The Diagnostic Role of Nuclear Medicine in Haematological Malignancies

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Abstract

Lymphomas are malignancies of the haematological system and normally originate and disseminate through the lymphatic system. Radionuclide methods have been in use for the past several decades in the management of lymphoma. Initially lymphoscintigraphy was used for identifying lymph node involvement in lymphoma. However the advent of CT and MRI saw lymphoscintigraphy relegated to the side line. Subsequently, the recognition of post therapy residual mass of fibrous tissue, looking like lymphoma on CT and MRI has lead to a resurgent interest in the functional nuclear medicine diagnostic procedures, especially imaging with Ga-67 citrate and Tc-99m MIBI. Whilst these could be used in a small number of difficult patients, often post therapy; the advent of F-18 FDG PET has lead to an overwhelming increase in the use of radionuclide techniques. Positron emission tomography (PET) is a novel functional imaging technique that can use a glucose analog (2-fluoro-2-deoxy-D-glucuse [FDG]) radiolabeled with the positron emitter fluorine-18 to evaluate glycolytic activity, which is greater in malignancies, including lymphoma. Several studies have suggested a role for FDG-PET in the diagnosis and follow-up of patients with lymphoma, and it is rapidly becoming a standard procedure for lymphoma management. PET provides several inherent advantages over other nuclear imaging techniques. The short half-life of FDG allows patient convenience and improved imaging characteristics. With modern dedicated PET machines, a resolution of approximately 5 mm can be achieved, and the ability to co-register PET with anatomic computerized tomography (CT) imaging allows for ease of interpretation. Moreover, using a quantitative approach to interpretation with the standardized uptake value (SUV) (ratio of activity per volume unit over injected activity per body mass), PET imaging appears to be more precise than conventional scintigraphy and is rapidly becoming an essential part in the management of lymphoma.

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Introduction

Lymphomas include a wide range of malignancies originating in the lymphoid tissue, which include Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). HD is one of the most common malignancies in the young adult, while NHL is most common in a more elderly age-group. There are a few known aetiologies like the Epstein-Barr virus for Burkett's lymphoma and radiation for lymphomas related to radiation exposure. But the aetiology of the majority of lymphomas remains unknown. For HD, the most common presenting feature is painless enlargement of lymph nodes with less common involvement of other body organs. About one third of patients of HD would have fever, weight loss and drenching night sweat. These are called “B” symptoms. B symptoms can also be found in non-cancerous states such as tuberculosis (TB). NHL is characterized by the presence of malignant cells in any area of the lymphoid system in the body, including lymph nodes, bone marrow, spleen, gastrointestinal tract and skin with the bone marrow being often involved. NHL does not tend to spread to contiguous lymph nodes. In NHL the clinical course and prognosis are strongly associated with histology. NHL is broadly divided into B and T- cell lymphoma, with diffuse B-cell lymphoma being the most common type of lymphoma according the Revised European American Lymphoma (REAL) classification. Compared to other malignancies in oncology; both HD and NHL are the most curable malignancies, with cure rates almost approaching 90% for Hodgkin's disease and up to 50% for high grade non-Hodgkin's lymphomas. The major objectives of radionuclide imaging in lymphoma management are to enable the clinician to minimise treatment for patients with localised responsive disease with simultaneous minimization of the therapy side effects; or to maximize treatment for patients with more advanced disease, which is poorly responsive to first-line treatment. These can be achieved through improving the accuracy of initial staging, defining response to treatment, and refining follow-up after successful completion of treatment. The role of nuclear

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medicine imaging procedures in the evaluation of lymphoma and other haematological malignancies will be addressed here, comparing each one individually with the other; as well as to other radiological investigations used in clinical practice.

A. Radionuclide Imaging of Lymphoma

1. Gallium-67 (Ga-67) scintigraphy:

Gallium-67 citrate (Ga-67) was introduced for the first time as a tumour seeking agent in the year 1969 by Edwards and Hayes in Hodgkin's disease (1). The evolution of technology of Gamma camera imaging and the introduction of single photon emission computed tomography (SPECT), and the increase in the administered dose of Gallium-67, have all contributed to a gradual improvement in the quality of Gallium imaging since its introduction as an imaging agent in 1969.

