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RECOMMENDATIONS

Appropriate indications for positron emission tomography/computed tomography, 2015

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These recommendations are intended to serve an important and relevant role in advising referring physicians on the appropriate use of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and non-^{18}F-FDG positron emission tomography/computed tomography (PET/CT), which can be a powerful tool in patient management in oncology, cardiology, neurology and infection/inflammation. PET is a non-invasive molecular imaging tool that provides tomographic images and quantitative parameters of perfusion, cell viability, proliferation and/or metabolic activity of tissues. These images result from the use of different substances of biological interest (sugars, amino acids, metabolic precursors, hormones) labelled with positron-emitting radionuclides (PET radiopharmaceuticals). Fusion of the aforementioned important functional information with the morphological detail provided by CT as PET/CT provides clinicians with a sensitive and accurate one-step whole-body diagnostic and prognostic tool, which directs and changes patient management. Hence PET/CT is currently the most widely used molecular imaging technology for a patient-tailored treatment approach. In these recommendations we outline which oncological and non-oncological indications are appropriate for PET/CT. Once each combination of pathology and clinical indication is defined, a recommendation is given as: 1. Recommended; 2. Recommended in select cases; 3. May be considered; or 4. Not recommended.

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1. Introduction

Positron emission tomography (PET) is a non-invasive molecular imaging tool that provides tomographic images and quantitative parameters of perfusion, cell viability, proliferation and/or metabolic activity of tissues. These images result from the use of different substances of biological interest (sugars, amino acids, metabolic precursors, hormones) labelled with positron-emitting radionuclides (PET radiopharmaceuticals). Fusion of the aforementioned important functional information with the morphological detail provided by computed tomography (CT) as PET/CT provides clinicians with a sensitive and accurate one-step whole-body diagnostic and prognostic tool, which directs and changes patient management.

Several studies have demonstrated the superiority of combined PET/CT over either modality alone, and for many indications this is generally accepted as the gold standard for imaging in oncology.[1] The value of PET/CT imaging has been best demonstrated in the setting of oncology with the use of ^{18}F-fluorodeoxyglucose (^{18}F-FDG). FDG is an analogue of glucose and is taken up by cells via the first stages of the normal glucose pathway and trapped inside cells with high glycolytic activity. Tumour uptake therefore correlates with tumour growth and viability, providing metabolic quantification and frequently useful information regarding tumour characterisation, patient prognosis and monitoring of the therapeutic response. Evidence is also rapidly accumulating for many indications in the fields of cardiology, neurology and infection imaging with existing tracers, and future growth is expected, given the numerous possibilities created by new tracers.

The rapid growth in PET/CT imaging worldwide, with the continual evolution of technology and clinical indications, makes

it difficult to ensure its optimal use. When used appropriately, PET/CT frequently provides powerful clinical information that improves patient outcomes and may lead to significant savings in the overall management costs of patients (e.g. by avoiding the cost of futile surgery and/or chemotherapy). Its inappropriate use has the potential risk of unjustifiable additional costs in patient management. There is frequently confusion among referring clinicians (and even imaging specialists) about the role of PET/CT in the management of a multitude of oncological and non-oncological conditions. The College of Nuclear Physicians (CNP) is the examining body for all nuclear medicine specialists in training. It is therefore also the body primarily responsible for the examination of PET/CT training in this country. In order to address these challenges, the CNP made the decision in late 2014 to draw up this document to provide guidance to referring clinicians (especially oncologists), nuclear medicine physicians, radiologists, and health insurers. This document strives to include recommendations on current indications for the use of PET/CT that represent the state of knowledge at the time of writing, and taking into account tracer availability in South Africa (SA). These indications are (for the most part) restricted to conditions where there is sufficient evidence of patient benefit, improved outcomes and altered management strategies and will be updated periodically as new evidence emerges.

It should be noted that recommendations and guidelines regarding the use of FDG-PET and PET/CT in oncology (and other fields) are available from several international professional organisations, such as the European Association of Nuclear Medicine (EANM) (http://www.eanm.org/publications/guidelines/index.php?navId=37), the Society of Nuclear Medicine and Molecular Imaging (SNMMI) (http://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=6414), the British Nuclear Medicine Society (BNMS) (http://www.bnms.org.uk/procedures-guidelines/bnms-guidelines-overview/) and the International Atomic Energy Agency (IAEA) (http://www.iaea.org/Publications/index.html), among others. Readers who seek further information are referred to these guidelines for more detailed information. This document is not intended to replace these documents, but aims to integrate and adapt this information to the SA context.

1.1 Indications and recommendations

The decision to approve an indication should ideally be made on an individual basis for each cancer type at the nuclear medicine physician's discretion. It is inadequate to make a decision on the appropriateness of PET/CT based on pathology alone; rather, an explicit clinical question needs to be defined. Oncology-related indications have been categorised into screening, diagnosis, staging, early response assessment, restaging/response post therapy, suspected recurrence, surveillance, radiotherapy planning, and in some cases peptide receptor radiation therapy (PRRT) planning. These are further defined below:

- Screening – search for tumour in patients with increased risk but no known evidence of cancer
- Diagnosis – for better definition of pathology in patients with known/suspected cancer
- Staging – assessment of tumour spread in untreated patients with known cancer
- Early response assessment – assessment of therapy efficacy during treatment, allowing for the possibility of prognostication or changing ineffective therapy before its completion
- Restaging – this refers to two possible scenarios: (*i*) assessment of tumour function and spread after completion of therapy; and (*ii*) assessment of tumour function and spread in a patient with confirmed recurrence of disease
- Suspected recurrence – assessment of tumour recurrence in patients with evidence (e.g. clinical, biochemical, or radiological) for tumour relapse
- Surveillance – routine follow-up scanning of patients in apparent remission
- Radiotherapy planning – use of functional (PET) and anatomical (CT) information for definition of external-beam radiotherapy treatment volumes
- PRRT planning – a molecularly targeted radiation therapy involving the systemic administration of a radiolabelled peptide designed to target with high affinity and specificity receptors overexpressed on tumours.

Once each combination of pathology and clinical indication is defined, a recommendation is given as: 1. Recommended: 2. Recommended in select cases; 3. May be considered; or 4. Not recommended. Further information is set out below in order to provide clarity on how each of these recommendations was determined, as well as their meaning in terms of future decision making:

1. **Recommended:** PET/CT is generally appropriate for this indication. There is a strong base of evidence supporting its use and/or it is currently recommended by international clinical guidelines.
2. **Recommended in select cases:** PET/CT is appropriate for this indication in cases meeting clearly defined criteria. In this specific context there is a strong base of evidence supporting its use and/or it is currently recommended by international clinical guidelines.
3. **May be considered:** PET/CT is generally not appropriate for this indication; however, it may be appropriate in individual cases with a strong motivation. Typically there may be some evidence or a strong rationale to support the use of PET/CT in special circumstances.
4. **Not recommended:** PET/CT is generally not appropriate for this indication. Typically there is a low level of evidence and/or weak rationale for its use, and it is not endorsed by international clinical guidelines.

1.2 The SA context

The vast majority of professional international guidelines also apply to the SA setting, without the need for adaptation. However, cancer patients tend to present later (especially in the public sector) with more advanced disease, and may therefore require imaging with PET/CT earlier in their management. In light of the relatively high incidence of HIV and tuberculosis (TB) co-infection, some special considerations apply. This patient group may simultaneously present with a wide range of malignant and infective conditions, which may be difficult to distinguish with ^{18}F-FDG PET. It is therefore imperative that referring physicians include pertinent information such as HIV status, CD4 count, viral load, diagnosis of previous or current TB, and current or past therapy with highly active antiretroviral therapy and/or anti-TB drugs.[2]

1.3 Cost-effectiveness

Data on the cost-effectiveness of PET/CT are limited, with even fewer studies obtained in the context of a middle-income country such as SA. However, many of the published data demonstrate a cost-effective role for PET/CT for particular oncology-related indications.[3] In some clinical scenarios the use of PET/CT can even lead to an overall reduction in the cost of patient management. This typically occurs through the avoidance of expensive invasive diagnostic procedures, the minimisation of futile surgery and the early cessation of

ineffective chemotherapeutic regimens. Unlike anatomical imaging, PET can predict the efficacy of chemotherapeutic regimens early in the course of therapy, enabling costly but ineffective therapy to be altered early, with benefits to patients and reduced costs. Cost-effectiveness studies should ideally reflect local disease prevalence (both oncology and inflammatory conditions that may give rise to reduced specificity) and local costs. In SA, while data are currently limited, there is already some evidence that PET can be cost-effective and can even reduce the overall cost of treatment.[4] From a practical perspective there is a need to make decisions regarding the likely cost-effectiveness of PET/CT locally that are based on available local and international data, as comprehensive SA cost-effectiveness studies are not expected to be available in the immediate future. During the development of these guidelines there has also been a focus on the appropriateness of clinical indications within the context of the relatively cost-constrained environment of a middle-income country.

