PERGAMON

European Journal of Cancer 38 (2002) 2157–2172

European Journal of Cancer

www.ejconline.com

Gamma camera imaging in malignancy

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Received 19 February 2002; accepted 15 March 2002

1. Introduction

The aim of this article is to describe the current applications of gamma camera imaging in oncology with some references to potential uses currently under investigation. Initially, the basic principles and techniques will be described, followed by a general discussion of routine and novel radiopharmaceuticals. How nuclear medicine can assist in answering typical clinical questions from oncologists will then be discussed. Finally, current and potential applications of nuclear medicine imaging for each body system will be covered.

2. Basic principles and techniques

Nuclear medicine imaging includes gamma camera imaging (GCI) and positron emission tomography (PET). The basic nuclear medicine procedure involves injection of an appropriate radionuclide usually bound to a biologically active ligand, e.g. iodine-131 labelled meta-iodobenzylguanidine (MIBG). After a suitable time for the ligand to be incorporated into the target organ(s), imaging is performed. Requirements for good quality imaging are radiopharmaceutical stability, specific, avid target binding, adequate delivery of the radiopharmaceutical to the target organ (including enough radionuclide for imaging and adequate blood supply), ability to reach the extracellular space (i.e. molecule small or lipid-soluble enough to cross the endothelium) and background tissue clearance, improving target to background signal ratio.

When designing a new nuclear medicine study, the radionuclide is chosen with regard to its ability to bind to the ligand, physical half-life (which affects radiation dose to the patient and allows sufficient time for radiopharmaceutical production, target organ incorporation and imaging) and the emission spectrum (affecting radiation dose and camera requirements). Some radionuclides are biologically active without prior need for a ligand, e.g. gallium-67. If required, the ligand is chosen according to the biological process or function of interest. Nuclear medicine imaging does not have the resolution of anatomical imaging such as magnetic resonance imaging (MRI) or computed tomography (CT). If detailed anatomical information is required then nuclear medicine by itself is not the imaging modality of choice. However, great advances have been made with fusion of nuclear medicine images with CT or MRI, the combination giving accurate anatomical localisation of function [1]. The great advantage of nuclear medicine imaging is its functional nature, as for example, its ability to assess whether a residual mass after therapy for lymphoma contains viable tumour or its ability to detect small melanoma metastases. In these situations, anatomical imaging alone relies on size, which has been shown to have low accuracy [2]. Fusion images offer the advantages of co-registering anatomy and function.

PET is a sub-category of nuclear medicine imaging that uses positron-emitting radionuclides. The decay of these radionuclides involves the emission of a positron from the atomic nucleus. The positron annihilates with an electron within a few mm of the nucleus resulting in the emission at the point of annihilation of two gamma photons whose paths are 180° to each other. The coincident detection of these two photons promotes improved resolution compared with single photon imaging with conventional gamma-emitting radionuclides.

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0959-8049/02/$ - see front matter
PII: S0959-8049(02)00412-4

However, more complex and expensive equipment is required for coincidence detection. Positron emitting radionuclides usually have short physical half-lives. This is an advantage in that a greater specific activity can be injected for a particular patient radiation dose. This allows a greater photon flux and, consequently, higher count statistics leading to greater sensitivity. Disadvantages of a short half-life are limited time for ligand radiolabelling, tissue incorporation and imaging, and greater radiation doses to the staff.

The coincident gamma photons of PET have a much higher energy (511 KeV) than conventional gamma-emitting radionuclides used in imaging (80–300 KeV) and, consequently, for their detection, require detectors with thicker scintillation crystals than that present in a typical gamma camera. Nevertheless, modifications have been developed to allow conventional gamma cameras to image positron-emitting radionuclides. One is the use of a thicker crystal and coincidence circuitry (see Section 6.7), whilst another is to fit a collimator capable of handling high-energy photons [3,4]. The main drawbacks of such gamma camera adaptation are an increase in the cost and complexity of the camera and some loss of image resolution for conventional imaging. Moreover, the resolution and image quality of positron imaging is inferior to that of a dedicated PET camera [1]. The former can typically only detect lesions greater than 10 mm in size, while the latter can detect lesions down to 4 mm in size. Dedicated PET cameras, particularly hybrid PET-CT cameras, can perform studies much faster than adapted gamma cameras, increasing the number of patients that can be evaluated and reducing motion artefact. In oncology, detection of small positive tumour deposits is vital for the most accurate staging. As this requires optimal resolution and image quality, dedicated PET is essential leading to the belief that in oncology gamma camera PET is not an adequate substitute. Dedicated PET and its applications are discussed elsewhere in this journal so this article will concentrate on the non-PET nuclear medicine techniques in oncology imaging, but will refer to PET in the discussion of the current imaging of the body systems.

3. Gamma-emitting radionuclides

Radionuclides used in gamma camera imaging include technetium-99m (99m-Tc), indium-111, iodine-123, iodine-131, 201-thallium-201, gallium-67 and selenium-53 [5].

99m-Tc is the most widely used as it has a favourable emission energy of 140 KeV, is cheap, easily available and can be bound to many ligands. The half-life of 6.02 h is excellent for same day imaging, but is inadequate if imaging is required for 24 h or more. Indium-111 is more expensive, but has a favourable emission spectrum, good binding characteristics and a longer half-life allowing delayed imaging.

Iodine-131 has a long half-life of 8 days and can be bound to many ligands, including proteins, but is also useful in thyroid cancer as an inorganic iodide. However, it emits a gamma photon, which is only moderately favourable for imaging and also has a beta particle emission resulting in increased local radiation dose. This can be exploited for radiopharmaceutical therapy of thyroid and other cancers. For imaging, however, this is a disadvantage. Iodine-123 has a favourable half-life and gamma emission energy, resulting in improved imaging and less radiation dose to the patient compared with iodine-131, but is much more expensive.

Gallium-67 has a complex emission spectrum, which results in some image degradation. The long half-life increases patient dose but does allow delayed imaging which is generally necessary. Selenium-53 has only a limited range of applications as it has a very long half-life of 50 days, which gives a high radiation dose and poor counting statistics. When labelled to nor-cholesterol, adrenal cortex pathology can be assessed. However, this radiopharmaceutical is not commercially available at present.

4. Radiopharmaceuticals

Many commonly used radiopharmaceuticals are prepared immediately prior to use by adding the isotope to 'cold' kits available commercially. Radiopharmaceuticals for use in oncology can be loosely categorised as non-specific or specific. An example of a non-specific agent is Tc-99m-sestamibi, which is incorporated into a variety of tumours, such as parathyroid neoplasms and some breast tumours. Specific agents include monoclonal antibodies, antibody fragments or peptides specific for tumour antigens or tumour receptors.

4.1. Classes of radiopharmaceuticals

4.1.1. Unbound isotopes or simple compounds

Pertechnetate is the chemical form of Tc-99m produced by commercial generators. It is an iodine analogue and consequently accumulates in the thyroid gland, salivary glands and gastric mucosa and is excreted in urine [5]. A wide range of Tc-99m-based radiopharmaceuticals are used in oncology.

Gallium-67 is a ferric ion analogue. Following injection, it binds to circulating transferrin and is incorporated into many tumours and areas of inflammation as a result of binding to local transferrin receptors [5]. In oncology, Ga-67 is mainly used for imaging lymphoma, but uptake is also seen in melanoma and, to a lesser degree, in hepatocellular carcinoma, lung cancer, mesothelioma, head and neck tumours and sarcomas. How-

ever, with the increasing availability and superior imaging properties of fluorine-18-labelled deoxyglucose (FDG PET), the need for Ga-67 is decreasing.

Thallium-201, a potassium analogue, non-specifically accumulates in viable tumour of many types [5]. Thallium uptake has been described in brain tumours, correlating well with tumour grade, breast cancer, bone and soft-tissue tumours, thyroid cancer, Kaposi's sarcoma, lung cancer, lymphoma and head and neck tumours. However, Thallium-201 has a low energy emission and, consequently, suboptimal imaging characteristics.

