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

Nuclear medicine techniques allow imaging of pathophysiology.

A Ellmann, MB ChB, MSc, MMed (NucMed); **J Holness**, MB ChB, MMed (NucMed), FCNP (SA)

Division of Nuclear Medicine, Department of Medical Imaging and Clinical Oncology, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

Corresponding author: *A Ellmann (ae1@sun.ac.za)*

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 These two modalities have largely been replaced by PET/CT.[3]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.

The use of FDG-PET/CT in lymphoma patients is well established for several indications, e.g. staging, evaluating therapy response, and restaging after therapy. It is also of value in suspected disease recurrence and for radiotherapy planning. This is useful in both Hodgkin and high-grade non-Hodgkin lymphomas, including diffuse, large B-cell lymphoma, plasmablastic lymphoma, mantle-cell lymphoma, high-grade follicular lymphoma, anaplastic large-cell lymphoma and Burkitt's lymphoma. These subtypes typically demonstrate intense uptake of FDG. PET/CT scans should not be routinely requested in the management of patients with low-grade lymphomas, except to evaluate treatment response. In such cases a baseline (pre-treatment) study is necessary to determine whether the tumour is FDG avid or not, as a significant proportion of low-grade lymphomas take up only minimal FDG, resulting in poor sensitivity. In such cases, PET/CT should not be used for follow-up after treatment.

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.[4-6] 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.

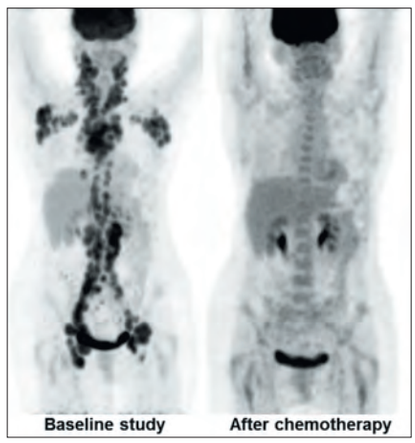

Fig. 1. Whole body PET MIP views in a 63-year-old woman with follicular lymphoma, scanned before and after completion of chemotherapy. A baseline F-18 FDG-PET/CT scan shows extensive disease, with widespread lymph node involvement above and below the diaphragm. The follow-up scan after completion of chemotherapy shows a complete response.

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.[7] 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.[8]

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

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

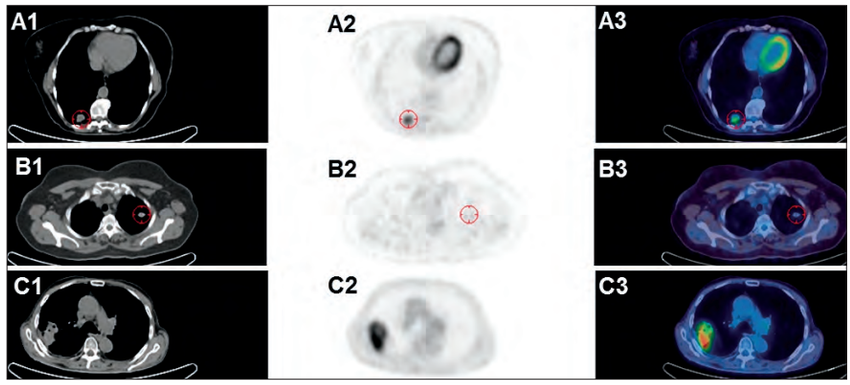

Fig. 2. Transaxial views of 3 cases referred for PET/CT to evaluate SPN. Case A: true positive, with FDG uptake in histologically proven adenocarcinoma. Case B: true negative, with absent FDG uptake in proven tuberculosis. Case C: false positive, with avid FDG uptake in tuberculosis. (A1 - C1 CT slices;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

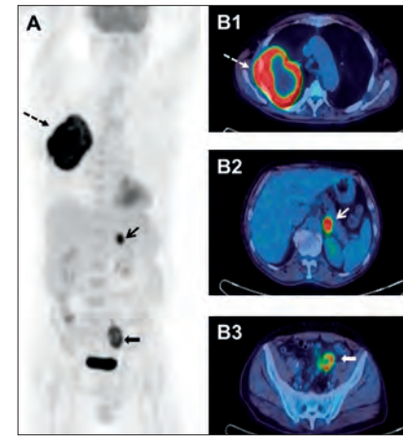

Fig. 3. Whole body FDG-PET/CT MIP view (A) and transaxial fused images (B) in a 62-year-old man who presented with a 4-month history of weight loss and right-sided chest pain. CT detected a mass in the right upper lobe of the lung confirmed to be a non-small-cell carcinoma. He was referred for PET/CT 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).

