



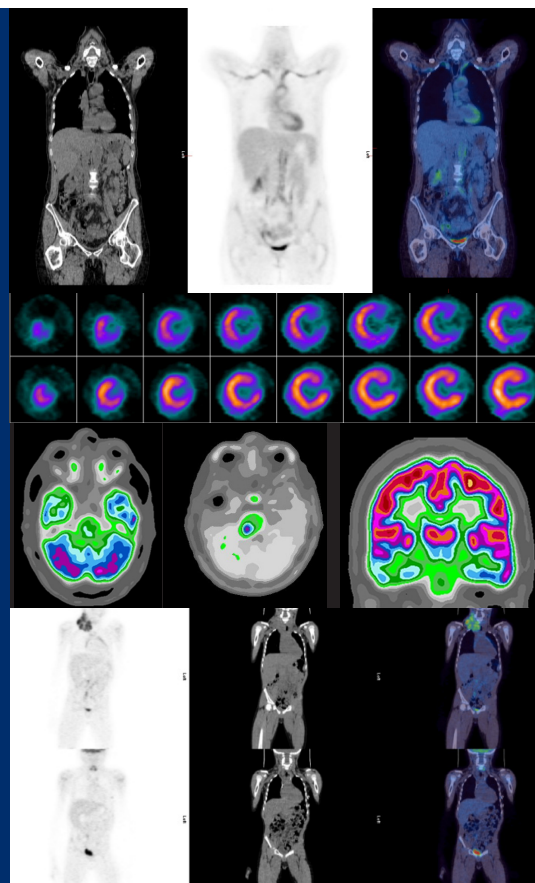
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Radiology

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Evidence-based indications for the use of PET-CT in the UK 2013



A report from:

Royal College of Physicians of London
Royal College of Physicians and Surgeons of Glasgow
Royal College of Physicians of Edinburgh
The Royal College of Radiologists
British Nuclear Medicine Society
Administration of Radioactive Substances Advisory Committee

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1. Introduction

This guidance comprises an up-to-date summary of relevant indications for the use of positron emission tomography – computed tomography (PET-CT), where there is good evidence that patients will benefit from improved disease assessment resulting in altered management and improved outcomes. This document supersedes the previous *Evidence-based Indications for the use of PET-CT in the United Kingdom* guidance published by the Royal College of Radiologists in February 2013. New indications and key references are highlighted in red ink for ease of identification. The document will be updated annually.

The indications are divided into oncological and non-oncological applications then body area/system. This list is not exhaustive and there are cases where PET-CT may be helpful in patients who have equivocal or definite abnormalities on other imaging where PET-CT may alter the management strategy if found to be 'positive' or 'negative'; for example, radical or high-risk surgery. PET-CT would be appropriate in such patients at the discretion of the local Administration of Radioactive Substances Advisory Committee (ARSAC) certificate holder.

2. Indications for ^{18}F -fluorodeoxyglucose (FDG) PET-CT

Oncology applications

Brain

- Identifying the grade of malignancy where there is uncertainty on anatomical imaging and functional assessment would assist biopsy.
- Suspected relapse where MR is equivocal to inform decisions regarding surgery or radiotherapy planning.
- Assessment of suspected high-grade transformation in low-grade glioma.
- Differentiation of cerebral tumour from atypical infection in immuno-compromised patients with indeterminate lesions on MR/CT.

Head and neck tumours

- Staging of patients where staging is difficult clinically; for example, patients with trismus or where there is uncertainty on other imaging or equivocal findings that would preclude radical treatment.
- Staging or restaging of patients with a high risk of disseminated disease such as advanced loco-regional disease and primary sites with a high propensity for disseminated disease such as nasopharyngeal cancer.
- To identify the primary site in patients presenting with metastatic squamous cell carcinoma in cervical lymph nodes, with no primary site identified on other imaging.
- Response assessment 3–6 months post chemo-radiotherapy in patients with indeterminate appearances on conventional imaging following treatment.
- To differentiate relapse from treatment effects in patients suspected to have tumour recurrence.

