Nuclear medicine in oncology 2: Breast, prostate, and cervical cancer, melanoma, and neuro-endocrine tumours

Nuclear medicine approaches to cancer detection, staging and treatment.

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Breast and prostate cancer

Bone scan

For 40 years a bone scan has been one of the most sensitive methods for the evaluation of the presence and localisation of skeletal metastases resulting from breast and prostate cancer. The accuracy of conventional bone scans is about 80%. The use of single photon emission computed tomography (SPECT) increases the accuracy to 88%, and by combining SPECT with computed tomography (CT) (SPECT/CT) the overall accuracy rises to 92%.[1,2]

Prostate cancer is now established as one of the cancers with false-negative results on FDG-PET/CT.

Although a bone scan is relatively inexpensive, delivers a low radiation dose, is widely available and is able to assess the whole skeleton, the specificity is limited by the number of benign pathologies that may mimic metastatic diseases, e.g. degenerative disease in the spine or solitary rib fractures. Also, very small-volume skeletal metastases may not be detected; therefore other imaging techniques, e.g. magnetic resonance imaging (MRI), may be more sensitive.[2]

Currently, the use of bone scans for the diagnosis of bone metastases is limited to higher-risk groups, e.g. for clinical Stage 2b, 3 or 4 breast cancer patients or those in whom the prostate-specific antigen (PSA) is elevated (>20 ng/ml). Twenty to fifty per cent of patients with metastatic bone lesions are asymptomatic.[1] (Fig. 1.)

A bone scan can also be used to monitor treatment response. Tumour progression is usually seen in the form of an increasing number of lesions. Over a period of 6 months or more, a positive response is indicated by a decrease in the tracer uptake or number of lesions; however, this does not apply in the first few months after successful treatment. Reparative calcification in a lesion, including small previously non-visualised lesions, may increase tracer uptake, i.e. the flare phenomenon.

Breast, prostate and cervical cancer and malignant melanoma

PET/CT

There has been a tremendous expansion of applications for positron emission tomography (PET) in the last few years, relating to improved tracer quality and development of combined PET/CT technology. In practice, PET imaging is always combined with CT. The CT scan provides anatomical detail (size and location of the tumour, mass, etc.), while a PET scan provides metabolic detail (cellular activity of the tumour, mass, etc.), enabling PET/CT to produce a fused data set. Consequently, the management of more than 33% of patients imaged has changed.[3] Indications can be broadly categorised into diagnosis, staging, monitoring of response to treatment, and investigation of residual tumour tissue or suspected recurrence (restaging). (Table 1.)

In practice, PET imaging is always combined with a CT.

2-[18F]-fluoro-2-deoxy-D-glucose (FDG) is still the most commonly available tracer approved for routine clinical use. It is an altered glucose molecule that can show physiological and pathological metabolic activity.[4] (Table 2.)

Nodal metastasis is an independent prognostic factor in cervical cancer patients who are being treated with primary radical surgery

Table 1. Timing of PET/CT imaging*

Timing of imaging for recurrence should be limited to the following:	
Surgery	• Up to 36 hours after surgical procedure • Thereafter, wait 3 months following surgery for local imaging • Distal metastatic disease is not affected by local surgery
Chemotherapy	Minimum of 10 - 14 days after the last dose of chemotherapy
Radiation therapy	Minimum of 6 - 8 weeks following radiation
Radiation frequency ablation (RFA)	Within 36 hours of RFA, or thereafter a minimum of 3 months before imaging

*The appropriate timing of restaging with PET/CT varies with type of therapy, principally due to post-treatment inflammatory response and bone marrow hyperplasia.

Imaging should be used with caution in patients who are diabetic or who have recently used high doses of corticisteroids.