The mechanism of Ga-67 uptake:

The exact mechanism of tumour tissue uptake of Ga-67 is not known. Several explanations have been postulated. These are as follows:

1. Related to Gallium: Upon its intravenous injection, Ga-67 is largely bound to transferrin, which is basically an iron transport protein; hence both of them compete with each other for binding to this protein (2). Ga-transferrin complex then binds to a cell surface transferrin receptor and gets internalized by absorptive endocytosis. The tansferrin receptor appears to be the major mechanism by which tumour cells concentrate Ga-67. Binding of Gallium to ferritin, to macromolecules within the intracellular organelles in tumours as well as to the intracellular lactoferrin also contribute to the uptake of Gallium by the tumour tissue (3-5).
2. Related to Tumour cells: Cellular uptake of Ga-67 is linked to the metabolic activity which is directly related to ATP metabolism in these cells(6). After its entry into the cell, Gallium is mostly transferred from transferrin to ferritin, for which it has a higher affinity than either transferrin or lactoferrin.
3. Tumour blood supply: Increase in tumour uptake is also due to the increased blood supply and increased membrane permeability found in malignant tissue. Normal Gallium localization is seen in the liver, spleen, bone marrow, bone growth plates, and colon, with relatively less intense uptake in lacrimal and salivary glands and breast tissues. This uptake is related to the presence of transferrin receptors at these sites. Activity outside these areas is considered abnormal and may suggest active disease (Figure 1).

Figure 1. Whole body Ga-67 citrate scan. Anterior (left) and Posterior (right) images showing small bowel uptake due to a small bowel lymphoma.

The treatment of lymphomas normally depends on the histological subtype and tumour stage. Computed tomography (CT) plays a major role in staging the disease and in few instances it is also complimented by magnetic resonance imaging (MRI). Nevertheless histological examination of bone marrow still remains a mandatory requirement before initiating therapy. Gallium has a small role in the initial staging of lymphoma. However Gallium seems to have a bigger role in the evaluation of treatment response.

Gallium-67 imaging is performed at 72 hours to provide a favourable target to background ratio following an intravenous injection of 150-300 MBq Ga-67 to the adult and a dose of 3 MBq/kg of body weight to children. A medium energy, high resolution, parallel hole collimator is used. Planar imaging is performed using a matrix size of 256 x 256. Images are obtained in anterior and posterior projections of the chest (2,000,000 counts per view) with arms up, abdomen/pelvis (with and without the liver in the field of view 1,500,000 counts per view), and the thighs (imaged for the same amount of time as the abdomen/pelvis). Lateral views of the head and neck are obtained as well (6000,000 counts per view on one side, followed by the same amount of time for the other side). Single photon emission computed tomography (SPECT) imaging is then performed using matrix size of 64 x 64 and 50-70 seconds per projection. Images are obtained from the nasopharynx to the lung bases, and then from the lung bases through the pelvis. The final data is reconstructed in axial, coronal, and sagittal planes using parameters specific for each camera (7).

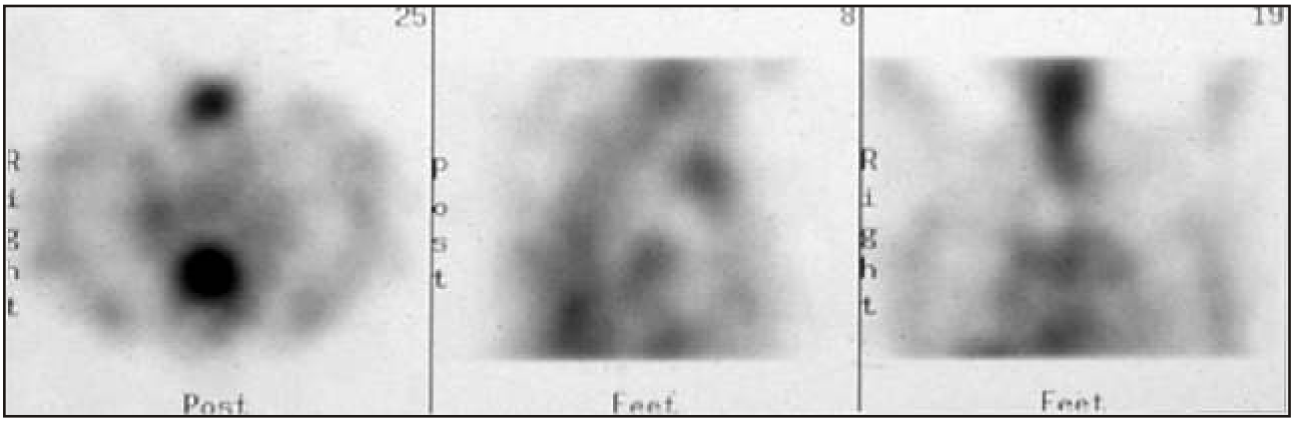

Figure 2. Tomographic Ga-67 citrate SPECT images with slices through the chest showing hilar lymphadenopathy

