Radionuclide imaging in cancer management

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Imaging, both anatomical and metabolic, has a major role in the optimal management of patients with cancer at different stages in the course of the disease. Complete surgical excision gives the patient the best chance of a curative treatment for most cancers, but many patients are found to be inoperable at surgery or relapse soon after major surgery has been performed. This usually indicates that primary ‘curative’ surgery was inappropriate.

The important question at initial diagnosis is usually ‘is the tumour localised or is it disseminated?’; in most cases, the answer will determine whether a tumour is resectable and potentially curable or has disseminated to such an extent that primary surgery is inappropriate or chemotherapy and/or radiotherapy is a necessary adjunct before or after surgery. Metabolic radionuclide imaging is increasingly shown to be cost-effective by reducing the frequency of unnecessary surgery with the high associated health care and clinical costs. Though surgery remains of prime importance, chemotherapy and radiotherapy are increasingly used as alternatives for the primary treatment of cancer as well as adjuvants to surgery. Neo-adjuvant chemotherapy is an attempt to downstage an inoperable tumour to one that can be treated surgically with a hope of curative resection. Metabolic imaging is also used to predict and measure an early response to chemotherapy or radiotherapy in order to monitor and tailor treatment regimens. In some cases, metabolic imaging provides sufficient accurate information by itself, while at others it is complementary to anatomical imaging with computed tomography (CT) or magnetic resonance imaging (MRI).

The approach to tumour staging is similar in different cancers:

- **T stage**: the primary lesion which usually relates the size of the tumour, and is largely determined by anatomical imaging methods.
- **N stage**: spread to regional lymph nodes.
- **M stage**: metastatic spread to other parts of the body.

### Key Points

The role of imaging in cancer management is:

- To distinguish benign from malignant masses
- To stage the disease (local, nodes and metastases)
- To detect recurrence of tumour
- To direct biopsy
- To select or plan therapy
- To monitor and predict therapeutic response
The N and M stages are those in which metabolic imaging has its most useful impact. Most tumours eventually decrease in size with effective treatment, but the process can be slow and incomplete. The tumour may be 'dead' but replaced by scar or necrotic tissue, and this may be hard to assess on a purely anatomical basis. Metabolic imaging has an important role in determining the viability of residual tumour in post-treatment masses, particularly as treating a scar with chemotherapy is expensive and clinically inappropriate.

Imaging strategy

The imaging strategy is usually a combination of anatomical and metabolic imaging, but depends on the type of cancer, the stage of the disease and the management decision to be made. Understanding the strengths of the different imaging approaches in each clinical situation is important in order to 'tailor' the strategy to be as accurate as necessary and yet cost-effective. Most anatomical imaging methods (x-ray, CT, MRI, ultrasound) provide information about the site and location of the tumour, and the involvement of other structures, which is usually critical to deciding on optimal therapeutic plans. Metabolic imaging provides information on the viability and metabolic activity of the tumour mass. Metabolic and anatomical imaging should not be considered as competing methods; the challenge is to use the information provided by both approaches in order to improve management and outcome. Table 1 summarises how information from anatomical and metabolic imaging is largely complementary and effective when used together. Coregistration of the two imaging data sets will even provide integrated anatomical and metabolic images, as shown in Fig 1.

The cancer cell and oncological tracers

Radionuclide tracers that are used for metabolic cancer imaging are designed to detect the abnormal characteristics of the cancer cell. More specific tracers are now being developed that reflect a single abnormal function of the cancer cell or a specific metabolic pathway. Characteristics of cancer cells that can be detected by radionuclide imaging, and which enable metabolic imaging to be effective, are summarised in Table 2.