Thyroid carcinoma

- Assessment of patients with elevated thyroglobulin levels and negative iodine scintigraphy with suspected recurrent disease.
- To evaluate disease in treated medullary thyroid carcinoma associated with elevated calcitonin levels with equivocal or normal cross-sectional imaging, bone and octreotide scintigraphy – see below for alternative PET imaging with ^{68}Ga -DOTA-octreotate (DOTATATE), DOTA-1-Na $^{3-}$ octreotide (DOTANOC) or DOTA-octreotide (DOTATOC).

Lung carcinoma

- Staging of patients considered for radical treatment of non-small cell lung cancer:
 - Specifically patients with mediastinal nodes <1cm on CT or mediastinal nodes between 1–2 cm on CT and patients with equivocal lesions that might represent metastases such as adrenal enlargement.
- Characterisation of a solid solitary pulmonary nodule 10 mm or greater in size:
 - Especially in the case of failed biopsy, a technically difficult biopsy or where there is a significant risk of a pneumothorax in patients with medical co-morbidities.
 - Smaller nodules in the upper lobes may be considered after discussion with the local ARSAC certificate holder if biopsy and /or CT follow-up are not appropriate.
- Assessment of suspected disease recurrence:
 - To differentiate between treatment effects and recurrent cancer.
- Staging of patients with small cell lung cancer with limited disease on CT being considered for radical therapy.

Pleural malignancy

- To guide biopsy in patients with suspected pleural malignancy:
 - With pleural thickening; FDG is less likely to be useful in patients presenting with a pleural effusion only or with a history of previous pleurodesis.
- To exclude extra-thoracic disease in proven mesothelioma in patients considered for multimodality treatment including radical surgery/decortication.

Thymic tumours

- Staging of patients considered for surgical resection
- Assessment of indeterminate thymic lesions if being considered for radical treatment

Oesophago-gastric carcinoma

- Staging/restaging of patients with oesophageal or oesophago-gastric carcinoma, suitable for radical treatment, including patients who have received neo-adjuvant treatment.
- Evaluation of suspected recurrence of oesophago-gastric tumours when other imaging is negative or equivocal.

Gastrointestinal stromal tumours

- Staging prior to treatment in patients who are likely to require systemic therapy.
- Response assessment to systemic therapy.

Breast carcinoma

- Assessment of multi-focal disease or suspected recurrence in patients with dense breasts.
- Differentiation of treatment-induced brachial plexopathy from tumour infiltration in symptomatic patients with an equivocal or normal MR.

- Assessment of extent of disease in selected patients with disseminated breast cancer before therapy.
- Assessment of response to chemotherapy in patients whose disease is not well demonstrated using other techniques; for example, bone metastases.

Hepato-pancreatico-biliary cancers

- Staging of patients with potentially operable pancreatic adenocarcinoma where cross-sectional imaging is equivocal for metastatic disease and a positive PET-CT would lead to a decision not to operate.
- Staging of potentially operable primary hepato-biliary malignancy (cholangiocarcinoma, gallbladder carcinoma or hepatocellular carcinoma) where cross-sectional imaging is equivocal for metastatic disease, who are fit for resection and a positive PET-CT would lead to a decision not to operate.
- Suspected recurrence of hepato-pancreatico-biliary cancer in selected patients, where other imaging is equivocal or negative, taking into consideration that up to 30% of pancreatic adenocarcinomas and up to 50% of differentiated hepatocellular carcinomas may not be FDG avid.

See below for other tracers that may be helpful in staging.

Colorectal carcinoma

- Staging of patients with synchronous metastases at presentation suitable for resection or patients with equivocal findings on other imaging; for example, pulmonary or liver lesions.
- Restaging of patients with recurrence being considered for radical treatment and/or metastatectomy.
- Detection of recurrence in patients with rising tumour markers and/or clinical suspicion of recurrence with normal or equivocal findings on other imaging.
- Evaluation of indeterminate pre-sacral masses post-treatment.

