

Four randomised controlled trials of ELND showed no overall survival advantage and the international trial on selective lymphadenectomy will not be published until 2006.

To add to the controversy, two publications from the Skin Cancer and Melanoma Unit have suggested an iatrogenic complication (ie a complication resulting from the treatment itself) of selective lymphadenopathy – namely an increased incidence of in-transit disease. The hypothesis is that synchronous wide excision of the primary tumour and local lymphadenopathy means that the normal lymphatic flow is disturbed and obstructed so that melanoma cells become entrapped within lymphatic channels – and there they will progress to form tumour nodules in the skin and subcutaneous tissue.

However, there is a positive corollary to the above warning. Dr Eleanor Moskovic in the Department of Radiology at the Royal Marsden has shown that elective inguinal node dissection for squamous carcinoma of the vulva can be replaced by ultrasound surveillance and ultrasound-guided fine-needle aspiration cytology when the nodes look suspicious. Selective lymphadenectomy can be undertaken based on the identification of nodal deposits as small as 4 mm. We have now started an identical surveillance programme for melanoma after wide excision.

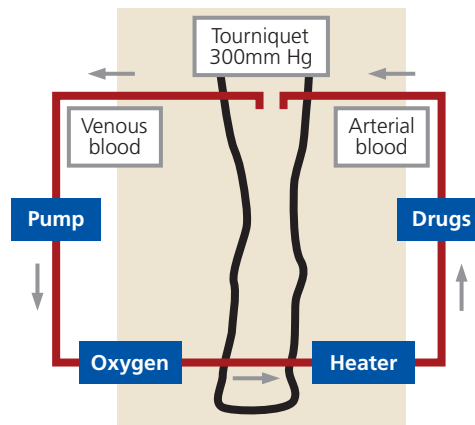
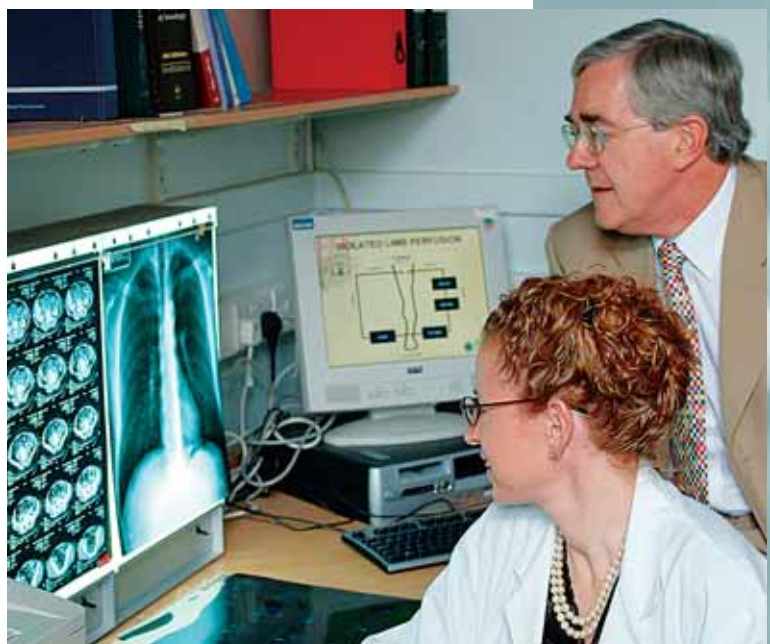


Figure 3. Hyperthermic isolated limb perfusion.

Where does this leave us? The future

Despite step-by-step improvements in our understanding of melanoma and its treatment, the reality is that this devastating disease is largely brought about by excessive exposure to UV radiation, particularly during childhood and teenage years. Melanoma is essentially a preventable disease, and as such, priorities for the future should include a national programme of public education about the disease, as well as a national programme of early diagnosis.

