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ARTICLE

Cancer imaging—making the most of your gamma camera

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Abstract

As MRI threatens the use of bone scintigraphy for skeletal metastases and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) emerges as the main focus in nuclear oncology, the future role of the gamma camera in cancer imaging appears unclear. However, there is a range of pre-existing conventional gamma camera techniques that have incremental benefit over CT and other structural imaging techniques, but are yet to be fully exploited in the care of cancer patients. This article reviews some of the more advanced conventional nuclear medicine techniques for cancer imaging. Often gamma camera techniques perform close to ^{18}FDG-PET or provide complementary information. Where ^{18}FDG-PET is diagnostically superior, the incremental cost-effectiveness gain of ^{18}FDG-PET over conventional gamma camera techniques has not always been fully evaluated.

Keywords: *Gamma camera; tumour imaging; angiogenesis; receptor imaging; sentinel node.*

Introduction

Over the last few decades, the main clinical impact of gamma cameras within oncology has been in the diagnosis of skeletal metastases by bone scintigraphy. However, this role is now threatened by the use of magnetic resonance imaging (MRI), not only in the assessment of the cancer patient with local bone pain but also in skeletal staging. Furthermore, the emergence of clinical positron emission tomography (PET), along with the increased impetus provided by the development of combined PET/CT systems, might suggest that PET, rather than conventional nuclear medicine, will be the mainstay of functional imaging of cancer into the future. So what are the likely roles of the gamma camera in cancer imaging for the near future?

The strength of nuclear medicine is the ability to assess tissue function and there are many aspects of tumour biology that can be usefully evaluated by gamma camera imaging techniques for diagnosis, staging and therapy monitoring. The performance of many of these techniques exceeds that of structural imaging methods such as CT, and in many cases, is close to that of ^{18}F-fluorodeoxyglucose (^{18}FDG)-PET. Furthermore, for many applications where PET has proved more effective, the case for improved cost-effectiveness for PET remains to be made. Focussing primarily on common tumours, this article reviews some of the more advanced conventional nuclear medicine techniques for cancer imaging that enable gamma cameras to be used to maximum effect.

Angiogenesis

The development of a tumour vasculature through processes of angiogenesis is an important biological event for the growth and metastasis of cancers. Increased vascularity is associated with a poor outcome for many tumour types. Increased vascularity will, in turn, result in increased delivery of radiotracers to tumour tissue. Thus tracers that are highly extracted from the blood during the first pass will accumulate within tumours in

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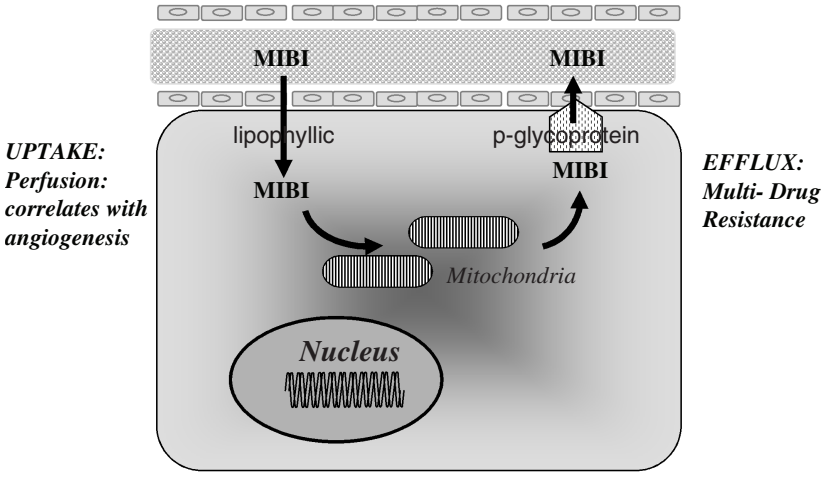