Urological malignancy

- Assessment of metastatic renal and ureteric carcinoma in difficult management situations or when standard imaging is inconclusive.
- Assessment of renal carcinoma at staging in selected cases with equivocal findings on other imaging (recognising that ~50% of renal cell carcinoma may not be FDG avid and that the tracer is excreted into the urinary tract).
- **Assessment of advanced muscle-invasive bladder carcinoma which has the potential for radical treatment.**

Gynaecological malignancy

- Staging or restaging of patients with vulval or uterine (cervix/endometrium) carcinoma considered for exenterative surgery.
- Staging **and restaging** of patients with locally advanced cervical cancer being considered for radical chemo-radiotherapy.

- Suspected recurrence of vulval, endometrial or cervical carcinoma when other imaging is equivocal.
- Detection of tumour in selected patients with ovarian carcinoma who have rising CA125 levels and equivocal or negative imaging.

Testicular

- Assessment of recurrent disease in patients with metastatic seminoma or teratoma with elevated or rising tumour markers and equivocal or normal anatomical imaging.
- Evaluation of residual masses for patients with seminoma and teratoma, although mature differentiated teratoma may not be FDG avid and cannot be excluded with a negative scan.

Anal and penile carcinoma

- Staging of selected patients considered for radical treatment with equivocal imaging.

Lymphoma

- Staging of patients with Hodgkin's disease (HD) and aggressive non-Hodgkin's lymphoma (NHL) and as baseline for comparison with treatment response scan.
- Staging of patients with early-stage follicular lymphoma (FL) considered for radiotherapy treatment.
- Interim response assessment of patients with HD and aggressive NHL after two cycles of chemotherapy to exclude progression. If there is complete metabolic response (CMR) (score 1 or 2 using Deauville criteria) there is no requirement for an end of treatment remission assessment.
- End of treatment remission assessment of HD and aggressive NHL. Not required for patients with CMR on interim scans.
- Evaluation of suspected relapse for FDG-avid lymphomas in symptomatic patients.
- Assessment of response to second line treatment and subsequent treatments for FDG-avid lymphoma.
- Staging of suspected post-transplant lymphoproliferative disorder (PTLD).
- Prior to bone marrow transplant to assess volume of disease and suitability for transplant.
- To determine extent and identify a suitable biopsy site in patients with low-grade lymphomas in whom there is suspected high-grade transformation.

Myeloma

- Assessment of patients with apparently solitary plasmacytoma or patients with ambiguous lytic lesions on skeletal survey.
- Suspected relapse in patients with non-secretory myeloma or predominantly extramedullary disease.

Skin tumours

- Staging of patients with known disseminated melanoma to assess extent of disease prior to treatment.

- To assess for distant disease in patients with melanoma when radical dissection is contemplated (nodal or metastatic disease).
- To assess response to isolated limb infusion for malignant melanoma.
- ***Not indicated for early-stage patients who should undergo sentinel node biopsy.***
- To exclude systemic involvement in skin lymphomas.
- To exclude primary malignancy where dermatomyositis suspected to represent a paraneoplastic manifestation.

Musculoskeletal tumours

- Assessment of suspected malignant transformation within plexiform neurofibromas in patients with neurofibromatosis type 1 with delayed imaging recommended at four hours where there is uptake at 60–90 minutes.
- Staging of high-grade sarcomas, unless already proven to have metastatic disease, especially Ewing's sarcoma, rhabdomyosarcoma, leiomyosarcoma, osteosarcoma, malignant fibrous histiocytoma, synovial sarcoma and myxoid liposarcoma.
- Pre-amputation in the setting of a high-grade sarcoma where the detection of distant disease will alter the surgical management.
- To stage patients with metastatic sarcoma considered for liver or lung metastatectomy where anatomical imaging has not identified any extra-thoracic or extra-hepatic disease which would preclude surgery.
- Response assessment in high-grade sarcomas.

Paraneoplastic syndromes

- To detect an occult primary tumour in selected patients with non-metastatic manifestations of neoplastic disease when other imaging is negative or equivocal.

