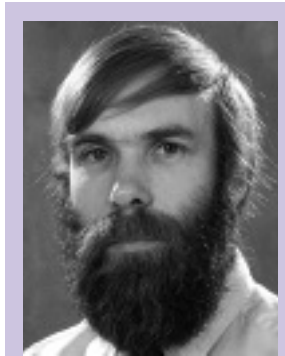


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*Peter Hoskin*



# Positron emission tomography (PET) – a diagnostic imaging technique

by Dr Wai Lup Wong and Professor Peter Hoskin

## Background

Many patients with lymphoma can now expect to be cured of their disease. However some patients either do not respond to their initial treatment or relapse after an initial remission. Improvements in the treatment of Hodgkin lymphoma (HL) – formerly known as Hodgkin's disease – and non-Hodgkin lymphoma (NHL) rely not only on new therapies, but also on accurate assessment of the disease extent to enable a more appropriate choice of treatment plan.

*(If you would like more information about the different types of lymphoma, please call the Helpline.)*

In the United Kingdom, computed tomography (CT) is the primary imaging technique for the assessment of lymphoma patients. It has largely replaced lymphangiography, gallium scanning and staging laparotomy. CT assessment of disease is based on detecting changes in anatomical appearance of a tissue or organ. It cannot however reliably and consistently distinguish active lymphoma from inflammatory changes triggered by the immune system. This poses a particular problem when tumour is harboured within normal sized lymph glands and also when it is within extra-nodal organs such as the liver, spleen and bone marrow. Furthermore, following chemotherapy and radiotherapy it

can be impossible to distinguish between scar tissue and persistent active disease.

## Principles of positron emission tomography

Positron emission tomography (PET) has recently become available to patients in the UK. Unlike x-rays, computed tomography (CT), magnetic resonance (MR) and ultrasound which produce anatomical images, PET provides a means of diagnosing cancer based on altered tissue metabolism. This 'functional' imaging technique relies on a radioactive substance that decays by positron emission (see later). Although a range of PET tracers

exists, the overwhelming majority of clinical studies are performed in conjunction with a form (an analogue) of glucose, [ $^{18}\text{F}$ ]-2-fluoro-2-deoxy-D-glucose (FDG). The radiotracer is given intravenously to the patient and is taken into cells. The cell recognises it as being 'foreign' and as a consequence it is trapped early on in the metabolic pathway. Malignant cells trap more radiotracer compared with non-malignant cells and the local tracer concentration can be measured in the body by exploiting the fact that these unstable tracers decay by giving off tiny positively charged particles (positron emission). Positrons travel short distances in tissue before colliding with other tiny negatively charged particles (electrons). The annihilation reaction when they collide results in two photons (gamma rays) or minute bursts of energy of 511keV each emitted at approximately 180 degrees to each other. These photons are detected by opposing detectors. A computer reassembles the signals into images, which represent radiotracer uptake in the part of the body scanned (see figure 1).

Depending on the radiotracer used different aspects of tissue metabolism and organ function can be measured such as distribution of blood flow, oxygen utilisation, protein synthesis and glucose consumption. Cancer cells have greater avidity for glucose than normal cells. This observation was made by Nobel prize laureate Professor Otto Warburg and his colleagues in the 1920's. The glucose analogue, FDG, can be used to exploit the differences in glucose metabolism between cancer cells and normal cells.

Positron emission tomography with FDG (FDG PET) has shown promise in the imaging of a variety of malignant tumours. It has been used successfully in detecting sites of a number of cancers including breast, lung, colorectal, head and neck, oesophageal, stomach and brain tumours.

Increased FDG uptake in lymphoma was first demonstrated by Dr Robert Paul, in 1987, at the Turku University Hospital in Finland. Subsequent studies have confirmed the effectiveness of FDG PET for not

only detecting primary lymphoma but also recurrent disease.

In a pilot study from the University of California, Los Angeles<sup>1</sup>, 18 patients with lymphoma were accurately staged or restaged using FDG PET. It detected not only more sites of nodal disease but also unsuspected disease in a transplanted kidney after conventional work-up investigations which included CT and MR.

These results are supported by a further study of 71 patients from the University Hospital, Zurich<sup>2</sup>, which suggested that FDG PET was more accurate than CT for restaging NHL and HL. This study demonstrated the clear advantage of FDG PET for the assessment of the mass which persists following treatment.