The Role of Ga-67 scans in lymphoma evaluation:

The main indications for Gallium-67 scintigraphy in lymphoma patients are as follows: (i) to monitor response to therapy, (ii) to distinguish viable residual tumour from post-therapy non-tumoural necrotic/fibrous tissue and (iii) to detect tumour recurrence at an early stage. Gallium scan has also been used to predict tumour response to therapy (8-10). Besides, One of the advantages of Gallium scan is that it provides a whole body spatial distribution profile of radio-tracer in one image, while CT provides only regional tomographic information at a time (11).

The ability of Ga-67 imaging to detect tumour is dependent on the histology of the lymphoma, the anatomical location of the lesion, its relation to the organ(s) that physiologically concentrate Gallium and the technical factors which affect image quality with Gallium. Ga-67 is more sensitive in HD and aggressive lymphomas than in low grade lymphomas. It picks up lesions easily which are greater than 2 cm in diameter. The lesion detection is much better if it is situated in the mediastinum. Keeping in view the above cited factors, appropriate patient selection is an important first step for maximizing the success rate of Ga-67 scanning in lymphoma.

Lesions larger than 5 cm and especially those larger than 10 cm, leave residual scars following therapy. Approximately up to 50% of patients of lymphoma will have residual mediastinal mass regardless of the mode of therapy. CT scanning cannot differentiate between viable (residual tumour) and non-viable (post therapy necrotic/fibrous masses) tumour tissue (12). But, persistence of Gallium-avid abnormality would indicate residual viable tumour or relapse after treatment(8, 13). Kostakoglu and colleagues have reported a sensitivity and specificity of 96% and 80% for Ga-67 SPECT in the detection of lymphoma *vis a vis* CT, which has a sensitivity of 68% and 60% respectively (14). To avoid the effect of therapy on Ga-67 uptake, that may lead to a false negative result; the scan should be performed at least three weeks after the last cycle of therapy(15).

Some studies have reported the role of Ga-67 scanning in predicting disease-free survival and/or survival after treatment for lymphoma. A good correlation has been reported between Ga-67 uptake and disease prognosis in many studies(16-18). Ga-67 scan performed as early as after the first cycle of chemotherapy allows patient stratification according to their predicted long-term outcome(19-21). A positive Ga-67 scan during the early part of a treatment course may represent those patients who will not respond to that treatment and may benefit from a change in treatment. However it is not entirely clear how early in the course of treatment a Ga-67 scan should be performed which would predict tumour response.

In summary, Ga-67 imaging of lymphoma provides information regarding the presence or absence of active lymphoma. Most importantly, the positive predictive value for the presence of active disease has consistently been shown to be greater than that for morphologic imaging techniques (such as CT and MRI), primarily due to the presence of residual mass in treated lymphoma. Hence with careful selection of patients, appropriate imaging protocols and meticulous correlation with morphological imaging, Ga-67 scintigraphy may still play an important role in the management of patients with lymphoma.

2. Positron Emission Tomography and lymphoma:

Positron emission tomography (PET) scanning, using F-18 Fluorodeoxyglucose (F-18 FDG) has recently emerged as a powerful functional imaging tool for assessment of patients with HD and NHL. FDG is transported into the cell via the normal glucose transport mechanism as glucose and phosphorylated by the hexokinase to FDG-6-phosphate. However, in contrast to glucose-6-phosphate, which further metabolizes to C02 and H20, FDG-6-phosphate remains intact in the tissue for an extended period of time. With time more and more FDG accumulate intracellularly. This unique metabolic behavior makes radiolabeled deoxyglucose an excellent candidate for mapping regional function, especially in the malignant tissue. Because intracellular accumulation of FDG reflects the glycolytic metabolic rate in malignant cells, which is significantly higher than normal cells(22), F-18 FDG-PET imaging is considered as a metabolic study that provides functional characteristics, which would differentiate malignant tissues from normal ones. Although high F-18 FDG-avidity has been reported in most types of lymphomas, there are still

Author	Ref.	(n)	Lymphoma type	Sensitivity (%)	Specificity (%)
Bangerter et al. (1999)	(57)	89	Mixed	96	94
Buchmann et al. (2001)	(58)	52	Mixed	99	100
Najjar et al. (2001)	(59)	36	NHL	87	100
Weihrauch et al. (2002)	(60)	22	HD	88	100
Sasaki et al. (2002)	(61)	43	Mixed	92	99
Hong et al. (2003)	(62)	30	Mixed	93.3	100

(n): is the number of patients in the study.

