Nuclear Medicine Applications in Hemato-Oncology

İlknur AK*, Zafer GÜLBAŞ**

* Department of Nuclear Medicine, Osmangazi University Medical Faculty,
** Department of Haematology, Osmangazi University Medical Faculty, Eskişehir, TURKEY

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INTRODUCTION

In nuclear medicine, the development of new radionuclide tracers and the improvement of equipment for imaging during the past decades has enable a more functional approach based on metabolic imaging rather than morphology-related techniques. Although radiography, ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) are still the methods of choice to evaluate the patient with cancer, they have certain limitations in superficially growing tumours, small lymph node metastasis, enlarged lymph nodes containing inflammation instead of tumour, in the assessment of the viability of previously treated lesions and the diagnosis of tumour relapse. There is ample evidence that nuclear medicine techniques may provide complementary information with respect to anatomical imaging. Tumour localising radiopharmauceuticals such as gallium-67 (Ga-67), thallium-203 (Tl-201), technetium-99m (Tc-99m) labelled Sestamibi and radiolabelled somatostatin analogues have an established role in clinical oncology using a specific aspect of tumour biochemistry and pathophysiology. As metabolic imaging, F-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography (PET) has opened a new field of imaging in oncology. This technique is being used for initial diagnosis, assessing diseases extension and prognosis, planning and monitoring treatment and detecting the recurrent disease.

In this review, the basic principles and current knowledge of most important nuclear medicine techniques in haematologic oncology, focusing primarily on lymphomas, are summarised and their value in clinical practice is discussed.

Hemato-Onkolojide Nükleer Tıp Uygulamaları

Anahtar Kelimeler: F-18 florodeoksiglikoz, Pozitron-emisyon tomografisi, Ga-67, Tc-99m-metoksi-2-isobutilisonitril, Lenfoma, Multipl miyeloma.

Key Words: F 18 Fluorodeoxyglucose, Positron-emission tomography, 67Ga, Tc-99m-Methoxy-2-isobutylisonitrile, Lymphoma, Multiple myeloma.

F-18 FDG PET

PET has opened a new field in clinical imaging as it is unique in its ability to per-

form imaging of blood flow or metabolic processes, thereby differing from the more conventional morphological or anatomical imaging methods, including radiography, US, CT, MRI and even single-photon emission tomography (SPET). Up to a few years ago, PET was known as a very expensive research tool-using positron emitting radiopharmaceuticals to study metabolic processes in vivo. Recent developments in detector technology enabled the detection of the distribution of positron emitting radionuclides inside the human body through dual-headed gamma camera systems[1]. These much cheaper cameras did move the focus of PET from research to clinical applications. Over the last decade its applications in clinical neurology, cardiology and especially in clinical oncology have increased considerably, paralleled by an increasing availability of PET cameras. The improved availability of F-18 FDG which, is by far the most commonly used PET agent, has promoted clinical PET. At present, PET is the most growing area of medical imaging because of its considerable power. PET imaging provides qualitative, semiquantitative and quantitative information on tumour physiology. Clinical FDG studies are generally analysed using semiquantitative and qualitative data. A standardized uptake value (SUV) is a semiquantitative index of glucose utilization that is obtained by normalizing the accumulation in the region-of-interest (ROI) to the injected dose and patients body weight.

The use of fluorine-18 2-fluoro-2-deoxy-D-glucose (F-18 FDG) in tumour imaging is based on the observations by Warburg in the 1920s that neoplastic cells exhibit increased glucose metabolism compared with normal cells[2]. The glucose analogue 2-deoxy-D-glucose is transported into the cell in the same way as glucose. In the cell, it is phosphorylated to deoxyglucose-6-phosphate by hexokinase, like normal glucose. However, in contrast with glucose, glucose-6-phosphate isomerase does not react with deoxyglucose-6-phosphate, so further metabolism is not possible. In addition, deoxyglucose-6-phosphate shows a slow clearance from the cell, which is caused by low membrane permeability. Furthermore, due to the very low concentration of glucose-6-phosphatase in the malignant cell, degradation of deoxyglucose-6-phosphate is minimal. Thus, deoxyglucose-6-phosphate is trapped in the cell. If deoxyglucose-6-phosphate labelled with F-18, which is a positron-emitting radionuclide with a physical half-life of 110 min, can be imaged by PET. This trapping mechanism of deoxyglucose-6-phosphate in malignant cells is the rationale for the common use of F-18 FDG in oncology.

Glucose transporters (GLUTs), presented on membranes of almost all cells, are the main pathway for glucose and F-18 FDG to enter the cell. The increased uptake of glucose following malignant transformation is explained by an increase in the activity of existing GLUTs, by the biosynthesis of a new class of transporters or by an increase in the normal cellular enzymes[3]. The rapid and high uptake of glucose by the GLUTs correlates with the high glycolytic activity of tumour cells and overexpression of GLUT 1 and GLUT 3 genes is responsible for increased uptake of glucose in malignancies[4,5]. Malignant cells also have larger amounts of hexokinase than is present in normal cells. Nevertheless, F-18 FDG uptake is not specific for neoplastic cells. Autoradiographically, intratumoural F-18 FDG distribution in certain tumours is even highest in the reactive inflammatory tissue, i.e. the activated macrophages and leukocytes surrounding the neoplastic cells[6,7]. A high uptake of F-18 FDG reflects an increased glycolytic metabolic rate in the cells. Inflammatory cells such as activated lymphocytes, neutrophils and macrophages have increased glucose utilisation and increased F-18 FDG uptake has been demonstrated in experimental infectious and inflammatory lesions[6]. Adenopathy associated with granulomatous disease such as sarcoidosis, tuberculosis, histoplasmosis can demonstrate increased F-18 FDG uptake[8]. Benign conditions usually have lower

uptake than malignancy but there is overlap. Although it can increase false-positive results and reduce the specificity of PET in oncology, F-18 FDG PET can be exploited for imaging infection and inflammation.

Hodgkin's Disease and Non-Hodgkin's Lymphoma

During recent decades there has been a steady improvement in the management and survival of both Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). This has resulted from new chemotherapeutic approaches and imaging techniques. In 1987, Paul became the first to describe imaging lymphoma with FDG[9]. It has been shown that the F-18 FDG uptake of NHL is obviously directly correlated with the degree of tumour malignancy[10]. It is known that there is higher F-18 FDG uptake in patients with high-grade compared with low-grade NHL[11]. Furthermore, Okada et al have demonstrated a positive correlation between the proliferative activity of malignant lymphoma and the intratumoural F-18 FDG accumulation[12]. They also reported that the response to therapy and the mean survival time were reduced in patients who initially exhibited a high metabolic rate, i.e. a high F-18 FDG uptake in PET scans.