Fluorine-18 is a hydroxyl analogue that is avidly accumulated in metabolically active bone [5]. Consequently, it is an excellent radiopharmaceutical for detecting bone metastases. However, Tc-99m-based bone agents are also excellent, but cheaper and easier to use.

4.1.2. More complex, but non-specific compounds

The PET radiopharmaceuticals FDG, F-tyrosine, carbon-11-methionine and oxygen-15-labelled water would fit into this category, but will be covered elsewhere [5].

Sestamibi and tetrofosmin are lipophilic cationic compounds, which despite having complex structures have very similar biodistributions to thallium and are routinely used for myocardial imaging [5]. An advantage of these compounds is that they are stably labelled with technetium giving better imaging characteristics. They are also easily prepared from commercial kits. The presumed mechanism of cellular uptake is by passive diffusion across the cell membrane followed by binding to mitochondria. These compounds are also substrates for P-glycoprotein, which mediates their elimination from cells [3] (Fig. 1). They are therefore surrogates for a range of chemotherapeutic agents and have the potential through imaging of predicting tumour response to chemotherapy, since the level of uptake appears to be inversely dependent on the P-glycoprotein expression of the tumour [6,7]. The commonest applications in oncology are in parathyroid (Fig. 2) and breast (Fig. 1) malignancies, but sestamibi uptake is also seen by lung carcinoma, sarcomas and lymphoma. A disadvantage is biliary and gut secretion which may obscure any abdominal tumour deposit [3].

Bone-seeking radiopharmaceuticals include the diphosphonates such as methylene diphosphonate (MDP) and the less commonly used pyrophosphates [6]. These are easily labelled with technetium and bind to calcium phosphate and hydroxy-apatite, giving images that portray bone turnover. Bone metastases have increased vascularity and more amorphous calcium phosphate and, consequently, bind these agents to a greater extent than normal bone (Fig. 3). Other sites of calcium deposition may also bind them. Consequently tumours, or their metastases, that accumulate calcium may also accumulate

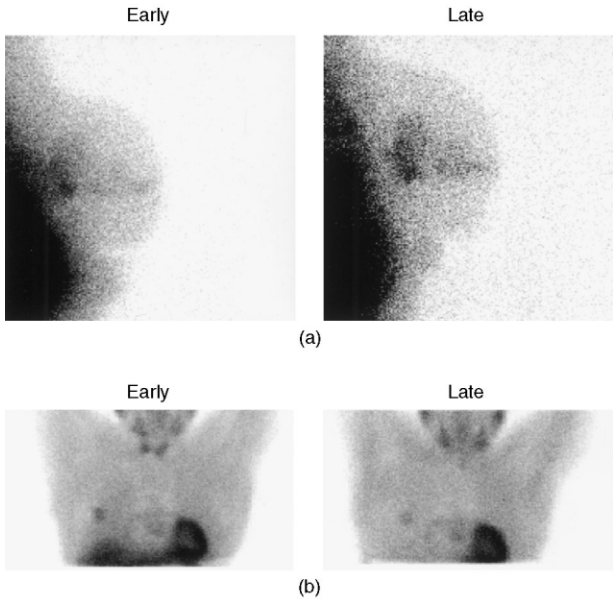

Fig. 1. Tc-99m-sestamibi images acquired 20 min (left panels) and 120 min (right panels) following injection in two separate patients with breast cancer. (a) Patient with a tumour showing a target-to-background ratio which increased from 1.65 to 1.99; (b) patient with a tumour showing a target-to-background ratio which decreased from 2.25 to 1.52. The tumour in patient a stained weakly for Pgp, while that of patient b stained strongly (Permission *J Nucl Med*).

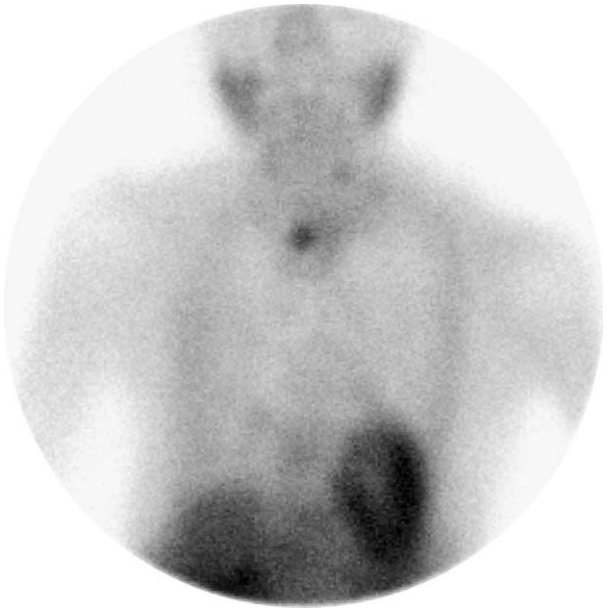

Fig. 2. A delayed (2-h) Tc-99m-sestamibi scan of the upper body and neck of a patient with hyperparathyroidism showing retention of radiotracer in a focus close to the thyroid gland, consistent with a parathyroid adenoma. The thyroid, but not salivary glands, eliminates the radiotracer soon after uptake as a result of the presence of physiological P-glycoprotein. Note the physiological uptake in the myocardium, for which this radiotracer is more commonly used.

these agents, e.g. osteo- and chondro-sarcomas, ovarian and mucinous tumours.

Tc-99m-annexin is a new radiopharmaceutical that is creating much interest in the nuclear medicine community. Annexin binds to phosphatidylserine. This is normally present on the inner leaflet of cell membranes. When a cell undergoes apoptosis or is irreversibly injured, phosphatidylserine is expressed on the external surface of the cell membrane [8]. Consequently, annexin uptake is a marker of cell death and has been described in tumours in response to therapy, myocardial infarction, autoimmune diseases and transplant rejection [8,9]. However, Tc-99m-annexin has not yet been approved for routine use.

Tc-99m-hexamethylpropyleneamine oxime (HMPAO) is a Tc-99m-labelled, lipophilic compound that has a high first pass uptake in the brain [6]. This radiopharmaceutical is trapped intracellularly, possibly by glutathione-mediated conversion to a hydrophilic compound. Uptake is dependent on regional blood flow and cellular activity. Although uptake is seen in cerebral tumours, PET with FDG and C-11-methionine gives superior images.

Tc-99m-dimercaptosuccininic acid (DMSA) is a radiopharmaceutical routine used to image the renal parenchyma. It is a trivalent compound but can be converted to pentavalent DMSA by adding oxygen and alkali to a kit normally used to produce trivalent DMSA [10]. Through an unknown mechanism, pentavalent Tc-99m-DMSA accumulates in a number of tumours, especially medullary thyroid carcinoma and chondrosarcoma, but also thyroid and lung carcinoma, brain tumours and aggressive fibromatosis [11–14].

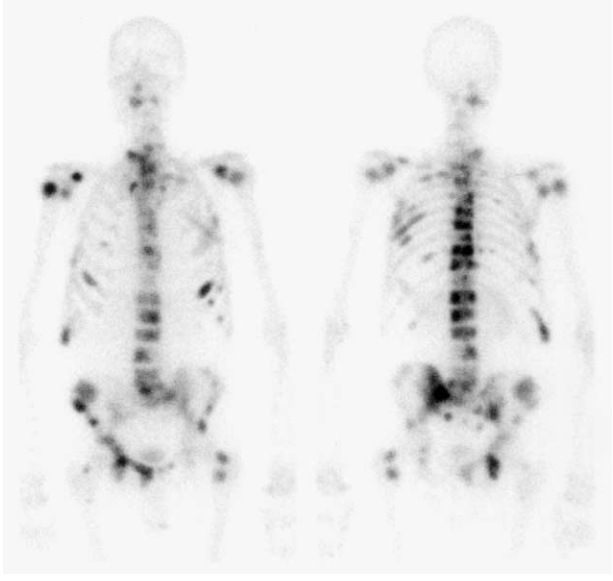

Fig. 3. Tc-99m-MDP bone scan in a patient with carcinoma of the prostate and widespread skeletal metastases.