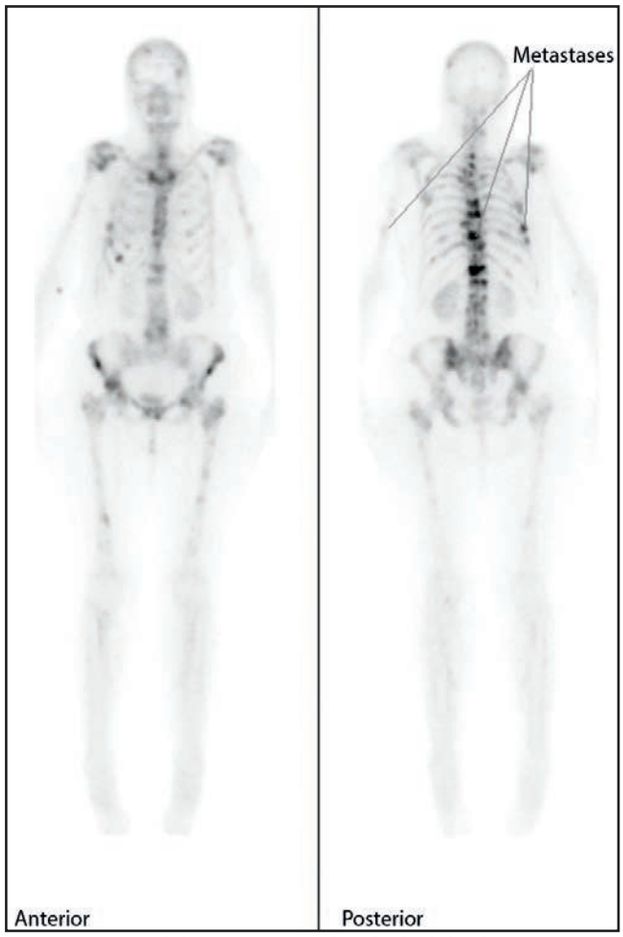

Fig. 1. Patient with breast cancer and multiple skeletal metastases.

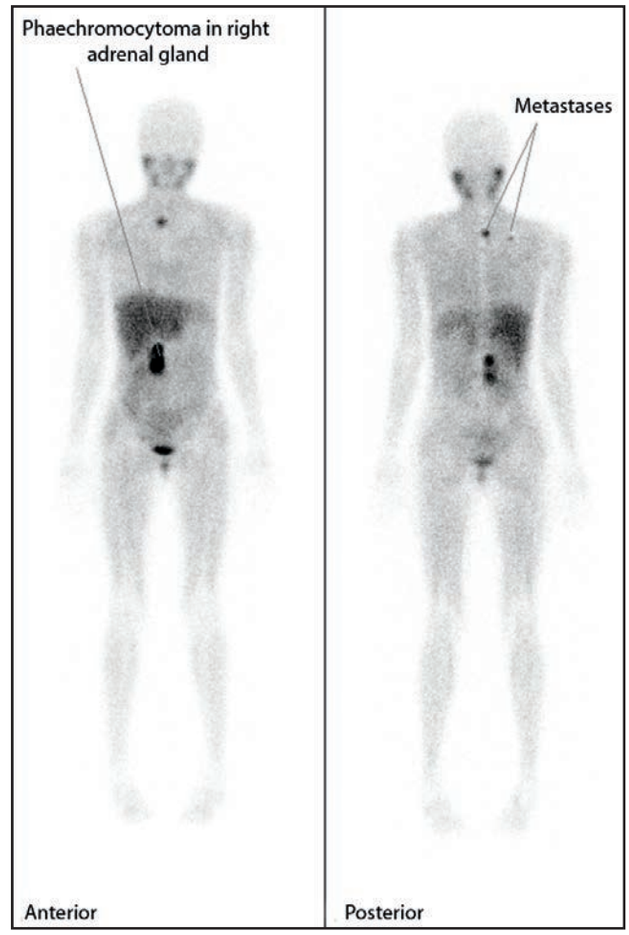

Fig. 3. MIBG scan of a patient with a phaeochromocytoma.