2. ^{18}F-FDG PET: Oncology

2.1 Central nervous system (CNS) tumours

2.1.1 Screening

FDG PET/CT is **not recommended**.

2.1.2 Diagnosis

- FDG PET/CT is **not recommended** for grading of brain tumours.[1]
- FDG PET/CT is **recommended in select cases** for distinguishing cerebral tumour from atypical infection in HIV-positive (HIV+) patients when anatomical imaging is inconclusive.[2,3] The greatest utility of FDG PET/CT may be in distinguishing infection from primary CNS lymphoma.[3]
- FDG PET/CT **may be considered** to provide optimal targets for stereotactic biopsy as it may increase the diagnostic yield from this procedure.[1]

2.1.3 Staging

- FDG PET/CT is **not recommended** for staging.

2.1.4 Early response assessment

- FDG PET/CT **may be considered** to assess response to chemotherapy.[1]

2.1.5 Restaging/response post therapy

- FDG PET/CT is **not recommended** for restaging post therapy.[1]
- FDG PET/CT is **not recommended** for restaging of confirmed recurrence.

2.1.6 Suspected recurrence

- FDG PET/CT is **recommended in select cases** to distinguish between suspected tumour recurrence and radiation necrosis when magnetic resonance imaging (MRI) is inconclusive.[1,4]

2.1.7 Surveillance

- FDG PET/CT is **not recommended** for routine surveillance.[1]

2.1.8 Radiotherapy planning

- FDG PET/CT is **not recommended** for radiotherapy planning.[1]

2.1.9 Plexiform neurofibroma

2.1.9.1 Diagnosis

- FDG PET/CT **may be considered** in patients with suspected malignant transformation of plexiform neurofibroma in neurofibromatosis type 1.

2.2 Head and neck cancer

The head and neck cancers include malignancies arising from the lining of the upper aerodigestive tract such as the oral cavity, pharynx, larynx, paranasal sinuses and major salivary glands. Thyroid and central nervous system malignancies are excluded.

2.2.1 Screening

- FDG PET/CT **may be considered** for screening for a second primary tumour. Second primary tumours can occur in up to 27% of head and neck squamous cell cancer patients, most frequently in the head and neck region, oesophagus and lungs.

2.2.2 Diagnosis

- FDG PET/CT is **recommended in select cases** for detection of an occult primary tumour site in patients presenting with cervical nodal metastases. (See 2.9, Malignancy of undefined primary origin and provisional carcinoma of unknown primary.)

2.2.3 Staging

- PET/CT is **recommended in select cases** for initial staging in patients with suspected advanced-stage disease, or tumours with a high propensity for spreading (such as naso- and hypopharyngeal carcinomas).[1]

2.2.4 Restaging/response post therapy

- FDG PET/CT is **recommended** for treatment response assessment.[2]

2.2.5 Suspected recurrence

- FDG PET/CT is **recommended** for detection of recurrence in patients suspected clinically or on conventional imaging of having recurrent disease (locoregional or distant).[3]

2.2.6 Surveillance

- FDG PET/CT is **not recommended** in asymptomatic patients where there is no suspicion of recurrence.

2.2.7 Radiotherapy planning

- FDG PET/CT is **recommended** for radiation therapy planning.[4]

2.3 Thyroid cancer

2.3.1 Screening

- FDG PET/CT is **not recommended** for screening at-risk populations.

2.3.2 Diagnosis

- FDG PET/CT is **not recommended** for the diagnosis of thyroid cancers.

2.3.3 Staging

- The routine use of FDG PET/CT in differentiated thyroid carcinoma is **not recommended**.[1]
- FDG PET/CT is **recommended in select cases** for the assessment of the extent of disease in patients with Hurthle cell carcinomas.[1,2]

2.3.4 Restaging/response post therapy

- FDG PET/CT is **recommended in select cases** in evaluation of treatment response following systemic or local therapy of metastatic or locally invasive disease in poorly differentiated thyroid cancers and invasive Hurthle cell carcinomas.[2,3]

- FDG PET/CT **may be considered** in medullary thyroid cancer to detect additional sites of disease in the context of a detectable calcitonin post thyroidectomy.

2.3.5 Suspected recurrence
- FDG PET/CT is **recommended in select cases** of differentiated thyroid cancer for detection of residual or recurrent disease when serum thyroglobulin is elevated and radioiodine scan is negative.[4]
- FDG PET/CT **may be considered** for suspected recurrence in treated medullary thyroid cancer, presenting with elevated calcitonin or carcinoembryonic antigen with normal or equivocal conventional imaging and octreotide scintigraphy. (Alternative PET-CT imaging with ^{68}Ga-DOTATATE/NOC/TOC is recommended in these select cases).

2.3.6 Surveillance
- FDG PET/CT is **not recommended**.

2.3.7 Radiotherapy planning
- FDG PET/CT is **not recommended**.

2.4 Thymoma and thymic carcinoma

2.4.1 Screening
- FDG PET/CT is **not recommended**.

2.4.2 Diagnosis
- FDG PET/CT **may be considered** as part of the work-up of anterior mediastinal mass, to detect other lesions.[1] In addition, FDG PET/CT may assist in differentiating thymoma from thymic carcinoma.[2]
- FDG PET/CT is **not recommended** to distinguish thymic hyperplasia from thymoma.[1]

2.4.3 Staging
- FDG PET/CT is **not recommended** for staging of thymoma.[2,3]
- FDG PET/CT **may be considered** for staging of thymic carcinoma.[1]

2.4.4 Restaging/response post therapy
- FDG PET/CT **may be considered** for restaging of thymic carcinoma post therapy.[1] In such cases a baseline PET/CT is required.
- FDG PET/CT **may be considered** to assess treatment response in patients with unresectable Masaoka stage III or IV thymoma.[4] In such cases a baseline PET/CT is recommended for comparison.[2]
- FDG PET/CT is **not recommended** for response assessment in thymic carcinoma.

2.4.5 Suspected recurrence
- FDG PET/CT **may be considered** to detect suspected recurrence of thymoma or thymic carcinoma if CT findings are inconclusive.[3]

2.4.6 Surveillance
- FDG PET/CT is **not recommended** for routine follow-up.

2.4.7 Radiotherapy planning
- FDG PET/CT is **not recommended** for radiotherapy planning in thymoma or thymic carcinoma.

2.5 Breast cancer

2.5.1 Screening
- FDG PET/CT is **not recommended**.

2.5.2 Diagnosis
- FDG PET/CT is **not recommended** for routine use in diagnosis.
- FDG PET/CT **may be considered** in selected patients with dense breasts, where the sensitivity of mammography is poor.[1]

2.5.3 Staging
- FDG PET/CT is **recommended in select cases** for initial staging of patients with locally advanced or metastatic breast cancer or inflammatory breast cancer as an adjunct to conventional imaging, when conventional studies (such as CT or bone scan) are equivocal.[1]

2.5.4 Restaging/response post therapy
- FDG PET/CT is **recommended in select cases** for assessment of response to therapy in patients whose disease is not well demonstrated on conventional imaging.[2]
- FDG PET/CT is **recommended in select cases** for differentiation of treatment-induced brachial plexopathy from tumour infiltration in symptomatic patients with an equivocal or normal MRI scan.[1]

2.5.5 Suspected recurrence
- FDG PET/CT is **recommended** in assessment of suspected recurrent disease (clinically/radiological/tumour markers/surrogate tumour markers).[3,4]

2.5.6 Surveillance
- FDG PET/CT is **not recommended**.

2.5.7 Radiotherapy planning
FDG PET/CT is **not recommended**.

2.6 Lymphoma

2.6.1 Hodgkin's lymphoma (HL)

2.6.1.1 Screening
- FDG PET/CT is **not recommended**.

2.6.1.2 Diagnosis
- FDG PET/CT **may be considered** to identify amenable biopsy sites if these are not clinically apparent in a patient with suspected lymphoma.[1]

2.6.1.3 Staging
- FDG PET/CT is **recommended** for routine staging (including marrow staging) of HL.[1]
- *If contrast-enhanced CT (ceCT) is used as part of staging, this should ideally occur in a single visit, in combination with PET/CT (i.e. cePET/CT), only if it has not already been performed.*[1]

2.6.1.4 Early response assessment
- The use of interim PET/CT to detect early treatment response in HL **may be considered**.[1,2]
- FDG PET/CT **may be considered** for interim response assessment of patients with HD 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 response scan.

2.6.1.5 Restaging/response post therapy
- FDG PET/CT guidelines for restaging of biopsy-confirmed recurrence are similar to those for staging above.
- FDG PET/CT at completion of therapy is **recommended** in HL as the preferred restaging method and is prognostic of treatment

success and subsequent survival (assessment should be made using Deauville criteria).[1,3]
- FDG PET/CT is **recommended** at completion of salvage therapy in primary resistant HL and relapsed classic HL as the preferred restaging method.[4] The achievement of PET negativity following salvage is a good prognostic indicator for outcome following autologous stem cell transplant (ASCT) in HL. Residual FDG-positive disease after ASCT is a poor prognostic factor.
- FDG PET/CT is **recommended in select cases** to determine treatment response in HL, when deciding whether patients with advanced HL who have completed BEACOPP escalated require radiotherapy.

