[^{18}F]FDG PET/CT Imaging Manual

Imaging manual for [^{18}F]FDG PET/CT staging, response monitoring and central review in the HOVON trials

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Introduction: [^{18}F]FDG PET/ CT staging and response monitoring

For accurate assessment, [^{18}F]FDG PET/CT scans have to be performed according to the guidelines of the EANM (1) and assessed visually according to the Lugano 2014 criteria (2) and quantitative for assessing metabolic tumor volume (MTV) and other radiomics features (3).

As [^{18}F]FDG-PET/CT is considered to be the most sensitive imaging modality for staging, re-staging as well as for therapy response assessment in Hodgkin lymphoma and in various non-Hodgkin lymphomas, this technique is used for the evaluation of treatment.

Standardization of PET/CT is essential for international multi-center trials to ensure that results are comparable between and within centers and that the results can be transferred into clinical practice at the conclusion of the trial. For quality assurances and assessment of acquisition and reconstruction parameters, EARL 1 accreditation is required. EARL 2 accreditation is highly recommended. Details can be found on the EARL website: https://earl.eanm.org or given after contacting the EANM office by email: earl@eanm.org.
Recommendations for patient preparation, [^{18}F]FDG administered activity, imaging procedure and reconstruction have been updated in the EANM 2.0 guidelines from the EANM 1.0 guidelines (5). Imaging procedures should be performed according to the EANM [^{18}F]FDG PET/CT guidelines version 2.0 (2015) (1). By applying a 7mm FWHM Gauss filter, EARL-2 compliant reconstructed studies may be converted into EARL-1 compliant studies for standardized uptake value (SUV) and metabolic tumor volume (metabolic tumor volume ((MTV) calculations (4).
In the paragraphs below, relevant differences between EANM 1.0 and EANM 2.0 guidelines will be briefly indicated.

In accordance with the guidelines a PET/CT scan from mid-thigh to skull base is required when there are no symptoms beyond the scan range. If deemed appropriate, a whole-body scan from head to toes can be performed. The CT as part of the PET/CT is a low dose CT without iodine contrast (its purpose is attenuation correction and anatomical localization of PET findings). It is important to have an **unenhanced** CT scan at all times for attenuation correction. The use of iodinated contrast will affect SUV values when used for attenuation correction.
An additional contrast enhanced CT (CECT) of the neck, thorax and abdomen should be performed for radiological assessment at baseline, preferably combined with the PET/CT investigation for optimal lesion localization. PET/CT-scans at follow up are not routinely combined with CECT. The use of an additional CECT of the neck, thorax, and abdomen can be considered in cases where pathological uptake at PET/CT imaging during response assessment needs further interpretation.
Recommendations for (minimal) [^{18}F]FDG administered activity can be found in the EANM guidelines 2.0 (1) The required interval between the [^{18}F]FDG administration and the acquisition start is 60 minutes. Scans acquired outside the 55 -75 minutes time window after the injection will not be eligible. There should be no more than 15 minutes difference in time of the start of the scan after injection of [^{18}F]FDG between staging and response evaluation scans.

The interim [^{18}F]FDG-PET/CT scans should be performed as close to the start of the next cycle and at least 10 days after the last chemotherapy.

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Necessary:
- PET/CT scanner with EARL 1 and/or EARL 2 accreditation (4)
- [^{18}F]FDG activity according to EANM guideline 2.0 (1).
- I.v. canula for intravenous administration
- Materials for blood glucose measurement

Patient preparation

A short outline of recommendations is listed below. Full details can be found in the EANM [^{18}F]FDG PET/CT guidelines 2.0 (2015). Additionally, the application of newly developed antidiabetic medications and can be considered, if undue effects on visual lesion detection and (semi)quantitative measurements have been adequately excluded.

Nondiabetic patients should not consume any food or liquids other than plain (unflavoured) water for at least 4 hours (EANM 2.0) or at least 6 hours (EANM 1.0) prior to [^{18}F]FDG injection.
In practice, this means that patients scheduled to undergo the [^{18}F]FDG-PET/CT study in the morning should not eat after midnight and preferably should have only a light meal (no alcohol and only a small amount of carbohydrates) during the evening prior to the FDG PET/CT study. Those scheduled for an afternoon [^{18}F]FDG-PET/CT study may have a light breakfast at least 4 hours prior to the time of their PET/CT examination appointment.

For **diabetic patients**, it is recommended to fast for at least 4 hours prior to tracer injection but a personalized approach should be followed to secure serum glucose levels of <11 mmol/l prior administration of [^{18}F]FDG.

Adequate pre-hydration is important to minimize radiation dose to the patient, so drinking at least 500 ml of water before the injection of [^{18}F]FDG is recommended.

In order to avoid brown fat activation, it is recommended to place the patient in a heated room (typically between 20-23°C) prior to and after injection with [^{18}F]FDG. Give the patient extra blankets if necessary. Optionally, 20 mg propranolol per os, one to two hours before FDG injection can be administered.

