* in the event of potentially curable relapse (for FDG avid tumours)
- *Establishing and localizing disease sites as a cause for elevated serum markers* (e.g. colorectal, thyroid, ovarian, cervix, melanoma, breast and germ–cell tumours)
- *Image guided biopsy (e.g. brain tumours) and radiotherapy planning*

Data that should accompany the request for a PET/CT study

- Indication, reason for request of PET or PET/CT study (see **Indications**)
- Height and body weight (these must be determined precisely in the case of SUV measurements, see below). With serial studies in the same patient, weight must be measured directly prior to *each* PET study because body weight often changes during course of disease.

- (If known) tumour type, tumour sites that have already been noted
- Oncology prior history, relevant co-morbidity (especially inflammation)
- Diabetes mellitus (including medication)
- Results of other imaging tests (especially CT, MRI).
- In case of therapy evaluation: type and date of last therapeutic intervention
- Allergy for contrast agents
- Renal function

Radiopharmaceutical

Product	: [¹⁸ F]-fluorodeoxyglucose (FDG)
Nuclide	: Fluorine-18
Dosage	: Dependent on the system and the patient’s weight. (See Performing the PET/CT study).
Administration	: Intravenous
Synthesis and Quality Control	: Conform the European Pharmacopeia

Patient preparation

The main purpose of the patient preparation is the reduction of tracer uptake in normal tissue (kidneys, bladder, skeletal muscle, myocardium, brown fat) while maintaining and optimizing tracer uptake in the target structures (tumour tissue). In the following, a generally applicable protocol is outlined:

- Patients are not allowed to consume any food or sugar for at least 6 h prior to the start of the PET study (i.e. with respect to time of injection of FDG). In practice, this means that patients scheduled to undergo the PET study in the morning should not eat after midnight and preferably have a light meal (no alcohol) during the evening prior to the PET study. Those scheduled for an afternoon PET study may have a light breakfast before 8.00 a.m. (i.e. up to two sandwiches, no sugars or sugar containing sandwich filling). Medication can be taken as prescribed.
- Adequate pre-hydration is important to ensure a sufficiently low FDG concentration of FDG in urine (less artefacts) and for radiation safety reasons (for example, 1 l of water in the 2 h prior to injection; where necessary, account for volume of water in oral contrast medium for a diagnostic CT scan).

- Parental nutrition and intravenous fluids containing glucose should be discontinued at least 4 h before the PET/CT examination. In addition, the infusion used to administer intravenous pre-hydration must not contain any glucose.
- During the injection of FDG and the subsequent uptake phase the patient should remain seated or recumbent and silent to minimise FDG uptake in muscles. For a brain examination with FDG, injection should take place in a darkened and quiet room and the patient should stay there for the subsequent uptake phase to avoid areas of enhanced uptake due to brain activation. The patient should be kept warm starting at 30–60 min before the injection of FDG and throughout the following uptake period and PET examination to minimise FDG accumulation in the brown fat (especially relevant if the room is air conditioned). Moreover, all patients must avoid (extreme) exercise for at least 6 h before the PET study (for example, they must not cycle to the hospital).
- In case of pregnancy: see the Society of Nuclear Medicine Procedure Guidelines for General Imaging Version 3 or national guidelines.

The following recommendations apply to patients with diabetes mellitus:

type II diabetes mellitus (controlled by oral medication)

- the PET study should preferably be performed in the late morning
- patients must comply with the fasting rules indicated above
- patients continue to take oral medication to control 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 medical doctor
- 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.

It is good practice to check the blood glucose level of the patient on arrival at the imaging centre to ensure the patients' sugar is not too low or high, since this may obviate an unnecessary wait.

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.

Extra notes

- A transurethral catheter is placed only if required (expected urinary activity prohibiting appropriate image interpretation), and this should preferably be done before FDG is administered. Administration of a diuretic (furosemide) can be considered in the case of small pelvic tumours, but it is not necessary to use this routinely. Clinical experience suggests that proper prehydration avoids most potential reading errors and that delayed imaging or furosemide intervention is very rarely necessary
- There is no reason for routine administration of sedatives (e.g. short-acting benzodiazepines). Sedatives can be considered in the case of tumours in the head and neck region to reduce muscle uptake or in anxious claustrophobic patients. In the case of children, sedation may be required depending on the age or the tumour type. A number of agents have been tried and are being tested (e.g. beta-blockers) to reduce brown fat uptake. If an agent is to be used as part of a clinical trial it needs to be effective and must not affect tumour uptake of the radiopharmaceutical. Patients should be instructed not to drive a car after sedation.
- Blood glucose level must be measured prior to administering FDG. A Glucometer or a similar bedside device (capable of performing overall euglycaemia measurements) can be used for this purpose, but a blood glucose test *must* be performed with a calibrated and validated method if plasma glucose level is used as correction of SUV measurements [27]:
 - If plasma glucose level is <7 mmol/l (or <120 mg/dl) the FDG PET study can be performed
 - If plasma glucose level is ≥ 7 mmol/l (or >120 mg/dl) the FDG PET study must be rescheduled or the patient excluded depending on the patient circumstances and the trial being conducted.
 - In case the study cannot be rescheduled or when elevated glucose levels cannot be ruled out, blood glucose levels must always be measured using a calibrated and validated method and SUV must be reported with and without glucose correction. Note that specifically in response-assessment studies blood glucose levels may change with the therapy and it is strongly recommended to measure blood glucose levels using validated and calibrated methods (no bedside devices) during all sequential PET examinations.
 - Reduction of the blood glucose level by administration of insulin can be considered, but the PET/CT examination should also be postponed depending on the type and route of the administration of insulin. 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 4 h.

- When diagnostic contrast-enhanced CT with intravenous contrast media is to be performed (after the PET/CT examination), indications, contraindications and restrictions have to be assessed by a qualified physician/radiologist. Medication that interacts with intravenous contrast (e.g. metformin for the treatment of diabetes) and relevant medical history (e.g. compromised renal function) have to be taken into consideration.
- For CT of the abdomen or pelvis, an intraluminal gastrointestinal contrast agent may be administered to improve the visualisation of the gastrointestinal tract in CT (unless it is not necessary for the clinical indication or it is medically contraindicated). Contrast agents must only be used in accordance with the recommendations given in paragraph **Other acquisition parameters**, CT-protocol.