2.6.2 Non-Hodgkin's lymphoma (NHL)

2.6.2.1 Screening
- FDG PET/CT is **not recommended**.

2.6.2.2 Diagnosis

FDG PET/CT **may be considered** for identifying amenable biopsy sites if not clinically apparent in a patient with suspected lymphoma.[1]

2.6.2.3 Staging
- FDG PET/CT is **recommended** for routine staging of FDG-avid nodal lymphomas (diffuse large B-cell; follicular; mantle-cell; Burkitt's; nodal marginal zone; lymphoblastic; anaplastic large T-cell; natural-killer/T-cell; angioimmunoblastic T-cell; peripheral T-cell).[1,3]
- FDG PET/CT is **recommended** for routine staging of primary extranodal diffuse large B-cell lymphoma (DLBCL).[3]
- FDG PET/CT is **not recommended** for routine staging of non-FDG-avid nodal lymphomas (lymphoplasmacytic lymphoma/Waldenström's macroglobulinaemia, chronic lymphocytic leukaemia/small lymphocytic, marginal zone splenic, marginal zone unspecified).
- FDG PET/CT **may be considered** for staging of primary cutaneous NHLs except for stage IA disease and in lymphomatoid papulosis. FDG PET may have poor sensitivity for cutaneous lesions in these disorders and have a higher rate of false-negatives in detecting involved lymph nodes.[1]
- FDG PET/CT is **not recommended** for staging of mucosa-associated lymphoid tissue (MALT) marginal zone lymphoma or enteropathy-type T-cell lymphoma.
- FDG PET/CT **may be considered** in primary CNS lymphoma to exclude occult systemic lymphoma.
- *If contrast-enhanced CT (ceCT) is used as part of staging, this should ideally occur in a single visit, in combination with PET/CT (i.e. cePET/CT), only if it has not already been performed.*[1]

2.6.2.4 Early response assessment

FDG PET/CT **may be considered** for assessment of response to initial therapy in NHL. There is as yet insufficient evidence to endorse the routine use of interim PET/CT in NHL to determine response to initial treatment.

2.6.2.5 Restaging/response post therapy
- FDG PET/CT guidelines for restaging of biopsy-confirmed recurrence are similar to those for staging above.
- FDG PET-CT is **recommended** for remission assessment in FDG-avid nodal NHL lymphoma and primary extranodal DLBCL after completion of therapy (assessment should be made using Deauville criteria).[1]
- FDG PET/CT is **recommended in select cases** for restaging of non-FDG-avid nodal lymphomas (lymphoplasmacytic lymphoma/Waldenström's macroglobulinaemia, chronic lymphocytic leukaemia/small lymphocytic, marginal zone splenic, marginal zone unspecified), if there is suspicion of aggressive transformation.[3]

2.6.2.6 Suspected recurrence
- FDG PET/CT is **recommended in select cases** to detect suspected relapse of FDG-avid nodal lymphoma, when no clinically apparent biopsy sites are available. Imaging features suggestive of relapse require histological confirmation. A negative PET in this context has a high negative predictive value.[1]

2.6.2.7 Surveillance
- FDG PET/CT is **not recommended** for routine follow-up of successfully treated NHL.[1,3]

2.6.2.8 Radiotherapy planning
- FDG PET/CT is **may be considered** in radiotherapy treatment planning in NHL, although there is currently insufficient evidence to support its routine use.

2.7 Langerhans cell histiocytosis (LCH)

2.7.1 Screening
- FDG PET/CT is **not recommended**.

2.7.2 Diagnosis
- FDG PET/CT is **not recommended** for diagnosis of LCH.

2.7.3 Staging
- FDG PET/CT **may be considered** for determining extent of disease at baseline.

2.7.4 Restaging/response post therapy
- FDG PET/CT **may be considered** to assess response to treatment. When used for this indication, a baseline scan is recommended.

2.7.5 Suspected recurrence
- FDG PET/CT **may be considered** for detecting suspected recurrence of disease.

2.7.6 Surveillance
- FDG PET/CT **may be considered** for routine surveillance. An optimal strategy has not been determined; radiation dosimetry is especially important in paediatric patients.

2.7.7 Radiotherapy planning
- FDG PET/CT is **not recommended** for radiotherapy planning.

2.7.8 Non-Langerhans cell histiocytoses (NLCH)
- FDG PET/CT is **recommended** to determine the extent of disease, and for monitoring treatment response and surveillance in Erdheim-Chester disease.
- As rare disorders, no clinical guidelines exist for other non-Langerhans cell histiocytic disorders (e.g. Rosai-Dorfman disease, haemophagocytic lymphohistiocytosis, Kikuchi disease). Utility of FDG PET/CT has been described in many of these conditions, however. Because of the inflammatory nature of lesions in histiocytic disorders, sites of disease are expected to be FDG-avid. As such FDG PET/CT **may be considered** for the same indications

as listed under LCH, where the results of the scan will affect management.

2.7.9 Other lymphoproliferative disorders

- FDG PET/CT **may be considered** in *staging* and *restaging* of post-transplant lymphoproliferative disorder.
- FDG PET/CT **may be considered** in *staging* and *restaging* of other lymphoproliferative disorders, such as lymphomatoid granulomatosis and Castleman disease. As rare disorders, evidence for the utility of FDG PET/CT in these conditions is limited.

2.8 Multiple myeloma

2.8.1 Screening

- FDG PET/CT is **not recommended**.

2.8.2 Diagnosis

- FDG PET/CT **may be considered** under certain circumstances when standard workup is ambiguous or inconclusive.[1] FDG PET/CT **may be considered** to distinguish between patients with definite active myeloma (FDG-positive) and patients with monoclonal gammopathy of unknown significance or smouldering disease (both of which are FDG-negative).[2]

2.8.3 Staging

- FDG PET/CT is **recommended in select cases** for patients with apparently solitary plasmacytoma to exclude early bone marrow involvement, but cannot be used as a substitute for conventional imaging methods.[2]
- FDG PET/CT **may be considered** to exclude extensive or extramedullary disease if this will impact therapeutic decisions.[3]

2.8.4 Restaging/response post therapy

- FDG PET/CT is **not recommended** for restaging of multiple myeloma after definitive therapy.
- FDG PET/CT **may be considered** to assess treatment response in multiple myeloma.[4] If used in this context, a baseline PET/CT is recommended.

2.8.5 Suspected recurrence

- FDG PET/CT is **recommended in select cases** for suspected relapse in patients with non-secretory myeloma or predominantly extramedullary disease.

2.8.6 Surveillance

- FDG PET/CT **may be considered** for routine follow-up of multiple myeloma as clinically indicated.[4]

2.8.7 Radiotherapy planning

- FDG PET/CT is **not recommended** in radiotherapy planning of plasmacytoma or multiple myeloma (insufficient evidence).

2.9 Malignancy of undefined primary origin (MUO) and provisional carcinoma of unknown primary (CUP)

2.9.1 MUO

MUO is metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, *before comprehensive investigation*. Investigations that form the recommended initial work-up of MUO are covered by several international guidelines.

2.9.2 Provisional CUP

Provisional CUP is metastatic epithelial or neuroendocrine malignancy identified on the basis of histology/cytology, with no primary site detected *despite a selected initial screen of investigations*, before specialist review and possible further specialised investigations.

2.9.3 Confirmed CUP

Confirmed CUP is metastatic epithelial or neuroendocrine malignancy identified on the basis of final histology, with no primary site detected despite a selected initial screen of investigations, specialist review, and further specialised investigations as appropriate.

2.9.4 Screening

- FDG PET/CT is **not recommended**.

2.9.5 Diagnosis

2.9.5.1 MUO

- FDG PET/CT is **not recommended** in the routine investigation of these patients.[1,2]

2.9.5.2 Provisional CUP

- FDG PET/CT is **recommended in select cases** in patients presenting with cervical lymphadenopathy with no primary tumour identified on ear, nose and throat panendoscopy *if radical treatment is considered to be an option*.[3]

2.9.6 Staging

2.9.6.1 Provisional CUP

- FDG PET/CT **is recommended in select cases** to detect disease amenable to local or regional therapy[3] or when curative therapy is planned,[4] such as in the case of extracervical presentation of a *single metastatic lesion* and a negative conventional work-up.

2.9.7 Restaging/response post therapy

- FDG PET/CT is **not recommended** to assess response to initial treatment.

2.9.8 Suspected recurrence

- FDG PET/CT is **not recommended** to restage after completing therapy.

2.9.9 Surveillance

- FDG PET/CT is **not recommended** for surveillance.

2.9.10 Radiotherapy planning

- FDG PET/CT is **not recommended** for radiotherapy planning.