Initial studies suggested more rapid uptake in high grade NHL, whereas low grade NHL was not at all visible on PET. Subsequent studies and our own experience suggest this not to be the case. FDG PET can be equally as effective for low grade and intermediate grade NHL as it is for high grade NHL.

## Current clinical use of FDG PET

FDG PET scanning is not necessarily for all patients and indeed currently is used only for a selected minority. For most patients CT scanning will give all the information that is required to enable accurate staging when the patient is first diagnosed and information on response to treatment.

FDG PET scanning could potentially be used in the following steps in lymphoma management:

- initial staging: FDG PET may identify more sites but this does not always mean that the stage of the lymphoma will be affected

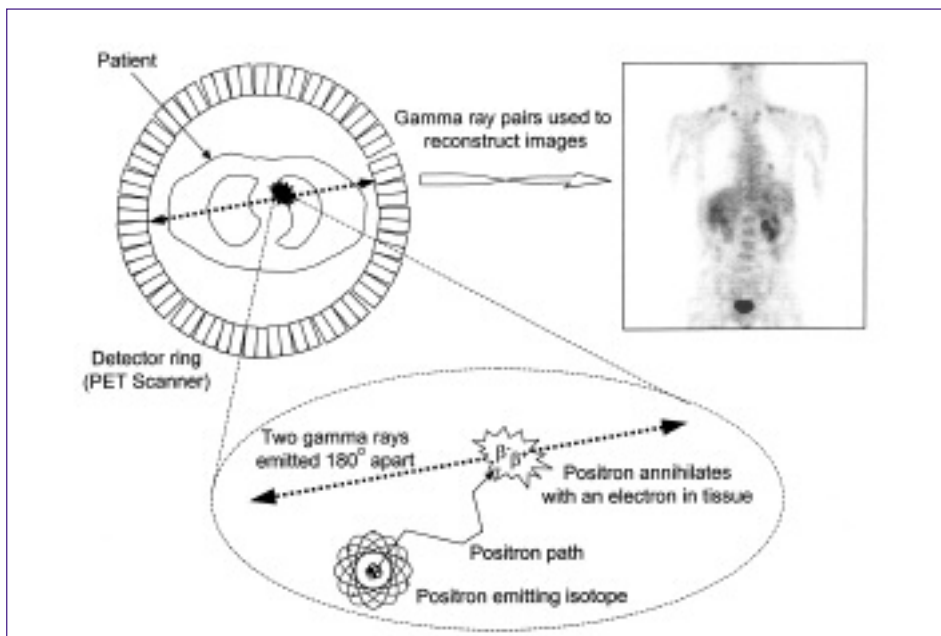


Figure 1 Schematic representation of the principles of PET imaging

## References

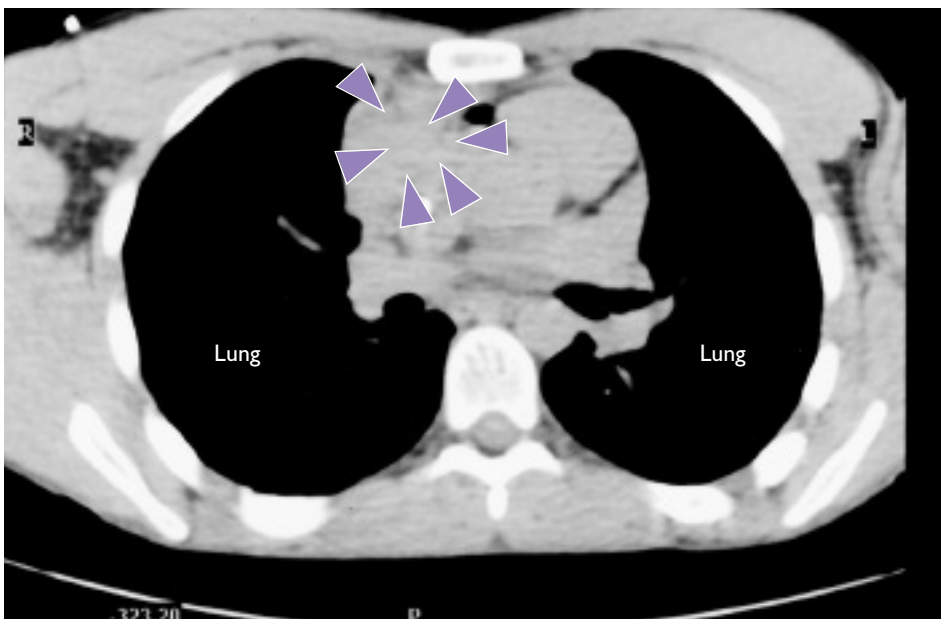
- <sup>1</sup> Hoh et al. (1997) Journal of Nuclear Medicine 38:343-348
- <sup>2</sup> Stumpe KDM et al. (1998) Journal of Nuclear Medicine 25:721-728