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

Required materials

- (Ideally) a triple-channel system (=standard system with three-way tap to enable saline flush) for administering the tracer and flushing with physiological saline. However, if automated bedside administration systems are being used then other types of lines may be required to obtain the same flushing and administration results.
- Bedside glucose meter, to check serum glucose, especially in patients susceptible to hyperglycaemia (diabetics, patients taking corticosteroids). Note that many (other) bedside methods do not have sufficient precision to be used for SUV correction [27].
- Weighing scales that are accredited and checked at least annually.

Clinical information required for scan procedure and interpretation

- Before the PET/CT examination the following clinical data should be available: a history focused on the patients disease and localisation of disease, date of diagnosis, type of verification of diagnosis (biopsy results, time of biopsy, histopathological report) and prior therapies (surgery, radiation therapy, chemotherapy, administration of bone marrow stimulants and steroids), current medication and previous imaging results

- Relevant comorbidity: diabetes, concurrent inflammatory disease.
- Prior therapy: nature and timing of last relevant surgery, radiation, chemotherapy, bone marrow stimulants and steroids. In clinical trials, the study protocol should define the interval between administration of such substances and the PET study. For clinical practice several recommendations have been published [7] (see also e.g. JNM Supplement 2009). A minimum interval between the last dose (chemotherapy) and the PET study should be 10 days, if possible, or probably as close to the next treatment administration as possible.
- Date at which results of the PET or PET/CT study must be available.
- Ability of the patient to lie still in the PET or PET/CT system for the duration of the examination (20–45 min)
- History of claustrophobia
- Ability to put his/her arms over the head

Precautions

See Society of Nuclear Medicine Procedure Guidelines for General Imaging Version 3

Radiation exposure

- The radiation dose with PET/CT or PET is the combination of the radiation exposure caused by the radiopharmaceutical and the CT study (or the external transmission sources). Radiation dose of diagnostic CT has been a matter of debate over the last years, particularly for paediatric examinations. It is difficult to state a mean dose for a CT scan because of the variety of applications, protocols, and CT systems. Especially for children but also for adults it is of importance to optimise the radiation exposure with respect to the diagnostic question. In recent years there has been much effort to minimise the radiation dose related to a conventional CT-or PET-examination.
- The radiation dose of FDG is approximately 2×10^{-2} mSv/MBq according to ICRP publication 106 [28], i.e. about 3–4 mSv for an administered activity of 185 MBq. The radiation exposure related to a CT performing a PET/CT examination depends on the intention of the CT carried out and may differ from case to case: the CT can be performed as a low-dose CT (with lower voltage and current) to be used for attenuation correction and localisation of PET lesions. Alternatively (or additionally) a diagnostic CT can be indicated (in most cases with intravenous contrast agent application and deep inspiration in case of a chest CT)

for a full diagnostic CT examination. The effective CT-dose could range from 1–20 mSv and may be even higher for a high resolution diagnostic CT scan. Given the variety of CT systems and protocols the radiation exposure for a PET/CT examination should be estimated specific to the system and protocol being used and an expert from radiology or guidelines provided by the European radiological societies should be consulted regarding effective dose from the CT examination.³

- The choice of the imaging protocol used strongly depends on the clinical question and must be discussed for every single case. In this respect, special attention is required in case of paediatric applications. For the optimisation of PET/CT examinations, dose reduction techniques should be considered.

Performing the PET/CT study

Preparation and execution

- In case of manual administration:
 - An indwelling intravenous device is used to administer the 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.
 - Flush and rinse out the administration syringe with at least 10 ml of normal saline (NaCl 0.9%) using the three-way valve.
- In case of automated administration:
 - Make sure that the automated system and procedures assures a net administered FDG activity within 3% accuracy (this must be ensured by manufacturer and verified by the user), i.e. the actual administered activity may not deviate more than 3% from that indicated by the reading of that device or used dose calibrator. Follow instructions given by the manufacturer.
- The administration system can be removed after intravenous administration (unless CT contrast agent is to be administered subsequently by intravenous injection).
- The ambient conditions in the waiting room must be relaxing and warm. Give the patient extra blankets if necessary.
- Tell the patients to lie or sit as calmly as they can, and not to talk. Provide comfortable beds or chairs. They may go to the toilet while waiting, preferably after the first 30 min p.i. Ask the patient to use the bathroom 5 min before the start of the PET study.
- An intense bladder or ureter activity concentration can impair the interpretation of lesions in the pelvis and retroperitoneum. Hydration and loop diuretics (e.g. furosemide i.v.) may be used to reduce bladder activity and radiation exposure to the bladder. Therefore, 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 intravenously, if such fluid load is not medically contra-indicated. This is of course dependent on the patients other clinical conditions, e.g. impaired renal function or poor cardiac function, where this amount of fluid may be contraindicated.
- The recommended interval between FDG administration and the start of acquisition is 60 min. However, for certain clinical trials this may change depending on the disease and aims of the study. This should then be clearly stated in the study protocol. The actual interval should be recorded, i.e. the time of FDG injection (administration) should be reported. Please be aware that this is usually not equal to the FDG activity assay or calibration time. Note that consistency of SUV measurements (in-house and compared with literature) depends on strict application of the interval schedule and therefore a 60-min interval is recommended. When repeating a scan on the same patient, *especially in the context of therapy response assessment*, it is *essential* to apply the same interval (tolerance ± 5 min). In addition, use of the same PET or PET/CT system and identical acquisition and reconstruction settings must be applied when making multiple scans of the same patient.
- Scan trajectory: for most oncology indications, a whole-body scan is sufficient. 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. Whole-body PET/CT offers the opportunity for whole-body staging/re-staging. For most oncology indications, skull base-to-mid thigh tumour imaging is sufficient. Extended whole-body examinations are performed in tumours that show a high probability of metastases in the head, skull, brain, cranium, and in the lower extremity. Limited-area tumour imaging can be considered for follow-up examinations, if the disease is restricted to a

³ It should be noted that the entity "effective dose" does not necessarily reflect the radiation risk associated with this nuclear medicine examination. The effective dose values given in this guideline are used to compare the exposure due to different medical procedures. If the risk associated with this procedure is to be assessed, it is mandatory to adjust the radiation-associated risk factors at least according to the gender and age distribution of the institution's patient population.

defined region (i.e. solitary pulmonary nodule, suspicion of lung cancer, examination of hilar lymph nodes, head and neck tumours, assessment of therapy response).