One of the most important factors influencing relapse-free and overall survival of lymphoma patients (in addition to histologic appearance) is extension of disease and accurate initial staging is essential for optimising therapy and determining the prognosis. Conventional modalities for staging lymphoma include physical examination, CT of the chest, abdomen and pelvis, bone scintigraphy and bone marrow biopsy. Although CT scan and MRI or US of these sites is the best imaging technique to provide detaied information about the relationship between organs and vascular structures, the criteria for adenopathy is based on size alone. They have certain limitations especially in small lymph node metastasis, enlarged lymph nodes containing inflammation instead of tumour, and in the assessment of the viability of previously treated lesions. In addition, CT has limited sensitivity for detection of spleen, liver and bone marrow involvement.

Whole body F-18 FDG PET has been proven to be a very effective imaging modality for staging of many malignant tumours. Because PET images have a fairly high resolution (6 mm), even small lesions with an increased F-18 FDG uptake can be detected[1]. It is known that morphologic imaging modalities miss a considerable number of tumour sites in both lymph nodes and organs. On the other hand, morphologic imaging modalities are used to evaluate a given region of the body rather than the entire body. Metastases outside the imaging field are missed. Whole-body PET scanning frequently can detect previously unsuspected distant metastases, thereby sparing incurable patients from futile treatment protocols[13]. Clinical-pathologic correlation studies and meta-analyses have confirmed that PET scanning provides much more accurate staging in malignancies than structural imaging alone[14].

Criteria for pathologic findings with F-18 FDG PET study in patient with lymphoma are unifocally or multifocally uptake in the regions of lymph node. Bone marrow or focal soft-tissue uptake beyond areas of normal FDG accumulation is abnormal. Splenic uptake may be either diffuse or unifocal or mutifocal in splenic lymphomatous involvement. The sensitivity of F-18 FDG PET for staging lymphoma, being in the range of 80-100%, was found to be at least as good as that of CT[15-22]. In the thorax and especially abdominal region, F-18 FDG PET proved to be superior to CT in staging malignant lymphomas. F-18 FDG PET also superior to CT for detection of extranodal lymphoma. In a study, investigating a group of 100 HL patients undergoing laparotomy, Munker et al, demonstrated that CT had a low sensitivity of only 37% for detection of splenic and similarly of liver involvement with HL[23]. Thill et al reported that F-18 FDG PET found 25%

more lesions in HD and NHL[24]. The staging by the bone marrow requires invasive biopsy and aspiration, but the sensitivity for detecting bone marrow disease is limited by sampling error. Although MRI appeares to be the most sensitive imaging technique, whole-body MRI is not practical as a screening test and should be reserved for areas that are of clinicall suspect[25]. PET is also suitable for identifying bone marrow involvement with a high positive predictive value and is more sensitive and specific than bone scintigraphy.

Monitoring of antitumour therapy is currently evaluated by sequential determinations of tumour size using morphologic imaging modalities (USG, CT, MRI). The definition of tumor response or progression, using anatomic imaging modalities, is based on size criteria and can not differantiate between active tumour and fibrosis. Despite the good response to therapy, residual mass can be demonstrated radiologically in up to 80% of patients with HD and in up to 40% of NHL patients after completion of treatment[26,27]. These residual mass may consist of fibrotic tissue or viable tumour. These modalities do not necessarily reflect the quantity of remaining viable tumour cells and residual tumour mass cannot be differentiated from scar. The interpretation of persistent residual masses detected by CT is a major clinical problem, especially in mediastinal and abdominal bulky disease. Although residual masses are usually considered to be persistant disease, a maximum of 18% of residual masses are found to harbor viable lymphoma after therapy[27]. MRI has not been able to fulfil the reliable distinction between malignant and fibrotic or necrotic lymphoma tissue[28,29]. The disease activity may have completely resolved after therapy, but residual mass persist on morphologic imaging. Tumour volume reduction measured by CT or MRI is only a late sign of effective therapy[30].

There is now considerable evidence that F-18 FDG PET after first line chemotherapy is very useful in assessing the significance of residual masses and identifies those patients with insufficient response to treatment and hance poor clinical outcome[11,29,31-33]. A positive study may indicate the need for additional radiotherapy or more aggressive second-line protocols, whereas a negative study may obviate unnecessary, potentially harmful treatment. In patients with a positive PET scan after chemotherapy an early relapse occurs in up to 100%, while more than 80% of patients with a negative PET will have a long-term remission. The overall review of the literature included 581 patients evaluated for recurrence, the sensitivity and specificity of FDG PET was 87% and 93%, respectively, compared with 92% and 10% for CT[34]. Most studies show that FDG-PET is significantly correlated with patient outcome whereas there is much weaker or even no correlation for CT. Cremerius et al have reported that F-18 FDG PET have significantly higher specifity and positive predictive value (PPV) than CT for assessing residual disease in 27 patients with lymphoma[11]. The specificity and PPV for PET were 92% and 94%, respectively, whereas for CT they were 17% and 60%, respectively. In other study by Naumann et al the prognostic value of F-18 FDG PET in the assessement of posttreatment residual masses was evaluated[35]. They studied 58 patients with HD or NHL who had posttherapeutic complete remission with residual masses indicated by CT. Patients with a PET-positive residual mass had a recurrence rate of 62.5% (5/8 patients), whereas patients with PET-negative residual mass showed a recurrence rate of only 4% (2/50 patients). No recurrence occurred in any of the 39 HD patients with a negative PET scan. They reported that a positive FDG-PET study correlated with a poorer progression-free survival ($p < 0.00001$). Both NPV and PPV were 100%.

In a study Spaepen et al, the value of a mid-treatment F-18 FDG-PET scan to predict clinical outcome in patients with aggressive NHL was assessed[36]. Seventy newly diagno-

sed patients with aggressive NHL, who were treated with doxorubicin-containing chemotherapy, underwent a F-18 FDG-PET scan at midtreatment. At midtreatment, 33 patients showed persistent abnormal F-18 FDG uptake and none of these patients achieved a durable complete remission (CR), whereas 37 patients showed a negative scan; 31/37 remained in CR, with a median follow-up of 1107 days. Only 6/37 patients either achieved a partial response or relapsed. These results suggest that early restaging F-18 FDG PET is an important prognostic factor to outcome a may be used to tailor induction chemotherapy in patients with aggressive NHL. In another study of Spaepen et al, after first line chemotherapy in 93 patients, 83.5% of patients with negative F-18 FDG findings remained in CR after a median follow up of 653 d[37]. Only 16% of patients had relapse of disease after negative F-18 FDG PET findings, with a median progression-free survival (PFS) of 404 d. In 26 patients, F-18 FDG PET showed persistent uptake, all of whom relapsed, with a median PFS of 73 d. According to the their results, persistent abnormal F-18 FDG uptake after first-line chemotherapy in NHL is highly predictive for residual or recurrent disease. In relapsing patients, PFS was significantly shorter after a positive scan than after a negative scan. Reske reported the results of analysed the 15 recently published studies reporting the results of differentiation of viable lymphoma from scar tissue in 723 patients[38]. Sensitivity of FDG-PET for detection of active disease was 71-100%, and the specificity was 69-100%. Accordingly, F-18 FDG PET had a high negative predictive value of 80-100%. In contrast, the specificity and PPV of CT were low (4-31% and 19-60%, respectively, except in one study in which the PPV was 82%).