2.10 Paraneoplastic neurological syndrome (PNS)

2.10.1 Screening

The optimal strategy for tumour screening in the context of a PNS is directed based on the most likely primary. Most likely primary site is assessed on (among other factors) the clinical syndrome and type of paraneoplastic antibody detected:[1]

2.10.1.1 Likely small-cell lung cancer

- FDG PET/CT is **recommended** if an initial CT thorax is negative.

2.10.1.2 Likely thymoma

- FDG PET/CT is **recommended** if an initial CT thorax is negative.

2.10.1.3 Likely breast carcinoma
- FDG PET/CT is **recommended** if mammography and MRI breast are negative.

2.10.1.4 Likely teratoma
- FDG PET/CT is **not recommended**.

2.10.1.5 Likely ovarian carcinoma
- FDG PET/CT **may be considered** if transvaginal ultrasound ± CT-pelvis/abdomen are negative.

2.10.1.6 Likely testicular tumour
- FDG PET/CT is **not recommended**.
- If *no paraneoplastic antibodies* are detected, the patient has a classic PNS, and the neurological condition is deteriorating, total-body FDG PET/CT, is **recommended** if initial recommended investigations directed towards a likely primary site are negative.[1]
- Because of the high negative predictive value of initial PET/CT, the repeated use of FDG PET/CT **may be considered** as part of screening in patients with PNS and paraneoplastic antibodies in whom no primary tumour has been identified at baseline, if suspicion of a malignancy remains high.[2]

2.11 Melanoma

2.11.1 Screening
- FDG PET/CT is **not recommended**.

2.11.2 Diagnosis
- FDG PET/CT is **not recommended**.

2.11.3 Staging
- FDG PET/CT is **not recommended** in early-stage patients (AJCC stages I and II).
- FDG PET/CT is **recommended in select cases** for detection and localisation of potential extranodal metastatic lesions in initial evaluation of patients with clinically suspected advanced-stage disease (AJCC stage III and IV),[1] and for staging of patients with known disseminated melanoma to assess extent of disease prior to treatment.[1]
- FDG PET/CT **is recommended in select cases** where metastasectomy is planned, to exclude disease that might make surgery inappropriate.[2]

2.11.4 Restaging/response post therapy
- FDG PET/CT is **recommended in select cases** for evaluation of the extent of metastatic disease burden in recurrent disease following treatment.[3]
- FDG PET/CT is **recommended in select cases** to assess response to isolated limb infusion.[4]

2.11.5 Surveillance
- FDG PET/CT is **not recommended** for routine follow-up.[3]

2.11.6 Suspected recurrence
- FDG PET is **recommended in select cases** of suspected recurrence where symptom-guided conventional imaging is equivocal.[3]

2.12 Lung cancers

2.12.1 Non-small-cell lung cancer (NSCLC)

Definition: Solitary pulmonary nodule (SPN): a single, well-circumscribed, radiographic opacity ≤3 cm in diameter that is completely surrounded by aerated lung (i.e. not touching mediastinum or hilum), not associated with atelectasis, hilar enlargement, or pleural effusion.

2.12.1.1 Screening
- FDG PET/CT is **not recommended** for screening at-risk populations.

2.12.1.2 Diagnosis
- FDG PET/CT is **recommended in select cases** in the investigation of a solid, non-calcified SPN ≥8 mm in diameter that is suspicious for malignancy.[1] FDG PET/CT has a good negative predictive value in this context, which allows for radiological follow-up of low-risk patients. The positive predictive value of FDG PET/CT in identifying malignant nodules is generally good but is reduced in regions with a high prevalence of infectious lung disease (e.g. TB);[2] it is not possible to reliably distinguish between infective and malignant nodules on the basis of PET.[1]

2.12.1.3 Staging
- FDG PET/CT is **recommended in select cases** as part of staging for patients with potentially curable disease (on CT staging) and who are fit for definitive therapy.[1]

2.12.1.4 Restaging/response post therapy
- FDG PET/CT **may be considered** after induction therapy to exclude progression of disease.[1]
- For patients with biopsy-confirmed recurrence PET/CT **may be considered** for restaging to assist selection of therapy.

2.12.1.5 Suspected recurrence
- FDG PET/CT **may be considered** when findings on follow-up CT are equivocal for neoplasm. When used in this context, biopsy confirmation is necessary for positive PET findings.[1]

2.12.1.6 Surveillance
- FDG PET/CT is **not recommended** for routine follow-up of NSCLC.[1]

2.12.1.7 Radiotherapy planning
- FDG PET/CT **may be considered** to assist radiotherapy planning, especially when there is significant atelectasis or when intravenous (IV) contrast is contraindicated.[1]

2.12.2 Small-cell lung cancer (SCLC)

2.12.2.1 Screening
- FDG PET/CT is **not recommended** for screening populations at risk.

2.12.2.2 Diagnosis
- FDG PET/CT is **recommended in select cases** for the investigation of a solid, non-calcified SPN ≥8 mm in diameter that is suspicious for malignancy.[1] FDG PET/CT has a good negative predictive value in this context, which allows for radiological follow-up of low-risk patients. The positive predictive value of FDG PET/CT in identifying malignant nodules is generally good but is reduced in regions with a high prevalence of infectious lung disease (e.g. TB);[2] it is not possible to reliably distinguish between infective and malignant nodules on the basis of PET.[1]

2.12.2.3 Staging
- FDG PET/CT is **recommended in select cases** as part of staging for patients with suspected limited-stage disease, who are potential candidates for radical management and in whom the detection of occult disease would alter management.[3]

2.12.2.4 Restaging/response post therapy
- FDG PET/CT is **not recommended** for response assessment in SCLC.
- PET/CT is **not recommended** for restaging of confirmed recurrence.

2.12.2.5 Suspected recurrence
- FDG PET/CT is **not recommended** after definitive therapy.

2.12.2.6 Surveillance
- FDG PET/CT is **not recommended** for routine follow-up of SCLC.[3]

2.12.2.7 Radiotherapy planning
- FDG PET/CT **may be considered** to assist radiotherapy planning.[3]

2.13 Primary pleural malignancy/mesothelioma

2.13.1 Screening
- FDG PET/CT is **not recommended**.

2.13.2 Diagnosis
- FDG PET/CT is **not recommended** for routine diagnosis of mesothelioma.
- FDG PET/CT **may be considered** in patients with suspected primary pleural malignancy, in whom conventional imaging and pleural biopsy are inconclusive, in order to guide choice of biopsy site. In these cases PET/CT should be performed prior to talc pleurodesis.

2.13.3 Staging
- FDG PET/CT is **recommended in select cases** for staging of patients being considered for surgery as part of a curative strategy, who have clinical stage I - III disease with epithelial or mixed histology.[4] In these patients, PET/CT should be performed before any pleurodesis.

2.13.4 Restaging/response post therapy
- FDG PET/CT is **not recommended** to assess treatment response.
- FDG PET/CT is **not recommended** to restage patients after definitive therapy.
- FDG PET/CT is **not recommended** for restaging of biopsy-confirmed recurrence.

2.13.5 Suspected recurrence
- FDG PET/CT **may be considered** to detect suspected recurrence in mesothelioma.

2.13.6 Surveillance
- FDG PET/CT is **not recommended** for routine follow-up after definitive therapy.

2.13.7 Radiotherapy planning
- FDG PET/CT **may be considered** in radiotherapy planning.

2.14 Gastrointestinal tract (GIT)

2.14.1 Oesophageal cancer

2.14.1.1 Screening
- FDG PET/CT **is not recommended.**

2.14.1.2 Diagnosis
- FDG PET/CT is **not recommended** for the diagnosis of oesophageal cancer.[1]

2.14.1.3 Staging
- FDG PET/CT is **recommended in select cases** for staging in patients being considered for radical therapy.[2]

2.14.1.4 Restaging/response post-therapy
- FDG PET/CT is **recommended in select cases** for restaging after neoadjuvant treatment in patients being considered for radical therapy.[2]

2.14.1.5 Suspected recurrence
- FDG PET/CT is **recommended in select cases** to detect recurrence when other imaging is negative or equivocal.[2]

2.14.1.6 Surveillance
- FDG PET/CT **may be considered** for routine follow-up of patients given the high incidence of recurrence.

2.14.1.7 Radiotherapy planning
- FDG PET/CT **may be considered** for radiotherapy planning as several studies have shown a good correlation between FDG-PET and pathology-based tumour length.

2.14.2 Gastric cancer

2.14.2.1 Screening
- FDG PET/CT is **not recommended**.

2.14.2.2 Diagnosis
- FDG PET/CT is **not recommended** for the diagnosis of gastric cancer. Diagnosis is established by endoscopy and biopsy.

2.14.2.3 Staging
- FDG PET/CT **may be considered** for staging owing to an increased detection of nodal and distant metastatic disease.[1]

2.14.2.4 Restaging/response post therapy
- FDG PET/CT **may be considered** for restaging after definitive therapy.[1]
- FDG PET/CT **may be considered** for assessing the response to preoperative chemotherapy.

