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Editorial

Cancer imaging with radiolabelled antibodies and peptides

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Cancer imaging

Radiology requires a mass of tissue, displacing tissue, infiltrating tissue, for contrast. Nuclear Medicine does not require a mass. It exploits the subtle differences between the cancer cell and the normal cell for identification. There is also an amplification factor. For example, antigen expression may be 500–50,000 per cell and receptor expression may be between 500 and 10,000 per cell. There is an affinity factor, antigen binding to antibody of the order of 10^9 and receptor binding between 10^{10-14} L/mol. There is also the residence time so that which binds stays. These are the bases of cancer imaging with Nuclear Medicine. Tumour detection as a result of this amplification process means that a radioactive pinhead is detectable if it has enough activity on it. For tumours less than 1.5 cm in diameter, size is not the determinant of detection.

There are two directions for cancer imaging in Nuclear Medicine: one, which may be termed the 'Catch-All', is to have increasingly sensitive but non-specific (or only context-specific) agents such as the bone scan, gallium-67 and Positron Emission Tomography with F-18 DG. These react with inflammation, granuloma and infection as well as tumours. The other is the 'Catch-One' approach to make an agent as specific and sensitive as possible. There are agents which bind the tumours rather than inflammatory tissue, such as Thallium 201, Tc-99m MIBI and In-111 Octreotide. There are agents that are class-specific, such as I-123 MIBG, binding to neuro-endocrine tumours. There are those that are type-specific, for example an antibody against lymphoma will only bind to lymphoma and not other cancers and that used for colorectal cancer, called Tc-99m PR1A3 (Cancer Research UK), which only binds to colorectal cancer. It is in both murine and humanised form.

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Radioimmunoscintigraphy

The requirements for radioimmunoscintigraphy are:

1. An antigen as specific as possible to the cancer.
2. A monoclonal antibody against the antigen.
3. The best radiolabel, which is usually Tc-99m.
4. A radiolabelling method that preserves binding efficiency.
5. An optimal imaging system and image data analysis.

There are many antibodies available for particular cancers (Table 1).

The rules of radioimmunoscintigraphy are quite straightforward:

1. Specific antibody uptake increases with time. An image at 5––10 minutes after injection provides a tumour-free template with which later images can be compared.
2. Non-specific uptake after the initial distribution decreases with time as the level of the antibody falls in the blood.
3. The higher the count rate, the better the detection.

Cancer imaging of lymph nodes with radiolabelled monoclonal antibodies, peptides or FDG PET allows one to overcome a problem with radiology of calling a 1 cm or smaller node „normal". In order to enlarge a lymph node beyond 1 cm in diameter, the cancer must have been present in a previously normal-sized node and such cancers can be detected using these techniques.

Table 1. Radioimmunoscintigraphy in malignant disease

Colorectal cancer	Anti CEA, B72-3, PR1A3, huPR1A3
Breast cancer and ovarian cancer	HMFG1, HMFG2, huHMFG1, SM3, B72.3
Prostate cancer	Anti PSMA, In-111 Prostascint, Tc-99m MUJ 591
Melanoma	225-225 anti high molecular weight melanoma antigen Tc-99m (Fab)2

Radiotherapy planning is conventionally done from images on X-ray CT and recurrences tend to occur at the centre of the tumour, where radio-resistant anoxic cells occur. Conformational planning however becomes closer and closer to the 3D mass shown on CT scanning. It may be predicted that recurrences will start to appear at the tumour edge, because the biological extent of the cancer exceeds the physical extent, as can be demonstrated by radioimmunoscintigraphy, radiopeptide imaging and by FDG PET.

Axillary node involvement in breast cancer

As the breast-screening programme brings in more women with small breast cancers, is axillary clearance still appropriate? Up to 50% of women with operable breast cancer have an „unnecessary" axillary clearance with associated morbidity in that the histology shows no cancer in the nodes. In order to image breast cancer with monoclonal antibodies, serial imaging is essential with an early image at 5–10 minutes to provide the template of a normal study. Imaging may also be undertaken at 5 hours but must be undertaken at 22–24 hours. The late image is then compared, using a change detection analysis technique, also called kinetic analysis with probability mapping. The matrix of 5×5 pixels is made and the middle pixel is centred on each of the pixels of the early and late image. In this way one is able to compare each pixel of each image and calculate the significance of the difference for each. These results can then be represented as significant differences, which are colour coded $P < 0.001$ red, $P < 0.01$ orange, $P < 0.05$ green, $P > 0.05 < 0.1$ in blue. By applying change detection analysis to monoclonal antibody imaging in this way, typically 90% of involved but impalpable axillary nodes can be detected [1–3]. This enables a strategy to be developed (Table 2). If palpation and cytology are positive in the axilla then axillary clearance is undertaken, but if no lymph node is palpable then imaging is performed. If the image is positive then there is axillary clearance, but if the imaging is negative then a Sentinel Node study is performed. If the Sentinel node is positive on histology, there is axillary clearance whereas if the Sentinel node is negative on histology no axillary clearance is performed. This assessment means that axillary clearance is not performed unless the triple evaluation is negative. It is also a problem with Sentinel Nodes that false negatives may occur if a lymph node is totally replaced with cancer cells, such nodes are the easiest for the imaging technique to find, hence the importance of combining the two modalities.