Evaluation of response to therapy involves careful comparison of pre- and posttreatment F-18 FDG PET scans. Imaging 1-2 week after completion of therapy is recommended[39]. The relationship between radiotherapy and changes in tumour F-18 FDG uptake of tumour has yet not to be established[40,41]. Some data suggest that radiotherapy may induce early acute inflammatory hypermetabolism that can be confused with tumour hypermetabolism. A fair comprimise may be to recommend F-18 FDG PET imaging 4-6 months after completion of radiotherapy. This would allow for assessement of early recurrence. If inflammatory hypermetabolism is confusing, a follow-up scan may be required[42].

It is important to distinguish between responders to standard approaches and nonresponders who may benefit from an early change to an alternative treatment in patients with lymphoma. Early recognition of the resistance to chemotherapy can also result in lower cumulative treatment toxicity and tumour burden at start of salvage therapy. If F-18 FDG PET study is performed during the course of chemotherapy, images can be obtained as early as 1 or 2 cycles of therapy. Several studies reported that F-18 FDG PET could distinguish responders from nonresponders early into the chemotherapy or immunotherapy in patients with lymphoma[36,43-45]. Kostakoglu et al reported that F-18 FDG PET has a high prognostic value for evaluation of therapy as early as after 1 cycle in aggressive NHL and HD[45]. Ninety percent of patients with positive F-18 FDG PET findings after 1 cycle had disease relapse with a median PFS of 55 mo, whereas 85% of patients had negative PET studies remained in CR after a minimum follow-up of 18 mo. The PFS was significantly different between patients with positive and negative F-18 FDG PET studies after 1 cycle of treatment. Sensitivity, specificity, and accuracy of F-18 FDG PET for first cycle versus completion of chemotherapy were 82%, 85%, and 97%, respectively, versus 46%, 90%, and 70%, respectively. The authors concluded that the potential of F-18 FDG PET to predict outcome in patients with aggressive lymphoma and HD early during the therapy was most likely due to the sensitivity of these lymphomas to chemotherapy. These results are similar to others for early

chemotherapy assessment but dramatically lower for posttherapy assessment[37,46,47]. Romer et al have investigated extent and time course of changes in F-18 FDG uptake of tumour in response to chemotherapy at baseline and 1 and 6 week after the initiation of therapy. One week after, tumour F-18 FDG uptake decrease by 60%. A further decrease of 42% was observed at 6 week, resulting in a total decrease of 79% from baseline. As a result, standard chemotherapy of patients with NHL causes a rapid decrease of tumour F-18 FDG uptake as early as 1 week after treatment. Early characterization of chemosensitivity of lymphoma cells by F-18 FDG PET may direct further therapy and predict prognosis.

Imaging devices able to detect the annihilation radiation from positron emitters but unable to depict single-photon-emitting radionuclides are referred to as dedicated PET scanners. Because of the cost and limited availability of dedicated PET scanners, the new device called coincidence mode gamma camera for imaging F-18 FDG became commercially available. This innovation provides the opportunity to implement FDG PET studies in virtually any nuclear medicine department. F-18 FDG imaging in the coincidence mode may cause low contrast resolution as compared with images obtained using dedicated PET scanners[48]. There are several studies on F-18 FDG CI in lymphomas[45,49-51]. In general, the results of F-18 FDG coincidence imaging (CI) in tumours > 15 mm seem to be comparable to those of dedicated PET, while in tumours < 15 mm, the relative sensitivity of F-18 FDG CI is approximately 80%. However, most low-grade tumours with a diameter of less than 1 cm cannot be detected.

In hyperglycaemia, F-18 FDG competes with blood glucose, resulting in its decreased uptake in neoplastic cells. PET studies are performed when the subject is in a fasting state. The goal is to have low insulin and low blood sugar levels, preferably to less than 120 mg/dL. This optimises tumour uptake and minimizes F-18 FDG uptake into the skeletal muscle. Thus, a 4 to 12-hour fasting period is recommended for examining patients with FDG PET. The effect of diabetes on the uptake of FDG is not fully elucidated. It is known that steroids, in the majority of therapeutic approaches of malignant lymphoma, lead to lower F-18 FDG accumulation in malignant lymphoma than in the surrounding tissues, because of their antiinsulin effect of carbonhydrate metabolism. F-18 FDG uptake of the thymus may occur particularly after therapy, and can be misleading for the presence of mediastinal disease[52]. Enhanced marrow uptake of the F-18 FDG may be seen following chemotherapy, especially when marrow-stimulating drugs (such as colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, macrophage colony-stimulating factor) have been administered[53].

To date, no side effects due to F-18 FDG injection have been reported. The patient dose is 0.027 mSv/MBq administered, which is in the same magnitude of a CT scan or a bone scan[54].

Multiple Myeloma (MM)

In MM, traditional staging depends heavily on the extent of disease evident on a radiologic full skeletal survey. Radiographs can significantly underestimate the extent and magnitude of bone and bone marrow involvement[55]. MRI is extremely useful for assessing suspected disease sites but is cumbersome as a whole-body screening technique[56]. CT is also useful for evaluation of regional or focal disease[57]. MRI and CT frequently do not readily distinguish between active disease and scar tissue, necrosis, bone fracture, or benign disease. A reliable whole-body technique with both functional and morphologic information is necessary to identify the extent and activity of MM for staging and monitoring purposes.

Very little information is available regarding the diagnostic utility F-18 FDG PET in

MM[58-62]. Jadvar et al reported that F-18 FDG PET can detect early marrow involvement of MM and is useful in assessing the extent of active disease at the time of initial presentation and in evaluating treatment response. In evaluating of 9 patients, PET detected multiple hypermetabolic lesions in one patient with a negative bone scan and concordant positive skeletal radiographic survey[59]. F-18 FDG PET also detected a few early marrow lesions with subtle radiographic changes while all radiographically aggressive lytic lesions corresponded to intense hypermetabolism on PET. In three patients with both pre- and posttherapy FDG PET scans, PET demonstrated a favourable treatment response, by showing a decline in lesion metabolic activity (n= 1), or progression of disease, by showing development of new lesions or higher lesion glucose metabolism (n= 2), concordant with the clinical evaluation, while the other imaging studies showed no discernible interval changes. Orchard et al reported the F-18 FDG PET in three patients with MM, each representing a particular clinical situation in which this imaging modality offered advantages over plain radiography, CT or MRI[62].