- The patient should be positioned with the arm elevated over the head to avoid beam hardening artefacts as well as artefacts caused by truncation of the field of view. For the examination of head and neck tumours, a two-step protocol is recommended (head and neck portion and from the apex of the lung through mid thigh) with the appropriate acquisition and reconstruction parameters adapted for the protocol. Alternatively, the arms can be positioned along the side for head and neck imaging. If the FDG PET/CT data are used for radiation planning, the examination should be carried out in the radiation position using the same dedicated radio-opaque positioning devices as used in the radiotherapy department (e.g. same table tops, laser alignment, immobilisation measures, etc.).
- Scan acquisition depends on various factors, including the system type and acquisition mode (2D, 3D). For CT settings in case of PET/CT, CT whole-body or low-dose CT, see **Other acquisition parameters**, CT-protocol. 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.
- 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, used for attenuation correction purposes, because of its potential influence on SUV calculation.
- In the case of single slice or 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 systems with more than two slices. The CT-AC scan can then be carried out while the patient continues to breath shallowly.
- 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 in case quantification of the PET study will be performed or is required.
- Recommendations for FDG activities are based on 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 ($\pm 10\%$). In the case of 3D scans: ca. 2.5 MBq/kg body weight ($\pm 10\%$). In paragraph *Permitted protocol alterations regarding FDG activity* detailed recommendations and permitted alter-

tions of the administration protocol are given, including those for systems that apply a 50% bed overlap.

- For children (<19 years), FDG activity *must* conform to the EANM recommendations given in the EANM paediatric dosage card [29].
- Specifications of transmission scans based on a Ge-68 line source: >2 min per bed position. In paragraph **Other acquisition parameters**, CT-protocol, recommendations are given for the CT-AC.

Permitted protocol alterations regarding FDG activity

When using systems with a high count rate capability (LSO, LYSO, and GSO-based cameras with or without time of flight), the administered FDG activity and scan duration for each bed position must be adjusted so that the product of the FDG activity and scan duration +10% is equal to or greater than the specifications set out below. Therefore, one may decide to apply a higher activity and reduce the duration of the scan or, *preferably*, use reduced activity and increase scan duration, thereby keeping ALARA principles in mind as well.

- The figures for systems with bed overlap of <25% are:
 - Product of MBq/kg \times min/bed >27.5 for 2D scans
 - Product of MBq/kg \times min/bed >13.8 for 3D scans. The dosage is then calculated as follows:
 - FDG activity in MBq for 2D scans = $27.5 \times \text{weight}/(\text{min}/\text{bed})$
 - FDG activity in MBq for 3D scans = $13.8 \times \text{weight}/(\text{min}/\text{bed})$
- And for systems with a bed overlap of 50%:
 - Product of MBq/kg \times min/bed >6.9 (3D only)
 - FDG activity in MBq = $6.9 \times \text{weight}/(\text{min}/\text{bed})$
- The specifications indicate that heavier patients receive a higher FDG activity. A short scanning duration per bed position should also be offset by a higher FDG activity [3, 30]. Two model calculations are given in Appendix I to clarify the situation.
- For obese subjects (>90 kg), increase of scanning time (time per bed position) rather than increase of FDG activity is recommended to improve image quality. A recent publication suggests that FDG activities higher than 529 MBq for patients above 90 kg should not be applied for LSO systems [31]. Therefore, it is recommended to keep administered activity below 530 MBq.
- A maximum allowed FDG activity may be imposed by national law. In the latter case, increase of scanning time should be applied to keep FDG activity within legal limits.
- 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 FDG activity 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.

- In all cases the administered activity should not result in count rates above the count rate capability of the PET or PET/CT system being used. Increase of scan duration should then be applied to improve image quality.

Other acquisition parameters

Emission scans:

- Online randoms correction should be based on ‘delayed coincidence time window’ technique or randoms correction using a model based on (block) singles count rates
- Indication of the correct isotope, the patient’s height and body weight, and the FDG activity administered. Please also note *and report* assay activity (=FDG activity) and assay time (=activity calibration time). In addition, indicate time of injection (usually not equal to assay time or activity calibration time) should be noted *and reported*.
- Decay correction must be ‘on’ (see also “[Image reconstruction](#)”).

CT-protocol

- The CT in the framework of a PET/CT examination comprises the topogram and the helical CT scan.
- If a CT is solely performed for attenuation and scatter correction and co-localisation, the acquisition parameters (tube current, voltage, slice thickness, rotation time, and pitch) should be selected in order to minimise the radiation exposure for the patient.
- For a diagnostic contrast-enhanced CT, standard CT milliamperere-seconds settings or those given by the radiological societies/radiologist should be used. The modulation of the tube current can be used to lower the radiation exposure of the patient. Depending on the clinical question, intravenous and/or oral contrast agents may be used. It might be useful to perform a diagnostic CT only for portions of the body, whereas for the rest of the body a low-dose CT is performed for attenuation correction and co-localisation. High intravenous concentrations of contrast material may cause artefacts on the reconstructed PET image and affect quantification and should thus not be applied during the

CT-AC in case quantification (i.e. SUV) is performed (but may be used after concluding the PET/CT examination during an additional diagnostic CT). In case of PET/CT scans without need for quantification, intravenous contrast agents may be used directly (i.e. this CT may also be used for attenuation correction purposes) during the PET/CT study because the impact on visual image quality and interpretation is modest. However, deep inspiration at chest CT will obviously cause misregistration and artifacts if low-dose CT (with normal breathing) is replaced by such a diagnostic deep inspiration CT.