Prostate cancer

The clinical questions are:

1. What is the extent of prostate cancer when radical surgery or radioactive implant seeds are proposed at treatment?
2. Where is the disease when PSA is rising and the bone scan and radiology are normal?
3. What is the significance of PSA that is not zero but rising within the normal range after radical prostatectomy or radical radiotherapy?

Table 2. Strategy for axillary nodes in breast cancer

Palpation and Cytology Positive:	Axillary Clearance
Palpation Negative:	Image Axilla
Imaging Positive:	Axillary Clearance
Imaging Negative:	Sentinel Node study
Sentinel Node Positive Histology:	Axillary Clearance
Sentinel Node Negative Histology:	No Axillary Clearance

FDG has low uptake in prostate cancer and is unreliable. It is only of benefit in highly malignant spreading prostate cancer and does not answer these questions. However they can be answered by using radiolabelled monoclonal antibodies. These react with a Prostate Specific Membrane Antigen, PSMA, which has an intra-cellular domain against which Prostascint (In-111 CYT 356) and the Technetium-99m labelled equivalent labelled in our department [4]. There is an extra cellular antigen domain against which the antibody MUJ 591 reacts. This is labelled with I-131 in the USA [5] and with Technetium-99m in our laboratory [6]. Using the Technetium-99m agent the protocol is imaging at 10 minutes and 24 hours. Using the Indium-111 agent the imaging is at 10 minutes, 24 and 48 hours, reviewed by Britton et al. [7].

A new protocol has been developed in this department using double radionuclide energy imaging. On Day 1 a bone SPET 3 hours post-injection of Tc-99m MDP is made as well as the conventional planar images and simultaneously a pelvic SPET one hour post-injection of Indium-111 CYT 356 using the two energy double radionuclide approach. This allows direct co-location of the two images. On day 3 a blood pool image SPET 10 minutes post-injection of pyrophosphate followed by Tc-99m, with simultaneous pelvic SPET for Tc-99m and Indium-111 Prostascint. The images are then displayed. The bone scan image allows co-location of the prostate images with anatomical features, and the blood pool image allows the differentiation of involved lymph nodes from tortuous blood vessels that occur in old men with prostate cancer. This technique has been refined with the G E Hawkeye System, which adds a CT scan with the same equipment for direct co-location. The CT scan is of moderate quality but allows co-location with a high resolution CT or MRI study if that is also performed on the patient. With this new protocol the accuracy of Prostascint studies is increased from 70–80% as reported to over 90% in a preliminary evaluation.

Radionuclide receptor imaging

A receptor accepts a chemical agent such as a hormone, a neurotransmitter, a cytokine or other biologically active peptides. The binding process initiates a series of reactions within the cell so that information is moved chemically from the cell surface to the nucleus. This process is called signal transduction. Thus it is that although the nucleus controls the cell, it is the cell environment that controls the nucleus through signal transduction from receptor to nucleus. For Nuclear Medicine then one should image the receptor or the altered receptor in the cancer cell. There are over 100 biologically active peptides involved in cancer and nuclear medicine is only using about a dozen, of which only four are commercially available.

The concept of receptor binding of a molecule is essentially the action or interaction of a binder and a bindee. This relationship is true for hormones and their receptors, enzymes and their substrates, antigens and their antibodies and biologically active agents and their binding sites. What is required for tissue charac-

terisation is an optimised binder, which has high density on the cell, homogeneity of expression between the cells, as specific as possible and independent of the grade of the cancer. The properties of the bindee should be of high avidity, small with stable labelling, as specific as possible and having renal excretion rather than gut excretion. To use a receptor binding radionuclide ligand for imaging or therapy it is required to know which tumours have which receptors and which radionuclide ligands bind to which receptors. Therefore prior imaging with the same radionuclide ligand is required before radionuclide therapy. Thus one can obtain a prediction of a therapeutic response before initiating therapy, an important concept in oncology.

