Review

New diagnostic imaging procedures in Hodgkin's disease

M. Bangerter,1 M. Griesshammer,1 T. Binder,1 M. Hafner,1 H. Heimpel,1 S. N. Reske2 & N. Frickhofen1

1Department of Internal Medicine III and 2Department of Nuclear Medicine, University of Ulm, Germany

Summary

A variety of new diagnostic imaging methods have been developed in recent years for patients with Hodgkin's disease in an attempt to improve the detection of spleen and bone marrow involvement within the scope of staging and to discriminate between fibrosis and vital lymphoma after treatment.

Somatostatin receptor scintigraphy has been performed only in a small number of patients to date and further studies must be conducted. Magnetic resonance imaging (MRI), as the established method, has shown its potential in several studies in detecting both spleen and bone marrow involvement; MRI investigations, however, only visualize a limited portion of the body and therefore must be performed in areas of clinically suspected disease. Immunoscintigraphy with radiolabeled antibodies is still in a preclinical or at most early clinical stage of evaluation and first results have to be confirmed in a controlled trial. Positron emission tomography (PET) with $^{18}$F-fluorodeoxy-glucose (FDG) is a technique which is still not a routine clinical procedure. However, whole-body FDG-PET seems to be a promising method in staging and follow-up of lymphoma, because it offers the unique capability of visualising metabolic activity throughout the entire body. Long-term multicenter studies are necessary to confirm these promising initial data. In the future, whole-body FDG-PET will probably be the technique of choice for immunoscintigraphic studies with radiolabeled monoclonal antibodies and studies on the pharmacokinetics of cytostatic compounds.

Key words: imaging procedures, immunoscintigraphy, MRI, positron emission tomography, somatostatin receptor scintigraphy

Introduction

Accurate anatomic staging in newly diagnosed Hodgkin's disease is essential for determining appropriate treatment and prognosis. Over the last twenty years, staging of Hodgkin's disease has been based on the Ann Arbor classification [1]. This classification utilizes the spread of Hodgkin's disease as evaluated by imaging methods and biopsies. For this purpose a variety of techniques are available: non-invasive imaging methods such as plain film radiography, lymphography, computed tomography and ultrasound; and invasive methods, such as bone marrow biopsy, biopsy of enlarged lymph nodes and staging laparotomy.

In approximately one-third of the patients initially presenting with apparently localized supradiaphragmatic disease by non-invasive methods, infradiaphragmatic involvement is discovered by laparotomy [2]. Splenic involvement remains largely undetected using ultrasound and computed tomography [3], due to poor sensitivity (33%) and specificity (76%) [4]. As a consequence of these low accuracy rates, many patients with Hodgkin's disease require invasive staging laparotomy with splenectomy.

A number of studies have demonstrated that knowledge of bone marrow involvement is important for planning treatment, especially in patients with early stage disease [5]. It must be kept in mind, that bone marrow biopsies from the posterior iliac crest represent only an extremely small sample of the total marrow volume and Hodgkin's disease is characterized by a focal bone marrow involvement.

Treatment of Hodgkin's disease frequently results in residual masses detected radiologically. The reported incidence varies between 12% and 88% [7]. Some of these patients will have been cured of their disease, while others have residual active lymphoma. So far, computed tomography remains unable to determine whether a residual mass represents merely fibrosis or active lymphoma.

In an attempt to improve the detection of spleen and bone marrow involvement and to discriminate between fibrosis and vital lymphoma after treatment, new diagnostic imaging procedures have been developed in recent years. The following article will review these new diagnostic imaging methods and point out their potential in the management of patients with Hodgkin's disease.

Somatostatin receptor scintigraphy

The presence of high-affinity somatostatin receptors has been demonstrated in a variety of endocrinologi-
cally active neoplasms (carcinoids, pheochromocytomas, medullary thyroid carcinomas) and subsequently used for in vivo and in vitro detection of these tumors [8]. Recently, somatostatin receptors were also found in Hodgkin’s and non-Hodgkin’s lymphomas [8]. Somatostatin receptor-positive tumors can be visualised in vivo by gamma-camera scintigraphy after injection of $^{123}$I- or $^{111}$In-labeled octreotide analogs.

Studies utilizing somatostatin receptor scintigraphy in Hodgkin’s disease are rare and only a small number of patients have been studied. The majority of studies were performed in patients with non-Hodgkin’s lymphoma [9–11]. Bares et al. [9] state that somatostatin receptor scintigraphy with $^{111}$In-labeled octreotide is useful for the detection of supradiaphragmatic manifestation of lymphoma. The majority of infra diaphragmatic lesions remained undetectable in their study because of the superposition of high radioactivity concentrations in the spleen, kidney, liver and bowel. In their study, somatostatin receptor scintigraphy was compared to positron emission tomography (PET) and $^{18}$F-labeled deoxyglucose (FDG). FDG-PET provided a better tumor contrast and higher detection rate. Single photon emission computed tomography (SPECT) would probably have improved image quality; however, at the present time, SPECT is not practical in a clinical setting because an extended acquisition time of 30–60 min per body area is needed.

**Magnetic resonance imaging (MRI)**

Magnetic resonance imaging (MRI) is an imaging technique that avoids patient exposure to radiation, but it is contraindicated in patients with pacemakers due to the use of magnetic fields. This method has the potential to detect organ infiltrations, which appear as changes in calculated relaxation times. MRI, if performed as part of the staging for lymphoma, is clearly useful in demonstrating enlarged lymph nodes, and is quite comparable to computed tomography [12].