Figure 1 **Uptake and efflux mechanisms for ^{99m}Tc-MIBI in tumours.**

proportion to the tumour blood flow. Examples of such tracers that are more commonly used for tumour imaging are ^{99m}Tc-methoxyisobutylisonitrile (MIBI) and ^{201}Tl-thallous chloride. MIBI is highly extracted in tumours on account of chemical lipophyllicity and subsequent binding to mitochondria (Fig. 1). In breast cancer, uptake of this agent has been shown to correlate with histological markers of angiogenesis. The high tumour extraction of thallous chloride is due to the presence of sodium/potassium ATPase, a membrane pump that is present in most tissues. The high first extraction of both these tracers is also the basis for their more common utilisation as myocardial perfusion agents. For tumour imaging, ^{99m}Tc-MIBI has the added advantage of also being able to assess multi-drug resistance (MDR) (see below).

Lung cancer

Both ^{99m}Tc-MIBI and ^{201}Tl-thallous chloride demonstrate increased uptake in lung cancer. Reported sensitivity values for the detection of malignancy within lung nodules with either tracer are 85–100%. A recent direct comparison between ^{201}Tl-thallous chloride and ^{18}FDG-PET for characterisation of lung nodules showed no difference in diagnostic performance[1]. Alveolar cell carcinomas showed greater uptake of ^{201}Tl-thallous chloride than ^{18}FDG whilst PET was more sensitive to malignant nodules less than 2 cm in diameter. For mediastinal staging, ^{99m}Tc-MIBI and ^{201}Tl-thallous demonstrate superior diagnostic performance over CT but have not proved as effective as ^{18}FDG-PET[2,3]. However, the relative cost-effectiveness of ^{18}FDG-PET compared to gamma camera techniques for staging lung cancer has not been evaluated.

Breast cancer

A range of conventional gamma camera-based radiopharmaceuticals have been proposed for diagnosis and assessment of breast cancer, with ^{99m}Tc-MIBI being the most widely adopted agent. The reported diagnostic performance for detection of primary breast cancers ranges between 85 and 94% for sensitivity and 72 and 94% for specificity and is comparable to that of ^{18}FDG-PET[4]. False positive results occur with hyperproliferative breast disease and fibroadenoma. False negative results are more likely for impalpable lesions (sensitivity: 25–72%), thus mammoscintigraphy is unsuitable for screening. The ability of mammoscintigraphy to detect axillary metastases is poor with sensitivity values of between 55 and 84%. However, even the best diagnostic performance figures are unlikely to match the accuracy of sentinel node detection. Mammoscintigraphy is generally advocated as a second line test for patients with difficult mammograms due to radiographically dense breast tissue, previous surgery or prostheses. The cost-effectiveness of mammoscintigraphy has not been extensively evaluated but the technique may be more cost-effective than immediate surgical excision biopsy.

Thyroid cancer

Both ^{201}T-thallous chloride and ^{99m}Tc-MIBI have been advocated for the detection of metastases from thyroid cancer. Unlike conventional ^{131}I-iodide imaging, these alternative techniques do not require withdrawal of thyroxine replacement. However, ^{201}Tl-thallous chloride and ^{99m}Tc-MIBI uptake within a metastasis does not necessarily correlate with ^{131}I-iodide and cannot therefore predict a likely response to ^{131}I therapy. Therefore, ^{201}Tl-thallous chloride and ^{99m}Tc-MIBI imaging are usually reserved for patients with raised serum thyroglobulin but negative ^{131}I-iodide imaging for whom image confirmation of localised metastases may allow subsequent external beam radiotherapy. ^{201}Tl-thallous chloride and ^{99m}Tc-MIBI imaging are both less sensitive than ^{18}FDG-PET in this clinical situation but the relative

cost-effectiveness of these alternative approaches has not been evaluated[5].

^{99m}Tc-MIBI and ^{201}Tl-thallous chloride imaging can also be used to characterise solitary thyroid nodules that are "cold" on conventional ^{99m}Tc-pertechnetate thyroid imaging. Reported sensitivity values for the detection of malignancy are around 85–90% with a MIBI-positive nodule increasing the likelihood of malignancy by 7.8 times[6]. However, uptake of MIBI within follicular adenomas produces lower specificity values of approximately 75%. Nevertheless, the technique may be useful where percutaneous biopsy is difficult or has proved inconclusive, and is potentially cost-effective in this situation by reducing the number of surgical explorations for benign disease.