Table 1. Examples of recent studies showing the sensitivity and specificity of F-18 FDG-PET imaging in the initial staging of lymphoma.

Study	Ref.	(n)	Lymphoma type	Sensitivity (%)	Specificity (%)
Stumpe et al. (1998)	(63)	53	HD	86	96
		18	NHL	89	100
Cremerius et al. (1999)	(64)	72	Mixed	88	83
Bangerter et al. (1999)	(65)	36	Mixed	71	86
Nannmann et al (2001)	(66)	58	Mixed	100	93
Hueltenschmidt et al (2001)	(67)	63	HD	95	89
Guay et al (2003)	(68)	48	HD	79	97
Freudenberg et al. (2004)	(69)	27	Mixed	86	100

(n): number of patients in the study.

Table 2. List of recent studies showing the sensitivity and specificity of F-18 FDG-PET imaging in re-staging of lymphoma.

some controversy with regard to some of the subtypes of NHL(23).

It may be noted that F-18 FDG is taken up normally by tissues and organs showing high glucose metabolism, such as the brain, liver, myocardium, smooth muscles of bowel and skeletal muscles. Besides, the organs like kidneys, urinary bladder and intestines which excrete Ga-67 are also visualised during the imaging process. Macrophages and granulation tissues also concentrate FDG.

The most important contribution of F-18 FDG-PET imaging in the management of lymphoma is in staging the disease. F-18 FDG-PET is non-invasive, efficient and has the capability to image the whole body. It is highly sensitive, specific and accurate in staging patients with most histological types of HD and NHL (Table 1), which are in fact comparable with CT (24, 25). Hence it has been generally accepted today that F-18 FDG-PET should be added as a clinically valuable tool to other staging modalities (26-28). PET effectively distinguishes between viable tumour and necrosis or fibrosis in the residual masses found after treatment. Hence it can be used in lymphoma re-staging (29,30). This represents one of the most important roles of PET in refining the follow-up protocol after completion of treatment (Figure 3). Many recent studies have demonstrated high sensitivity and specificity for F-18 FDG-PET imaging in the lymphoma re-staging (Table 2). PET/CT system that produces co-registered (functional and anatomical images) further improves the diagnostic accuracy of PET imaging alone. PET provides accurate early assessment of therapy response by demonstrating a rapid decline in FDG uptake or normalization of F-18 FDG PET scan after the first or second cycle of therapy that would help in tailoring or modifying therapy accordingly (31-46).

The role of PET for post-therapy surveillance without clinical or radiological evidences, and its impact in altering the management strategy, as well as its role in long-term follow-up need to be clarified with further evidence based studies.

