Nuclear medicine in oncology 1: Lymphoma, and cancer of the lung, colon, and oesophagus

Nuclear medicine techniques allow imaging of pathophysiology.

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Nuclear medicine provides an opportunity to image pathophysiology, while radiology mainly shows morphology. Over the last few decades hybrid imaging modalities have been developed in which nuclear medicine instrumentation has been combined with computed tomography (CT) and, more recently, with magnetic resonance imaging (MRI). This allows the clinician to combine the imaging of pathophysiology with the anatomical localisation of such lesions.

Conventional nuclear medicine imaging can be performed using various radiopharmaceuticals, mainly labelled with technetium-99m (Tc-99m), e.g. Tc-99m methylene diphosphonate (MDP) for skeletal scanning. In past decades, positron emission tomography combined with CT (PET/CT) has been used routinely for the assessment of solid tumours, including lymphomas, and lung and colorectal cancers.[1,2] The most frequently used PET radiopharmaceutical is fluorine-18 (F-18) fluorodeoxyglucose (FDG), which reflects cellular glucose metabolism.

Lymphoma
Traditionally, a CT scan was the standard imaging technique to evaluate patients with lymphoma. CT is now complemented by FDG-PET/CT as a metabolic imaging technique.

Before the availability of PET/CT in South Africa, the two nuclear medicine modalities most frequently used in lymphoma patients were skeletal scintigraphy to detect skeletal metastases and gallium-67 scanning to evaluate disease extent and tumour response following treatment. These two modalities have largely been replaced by PET/CT.[3]

The use of FDG-PET/CT is well established for several indications in patients with lymphoma, e.g. staging, evaluating therapy response, and restaging after therapy.

Lung cancer incidence has increased rapidly over the last few decades, with the 5-year survival still being relatively poor.

Staging. FDG-PET/CT can be used to evaluate the extent of disease. It offers improved accuracy over conventional CT staging and the opportunity for comparison with, and correct interpretation of, subsequent interim and restaging PET/CT. Several published papers have confirmed that lymphoma patients can be upstaged in as many as 20% of cases, while downstaging was reported in less than 10% of cases.

Treatment monitoring. Mid-treatment PET/CT is a powerful prognostic tool as an indicator of progression-free and overall survival. PET/CT is preferred to CT alone, as both metabolic and anatomical response can be measured. Metabolic response is evident at an earlier point than anatomical response. Findings are described as complete or partial metabolic response, no response or disease progression. These findings may be used to make decisions with regard to therapy, especially in cases of drug or radiotherapy toxicity or disease progression. Although an early response indicates a good prognosis, evidence is still lacking that a change in treatment following a PET/CT scan, showing poor/no response, improves outcome.

Restaging. Morphological changes on CT scanning were traditionally used to evaluate treatment response, a reduction in tumour size being a criterion. Residual masses may represent fibrotic scar tissue or viable lymphoma cells. The absence of FDG uptake after treatment with or without residual masses on CT scanning is highly predictive of progression-free survival and overall survival in both Hodgkin and aggressive non-Hodgkin lymphomas (Fig. 1). These studies should...
be performed at least 3 weeks after the last dose of chemotherapy and 3 months after radiotherapy. This allows the inflammation secondary to treatment to subside, as inflammatory processes can also concentrate FDG, thereby raising the potential of false positives.

Suspected recurrence. PET/CT is only indicated in patients with clinical, biochemical, or radiological evidence of recurrence. Routine scanning should not be performed for monitoring of otherwise well patients.

Radiotherapy planning. FDG-PET/CT may be used for radiotherapy planning, but patients should then be positioned on a flat bed in the therapy position. The metabolic findings are combined with the anatomical findings to determine the radiotherapy fields. Close liaison with radiation oncology is essential to ensure that patients are scanned in the correct therapy position, using the necessary immobilisation devices.