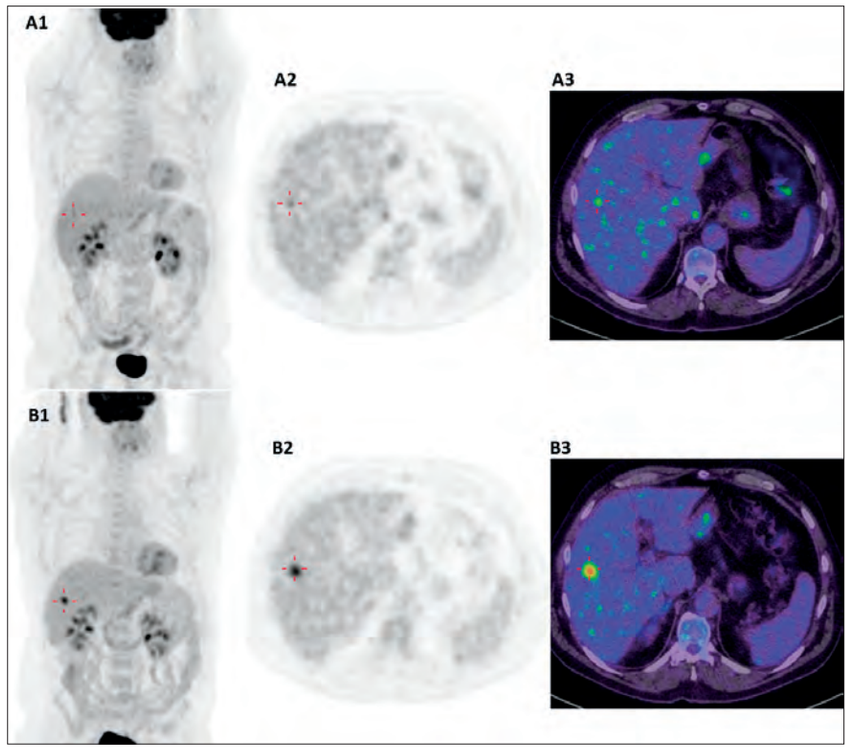

Fig. 4. Whole body FDG-PET/CT in a 62-year-old patient after left hemicolectomy and chemotherapy for colon carcinoma. The patient presented with a single liver metastasis, which was treated with radiofrequency ablation. MIP view (A1) of follow-up FDG-PET/CT study; transaxial (A2) and fused (A3) views 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.

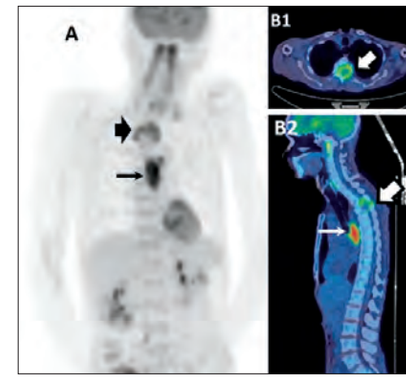

Fig. 5. Whole body FDG-PET/CT MIP view (A), transaxial (B1) and sagittal (B2) fused images in a 64-year-old man with oesophageal carcinoma (thin arrows) and vertebral involvement (thick arrows), which rendered him inoperable.

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

Tumour	Indication	Comments
Lymphoma	Staging	• Indicated in Hodgkin and high-grade diffuse large B-cell lymphoma • Not indicated in indolent lymphomas, except if to be used for therapy response
	Therapy response	• Indicated in Hodgkin and diffuse large B-cell lymphoma • To be used in indolent lymphomas only if positive on baseline study
	Suspected recurrence	• Characterisation of masses after treatment of Hodgkin and non-Hodgkin lymphomas with proven FDG avidity
Lung carcinoma	Diagnosis	• Characterisation of SPNs
	Staging	• NSCLC if considered for curative treatment • SCLC: In early-stage disease
	Response evaluation	• NSCLC: Following neoadjuvant chemotherapy to evaluate operability • NSCLC: During definitive radiotherapy/chemotherapy to adapt dose according to response
	Radiotherapy (RT) planning	• NSCLC: Define RT treatment fields
Colorectal carcinoma	Staging	• M staging – indicated • T staging – not indicated • N staging – not indicated
	Recurrence	• Rising tumour markers • Equivocal findings on anatomical imaging • Exclude other metastases in patients for metastatectomy or resection of local recurrence
Oesophageal carcinoma	Staging	• M staging
	Response evaluation	• Assess response after neoadjuvant therapy prior to surgery
	Suspected recurrence	• Identify disease amenable to locoregional therapy
	Radiotherapy planning	• Assist in defining target volume