- assessment of initial response to chemotherapy: FDG PET may give an earlier indication than CT or MR when a patient is responding well or conversely when the chemotherapy is not working sufficiently well
  - assessment of final response to treatment: in particular FDG PET is valuable in distinguishing active tumours from inactive residual
- lumps seen on CT or MR scans (see below)
  - follow up: FDG PET may well have a future role in follow up but this is an area which has not been greatly explored to date
  - radiotherapy planning is another future area currently being investigated; more accurate definition of the extent of disease

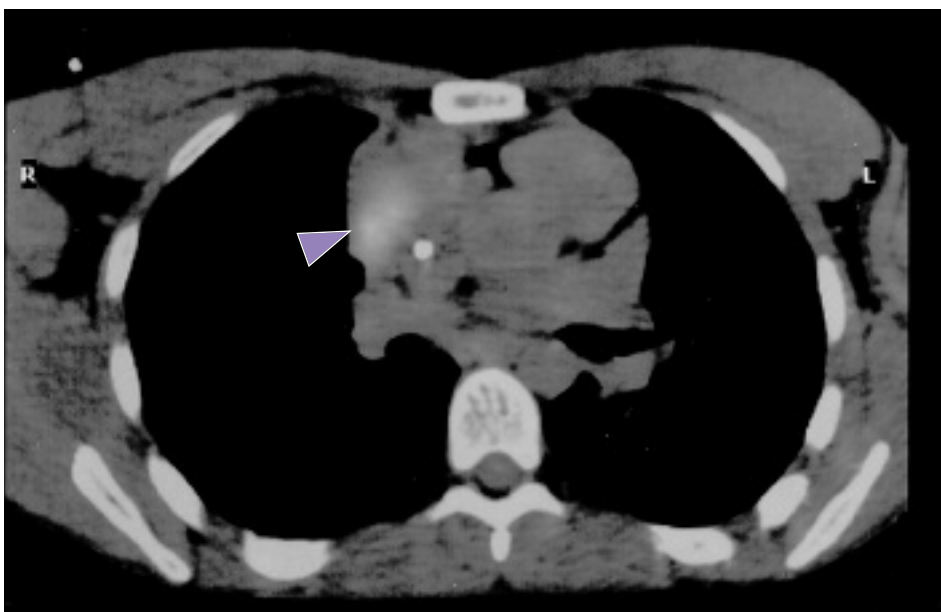
may enable more accurate definition of the areas that require radiotherapy.

FDG PET is particularly useful in those cases where the results of CT scans are uncertain or contradict other features of the lymphoma. Here it can give supplementary information and help further management of disease.

A relatively common problem where FDG PET scanning is being increasingly used is in those patients who, after a course of chemotherapy, are found to have some reduction in the size of a lymphoma swelling but it does not go away completely. It is then often difficult to be sure whether this contains active lymphoma, which would result in that patient's relapse and need for further treatment. Frequently, the residual lump simply reflects scar tissue from the disturbed architecture of the original lymph glands, needing no further treatment and which, given time, will slowly shrink back. Clinical



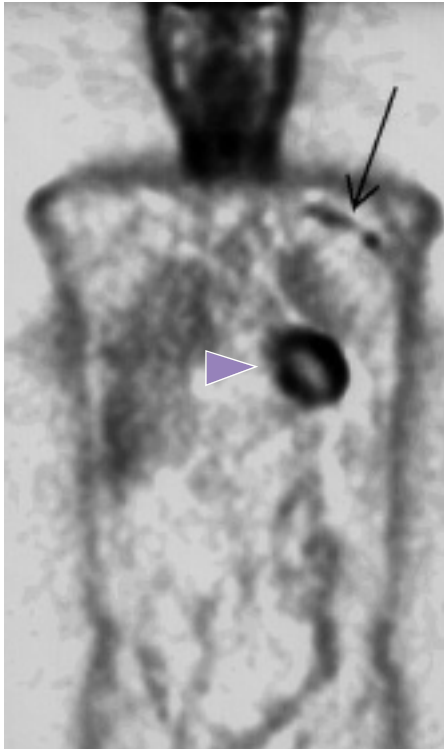
**Figure 2a** CT scan showing a residual mass (arrowheads) remaining in the mediastinum after chemotherapy