- Oral contrast agents allow a better delineation of the gastrointestinal tract. Positive contrast material (like diluted barium) as well as negative contrast material (for example water) can be used. High intraluminal concentrations of barium or iodinated contrast agents can cause an attenuation correction related artefact in the PET images resulting in an overestimation of FDG accumulation at those sites. These artefacts can be avoided by using negative contrast agents. However, administration of water only as negative intraluminal contrast agent itself is associated with a fast resorption and can cause increased nonspecific FDG accumulation in the bowel. In case quantification of the PET/CT studies is required, it is recommended to use diluted positive contrast agents only. The concentration of diluted positive contrast agents should be low enough to guarantee absence of attenuation correction artefacts, which should be verified for each combination of PET/CT system, PET/CT image reconstruction software and contrast agent being used.
- Ensure that the patient is lying within the CT-AC field of view (FOV) and in the same position as during emission scanning.

Pitfalls

- In some PET/CT systems, 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. When available, truncation corrections algorithms may be applied during image reconstruction (and/or during processing of CT used for attenuation correction). However, one needs to demonstrate that quantification is not affected by CT truncation even when truncation corrections are applied. As the amount of truncation may vary across scans and subjects, it will be difficult to ensure proper quantification across scans and subjects. It is therefore *strongly recommended* to avoid any CT truncation. It should be noted that CT

truncation may occasionally seriously affect the scatter correction and may lead to non-quantitative results.

- When using Ge-68 transmission sources, they must be replaced on time (i.e.: at least once every 18 months) and/or following the manufacturer's recommendations. It is recommended to compensate for the decay of transmission scan sources over time by increasing transmission scan durations, e.g. by performing transmission scans based on total number of collected counts, if possible [32].
- Make sure that all clocks (of dose calibrator and PET or PET/CT system) are synchronized. Consult your local service engineer when needed. Clocks should be synchronised with the official local time within 1 min (in case of FDG studies).

Image reconstruction

PET image reconstruction

The PET emission data must be corrected for geometrical response and detector efficiency (normalisation), system dead time, random coincidences, scatter, and attenuation. Some of these corrections (for example attenuation correction) can be directly implemented in the reconstruction process. In all cases, all corrections needed to obtain quantitative image data should be applied during the reconstruction process. Data acquired in the 3D mode can be reconstructed directly using a 3D-reconstruction algorithm or rebinned in 2D data and subsequently be reconstructed with a 2D-reconstruction algorithm. Iterative reconstruction algorithms represent the current standard for clinical routine and have meanwhile replaced filtered backprojection algorithms for PET reconstruction. It is good clinical practice to perform reconstructions with and without attenuation correction to tackle potential reconstruction artefacts caused by a CT-based attenuation correction. For clinical cases, reading the reconstructed 3D volume data set is visualized in transaxial, coronal, and sagittal slices, but also the maximum intensity projections should be available.

Further standardisation of reconstruction settings is necessary in order to obtain comparable resolutions and SUV recoveries and make SUVs interchangeable, i.e. reconstructions are chosen such to achieve convergence and resolution matching across various PET and PET/CT systems and sites, especially *within a multi-centre setting* [15, 30, 33]. However, also for clinical practice, strict standardisation is needed to provide the same quality of care across sites and to allow for exchange and use of quantitative PET information elsewhere. Some indicative reconstruction settings are suggested in Appendix II. However, most

importantly, reconstructions should be chosen so that they meet the multi-centre QC specifications for both calibration QC and image quality/SUV recovery QC, as described in “Quality control and inter-institution cross-calibration”.

Exceptions/special features

Various new types of cameras are coming into 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. The convergence and overall final image resolution must also match this study protocol QC specification. Compliance with these requirements must be demonstrated by means of the tests described under Quality Control and inter-institution cross-calibration in “Quality control and inter-institution cross-calibration”. Calibration and activity recovery coefficients may not deviate from multi-centre standard specifications by more than 10%. These specifications are given in “Quality control and inter-institution cross-calibration”. In other words: any combination of acquisition and reconstruction protocol and/or settings which meets the multi-centre QC specifications given later and especially those for the (absolute) activity (or SUV) recovery coefficients is allowed.

CT image reconstruction

The CT data that are acquired during the PET/CT scanning session are usually reconstructed by use of filtered back projection or a similar algorithm. Depending on the CT-protocol and the diagnostic question separate CT reconstructions for the PET attenuation correction and for the diagnostic CT are performed. The reconstructions differ in their slice thickness, slice overlap, filter, etc. In addition to the reconstruction kernel that modulates the image characteristics within the slices (i.e. spatial resolution, edge enhancement and noise texture), a longitudinal filter in the z-dimension is used to optimise the resolution in the z-direction and to modify the slice-sensitivity profiles. The measured attenuation values are normalized to the density of water in order to assign a device-independent numeric value in the framework of the reconstruction.

$$\text{CT - value} = \text{HU} = \frac{1000(\mu - \mu_{\text{water}})}{\mu_{\text{water}}}$$

This procedure additionally reduces the dependency of the attenuation values from the radiation energy. In modern CT-tomographs, the spatial resolution in the z-dimension is almost as high as the transaxial resolution and almost isotropic

allowing image visualisation in coronal and sagittal views in a high quality. Additionally, post-processing like volume rendering or maximum intensity projections (MIPs) benefit from the high quality of the raw data.

Reporting

Reporting PET findings and SUV calculations

The reconstructed PET and CT images are assessed from a computer screen. The software packages for current PET/CT systems enable visualisation of PET, CT, and PET+CT fusion images in the axial, coronal, and sagittal planes as well as maximum intensity projections in a 3D cine mode. FDG PET images can be displayed with and without attenuation correction. On all slices (of the attenuation corrected data) quantitative information with respect to size and FDG uptake can be derived. Images must be evaluated using software and monitors approved for clinical use in radiology and nuclear medicine. Characteristics of monitor and settings should be in line with published standards (e.g. the Medical Electrical Safety Standards (IEC 60601-1/EN 60601-1), the Medical ECM Standards (IEC 60601-1-2, EN 60601-1-2) or national guidelines). Moreover, environment conditions (background light) must be at appropriate levels to ensure adequate image inspection.