Dr Eleanor Moskovic and Mr Meirion Thomas evaluate tracer distribution in a patient





Nuclear Medicine

Rapid advances in the diagnosis and treatment of cancers

The development of combined positron emission tomography (PET)/computed tomography (CT) scanners is a major step forward in the detection of cancer and in evaluating response to treatment.



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Two key areas of rapid development in nuclear medicine

Nuclear medicine involves the use of radioactive isotopes in the diagnosis and treatment of many diseases but has an especially important role in oncology. Whilst many diagnostic and therapeutic nuclear medicine techniques are used in day-to-day routine patient management there are two key areas that have shown rapid recent development, with evidence of improvement in patient management and care.

- Positron emission tomography (PET) scanning uses radiopharmaceuticals such as ^{18}F -fluorodeoxyglucose (FDG) to detect abnormally increased glucose metabolism in malignant cells to help to pinpoint cancer more sensitively and to monitor treatment more effectively. The most recent advance in this modality is in the development of combined PET/CT scanners that can monitor tumour function (PET) as well as detect structural changes (CT) in a single scan, maximising the advantages of each type of scan.
- Targeted radionuclide therapy employs a number of different radiopharmaceuticals that can specifically target cancer cells, resulting in a therapeutic radiation dose to tumour tissue rather than normal tissues. Whilst this technique has been successfully employed for many years in a number of rare cancers including thyroid and neuroendocrine tumours, novel agents have now been developed for a wider range of common tumours, including lymphoma.

Combined PET/CT imaging

The Royal Marsden installed one of the first PET/CT scanners in the NHS in February 2004.

There is evidence that the extra information gained from combined PET/CT imaging is incremental and complementary to standard imaging in a number of cancers and positively affects patients' clinical management in as many as 30% of cases compared to standard techniques.

Work is currently underway at the Royal Marsden PET/CT Unit in collaboration with Professor Janet Husband (Head of the Department of Diagnostic Radiology) and a number of clinical units to further evaluate the role and efficacy of FDG-PET in a number of clinical situations, in order that the use of this valuable resource can be optimised to help tailor treatment protocols in individual patients.

Recurrent colorectal cancer

In collaboration with Professor David Cunningham and colleagues in the Gastrointestinal Unit, this project is prospectively evaluating the contribution of FDG-PET in clinical decision-making in patients in whom there is suspicion of recurrent cancer as a result of a positive tumour marker blood test (carcino-embryonic antigen – CEA), but in whom standard imaging tests such as CT are negative.

Lung cancer

In collaboration with Dr Mary O'Brien and colleagues in the Royal Marsden's Lung Unit, this project is evaluating the contribution of FDG-PET/CT to the speed with which therapy is instigated when used early on in the investigation pathway. By using FDG-PET/CT at an early stage soon after diagnosis it is possible that patients' treatment pathways will be accelerated with a reduction in delay to first treatment.

Figure 1 shows a combined FDG-PET/CT scan (PET colour scale, CT grey scale) of a patient with lung cancer. The tumour (colour) can easily be differentiated from collapsed lung distal to the tumour (grey) that is not involved by cancer. This type of information may be very helpful in planning radiotherapy, with the potential to delineate more accurately the boundaries of the tumour compared to using CT alone.

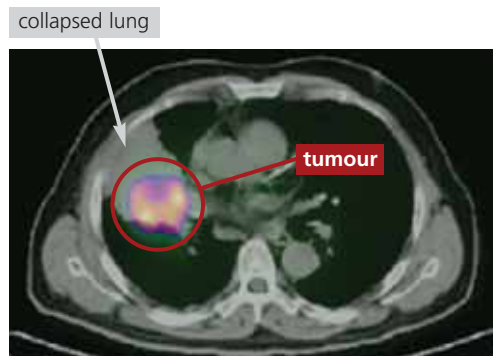
Oesophageal cancer

Many patients with apparently operable oesophageal cancer relapse after surgery because of small areas of disease, which were undetectable by conventional investigation at the time of surgery. FDG-PET is being used to routinely stage patients with apparently operable oesophageal cancer to measure its impact on subsequent patient management (in collaboration with Mr William Allum, Gastrointestinal Unit). It is possible that a number of patients will be able to avoid futile surgery and receive more appropriate treatment, eg chemotherapy. A further project is planned in collaboration with Dr Diana Tait in the Department of Radiotherapy to evaluate the role of FDG-PET in planning radiotherapy in oesophageal cancer.