Some factors like the degree of metabolic activity, lesion

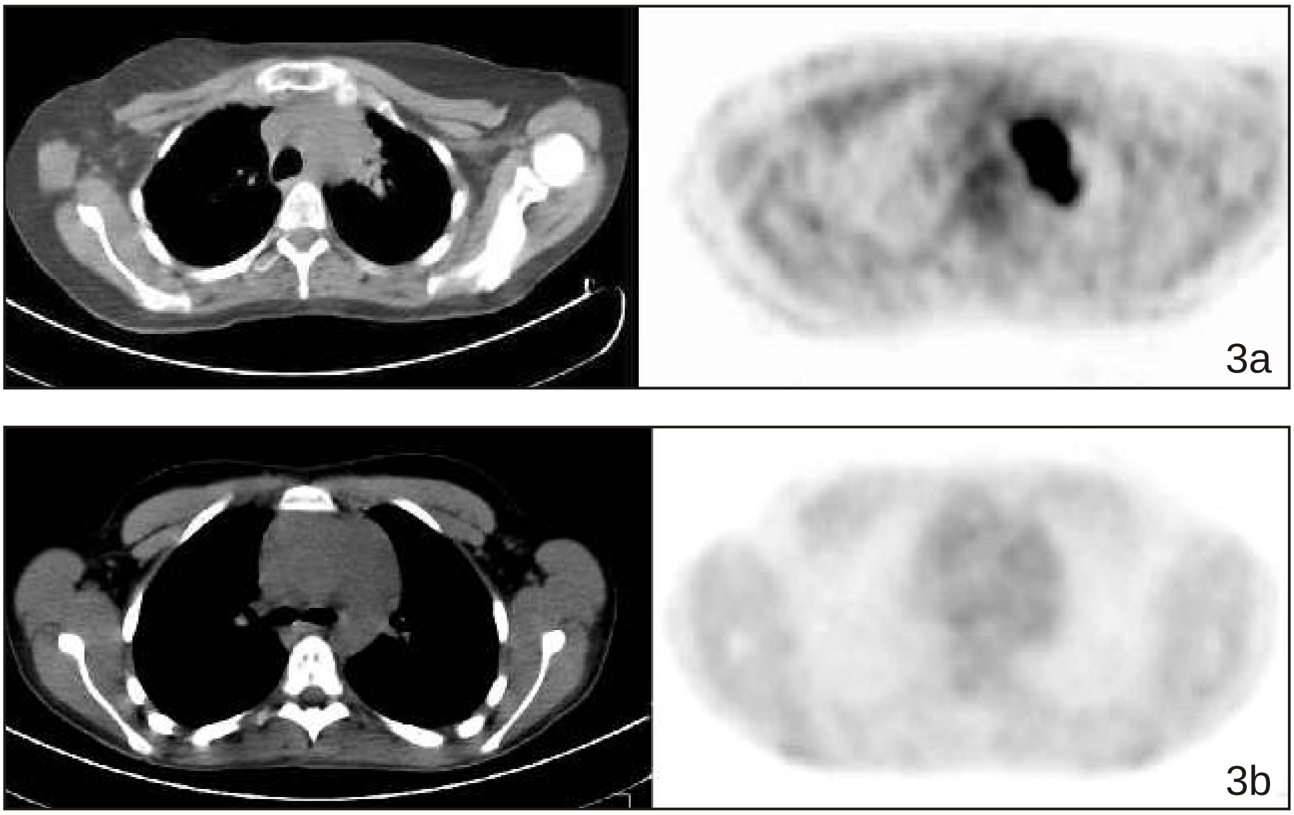

Figure 3. Patient with Hodgkin's disease CT and PET (a) Pre-treatment scans show a mediastinal mass which is metabolically very active on F-18 FDG PET. (b) Post-treatment scans. After 12 months treatment there is a residual mass on CT but PET confirms clearance of all disease. (Images courtesy of Dr. Gary Cook, Royal Marsden Hospital, Sutton UK)

size, and physiological uptake in normal tissue may lead to false results, and these have to be carefully considered during interpretation of scan results. These pitfalls account for the non-specificity of PET. Hence the results of PET studies should be interpreted in conjunction with the overall clinical context and results of morphological investigations like CT and MRI. This approach has dramatically improved the specificity and diagnostic accuracy of PET studies.

In recent years, new tracers based on DNA turnover, such as F-18 fluoro-levotyrosine (FLT) have been suggested as more specific radiotracer than F-18 FDG. However uptake of FLT by the normal bone marrow and liver may still make staging difficult. Despite several shortcomings PET remains one of the most important investigative tools in the management of lymphoma, along with CT and MRI with comparable sensitivity and specificity (27).