Indium-111 Octreotide in gastro-endocrine tumours appears to be cost beneficial in patients with carcinoid, para-ganglioma and gastrinoma, but less so in medullary thyroid carcinoma and insulinoma [8]. Alternative peptides include I-123 labelled vaso active intestinal peptide, a stimulatory peptide [9]. Radiolabelled alpha-melanocyte stimulating hormone for melanoma, Cholecystokinin for gastrointestinal cancers and Bombesin for Lung cancer, are being evaluated. Interleukin 2 has been labelled with Tc-99m or I-123 [10]. This binds to activated T cells which surround the melanoma. For example melanoma therapy with Interleukin 2 may be confined to those melanomas that show good uptake of Interleukin 2 labelled with Tc-99m [11]. In fact in Oncology infusions of various Cytokines for cancer therapy are used increasingly. Some patients respond and some do not. Is it not time for evidence of uptake in the tumour environment to be obtained using a radiolabelled Cytokine to predict efficacy before expensive and maybe ineffective treatment is undertaken?

Tc-99m Depreotide is a good peptide for imaging lung cancer and some neuro-endocrine tumours [12].

Radionuclide imaging and therapy

The advantage of radionuclide therapy over chemotherapy in cancer is that one is able to find and treat the individual. Most cancer surgery and radiotherapy is based on the physical extent of the disease and not the biological extent. Most cancer chemotherapy is based on the clinical trials of the many and may or may not work in the individual. For example if 30% of patients respond to a particular chemotherapy it means that 70% have side effects and no therapeutic benefit. Radiolabelling and imaging of chemotherapy agents may be an answer to this problem. In Nuclear Medicine it is answered by having an imaging radionuclide that is gamma emitting and this gamma emitting radionuclide is then substituted with a therapy radionuclide, which may be beta or alpha emitting on the same agent. In this way only those patients are exposed to radiation therapy that have demonstrated by imaging significant and specific tumour uptake. Those patients that do not demonstrate this should not receive radionuclide therapy. Thus thyroid cancer should not be treated with I-131 therapy unless there has been evidence previously obtained of iodine avidity of the cancer [13]. The various agents are summarised in Table 3. For neuro-endocrine tumours one can fallow this imaging strategy (Table 3). Unfortunately, the availability of Y-90 Octreother is dependent on the outcome of a multicentred trial and the availability of Y-90 Lanreotide therapy is also uncertain. It is possible to image the Bremstrahlung radiation from the Y-90 and show that it confirms location of the therapy with the Indium-111 Octreotide image positive sites.

Table 3. Cancer find and treat the individual

Tumour	Imaging	Therapy
Thyroid cancer	I-123, I-131	I-131
Neuro Endocrine	I-123-MIBG	I-131 MIBG
Neuro Endocrine	In-111 Octreotide	Y-90 Octreotide
	Tc-99m MDP	Re-188 EHDP
Non Hodgkin's	I-131 Anti CD-20*	I-131 Anti CD-20
lymphoma	In-111 Retuximab*	Y-90 Retuximab
Prostate cancer	In-111 Prostascint	Y-90 anti-PSMA
Breast cancer	Tc-99m Herceptin	Herceptin

*Dosimetry and imaging

A new approach developed by DeChristoforo et al. [14, 15] has been the development of Tc-99m EDDA-HYNIC-TOC. They have shown that 140 patients who were Indium-Octreotide avid showed uptake of the Technetium 99m Octreotide «Tectoc» equal to or greater than that of the Indium-111 Octeotide. They also showed new sites with the Technetium agent in 10% of patients. This agent then opens the possibility of substituting Tc-99m with Re-188 Beta emitter (Half Life 17 hours 2.2 MeV, 11 mm range) as a radionuclide therapy.

Conclusions

1. This type of imaging depends on identifying differences between the cancer cell and the normal cell.
2. This imaging identifies sheets, ribbons, plaques and infiltration of Cancer that cannot be identified radiologically because of their lack of mass. There are implications for radiotherapy planning.
3. This imaging is positive in dormant cancer cells.
4. Cancer imaging prior to radionuclide therapy excludes those patients who will not respond (unlike chemotherapy) and those who will take up the therapy agent and are likely to respond.
5. The Cancer imaging and therapy will progress as genetically engineered and synthetic molecules mimicking the properties of monoclonal antibodies and peptides become available. This will help to overcome regulatory problems. The future is bright.

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