Cancer of the lung
Lung cancer incidence has increased rapidly over the last few decades, with the 5-year survival still being relatively poor. Imaging plays an integral role in the evaluation of patients with lung cancer. FDG-PET/CT is now an accepted part of the imaging assessment. It is useful in characterising solitary pulmonary nodules (SPNs), staging disease, monitoring treatment response and for radiotherapy planning. Its primary role is in potentially operable non-small-cell lung carcinoma (NSCLC) and in cases of early-stage small-cell lung carcinoma (SCLC). There is poor uptake of FDG in bronchoalveolar carcinoma, some adenocarcinomas and well-differentiated neuro-endocrine tumours. Neuro-endocrine tumours are better evaluated with somatostatin analogue imaging.

PET/CT should not be routinely requested in the management of patients with low-grade lymphomas, except to evaluate treatment response.

Solitary pulmonary nodules. FDG-PET/CT is the most accurate, non-invasive imaging modality for the evaluation of SPNs (Fig. 2). The combination of the anatomical and metabolic images combines the sensitivity of the CT and the specificity of the PET, resulting in improved overall accuracy. PET/CT may produce false-positive results, specifically in inflammatory conditions, including tuberculosis. It may be false negative in lesions smaller than 1 cm and in tumour types with a low-glucose metabolism, e.g. bronchoalveolar carcinoma.

Tumour staging. The initial staging of a patient with NSCLC is important, as it has therapeutic and prognostic implications. CT remains the initial study for staging, but it frequently produces false-negative results when lymph nodes are smaller than 1 cm. PET/CT has a higher diagnostic accuracy than CT alone, although it cannot replace histological confirmation of nodal involvement. It serves as a roadmap to identify nodal areas for tissue diagnosis.

Distant metastases of NSCLC frequently involve the adrenal glands, brain, liver and skeleton. It is important to identify metastases, as this has a significant influence on the choice of therapy (Fig. 3). Although skeletal scintigraphy using Tc-99m MDP is sensitive for detecting skeletal metastases, FDG-PET/CT has a higher sensitivity and specificity.

It is difficult to detect brain metastases with FDG-PET/CT because of the high glucose consumption in the normal brain. Brain metastases are therefore better detected using contrast-enhanced CT or MRI. As PET/CT has superior accuracy in the detection of lymph node involvement and distant metastases, it has resulted in fewer futile thoracotomies in a significant number of patients.

Monitoring treatment response. As metabolic changes reflect treatment response more sensitively than morphological changes, the use of PET/CT in the evaluation of treatment response is well established. Residual masses on CT may be due to tumour fibrosis or residual tumour tissue. These can be differentiated using PET/CT.

Radiotherapy planning. Radiotherapy is a key treatment modality in patients with both NSCLC and SCLC. The metabolic information obtained from a PET scan can be incorporated into the radiation treatment plan, enabling more accurate treatment plans to be drawn up than when using CT alone.

Colorectal carcinoma
This malignancy is one of the common neoplastic diseases, with early diagnosis being key to long-term survival. If the disease is localised, surgery is the treatment of choice. In patients with locally advanced
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disease, prognosis can be improved by using neoadjuvant chemo-radiotherapy. It is therefore important to accurately stage the disease and to detect local or distant recurrence timeously. Many imaging modalities are available for this purpose, including FDG-PET/CT as a metabolic tracer.[9,10]

Using FDG-PET/CT in the pre-operative staging of disease may be potentially advantageous, but a substantial impact on clinical management has not yet been demonstrated. FDG-PET/CT has been recognised as appropriate in the restaging of patients with suspected recurrence when elevated serum tumour markers (e.g. carcino-embryonic antigen (CEA)) are found, when conventional imaging is non-diagnostic and in apparently isolated local recurrence or metastases prior to surgery (Fig. 4). FDG-PET was shown to result in a change in clinical management

Fig. 2. Transaxial views of 3 cases referred for PET/CT to evaluate SPN. Case A: true positive, with FDG uptake in histologically proven adenocarcinoma. Case B: true negative, with absent FDG uptake in proven tuberculosis. Case C: false positive, with avid FDG uptake in tuberculosis. (A1 - C1 CT slices; A2 - C2 FDG-PET slices; A3 - C3 fused images.)