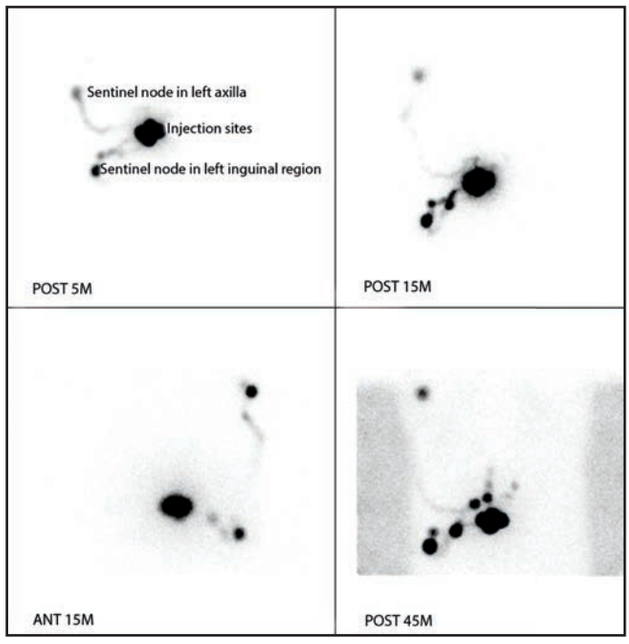

Fig. 2. Sentinel node imaging of a patient with malignant melanoma on the back.

or radiotherapy. Because advanced imaging technologies are not available in many countries where cervical cancer is prevalent, the International Federation of Gynecology and Obstetrics staging system does not consider pelvic or para-aortic lymph nodes in their staging criteria. Although PET/CT is not routinely indicated in patients with cervical cancer, the literature increasingly supports its use for (*i*) assessing prognosis and primary staging; (*ii*) determining the treatment goal (curative or palliative) in lymph node metastases; (*iii*) assessing treatment response after chemo-radiation; and (*iv*) documenting recurrent cervical cancer, unexplained post-treatment elevations in tumour markers, and follow-up after salvage therapy.[5]

Prostate cancer is now established as one of the cancers with false-negative results on FDG-PET/CT. Other radiopharmaceuticals are currently being used more successfully for PET/CT imaging of prostate cancer. Unfortunately, these are currently not available in South Africa.

Breast cancer, malignant melanoma and cervical cancer

Sentinel lymph node imaging

Sentinel lymph node (SLN) imaging is widely used by surgical oncologists as an alternative to elective lymphadenectomy for patients with clinically negative regional lymph nodes who are at high risk for nodal metastases. The objective of SLN imaging is the identification of the most likely first (sentinel) node to which malignant cells could spread.

In SLN imaging radiolabelled colloid particles are injected into the tumour and imaged as they migrate along the lymphatic system. These particles accumulate in the first lymph node they encounter. This simulates what happens to tumour cells that spread to a lymph node.

For patients with clinically negative axillary nodal basins, axillary lymph node dissection has been replaced by sentinel lymph node biopsy (SLNB) as the procedure of choice for lymph node staging in breast cancer.

SLNB was introduced during the last decade as a standard staging procedure in primary melanoma in cases of tumour thickness of ≥1 mm. Reported rates of SLN metastasis are 12 - 20% for 1 - 2 mm melanomas, 28 - 33% for 2 - 4 mm melanomas, and 28 - 44% for melanomas >4 mm.[6] (Fig. 2, Table 3.)

SPECT/CT offers increased spatial resolution and anatomical localisation when compared with planar imaging. This is of particular importance when there is unpredictable drainage to lymph nodes, SLNs are close to the injection site, extra-axillary SLNs are present, or SLNs are not identified on conventional planar images because of soft-tissue attenuation.[7,8]

Neuro-endocrine tumours (NETs) comprise a rare group of neoplasms with a variable natural history and prognosis.