Blood glucose level must be measured prior to the administration of [^{18}F]FDG. A glucose meter (or glucometer) or a similar bedside device capable of performing blood glucose measurements can be used for this purpose.
If the plasma glucose level is lower than 11 mmol/L (about 200 mg/dL), the [^{18}F]FDG-PET/CT study can be performed. (In EANM 1.0 guidelines the recommended maximal plasma glucose level was 7.0 mmol/L).

Height and body weight must be determined precisely in the case of SUV measurements. Patient height is an essential parameter for SUV calculations adjusted for lean body mass (SUL) instead of adjusted to body weight.
Weight must be *measured directly prior to each* FDG PET/CT examination (also in the case of longitudinal studies) because body weight often changes during the course of disease.

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Patients should void immediately prior to the PET/CT scan to reduce bladder activity.

The patient should be able to lie still in the PET/CT system for the duration of the examination (20 – 45 min for standard PET systems, 5-10 min for long-axial field-of-view (LAFOV) PET systems). **If possible, the patient should put his/her arms above the head;** proper support devices (e.g. foam pallets) provided by the manufacturers should be employed whenever feasible.

Recommendations for [^{18}F]FDG administered activity

[^{18}F]FDG activity according to EANM Guideline 2.0 2015 (in short)[1]

For systems that apply a PET bed overlap of ≤30 %, the recommended administered activity is calculated as follows:
[^{18}F]FDG (MBq)=14 (MBq·min·bed^{-1}·kg^{-1}) × patient weight (kg)/emission acquisition duration per bed position (min·bed^{-1})
or:
[^{18}F]FDG (MBq)=1050 (MBq·min·bed^{-1}·kg^{-2}) × (patient weight (kg)/75)^2/emission acquisition duration per bed position (min·bed^{-1}).

For systems that apply a PET bed overlap of >30 %, the recommended administered activity is calculated as follows:
[^{18}F]FDG (MBq)=7 (MBq·min·bed^{-1}·kg^{-1}) × patient weight (kg)/emission acquisition duration per bed position (min·bed^{-1})
or:
[^{18}F]FDG (MBq)=525 (MBq·min·bed^{-1}·kg^{-2}) × (patient weight (kg)/75)^2/emission acquisition duration per bed position (min·bed^{-1}).

In practice this translates in a minimal activity of 3 MBq/kg for a 2 to 3 min acquisition per bed position in case of more than 30% bed overlap and a 6 MBq/kg activity for a 2 to 3 min acquisition per bed position in case of less than 30% bed overlap. In case of flow motion technology, choose a speed that results in a 1 m axial coverage in about 15 to 20 min with a 3 MBq/kg activity.

Notes:
*Patient >90 kg: increase emission acquisition time per bed rather than increasing administered [^{18}F]FDG activity.
*Maximum activity of 530 MBq [^{18}F]FDG for L(Y)SO systems
*After [^{18}F]FDG administration: Flushing of the i.v. canula with 10-20 ml NaCl 0.9% (or measurement of residual activity of [^{18}F]FDG in syringe).
*[^{18}F]FDG activity and acquisition time for the newest LAVOF PET systems are currently subject for validation. 3 MBq/kg patient weight with acquisition time of 8 minutes is suggested as current recommendation.
*[^{18}F]FDG activity and acquisition time can be optimized for e.g. new LAFOV and/or highly sensitive digital PET systems according to a protocol as defined by EARL (6, 7)).

Incubation time (time between [^{18}F]FDG administration and start [^{18}F]FDGPET/CT scan): 55-70 min

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PET acquisition protocol

The PET emission data must be corrected for geometrical response and detector efficiency (normalisation), system dead time, random coincidences, scatter and attenuation. It is good clinical practice to perform reconstructions with and without attenuation correction to identify potential reconstruction artefacts caused by the CT. Both attenuation corrected (AC PET) and non-attenuation-corrected PET (NAC PET) images should be available for interpretation. Lesions seen on the AC PET images may need to be checked on the NAC PET images, particularly when adjacent to highly attenuating materials, for example contrast agents or metal implants. For SUV measurement standardized reconstruction parameters are necessary to obtain a standardized and harmonized SUV recovery. For quantitative purposes, EARL1-approved reconstruction settings should be used/available.

Scanning protocol: Supine position, head first. Torso imaging (skull base to mid-thigh). Acquisition duration per bed position according to the administrated activity of [^{18}F]FDG (see above).

The final reconstruction protocol and settings should be based on an actual EARL1 (or EARL2) accreditation and the optimal settings differ between individual systems and system models.

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Image reconstruction

[^{18}F]FDG-PET/CT images must be reconstructed using an iterative algorithm and with attenuation correction using non-contrast-enhanced CT images and by using the EARL-1 and/or EARL-2 approved acquisition and reconstruction settings (as determined during the EARL accreditation process).

Note: By applying a 7mm FWHM Gauss filter, EARL-2 compliant reconstructed studies may be converted into EARL-1 compliant studies for standardized uptake value (SUV) and MTV calculations (4).

Image analysis and interpretation

Image data should be stored on an approved PACS system and in DICOM format. The presence or absence of abnormal [^{18}F]FDG accumulation on the PET images, especially focal accumulation, in combination with intensity of uptake and anatomical size should be evaluated (2).