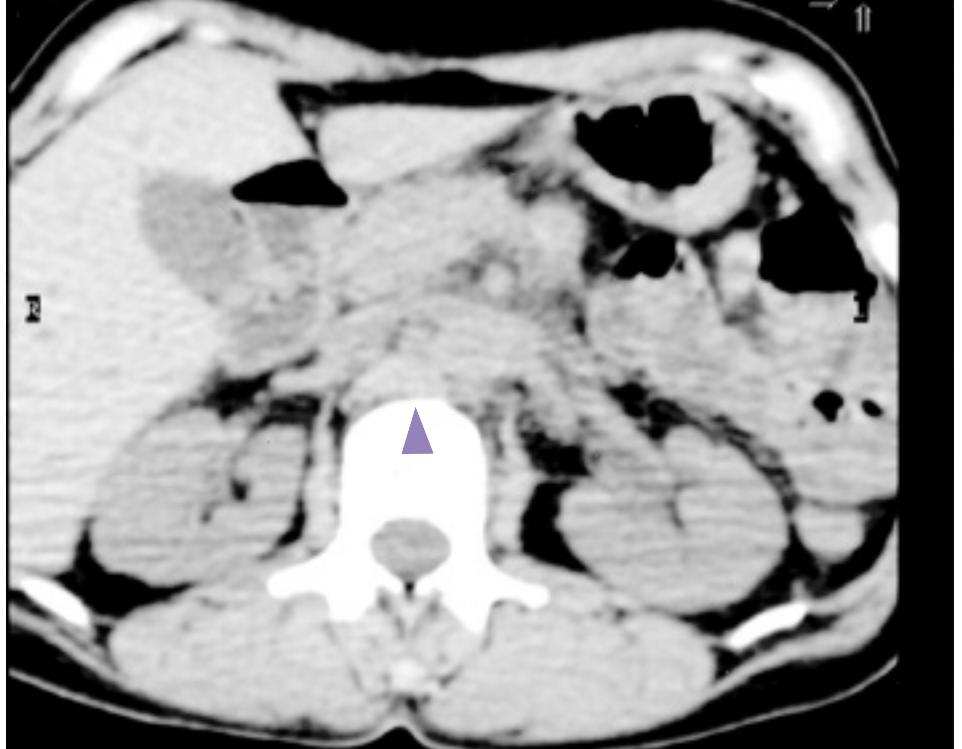
**Figure 2b** FDG PET shows increased uptake in exactly the same site (arrowhead) as the mass on the CT scan indicating active disease.