Carcinoma of unknown primary

- Detection of the primary site when imaging and histopathology has failed to show a primary site, where the site of tumour will influence choice of chemotherapy.

Neuroendocrine tumours

- Staging or restaging of selected patients with poorly differentiated neuroendocrine tumours prior to treatment with negative or normal metaiodobenzylguanidine (MIBG) and octreotide scans.
- Assessment of possible multifocal disease in patients with paraganglioma considered for surgery.

Rare tumours in children and young adults

- Staging of osteosarcoma and response to chemotherapy.
- Staging and response assessment of Ewing's sarcoma.
- PET-CT may be helpful on an individual case basis in paediatric or adolescent patients with:

- Wilms' tumours
- MIBG-negative neuroblastoma
- Hepatoblastoma
- Langerhans' cell histiocytosis.

Non-oncological applications

Neurological applications

- Pre-surgical assessment of medically refractory complex partial seizures where MR is normal, equivocal or conflicts with EEG localisation.
- Evaluation of memory loss/neurological signs suggestive of dementia and differentiation of types of dementia in selected patients.

See below for Amyloid imaging which may be helpful in highly selected patients with suspected dementia.

Cardiological indications

- Assessment of myocardial viability in patients with ischaemic heart failure and poor left ventricular function being considered for revascularisation, usually in combination with perfusion imaging with sestamibi/tetrofosmin or ammonia/rubidium.

Vasculitis

- Evaluation of suspected vasculitis in selected cases; for example, to determine the extent and distribution of the disease activity or to exclude underlying malignancy which may be a paraneoplastic phenomenon, resulting in atypical presentations of vasculitis.
- PET-CT would not be indicated in all patients with giant cell arteritis but is of use in patients where conventional investigations are unhelpful and treatment would be altered if ongoing inflammatory disease is confirmed.

Sarcoidosis

- Assessment of activity and distribution of disease at baseline in highly selected cases where there is diagnostic uncertainty using conventional imaging (e.g. suspected cardiac sarcoidosis).
- Assessment of disease response where other measures to monitor response are unhelpful and/or in patients with disease resistant to treatment.

Infection imaging

- Detection of site of focal infection in immuno-compromised patients or problematic cases of infection.
- Evaluation of vascular graft infection in selected cases provided sufficient time has elapsed since surgery.

Pyrexia of unknown origin (PUO)

- To identify the cause of a PUO where conventional investigations have not revealed a source.

3. Non-FDG tracers for clinical practice

The role of FDG in a range of malignancies is established, but there are limitations to using FDG for imaging some tumours. Non-FDG tracers can be used to image a limited number of tumours which would have little impact on the total number of patients scanned with PET-CT cameras, but are important for patient care. The exceptions are the potential use of choline derivatives for imaging prostate cancer and the use of amyloid tracers for assessment of patients with cognitive impairment/dementia.

Fluorinated tracers can be produced in a regional cyclotron and transported such as FDG, fluoro-choline. Generators that are used to produce radionuclides such as ^{68}Ga Gallium can be purchased and the tracers produced in nuclear medicine department radiopharmacies, although these tracers are not yet widely available. Other short-lived tracers such as ^{13}N -ammonia and ^{11}C -labelled compounds are produced in a cyclotron which needs to be on the same site as the scanner.

It is recognised that cyclotron and generator-produced tracers will be available in few specialist centres but that fluorinated tracers may become more widely available. The rationale for using alternative tracers to FDG for these indications is highlighted in italics.