In another study by Durie et al, F-18 FDG PET scans were obtained in 66 patients with MM and related monoclonal diseases, with 25 patients having 2 or more scans[60]. The results were compared with routine clinical and staging information, including CT and MRI scans. The 16 previously untreated patients with active myeloma all had focal or diffusely positive scan findings. Four (25%) of 16 previously untreated patients with positive F-18 FDG PET findings had negative full radiologic surveys. Another 4 (25%) of 16 patients had focal extramedullary disease. This was confirmed by biopsy or other imaging techniques. Extramedullary uptake also occurred in 6 (23%) of 26 patients with relapse. This extramedullary uptake was a very poor prognostic factor both before treatment and at relapse. For example, median survival was 7 mo for patients with disease relapse. Persistent positive F-18 FDG PET findings after induction therapy predicted early relapse. In 13 (81%) of 16 patients with relapsing disease, new sites of disease were identified.

Briefly, whole-body F-18 FDG PET reliably detects active MM. Residual or recurrent disease, especially extramedullary disease, after therapy detected by F-18 FDG PET, is a poor prognostic factor in MM. Although high-resolution CT and MRI have allowed the identification of myeloma sites in patients with negative radiography findings, F-18 FDG PET has the advantage of allowing whole-body screening as well as distinguishing between new active disease and old disease, scar tissue, necrotic tissue. It is likely that whole body F-18 FDG PET can usefully complement these imaging modalities in patients with MM.

GALLIUM-67 (Ga-67) SCINTIGRAPHY

The mechanism of Ga-67 uptake in the tumours remains incompletely understood and represents multiple mechanisms rather than a single one. Firstly, the arrival of Ga-67 in the interstitiel fluid space can be attributed to the increased permeability of newly formed vessels and increased vessel wall permeability accounts for the localisation of Ga-67 in tumour tissue[63]. In 1980, Hoffer postulated that Ga-67 is likely to bind several iron-binding serum proteins such as transferrin, ferritin and bacterial siderophages[64]. Larson et al postulated the transferrin receptor hypothesis[65]. Increased metabolic activity of the tumour cells requires high iron uptake, and that this requirement leads to an increased number of transferrin receptors. This would explain why Ga-67 uptake by tumour cells is enhanced. Ga-67-transferrin complex is incorporated into the vesicle by endocytosis, which migrates into the cytoplasm followed by fusion with lysosoms. Intracellular Ga-67 binds to cytoplasmic proteins (possibly bound to ferritin) and macromolecules within the organelles. Another postulated mechanism is lactoferrin theory. Lactoferrin is a macromolecule with a structure si-

milar to transferrin and present in lactating breast, neutrophil leukocytes, bone marrow, spleen and genital, salivary and nasopharengeal secretions[66]. Ga-67 is not specific for tumour. It also accumulate in the inflammatory processes. Due to the increased permeability of the vessel walls, high concentration of lactoferrin in leukocytes, direct bacterial uptake and some intracellular substance such as keratin poysulphate, Ga-67 accumulates in the inflammation site[67-70].

After administration into the vascular system, Ga-67 bound iron-binding serum proteins complex is taken up in the liver, skeleton, lachrymal and salivary glands and lactating breast. Around 20% of the Ga-67 activity is excreted in the first 24 hours by the kidneys. After 24 hours, Ga-67 is excreted in the bowel, with a half-life of 25 days[64]. Because Ga-67 is excreted in the colon, delayed imaging as late 10-15 day after administration may be necessary for evaluation of abdomen, allowing bowel activity to clear while pathologic uptake persist. For this purpose, laxatives are often used. Thymic uptake can occur, especially with thymic hyperplasia after chemotherapy or radiotherapy. It is not uncommon in children, may be in adults. In a study of children with NHL, 43% of the patients showed mediatinal uptake posttherapy in the absence of disease[71]. Ga-67 uptake of the thymus appeared 1 to 8 months following the end of chemotherapy and persisted for 2 to 59 months. Progressive widening of the mediastinum on chest x-ray is the cause for suspicion and requires further evaluation[72]. Enhanced salivary gland uptake after radiotherapy usually indicates radiation sialadenitis. Increased transferin saturation resulting from parenteral iron therapy can increase renal excretion and decrease activity in bone marrow and reticuloendothelial system[73]. The recent radiation or chemotherapy can temporarily decrease tumour uptake[74]. Ga-67 injection should follow chemotherapy by 1-2 week.

Ga-67 scintigraphy has been routinely and extensively used to evaluate the patients with lymphoma for more than 20 years. Ga-67 imaging has a role at the staging of lymphoma[28,75-80]. Because Ga-67 scanning provides whole body screening, it can identify extent of disease in a single examination. It is known that the sensitivity of the Ga-67 scintigraphy is higher in HD than that of NHL. Reported sensitivity is typically greater than 90% for HD and greater for 75% for NHL[81-83]. In NHL, gallium avidity correlates with histology and tumour grade. In low grade NHL, Ga-67 uptake is low compared with high grade and intermediate NHL. Small noncleaved cell and diffuse large cell lymphomas routinely demonstrate Ga-67 uptake[84]. The documentation of Ga-67 avidity of the tumour before treatment is necessary for meaningful scintigraphic follow-up after therapy. In patient with a nonavid tumour, Ga-67 imaging is not useful. Failure to establish the tumour's avidity before treatment can lead to misinformation if negative posttreatment Ga-67 imaging is interpreted as indicating the absence of disease[85].

Persistent abnormalities are identified on physical examination, chest radiography or CT, which cannot reliably distinguish fibrotic mass and residual lymphoma. Although MRI has limited ability to distinguish active tumour from fibrotic mass, Ga-67 scintigraphy can contribute to patient management primarily by detecting residual disease or relapse after treatment, monitoring response during therapy[86-88]. Being a viability agent, taken up by lymphomatous, but not by necrotic or fibrotic tissue, it is used to assess the nature of a residual mass after treatment. It is used with high sensitivity and specificity for diagnosis of recurrence after a continuous clinical remission, which is achieved after successful treatment. Disappearance or decreases of Ga-67 uptake after treatment usually corresponded to a disappearance or regression of the tumour as ascertained by other methods. When the treatment was shown to be ineffective, Ga-67 uptake persisted or even became more prominent. When during follow-up, a new concentration of

Ga-67 appeared at the original location or elsewhere, a relapse was extremely likely[28,82,88-91]. In a study by Zinzani et al, thirty-three patients with HD or high-grade NHL presenting with bulky mediastinal disease were studied with CT, Ga-67 scan, and MRI at diagnosis, after two-thirds of their chemotherapy, at the end of chemotherapy, and after radiotherapy[88]. After treatment, all patients with Ga-67 negative (30/33) disease are still in continuous complete response. Among the three Ga-67 positive patients, two relapsed within one year and another one is still alive without evidence of disease. Regarding MRI, two patients were found to be positive, one of them concomitant with Ga-67 positivity; both patients survived in complete response.