Multiple myeloma

Whole body imaging with ^{99m}Tc-MIBI is emerging as a technique that can overcome some of the limitations of bone scintigraphy and skeletal surveys in multiple myeloma. Uptake can be focal or diffuse or both (Fig. 2). The intensity of uptake correlates with serum indices of disease activity and prognosis such as C-reactive protein, calcium and beta2-microglobulin[7]. Focal lesions with or without diffuse marrow uptake imply progressive disease. Early imaging at 10 min minimises the likelihood of false negative finding due to MDR (see below). As yet, there have been no study series directly comparing ^{99m}Tc-MIBI with ^{18}FDG-PET or MRI.

Sarcoma

The primary role of ^{99m}Tc-MIBI and ^{201}Tl-thallous chloride imaging is the evaluation of response to pre-operative chemotherapy or radiotherapy for which baseline (pre-treatment) and post-treatment examinations are required. ^{18}FDG-PET has been shown to be more sensitive to residual tumour (98% vs. 82%)[8] but it is unclear whether this diagnostic advantage translates to improved cost-effectiveness.

Glioma

^{99m}Tc-MIBI and ^{201}Tl-thallous chloride uptake correlate with tumour grade and both imaging techniques have been shown to be accurate in distinguishing radiation necrosis from recurrent tumour, a problematic area for MRI. The few studies directly comparing ^{201}Tl-thallous chloride and ^{18}FDG-PET to date have not shown a significant difference in diagnostic accuracy[9].

Lymphatic drainage

The spread of cancer to regional lymph nodes appears to occur in an orderly fashion such that the first lymph node in a nodal bed to receive drainage from a tumour will show metastasis if any lymphatic spread has occurred. This is known as the sentinel node concept and identification of the sentinel node allows its removal and histological examination for the presence of tumour. If no tumour is found, dissection and removal of the remaining nodes in that group can be safely avoided.

Radionuclide sentinel node detection was first used for malignant melanoma but more recently greater emphasis has been placed on the role of this technique in breast cancer with emerging applications in head and neck, colon and vulval cancers. Detection rates are extremely high (92–100%) and for breast cancer the absence of metastasis in a sentinel node has a negative predictive value of greater than 98%[10]. Although sentinel node detection can be performed using an injection of blue dye alone, detection rates are significantly higher using blue dye as well as lymphoscintigraphy with gamma camera imaging and use of an intra-operative probe. By allowing the histopathologist to concentrate on the node most likely to contain tumour, sentinel node detection results in a greater incidence of micrometastases when compared to conventional axillary node dissection. The ability to detect micrometastases also makes sentinel node detection more sensitive to nodal disease than ^{18}FDG-PET, both for melanoma and breast cancer. Recent evidence confirms the prognostic significance of such nodal micrometastases.

The techniques advocated for sentinel node detection have varied, particularly in the radiopharmaceutical used and, for the breast, in the site of injection. It is important to realise that there is a learning curve both for the imaging specialist and the surgeon and a number of cases should be undertaken with complete nodal dissection for validation of the technique prior to routine use. The commonest agents used are ^{99m}Tc-antimony sulphide colloid which, on account of its smaller particle size (15–50 nm), demonstrates faster transit than filtered ^{99m}Tc-sulphur colloid (particle size 100–200 nm). The principal sites for injection in breast cancer are peritumoural (four sites) or subdermal, or a combination of both. The rates of axillary node detection are similar regardless of the injection technique, however, a greater incidence of internal mammary node detection is found with peritumoural injection. For melanoma, unexpected patterns of lymphatic drainage, including crossing the mid-line, are common, particularly for lesions in the head and neck or on the back. The need to operate on a radioactive patient may initially create concern amongst operating department staff but it has been estimated than the radiation dose to the hands of a surgeon performing 30 nodal dissections with sentinel node detection is equivalent to one year's background radiation and exposure to pathology staff is negligible.