The presence or absence of abnormal FDG accumulation in the PET images, especially focal accumulation, in combination with their size and intensity are evaluated. Absence of such accumulation is particularly significant if other tests have revealed findings such as anatomical abnormalities. Where necessary, 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. For response assessment, the images should be viewed over the same dynamic grey scale or colour scale range, i.e. a fixed colour scale e.g. from SUV=0 to 10 is recommended.

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.

Standardized uptake values are increasingly used in clinical studies in addition to visual assessments. SUV is a measurement of the uptake in a tumour normalized on the basis of a distribution volume. It is calculated as follows:

$$\text{SUV} = \frac{\text{Act}_{\text{voi}}(\text{kBq/ml})}{\text{Act}_{\text{administered}}(\text{MBq})/\text{BW}(\text{kg})}$$

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

$$\text{SUV}_{\text{glu}} = \frac{\text{Act}_{\text{voi}}(\text{kBq/ml})}{\text{Act}_{\text{administered}}(\text{MBq})/\text{BW}(\text{kg})} \times \frac{\text{Gluc}_{\text{plasma}}(\text{mmol/l})}{5.0(\text{mmol/l})}$$

In these calculations, Act_{voi} is the activity measured in the volume of interest (see “Definitions for volumes of interest (VOI) and regions of interest (ROI)”), $\text{Act}_{\text{administered}}$ is the administered activity corrected for the physical decay of FDG to the start of acquisition, and BW is body weight. Patient height, weight, and gender should be reported to allow for other SUV normalisations (LBM, BSA). The latter is of importance to meet EORTC recommendations [13] and, for response assessment studies, when large changes in body weight occur during the course of the treatment. As stated earlier, it is recommended to measure plasma glucose levels using validated methodology and calculate SUV with and without plasma glucose correction in all response monitoring assessment studies (“Patient preparation”, extra notes). Note that the measured glucose content ($\text{Gluc}_{\text{plasma}}$) is normalised for an overall population average of 5.0 mmol/l so that the SUVs with (SUV_{glu}) and without (SUV) correction of glucose content are numerically practically identical (on average) [3].

Interpretation and pitfalls

Interpretation criteria

- A physiological and variable FDG accumulation can be observed to a certain degree in most viable tissue: brain, myocardium (in which the FDG accumulation can be high in the fasting state), breast, liver, spleen, stomach, intestine, kidneys, urine, skeletal muscle, lymphatic tissue, bone marrow, salivary glands, thymus, uterus, ovaries, testicles, and brown fat.
- In whole-body PET/CT examinations the brain shows a high FDG accumulation. For the detection of brain metastases FDG PET is therefore only of limited value. In consequence FDG PET is usually not used for the primary detection or exclusion of brain metastases.
- An increased FDG uptake is observed in neoplastic lesions, granulation tissue (e.g. wound healing), infections and other inflammatory processes.
- Patterns of FDG uptake, established CT-morphological criteria as well as correlation with patient history, physical examination and other imaging modalities may be helpful for the differentiation between malignant and benign lesions. Semi-quantitative parameters (for example SUV) gain increasing importance for

therapy response monitoring and for assessing the prognosis of patients.

- Detection limits obviously depend on the degree of contrast between the tumour and its immediate surroundings. Sensitivity of FDG PET is much lower in diabetic patients. There is no single detection limit for FDG PET since 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. Although it is impossible to give 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 when the diameter of the tumour is less than 6 mm. Non-specific, non-physiological uptake is based on inflammatory processes or uptake in brown fat (neck, upper mediastinum, para-vertebral region). 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 sternotomy will remain visible for months. The resolution of FDG PET for bone fractures is more or less the same as has been established for skeletal scintigraphy.

Additional remarks

- Though there are no conclusive data on the optimum interval between chemotherapy and PET, an interval of at least 10 days 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 (due to enhanced bone marrow uptake) do not last for more than 2 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 due to radiation-induced inflammation, it is best to wait for about 3 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 3 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. 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 [30, 33]. This recommendation is an attempt to increase uniformity of FDG PET investigations in multi-centre studies and for routine clinical applications. It is therefore also essential that the equipment used is comparable. This can be achieved by means of (cross-) calibration, as described in “[Quality control and inter-institution cross-calibration](#)”.

Documentation and report

- Examination label
- Clinical information:
 - Indication for PET/CT-examination
 - Relevant patient history
 - Information relevant for reimbursement
- PET/CT-Examination and imaging protocol
 - Radiopharmaceutical with applied activity, purity, injection type and site (localisation of injection), time of injection, uptake time, body weight (for each longitudinal study) and height, gender
 - Information concerning medication administered as preparation of the PET scan
 - Field of view and patient positioning: whole-body PET/CT, skull base to mid thigh, limited area and position of the arms
 - Blood glucose level before the examination and used methodology to obtain blood glucose
 - CT-protocol: low-dose or/and diagnostic CT, contrast agent application (oral, intravenous, information on concentrations and volumes, native, arterial, portal-venous), scanned portion of the body
- Clinical report
 - Quality of the PET/CT-examination: i.e. limited due to motion artefacts, FDG accumulation in muscles and/or brown fat, hyperglycemia, CT-related artefacts, high patient body weight
 - Description of the localisation, the extent and the intensity of pathological FDG accumulations related to normal tissue. Description of relevant findings in CT and their relation to pathological FDG accumulations. FDG accumulation should be reported as mild, moderate, or intense and compared to the background uptake in e.g. the liver parenchyma (mean SUV: 2.0–3.0; maximum SUV: 3.0–4.0). However, criteria for visual interpretation must be defined for each study protocol and/or type of cancer because they may differ for different tumour locations and types. Some criteria have

already been proposed [7, 34]. The CT part of the PET/CT report must describe all findings (even in the case they are PET negative), and exception being that the CT is only used for attenuation correction.