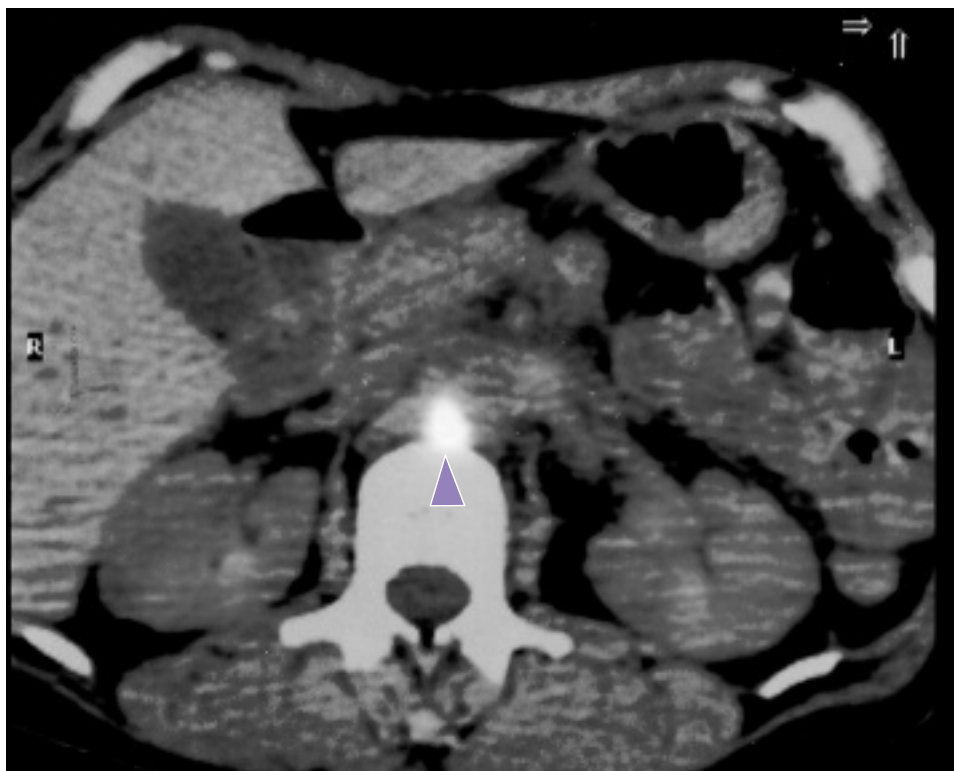
**Figure 2c** Side view, arrowhead indicates active disease in the same site



**Figure 3** Whole body FDG PET  
Increased uptake is seen along the tract of the HICKMAN®\* catheter (arrow) due to an infection. Normal intense uptake can be seen in the heart (arrowhead).



**Figure 4a** CT scan through the abdomen. Arrowhead points to a residual mass in the abdomen following chemotherapy. It was uncertain or not whether this was active lymphoma



**Figure 4b** FDG PET confirms residual mass is active disease (arrowhead)

experience suggests that FDG PET can, with a high degree of accuracy, determine between residual masses containing viable tumour where further treatment will be required to achieve a cure and those which no longer have active lymphoma within them and where additional and unnecessary side-effects from treatment can be avoided. FDG PET alone is rarely of value and should be used in conjunction with the clinical history, examination and information from blood tests and other scans.

A second scenario in which FDG PET can be valuable is in the case of someone who has striking symptoms of lymphoma, often having been previously treated for the disease and apparently cured. The combination of weight loss, night sweats and fevers are well recognised, as is the rare but striking symptom of intractable itch or alcohol induced pain. Other findings that may alert the clinician to

underlying lymphoma activity can be changes in the blood count or increased blood viscosity (high ESR) developing at a routine follow up visit. These changes will usually result

in a CT scan being performed but on occasions this will be negative and the symptoms or other findings will persist. In this group of patients FDG PET can also be of considerable

\*Hickman® is a registered trade mark of C. R. Bard, Inc

value. A negative FDG PET scan in this circumstance can provide much reassurance that there is no evidence of active lymphoma and an alternative cause for their symptoms can be sought.

However, FDG PET images lack anatomic detail and limit their use for planning radiotherapy treatment. With the advent of integrated PET CT scanners which superimpose the PET image on a CT image it is now possible to consistently and reliably relate the site of PET uptake to underlying anatomy.

An example of the value of FDG PET CT is shown in figures 2a, 2b and 2c. A patient who had nodular sclerosing stage 3 Hodgkin lymphoma in nodes within the chest, in the mediastinum and abdomen was given six courses of ABVD chemotherapy. After this treatment a CT scan (figure 2a) showed a mass remaining in the mediastinum (figure 2a arrowheads), although there were no signs of disease elsewhere. FDG PET CT (figures 2b and 2c) showed persistent active disease within the mediastinum (figure 2b and 2c arrowheads) which led to the patient having further radiotherapy to the chest. If the FDG PET CT showed no active disease the patient would have had no further treatment.

As with any sophisticated and relatively new technique there are pitfalls which are being recognised and may result in misinterpretation of the PET scan. It does seem that false positive scans can be obtained but that overall a negative scan is much more informative and is a far more reliable observation.

False positive scans can occur because of metabolically active tissue taking up the tracer FDG in high concentrations. This may be seen post-operatively, in a focus of infection or inflammation and as seen



Figure 4c Side view showing site of active disease (arrowhead)

occasionally in patients with haematological malignancies when areas of new bone marrow develop outside the normal bone architecture. An important example of this, in a patient receiving treatment for lymphoma with infection related to a Hickman® catheter, is shown in figure 3.