3. Uses of other radiopharmaceuticals for imaging lymphoma

(i) Thallium-201 Chloride

Thallium-201 (Tl-201) is a potassium analogue that is actively taken up by viable tumour cells in proportion to the activity of the sodium-potassium adenosine triphosphatase pump. The cellular uptake is not solely related to cell biology in the tumour. There are many other factors which contribute to Tl-201 uptake by tumour cells, which include: (i) blood flow, (ii) tumour type, (iii) viability of tumour cells, (iv) co-transport system, (v) vascular permeability and (vi) cell membrane permeability. Although not very widely used, Tl-201 imaging may have a significant role in certain specific clinical settings in the management of lymphoma, especially cerebral lymphoma (50). There is generally very intense FDG uptake in the brain because the brain's only energy source is glucose. The total uptake in the brain is approximately 6% of the injected dose of F-18 FDG. Hence F-18 FDG may not be the most appropriate radiopharmaceutical to detect cerebral lymphoma. It has been reported that both Gallium-67 as well as F-18 FDG have reduced avidity for low grade lymphomas. Under this setting, Tl-201 has shown to have better utility value for imaging low-grade lymphomas (47-49). Several studies have suggested the usefulness of Tl-201 brain SPECT to differentiate lymphoma from infectious processes and to determine the timing for biopsy or empirical therapy for patients with AIDS-related brain lesions (50). Limitations of diagnostic accuracy occur in the head and neck lesions that are smaller than SPECT resolution (6-8mm) allows to detect, lesions close to orbitae, skull base, scalp or in lymphoma with diffuse leptomeningeal spread. In a series of HIV-infected patients, Tl-201 SPECT was able to accurately differentiate primary brain lymphoma from other causes of focal CNS lesions in most patients; however, both false positive and false negative results occurred. By combining Tl-201 SPECT with serum Toxoplasma IgG, diagnostic accuracy was shown to improve (51). A few reports also have suggested that Tl-201 brain SPECT is unreliable for differentiating primary

Figure 4. Whole body Tc-99m MIBI images showing uptake in two mediastinal nodes of a patient with non-Hodgkins B cell lymphoma.

lymphoma from non-malignant brain lesions in patients with AIDS. In such cases early brain biopsy is necessary to establish a definitive diagnosis when appropriate (52)

(ii) Sestamibi:

The mechanism of Tc-99m MIBI uptake by the tumour involves binding of MIBI to cytosol in the tumour cells (Figure 4). The cationic charge and lipophilicity of Tc-99m MIBI, mitochondrial and plasma membrane potentials of tumour cells and cellular mitochondrial content, all play some part in tumour uptake of this agent. The uptake of MIBI has also been attributed to certain indirect phenomena such as increased tumour blood flow and capillary permeability. In addition, the retention of Tc-99m MIBI in cells depends on the activity of the 170 kDa Pgp coded on the MDR1 gene, which functions as an ATP-dependent efflux pump for many cytotoxic substances, mostly lipophilic cations. A few studies have demonstrated the relationship between Tc-99m MIBI tumour uptake and Pgp expression and implied some potential for Tc-99m MIBI scintigraphy as a non-invasive imaging test for assessing Pgp expression. Low and high Tc-99m MIBI tumour uptakes are thought to be consistent with relatively high and low Pgp expressions, respectively and the mechanism of chemotherapy resistance in malignant lymphomas is thought to involve MDR-Pgp expression. In a prospective study using Tc-99m MIBI scan to predict Pgp expression and chemotherapy response in malignant lymphomas Liang and colleagues have reported that positive Tc-99m MIBI scans accurately predicted chemotherapy response in all 15 (100%) patients with good response and negative Pgp expression and also in six (60%) patients with poor response and positive Pgp expression (53). Resistance of malignant tumours to chemotherapy agents or what is called multi-drug resistance (MDR) is a major cause of treatment failure. MDR is associated with P-glycoprotein (PgP) over-expression in tumour cells (54). Tc-99m sestamibi is a lipophilic cation which accumulates in tumour cells with low PgP expression, and hence can predict tumour response to therapy(55,56). Tc-99m sestamibi also has been used in low-grade lymphomas(57).

(iii) Somatostatin receptor scintigraphy (SRS) and lymphoma:

SRS is performed after injection of about 111-222 MBq In-111 DTPA Octreotide followed by planar and SPECT imaging at 4 and 24 hours. The normal bio-distribution includes thyroid, liver, spleen, bowel, kidneys and urinary bladder. SRS has been used for tumour imaging for more than two decades. High somatostatin receptor expression has been found in most low and intermediate grades of NHL and in the majority of high-grade NHL(58). However the sensitivity of the test is higher in Hodgkin's lymphoma as compared to non-Hodgkin's lymphoma (59,60). In-111 Octreotide accumulates in inflammatory cells such as lymphocytes and macrophages present at the infection or inflammatory sites, which may affect the specificity of the SRS (61-63). In addition, its normal physiological distribution in several organs in the body also affects its sensitivity. Because of this limited sensitivity, SRS is recommended only in selected cases of low-grade NHL. SRS offers complementary information to morphological imaging and may be used as a guide for radionuclide therapy for lymphomas.