Tyrosine labelled with iodine or fluorine can demonstrate protein synthesis and consequently cell proliferation. Inflammation is not tyrosine avid. Tyrosine has been used to stage soft tissue sarcomas [15,16].

Folate receptors are overexpressed in many tumours [3]. Folate can be labelled with a variety of radionuclides and potentially used to image such receptors. Pegylated liposomes may also be radiolabelled and are taken up by many tumours [17]. However, as yet, no definite role has been established for these radiopharmaceuticals.

In oncology, many normal biological functions need to be monitored in order to avoid complications of both therapy and the disease process itself. Trivalent DMSA and mercaptoacetyl triglycine (MAG3) are used for assessing renal function, maccroaggregated albumin and a variety of aerosols and gases are used to assess pulmonary function, especially pulmonary embolism. Technetium-99m-labelled red cells can assess cardiac ejection fraction or confirm a liver lesion as a haemangioma. Technetium-99m-labelled colloid can be used for sentinel node detection, demonstration of haemopoietic bone marrow and liver and spleen morphological changes, e.g. splenunculi. Hydroxyethyliminoacetic acid (HIDA) demonstrates biliary function and obstruction.

4.1.3. Specific radiopharmaceuticals

There are a wide range of hormones, including precursors or analogues, which specifically bind to tumour receptors and can be radiolabelled. The two commonly used radiopharmaceuticals are MIBG (an analogue of noradrenaline) and pentetreotide (an analogue of somatostatin) [6].

MIBG uptake appears to be via the type 1 active amine transport mechanism with localisation in presynaptic adrenergic neurons [6]. Uptake is seen within neuroblastomas, phaeochromocytomas (Fig. 4), paragangliomas, ganglioneuroblastomas and ganglioneuromas. Uptake is also seen within many normal tissues with adrenergic supply including heart, salivary glands and spleen. MIBG can be labelled both with I-131 and I-123. The former is cheaper and because of its beta emission may also be useful in therapy. The latter, though more expensive, gives better image resolution and lower radiation dose and is generally preferred, especially for children.

Octreotide (or, for imaging, the analogue pentetreotide) is the most commonly used of a family of somatostatin analogues, other examples being lanreotide and depreotide [18,19]. So far, five somatostatin receptors have been identified. Octreotide particularly binds to receptors 2 and 5 [20]. Somatostatin receptors are expressed by a variety of tumours, which can be categorised into carcinoids (Fig. 5), neuroendocrine tumours including phaeochromocytomas, medullary thyroid carcinoma and small cell lung cancer, CNS

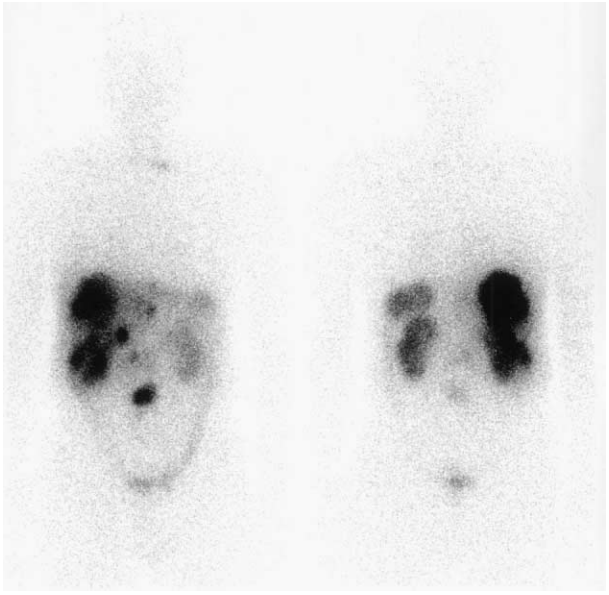

Fig. 4. Whole body I-123-MIBG scan in a patient with a large right adrenal phaeochromocytoma. No extra-adrenal disease is present.

tumours including pituitary adenomas, astrocytomas, meningiomas, and neuroblastomas, and other tumours including lymphoma, breast, lung and renal cell carcinoma [20]. Pentetreotide, a five-residue peptide, can be labelled with a variety of radionuclides, including indium-111 and iodine-123 for diagnosis and with radionuclides such as iodine-131 and yttrium-90 for therapy. Depreotide can be labelled with technetium-99m. Although inferior to pentetreotide with respect to neuroectodermal tumours, depreotide has Food and Drug Association (FDA) approval for use in lung cancer, in particular for characterising lung nodules [21]. A disadvantage is high liver uptake, making assessment of adrenal and liver metastases difficult.

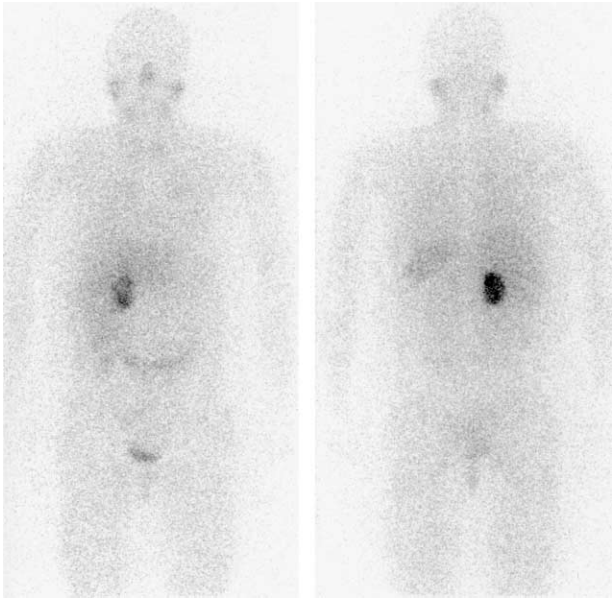

Fig. 5. In-111-pentetreotide whole body scan in a patient with extensive carcinoid metastases. There is extensive disease throughout the liver, plus a prominent deposit in the abdomen and extraabdominal disease in the form of an involved left supraclavicular lymph node. Splenic, renal and urinary activity is physiological.

Many other peptide hormones or their analogues can be labelled with a wide range of radionuclides [20,22]. An excellent review of this subject has been written by Heppeler and colleagues [22]. These hormones include melanocyte-stimulating hormone, luteinising-hormone releasing hormone LHRH, VIP, CCK-B/gastrin, glucagon-like peptide, opiates, neurotensin, bombesin and substance P. The clinical value of imaging with these latter peptide hormones is uncertain and needs further research.

Norcholesterol accumulates within adrenocortical cells and adrenocortical tumours, where it is esterified, but not metabolised into adrenal hormones [6]. Norcholesterol can be labelled with I-131 or with selenium-75. However, the selenium compound is no longer economically viable and is consequently no longer available [23,24].

Cyclic pentapeptides can be labelled with technetium-99m and bind to the neovascular $\alpha v\beta 3$ integrin receptor, which is expressed during angiogenesis. Trials are needed to determine if there is a role for this radiopharmaceutical [9].

Monoclonal antibodies and antibody fragments can be labelled with technetium, indium or iodine [25]. The antibody fragments may show superior imaging characteristics, with faster background clearance, improved capillary permeability into the target tumours and less antigenicity. However, radiolabelling may interfere with antigen binding [6]. Antibody bound to biotin and avidin may magnify the signal to improve sensitivity [26]. The FDA has approved some radiolabelled antibodies for imaging, including *Oncoscint*, a whole murine IgG antibody targeted to TAG-72, which is expressed by colorectal and ovarian malignancies, carcinoembryonic antigen (*CEA*)-*scan*, an antibody fragment against CEA antigen, which has approval for colorectal carcinoma and *Prostascint* which is a murine immunoglobulin reactive with prostate-specific antigen. TAG-72 and CEA are antigens expressed on other tumours, but the FDA has only approved their use for the above indications [27,28].