Ga-67 scan also predicts disease-free survival and overall survival after treatment. Ionescu et al assessed relapse and survival, and the predictive value of restaging gallium scan of patients with a residual mass on CT scan after induction chemotherapy in 53 newly diagnosed HD patients[90]. Ga-67 scan was performed after chemotherapy (3 or 4 courses) and always before consolidative radiotherapy. At median follow-up period of 36 months, freedom-from-progression rate was 86% versus 19% ($p< 0.0001$) for patients with negative vs. positive Ga-67 scans, respectively. The five-year overall survival rate was 68% and higher in negative Ga-67 scanning groups (91%) than that of positive (25%). The specificity of Ga-67 scanning was 91% and the sensitivity 72% with a PPV of 81% and a NPV value of 86%. They reported that the evaluation with Ga-67 scan after induction chemotherapy identifies chemosensitive patients among those with poor-prognosis mediastinal HD. Although relapse may occur in patients with negative Ga-67 scan, a positive Ga-67 scan is highly predictive of failure and poor outcome, and treatment should thus be modified. In another study by King et al, assessing the prognostic importance of restaging Ga-67 scans following induction chemotherapy for advanced Hodgkin's disease, the four-year actuarial relapse-free survival rate was 75% for patients with negative restaging gallium scans compared with 8% for those with positive restaging scans ($p< 0.001$)[92]. The four-year actuarial overall survival rate was 100% for those with negative scans compared with 51% for gallium-positive patients ($p= 0.001$). The negative and positive predictive values for Ga-67 scanning are 92% and 90%, respectively, compared with values of 48% and 83% for CT scanning. According to the their results, Ga-67 scanning is clearly superior to CT in this regard. Patients with advanced HD who have positive restaging Ga-67 scan after induction chemotherapy should be classified as induction failures and are highly unlikely to be cured with involved-field low-dose radiotherapy.

Israel et al have reported that Ga-67 scintigraphy demonstrates early the effect of treatment in patients with aggressive NHL and it is a better predictor than pretreatment risk factors of both response rate and failure-free survival[93]. Positive Ga-67 early during treatment may be used as an independent test in selecting patients who will not respond favourably to current protocol treatment for early therapeutic modifications[93].

Gastric lymphoma of mucosa-associated lymphoid tissue (MALT) is by far the most common extranodal primary NHL. Gastric MALT lymphoma can be classified as low-grade (LG) or high-grade (HG). Low-grade gastric MALT lymphoma can be cured by eradication of *Helicobacter pylori*; but radiotherapy and/or chemotherapy and/or surgery are the major methods of treatment for the HG gastric MALT lymphoma. However, it is difficult to differentiate these two groups by clinical parameters and endoscopic findings. Hsu et al assessed the value of Ga-67 scintigraphy in differentiating the LG gastric MALT lymphoma from the HG gastric MALT lymphoma[94]. In the LG group, nine patients had negative results and three patients had positive results. In the HG group of nine patients, all

patients had positive results. They have reported that the Ga-67 scintigraphy is of good clinical value for the differentiation of the LG gastric MALT lymphoma and the HG gastric MALT lymphoma.

Although the suboptimal photon energy of Ga-67 leading to noisy images, limited detection of abdominal disease secondary to marked physiologic hepatic and colonic activity and multiple visits to the imaging facility on concecutive days, the Ga-67 scan remains the preferable imaging technique for monitoring and differentiating the eventual active residual tumour in patients with lymphoma. However, the introduction of F-18 FDG PET, which provides images of superior quality, may have an impact on the current role of Ga-67 scanning in the management of patients with lymphoma[51,80,95-98]. F-18 FDG-PET seems to share with Ga-67 scan the advantages of a tumour viability agent. It appears to be more sensitive for detecting nodal and extra nodal sites of disease than Ga-67 scan and may have predictive value during and after therapy for lymphoma[95]. Shen et al reported that F-18 FDG PET had a higher sensitivity and detected significantly more disease sites when compared with Ga-67 scintigraphy in the initial evaluation of this group of patients[98]. In their study, before any therapy, 25 contemporaneous F-18 FDG PET and Ga-67 scintigraphies were performed on patients with either NHL (n= 16) or HD (n= 14). The sites of disease were correlated on a site-by-site basis in corresponding areas of F-18 FDG PET and Ga-67 scintigraphy. Discordant F-18 FDG PET and Ga-67 scintigraphic findings were correlated with CT/MRI and clinical evaluation. F-18 FDG PET detected malignant lymphoma in 24/25 patients with sensitivity of 96% and Ga-67 scintigraphy detected malignant lymphoma in 18/25 patients with sensitivity of 72%). F-18 FDG PET upstaged 6 patients in whom Ga-67 scintigraphy detected disease sites partially. In a study by Kostakoglu et al., the accuracy of F-18 FDG CI and Ga-67 scintigraphy was compared to identify disease sites in patients with HD and intermediate and high-grade NHL at initial diagnosis or clinical recurrence[80]. Sites of disease were correlated on a site-by-site basis on FDG CI and Ga-67 images. F-18 FDG CI was positive at all 158 sites in 51 patients compared with 113 sites in 41 positive studies with Ga-67 scintigraphy. Ga-67 scans failed to demonstrate disease at 45 sites (35.7%). F-18 FDG CI revealed higher stage disease in 13 patients compared with Ga-67 imaging. Authors have reported that FDG CI has significantly higher site and patient sensitivity than Ga-67 scintigraphy in imaging aggressive lymphoma and HD before therapy (100% vs. 71.5% and 100% vs. 80.3%, respectively). Rini et al have reported that, in newly diagnosed Hodgkin's disease, F-18 FDG PET accurately diagnoses splenic involvement and is significantly more sensitive and accurate than Ga-67 for this purpose[97]. While reported sensitivity, specificity, and accuracy for F-18 FDG were 92%, 100% and 97%, respectively, 50%, 95%, and 78% for Ga-67, respectively. In addition, whole body F-18 FDG PET has several advantages over whole body Ga-67 imaging. Imaging can be started 1 h after injection of the tracer, allowing for rapid reporting. Whole-body F-18 FDG PET images are obtained within 60 min, with clearly superior image quality and resolution compared to whole-body tomographic gallium images. F-18 FDG has better tracer kinetics because the F-18 FDG molecule is much smaller than the relatively large Ga-67 transferrin complex, leading to higher lesion-to-background ratios at early time points. Contrary to gallium scanning, there is low uptake of the F-18 FDG in the liver, the abdomen and the bone marrow, resulting in optimal imaging conditions. Moreover, the radiation dose to the patient is lower.

