Figure 2

radiological features, together with tumour markers in 122 patients who presented with or developed calcification within metastatic ovarian cancer. Changes in soft tissue lesion size and the development of calcification have been correlated with histopathology and outcome. The study group was compared with a control group of 1577 patients who had a CT scan performed at least once during follow-up. A positive relationship between calcification and tumour sub-type was identified with serous tumours, which represented 60% of the calcified group, against 30% in the control. Patients with calcification were generally higher stage than the control group but lower grade. They also had a poorer survival rate.

There did not seem to be any relationship between the development of calcification and chemotherapy and thus it is unusable as a marker of response. Reliable assessment of metastatic ovarian cancer still remains extremely difficult and it is contended that for this disease trial data should be subjected to external panel review.

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Radiopharmaceuticals in monitoring cancer

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Introduction

Normal cells have three basic outcomes: differentiation, division and death. Cancer cells usually have reduced differentiation, increased division and mechanisms to avoid programmed cell death, apoptosis. These properties can be used to monitor cancer by nuclear medicine imaging.

Differentiation

Thyroid cancer cells show a reduced ability to take up radio-iodine compared with normal cells. Thus, all normal thyroid tissue has to be ablated surgically and with radio-iodine in order that the papillary or follicular thyroid cancers show uptake on radioiodine images and for thyroglobulin, Tg, to be a useful serum marker. Monitoring of thyroid cancer used to be done with a tracer amount of radioiodine ^{131}I. It was found that administration of amounts greater than 185 MBq, 5 mCi may cause stunning, reducing the of effectiveness of the large dose of ^{131}I given for therapy, (5–6 GBq, 150 mCi). However, 185 MBq (or less) ^{131}I gives a poor count rate signal, so that weakly iodine-avid malignant disease may not be detected. If the Tg is raised, some authorities are giving ^{131}I therapy in the absence of proof of iodine uptake. Some 50% of such patients show no uptake

on the post-therapy dose scan. Those patients have received a large amount of unnecessary radiation, hospitalization and temporary hypothyroidism while off trioiodothyronine. Such practice is against the radiation rules for the justification of the administration of radioactive materials to patients. The answer is to monitor with a dose of the gamma remitting ^{123}I (185 MBq, 5 mCi), which gives a similar count rate as a therapy dose of ^{131}I, but half the radiation dose of 185 MBq, 5 mCi of ^{131}I. Then there is no stunning, so that iodine-avid disease can be treated. With this dose of ^{123}I, but not the trivial doses of ^{123}I used previously of less than 20 MBq, 0.5 mCi, a patient who is negative on ^{123}I is not treated by radioiodine in spite of a raised Tg. The effectiveness of this approach in deciding when ^{131}I therapy is needed has been shown with a Tg-positive, ^{131}I tracer scan-negative, ^{123}I image-positive, ^{131}I post-therapy scan-positive disease and a Tg-positive, ^{131}I tracer-negative, ^{123}I image-negative, ^{131}I post-therapy scan-negative disease. Thus, ^{123}I (185 MBq) and Tg combination protocols are being introduced to monitor thyroid cancer[1].

Many neural crest APUDoma tumours maintain their Uptake-1 mechanism for noradrenaline storage in chromaffin granules. ^{123}I MIBG, metaiodobenzylguanadine, a noradrenaline analogue, may be used at an administered dose of 185 MBq, 5 mCi, to monitor malignant pheochromocytoma, paragangliomas and about 50% of abdominal carcinoids. However, usually once the diagnosis of MIBG-avid tumour is made then ^{131}I MIBG therapy (7.4 GBq, 200 mCi) is given and the post-therapy scan at 4 days is used to show continuing MIBG avidity. This therapy is repeated every 6 months until 45 GBq, 1.2 Ci is given to the patient, or else a satisfactory response has occurred, or else loss of MIBG avidity is demonstrated.

Bone metastases usually induce osteoblastic activity, so serial bone scans may be used to monitor response or more usually failure of response to treatment. In which case, evidence of widespread painful bone metastases from prostate or breast cancer on the bone scan may indicate the need for therapy with ^{89}Sr or ^{153}Sm-EHTMP Beta-emitting radionuclides.