2.14.2.5 Suspected recurrence
- FDG PET/CT is **not recommended** in cases of suspected recurrence.[1]

2.14.2.6 Surveillance
- FDG PET/CT **may be considered** in the post-treatment surveillance of patients.[1]

2.14.2.7 Radiotherapy planning
- FDG PET/CT is **not recommended**.[1]

2.14.3 Pancreatic adenocarcinoma

2.14.3.1 Screening
- FDG PET/CT is **not recommended**.

2.14.3.2 Diagnosis
- FDG PET/CT is **not recommended** as it offers no benefit over the current primary diagnostic tools in diagnosing pancreatic cancer.

2.14.3.3 Staging
- FDG PET/CT **recommeded in select cases** for staging of patients with potentially operable pancreatic adenocarcinoma where conventional imaging is equivocal, and a positive PET/CT would lead to a decision not to operate.[2]

2.14.3.4 Early response assessment
- FDG PET/CT is **not recommended**.[1]

2.14.3.5 Restaging/response post therapy
- FDG PET/CT is **not recommended**.[1]

2.14.3.6 Suspected recurrence
- FDG PET/CT **may be considered** in cases of suspected recurrence, where other imaging is equivocal or negative.[2]

2.14.3.7 Surveillance
- FDG PET/CT **may be considered** in the post-treatment surveillance of patients.[1]

2.14.3.8 Radiotherapy planning
- FDG PET/CT **may be considered** for target volume delineation and dose intensification.[1]

2.14.4 Colorectal cancer

2.14.4.1 Screening
- FDG PET/CT is **not recommended**.

2.14.4.2 Diagnosis
- FDG PET/CT is **not recommended** for the diagnosis of colorectal cancer.[1]

2.14.4.3 Staging
- FDG PET/CT is **recommended in select cases** for patients in whom potentially resectable metastases have been detected on conventional imaging.[3]
- FDG PET/CT **may be considered** in patients in whom conventional imaging is equivocal.[2]

2.14.4.4 Early response assessment
- FDG PET/CT **may be considered** during chemotherapy in advanced colorectal cancer to identify ineffective treatment in non-responders.[4]

2.14.4.5 Restaging/response post therapy
- FDG PET/CT is **recommended in select cases** for restaging of patients with confirmed recurrence being considered for radical treatment and/or metastatectomy.[1,2]
- FDG PET/CT **may be considered** after local ablative therapy of liver metastases to identify residual tumour at an early stage.[2]
- FDG PET/CT **may be considered** after preoperative radiotherapy for rectal cancer as ^{18}F-FDG PET/CT has been shown to correlate better with pathology than conventional imaging.[4]
- FDG PET/CT **may be considered** for the evaluation of indeterminate presacral masses post treatment.

2.14.4.6 Suspected recurrence
- FDG PET/CT is **recommended** to detect recurrence in cases of rising tumour markers.
- FDG PET/CT **may be considered** in cases of clinically suspected recurrence with equivocal findings on other imaging.[2]

2.14.4.7 Surveillance
- FDG PET/CT **may be considered** for routine follow-up of patients, as in limited studies it has been shown to detect recurrence at an earlier stage.

2.14.4.8 Radiotherapy planning
- FDG PET/CT is **not recommended** for radiotherapy planning.[1]

2.14.5 Anal cancer

2.14.5.1 Screening
- FDG PET/CT is **not recommended**.

2.14.5.2 Diagnosis
- FDG PET/CT is **not recommended**.

2.14.5.3 Staging
- FDG PET/CT is **not recommended** for routine use as it has not been validated and it should not replace diagnostic CT.
- FDG PET/CT **may be considered** for node-positive disease and T2-4 N0 disease to confirm staging before surgery.

2.14.5.4 Restaging/response post therapy
- FDG PET/CT **may be considered** for restaging of patients with persistent, progressive or recurrent disease who are being considered for salvage surgery.

2.14.5.5 Suspected recurrence
- FDG PET/CT is **not recommended**.

2.14.5.6 Surveillance
- FDG PET/CT is **not recommended**.

2.14.5.7 Radiotherapy planning
- FDG PET/CT **may be considered**.

2.15 Hepatobiliary cancers (hepatocellular carcinoma (HCC), gallbladder carcinoma and cholangiocarcinoma)

2.15.1 Screening
- FDG PET/CT is **not recommended**.

2.15.2 Diagnosis
- FDG PET/CT is **not recommended**.

2.15.3 Staging
- FDG PET/CT is **not recommended** for routine staging of HCC.
- FDG PET/CT **may be considered** to detect distant and nodal metastases in patients with biliary cancer and otherwise potentially resectable disease.[1] There is, however, a high risk of false-negative studies in mucinous adenocarcinomas.

2.15.4 Restaging/response post therapy
- FDG PET/CT is **not recommended** for restaging of confirmed recurrence of HCC or biliary cancer.

- FDG PET/CT is **not recommended** to assess treatment response in HCC or biliary cancers (insufficient evidence).

2.15.5 Suspected recurrence
- FDG PET/CT is **not recommended**.

2.15.6 Surveillance
- FDG PET/CT is **not recommended** in routine follow-up of patients with treated HCC or biliary cancers.

2.15.7 Radiotherapy planning
- FDG PET/CT is **not recommended** in radiotherapy planning for HCC or biliary cancers.

2.16 Sarcoma (GIST is treated separately, see 2.17)

2.16.1 Screening
- FDG PET/CT is **not recommended**.

2.16.2 Diagnosis
- FDG PET/CT is **not recommended** in the routine diagnosis of sarcoma.
- FDG PET/CT **may be considered** to detect malignant transformation in patients with neurofibromatosis 1 (see section on plexiform neurofibroma).

2.16.3 Staging
- FDG PET/CT is **recommended in select cases** in patients with soft-tissue sarcoma and suspected isolated metastases who are potential candidates for curative surgery.[2]
- FDG PET/CT **may be considered** for staging of soft-tissue sarcoma, but does not replace established radiological investigations.[2] FDG PET/CT may be useful in prognostication and grading (since biopsy may not be representative)[2] and is especially beneficial in high-grade extremity lesions that are larger than 3 cm, firm and deep.
- FDG PET/CT **may be considered** in staging of Ewing's sarcoma and osteosarcoma.
- FDG PET/CT **may be considered** in staging of chordoma.

2.16.4 Restaging/response post therapy
- FDG PET/CT **may be considered** for restaging of recurrent rhabdomyosarcoma but does not replace established radiological investigations.[2]
- FDG PET/CT **may be considered for** restaging after definitive therapy of soft-tissue and skeletal sarcomas (provided a baseline scan was obtained).
- FDG PET/CT **may be considered** for assessing response to treatment in both skeletal and soft-tissue sarcomas. In such cases comparison with a baseline scan is required.
- FDG PET/CT **may be considered** after neoadjuvant therapy of high-grade osteosarcoma to assess resectability (in comparison with a baseline PET/CT study).

2.16.5 Suspected recurrence
- FDG PET/CT **may be considered** for detection of suspected recurrence of sarcoma in order to guide biopsy.[2]
- FDG PET/CT **may be considered** prior to radical amputation for recurrent soft-tissue sarcoma to exclude other sites of disease.

2.16.6 Surveillance
- FDG PET/CT is **not recommended** for routine follow-up of previously treated patients with soft-tissue sarcomas.
- FDG PET/CT **may be considered** for post-therapy surveillance of treated Ewing's sarcoma and osteosarcoma.

2.16.7 Radiotherapy planning
- FDG PET/CT **may be considered** in radiotherapy planning of high-grade sarcomas. This is based on minimal evidence but a strong rationale.[2]

2.17 Gastrointestinal stromal tumour (GIST)

2.17.1 Screening
- FDG PET/CT is **not recommended**.

2.17.2 Diagnosis
- FDG PET/CT is **not recommended**.

2.17.3 Staging
- FDG PET/CT is **recommended in select cases** for GIST prior to the initiation of imatinib (Gleevec) therapy in patients with tumours that are *marginally resectable or with risk of significant morbidity*,[3] but may yet undergo curative surgery. In these cases, PET/CT may assist in making a timely decision for or against surgery.[3] PET/CT does not replace CT or MRI in staging these patients.
- FDG PET/CT **may be considered** in patients with definitively unresectable disease who will be started on imatinib, as a baseline measure against which future PET/CT for treatment response might be performed.[3]
- FDG PET/CT **may be considered** for staging of GIST patients with allergy to CT contrast and inconclusive MRI.

2.17.4 Restaging/response post therapy
- FDG PET/CT is **recommended in select cases** for patients who *may be future candidates for curative resection*, to assess initial treatment response after 2 - 4 weeks of imatinib therapy, if the tumour shows uptake on baseline PET/CT.[4]
- FDG PET/CT is **not recommended** for routine restaging of patients who undergo definitive therapy (surgery).[4]

2.17.5 Suspected recurrence
- FDG PET/CT **may be considered** for detecting suspected recurrence of previously definitively treated GIST, when CT or MRI is ambiguous.