Tc-99m-MIBI IMAGING

Tc-99m-2-hexakis-2-methoxysobutylisonitrile (Tc-99m MIBI) is a lipophilic and cationic radiopharmaceutical initially, proposed as a Tl-201 substitute for myocardial ima-

ging but during their worldwide application for myocardial scintigraphy they were accidentally found to accumulate in tumours. Although exact uptake mechanism has not been completely elucidated, experimental in vitro studies consistently show that the mechanism of Tc-99m MIBI uptake in cultured tumour cell lines is characterised by a marked binding to mitochondria and a potential-dependent transmembrane distribution[99,100]. The concentration of Tc99m-MIBI in tumour cells is a function of a passive, membrane potential-dependent influx into the cell, and a reversible accumulation within mitochondria of both normal and malignant cells. Carvalho et al found that approximately 90% of Tc-99m MIBI activity occurs within the mitocondria[101]. Lipophilic properties of Tc-99m MIBI facilitate diffusion through membranes, while the positive charge leads to their concentration at negative membrane potentials[102-104]. Since 1987, detecting the accumulation of Tc-99m MIBI in lung metastases of a thyroid carcinoma during cardiac imaging by Müller et al, Tc-99m MIBI has been used in clinical practice for detection of various tumour including breast, brain, thyroid, bone tumours and MM[105-110].

The ability of cancer cells to become simultaneously resistant to multiple classes of chemotherapic drugs that can be structurally and mechanistically unrelated, a trait known as multidrug resistance (MDR), remains a significant impediment to successful chemotherapy. Classical MDR regards altered membrane transport that results in lower cell concentrations of cytotoxic drug and is related to the over expression of a variety of proteins that act as ATP-dependent extrusion pumps[111]. P-glycoprotein (Pgp), encoded by the MDR1 gene, is an energy dependent plasma membrane efflux pump, which actively transports a variety of drugs and substances out of cells. Because of the a number of anti-cancer drugs are recognized as substrates by Pgp, a member of the ATP-binding cassette family of transporters, which is overexpressed in resistant tumours and actively extrudes a variety of compound from cells, many chemotherapeutic regimens may become ineffective in patients with acute leukaemia[112]. Identification of the presence of the MDR1 phenotype at an early stage, preferably before beginning cytotoxic chemotherapy, could lead to therapeutic strategies to circumvent or overcome it, such as modulation by various inhibitors or use chemotherapeutics not involved in MDR1 phenotype.

The quantity of uptake of Tc-99m MIBI in tumour cells is a function of a passive, membrane potential-dependent influx into and a P-glycoprotein-controlled efflux out of the tumour cell. The efflux rate Tc-99m MIBI was found directly correlated with Pgp levels in untreated breast cancer patients and the enhanced tracer efflux predicts lack of tumour response to neo-adjuvant therapy in patients with locally advanced breast cancer[113,114]. Several studies have indicated a potential use of Tc-99m MIBI for in vivo identification of the MDR1 phenotype in patients with solid tumours[115-118].

Assessing the drug resistance of leukaemia cells and therefore, prospective identification of patients with MDR1 phenotype is also important for treatment of leukaemia. Tc-99m-MIBI bone marrow imaging, as a functional imaging, can give in vivo information about the functional expression of MDR phenotype in patients with leukaemia[119-122]. Gruber et al have reported that Tc-99m MIBI with a high sensitivity can detect rather low levels of MDR1 gene expression in clinical samples[111]. In their study, the leukaemic cells from ten patients with acute myelocytic leukaemia were used, 5 with undetectable MDR1 gene expression and 5 with MDR1. The median Tc-99m MIBI accumulation (% of added radioactivity) is higher in MDR1-negative cells than that of MDR1-positive cells (0.89% and 0.34%, respectively, p= 0.01). In another study, Kostakoglu et al reported an inverse correlation between the levels of Pgp

and Tc-99m MIBI imaging in patients with haematological malignancy[120]. In our a recent study, we assessed the relationship between the degree of Tc-99m MIBI uptake of bone marrow and the level of Pgp expression determined by flow cytometry to demonstrate a prospective identification of patients with MDR1 phenotype in patients with leukaemia[122]. A total of 26 patients with newly diagnosed and un-treated leukaemia were included the in the study. Flow cytometry was performed for determining the Pgp expression of the blast cells in the bone marrow aspiration samples. There was a statistically significant inverse relationship between the Pgp level in numeric values and Tc-99m MIBI uptake of bone marrow. These data indicate that an increased level of Pgp expression is correlated with a low accumulation of Tc-99m MIBI in bone marrow of patients with leukaemia.

Multiple myeloma is an immunoproliferative disease characterized by infiltration of monoclonal plasma cells in the bone marrow compartment, suppression of normal haematopoiesis. The prognosis of patients has improved since the introduction of new therapeutic approaches; however, MM is still a fatal malignancy. The percentage of myeloma cells in bone marrow is subsequently an important index of disease in patients with MM. Specific and reliable laboratory examinations are required to evaluate its aggressivity and extent[123]. Fonti et al showed the localization of Tc-99m MIBI inside the plasma cells infiltrating the bone marrow by micro-autoradiography. They also found a positive and significant correlation between tracer uptake values obtained in each patient and the percentage of plasma cell infiltration ($r= 0.66$, $p< 0.0001$). In our recent study, we assessed the relationship between degree of Tc-99m MIBI uptake and the percentage of CD38/CD138 expressing myeloma cells in the bone marrow of patients with MM[124]. The uptake of Tc-99m MIBI in the bone marrow was evaluated using a qualitative and also a semiquantitative scoring for the bone marrow in areas that included the proximal femurs, anterior iliac crest and sternum. The percentage of CD38/CD138 expressing myeloma cells in bone marrow ranged from 5% to 85%, with a mean value of 48%. There were a statistically significant positive correlation between the percentage of CD38/CD138 expressing plasma cells in bone marrow and both mean qualitative ($r= 0.689$, $p= 0.005$) and semiquantitative ($r= 0.669$, $p= 0.006$) results of Tc-99m MIBI uptake. A significant positive correlation was also found between the results of Tc-99m MIBI imaging and the various activity markers of disease including erythrocyte sedimentation rate, β_2-microglobulin and C-reactive protein levels. Alexandrakis et al have also reported a positive correlation between Tc-99m-MIBI intensity and C-reactive protein, erythrocyte sedimentation rate, β_2-microglobulin, interleukin-6 (IL-6), soluble IL-6 receptor, serum calcium and bone alkaline phosphatase[110]. According to the their results, more extensive disease activity, as determined by high levels of CRP, β_2M, IL-6 and sIL-6r correlated with a higher uptake of the Tc-99m MIBI.