Historically, early-stage, and Stage 1a and 1b cervical cancer patients with low-risk pathological features were treated by means of radical hysterectomy and pelvic lymph node dissection. The risk of lymph node metastases in these women is approximately 15%. Over 80% do not benefit from a pelvic lymphadenectomy, but may suffer from adverse complications such as lymphoedema, lymphocyst formation, neurovascular and ureteral injury, or secondary blood loss. In addition, as the cervix is a midline structure with complex lymphatic drainage, it is not possible to predict the location of metastatic spread reliably. Therefore, SLN assessment is becoming an integral component of definitive surgical management for prognostication and the planning of adjuvant therapy. This is particularly desirable for young women who wish to preserve both ovarian and sexual function. Conversely, women with lymph node metastases may be offered primary or adjuvant chemo-radiation in an attempt to improve survival. According to the recent literature, both the sensitivity and negative predictive values approach 100%.[9]

Neuro-endocrine tumours

Neuro-endocrine tumours (NETs) comprise a rare group of neoplasms with a variable natural history and prognosis. They are derived from endocrine stem cells of the amine precursor uptake and decarboxylation (APUD) system, and can potentially cause

Table 2. Indications for the use of FDG-PET/CT

	Primary diagnosis	Staging	Restaging
Breast cancer	No role No role for carcinoma *in situ* Limited to patients with infiltrating ductal carcinoma	Only indicated if there is significant chance of distal disease as determined by axillary dissection, or where conventional imaging is equivocal	Suspected local or regional recurrence Suspected nodal or distal metastatic recurrence Differentiate post-therapeutic fibrosis from recurrent or residual tumour
Malignant melanoma	No role in primary diagnosis, which is primarily a surgical/histological diagnosis	Indicated for patients with clinical features suggestive of Stage 3 and 4 disease where there is a high incidence of distal nodal and metastatic disease Solitary distal metastasis on conventional imaging where metastatectomy is considered. PET/CT is used to exclude additional lesions which would preclude surgery	Modality of choice for identification/detection of recurrent nodal and distal metastatic disease Differentiate post-therapeutic fibrosis from recurrent or residual disease

Table 3. Advantages and disadvantages of sentinal node imaging

Advantages	Disadvantages
Identification of all draining lymph nodes and all draining basins Identification of sentinel and second-tier lymph nodes Identification of unpredictable lymph nodes: • in-transit nodes (i.e. lymph nodes located between the primary tumour site and a drainage basin) • greater variability in lymphatic drainage pathways in the head and neck or trunk Avoid unnecessary lymphadenectomies and the resulting complications, i.e. lymphoedema, delayed wound healing, infection, and pain	False negative • lymphatic channels may be obstructed by tumour • lymph node may be invaded by tumour

Table 4. Expression of somatostatin receptors and sympathoadrenal tumours

High expression of receptors and sympathoadrenal system tumours	Low expression of receptors	Non-neoplastic pathology
Phaeochromocytoma	Breast carcinoma	Autoimmune diseases
Neuroblastoma	Melanoma	Granulomas
Ganglioneuroma	Lymphoma	Thyroid-associated ophthalmopathy
Paraganglioma	Prostate cancer	Post-radiation inflammatory disease
Gastroenteropancreatic tumours (GEP) (e.g. carcinoids, gastrinoma, insulinoma, glucagonoma, VIPoma, etc.)	Non-small-cell cancer Sarcoma Renal cell carcinoma	Bacterial infections
Medullary thyroid carcinoma	Differentiated thyroid carcinoma	
Pituitary adenoma	Astrocytoma	
Merkel cell carcinoma	Meningioma	
Small-cell lung cancer		

clinical syndromes due to hypersecretion of biogenic amines and polypeptides. Diagnosis is challenging and often delayed for a mean duration of up to 9 years owing to non-specificity or lack of symptoms. At diagnosis metastatic disease is frequently encountered, but detection can be problematic owing to the small size of the primary tumour and the metastases. (Table 4.)