Standardized uptake value (SUV) is increasingly used in clinical studies in addition to visual assessments. SUV is a measurement of the uptake in a tumor, normalized to the distribution volume. In case of [^{18}F]FDG, SUV is normalized to body weight (SUV/bw). These SUV measurements will be used in addition to visual analysis.
Note: For accurate SUV calculation it is essential that the net administered activity at the time of injection is accurately recorded.
Note 2: SUV normalized to lean body mass (LBM) is referred to as SUL and is a recommended quantitative measure of [^{18}F]FDG uptake. SUL should preferably be calculated alongside SUV. Not all

research protocols require the calculation of SUL. However, if desired at a later stage, SUL parameters can easily be derived from SUV if patient's height has been recorded. For further details see EANM 2.0 guidelines (1).

Note 3: Metabolic tumor volume (MTV) is recognized as an important prognostic parameter in lymphoma. Lesion selection and segmentation can be performed at a chosen cut-off level, e.g SUV 4 (4). Total lesion glycolysis (TLG) can be calculated from MTV and SUV parameters.

Note 4: By applying a 7mm FWHM Gauss filter, EARL-2 compliant reconstructed studies may be converted into EARL-1 compliant studies for SUV and MTV calculations (4).

[18F]FDG PET/CT visual assessment

At staging, abnormal [18F]FDG uptake will be assessed using the Lugano criteria (2).

Visual assessment during follow-up will be performed using the criteria defined according to the Deauville 5 point scale (2).

1= No uptake.
2= Uptake ≤ mediastinal blood pool.
3= Uptake > mediastinal blood pool but ≤ liver.
4= Uptake moderately more than liver uptake, at any site involved at baseline.
5= Markedly (> 2 times) increased uptake at any site involved at baseline vs liver and/or and new sites of disease estimated to represent lymphoma
X= New areas of uptake unlikely to be related to lymphoma. For response criteria and definitions see appendix B.

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Data to be uploaded for central review

PET
- Axial EARL1 (and EARL2) reconstruction (slice thickness 5/slice interval 4)
- Axial AC PET (5/4)
- Axial NAC PET (5/4)
- Axial low-dose CT applied for attenuation correction (3/3)

CT
- Axial (3/3)
- Coronal head / cervical spine (3/3)
- Sagittal head / cervical spine (3/3)
- Coronal thorax/abdomen/upper extremities (3/3) (including pelvis)
- Sagittal thorax/abdomen/upper extremities (3/3)
- Coronal legs (3/3)

All PET/CT scans **AND** the local [^{18}F]FDG PET/CT reports **AND** the completed Send form have to be sent preferably via any form of digital transfer (e.g. surf file sender) or via CD-rom to:

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P.O. Box 7057
NL – 1007 MB Amsterdam
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Tel: +31 20 4445057
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Central PET review instructions

Within de HOVON datacenter, the Keosys imaging system will be used to exchange imaging data and reporting of a central review. The PET/CT and CECT scans will be collected and reviewed by nuclear medicine physicians and radiologists of the HOVON Imaging working group. For central review, preferably all [^{18}F]FDG PET scans, with and without attenuation correction and EARL2 reconstruction, the low dose CT used for attenuation correction and if performed the contrast-enhanced CT scan(s) will be uploaded to the HOVON imaging platform.

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[^{18}F]FDG PET/CT-scan send form

On the CD-ROM or CD-ROM label, please report the HOVON patient number, patient's year of birth and the protocol phase.
Please note that the name and all data that can lead to direct identification of the patient should be omitted. **Please don't remove or alter the following DICOM headers of the PET-CT scan;**

0008,0020	Study Date
0008,0021	Series Date
0008,0022	Acquisition Date
0008,0023	Image Date
0008,0031	Acquisition Time
0008,103E	Series Description
0008,0032	Acquisition Time
0008,0060	Modality
0010,1020	Patient's Height
0010,1030	Patient's Weight
0018,0031	Radiopharmaceutical
0018,0050	Slice Thickness
0018,1072	Radiopharmaceutical Start Time
0018,1074	Radiopharmaceutical Stop Time
0018,1075	Radionuclide Half Life
0018,1078	Radiopharmaceutical Physical Decay Time
0018,1181	Collimator type
0018,1210	Convolution Kernel
0018,5100	Patient Position
0020,0013	Instance Number
0020,0032	Image Position (Patient)
0020,0037	Patient Orientation
0020,0052	Frame of Reference UID
0020,1041	Slice Location
0028,0010	Rows
0028,0011	Columns
0028,0030	Pixel Spacing
0028,1052	Rescale Intercept
0028,1053	Rescale Slope
0054,0081	Number of Slices
0054,0412	Referenced PET Radioactivity Measured Values Sequence
0054,0414	Referenced ROI Energy Values Sequence
0054,1001	Units
0054,1102	Decay Correction
0054,1103	Reconstruction Method
0054,1330	Image Index

In case of any questions: c.karga@amsterdamumc.nl, g.zwezerijnen@amsterdamumc.nl

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