Fig. 3. Whole body FDG-PET/CT MIP view (A) and transaxial fused images (B) in a 62-year-old man who presented with a 4-month history of weight loss and right-sided chest pain. CT detected a mass in the right upper lobe of the lung confirmed to be a non-small-cell carcinoma. He was referred for PET/CT for staging, for possible surgical resection of the primary tumour. View B1 demonstrates uptake of FDG in the primary tumour with a necrotic centre (dotted arrow in A and B1). A mid-abdominal transaxial cut (B2) demonstrates a metastasis in the left adrenal gland (thin solid arrow). In addition, an abnormal FDG concentration is noted in a soft tissue mass in the left iliac fossa, also showing central photopenia consistent with necrosis (bold solid arrow in A and B3).

Fig. 4. Whole body FDG-PET/CT in a 62-year-old patient after left hemicolecctiony and chemotherapy for colon carcinoma. The patient presented with a single liver metastasis, which was treated with radiofrequency ablation. MIP view (A1) of follow-up FDG-PET/CT study; transaxial (A2) and fused (A3) views demonstrated a small area of doubtful significance in the right lobe of the liver (A1 - A3). A follow-up study 3 months later confirmed recurrence of the lesion in the liver (B1 - B3). The lesion is indicated with a red + sign.

Fig. 5. Whole body FDG-PET/CT MIP view (A), transaxial (B1) and sagittal (B2) fused images in a 64-year-old man with oesophageal carcinoma (thin arrows) and vertebral involvement (thick arrows), which rendered him inoperable.
in about 30% of patients with recurrent colorectal cancer. This was due to the detection of early recurrence with metabolic changes in normal-sized structures before morphological changes occurred, or in lesions missed on contrast-enhanced CT because of altered morphology due to previous surgery.

**FDG-PET was shown to result in a change in clinical management in about 30% of patients with recurrent colorectal cancer.**

PET has been shown to be more sensitive than conventional imaging for detecting extrahepatic metastatic disease in patients considered for liver metastasectomy, and has the potential to alter treatment in up to 27% of patients. The use of FDG-PET/CT is also advantageous in the restaging of recurrent colorectal cancer because of the identification of additional unexpected metastatic sites, leading to upstaging of the disease. PET/CT has a higher sensitivity than CT in the abdominal cavity, and for detecting metastatic lymph nodes and peritoneal involvement. PET/CT is also of value for the detection of unexpected extra-abdominal metastases, mainly in the lungs.

**Oesophageal carcinoma**

Oesophageal cancer is very prevalent in South Africa. FDG-PET/CT is not generally used in the diagnosis of oesophageal carcinoma, as endoscopy (with ultrasound) is the standard technique. PET/CT has a low sensitivity for locoregional lymph node metastases, but is valuable for the detection of distant metastases (M staging), as this is crucial for the differentiation between locoregional and systemic disease (Fig. 5). The use of PET/CT led to the upstaging of patients in as many as 20% of cases, with downstaging in 5%.