Verluma, an antibody fragment against an antigen expressed on many carcinomas, including small and non-small cell lung carcinoma, breast, ovary, colorectum and prostate, has FDA approval for diagnosing small cell lung cancer. Anti-αFP has been used to image germ cell tumours and hepatomas [29,30]. Other imaging antibodies under investigation include anti-CD20, anti-CD-31, anti-CD-34 and anti-CD-36. Anti-factor VIII-Ra may be useful in detecting angiogenesis [31]. Anti-$\alpha v\beta 3$ has been paramagnetically labelled for MRI

for imaging angiogenesis. Although this approach with MRI provides detailed functional morphology, nanomolar concentrations of antibody are required for a detectable signal. In contrast, nuclear medicine techniques can detect picomolar concentrations of antibody. The current role of antibodies in oncology imaging is uncertain and requires further evaluation. The potential is wide, limited only by production of suitable antibodies and by the performance of suitable trials.

Antisense oligonucleotides can also be labelled with radionuclides including technetium-99m, indium-111 and fluorine-18. In 1994, Dewanjee and colleagues produced images in a rat using an antisense oligonucleotide and since then an antisense oligonucleotide to the *MDR* gene has been produced [32]. This is a technique which has great potential for detecting viruses, cancer-specific genes and the presence of messenger RNA *in vivo*, but has not been assessed in clinical trials. An excellent review of this subject has been written by Gauchez and colleagues [33]. Antisense oligonucleotides may also potentially be used in therapy. Preliminary imaging with the nucleotide may be useful to predict whether the therapy would be effective. However, there are multiple technical difficulties with this technique and much work will need to be done if it is to become clinically useful.

Molecular Imaging involves the detection of compounds and processes *in vivo*, including antibodies and antisense oligonucleotides as well as other cellular compounds, using a variety of techniques including nuclear medicine. An excellent review of this related topic has been written by Weissleder and Mahmood [34].

5. The clinical role of nuclear medicine

The following issues need to be considered:

1. Screening
2. Diagnosis, including detection of unknown primary
3. Staging
4. Grading
5. Prognosis
6. Guiding therapy, including sentinel node detection and assessing suitability of radiopharmaceutical therapy
7. Detecting response
8. Detecting recurrence
9. Paraneoplastic syndromes
10. Effects of therapy on normal tissues.

5.1. Screening

Nuclear medicine has no role for screening the general population. Although specific nuclear medicine probes can detect multiple disease processes, nuclear medicine is unsuitable for screening large numbers of patients because of the high cost and radiation burden to the population. Whether there is a role for screening selected populations, such as those presenting with deep venous thrombosis (DVT) or hepatitis-B-positive individuals has not been clinically evaluated. FDG PET detects many common tumours and patients with DVT, with no apparent risk factors. Patients with suspected paraneoplastic syndromes are at risk of occult malignancy. Similarly, patients with hepatitis-B are at risk of developing hepatomas. The authors speculate that FDG may have a role for screening these selected populations, but this obviously requires clinical evaluation.

5.2. Primary diagnosis, including detection of unknown primaries

The histological definitive diagnosis of a mass is a clinical problem poorly addressed by nuclear medicine. Despite having probes for many tumours, nuclear medicine is unlikely to replace biopsy and histology for definitive primary diagnosis in clinical practice. For instance, although a thyroid mass will avidly take up radioactive iodine, this technique does not differentiate papillary from follicular carcinoma, i.e. despite having a specific marker for melanocyte stimulating hormone receptors, a suspected melanoma should be treated by excision biopsy with histological examination rather than any nuclear medicine investigation.

Although not able to give a definitive histological diagnosis, nuclear medicine may give a diagnosis that is accurate enough to guide management. For instance, both FDG PET and Tc-99m-depreotide have been used to determine whether a solitary pulmonary nodule is benign or malignant and truly solitary. Sestamibi has been used in a similar way for detecting whether a breast lesion is benign, malignant or multi-focal when other imaging analyses have been inconclusive [35].

For the patient with multiple metastases from an unknown primary, FDG PET may demonstrate multiple sites of disease. However, determining which site is the primary may be very difficult. The clinical significance of identifying all sites of disease in this circumstance is also doubtful.

5.3. Staging

Nuclear medicine is an excellent modality for staging cancer. Its advantages are as follows: the whole body can be examined easily, there is good patient compliance and tolerance of the procedure, in difficult cases and if motion artefacts are seen then further images are easily obtained and tumour detection with nuclear medicine is not reliant on size criteria. Current practice in CT staging of lung cancer is to assume a lymph node within the med-

iastinum of greater than one centimetre contains metastatic disease, whereas lymph nodes less than one centimetre do not. This has been shown in numerous studies to be incorrect and the same principle applies with other tumour types [2]. Nuclear medicine techniques rely on the isotope activity bound to a metastatic deposit, not its size [1]. Consequently, for avid tumours, small metastases can be detected. The best example of this is FDG PET imaging of melanoma. Wagner and colleagues found they could detect nodal metastases greater than 80 mm^3 with 90% accuracy, i.e. metastases 4–5 mm in diameter [36]. FDG PET is the most useful radiopharmaceutical in many tumours. However, the same principle applies to all radiopharmaceuticals, i.e. avid tumour uptake leads to greater sensitivity to smaller deposits.

5.4. Grading tumours

Grading cancer is not a common application of nuclear medicine techniques. However, many tumours are heterogeneous in their grading and activity. Nuclear medicine techniques can indicate sites of more active, higher grade tissue and, consequently, identify the optimal sites for biopsy. The best example of this is FDG and methionine imaging of cerebral tumours. Methionine imaging identifies viable tumour. Correlation with FDG uptake in the region estimates grade, with the highest uptake of FDG seen in the higher grades. Gallium uptake in non-Hodgkin's lymphoma also correlates with the grade of tumour.

A potential application for nuclear medicine in grading tumours is the use of labelled antibodies and antisense oligonucleotides as there is the possibility of detecting antigen expression, viruses, oncogenes and messenger RNA *in vivo*. However, this is still a theoretical application with no established clinical role [33].

5.5. Prognosis

A combination of staging and grading tumours can be useful in prognosis, the better examples being melanoma and cerebral tumours, as mentioned above.

Characterising antigen expression can also predict prognosis. CEA expression in medullary thyroid carcinoma is associated with a poor prognosis, while octreotide uptake is associated with a better prognosis [20]. Admittedly, antigen expression can also be assessed on pathology specimens. However, many tumours are heterogeneous. *In vivo* nuclear medicine techniques assess the whole tumour, while pathology specimens are only samples and sampling error can occur.

5.6. Guiding therapy

Sentinel node detection is a technique of increasing interest to oncology surgeons. The technique involves injection of radiolabelled colloid around the tumour. Sequential images are then obtained until the first draining lymph node is identified and marked on the overlying skin. The surgeon can then use a hand-held, sterile gamma probe to find and excise the sentinel node for more accurate staging and determination of the need for wide excision.

The technique identifies the lymphatic drainage of a region in the individual patient. The advantages of the technique are improved staging of tumours, potential limitation of excision and any postsurgical complications and an indication of where the pathologist should concentrate his/her attention to detect micrometastases. For example, when excising a breast malignancy, the pathologist concentrates their attention on the sentinel node and less attention is focused on the other 10–30 nodes excised [37,38].

The technique does not identify whether tumour has spread, but does identify where the tumour is likely to spread. This technique is particularly useful in tumours that normally spread through lymphatics, but in which the drainage may be unpredictable. These include tumours of the breast, penis, melanoma, vulva and gastrointestinal tract, especially oesophagus [36,39].

Low sestamibi uptake or rapid clearance of sestamibi has been correlated with a high expression of P-glycoprotein (Pgp), particularly in breast malignancy, although Pgp is seen in many cell types. Pgp expression implies a resistance to a number of chemotherapeutic agents such as the taxanes [3,6,7]. Whether sestamibi can be used to guide chemotherapy regimes needs further study.

Imaging with a radiopharmaceutical with therapeutic potential can determine if a tumour is avid for, and consequently suitable for, radiopharmaceutical therapy. The best examples of this approach are octreotide and MIBG assessment and treatment of carcinoid tumours.

Image fusion with anatomical imaging can help guide radiotherapy planning [40].