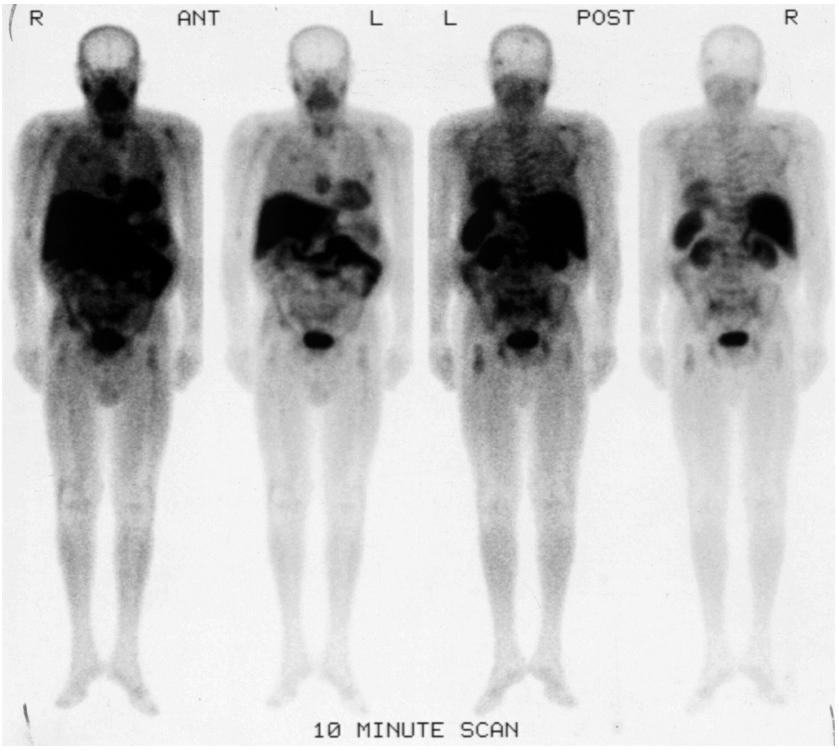

Figure 2 **^{99m}Tc-MIBI images in a patient with multiple myeloma demonstrating diffuse bone marrow uptake and focal lesions including site in the skull, ribs, sternum and upper femurs.**

Tumour receptor status

The levels of expression of particular receptors on the surface of cancer cells will, to some extent, determine the biological behaviour of that cancer which, in turn, will relate to prognosis and response to therapy. Although receptor status can be assessed using histological or molecular analyses, the spatial and temporal heterogeneity of receptor expression in tumours implies a benefit for imaging evaluations of receptor expression. Imaging can assess the receptor status of whole tumours at multiple sites and at several time points. On the other hand, tissue biopsy may miss receptor expression due to sampling error and multiple biopsies are likely to be undesirable or impracticable. The expression of a range of receptors of prognostic or therapeutic significance can be assessed using gamma camera-based radiopharmaceuticals and, for many of these agents, there is no widely available positron emitting equivalent.

P-glycoprotein-mediated MDR

Drug resistance creates a major obstacle to the success of chemotherapy for patients with cancer. The classic form of MDR results from the expression of a transmembrane P-glycoprotein (Pgp) encoded by the human *mdr1* gene. Pgp acts as an energy-dependent drug efflux pump that reduces the intracellular accumulation of chemotherapeutic drugs and its expression has been shown to be associated with a poor prognosis. ^{99m}Tc-MIBI is also a substrate for Pgp and, although initial tumour uptake of this agent is perfusion-dependent (see above), the degree of washout of MIBI between early and late images provides an indicator of Pgp-mediated MDR expression (Fig. 1). Indeed, high washout rate and low residual uptake on late images have been shown to correlate with histological assessments of Pgp expression and to predict for chemo-resistance and poor prognosis in many tumours, including lung cancer, breast cancer and myeloma[11].