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**Table 1. Summary of role of FDG-PET/CT in different tumour types**

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Indication</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Lymphoma</td>
<td>Staging</td>
<td>• Indicated in Hodgkin and high-grade diffuse large B-cell lymphoma</td>
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<tr>
<td></td>
<td></td>
<td>• Not indicated in indolent lymphomas, except if to be used for therapy response</td>
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<tr>
<td>Lung carcinoma</td>
<td>Diagnosis</td>
<td>• Characterisation of SPNs</td>
</tr>
<tr>
<td></td>
<td>Staging</td>
<td>• NSCLC if considered for curative treatment</td>
</tr>
<tr>
<td></td>
<td>Response evaluation</td>
<td>• NSCLC: Following neoadjuvant chemotherapy to evaluate operability</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy (RT) planning</td>
<td>• NSCLC: Define RT treatment fields</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>Staging</td>
<td>• M staging – indicated</td>
</tr>
<tr>
<td></td>
<td>Recurrence</td>
<td>• Rising tumour markers</td>
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<tr>
<td></td>
<td></td>
<td>• Equivocal findings on anatomical imaging</td>
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<tr>
<td></td>
<td></td>
<td>• Exclude other metastases in patients for metastatectomy or resection of local recurrence</td>
</tr>
<tr>
<td>Oesophageal carcinoma</td>
<td>Staging</td>
<td>• M staging</td>
</tr>
<tr>
<td></td>
<td>Response evaluation</td>
<td>• Assess response after neoadjuvant therapy prior to surgery</td>
</tr>
<tr>
<td></td>
<td>Suspected recurrence</td>
<td>• Identify disease amenable to locoregional therapy</td>
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<tr>
<td></td>
<td>Radiotherapy planning</td>
<td>• Assist in defining target volume</td>
</tr>
</tbody>
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FDG = fluorodeoxyglucose; PET/CT = positron emission tomography combined with computed tomography; SPNs = solitary pulmonary nodules; NSCLC = non-small-cell lung carcinoma; SCLC = small-cell lung carcinoma.
PET/CT has been validated as a surrogate marker for therapy response assessment. Its appropriate use for evaluating response to therapy has not been well defined, but it does correlate with clinical response and survival.

If tumour recurrence is suspected, PET/CT provides the most accurate whole body restaging tool, significantly better than conventional imaging using CT and endoscopic ultrasound.

When PET was used in radiotherapy planning it resulted in changes in target volumes, as areas with high metabolic activity were also included.

Table 1 provides a summary of the various internationally accepted indications for the use of FDG-PET/CT in the tumours described in this paper.

**References**


**Summary**

- Nuclear medicine imaging procedures evaluate physiology and pathophysiology, and do not show morphology.
- In oncology, PET/CT primarily using F-18 FDG plays a significant role in various aspects of the evaluation of these patients, including diagnosis, staging, restaging and therapy response evaluation.
- FDG-PET/CT is useful in both Hodgkin and high-grade non-Hodgkin lymphomas, but should not be routinely requested in the management of patients with low-grade lymphomas.
- FDG-PET/CT offers improved accuracy over conventional CT in the staging of lymphomas, while mid-treatment PET/CT is a powerful prognostic tool as indicator of progression-free and overall survival.
- In both Hodgkin and aggressive non-Hodgkin lymphomas the absence of FDG uptake after treatment with or without residual masses on CT is highly predictive of progression-free survival and overall survival. Using only morphological changes on CT is not accurate, as post-therapy fibrosis may also cause a residual mass.
- FDG-PET/CT is the most accurate, non-invasive imaging modality for the evaluation of SPNs.
- PET/CT has a higher diagnostic accuracy than CT alone in non-small-cell lung carcinoma, as it can identify lymph node involvement in normal-sized lymph nodes, and therefore serves as a roadmap to identify areas accessible for tissue diagnosis.
- The use of FDG-PET/CT in staging of non-small-cell lung carcinoma has resulted in fewer futile thoracotomies in a significant number of patients, as more extensive disease was found than expected from the diagnostic CT scan.
- In colorectal carcinoma the use of FDG-PET/CT is appropriate in the restaging of patients with suspected recurrence when elevated tumour markers are found, when conventional imaging is non-diagnostic, and in apparently isolated local recurrence or metastases prior to surgery.
- FDG-PET/CT is not generally used in the diagnosis of oesophageal carcinoma, but is valuable in the detection of distant metastases (M staging).