Areas of increased uptake, however, in a site previously involved with lymphoma which has failed to resolve completely is unlikely to represent a false positive finding and this illustrates the importance of interpreting the FDG PET scan alongside other imaging. Figures 4a, 4b and 4c illustrate a patient with stage 3 non-Hodgkin lymphoma. Following six courses of RCHOP\* chemotherapy, CT showed small lymph nodes remaining in the abdomen (figure 4a arrowhead).

FDG PET confirmed that there was still active disease (figures 4b and 4c, arrowheads) in these nodes. The patient went on to have high dose chemotherapy (ESHAP\*) followed by an autologous bone marrow transplant. The patient would not have received further treatment if the FDG PET CT had shown no active disease.

## Clinical trials in FDG PET

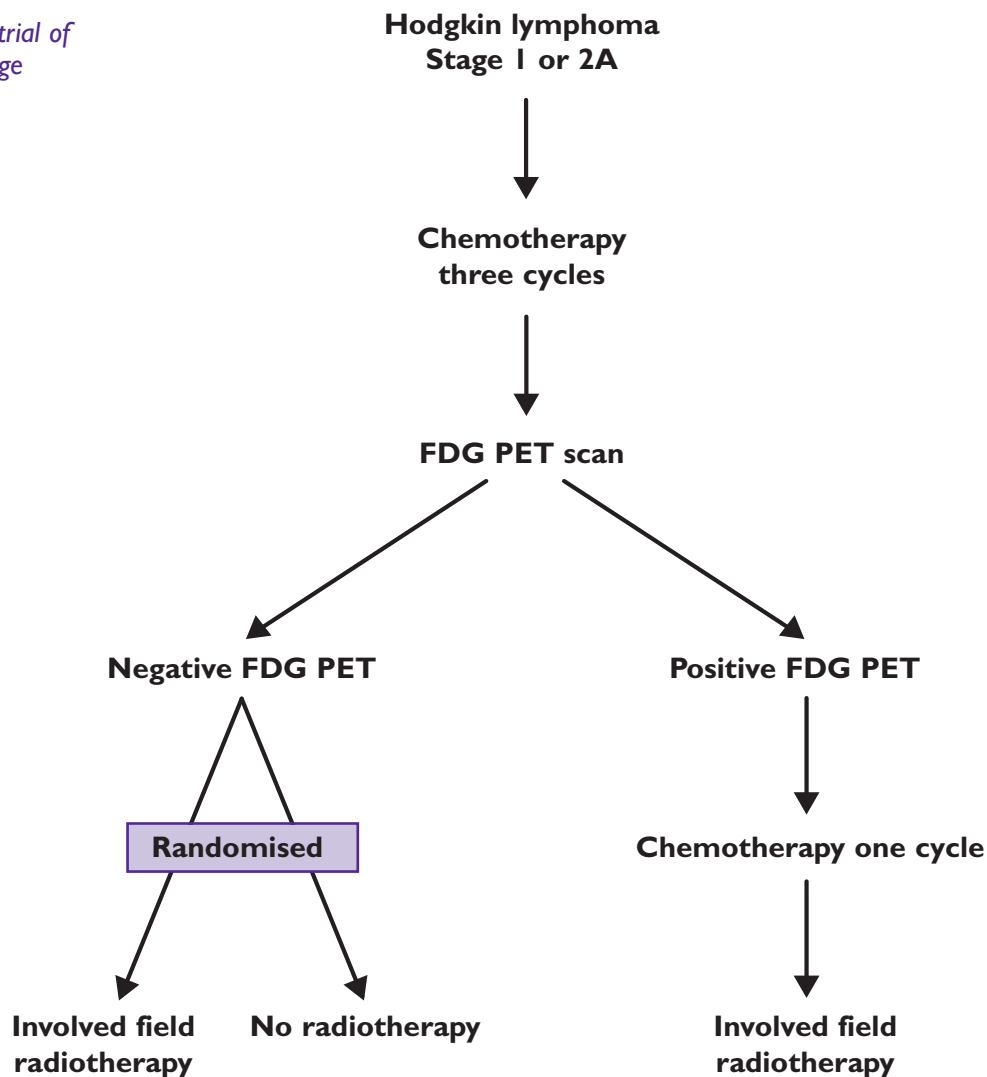
It is vital that any new technique such as this is carefully evaluated in clinical trials so that its true accuracy and relative value alongside current techniques can be critically and objectively assessed. The effect of FDG PET in the management of early stage Hodgkin lymphoma is being evaluated in a multicentre trial which is being undertaken throughout the United Kingdom. It has been developed by the National Cancer Research Institute (NCRI) Lymphoma Group and is approved by the National Cancer Research Network (NCRN) with funding from the Leukaemia Research Fund.