In another study, Pace et al have evaluated the incidence of various patterns of diffuse Tc-99m MIBI uptake in patients with MM, to assess their relationship with clinical status and stage of disease, and to try to clarify the meaning of the diffuse bone marrow uptake of Tc-99m MIBI[125]. According to the their result, presence of focal uptake or intense diffuse bone marrow uptake suggests that the patient has active and advanced stage disease, while a negative scan in a patient with MM clearly indicates remission. Several studies showed that focal myeloma bone lesions are detected with great sensitivity and sensitivity by localised increased uptake o Tc-99m MIBI, compared with conventional radiological procedures[126-129]. A study carrying out in 46 myeloma patients (15 at diagnosis, 14 during conventional chemotherapy, and 29 following high-dose sequential therapy and autologous peripheral blood progenitor support) Tc-99m MIBI scans recognized

a higher number of myeloma lesions at diagnosis[128]. MIBI scans remained positive in all patients during conventional chemotherapy, and there was a direct correlation between MIBI result and clinical outcome of patients following high-dose therapy. A diffuse MIBI pattern reflected a higher bone marrow plasma cell number. Histologically or cytologically verified soft tissue myeloma lesions were correctly diagnosed by MIBI scans, while all plain radiographs showed none of them.

As a result, Tc99m-MIBI bone marrow imaging may be a useful tool for predicting the levels of myeloma cells in bone marrow in diagnosis, evaluating the therapy response and monitoring of patients with MM. Tc-99m MIBI scintigraphy can detect bone marrow lesions in myeloma patients that cannot be detected by other imaging methods and that it can be useful especially in solitary myeloma to exclude other involved sites.

RADIOLABELLED SOMATOSTATIN RECEPTOR SCINTIGRAPHY

The somatostatin receptor (SSTR) scintigraphy is a sensitive and specific technique to show in vivo the presence and abundance of somatostatin receptors on various lesions. SSTR is a member of the superfamily of the G protein-coupled receptors. These are the surface receptors consisting of a chain of polypeptides with seven membrane-spanning domains. Somatostatin binding activates the inhibitory G protein followed by the inhibition of the stimulating adenylyl cyclase and a decrease in cAMP production[130]. These receptors are distributed in various quantities over many tissues such as in the several regions of the brain, anterior pituitary, the gastrointestinal tract, the adrenals, the pancreas, the thyroid and the kidneys. In general, various SSTRs remain present on malignant cells originating from tissue, which normally contains these receptors. Furthermore, tumours express these receptors in greater densities than normal tissue. The antiproliferative effects of the somatostatin are also mediated via SSTRs expressed on tumours as well as on normal tissue. Even tough almost all neuroendocrin tumours are well endowed with SSTRs; these receptors are also expressed to a varying degree in many common tumours[131]. The advent of molecular biology has showed a variable expression of SSTR on the various T and B-cell lines or lines deriving from lymphoma/leukaemia and human myeloma. Using autoradiographic studies, SSTR have been predominantly found in lymphoblastic areas of lymphoma, which represent the active part of the tumour. SSRTs are also present on activated lymphocytes, in inflammation and granulation tissue, sarcoidosis, tuberculosis, Grave's disease, Hashimoto's thyroiditis[132].

In order to visualise somatostatin receptor-containing tumours, a long-acting somatostatin analogue was required since the native somatostatin has a half-life in circulation of only 3 minutes[133]. Bauer et al developed the synthetic peptide octireotide, a somatostatin analogue[134]. This analogue, labelled with I-123, has been used for the scintigraphic detection of tumours containing SSTRs. Although tumours have been successfully detected, this radioactive agent has some drawbacks. I-123 Thy-octitreotide is rapidly cleared by the liver and biliary system, this results in accumulation of the radioactivity in the liver and the intestines. In vivo degradation and the short physical half-life are the other disadvantages[135]. Although all the native somatostatins bind the SSTR with high affinity, synthetic analogues have a tendency to bind the SSTR1 to SSTR5 with different affinities[136]. The most commonly used somatostatin analogues, octireotide, lanreotide and vapreotide, and its radiolabelled variants interact mainly SSTR2 and SSTR5[131]. In-111-DTPA-D-Phe1-octreotide (Octreoscan, Mallinckrodt Medical, St Louis, MO) and Tc-99m-detreotide (Neotect, Diatide, Inc, Londonberry, NH) is currently approved and avaible for clinical use in the United States. Octreoscan is increasingly widely used. Neotec is much less used and limited mainly to detect pulmonary neoplasms not detected by Octreoscan.

Normal scintigraphic features include visualisation of the thyroid, spleen, liver, kidneys and the pituitary gland. Also, urinary bladder and the bowel are usally visualised. The visualisation of the thyroid, spleen and pituitary gland is due to the receptor binding. There are some drawbacks in interpretation of SSTR scintigraphy. The intensity of uptake is more related to the density of receptors present in the tumour and also in the peritumoural blood vessels than actual tumour size. Furthermore, loss of receptors may occur after dedifferentiation of tumour cells or after chemotherapy. Thus, a negative scintigraphy could falsely suggest tumour regression[132]. Another problem is the uptake of radioligand by inflammatory, nonneoplastic conditions.

In a study by Lugtenburg et al, the results of SSTR scintigraphy in 126 untreated patients with HD were compared with those of physical and radiological examinations[137]. SSTR scintigraphy was positive in all patients. The lesion-related sensitivity was 94% and varied from 98% for supradiaphragmatic lesions to 67% for infradiaphragmatic lesions. It provided superior results for detection of HD localisations above the diaphragm in comparing with CT and USG. Fifteen of 63 patients (18%) in stage I and II upstaged to stage III and IV after SSTR scintigraphy. In the intraabdominal region, the CT scan was more sensitive than the SSTR scintigrahpy. In another study of these authors, SSTR scintigraphy was compared with conventional staging procedures for the initial staging of patients with low-grade NHL[138]. Fifty consecutive untreated patients SSTR scintigraphy findings were positive in 42 of 50 patients (84%). In 10 patients (20%), the SSTR scan revealed new lesions that had not been revealed by conventional staging procedures. These 10 patients were all upgraded to a higher stage. Consequently, the treatment plan would have been altered in 5 patients (10%). However, in 19 patients (38%), lesions apparent after conventional staging methods were missed by SSTR scintigraphy. The sensitivity of SSTR scintigraphy varied from 62% for supradiaphragmatic lesions to 44% for infradiaphragmatic lesions. They reported high specificity (98-100%).

These data support that SSTR scintigraphy as an imaging technique for the staging of patients with lymphoma. Although SSTR scintigraphy findings are positive in a large proportion of patients with low-grade NHL, it is recommended that SSTR scintigraphy for initial staging of patients with low-grade NHL only in selected conditions and not for the general work-up.