2.17.6 Surveillance
- FDG PET/CT is **not recommended** for routine follow-up in definitively treated disease or in patients on imatinib maintenance.[4]

2.17.7 Radiotherapy planning
- FDG PET/CT is **not recommended** in radiotherapy planning for GIST.

2.18 Genitourinary system

2.18.1 Renal cell carcinoma (RCC)
- FDG PET/CT **may be considered** for extrarenal metastases in staging and restaging.
- Currently there is insufficient evidence to support the use of FDG PET/CT in diagnosis, or surveillance post nephrectomy in RCC. FDG PET/CT in RCC for these indications is therefore **not recommended**.[1]
- FDG PET/CT may **be considered** for the assessment of tumour response to molecular-triggered therapies when there is minimal change in volume (on radiological assessment).[2]

2.18.2 Ureteric and urethral carcinoma

- Currently there is insufficient evidence to support the use of FDG PET/CT in ureteric and urethral cancers. Existing clinical guidelines do not include a role for FDG PET/CT in this condition.[3] FDG PET/CT in these malignancies is therefore **not recommended**.

2.18.3 Bladder cancer

No main clinical guidelines currently endorse a role for FDG PET/CT in bladder cancer.[4]

2.18.3.1 Screening

- FDG PET/CT is **not recommended**.

2.18.3.2 Diagnosis

- FDG PET/CT is **not recommended**.

2.18.3.3 Staging

- FDG PET/CT **may be considered** in the staging work-up of patients with muscle-invasive bladder cancer who are eligible for radical cystectomy when conventional CT and bone scintigraphy are negative or inconclusive for metastases.

2.18.3.4 Restaging/response post therapy

- FDG PET/CT is **not recommended** for response post therapy.
- FDG PET/CT **may be considered** for distant metastases in restaging.

2.18.3.5 Suspected recurrence

- FDG PET/CT is **not recommended**.

2.18.3.6 Surveillance

- FDG PET/CT is **not recommended**.

2.18.3.7 Radiotherapy planning

- FDG PET/CT is **not recommended**.

2.19 Male reproductive system

2.19.1 Testicular cancer

2.19.1.1 Screening

- FDG PET/CT is **not recommended**.

2.19.1.2 Diagnosis

- FDG PET/CT is **not recommended**.

2.19.1.3 Staging

- FDG PET/CT is **not recommended** for initial staging.

2.19.1.4 Restaging/response post therapy

- FDG PET/CT is **recommended in select cases**, in pure seminoma with residual tumour >3 cm and normal marker levels post chemotherapy: to detect viable residual tumour. In such cases, PET should be performed ≥6 weeks after last chemotherapy to reduce the incidence of false-positive results.[1]
- FDG PET/CT **may be considered** in pure seminoma with residual tumour <3 cm and normal marker levels post chemotherapy: to detect viable residual tumour. In this context, the positive predictive value of PET is lower and surveillance is preferred. If performed in such cases, PET should be performed ≥6 weeks after last chemotherapy to reduce incidence of false-positive results.

2.19.1.5 Suspected recurrence

- FDG PET/CT **may be considered** for detection of suspected recurrence of testicular cancer when other imaging techniques are not helpful.[2]

2.19.1.6 Surveillance

- FDG PET/CT is **not recommended** for routine surveillance of testicular cancer after definitive therapy.

2.19.1.7 Radiotherapy planning

- FDG PET/CT is **not recommended** for radiotherapy planning.

2.19.2 Penile carcinoma

2.19.2.1 Screening

- FDG PET/CT is **not recommended**.

2.19.2.2 Diagnosis

- FDG PET/CT is **not recommended**.

2.19.2.3 Staging (*ab initio* and biopsy-confirmed recurrence)

- FDG PET/CT **may be considered** in patients with palpable inguinal nodes and who have potentially resectable disease on CT or MRI; FDG detects pelvic lymph node- and distant metastases.[3]

2.19.2.4 Restaging/response post therapy

- FDG PET/CT is **not recommended**.

2.19.2.5 Suspected recurrence

- FDG PET/CT is **not recommended**.

2.19.2.6 Routine follow-up (surveillance)

- FDG PET/CT is **not recommended** for surveillance post definitive therapy.

2.19.2.7 Radiotherapy planning

- FDG PET/CT **may be considered** to assist planning of neoadjuvant radiotherapy (strong rationale).

2.19.3 Prostate cancer

- FDG PET/CT is **not recommended** in prostate cancer (please refer to section on non-^{18}F-FDG PET).

2.20 Female reproductive system

2.20.1 Cervical cancer

2.20.1.1 Screening

- FDG PET/CT is **not recommended**.

2.20.1.2 Diagnosis

- FDG PET/CT is **not recommended**.

2.20.1.3 Staging

- FDG PET/CT is **recommended in select cases** for initial staging, in locally advanced cervical cancer being considered for radical chemoradiotherapy.[1]

2.20.1.4 Restaging/response post therapy

- FDG PET/CT is **recommended in select cases** for restaging in locally advanced disease being considered for radical chemoradiotherapy.[2]

2.20.1.5 Suspected recurrence

- FDG PET/CT is **recommended in select cases** for detection of recurrent disease when other imaging is equivocal.[3]

2.20.1.6 Surveillance

- FDG PET/CT is **not recommended** for routine follow-up.

2.20.1.7 Radiotherapy planning
- FDG PET/CT **may be considered** for radiotherapy planning.[1]

2.20.2 Other gynaecological malignancies

2.20.2.1 Screening
- FDG PET/CT is **not recommended** for screening at-risk populations.

2.20.2.2 Diagnosis
- FDG PET/CT is **not recommended** for diagnosis of ovarian cancer.
- FDG PET/CT is **not recommended** for diagnosis of endometrial cancer.

2.20.2.3 Staging
- FDG PET/CT **may be considered** for staging of patients with endometrial cancer considered for surgery.
- FDG PET/CT **may be considered** for staging of patients with vulval carcinoma considered for surgery.[1]
- FDG PET/CT **may be considered** for staging of ovarian cancer, complementary to diagnostic CT in selected patients preoperatively.

2.20.2.4 Restaging/response post therapy
- FDG PET/CT **may be considered** for restaging of patients with endometrial cancer considered for surgery.
- FDG PET/CT **may be considered** for restaging of patients with vulval carcinoma considered for surgery.[1]
- FDG PET/CT is **not recommended** for assessing response to therapy.

2.20.2.5 Suspected recurrence
- FDG PET/CT is **recommended in select patients** for detection of tumour recurrence in ovarian carcinoma with rising CA125 levels and equivocal or negative conventional imaging.[4]
- FDG PET/CT is **recommended in select patients** for suspected recurrence of endometrial cancer when other imaging modalities are equivocal.
- FDG PET/CT **may be considered** for suspected recurrence of vulval carcinoma when other imaging modalities are equivocal.[1]

2.20.2.6 Surveillance
- FDG PET/CT is **not recommended** for routine follow-up.

2.20.2.7 Radiotherapy planning
- FDG PET/CT is **not recommended** for radiotherapy planning.

3. Non-^{18}F-FDG PET

3.1 Neuroendocrine tumours: Somatostatin receptor PET/CT (^{68}Ga-SSTR PET/CT)

Neuroendocrine tumours (NETs) comprise a heterogeneous group of neoplasms that arise from endocrine cells within glands (adrenal medulla, pituitary, parathyroid) or from endocrine islets in the thyroid, the pancreas, or the respiratory and gastrointestinal tract. When histology is available it is important to distinguish between well/intermediately differentiated NETs (Ki67 <20%) and poorly differentiated NETs (Ki67 >20%). FDG PET remains the preferred modality for staging a poorly differentiated NET. Well/intermediately differentiated NETs are likely to be better visualised with somatostatin receptor PET/CT using ^{68}Ga-DOTA-conjugated peptide PET/CT (^{68}Ga-SSTR PET/CT).[1] Routinely used PET tracers include Ga-68-DOTA-TATE/TOC/NOC.

The likelihood of tumour detection with ^{68}Ga-SSTR PET/CT can also be predicted to some extent based on tumour type:
- Tumours with high expression of receptors: gastroenteropancreatic tumours (e.g. carcinoids, gastrinoma, glucagonoma, VIPoma, etc.), functioning and non-functioning; sympathoadrenal system tumours; pituitary adenoma; medulloblastoma; Merkel cell carcinoma; small-cell lung cancer (mainly primary tumours) and meningioma.
- Tumours with variable expression of receptors: insulinoma, phaeochromocytoma, paraganglioma, neuroblastoma, ganglioneuroma and medullary thyroid carcinoma.
- Tumours with low expression of receptors: breast carcinoma, melanoma, lymphoma, prostate carcinoma, non-small-cell lung cancer, sarcomas, renal cell carcinoma, differentiated thyroid carcinoma, astrocytoma and ependymoma.

^{68}Ga-SSTR PET/CT and FDG PET/CT frequently have a complementary role given the heterogeneity in receptor expression at different tumour sites and the variable positivity of each for a given tumour grade and type.