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.

in about 30% of patients with recurrent colorectal cancer.[11] 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.[12]

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.[13] 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%.[14]

PET/CT has been validated as a surrogate marker for therapy response assessment.[15] 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

1. Akin O, Brennan SB, Dershaw D, et al. Advances in oncologic imaging: Update on 5 common cancers. CA Cancer J Clin 2012;62:364-393. [http://dx.doi.org/10.3322/caac.21156]
2. Facey K, Bradbury I, Laking G, Payne E. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. Health Technol Assess 2007;11(44).
3. Cheson BD. Role of functional imaging in the management of lymphoma. J Clin Oncol 2011;29:1844-1854. [http://dx.doi.org/10.1200/JCO.2010.32.5225]
4. Ambrosini V, Nicolini S, Caroli P, et al. PET/CT imaging in different types of lung cancer: An overview. Eur J Radiol 2012;81:988-1001. [http://dx.doi.org/10.1016/j.ejrad.2011.03.020]
5. Allen TL, Kendi ATK, Mitiek MO, Maddaus MA. Combined contrast-enhanced computed tomography and 18-fluoro-2-deoxy-D-glucose-positron emission tomography in the diagnosis and staging of non-small cell lung cancer. Semin Thoracic Surg 2011;23:43-50. [http://dx.doi.org/10.1053/j.semtcvs.2011.05.003]
6. Devaraj A, Cook GJR, Hansell DM. PET/CT in non-small cell lung cancer staging – promises and problems. Clin Radiol 2007;62:97-108. [http://dx.doi.org/10.1016/j.crad.2006.09.015]
7. Fletcher JW, Kymes SM, Gould M. A comparison of the diagnostic accuracy of 18F-FDG PET and CT in the characterization of solitary pulmonary nodules. J Nucl Med 2008;49:179-185. [http://dx.doi.org/10.2967/jnumed.107.044990]
8. Mac Manus MP, Hicks RJ. The role of positron emission tomography/computed tomography in radiation therapy planning for patients with lung cancer. Semin Nucl Med 2012;42:308-319. [http://dx.doi.org/10.1053/j.semnuclmed.2012.04.003]
9. Pelosi E, Deandreis D. The role of 18F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) in the management of patients with colorectal cancer. Eur J Surg Oncol 2007;33:1-6. [http://dx.doi.org/10.1016/j.ejso.2006.10.020]
10. Esteves FP, Schuster DM, Halkar RK. Gastrointestinal tract malignancies and positron emission tomography: An overview. Semin Nucl Med 2006;36:169-181. [http://dx.doi.org/10.1053/j.semnuclmed.2005.12.002]
11. Huebner RH, Park KC, Shepherd JE, et al. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. J Nucl Med 2000;41:1177-1189.
12. Park IJ, Kim HC, Yu CS, et al. Efficacy of PET/CT in the accurate evaluation of primary colorectal carcinoma. Eur J Surg Oncol 2006;32:941-947.
13. Lamen P, Stroobants S, Van Cutsem E, et al. Additional value of whole-body positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D glucose in recurrent colorectal cancer. J Clin Oncol 1999;17:894-901.
14. Bar-Shalom R, Guralnik L, Tsalik M, et al. The additional value of PET/CT over PET in FDG imaging of oesophageal cancer. Eur J Nucl Med Molec Imag 2005;32:918-924. [http://dx.doi.org/10.1007/s00259-005-1795-y]
15. Wolf MC, Stahl M, Krause BJ, et al. Curative treatment of oesophageal carcinoma: Current options and future developments. Radiation Oncology 2011;6:55. [http://dx.doi.org/10.1186/1748-717X-6-55]

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).