Table 1. Anatomical and metabolic imaging is complementary.

| Anatomical                              | Metabolic                                |
|-----------------------------------------|------------------------------------------|
| Limited ability to differentiate benign from malignant | Metabolic activity frequently categorises malignancy |
| Usually excellent for defining extent and site of disease | Extent of metabolic activity may define boundary between tumour and reactive inflammation |
| Identifies lymph nodes but cannot confirm presence or absence of tumour | Identification of malignant nodes is not size-dependent |
| Limited ability to assess early response | Metabolic response occurs before change in size |
| Post-therapy masses often non-diagnostic | Metabolic activity in masses will define viable tumour |
| Unable to assess surface receptors | Imaging of membrane receptors may be critical |
| Local site evaluation usual | Whole-body screening more feasible |

Table 2. Key differences in cancer cells that enable effective metabolic imaging.

- Increased metabolism, as reflected by enhanced glycolysis
- Increased amino acid transport
- Increased protein synthesis and DNA synthesis
- Specific surface membrane receptors
- Inadequate oxygenation (hypoxic)
- Specific surface membrane receptors
- Increased blood flow

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depends on developments in our understanding of the biology of cancer cell growth. Even now there is an extensive choice of radionuclide tracers to use in cancer with different mechanisms of action and differing degrees of specificity. Table 3 is a simple classification of oncological tracers.

Cancer masses may be visualised because they replace normal functioning cells. A good example is the 'cold' nodule in a thyroid due to a follicular carcinoma. The relative function of the follicular cancer cell is diminished com-

Fig 1. Fluorodeoxyglucose (FDG) positron emission tomography (PET) scan to identify extent of disease for treatment planning. Registered PET and magnetic resonance images show a main tumour mass corresponding to the deep lobe of the parotid. The 18F-FDG uptake outside the parotid indicates the site of local spread.

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Table 3. Classification of oncological radionuclide tracers.

| Non-tumour specific: |
|----------------------|
| • Tumour replacing normal tissue, eg liver metastases or thyroid tumour |
| • Normal tissue reacting to tumour, eg ⁹⁹ᵐTc-MDP bone scan |
| • Non-specific tumour uptake, eg ⁶⁷Ga, ²⁰¹TI, ¹⁸⁸F hypoxia agents |

| Tumour-specific tracers: |
|--------------------------|
| • Antigen antibody reactions (labelled monoclonal antibodies) |
| • Cell surface receptors, eg ¹¹¹In-octreotide |
| • Specific metabolic pathways, eg ¹³¹I or ¹²³I-MIBG |
| • Specific cell functions, eg ⁹⁹ᵐTc-MIBI for the p-glycoprotein pump in MDR |

FDG = fluorodeoxyglucose
MIBG = metaiodobenzylguanidine
MIBI = methoxyisobutylisonitrile
MDR = multidrug resistance
MDP = methane diphosphonate

pared with normal thyroid tissue and takes up radioiodine only when the thyroid-stimulating hormone level is raised². The replacement of Kupffer cells accumulating technetium-⁹⁹m (⁹⁹ᵐTc)-labelled colloid in the liver is another example, but now rarely used. Tumours may also be identified by the response of surrounding tissues. The radionuclide bone scan using ⁹⁹ᵐTc-methylene diphosphonate (MDP) is the best example³⁴ and is highly sensitive to the local osteoblastic bone reaction to the tumour. The bone scan remains the most sensitive method for detecting metastatic disease in bone, and is particularly important for managing patients with breast cancer, prostate cancer (Fig 2) and lung cancer, as well as many other cancers that originate in bone or metastasise to it⁵.