- *Limitations:* If necessary, confounding factors influencing sensitivity and specificity of the PET/CT examination should be noted: small lesions (partial volume effect), inflammatory changes, muscle activity, high blood glucose levels at the time of injection
- *Clinical context:* Addressing the findings with respect to the clinical questions asked in the context of the PET/CT examination
- *Complementary information:* Comparison with previous examinations should be part of the PET/CT report. PET/CT examinations are more valuable, if they are interpreted in the context of results of other imaging examinations (for example CT, PET, PET/CT, MRI, etc.) and relevant clinical data. If a PET/CT examination is performed in the context of the assessment of response to a therapy the extent and the intensity of the FDG uptake should be documented. The European Organisation for Research and Treatment of Cancer (EORTC) has published criteria for the assessment of therapy response with FDG as metabolic marker. The documentation of a change in intensity of the FDG accumulation with semi-quantitative parameters—expressed as absolute or relative change—can be used for dedicated clinical questions. At present, relative changes in SUV under therapy represent the most robust parameter. A focus must be put on the equivalence of the results achieved with respect to comparability of technical protocols and data analysis.
- *Summary and diagnosis*
 - If possible, a definite diagnosis should be stated whenever possible. Alternatively, an estimate of the probability of a diagnosis should be given.
 - If relevant, differential diagnoses should be discussed
 - If appropriate, repeat examinations and/or additional examinations should be recommended to clarify or confirm findings.

For further reading, also see the Society of Nuclear Medicine Procedure Guidelines for General Imaging.

Definitions for volumes of interest (VOI) and regions of interest (ROI)

Definition:

- The maximum SUV measure (SUV^{\max}) is required for each lesion as specified in the study protocol and/or as

considered clinically relevant. The voxel with maximum uptake should be determined as follows:

- This volume of interest equals the voxel with highest uptake in tumour/lesion. The maximum uptake should be defined on original reconstructed PET images, i.e. no additional rebinning, resampling, smoothing by the user is allowed.
- Use of a 2D peak ROI/VOI is recommended as well (providing SUV^{peak}). The volume of interest that should be generated is:
 - Approximately 1.2 cm diameter fixed size circular ROI (defined in axial plane), centred on the tumour area with highest uptake, as recently suggested in [12].
- Use of a 3D peak ROI/VOI (providing $SUV^{3D\text{peak}}$) may be determined (when possible) as follows:
 - 3D 1.2 cm diameter spherical VOI centred on area with maximum uptake ($SUV^{3D\text{peak}}$) may be defined [12].
- The following additional 3D volumes (volumes of interest, VOI) are frequently used [30, 35]. It is recommended, when possible, to include one of the following 3D volumes of interests during the data analysis and reporting:
 - 3D isocontour at 41% of the maximum pixel value adapted for background (A41)
 - 3D isocontour at 50% of the maximum pixel value (50)
 - 3D isocontour at 50% adapted for background (A50)
 - 3D isocontour at 70% of the maximum pixel value (70)
 - 3D isocontour at 70% adapted for background (A70)
- The isocontour described as A41 generally corresponds best with the actual dimensions of the tumour, but only for higher tumour-to-background values and homogeneous backgrounds. In practice, however, this VOI seldom results in useful tumour definition because of noise, inhomogeneities 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 for all sequential scans of the same patient.
- Other tumour segmentation methods have been described for tumour volumetry in literature, such as gradient-based methods [36], iterative methods [37], and fuzzy clustering/segmentation methods [38]. These, however, are not routinely used for determining SUVs and are not widely available. Yet these new methods may be used provided that at least the maximum uptake (SUV^{\max}) always and, for clinical trials, preferably 2D SUV^{peak} will be determined and reported as well.
- When VOIs are generated semi-automatically, 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 and $2D\text{ SUV}^{\text{peak}}$ should be used for reporting.

Quality control and inter-institution cross-calibration

PET quality control

Both physiological and physical factors influence the accuracy and reproducibility of ‘standard uptake values’ (SUV) in oncology FDG PET studies. Variations in PET camera calibration, image reconstruction, and data analysis and/or settings can have more than a 50% effect on the measured SUV [15]. The use of SUV in multi-centre oncology PET studies therefore requires an inter-institution calibration procedure in order to facilitate the exchangeability of SUVs between institutions. It is also important that all participating institutions use methodology that is as similar as possible. In order to ensure the exchangeability of SUVs, a minimum set of quality-control procedures must be carried out, such as:

- Daily quality control
- Calibration/cross-calibration of PET or PET/CT camera with the institution’s own dose calibrator or against another dose calibrator (e.g. that of an FDG provider) which is generally used to determine patient specific FDG activities
- Inter-institution cross-calibration and determining ‘activity recovery coefficients’

Note that these QC measures do NOT replace any QC measures required by national law or legislation or those recommended by local nuclear medicine societies. A brief summary of PET and PET/CT quality-control procedures, specifically recommended here to ensure accurate SUV quantification, is given below.

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 PET and PET/CT systems, the daily quality control includes tuning of hardware and/or settings. Thus both the

procedure and its name may be different between various PET and PET/CT systems. In all cases, all daily quality-control measures and/or daily setup/tuning measurements should be performed according to the manufacturer’s specifications. Users should check whether the daily quality control meets the specifications or passed the test correctly.

When available, a daily PET or PET/CT scan of a cylindrical phantom filled with a Ge-68 solution *may* be collected. Inspection of uniformity and quantitative accuracy of the reconstructed image may help to identify technical failures that were not detected using the routine daily QC procedures. In addition, sinogram data may be visually inspected to check detector failures.

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 dose calibrator or against another one which is used to determine patient-specific FDG activities [39]. If these FDG activities 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 activity of about 70 MBq, see below, as if it concerns an FDG activity needed for a clinical study). 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. Differences of up to 15% in the cross-calibration between PET camera and dose calibrator have been observed [15] 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 and PET camera used.