3.1.1 Screening
- ^{68}Ga-SSTR PET is not recommended for screening at-risk populations.

3.1.2 Diagnosis
- ^{68}Ga-SSTR PET **may be considered** for the detection of primary NETs (CUP-NETs).[2] *Carcinoma of unknown primary (CUP) is defined as a biopsy-proven secondary lesion without any evidence of primary site after physical examination and conventional imaging tests (MRI, CT and ultrasound).*
- ^{68}Ga-SSTR PET **may be considered** in the diagnostic work-up of patients with suspected NETs due to clinical symptoms, elevated levels of tumour markers or in indeterminate tumours suggestive of NET, especially in suspected thoracic or gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs).

3.1.3 Staging
- ^{68}Ga-SSTR PET is **recommended in select cases** for preoperative staging to localise primary tumours and detect sites of metastatic disease.[3]
- ^{68}Ga-SSTR PET **may be considered** for baseline staging of patients with GEP-NETs that will be managed medically or with an expectant strategy.
- ^{68}Ga-SSTR PET **may be considered** for staging of phaeochromocytoma, paraganglioma, bronchial carcinoid, neuroblastoma, medullary thyroid cancer, multiple endocrine neoplasia type 2, and Merkel cell cancer.

3.1.4 Early response assessment
- ^{68}Ga-SSTR PET **may be considered** after the first PRRT cycle used for treatment of NET, as a prognostic measure, although there is currently insufficient evidence for its routine use in this indication.

3.1.5 Restaging/response post therapy
- ^{68}Ga-SSTR PET **may be considered** for restaging and for treatment response evaluation, although there is insufficient evidence to recommend this routinely. In such cases, comparison with a baseline scan is recommended.[1]

3.1.6 Suspected recurrence

- ^{68}Ga-SSTR PET **may be considered** to follow up patients with known disease in order to detect recurrent disease when suspected clinically or due to rising tumour markers.

3.1.7 Surveillance

- ^{68}Ga-SSTR PET is **recommended** as part of routine follow-up of all GEP-NET tumours after 18 - 24 months if expression of somatostatin receptor 2a has been proven on tumour cells[2] or baseline ^{68}Ga-SSTR PET was positive (strong rationale).

3.1.8 Peptide receptor radiation therapy (PRRT)/radiotherapy planning

- ^{68}Ga-SSTR PET **may be considered** to determine SST receptor status visually as well as by using semiquantitative parameters such as standardised uptake value (patients with SST receptor-positive tumours are more likely to respond to octreotide therapy). This is based on limited evidence, and strong rationale.
- ^{68}Ga-SSTR PET is **recommended** to select patients with metastatic disease who are being considered for PRRT (with 177Lu or 90Y-DOTA-peptides).[1]
- ^{68}Ga-SSTR PET is **not recommended** for external beam radiotherapy planning In NET tumours.

3.2 Neuroendocrine tumours: ^{18}F-FDG PET/CT

- FDG PET/CT is **recommended** in proven malignant pheochromocytoma, for staging.[4]
- FDG PET/CT **may be considered** for follow-up post therapy in select cases of phaeochromocytoma (proven malignant; SDHB mutation; extra-adrenal primary; phaeochromocytoma/paraganglioma without relevant preoperative hormone secretion). In such cases, imaging should be repeated at least every 6 months during the first year and yearly afterward (lifelong), irrespective of negative biochemistry.
- FDG PET/CT **may be considered** in Merkel cell carcinoma, for staging.
- FDG PET/CT is **recommended** in staging of undifferentiated and non-secretory NETs of the thorax.
- FDG PET/CT **may be considered** as part of baseline workup of GEP-NETs[3] as a prognostic measure and for staging of poorly differentiated NETs.
- ^{68}Ga-SSTR PET and ^{18}F-FDG PET are likely to be complementary in NET imaging.

Neuroblastoma is addressed separately.

3.3 Musculoskeletal conditions: ^{18}F-sodium fluoride

3.3.1 Diagnosis

- ^{18}F-sodium fluoride (NaF PET/CT) **may be considered** in patients with back pain and otherwise unexplained bone pain; child abuse; abnormal radiographic or laboratory findings; osteomyelitis; trauma; inflammatory and degenerative arthritis; avascular necrosis; osteonecrosis of the mandible; condylar hyperplasia; metabolic bone disease; Paget's disease; bone graft viability; complications of prosthetic joints; reflex sympathetic dystrophy; distribution of osteoblastic activity before administration of therapeutic radiopharmaceuticals for bone pain.[1]

3.4 Prostate cancer (PCA)

PET tracers for PCA: ^{18}F-FDG, ^{18}F-fluoroethylcholine (^{18}F-choline), ^{18}F-NaF, ^{68}Gallium-labelled prostate-specific membrane antigen (^{68}Ga-PSMA).

3.4.1 Screening

- ^{18}F-FDG/^{18}F-choline/^{18}F-NaF/^{68}Ga-PSMA PET/CT is **not recommended** for screening.

3.4.2 Diagnosis

- ^{18}F-FDG PET/CT is **not recommended** for diagnosis. There is currently no evidence for using FDG in diagnosing prosate cancer.
- ^{18}F-choline PET/CT **may be considered** for guiding re-biopsy in highly selected patients suffering from clinically suspected PCA with repeated negative prostate biopsies.
- ^{18}F-NaF is **not recommended**.
- ^{68}Ga-PSMA **may be considered**.

3.4.3 Staging

- ^{18}F-FDG is **not recommended** for primary staging of PCA.
- ^{18}F-choline **may be considered** for staging high-risk PCA patients (prostate-specific antigen (PSA) >20 ng/ml and Gleason score 7) if findings on conventional imaging are equivocal and confirmation or exclusion of distant disease would directly influence patient management.[1]
- ^{18}F-NaF **may be considered** in high-risk PCA to detect bone metastases.[2]
- ^{68}Ga-PSMA **may be considered**.

3.4.4 Restaging/response post therapy

- ^{18}F-FDG PET/CT is **not recommended** for restaging after definitive therapy.
- ^{18}F-choline **may be considered** for restaging.
- ^{18}F-NaF is **not recommended** for restaging.
- ^{68}Ga-PSMA **may be considered** for restaging.
- ^{18}F-FDG PET/CT is **not recommended** for response post therapy.[3]
- ^{18}F-choline is **not recommended** for response post therapy.
- ^{18}F-NaF is **not recommended** for response post therapy.
- ^{68}Ga-PSMA **may be considered**.

3.4.5 Suspected recurrence

- ^{18}F-FDG PET/CT is **not recommended** for suspected recurrence.[4]
- ^{18}F-choline is **recommended in select cases** with suspected recurrence in patients with a rapidly rising PSA and indeterminate or equivocal conventional imaging, where the results would directly influence patient management.[4]
- ^{18}F-NaF is **not recommended** in suspected recurrence.
- ^{68}Ga-PSMA is **recommended in select cases** with suspected recurrence.[3]

3.4.6 Surveillance

- ^{18}F-FDG/^{18}F-choline/^{18}F-NaF or ^{68}Ga-PSMA PET/CT is **not recommended** for routine follow-up.

3.4.7 Radiotherapy planning

- ^{18}F-FDG PET/CT is **not recommended**.
- ^{18}F-choline **may be considered**.
- ^{18}F-NaF is **not recommended**.
- ^{68}Ga-PSMA **may be considered**.[3]

3.4.8 Potential therapy with ^{177}Lu-PSMA

- ^{68}Ga-PSMA PET is **recommended** for select patients being considered for PRRT with metastatic disease or recurrence that is hormone refractory or not suitable for chemotherapy.[3]

4. Paediatric oncology

4.1 Neuroblastoma

4.1.1 Screening

- FDG PET/CT is **not recommended** for screening at-risk populations.

4.1.2 Diagnosis

- FDG PET/CT is **not recommended** for the diagnosis of neuroblastoma.

4.1.3 Staging

- FDG PET/CT is **recommended in select cases** for staging if the tumour is not meta-iodobenzylguanidine (MIBG) avid or has a low affinity for MIBG. FDG PET/CT should be considered when the MIBG scan shows less disease than is seen on anatomical imaging or the clinical presentation suggests more extensive disease involvement.[1]

4.1.4 Restaging/response post therapy

- FDG PET/CT is **recommended in select cases** for restaging if the tumour is not MIBG avid or it has a low affinity for MIBG. FDG PET/CT should be considered when the MIBG scan shows less disease than is seen on anatomical imaging or the clinical presentation would suggest more extensive disease involvement.[1]
- FDG PET/CT is **recommended in select cases** for evaluating response to therapy in patients with MIBG-negative or poorly avid tumours.[2]

4.1.5 Suspected recurrence

- FDG PET/CT **may be considered** for suspected recurrence.

4.1.6 Surveillance

- FDG PET/CT is **not recommended** for routine follow-up.

4.1.7 Radiotherapy planning

- FDG PET/CT **may be considered** for radiotherapy planning.[3]

4.2 Wilms tumour

4.2.1 Screening

- FDG PET/CT is **not recommended**.