(iv) Radioimmunoscintigraphy with Labelled monoclonal antibodies:

Tc-99m labelled monoclonal antibodies (MoAb) consisting of a Fab' fragment of the LL2 antibody to CD22 receptor with high affinity for malignant B cells has been evaluated for imaging NHL(64,65). In a study done by Murthy and colleagues the overall lesion sensitivity of radioimmunoscintigraphy (RIS) for lymphomas was reported to be 89%. The study also reported a positive predictive value of the test around 96% (66). RIS is of great significance as an investigation prior to treatment when the treatment of lymphoma with radiolabelled MoAb is considered. SPECT acquisition is essential especially in the abdomen. RIS has better lesion delineation than Ga-67 for low-grade disease (67). Advances in PET may significantly reduce the clinical role of antibodies in imaging lymphoma.

(v) Bone scan and lymphoma:

Skeletal involvement in lymphomas is rare; bone scan using Tc-99m labelled methylene diphosphonate (MDP) can be used when there is bone pain. It is more reliable than plain radiograph in diagnosis of bone metastasis in lymphomas(68).

B. Multiple Myeloma and radionuclide imaging:

Multiple myeloma (MM) is a malignant clonal neoplasm of plasma cells of B-lymphocyte origin that commonly results in overproduction of large amounts of monoclonal immunoglobulins. The role of imaging in the work-up of patients with MM consists of studies that detect the effects of myeloma cells on the skeletal system, which is extensive bone re-absorption with severe inhibition of bone formation leading to bone fractures and bone pain (69). This makes MM an osteolytic tumour. MRI is extremely useful for assessing suspected disease sites but is cumbersome as a whole-body screening technique. Since bone scan using Tc-99m labelled methylene diphosphonate (MDP) relies on an osteoblastic reaction, it may underestimate the extent of the disease. MM usually shows 'cold' or photopenic lesions on bone scans. The generally planar radiograph is more sensitive than bone scan, particularly for osteolytic lesions. This limitation of Tc-99m MDP bone scan has led to search for other alternative radionuclides which would selectively concentrate in the tumour cells; such as Ga-67, Tl-201, Tc-99m sestamibi and F-18 FDG. Durie et al in a recent study have reported that whole-body F-18 FDG PET is probably the most accurate imaging tool for the evaluation of patients with MM (70).

C. Leukaemia and radionuclide imaging:

Although leukaemia is the single most common type of malignancy in children, patients afflicted with leukaemia are not very commonly evaluated by radionuclide techniques. Bone scintigraphy is sometimes performed in the diagnostic work-up of children with acute leukaemia and bone pain or when bone metastasis is suspected, although the high possibility of osteomyelitis due to immunosuppression from the disease and its therapy will reduce the specificity of the bone scan. The bone scan however, may significantly underestimate the extent of disease.

D. Polycythemia RubraVera (PV) and diagnostic role of nuclear medicine:

PV is a clonal, chronic progressive myeloproliferative disorder which is characterised by proliferation of all three bone marrow elements (erythroid, granulocytic and egakaryocytic) and by an absolute increase in the red blood cell mass. PV is sought to arise from a neoplastic clone of a pluripotent hematopoietic stem cell (71). The transitions from PV to postpolycythaemic myeloid metaplasia and acute leukaemia are common. An assessment of total red cell mass (using nuclear medicine technique) is essential for the diagnosis of PV and to separate it from a secondary polycythemia due to chronic airways disease or other causes.

The role of radionuclide technique is to measure the red cell volume (RCV) using the dilution principle. Both Tc-99m labelled RBC as well as Cr-51 labelled RBC has been used in the estimation of RBC mass (72).

E. Other Nuclear medicine studies in haematological malignancies

Radionuclide studies are also used in monitoring the effects of drug toxicity on organ function, especially of doxorubicin on cardiac function and plantinum based chemotherapeutic drugs such as Cisplatin on kidneys, both of which are used to treat acute leukaemias. Gated ventriculograhy studies (MUGA) offer more accurate and consistent results of left ventricular ejection fraction (LVEF) than sequential echocardiograms. Glomerular Filtration Rate estimation by Cr-51 EDTA offers much better and more accurate method for monitoring renal function compared to conventional creatinine clearance technique using biochemical methods.

These patients are susceptible to infection secondary to the immuno-suppression from chemotherapeutic drugs. As they are often neutropaenic, imaging methods for infection not depending on white cell function such as Ga-67 citrate or Tc-99m Infecton are preferred (72).

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