Indications for non-FDG tracers

^{11}C -Methionine (cyclotron-produced short-lived tracer)

- Assessment of tumour grade and extent in some patients with glioma for staging or suspected recurrence to target biopsy and plan treatment.
- *^{11}C -Methionine is superior at defining the extent of tumour in low and intermediate grade gliomas compared to FDG, which has limited use because of high uptake in normal brain.*
- Parathyroid tumour localisation in difficult cases where the tumour has not been found using conventional anatomical and functional imaging techniques.
- *^{11}C -Methionine has been reported as having better sensitivity for localising tumour than FDG in difficult cases.*

^{13}N -Ammonia (cyclotron-produced short-lived tracer) ^{82}Rb -Rubidium chloride (generator-produced short-lived tracer)

- Assessment of myocardial perfusion in patients with suspected ischaemic heart disease or to assess the extent of disease in patients with known coronary artery disease (CAD).
- Assessment of perfusion in selected patients with coronary anomalies with congenital disease, after surgery and with Kawasaki's disease.
- *$^{99\text{m}}\text{Tc}$ -labelled tracers (sestamibi, tetrofosmin) are widely available and have high sensitivity and specificity for the evaluation of CAD with Single Photon Emission Computed Tomography (SPECT). However, PET tracers have improved sensitivity in some situations, for example, in high-body mass patients where significant attenuation of the inferior and anterior walls limits assessment. ^{13}N -Ammonia allows quantitative assessment of myocardial perfusion to be performed and is better to assess disease in patients with balanced three vessel disease. Rubidium has improved image quality compared to $^{99\text{m}}\text{Tc}$ and may be cost-effective compared*

to ^{99m}Tc when there is a large throughput of patients (~5 cases/day Monday to Friday). Both PET tracers are associated with lower radiation dose than ^{99m}Tc tracers.

^{11}C -Choline or ^{18}F -fluoro-choline (both cyclotron-produced but ^{11}C short-lived, ^{18}F can be transported)

- Evaluation of equivocal findings on conventional imaging such as possible nodal or metastatic disease in patients with prostate cancer where confirmation or exclusion of distant disease would directly influence patient management.
- Suspected recurrence in patients with a rapidly rising prostate-specific antigen (PSA) and indeterminate or equivocal conventional imaging where the results would directly influence patient management.
- Assessment of patients with hepatocellular carcinoma (HCC) being considered for transplant or other radical treatment where the results would directly influence patient management.
- *FDG is not taken up by most prostate cancers. FDG is taken up but rapidly dephosphorylated and 'washes out' of the liver and not useful to image up to 50% of HCC. Choline transport and choline kinase enzymes are over expressed in many malignancies including prostate cancer and HCC. A substantial number of observational studies support the use of choline PET-CT to detect local and distant metastatic disease in prostate cancer with improved accuracy compared to CT and MR. ^{11}C -Choline is generally preferred to ^{18}F -fluorocholine because it is not excreted in urine but has limited availability. There are two forms of ^{18}F -fluorocholine available (fluoro-methyl choline and fluoro-ethyl choline) and neither has undergone validation in direct comparison with ^{11}C -choline.*
- *At present, there is limited evidence from observational studies suggesting ^{18}F -fluorocholine improves the accuracy of HCC detection in primary staging and recurrence. Liver transplantation can offer some patients a chance of cure but careful pre treatment assessment is essential. A multicentre prospective trial comparing the accuracy of fluorocholine PET-CT and FDG PET-CT in HCC is in progress.*

^{11}C -Acetate

- Assessment of HCC.
- *The combination of FDG and acetate for HCC has been demonstrated to identify more abnormalities to stage the disease than conventional imaging.*

^{68}Ga -labelled somatostatin receptor (SSR) imaging (generator produced)

- Staging and assessment of suspected recurrence in neuroendocrine tumours (NETs).
- *Most NETs have low uptake of FDG; however, tracers that bind to somatostatin receptors which are expressed by these tumours have high uptake. Somatostatin receptor (SSR) scintigraphy using SPECT tracers, for example ^{111}In -octreotide, has been in clinical use for a number of years. Newer peptides labelled with ^{68}Ga such as DOTATOC and DOTATATE show much higher affinity for NETs. Recently radionuclide treatments using SSR agents have resulted in improved quality of life and survival for patients with NETs and SSR imaging helps to select and manage patients for radionuclide therapy.*

^{18}F -FluoroDOPA (cyclotron-produced but transportable)

- Assessment of suspected congenital hyperinsulinism.
- Assessment in selected cases of NETs.