5.7. Detecting response to therapy

Monitoring response to therapy is a clinical scenario for which nuclear medicine is ideally suited. Anatomical imaging modalities require extensive necrosis or a change in size to detect response to therapy. Nuclear medicine techniques can detect an early change in tumour activity well before any anatomical change occurs [3]. An example of this was given by Front and colleagues, assessing the response of NHL patients treated with chemotherapy by gallium scan versus CT [41]. After one cycle of chemotherapy, 81% of patients with negative gallium scans had long-term remission, whereas 71% with positive images after one cycle of chemotherapy had treatment failure. Even after three and a half cycles of chemotherapy, CT was not predictive of outcome. These results are encouraging. More

impressive results may be expected with Hodgkin's disease and FDG as NHL is less gallium or FDG avid than Hodgkin's disease and FDG PET offers superior imaging to gallium scintigraphy. New cytostatic therapies, including those limiting angiogenesis, may result in no change of tumour size and, consequently, require functional imaging to detect a response [3,42,43].

Technetium 99m-labelled annexin is a promising new radiopharmaceutical for detecting cell death and may be very useful for detecting response to therapy [8,9]. Clinical trials are currently underway to determine the role of this radiopharmaceutical in the management of many tumours.

5.8. Detecting recurrence (restaging)

This is another application for which nuclear medicine is ideally suited and has advantages over anatomical imaging. After therapy, there is frequently residual necrotic tumour, scar tissue or recurrent tumour. Anatomical imaging has great difficulty in differentiating these. However, nuclear medicine techniques can detect active tumour versus inactive tissue [41]. Although FDG PET is the most common, often ideal, radiopharmaceutical for this application, many other radiopharmaceuticals may be used depending on the tumour type, for example, radioiodine in a patient with a rising thyroglobulin after ablative therapy for thyroid carcinoma.

5.9. Paraneoplastic syndromes

Hypertrophic pulmonary osteoarthropathy is detectable by bone scintigraphy before the periosteal calcification can be seen on any other imaging (Fig. 6). Assuming the chest X-ray is close to normal, ventilation and perfusion imaging remains an excellent test for detection of pulmonary emboli.

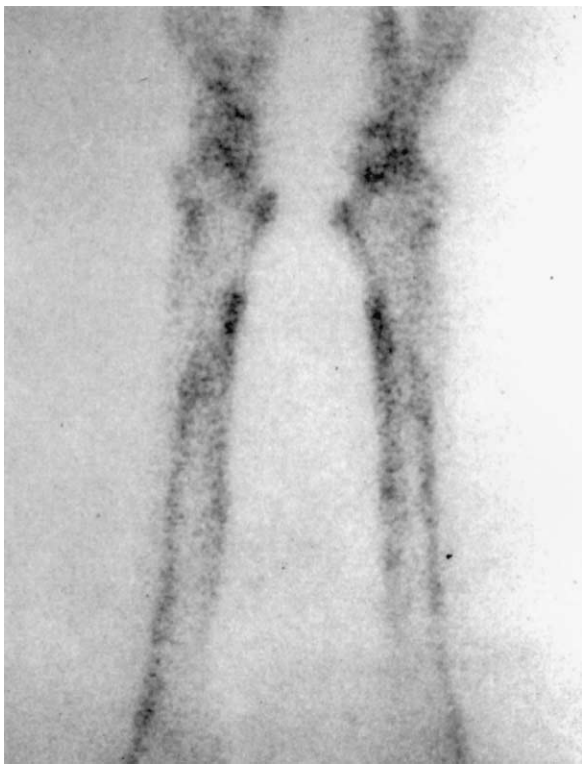

Fig. 6. Tc-99m-MDP bone scan in a patient with non-small cell lung cancer showing hypertrophic pulmonary osteoarthropathy. Note the prominent bilateral increased periosteal uptake.

5.10. Effects of therapy on normal tissues

All forms of tumour therapy may damage normal tissues. Nuclear medicine is excellent for quantifying and monitoring the function of normal tissues, including cardiac, biliary and renal function, extent of haemopoietic marrow, and demonstrating change in pulmonary function after radiotherapy.

6. Current and potential clinical uses of nuclear medicine with regard to specific tumours

6.1. Cerebral tumours

Optimal imaging of cerebral tumours currently involves a combination of C-11-methionine and anatomical imaging including CT and MRI. This combination provides the fine anatomical detail, particularly with MRI, with the functional information of methionine, effectively staging and grading the tumour, or differentiating radionecrosis from recurrent tumour. Methionine appears to be a superior agent to FDG for detection of viable tumours including gliomas and meningiomas [44–48]. FDG is less useful in assessing intracranial tumours due to high normal uptake in the cerebral cortex. As many cerebral tumours have varying grades of tumour at different sites, nuclear medicine has been used to identify the site of highest grade for biopsy. Tc-99m-HMPAO has a distribution of uptake in cerebral tumours similar to FDG and can be used in a similar manner. However, FDG is clearly superior to HMPAO.

A number of neuro-transmitters or analogues, such as octreotide and depreotide, are taken up by cerebral tumours. In rare, difficult cases, particularly after surgery, octreotide may be useful to detect meningiomas or functioning pituitary adenomas [49]. Non-functioning adenomas are less avid. Image fusion with CT or MRI would be useful in these cases.

6.2. Head and neck tumours

FDG has a clear role in staging head and neck tumours and detecting recurrence. A common clinical

problem in the head and neck region is determining the site of an unknown primary when the patient presents with a metastatic cervical lymph node. FDG PET, particularly with image fusion to CT or MRI, is the optimal imaging modality in this case. Sentinel node detection has potential for use in this region, particularly around the oral cavity, where lymphatic drainage may be unpredictable. However, whether this results in improved patient outcome has yet to be determined.

There is non-specific uptake by head and neck tumours of thallium and pegylated liposomes. Thallium is unlikely to be useful due to its imaging characteristics. Pegylated liposomes have potential application for delivering chemotherapeutic agents and prior imaging with radiolabelled liposomes may be useful to predict if uptake of this form of chemotherapy may occur [17].

6.3. Salivary tumours

Salivary glands accumulate and then secrete technetium and iodine and can be imaged with these radionuclides [5]. They are also normally seen with Tc-99m-sestamibi and I-123-MIBG scans. However, no specific role for nuclear medicine has been established with salivary tumours.

6.4. Thyroid

When assessing a thyroid mass, [Tc-99m]pertechnetate has traditionally been used for the identification of a non-specific 'cold' nodule, which carries a 10% likelihood of malignancy. However, ultrasonography, possibly followed by percutaneous biopsy, will give a specific diagnosis.

The treatment for papillary and follicular thyroid malignancy is 131-radioiodine, irrespective of whether metastases are present. Debulking the normal thyroid and tumour optimises uptake of radioiodine in the remaining tissue and is routinely performed in all cases. Consequently, nuclear medicine is not useful for initial staging. However, imaging performed a few days after administration of a therapeutic dose of radioiodine will document the presence of any metastases for later follow-up. If thyroglobulin levels rise after thyroid ablation, radioiodine can be readministered to treat recurrent disease and identify its position. If the thyroglobulin level continues to rise, FDG PET may identify any metastastic disease that cannot be identified with radioiodine. Anaplastic thyroid carcinoma may be more effectively staged with FDG [50].

6.5. Parathyroid

Parathyroid carcinoma is rare, unlike parathyroid adenomas and parathyroid hyperplasia which are much more common. All three conditions can be identified either with sestamibi or with a combination of pertechnetate and thallium [51,52]. The former is currently considered the superior technique. Sestamibi is taken up by both thyroid and parathyroid tissue. However, thyroid tissue contains Pgp, which mediates the elimination of sestamibi from the thyroid, but not from parathyroid tissue. Consequently, on delayed imaging, only parathyroid tissue is seen (Fig. 2). The normal parathyroids are too small to be seen. The technique is usually performed in a patient who has biochemical evidence of hyperparathyroidism and the imaging is performed to detect the site(s) of any parathyroid adenomas or parathyroid hyperplasia. The advantage over ultrasound is that patient can be scanned easily from the angle of mandible to the diaphragm, consequently allowing the detection of low-lying parathyroid tissue. Sestamibi scanning is particularly useful for identifying residual tumour if there is a persistently elevated parathormone level after initial surgery [53]. Occasionally, a thyroid adenoma may retain sestamibi due to loss of physiological Pgp. This is an uncommon appearance, in the context of hyperparathyroidism, and can usually be excluded by comparison with a pertechnetate scan of the thyroid performed the next day. FDG can detect adenomas, but is poor at detecting parathyroid hyperplasia [54].