In short, the procedure is as follows: A syringe is filled with approximately 70 ± 10 MBq of FDG solution and is re-measured in a calibrated dose calibrator (or the syringe is ordered from the pharmaceutical company). The FDG is then introduced into a calibration phantom with an exact known volume (<1%) filled with water, which results in a solution containing an exactly known activity concentration (Bq/ml). Homogenisation of the FDG in the phantom should be achieved by leaving an air bubble of approxi-

mately 10–20 ml within the phantom and subsequently shaking/mixing the phantom for a short period of time (10 min). 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 multi-bed acquisitions, see Appendix III). Once the activity has decayed (after an interval of 10 h or more), a transmission scan is performed without moving the phantom from its position in the PET or PET/CT system. 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 “Image reconstruction” on image reconstruction and Appendix II. 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 (<10%). A ‘standard operating procedure’ (SOP) is described in Appendix III.1 (Software and/or processing programs for (automated) analysis of the QC calibration experiments are available on request as research tool, r.boellaard@vumc.nl).

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 between centres as a result of differences in the reconstruction and data analysis methodology used. 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 standardized ‘anthropomorphic’ phantom containing spheres (tumours) of varying sizes. Phantoms such as these enable to verify SUV quantification under

clinically relevant conditions. The aim of the IQRC quality-control procedure is:

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

The IQRC quality-control procedure is carried out closely 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 “Definitions for volumes of interest (VOI) and regions of interest (ROI)”:

- 3D isocontour at 50% adapted for background correction (A50)
- 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. 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 normalized 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 Appendix III.2. (Software and/or processing programs for (automated) analysis of the QC image quality/recovery experiments are available on request as research tool, r.boellaard@vumc.nl).

The measured activity concentration recovery coefficients must meet the specifications given below. These specifications are based on recovery coefficients measured according to this protocol on various PET and PET/CT systems of different vendors [3].

Specifications for activity concentration recovery coefficients (RC) measured according the Image Quality QC SOP (Appendix III.2). Specifications are given for recovery

coefficients obtained using A50 VOI and the maximum pixel value only.

RC specification for A50

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

RC specifications for maximum pixel value

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

Minimum frequency of PET quality-control procedures

Procedure	Frequency
Daily QC	Daily
Cross-calibration	At least 1× 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 <i>always</i> following software adjustments (especially adjustments to the reconstruction and/or data analysis (region of interest) software/hardware) and relevant PET or PET/CT system hardware changes

CT quality control

- In general, QC for CT scanner (and CT part of PET/CT) are already defined by the radiological societies and software and procedures are usually incorporated in the scanner (software). It is recommended to follow the QC-CT guidelines as required by national law and/or as indicated by the (national) radiological societies.
- Several documents and reports on QC-CT have been published and are listed below for the readers' information. An overview of CT-QC is given in e.g. the "Equipment Specifications" and "Quality Control" sections of the American College of Radiology Practice Guideline for the Performance of Computed Tomography of the Extracranial Head and Neck in Adults and Children, the American College of Radiology Practice

Guideline for the Performance of Pediatric and Adult Thoracic Computed Tomography (CT), and the American College of Radiology Practice Guideline for the Performance of Computed Tomography (CT) of the Abdomen and Computed Tomography (CT) of the Pelvis and in the IPEM report 91. In addition, CT performance monitoring guidelines are also given in the American College of Radiology Technical Standard for Medical Physics Performance Monitoring of Computed Tomography (CT) Equipment.

Additionally recommended quality-control measures, specifically for PET or PET/CT systems

- Alignment of PET and CT images on a PET/CT system should be checked following manufacturer's procedure and frequency.
- Setup and normalisation for both PET and CT should be performed according to procedure and frequency as recommended by the manufacturer.
- All devices involved (PET and PET/CT camera's, dose calibrators, well counters, clocks, scales) should be maintained according to the manufacturer's recommendations. This includes preventive and corrective maintenance required to ensure correct and accurate functioning of the devices.
- Calibration of the above-mentioned devices should always be performed or correct (cross)calibration should be verified (by means of QC) after maintenance and software upgrades.
- Dose calibrators and well counters should be calibrated at least once per year.
- The accuracy of scales used to weigh patients should be checked.

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Appendix I: Examples of FDG activity calculations

Calculation of FDG activity to be administered, example 1:

- 3D system with a bed overlap of less than 25% (e.g. Siemens and GE cameras).
- Patient weighing 70 kg

- Scanning duration per bed position: 3 min per bed. The FDG activity to be administered is therefore: $13.8 \text{ (MBq/kg per min/bed)} \times 70 \text{ (kg)/3(min/bed)} = 13.8 \times 70/3 = 322 \text{ MBq}$.

Calculation of FDG activity to be administered, example 2:

- 3D PET or PET/CT system with 50% bed overlap (e.g. Philips cameras).
- Patient weighing 70 kg
- Scanning duration per bed position: 3 min per bed. The FDG activity to be administered is therefore: $6.9 \text{ (MBq/kg per min/bed)} \times 70 \text{ (kg)/3(min/bed)} = 6.9 \times 70/3 = 161 \text{ MBq}$.

Note: the scanner brands are solely given as examples. The key factors in determining the FDG activity are the mode of acquisition (2D or 3D), the time per bed position (time/bed) and the degree of bed overlap and, finally, the patient's weight.

In order to simplify implementation in a routine clinical setting, a Table in 10-kg steps may be used such as published by Boellaard et al. [3]. Note however that in the present guideline, a maximum FDG activity of 529 MBq for patients above 90 kg is recommended. Moreover, a maximum allowed FDG activity may be applicable by national law. In the latter case, i.e. for obese patients, increase of scanning time should be applied to obtain sufficient image quality and/or to remain within (national) legal limits.