Lymphoma

In collaboration with Professor David Cunningham and colleagues in the Lymphoma Unit, this project will prospectively evaluate the role of FDG-PET/CT in clinical decision making in patients who have received primary chemotherapy but who are left with a residual tumour mass in which it is not possible to differentiate residual active tumour, which requires further treatment with radiotherapy, from post-treatment scar tissue.

Further projects are underway or being planned to evaluate the role of FDG-PET/CT in radiotherapy planning. Areas of current interest include head and neck, lung and oesophageal cancer as well as lymphoma.



FDG-PET/CT in evaluating response to treatment

Monitoring tumour metabolism has the potential to be a more sensitive method in evaluating response to anticancer treatments, because changes in tumour metabolism often occur before a reduction in tumour size is seen – a parameter currently used to assess response with standard imaging methods. Many novel anticancer drugs act by inhibiting specific aspects of tumour metabolism rather than by the direct killing of tumour cells as occurs with standard chemotherapy. Successful treatment with these novel agents may therefore be more easily appreciated using techniques that measure tumour metabolism rather than size reduction of the tumour.

Figure 2 shows a patient with a gastrointestinal stromal tumour in the liver and pelvis (Figure 2a). Two months after starting imatinib treatment, the activity of the tumour has completely resolved (Figure 2b).

We are using FDG-PET/CT to measure treatment response to at least three novel anticancer agents in collaboration with colleagues in the Drug Development Unit. Although the mechanism of action of these drugs may differ, there is usually a common downstream effect on tumour glucose transport and metabolism that can be monitored by FDG-PET/CT.

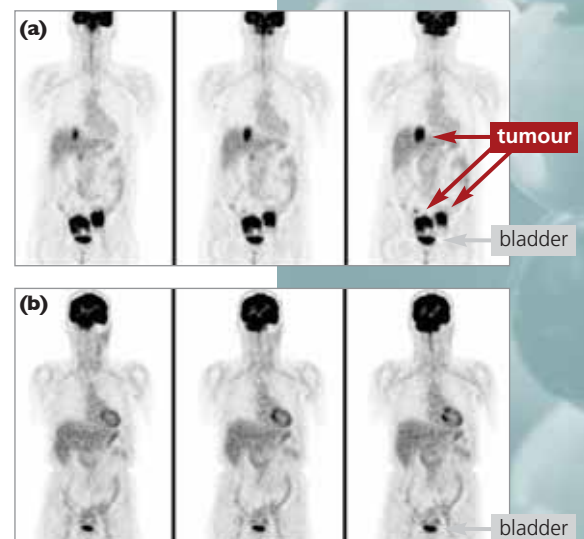


Figure 1. Combined FDG-PET/CT scan (PET colour scale, CT grey scale) of a patient with lung cancer. The tumour (colour) can easily be differentiated from collapsed lung distal to the tumour (grey) that is not involved by cancer.

Figure 2. (a) Patient with a gastrointestinal stromal tumour in the liver and pelvis. (b) Two months after starting imatinib treatment, the tumour has completely resolved.



Targeted radionuclide therapy

Targeted therapy using therapeutic radioisotopes offers several advantages compared with other cancer treatments. Acting systemically, this approach allows multiple tumour sites to be treated simultaneously with relative sparing of healthy surrounding tissues. As a result, toxicity is very low in comparison with other systemic therapies and treatment is well tolerated.