6.6. Medullary thyroid carcinoma

This is a rare tumour, but of great interest to nuclear medicine as it accumulates a range of radiopharmaceuticals, including pentavalent DMSA, gastrin, cholecystokinin and substance P [20,55]. As presentation is usually with biochemical evidence and/or a mass in the neck which can be biopsied under ultrasound guidance, the usefulness of nuclear medicine is uncertain, although detection of recurrence is potentially useful. CEA expression in medullary thyroid carcinoma has been associated with a poor prognosis, whereas somatostatin receptor expression is associated with an improved prognosis [20]. The latter may also indicate potential use of octreotide therapy. However, only 50% of medullary carcinomas express somatostatin receptors.

6.7. Lung

The optimal radiopharmaceutical for imaging lung cancer is FDG, which accurately stages both small and non-small cell lung cancers (Figs. 7 and 8), and is excellent for detecting tumour recurrence. False-positives can be seen with inflammatory lesions and as a result, interestingly, the specificity of FDG PET varies regionally depending on the local incidence of granulomatous lung lesions. However, the standardised uptake value (SUV) of infection is usually not as high as that of

neoplasia and, as with all tumour imaging, accuracy can be improved if clinical information and other imaging studies are available for comparison. False-negatives are occasionally seen with bronchoalveolar cell carcinoma and with carcinoids. Technetium-labelled depreotide has been approved for use in differentiating benign from malignant pulmonary nodules with high sensitivity [21]. The main advantage of depreotide is that it is a technetium labelled ligand and, consequently, available for use with standard gamma cameras. A disadvantage is significant liver and abdominal uptake, making assessment of metastases in the abdomen difficult.

6.8. Breast

FDG is the most useful radiopharmaceutical for detecting breast malignancy as it detects both soft tissue and bone metastatic deposits, while MDP and other phosphonates are excellent for detecting bone metastases [56]. Sestamibi is also taken up by the majority of breast tumours. In addition, poor uptake or rapid washout of sestamibi from a known tumour implies the presence of multidrug resistance and consequent resistance to chemotherapy [6,7]. Nuclear medicine techniques are not suitable for breast screening of the general population. However, sestamibi, FDG or MRI may be useful for differentiating difficult cases where mammography and ultrasound are inconclusive. Sestamibi was demonstrated to be particularly useful with a negative predictive value of 94% in cases where the anatomical imaging conclusion was 'probably benign', but in which the prevalence of malignancy was 10% [35]. These situations include patients with dense breast parenchyma and in lobular carcinoma.

A problem with nuclear medicine imaging of the breast is accurate localisation and biopsy of an abnormal finding is difficult, but this is a problem shared with MRI.

Sentinel node detection with technetium labelled nano-colloid is a technique which has the potential to limit the extent of axillary excision of breast malignancy and limit its subsequent complications, particularly lymphoedema [39]. Sentinel node detection has become popular, particularly with patients who are well educated about their disease and the therapeutic options they have. Clinical trials are in progress, but no definite conclusions have been determined on the long-term outcome for these patients [39].

6.9. Gastrointestinal tumours (non-endocrine)

For the more common malignancies of the oesophagus, stomach and colon, FDG is the radiopharmaceutical of choice for staging and detection of tumour recurrence. Sentinel node detection has been performed, particularly with respect to the oesophagus, but also the colon, with injection around the tumour sites via an endoscope. This is more likely to be useful for the oesophageal malignancies where lymphatic drainage is unpredictable. The clinical usefulness of this procedure needs to be assessed [57].

6.10. Neuroendocrine tumours

These are a group of tumours of particular interest to nuclear medicine as they express a variety of receptors and have varying types and levels of function [58]. An excellent review has been written by Behr and colleagues [20]. In-111-pentetreotide is the most useful radiopharmaceutical in this group of tumours and the only one currently approved for use. However, many other peptides are potentially useful and need to be examined.

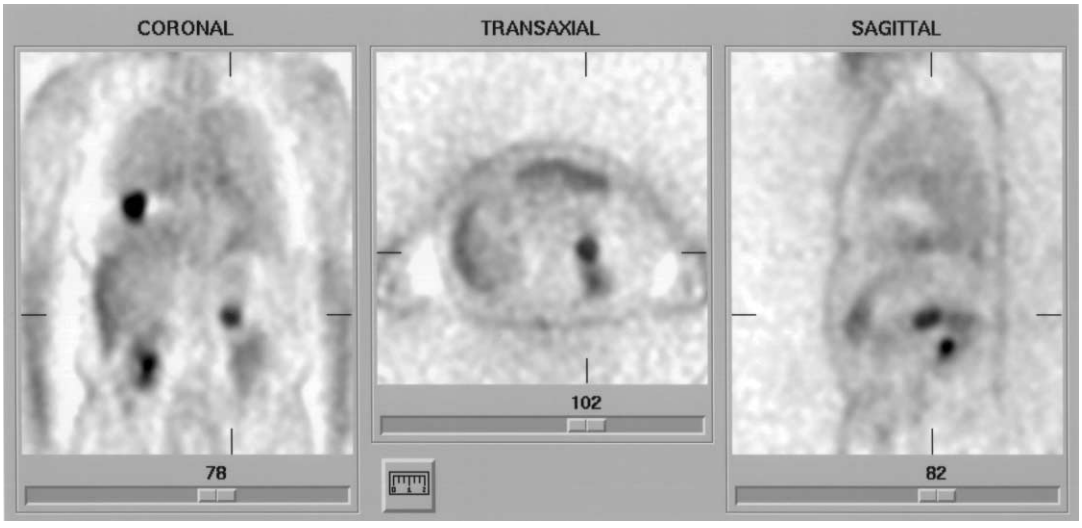

Fig. 7. Fluorine-18-labelled deoxyglucose (FDG PET) scan in a patient with lung cancer and a left adrenal metastasis. The lung primary is also clearly visible. Image acquired with a partial ring dedicated PET system (ECAT ART). Note physiological urinary activity in the kidneys.

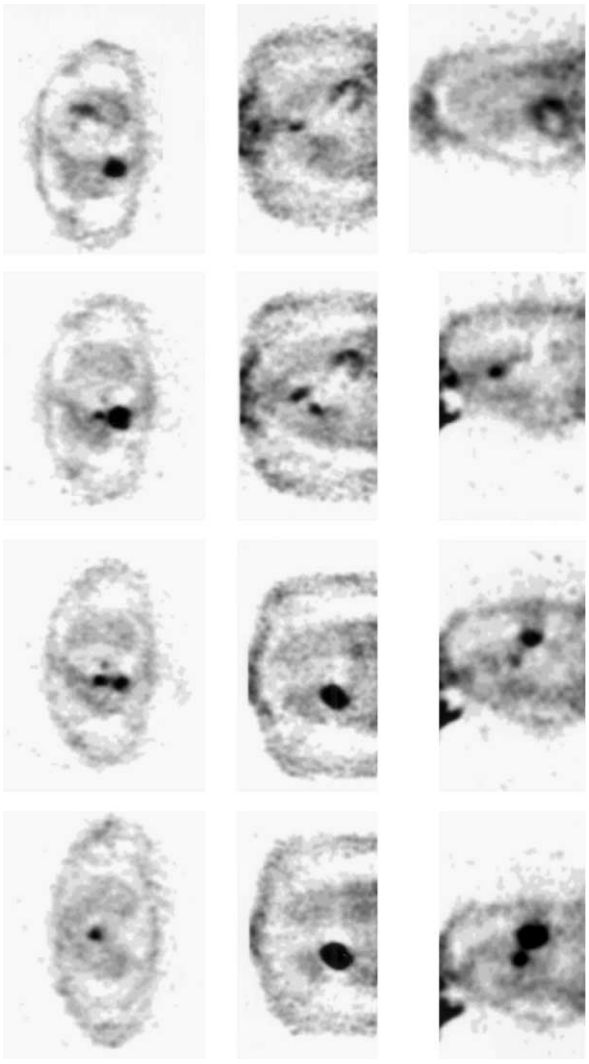

Fig. 8. Tomographic FDG images in a patient with carcinoma of the lung acquired with a gamma camera fitted with coincidence circuitry. The primary is located posteriorly in the right midzone and there is extension to the right hilar region. Physiological uptake in the myocardium is clearly visible. Uptake in the laryngeal region is also physiological and may be particularly prominent if the patient does not refrain from talking after the administration of EDO. Upper row: transaxial; middle row: coronal; lower row: saggital (courtesy of Dr K. K. Balan).