Somatostatin receptors

Somatostatin exerts an inhibitory effect on virtually all endocrine and exocrine secretions. Many tumours express somatostatin receptors, particularly endocrine gastrointestinal tumours such as carcinoids, insulinomas, gastrinomas, VIPomas, etc. Somatostatin receptor status can be determined *in vivo* by imaging with ^{111}In-Octreotide. Somatostatin-expressing tumour can therefore be detected and localised with this agent but receptor expression is variable and may be as low as 60% of cases for insulinoma. However, as a somatostatin analogue, Octreotide given in sufficient doses can induce tumour growth inhibition or tumour regression for tumours that express somatostatin, not only endocrine gastrointestinal tumours but also others such as small cell lung cancer[12]. Thus, even in tumour types that exhibit only a moderate

incidence of somatostatin receptor expression, ^{111}In-Octreotide can be useful in identifying those patients who might be suitable for Octreotide therapy.

Transferrin receptors

The gamma camera-based radiopharmaceutical ^{67}Ga-gallium citrate binds strongly to serum transferrin and consequently, tumours that express transferrin receptors demonstrate significantly increased uptake of this agent. However, transferrin-independent uptake also occurs. The predominant application for ^{67}Ga-gallium citrate has been the imaging of patients with lymphoma but this agent has also been used for evaluation of high-risk melanoma. For lymphoma imaging, ^{67}Ga-gallium citrate has incremental value over CT, especially in evaluation of a residual mass post-therapy. Nonetheless, interpretation of gallium images in the abdomen is complicated by physiological bowel uptake and the diagnostic performance of ^{67}Ga-gallium citrate is exceeded by that of ^{18}FDG-PET[13]. A potential future application that would be specific for ^{67}Ga-gallium citrate arises from the fact that certain chemotherapeutic agents such as cisplatin also bind to transferrin and transfer to cancer cells through transferrin receptors. Thus, ^{67}Ga-gallium citrate uptake could assess tumour delivery of such agents and hence predict for chemotherapeutic response in a range of tumours.

Na/I symporter

Although ^{131}I-iodide has been used for imaging and treating differentiated thyroid cancer for many years, only recently has it become apparent that the uptake of radioiodine is dependent upon expression of the sodium/iodide (Na/I) symporter. In general, Na/I symporter expression is reduced in thyroid cancer[14] but expression of the gene is up-regulated by thyroid stimulating hormone (TSH). Therefore, it is necessary to raise TSH levels prior to ^{131}I-iodide imaging by withdrawing thyroxine replacement. In a proportion of thyroid cancers, Na/I symporter expression is lost completely due to de-differentiation during oncogenesis. Such tumours do not take up radioiodine and may show no Na/I symporter gene expression *in vitro*. ^{201}Tl-thallous chloride and ^{99m}Tc-MIBI may be useful in detecting these tumours (see above).

Conclusion

Although ^{18}FDG-PET is the main focus of current interest in oncological nuclear medicine, there are many pre-existing conventional gamma camera techniques that have incremental benefit over CT and other structural imaging techniques, but are yet to be fully exploited in the care of cancer patients. The precise relationship between many of these techniques and ^{18}FDG-PET remains to be determined. Even when direct comparisons have shown that ^{18}FDG-PET diagnostic performance is superior to conventional nuclear medicine, the incremental benefit of ^{18}FDG-PET in terms of cost-effectiveness has not always been demonstrated. In other cases, conventional nuclear medicine can provide information that is complementary to ^{18}FDG-PET. Pending a complete roll-out of PET services, there is an opportunity to make the most of our gamma cameras.

Key points

- Many pre-existing conventional gamma camera techniques that have incremental benefit over CT are yet to be fully exploited in the care of cancer patients.
- Tumour imaging with ^{99m}Tc-MIBI and ^{201}Tl-thallous chloride can achieve results close to those of ^{18}FDG-PET.
- The incremental cost-effectiveness gain of ^{18}FDG-PET over conventional gamma camera techniques has not been fully evaluated.
- Radionuclide sentinel node detection is emerging as an important tool for many tumour types.
- Tumour receptor expression relates to prognosis and likely therapeutic response and can be assessed using a range of gamma camera techniques.

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