Currently, the use of bone scans for the diagnosis of bone metastases is limited to higher-risk groups, e.g. for clinical Stage 2b, 3 or 4 breast cancer patients or those in whom the prostate-specific antigen (PSA) is elevated (>20 ng/ml).

Standard anatomical techniques, such as CT and MRI, are routinely used for staging and restaging of NETs, with an overall sensitivity of 50 - 80%, depending on the size and site of metastatic lesions and the imaging protocol. In contrast, functional imaging techniques provide highly sensitive and specific diagnostic information, allowing whole-body screening suitable for tumour staging. Somatostatin receptor (SSTR) scintigraphy is a whole-body imaging technique used for diagnosis, staging and restaging of NETs. It is also used to establish if there is any merit in therapy with ^{90}Yttrium or ^{177}Lutetium-labelled somatostatin analogues.

Somatostatin is a regulatory peptide, with affinity for G-protein-coupled membrane-bound SSTR subtypes 1 - 5, including 2A and 2B, which are overexpressed in NETs. The compound ^{111}Indium DTPA-octreotide has an overall sensitivity of 80 - 90% for carcinoid and 50 - 70% for pancreatic NETs, and a high specificity of 88 - 97% for either group of NETs. The sensitivity is reduced if there is a lack of SSTR2 expression, as is seen in poorly differentiated NETs and insulinomas. SSTRs are not only expressed in NET, but are found in normal physiological structures and in other disease states such as inflammation or infection.

I^{123}- and I^{131}-labelled meta-iodobenzylguanidine (MIBG) is an analogue of norepinephrine. The mechanism of MIBG accumulation is a combination of uptake by the norepinephrine transporter and passive diffusion. MIBG imaging is reserved for tumours thought to be of enterochromaffin origin. The reported sensitivity is 55 - 85%, with a specificity of 95%. There are numerous medications that can affect the uptake of MIBG. These include opioids, tricyclic antidepressants, sypathomimetics, antihypertensives (beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors) and antipsychotics. Therapeutic doses of I^{131} MIBG may be used for the treatment of metastatic NETs that display MIBG avidity. (Fig. 3.)

Hybrid SPECT/CT cameras offer superior accuracy for localisation and functional characterisation of NETs compared with traditional planar and SPECT imaging.

The potential role of PET tracers in the functional imaging of NETs is also being increasingly recognised. In addition to FDG, newer positron-emitting radiopharmaceuticals such as Gallium^{68}-1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetra-acetic acid (DOTA) peptides show promise. Imaging can be completed within 2 hours, without delayed imaging on a subsequent day. This is in contrast to SSTR scintigraphy that routinely requires imaging at 4 and 24 hours. However,

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despite its obvious strengths, PET/CT has been slow to be adopted in routine clinical practice in South Africa owing to a combination of cost and availability. FDG-PET/CT has a role in the imaging of poorly differentiated NETs with more biologically aggressive behaviour.[10]

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Summary

- A bone scan is one of the most sensitive methods for the detection of the presence and localisation of skeletal metastases for breast and prostate cancer.
- FDG-PET/CT scans are indicated in patients with breast cancer for staging and restaging.
- FDG-PET/CT scans are indicated in patients with melanoma for staging and restaging.
- FDG-PET/CT has an increasing role to play in the management of patients with cervical cancer.
- Sentinel lymph node imaging is a standard staging procedure for patients with breast cancer and malignant melanoma.
- Sentinel lymph node imaging with SPECT/CT has an increasingly important role in the management of patients with cervical cancer.
- MIBG imaging is reserved for situations where the tumours are thought to be of enterochromaffin origin.
- MIBG therapy is an option for tumours that are proven to be MIBG avid.
- NETs often express somatostatin receptors and can be imaged using somatostatin analogues.
- NETs can be imaged with PET/CT using DOTA peptides.