Direct uptake of tracer into the tumour cell may reflect a generic characteristic of the tumour cell rather than be specific for an individual tumour. Several examples of this may be cited. Gallium-⁶⁷ (⁶⁷Ga) is widely used for staging lymphomas and monitoring their response to chemotherapy⁶. Uptake of thallium-²⁰¹ (²⁰¹TI) depends on the integrity of the sodium-potassium cell pump, which is enhanced in cancer cells. This tracer can be used for the assessment of primary and recurrent brain tumours, lung cancer⁷ and for recurrent thyroid cancer, particularly when stopping thyroxine medication is a problem. Fluorine-¹⁸ (¹⁸F)-fluorodeoxyglucose (FDG) with positron emission tomography (PET) visualises the increased glycolysis of the cancer cell which is mainly due to increased cell membrane transport of glucose and the increased hexokinase activity in most cancer cells. FDG-PET is the most rapidly growing application of metabolic oncology imaging in nuclear medicine and, where available as a clinical service, is having a major impact in managing lung cancer (Fig 3), colon cancer, lymphoma and many other malignancies⁸⁻¹⁰. ⁹⁹ᵐTc Sesta methoxyisobutylisonitrile (MIBI), another tracer finding a clinical role in oncology, appears to enter the cell and bind with the mitochondria. It is an example of a relatively non-specific tracer, and is having an important impact in breast cancer¹¹ and, more recently, in the management of non-small cell lung cancer (NSCLC). Agents that bind to hypoxic cells are becoming available, and may in the future have a role in assessing patients' suitability for radiotherapy¹².

In some instances, the non-specific reflection of cancer cell metabolism may be sufficient, but at other times it is

Fig 2. Bone scans in diagnosing and monitoring therapy: (a) The whole body scan demonstrates areas of intense uptake throughout the skeleton, diagnostic of metastases from the known carcinoma of the prostate; (b) the patient was treated with chemotherapy and a repeat scan a few months later shows significant improvement.

Fig 3. Fluorodeoxyglucose (FDG) in diagnosing malignancy and assessing nodal and metastatic spread: (a) Computed tomography (CT) of the thorax in a 73 year-old man shows a large mass at the right hilum and small lymph nodes (<1 cm) in the subaortic fossa which, by CT criteria, are negative for malignancy. Positron emission tomography (PET) demonstrates intense uptake in the right mid-zone with (b) further foci in the subarcinal region and (c), in the right parametrical region, left chest wall and a mid-vertebral body (FDG = fluorodeoxyglucose).
preferable to have a tracer specific to the tissue of origin. Taking advantage of the surface membrane antigen antibody reaction using radiolabelled iodine-131 ($^{131}$I), indium-111 ($^{111}$In) or $^{99m}$Tc monoclonal antibodies, particularly when antibody fragments are used, may be very effective, although they are as yet not widely applied in clinical practice.

Ovarian, colon cancer and melanoma are amongst those for which immunoscintigraphy is useful. The best example of a labelled compound that interacts with specific cell surface receptors is $^{111}$In-labelled octreotide (Fig 4), an analogue of somatostatin and highly specific for tumours of neuroendocrine or gastrointestinal origin. Other radionuclide tracers following specific metabolic pathways include $^{131}$I and $^{123}$I-metaiodobenzylguanidine (MIBG). These tracers were originally used to assess adrenaline storage in phaeochromocytomas but are now widely used in other tumours of neural crest origin.

An important function of these tracers is to show that subsequent therapy with large doses of radionuclide can be effective. As mentioned above, Sesta MIBI is primarily a non-specific tumour tracer particularly valuable in breast cancer. However, it also has a second – possibly more important – role in reflecting the activity of the $\gamma$-glutamyl transpeptidase function which is enhanced in patients with multidrug resistance, and this tracer may have an important place in identifying and managing patients with multidrug resistance.

The role of radionuclide imaging in cancer management and the various stages in the management of a cancer where it has a part to play are summarised in the key points.

Examples of metabolic imaging of different isotopes

1. It has been definitely shown that 18-FDG accurately characterises equivocal lung masses and that $^{99m}$Tc-Sesta MIBI will distinguish benign from malignant breast lumps. The latter is of particular importance in those patients in whom mammography is more difficult to interpret (eg younger women with dense breasts).