Alternatives to the use of radioactive iodine

Radioactive iodine, for example, has been the mainstay of post-surgical treatment for differentiated thyroid cancer for over 50 years. In addition to therapeutic beta particles, iodine also emits unwanted high-energy gamma rays, which pose a significant radiation hazard to staff and carers. Patients undergoing high-activity treatment must therefore be nursed for several days in dedicated, lead-lined isolation rooms. To overcome these constraints, there is growing interest in the use of alternative radioisotopes such as yttrium-90 (^{90}Y)

or alpha particle emitters, which might allow treatment to be delivered safely on an outpatient basis.

Designer radiopharmaceuticals

Recent advances have focused on designer molecules, selected to recognise and specifically target tumour cells. For example, several bone-seeking radiopharmaceuticals are now available to treat metastatic skeletal pain. Although effective for symptom palliation, these treatments have not been shown to prolong survival or to have an anti-tumour effect. In a bid to improve outcome, we are participating in the first international, multicentre clinical trial using an isotope of radium (^{223}Ra). This is an alpha particle emitting radioisotope predicted to deliver a tumouricidal radiation dose to bone metastases. The clinical programme is supported by the development of new methods for image quantification and alpha particle dosimetry by the

Radioisotope Physics Team in the Joint Department of Physics.

Radiolabelled peptides – their use for the treatment of neuroendocrine tumours

The Royal Marsden has extensive experience using ^{131}I meta iodobenzylguanidine (^{131}I mIBG) to treat refractory neuroendocrine tumours and is participating in a European study investigating the role of high activity mIBG therapy with chemotherapy in childhood neuroblastoma. However, only a minority of adult neuroendocrine tumours concentrate mIBG sufficiently well for this to be a realistic treatment option. By contrast, over 90% of neuroendocrine tumours over-express surface receptors for a range of neuropeptides, such as somatostatin. Targeted therapy using radiolabelled peptides directed against somatostatin surface receptors (SSR) offers a new treatment approach for these tumours. Procedures were developed in 2004 by Royal Marsden radiochemists to label SSR analogues with the isotope ^{90}Y . Over 100 patients have now been referred for ^{90}Y peptide therapy from the UK and abroad. An assessment programme has been established to monitor clinical outcomes, including quality of life assessment and will report later this year.

Targeted therapy using radiolabelled peptides directed against somatostatin surface receptors offers a new treatment approach for neuroendocrine tumours.

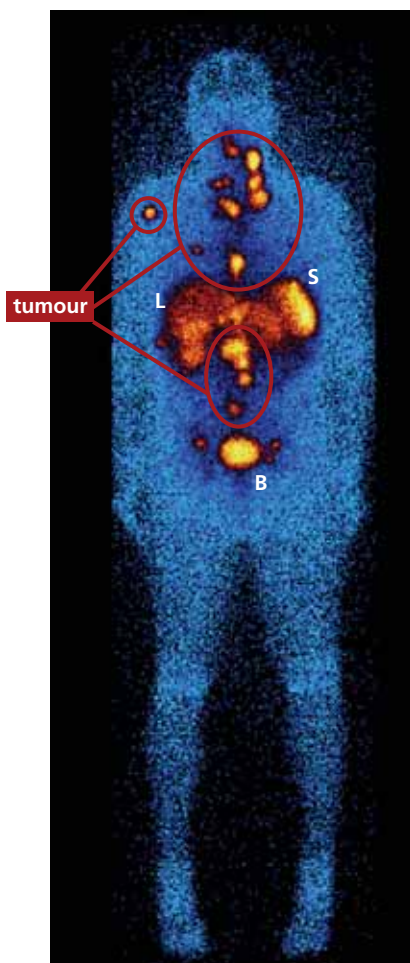
Figure 3 shows a post-therapy SSR peptide scan with physiological hepatic, splenic and bladder activity and extensive metastases.

Radioimmunotherapy

One of the most promising advances in radionuclide treatment is radio-immunotherapy using isotope-

Figure 3. Post-therapy SSR peptide scan with physiological hepatic, splenic and bladder activity and extensive metastases.