- *There is evidence that F-DOPA may have high uptake in some NETs, mainly carcinoids and it can be useful to guide surgery in cases of suspected congenital hyperinsulinism.*

¹⁸F-Fluoride bone imaging (cyclotron-produced but transportable)

- Assessment of benign and malignant diseases of bone in selected patients.
- *Sodium ¹⁸F-fluoride produces very high quality images of the skeleton with high uptake in bone and rapid clearance from blood. ¹⁸F-Fluoride has been evaluated against ^{99m}Tc-MDP planar and SPECT imaging in patients with suspected or known metastatic bone disease. These studies show it to be more sensitive and specific than ^{99m}Tc-MDP scintigraphy, and the addition of CT increases further the specificity of the test.*
- *Uptake times are shorter than conventional bone scintigraphy, 15–30 minutes versus 3–4 hours, and imaging times are shorter 15–30 minutes versus 30–60 minutes suggesting that ¹⁸F-fluoride imaging for some patients with bone disease may be an appropriate use of PET-CT.*

¹⁸F-Florbetapir (Amyvid) brain imaging (cyclotron-produced but transportable)

- *Use in highly selected patients with cognitive impairment where i) Alzheimers dementia (AD) is a possible diagnosis but this remains uncertain after comprehensive evaluation by a dementia expert and conventional imaging work-up and ii) where knowledge of the presence or absence of amyloid is expected to increase diagnostic certainty and influence patient management.*
- *At present ¹⁸F-Florbetabir is the only amyloid imaging agent commercially available in the UK. Currently there is a paucity of evidence of the impact of this tracer on clinical outcomes and the above indication is based on appropriate use criteria developed by the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association. Amyloid PET imaging detects the presence of human amyloid β deposition in the brain. Whilst amyloid plaques are one of the defining pathological features of AD, it is not specific and can be present as part of the normal ageing process and in other clinical syndromes. As a result it is essential that this test is only used in patients who have been fully assessed by an expert clinician and it is considered that ¹⁸F-Florbetabir imaging can contribute to diagnosis in combination with clinical assessment and other factors.*
- *Currently there is insufficient evidence to support the use of this technique except in the scenario defined above where the patient has persistent or progressive unexplained memory impairment confirmed by standard medical tests, an unusual clinical presentation and/or an atypically early age of onset.*
- *Inappropriate scenarios for use would include patients 65 years or older who meet standard definitions and tests for AD; where there is no clinical evidence of memory impairment (i.e. as a screening tool); to assess the severity of dementia; in asymptomatic patients with a family history of dementia; for non-medical reasons such as pre-employment screening.*

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General overview

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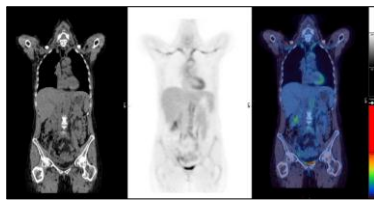
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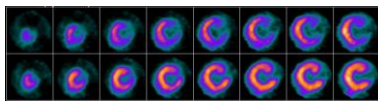
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Appendix: Explanation of figures on front cover



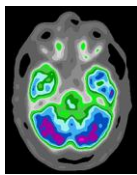
^{18}F -fluorodeoxyglucose (FDG) PET-CT image of vasculitis

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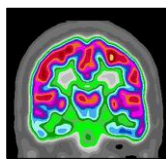
^{13}N -Ammonia stress-rest images of lateral ischaemia

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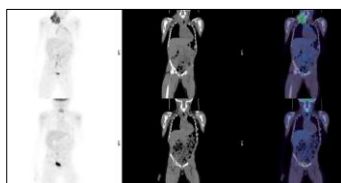
FDG and ^{11}C -Methionine axial images of low grade glioma

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FDG coronal image of right temporal epilepsy

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FDG PET-CT images of a child at staging and during treatment for Hodgkin lymphoma

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