2. The radionuclide bone scan remains a mainstay of staging advanced breast cancer to identify bone metastases. 18-FDG has been shown to reduce by up to a third the operation rate for oesophageal carcinoma by showing previously unidentified local and distant spread, and it alters the management in approximately 25% of patients with NSCLC.

3. For recurrent disease, $^{20}$TI differentiates recurrent brain tumour from scar or radiation necrosis only slightly less effectively than 18-FDG which is less widely available. When metastectomy is considered for the management of recurrent colon cancer, FDG imaging will reduce the surgical rate by 30% by the identification of more widespread disease. It can also be valuable when there is a rise of circulating markers with no identified site of disease in colon, testicular and thyroid tumours. $^{99m}$Tc pentavalent dimercaptosuccinic acid (DMSA) may also identify the site of recurrent medullary carcinoma when serum calcitonin is elevated.

4. Deciding on the optimal site of biopsy of brain and other tumours by targeting the metabolically most active site is useful. Sentinel-node biopsy in malignant melanoma and breast cancer using colloid tracers to identify the node pre- or perioperatively is a rapidly growing technique.

The expansion of therapy with radionuclides in cancer makes it particularly important to image these tumours before embarking on this complex, expensive and potentially dangerous therapy. Examples are:

- $^{131}$I for differentiated follicular thyroid carcinoma
- $^{131}$I-$^{123}$I-MIBG for medullary thyroid cancer and neuroblastomas
- $^{111}$In octreotide for gastric and neuroendocrine tumours.

Monitoring the effect of chemotherapeutic agents, the measurement of glomerular filtration rate and cardiac ejection fraction remains important in the safe treatment and monitoring of these patients.

The future

Future developments in techniques, but more particularly in new more specific radiotracers, will have an increasing impact on the care of patients with cancer. Increased availability of these tracers and particularly the increased availability of positron emitting tracers are likely to widen their use for the staging of common cancers, surveillance of cancers that have a high risk of recurrence, and the prediction and

Fig 4. Tracer scans in deciding on and planning radionuclide therapy. There is good $^{111}$In-octreotide uptake in the known metastatic foci in a 66 year old man with a history of carcinoid and known liver metastases. $^{111}$In-octreotide therapy would therefore be an option for this patient.
early detection of response to chemotherapy.

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Neurology and psychiatry

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The advances in neuroimaging using x-ray computed tomography (CT) and magnetic resonance imaging (MRI) are well known. Nuclear medicine has also seen a substantial increase in the application to neurology and psychiatry, using both positron emission tomography (PET) and single photon emission tomography (SPET). The major areas of progress will be reviewed in this article (Table 1).

Table 1. Nuclear medicine in neurology and psychiatry.

| Brain perfusion (rCBF) | Neurotransmission (neuroreceptors) | Oncology |
|------------------------|-----------------------------------|----------|
| Normal database        | Dopamine:                         | Tumour recurrence vs Necrosis |
| Stroke                 | post-synaptic                     |          |
| Epilepsy               | schizophrenia                      |          |
| Dementias              | pre-synaptic transporter          |          |
| Alzheimer              | Parkinson’s disease                | Lymphoma |
| frontal lobe           | Alzheimer’s disease                | vs Toxoplasma |
| multi-infarct          | Benzodiazepine:                   |          |
| Depression             | alcoholism                         |          |
| ME/CFS                 | 5-HT (serotonin):                 |          |
| Brain death            | schizophrenia                      |          |
| Head trauma            | Acetylcholine:                    |          |
| Encephalitis           | Alzheimer’s disease                |          |

Notes:
CFS = chronic fatigue syndrome
ME = myalgic encephalomyelitis
rCBF = regional cerebral blood flow

Cerebral blood flow imaging

Using conventional equipment, tomographic maps of cerebral blood flow can be routinely obtained. These provide good anatomical detail and important functional information (Fig 1). A normal database can be constructed (Graph 1). Cerebral blood flow imaging can be used to assess interventions either in