L - liver
S - spleen
B - bladder



antibody conjugates directed against tumour cell surface antigens. The CD20 antigen, for example, is a useful target in B cell non-Hodgkin's lymphoma (NHL). Building on previous experience using the anti-CD20 monoclonal antibody, rituximab, radio-labelled anti-CD20 antibodies have now been licensed to treat relapsed NHL. Low dose-rate radiation exploits the inherent radiosensitivity of haematological malignancies and acts synergistically with the biologically active antibody. Three patients with refractory NHL have now been treated using ^{90}Y labelled antibodies at the Royal Marsden.

The Radioisotope Physics Team is developing methods for ^{90}Y quantification to enable prospective individual treatment planning. This approach will be critical to improving the efficacy of radioimmunotherapy and has wider implications for targeted radionuclide therapy in general.

Figure 4 shows a post-therapy anti-CD20 antibody whole body scan with physiological liver and blood pool activity and extensive left axillary, mesenteric and iliac adenopathy.

The future

The unique availability of expertise in clinical PET, radionuclide therapy, radiochemistry and dosimetry physics at the Royal Marsden is encouraging research investment and partnership with industry. Future collaboration is planned that will bring together these aspects of current research interest. Further work is anticipated to develop targeted radionuclide dosimetry techniques for novel therapies with radiopharmaceuticals, using either PET/CT or single photon emission computed tomography (SPECT)/CT to improve the accuracy of these measurements.

The main areas of future research interest for PET/CT are concerned with utilising alternative radiopharmaceuticals to measure different aspects of tumour metabolism.

A new cyclotron and radiochemistry facility is being planned that will enable the production of novel radiopharmaceuticals that will be used in future research at the Royal Marsden and The Institute.

Examples include:

- ^{18}F -fluorothymidine to monitor increased DNA synthesis in tumours and changes in activity as a result of cytotoxic chemotherapy;
- ^{18}F -fluorocholine to measure abnormal cell membrane metabolism in cancer, including prostate cancer;
- Radiopharmaceuticals designed to measure tumour hypoxia (low oxygen levels), a factor that is known to cause resistance to radiotherapy in a number of cancers. Knowledge of the distribution of hypoxia within a malignant tumour is likely to impact on the way radiotherapy is planned and we are currently collaborating in trials with Dr Chris Nutting and colleagues in the Head and Neck Unit to determine the impact of hypoxia imaging on intensity modulated radiotherapy in head and neck cancers with the goal of improving tumour control.

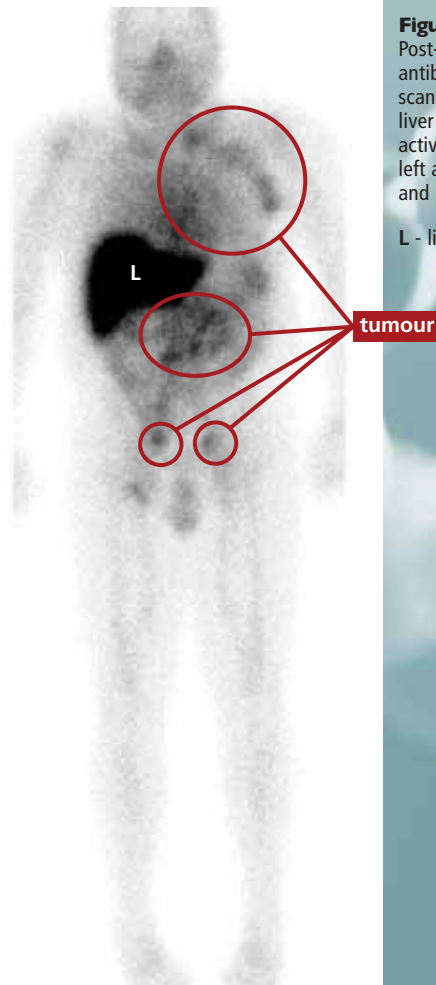


Figure 4. Post-therapy anti-CD20 antibody whole body scan with physiological liver and blood pool activity and extensive left axillary, mesenteric and iliac adenopathy.

L - liver