4.2.3 Diagnosis

- FDG PET/CT **may be considered** to identify a biopsy site.

4.2.4 Staging

- FDG PET/CT **may be considered**.

4.2.5 Early treatment response

- FDG PET/CT **may be considered**.

4.2.6 Restaging/response post therapy

- FDG PET/CT **may be considered** for restaging after completion of first-line treatment**.**
- FDG PET/CT **may be considered** for restaging of recurrent disease.

4.2.7 Suspected recurrence

- FDG PET/CT **may be considered**.

4.2.8 Surveillance

- FDG PET/CT is **not recommended** for routine follow-up.

4.2.9 Radiotherapy planning

- FDG PET/CT **may be considered**.

4.3 Hepatoblastoma

4.3.1 Screening

- FDG PET/CT is **not recommended** for screening at-risk populations.

4.3.2 Diagnosis

- FDG PET/CT is **not recommended** for diagnosis.

4.3.3 Staging

- FDG PET/CT **may be considered** for initial staging.[4]

4.3.4 Restaging/response post therapy

- FDG PET/CT **may be considered**.

4.3.5 Suspected recurrence

- FDG PET/CT **may be considered**.

4.3.6 Surveillance

- FDG PET/CT is **not recommended** for routine follow-up.

4.3.7 Radiotherapy planning

- FDG PET/CT **may be considered**.

4.4 Lymphomas

This topic is covered extensively in the adult context (see HL (2.6.1) and NHL (2.6.2)), and it is similar in the paediatric population.

4.4.1 Screening

- FDG PET/CT is **not recommended** for screening at risk populations.

4.4.2 Diagnosis

- FDG PET/CT **may be considered** for directing the surgeon to an appropriate biopsy site.

4.4.3 Staging

- PET/CT is **recommended** for routine staging. The baseline staging scan is also essential for accurate interpretation of scans for response assessment and restaging post therapy.

4.4.4 Early response assessment

- FDG PET/CT is **recommended t**o determine early treatment response in lymphoma. Interim FDG PET/CT during mid-therapy is prognostic of treatment response and survival in lymphoma.[3]

4.4.5 Restaging/response post theray

- FDG PET/CT at completion of therapy is **recommended** in lymphoma and is prognostic of treatment success and subsequent survival. It is the preferred restaging method of lymphoma (assessment should be made using Deauville criteria).[1,3]

4.4.6 Suspected recurrence

- FDG PET/CT is **recommended** in suspected recurrence of lymphoma.

4.4.7 Surveillance

- FDG PET/CT is **not recommended** for routine follow-up.

4.4.8 Radiotherapy planning

- FDG PET/CT **may be considered** in radiotherapy treatment planning.

5. Neurology

5.1 Dementia and mild cognitive impairment (MCI)

5.1.1 ^{18}F-FDG

- FDG PET/CT is **recommended in select cases** of dementia where the diagnosis remains in doubt after clinical and structural imaging work-up.[1] FDG PET/CT should not be used as the only imaging measure. FDG PET/CT is particularly useful in distinguishing moderate to severe Alzheimer's dementia (AD) from other neurodegenerative dementias (especially AD v. frontotemporal dementia).
- In patients with MCI (evaluated by a dementia specialist), FDG PET/CT **may be considered** if findings of a neurodegenerative pathology would affect management. An AD-like metabolic pattern on FDG PET in a patient with MCI is predictive of conversion to AD within several years.
- FDG PET/CT is **not recommended** in cases of cognitive decline due to suspected normal-pressure hydrocephalus, suspected Huntington's disease, suspected brain iron accumulation, motor neuron disease or parkinsonian syndromes.

5.1.2 Amyloid agents

- Amyloid PET (e.g. ^{18}F-florbetapir, ^{18}F-florbetaben, etc.) is **recommended in select cases**, in the clinical situations below for individuals with *all of the following characteristics*: (*i*) a cognitive complaint with objectively confirmed impairment; (*ii*) AD as a possible diagnosis but diagnosis uncertain after comprehensive evaluation by a dementia expert; and (*iii*) knowledge of the presence or absence of AD pathology is expected to increase diagnostic certainty and alter management.
  - Persistent or progressive unexplained MCI
  - Patients satisfy core clinical criteria for possible AD (not probable AD) because of unclear clinical presentation – either an atypical clinical course or an aetiologically mixed presentation
  - Progressive dementia and atypically early age of onset (≤65 years old).
- Amyloid PET is **not recommended** in the following clinical situations:
  - Patients with core clinical criteria for *probable* AD with typical age of onset
  - To determine dementia severity
  - Based solely on a positive family history of dementia or presence of apolipoprotein E (APOE)ε4
  - Cognitive complaint that is unconfirmed on clinical examination
  - In lieu of genotyping for suspected autosomal mutation carriers
  - In asymptomatic individuals
  - Non-medical use (e.g. legal, insurance coverage or employment screening).

5.2 Movement disorders

- FDG PET/CT is **not recommended** in routine work-up of Parkinson's disease (PD) or for differentiating PD from atypical parkinsonian syndromes (APS). While there is some evidence for the utility of FDG PET/CT in PD and APS, clinical guidelines do not yet endorse this indication as routine.
- In the investigation of movement disorders, FDG PET/CT **may be considered** in select clinical scenarios, to support or refute clinical impressions.[3] *Referral of such cases should be by movement disorder specialists. These studies should only be performed by centres with sufficient experience in interpreting such studies. Visual and quantitative analysis (in comparison with a locally derived normal database) is recommended.*

5.3 Seizure disorders

- FDG PET/CT is **not recommended** in routine work-up of epilepsy.
- FDG PET/CT **may be considered** in the presurgical work-up of medically refractory focal epilepsy, in cases where MRI and ictal scalp electroencephalogram do not identify a clear epileptogenic focus or where these investigations are discordant or inconclusive.[4] *Focal hypometabolism on interictal FDG PET can identify potential surgical candidates and assist in the decision to perform invasive intracranial recording. FDG PET/CT cannot be used to precisely identify surgical margins but assists in lateralisation and general localisation of epileptogenic foci. FDG PET appears to be predictive of surgical success in these patients.*

5.4 Psychiatric conditions

- With the exception of the neurodegenerative dementias, FDG PET/CT is **not recommended** for psychiatric conditions *per se*.

6. Cardiology

6.1 Myocardial viability

- FDG PET/CT is **recommended in select cases** for patients with left ventricular dysfunction due to coronary artery disease who are eligible for coronary revascularisation and have resting myocardial perfusion defects, in order to differentiate viable (i.e. hibernation) from non-viable myocardium (i.e. scar),[1] the rationale being that if myocardial viability (hibernation or inducible ischaemia) is present, the patient has a great probability of benefiting clinically from revascularisation.[2-4] FDG PET is ideally used in conjunction with perfusion imaging (sestamibi/tetrofosmin SPECT or ammonia/rubidium PET).

7. Infection and inflammation

Clinical indications have not yet been developed. Based on EANM/SNMMI Guideline for ^{18}F-FDG use in Inflammation and Infection (2013).[1]

- FDG PET/CT is **recommended in select cases** for the investigation of:
  - Sarcoidosis – for assessment of disease activity and distribution
  - Peripheral bone osteomyelitis (non-postoperative, non-diabetic foot)
  - Suspected spinal infection (spondylodiskitis or vertebral osteomyelitis, non-postoperative)
  - Fever of unknown origin (FUO) including true FUO (defined according to the criteria of Durack and Street, postoperative fever and recurrent sepsis, immunodeficiency (both induced and acquired)-related FUO, neutropenic fever, and isolated acute-phase inflammation markers (persistently raised C-reactive protein and/or erythrocyte sedimentation rate)[1,2]
  - Metastatic infection and high-risk patients with bacteraemia
  - Vasculitis – where conventional investigations are not helpful and treatment would be altered if confirmed
  - For diagnosis, and possible determination of the extent and distribution of the disease activity
  - To determine disease activity in confirmed medium- to large-vessel arteritis where treatment would be altered if ongoing inflammatory disease is confirmed

  - To exclude underlying malignancy in patients with atypical presentations of vasculitis that may be on a paraneoplastic basis.
- FDG PET/CT **may be considered** in:
  - Potentially infected liver and kidney cysts in polycystic disease
  - Potentially infected intravascular devices, pacemakers and catheters (provided sufficient time has lapsed since surgery)
  - AIDS-associated opportunistic infections, associated tumours and Castleman's disease
  - To assess metabolic activity in TB.
- FDG PET/CT is **not indicated** in the investigation of:
  - Diabetic foot infections
  - Joint prosthetic infections
  - Vascular prosthetic infections
  - Inflammatory bowel diseases
  - Endocarditis
  - FUO – prolonged (>3 weeks) hyperthermia (>38.3°C) with no specific aetiology identified despite extensive diagnostic work-up.[3,4]

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Because of space constraints, only selected references are provided, numbered separately for each section. A complete list of 350 references is available on request from the corresponding author.

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