The standard treatment for early Hodgkin lymphoma (stages I and 2A) is 4 cycles of ABVD\* chemotherapy followed by involved field radiotherapy. This is very effective and most patients are cured, however we are becoming increasingly aware of long-term complications from treatment in such patients. This trial is seeking to determine whether FDG PET can predict for early response to chemotherapy and define a group of patients who may need relatively little treatment and who can avoid radiotherapy. A small study from St Thomas' Hospital in London has suggested that such patients may be those who have a negative PET after only two cycles of chemotherapy.

This trial will test this. The outline is shown in figure 5 (next page). All patients will receive three cycles of

\* Please call the Helpline if you would like more information on the chemotherapy regimes mentioned here.

**Figure 5**  
Diagram of the new trial of  
FDG PET in early stage  
Hodgkin lymphoma



standard chemotherapy with ABVD. They will then have an FDG PET scan.

- Patients with a negative scan will be randomised to have either involved field radiotherapy or to have no further treatment. In this group of patients we will be looking to see whether there is any difference in outcome between those who receive radiotherapy and those who do not.
- In patients having a positive FDG PET scan, they will be given one more cycle of chemotherapy followed by involved field radiotherapy on the basis that they have less responsive disease which is still detectable on PET after three cycles of chemotherapy and it

would therefore not be safe to randomise them to less than standard treatment.

Unfortunately, at present, there are only a limited number of PET scanners in the country. The major part of the trial funding therefore is to enable all patients in the trial to travel to a PET centre for their scan; in many cases this will mean travel to London to St Thomas', Mount Vernon, or University College Hospital. Scanning may also be possible at Addenbrookes, Aberdeen University and Christie hospitals. New scanners are however being installed elsewhere and this will reduce the extent of travel for patients as the trial progresses.

The role of PET in diffuse large B-cell lymphoma is also being evaluated within the current CHOP14/CHOP21 trial which is another NCRI lymphoma CSG study with the primary aim of comparing two different schedules of CHOP chemotherapy.

In summary then, FDG PET has provided an important and useful additional tool in enabling us to identify sites of active lymphoma. It can alter the management of the treatment of a patient with lymphoma by allowing us to recommend with greater confidence further treatment where initial treatment has been unsuccessful or on the other hand, be reassuring that residual changes

on a scan do not represent active lymphoma and that no further treatment need be given.

The new trial in Hodgkin lymphoma will tell us whether it can also provide early information on response to chemotherapy and allow reduced treatment for some patients.

**Acknowledgements:** we would like to thank Dr M Lodge, physicist and Mr J Lowe, Superintendent Radiographer for their assistance with this article.

## Glossary

**Conventional work-up** for lymphoma usually includes various blood tests including full blood count, ESR, liver function tests, serum LGH, serum urea and electrolytes; CT (chest, abdomen, pelvis) and also bone marrow aspirate and biopsy for NHL patients

**Gallium scanning** was used prior to CT for assessing the extent of active lymphoma. It required several visits to the hospital and defined localised disease poorly compared with CT

**Gamma rays** are high energy, penetrating electromagnetic rays produced by some radioactive compounds

**KeV** stands for kiloelectron volt, a unit of energy

**Lymphadenopathy** is the medical description of enlarged lymph glands. They usually become enlarged when the area of the body which they drain is the site of infection. Occasionally lymphoma or metastatic cancer can cause swollen glands

**Lymphangiography** is the procedure whereby the lymphatic channels and glands can be rendered visible on x-ray film by means of an injection of a radio-opaque substance

**Mediastinum** is the space in the chest cavity behind the breast bone and in between the two lungs

**Stage** indicates the areas of the body affected by lymphoma

**Staging laparotomy** is surgical examination of abdominal contents together with splenectomy (removal of the spleen to assess for splenic involvement)