Carcinoid tumours are best imaged with In-111-pentetreotide, but can also be imaged with F-dopa [58]. I-123-MIBG is also taken up by carcinoids, but to a lesser extent than In-111-pentetreotide. These radiopharmaceuticals can be used for staging and for tumour recurrence. Uptake also indicates those tumours that may be responsive to radiopharmaceutical therapy. Carcinoids are not usually FDG-avid. Only 50% of insulinomas express somatostatin receptors. Although clinically not evaluated, glucagon-like peptide has potential for use with this tumour [20].

6.11. Adrenal gland

Both adrenocortical and adrenomedullary scintigraphy are reserved for patients with biochemical evidence of disease and inconclusive anatomical imaging, that is, elevated hormone or degradation products and no obvious mass on anatomical imaging or in the post-surgery clinical setting.

I-123-MIBG is the radiopharmaceutical of choice for detecting phaeochromocytomas and neuroblastoma, with uptake implying that I-131-MIBG may be a radiopharmaceutical therapy option [6].

Adrenocortical adenomas or hyperplasia are detected with norcholesterol usually labelled with 131-I as 53-Se is no longer available [23,24].

6.12. Exocrine pancreas

Pancreatic adenocarcinoma is a tumour with poor prognosis and limited therapy options once the initial tumour has become unresectable. FDG PET may be useful to detect liver and distal metastases. However, the majority of cases will be best evaluated by CT, MRI or laparoscopic techniques to detect whether a tumour is resectable or not. Consequently, nuclear medicine has little to offer. Tumour recurrence is usually detectable on anatomical studies. However, FDG may be of benefit in this situation. HIDA scans may be useful to assess biliary obstruction and stent function.

6.13. Liver

Differentiating benign from malignant masses within the liver is a common problem. Metastases are usually imaged with the same techniques as that of the primary involved, e.g. FDG for colon and lung cancer. Hepatoma, which is usually managed by a combination of anatomical imaging and biopsy, has been imaged with Anti-αFP and gallium [26]. However, hepatomas may show a specific, but insensitive, pattern of an initial cold defect on HIDA imaging, with 'filling in' over 2–4 h [5]. Haemangiomas may be characteristic on CT, ultrasound or MRI, but may also be atypical. Haemangiomas greater than one centimetre in size can easily be identified on labelled red cell studies with a high specificity [5]. This may be useful to confirm a lesion as a haemangioma, thus avoiding a biopsy and risk of significant haemorrhage. However, a negative red cell study is non-diagnostic. Although large hepatomas and angiosarcomas have been reported as positive on red cell scintigraphy, the majority of hepatomas are negative and the number of false-positive studies is extremely rare [5]. Technetium colloid scans show normal or increased uptake within focal nodular hyperplasia, although interpretation may be difficult if there is coincident cirrhosis or other infiltrating processes.

HIDA scans can be useful for detecting hepatocyte dysfunction or biliary obstruction. The latter is particularly useful when biliary anatomy has been altered due to previous therapy [5].

6.14. Kidney

Initial staging of renal tumours is usually accurately performed by CT, as the usual path of spread is typically local and also into inferior vena cava and lungs. MDP is useful for detecting bone lesions. However, renal metastases to bone are often lytic and photopenic on bone scintigraphy (Fig. 9). FDG is useful for staging both soft tissue and bone metastases. Local tumour recurrence is usually apparent on CT, but FDG may also be useful for detecting tumour recurrence. A disadvantage of FDG is its normal renal excretion, but this can be minimised by the administration of frusemide, and an experienced interpreter can usually differentiate renal excretion from tumour uptake. Somatostatin receptor expression has been described with renal malignancy, but no role for somatostatin receptor imaging has been established [60,61].

The commonest use of nuclear medicine imaging in renal malignancy is for measurement of differential renal function, most accurately with DMSA. MAG3 scintigraphy is able to assess outflow, drainage and whether obstruction is intrinsic, as for example in transitional cell carcinoma, or extrinsic, e.g. non-specific lymphadenopathy. Glomerular filtration rate is estimated from plasma clearance of Cr-51-ethylene diamine tetraacetic acid (EDTA) following intravenous (i.v.) injection.

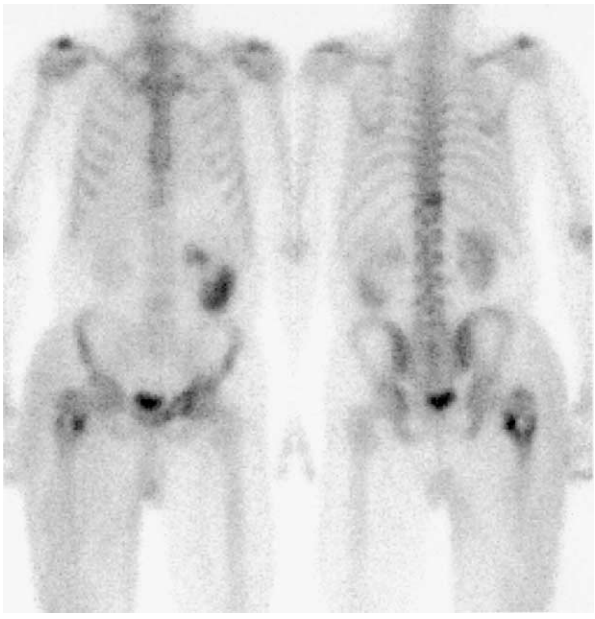

Fig. 9. Tc-99m-MDP bone scan in a patient with renal cell carcinoma showing lytic metastatic deposits in the proximal shaft of the right femur and left superior pubic ramus. There is a further deposit in the thoracic spine at T11. The left kidney shows a large parenchymal defect as a result of the primary and there is extensive soft-tissue swelling involving the right buttock and thigh.

6.15. Peritoneum

The extent of pseudo-myxoma peritonei has been evaluated with a radiolabelled antimucin monoclonal antibody. However, this is a rare tumour and no clear role for nuclear imaging has been established [61].

6.16. Ovary

As ovarian malignancy often presents late, detection of metastases or tumour recurrence is often easily detected on CT, US or MRI. However, in difficult cases, FDG may be useful. Colonic and urinary activity with FDG may make interpretation difficult.

6.17. Uterus and cervix

Nuclear Medicine has little to offer in the initial staging of these tumours as treatment is usually local excision at which time surgical inspection of the pelvic lymph nodes, possibly with biopsy, can be performed. However, for tumour recurrence, FDG PET may be useful [62]. As with all tumours in the pelvis and lower abdomen, colonic and urinary activity may make interpretation difficult.

6.18. Prostate

Initial staging of prostate cancer is still best performed with a digital examination, MRI and biopsy. Bone metastases are a common site of spread of prostatic malignancy and are easily detected with MDP. If there is concern about renal dysfunction at the time of bone scan, a renogram can be performed immediately following injection of MDP, the renal handling of which is very similar to DTPA, giving differential renal function and an assessment of drainage. FDG is also useful for staging and detecting tumour recurrence.

A new radiolabelled anti-PSA antibody, *Prostascint,* has been identified which detects soft tissue and bony metastases and has been approved for use in prostate malignancy [5]. However, it is not yet in common use. Bombesin receptors have been described in well differentiated carcinomas, but only rarely in hyperplasia [20]. Their use in clinical practice is unknown.