Division

Cancer cells divide frequently and outgrow normal tissues partly through better nutrition and partly by inhibiting the normal environmental reaction to invasion. Better nutrition is achieved by upregulation of glucose and amino acid transporter proteins. For glucose upregulation of the hexokinase enzyme which phosphorylates glucose also occurs. FDG ^{18}F deoxyglucose is a non-metabolizable analogue of glucose used with Positron Emission Tomography (PET) imaging for the detection of cancer vs. benign lesions. This is through the greater visual and measured uptake (SUV, Standard Uptake Value) and by demonstrating increased glucose uptake in lymph nodes either that have not regressed to

normal size on CT scan as after chemotherapy of Hodgkin's disease, or else in normal size nodes (1 cm or less on CT or MRI). It is clear that cancer has to be present in a normal-sized node before it can enlarge it to a greater than 1 cm diameter. The specificity of FDG PET (and ^{67}Gallium) is context-dependent, the presence of cancer (primary or recurrent) indicating uptake in a node is likely to be due to cancer.

The general approach is that a reduction of FDG uptake after chemotherapy indicates a response. Such a reduction in uptake usually precedes a reduction in tumour size seen radiologically. However, it has to be remembered that activated white cells are also hungry for glucose and that dying necrobiotic cells and the autolytic process are glucose-avid, as are granuloma[2]. An abscess or glandular enlargement due to infection may be mistakenly called recurrence. Cancer cells in a tumour mass are not uniform in response. The more anaplastic the clone of cells, the greater the initial expected glucose utilization and probably the greater reduction of uptake after therapy. It is not yet clear whether the average response of the tumour or the maximum response should be taken. In monitoring the response of cancer to chemotherapy using FDG the problem is further compounded that just as sick patients do not eat, so sick cells do not feed. Lack of FDG uptake thus may not equate with death or response to chemotherapy but with dormancy. In summary, the reduction of FDG uptake may give a false sense of benefit and no change of uptake may be due to an active, potentially beneficial inflammatory response rather than a lack of response to the therapy.

There are technical problems in evaluating response by quantitative imaging, reviewed by Hoekstra *et al.*[3]. There are no rigorous methods to determine the threshold to use to draw a region of interest around the tumour on the image. Say it is 37% of the peak tumour counts on the pre-treatment image. Should it be 37% on the post-treatment image, which may be inappropriate as therapy may have changed the environment as well as the tumour, or should it be what looks best? In the latter the subjective element creeps in. Furthermore, the reconstruction process, whether iterative or back-projection, relates the count content of each pixel to every other pixel. The statistical independence of each pixel is lost and thus the statistical requirement that a comparison must be made of independent variables is lost. An active environment, e.g. blood or heart activity will reduce the count rate in a neighbouring tumour, a stomach bubble or air in the gut will increase the apparent count rate in the neighbouring tumour. In principle quantification should be undertaken before reconstruction, as in the method called 'image surgery'[4] . The actual timing of the second PET scan is a problem in relation to chemotherapy and the optimum time to attempt to predict responsiveness may be different for different tumours, different regions and different patients[5]. It appears that ^{18}F amino acids such as methyl tyrosine (also as ^{123}I methyl tyrosine) may be more specific, as may radio-labelled purines and pyramidines, through being less

Table 1 EORTC 1999 Criteria for FDG response (abridged)

1	Assessment at baseline just before and response at 1–2 weeks after end of chemotherapy cycle
2	Progressive disease (PMD) FDG SUV >25% within tumour RO1 of baseline
3	Stable disease (SMD) FDG SUV <25% ⩾15%
4	Partial response (PMR) FDG SUV decrease of 15–25% after one cycle of chemotherapy or decrease over 25% for more than one cycle
5	Complete response (CMR) FDG SUV shows complete resolution within the baseline tumour RO1
6	Patlak kinetic approach is preferred. Reproducibility of FDG SUV is required.

FDG, ^{18}F Fluorodeoxyglucose; SUV, Standard Uptake Value.

affected by the inflammatory response when predicting and monitoring the effect of chemotherapy[6,7]. Nevertheless, FDG PET is being used to monitor breast cancer therapy successfully[8] and sarcoma[9]. General recommendations are made by EORTC[10] (Table 1), but the above caveats need to be noted.