RADIOIMMUNOTHERAPY

Up to now only myeloablative therapy followed by allogeneic stem cell transplantation can potentially cure patients with poor-risk relapsed low-grade NHL[139]. Radioimmunotherapy (RIT) is a new and apparently successful treatment modality for B-cell-NHL, particularly low-grade or transformed forms of this disease. Ongoing trials of immunotherapy and RIT continue to show excellent response rates in patients with relapsed or refractory NHL and remarkably favourable safety and toxicity profiles[140-143].

In the basic concept of the RIT, the cytotoxic radiation from therapeutic radioisotopes is delivered to tumours via antibodies that bind to tumour-specific or tumour-associated antigens. The antibodies often function as vehicle that carry the therapeutic radioisotopes to the tumour and have a cytotoxic effect of their own mediated by apoptosis, antibody-dependent cell- mediated cytotoxicity and complement-dependent cytotoxicity[144-147]. One obvious advantage of RIT compared with treatment with unconjugated anti-B-cell NHL mAbs, addition to both biologic and immunologic mechanisms of antitumour effects of these mAbs, the effects of targeted radiation play a role in the antitumour responses observed[148,149]. Another advantage is that with RIT, there is no need to target every tumour cell with a particular Ab to cause an antitumour effect at the cellular le-

vel. Even antigen-negative nontargated cells can be irradiated and killed by radiation from targeted neighbouring cells. This is not the case with unconjugated Abs, where each particular tumour cell must be targeted with the Ab for the antitumour effect to occur at the cellular level[150].

The goal of RIT is to target radiation to tumour tissue with radiolabelled monoclonal antibodies while limiting toxicity to normal cells. Radionuclide emission properties and the chemical stability of radioimmunoconjugates are important factors that contribute to the effectiveness of RIT. Radionuclides suited for RIT usually emit ß radiation for irradiation of the tumour. It is preferable for the radionuclide also to emit low-energy γ radiation in order to allow scintigraphic imaging. The promise of RIT of B-cell NHL became apparent after the 1987 report of DeNardo et al of the first patient treated with RIT[148]. They are used an I-131 labelled anti-B-cell lymphoma mAB. I-131 was the main radionuclide used for RIT, for decades. However, the physical properties of I-131 such as relatively low-energy ß radiation and high-energy γ radiation are not ideal for RIT. On the other hand, I-131 has some advantages including its low cost, the relatively simple radioiodination methods avaible for antibody labeling and the ability to obtain image of organ and tumour biodistribution with I-131 labeled mAbs, before or after RIT. Nevertheless, the results of RIT in patients with NHL with I-131 labelled antibodies have been very promising[151-153]. Rhenium-186 (Re-186) is another radionuclide suitable for RIT[154]. It has both ß- and γ-radiation. Low energy γ-radiation of Re-186 is ideal for imaging. Copper-67 (Cu-67) can also be chosen RIT[155,156]. Unlike some other radiometals, Cu-67 is not deposited in the skeleton or bone marrow. Because of the limited avaibility, it is not widely used. Another approach is the use of the α emitting radionuclides. Alpha paticles have a very limitted range in tissue (micrometres instead of millimetres). Bismut-213 (Bi-213) is used for RIT in patient with acute myelogenous leukaemia at Memorial Sloan-Kethering Cancer Center, New York[157]. Because of the very short range of the α particles, α-emitters not very suitable for treatment of bulky disease (in NHL) but could be useful for in micrometastatic disease[158]. Y-90 is now being used increasingly to radiolabel various mAbs. Because Y-90 is a pure ß emitter, there is negligible radiation exposure to treating personnel or relatives and outpatient's therapy can be performed even with very high doses of Y-90[159].

Two distinct approaches of RIT are used to deliver radioactivity to tumour: Nonmyeloablative low dose and the myeloablative high dose RIT approach[147,150]. In the nonmyeloablative approach, the radionuclides dose given does not result in the bone marrow ablation. Myelosuppression occurs two-three week after RIT and full recovery usually before 12 week after RIT. Only minimal nonhematologic toxicity is observed this approach. In myeloablative RIT, higher amount of radioactivity are administered[160]. This approach requires a haematopoietic, usually autologous, stem-cell transplant with peripheral blood stem cells or bone marrow. Significant second-organ toxicity is observed such as hepatic, gastrointestinal and at highest doses, also cardiopulmonary[160,161].

The Food and Drug Administration has approved Y-90 ibritumomab tiuxetan anti-B-cell NHL mAb (Zevalin; IDEC Pharmaceuticals) as the first commercially available radiolabelled antibody for cancer therapy in February 2002. It is a murine IgG1 kappa monoclonal antibody conjugated to tiuxetan (MXDTPA) that chelates Yytrium or indium and is directed against the CD20 molecules of B-lymphocytes[162]. This comes only a few years after the introduction of rituximab (Rituxan; IDEC Pharmaceuticals) into clinical practice as the first unconjugated antibody for cancer treatment, underscoring the success of both immunotherapy and RIT in the treatment of NHL. Zevalin contains a pure ß-emitting isotope; no protective patient or

staff isolation procedures are required. Toxicity is primarily haematological, transient, and reversible[163].

Several pilot and phase I/II trials have been reported using various radiolabelled mAbs directed against B-cell NHL[40,148,149,153,160,161,164]. Well-controlled phase II and III trials involving hundreds of patients have established its efficacy in these patients, ranging from the previously untreated to those refractory to chemo- and immunotherapy. In a phase III randomised study by Witzig et al, the novel radioimmunotherapy Y-90 ibritumomab tiuxetan was compared with a control immunotherapy, rituximab, in 143 patients with relapsed or refractory low-grade, follicular, or transformed CD20 (+) transformed NHL[142]. Patients received either a single intravenous dose of Y-90 ibritumomab tiuxetan 0.4 mCi/kg (n= 73) or rituximab 375 mg/m^2 IV weekly for four doses (n= 70). RIT Y-90 ibritumomab tiuxetan was well tolerated and produced statistically and clinically significant higher overall response rate and complete response compared with rituximab alone. Ma et al have reported that 90Y-labeled anti-CD19 antibody has efficacy comparable to 90Y-labeled anti-CD20 antibody in the treatment of mice bearing human lymphoma xenografts[140]. These data suggest that CD19-targeted RIT merits further study.

As a result, RIT has emerged as an important treatment modality for B-cell-NHL, particularly low-grade or transformed forms of this disease. Although many phase III trials have led to the introduction of RIT for B-cell NHL into clinical practice, new clinical trials will be needed to establish the role for this treatment modality in the standard management of B-cell NHL patients.

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Address for Correspondence:

İlknur AK, MD

Department of Nuclear Medicine
Osmangazi University Medical Faculty,
Eskişehir, TURKEY