Appendix II: Indicative reconstruction settings for current PET and PET/CT systems (as of mid 2009)

Here a number of *indicative* settings are given for different system types. These indicative settings usually provide results that meet closely the QC specifications as defined later in this guideline. In case these reconstructions cannot be set exactly as indicated below, settings may be set as close as possible to the ones listed below. However, note that reconstructions should be set such that they meet the multi-centre QC specifications for both calibration and image quality/SUV recovery as function of sphere size (see "Exceptions/special features")

Siemens/CTI systems:

- 2D or 3D OSEM reconstruction with sufficient convergence (generally, product of iterations and subset larger than 50 is sufficient)
- 5-mm FWHM Gaussian reconstruction filter in all directions or equivalent filters. In case of resolution modeling during reconstruction, a smoothing filter may be required to meet the multi-centre QC specifications. This filter may be applied afterwards (and/or thus create an additional dataset).

- matrix size of 128×128 up to 256×256
- zoom=1

General Electric systems:

- 2D or 3D OSEM reconstruction with sufficient convergence (generally, product of iterations and subset larger than 50 is sufficient)
- 5-mm FWHM Gaussian filter in all directions or equivalent filters. In case of resolution modeling during reconstruction, a larger filter may be required to meet QC specifications. This filter may be applied afterwards (and/or thus create an additional dataset)
- matrix size 128×128 up to 256×256
- zoom=1

Philips systems (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).
 - (3) For both use an image matrix size of 144×144

Appendix III: Standard operating procedures for quality control

Calibration QC of PET and PET/CT and information required for calibration report form

Materials

- About 30 to 70 MBq ^{18}F -FDG
- Cylindrical calibration phantom, any dimension but with exactly known volume
- PET or PET/CT system. Phantom volume of about 6–9 l, diameter from 15–25 cm.
- Dose calibrator (DC)

Site/other information

Site ID	=
System type and model	=
System software version	=
Volume of calibration phantom	= (ml)
Scan date	= (dd:mm:yyyy)
Scan time	= (hh:mm:ss)
Time difference between DC and PET	= (min:ss)
<i>OR</i>	
Time difference between official time* and PET	= (min:ss)
Time difference between official time* and DC	= (min:ss)

*Official time = atomic clock (may be taken from internet in case of FDG)

Preparation

- Prepare a 5 to 10 ml syringe with about 70 MBq FDG, provide the exact measured amount of FDG activity below
- FDG activity =(MBq) specified at(hh:mm:ss)
- Fill calibration phantom completely (with water) and then remove 10 ml water from the phantom
- Put the FDG in the phantom. Make sure that all activity is in the phantom by flushing the syringe a few times.
- Extensively shake the phantom to homogenize activity throughout the phantom

PET or PET CT scan acquisition

- Put phantom in the PET or PET/CT system
- Acquire a PET or PET/CT scan consisting of at least two PET bed positions. PET and PET/CT scan acquisition and reconstruction should be performed identically to patient studies as prescribed in the clinical protocol. However, somewhat longer acquisitions are recommended (e.g. 5 to 10 min per bed position acquisitions), include a standard transmission or (low-dose) CT for attenuation correction purposes.

Reconstructions

Reconstructions should be performed with attenuation, scatter, normalisation, decay, dead time corrections, i.e. all corrections required for quantification. Follow the instructions given in this guideline (“Image reconstruction”).

Analysis

Determine average activity concentration or SUV *within* the phantom. Verify that activity concentration and/or SUV are within 10% of expected values.

Pitfalls

- Make sure that all clocks (of dose calibrator and PET or PET/CT system) are synchronized. Consult your local service engineer when needed. Clocks should be synchronized with the official local time within 1 min (in case of FDG studies).
- Remaining activity in the syringe will result in incorrect verification of PET or PET/CT system calibration.
- If count rates exceed the limits of the PET or PET/CT system to allow for accurate quantification due to high dead time or randoms fractions, then this experiment

should be performed using a lower FDG activity and/or prepare the phantom a couple of hours in advance to allow for radioactive decay.

CRF/SOP image quality and activity concentration
recovery coefficient PET

Date =(dd:mm:yyyy)

Site ID =

Time difference between DC and PET = (min:ss)

OR

Time difference between official time and PET = (min:ss)

Time difference between official time and DC = (min:ss)

Materials

- Various ^{18}F -FDG activities in 2–5 ml syringes, two syringes with 20 MBq specified at expected phantom acquisition time.
- Bottle filled with exactly 1,000 ml
- NEMA NU2-2001 (“Patient preparation” of this NEMA standard) Image Quality phantom
- Dose calibrator (=DC)

Preparation

Stock/solution for spheres:

- Fill bottle with *exactly* 1,000 ml water
- Add 20 MBq ^{18}F -FDG. Make sure all activity is removed from the syringe into the phantom.

FDG activity =MBq specified at (hh:mm:ss)

Volume (of FDG in syringe) = (ml)

- Homogenize solution (20 MBq FDG in 1,000 ml)
- Fill *all* spheres of the NEMA NU2-2002 image quality phantom with this solution.

Filling of background compartment of image quality phantom:

- Fill background compartment completely with water
- Remove 30 ml water from the background compartment of the phantom
- Add 20 MBq FDG in the background compartment. Make sure all activity is removed from the syringe into the phantom.
- FDG activity =MBq specified at (hh:mm:ss)
- Homogenize the solution in the background compartment by shaking the phantom extensively.

PET or PET/CT Scans

- Acquire a routine quantitative whole-body FDG PET scan of at least two PET bed positions of the entire phantom. Follow instructions given in this guideline for the patient studies (i.e. standard acquisition parameters and scan durations).
- Acquire a quantitative whole-body FDG PET scan of one PET bed position of the phantom. Position the phantom such that spheres are located at the centre of the axial field of view. In this case, emission scans per bed position should take at least 10 min. All other scan parameters must be identical to those used during patient scanning and as recommended in this guideline.
- PET scan acquisition time = (hh:mm:ss)
- PET scan acquisition date = (dd:mm:yyyy)

Reconstructions

Reconstructions should be performed with attenuation, scatter, normalisation, decay, dead time corrections, i.e. all correction needed for quantification. Reconstructions need to be performed conform specifications given in this guideline. In case such a protocol is not in place, the recommendation for quantitative studies as provided by the vendor should be applied.

Analysis

Determine recovery coefficient as function of sphere using maximum pixel value and A50 VOI.

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.

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