6.19. Testes

These tumours have a highly predictable path of spread and, consequently, are easily staged and observed with CT. Nuclear medicine has little extra to offer in this initial staging. Anti-αFP has been used to

detect germ cell tumours and may be useful for detecting recurrence [29]. However, cardiac and renal function are often assessed by nuclear medicine techniques in these patients to avoid therapy-associated toxicity.

6.20. Lymphoma and myeloma

Both FDG and gallium are useful in assessing lymphoma, although FDG appears to be the superior radiopharmaceutical. The vast majority of lymphomas, both non-Hodgkin's lymphoma and Hodgkin's disease are FDG-avid [41]. Virtually all Hodgkin's disease and high-grade non-Hodgkin's lymphomas are also gallium-avid. However, some low and medium grade non-Hodgkin's lymphomas are gallium non-avid. Gallium has lower specificity within the abdomen due to physiological gastrointestinal activity, although delayed imaging, after colonic activity has been excreted, may allow the identification of tumour. Both these radiopharmaceuticals can stage lymphoma and detect whether residual tissue is viable tumour or scar tissue [41,63–65]. An additional advantage over anatomical imaging is the early detection of response to therapy. A common procedure is to perform PET scanning of lymphoma patients 3-to-4 weeks after their second course of chemotherapy. A negative scan implies good chemotherapeutic response and that continuation of the current therapeutic regimen is appropriate. A positive scan after two cycles implies a poor prognosis, suggesting a change of therapy may be appropriate.

In-111-pentetreotide also detects virtually all Hodgkin's disease and the majority of non-Hodgkin's disease. However, its role in lymphoma has not been evaluated and this agent is expensive [20].

FDG PET and gallium are able to indicate early response to therapy. However, it is important not to perform either study less than 3 weeks after chemotherapy in order to avoid false-negatives due to 'tumour stunning'. Although gallium is a sub-optimal radiopharmaceutical when compared with FDG, gallium scanning with a standard gamma camera is much more available than FDG.

Technetium colloid scans can be used to detect defects within the spleen and also for determining whether or not perisplenic masses or residual masses after splenectomy are splenunculi.

Although plain radiography is still the primary method of diagnosing bone lesions in myeloma, sestamibi has been used to assess staging of soft-tissue deposits and in assessing the response to therapy [66].

6.21. Skin

Melanoma in stage 1 is usually excised with skin thickness predicting prognosis. The most accurate method of detecting micrometastases in draining lymph nodes is sentinel node biopsy. However, for higher stages of melanoma, FDG is clearly the imaging modality of choice. Using dedicated PET, Wagner and colleagues found a greater than 90% accuracy in detecting melanoma nodal metastases larger than 80 mm^3, i.e. 4–5 mm [36]. Gamma camera PET is also sensitive, but does not have the resolution of dedicated PET and, consequently, is less likely to detect small lesions. FDG is excellent for detecting tumour recurrence.

Squamous and basal cell carcinomas are usually seen on exposed skin, including the face. These lesions may also spread along neurovascular pathways through complex anatomical areas. FDG is excellent for detecting and staging these lesions. Image fusion with CT and/or MRI would be particularly advantageous in these complex cases, both in initial staging and for detecting recurrence after surgery.

6.22. Bone and soft-tissue malignancy

For local staging of bone and soft-tissue tumours, MRI, and to a lesser extent, CT, are the imaging modalities of choice. Accurate identification of fascial compartments and neurovascular bundles is required for accurate surgical treatment. CT is also excellent for detecting lung metastases. Nuclear medicine techniques with MDP or other bone-seeking agents may detect bone and calcified soft-tissue metastases, such as osteosarcoma (Fig. 10) or chondrosarcoma, but the value of this is debatable as prognosis is frequently poor once metastases have occurred. Moreover, such metastases are also usually easily detected by other methods such as plain radiography or CT. Pentavalent DMSA has been described as useful in differentiating benign from malignant chondral tumours, but has yet to reach standard clinical practice [67]. Octreotide analogues and FDG have been used to assess sarcoma activity, but also have not yet reached clinical practice [68,69].

6.23. Paraneoplastic syndromes

Pulmonary embolism is a common complication of malignancy. If the patient presents with shortness of breath and a normal chest X-ray then ventilation/perfusion imaging remains an excellent method for detecting or excluding pulmonary emboli with only a minority of cases giving an indeterminate result. However, if the patient presents with chest pain, and/or an abnormal chest X-ray, then CT pulmonary angiography may be a better investigation. CT pulmonary angiography not only detects any pulmonary emboli, but also may find another cause of chest pain and explain the abnormality on plain film. Ventilation and perfusion images may be useful for detecting radiation damage to lungs and for planning lung resection of metastases.

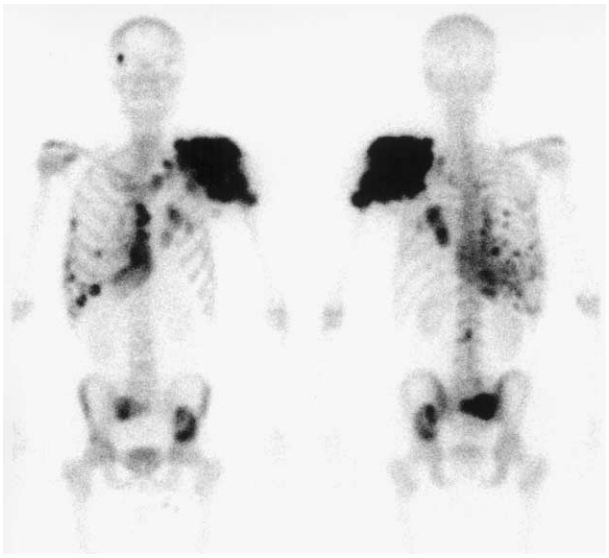

Fig. 10. Tc-99m-MDP bone scan in a patient with metastatic osteosarcoma. The primary, in the left shoulder, is MDP-avid. There are extensive osseous and soft MDP-avid soft-tissue metastases in the left lung and liver.

Hypertrophic pulmonary osteoarthropathy is detected earliest on bone scintigraphy, before a periosteal reaction is visible on plain film (Fig. 6). This condition is usually first seen around the ankles [70,71].

A marrow scan may be performed to demonstrate the presence or absence of normal haemopoietic marrow. This may be useful in conditions such as myeloma and lymphoma for explaining a non-fatty marrow signal on MRI scan. A defect may indicate a good site for marrow biopsy. Antigranulocyte antibodies have also been used to demonstrate haemopoietic marrow [72].

7. Conclusions

Nuclear medicine contributes significantly to the care of oncology patients. Although screening and initial diagnosis are not included in its main applications, gamma camera imaging and PET offer clear advantages in staging, guiding therapy, detecting response and detecting tumour recurrence, as well as assessing the effects of therapy on normal tissues. FDG is clearly a radiopharmaceutical of great benefit [73]. Technically, PET imaging can be performed with an adapted gamma camera (Fig. 10; compare with Fig. 7). However, whilst dedicated PET scanners are clearly superior in sensitivity, they are more expensive to purchase and operate. The best results are obtained when nuclear medicine imaging is used with clear knowledge of the patient's clinical details and interpreted in conjunction with other imaging techniques [58]. Image fusion with anatomical methods such as CT and/or MRI may improve diagnostic accuracy. Many ligands that are currently available or in development offer great potential, but their role needs to be established in clinical trails. Many techniques, in particular FDG PET, are expensive or not freely available and require further investigation with respect to cost-effectiveness. However, if costs were to come down, there is potential to re-write standard imaging protocols. For instance, for the common tumours of breast, lymphoma, colon, lung and head and neck, a PET scan may be performed for initial staging, with CT and/or MRI reserved for indeterminate lesions, instead of the current practice of staging with CT and/or MRI and using a PET scan for assessing the indeterminate lesions.

Acknowledgements

We wish to thank Mr N.J. Bird for help with the illustrations and Ms Nina Hedderick for secretarial assistance.

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