Both Tc-99m SestaMIBI (methoxy-isobutyl isonitrile), perhaps representing mitochondrial activity, and ^{201}Thallium, relating to cellular potassium uptake, have been used to monitor therapeutic response in small cell lung cancer[11] and in bone and soft tissue tumours[12].

The upregulation of receptors to take advantage of autocrine growth factors may be imaged with ^{111}In Octreotide analogues and more recently Tc-99m Octreotide analogues to monitor somatostatin receptor avidity in neuro-endocrine tumours. Absence of receptors on imaging will indicate absence of response to cold Octreotide and to ^{90}Y Dotatoc. The five somatostatin receptors confound the issue so that an ^{111}Indium Octreotide-negative scan may be ^{111}Indium Lanreotide-positive and such a tumour may respond to ^{90}Y Lanreotide. As there are over 100 biologically active peptides in the regulation of cell growth and division, many new radiolabelled peptides are being evaluated for monitoring cancer.

The architectural disruption of the malignant process brings antigens normally not exposed to blood to be upregulated and available for detection by imaging. Examples are murine and more recently humanized HMFG, a monoclonal antibody against the human milk fat globule, and murine and more recently humanized PR1A3, a monoclonal antibody that binds to colorectal cancer. Both may be radiolabelled with Tc-99m for determining recurrent disease and the response to radio or chemotherapy. Other tumour antigens are upregulated, such as prostate-specific membrane antigen (PSMA) in prostate cancer which remains fixed to the cell, unlike the prostate-specific antigen (PSA) which is increased in the serum. As well as for judging the operability of primary prostate cancer, antibodies against PSMA-labelled either with ^{111}Indium (Prostascint) or with Tc-99m may be used after surgery to judge whether a small change in PSA is significant, or, if the PSA is rising, the site of the soft tissue recurrences when the bone scan and other radiology are negative[13]. Receptor imaging and monoclonal antibody imaging of antigens present on the cancer cell have the advantage that these are still present in the dormant cancer cell during therapy but disappear with successful treatment. Furthermore, post-surgical or radiotherapy fibrosis can be distinguished from active or viable tumour using these agents, which may be difficult with CT or MRI. When cancer recurs as sheets, ribbons or plaques with very little mass it is very difficult to detect it radiologically. The nuclear medicine techniques identify the presence of cancer through differences between the cancer cells and their normal counterparts. Such identification does not depend on its physical mass. However, when a more malignant clone of cancer develops it may lose some receptors and antigens.

Death

Cancers have developed techniques to avoid apoptosis so that the p53 and related mechanisms fail to recognize the damaged DNA of the oncogene and thus fail to switch on the apoptotic mechanism. Treatment of cancer with chemotherapy and radionuclide therapy may trigger apoptosis in contrast to high dose external beam radiotherapy which breaks DNA strands and tends to cause necrosis. Tc-99m annexin is a marker of apoptosis. On the onset of apoptosis, phosphatidylserine which is on the inner side of the cell membrane, becomes exposed to the outer surface where it can combine with the peptide annexin. Trials have shown that this imaging agent can demonstrate immunologically induced apoptosis, for example in cardiac transplant rejection, but so far has been less successful in demonstrating whether chemotherapy is likely to be effective or not by imaging before and after the onset of the first course of chemotherapy. The principle, however, is a good one and it may be the key to determining the effectiveness of chemotherapy by demonstrating activation of apoptosis early in its course[14].

Other approaches include: the demonstration of hypoxia, for example with radiolabelled nitroimidazoles[15,16]; by showing multiple drug resistance or not as is in Tc-99m-sestaMIBI imaging[17]; and monitoring gene therapy with ^{123}I FIAU or ^{18}F FIAU, a uracil derivative[18].

Conclusion

The regular and reliable monitoring of cancer therapy using radiopharmaceutical-based imaging techniques is

still in its infancy, nevertheless, understanding the biological behaviour of cancer cells undergoing treatment will lead to one or more of the above approaches becoming successful.

Monitoring cancer questions

(1) How to detect cancer in lymph nodes less than 1 cm diameter?

(2) How to relate nuclear medicine imaging and measurements before, during and after therapy when the technical assumptions at each image time differ?

(3) What is the best measure for response to therapy before morphological change?

Is it apoptosis induction or loss of viability, as reduction in glucose utilisation appears insufficient?

Acknowledgement

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