As mentioned above, the sensitivity of ultrasound and computed tomography in detecting involvement of the spleen in Hodgkin’s disease is quite low (33%). The availability of MRI allows the detection of parenchymal focal disease localized chiefly in the spleen, as has been shown in a number of reports [13, 14]. Weissleder et al. [13] used superparamagnetic iron oxide as a contrast agent for MR to distinguish normal spleens from those diffusely infiltrated by lymphoma (four patients with Hodgkin’s disease). Superparamagnetic iron oxide changed MR signal intensity unambiguously in their study and they identified eight of eight lymphomatous spleens and 25 of 25 normal or enlarged spleens, that did not contain lymphoma.

An additional interesting application of MRI is its use in evaluating bone marrow involvement. Hodgkin’s disease has the potential of spreading in the bone marrow with focal deposits. It is obvious, that the small samples obtained at bone marrow biopsy may not be representative.

Preliminary data have shown that MRI appears to be a sensitive technique for the detection of bone marrow involvement in patients with Hodgkin’s disease [15–19], although to date no prospective randomized study in a consecutive group of newly diagnosed patients with Hodgkin’s disease has been performed to determine its accuracy and clinical effectiveness.

To our knowledge, only one study has used ‘whole-body’ MRI for staging patients with Hodgkin’s lymphoma (39 patients) [20]. Tesoro-Tess et al. [20] evaluated 39 previously untreated patients with chest, abdominal and pelvic MRI for initial staging. Sensitivity in this study for detecting spleen involvement was relatively low (60%). However, the number of patients with histologically confirmed spleen involvement was small. MRI assessment of bone marrow demonstrated good overall accuracy (83%). The high rate of diagnostic errors in younger patients was probably due to the presence of areas of large amounts of red marrow, which might slightly decrease the signal of MRI, thus simulating the presence of lymphoma. MRI findings influenced the staging in 15% of these patients. However, ‘whole-body’ MRI is not practicable in a clinical setting.

The mediastinum is frequently the site of residual tumor masses after treatment, especially in Hodgkin’s disease. Used for the evaluation of residual masses, MRI is able to differentiate between residual tumor activity and fibrosis [21–23]. Sensitivity ranges from 45% to 93% in assessing the activity of residual tumor, specificity from 0% to 90%. Hill et al. [21] evaluated the role of MRI compared with gallium-67 single-photon emission CT ($^{67}$Ga SPECT) in predicting relapse in residual masses after treatment in 21 patients with Hodgkin’s lymphoma. This study reported a high specificity (90%) but poor sensitivity (45%) in predicting relapse. The results for $^{67}$Ga SPECT were similar, apart from lower sensitivity (33%). The problems seen by Hill in the interpretation of signals were low-volume masses as well as postirradiation changes.

**Immunoscintigraphy**

Numerous publications have shown the potential interest of immunoscintigraphy in the management of patients with cancer, in particular gastrointestinal and ovarian malignancies, as well as melanomas [30]. Especially in colorectal and ovarian carcinoma there is strong evidence that immunoscintigraphy is able to detect recurrence up to several months earlier than other noninvasive methods such as computed tomography and MRI [31].

Several studies have dealt with radiolabeled monoclonal antibodies in lymphoma [32–35]; however, the number of patients with Hodgkin’s disease is low. In a report of 6 patients with advanced Hodgkin’s disease published by Falini et al. [32], in vivo binding of
131I-labeled Ber-H2 (CD 30) as monoclonal antibody to Hodgkin and Reed–Sternberg cells was assessed by immunohistological analysis of tumor biopsies and immunoscintigraphy. Only 50% of tumor sites were imaged by scintigraphy with 131I-labeled Ber-H2, although immunohistological studies showed Hodgkin and Reed–Sternberg cells in all tumor sites. In the study of Carde et al. [33], eight patients were injected with the monoclonal antibody HRS-1 radiolabeled with 131I and 123I. Six out of eight patients with histologically proven Hodgkin’s disease had a true positive scan. Da Costa et al. [34] used HRS-3 Hodgkin-associated monoclonal antibody in 18 patients for staging and restaging. Fourteen patients showed a true positive result. Nodal, splenic, bone marrow and muscle tissue was imaged. Involvement of many of these sites was previously unsuspected. Reske et al. [35] compared the results of immunoscintigraphy of the bone marrow with those of conventional bone scanning in 36 patients with lymphoma. Correspondence was documented in 31 out of 36 patients.

Positron emission tomography (PET)

PET is a form of computed tomography that produces images of biochemical and physiological processes in tissue. Tumors are visualized as areas of increased uptake of the tracer. Images can be presented in axial, sagittal or coronal planes. In oncology, the most thoroughly studied tracers are [18F]fluorodeoxy-glucose (FDG) and [11C]methionine.

Increased glycolysis in cancer results in significant accumulation of FDG in malignant neoplasms. The first PET studies in oncology dealt with the glucose metabolism of brain tumors and FDG-PET has been considered helpful for staging tumors. There are several reports on the association between uptake of FDG and the histological grade of the tumor, but few where the accumulation was correlated with the proliferative activity of the cancer. The uptake of FDG is clearly influenced by the plasma glucose level; hence, patients taking part in FDG-PET studies should be fasting.

Methionin is an essential amino acid which is required for protein synthesis, transmethylation reactions, and as a precursor in transamination pathways. Uptake of methionin is accelerated in cancer cells. The uptake of [11C]methionine accumulates physiologically in salivary glands, liver, pancreas and bone marrow. These normal hot spots may serve as landmarks in the study or confuse the interpreter.

Several other tracers have been suggested for use in cancer PET studies. [11C]Thymidine has been used in an attempt to assess the proliferation rate of tumors, but rapid metabolism of the tracer has complicated its use. Putrescine labelled with a positron-emitting label has also been proposed for tumor studies to assess the increased polyamine synthesis of cancer cells. Studies on the pharmacokinetics of cytostatic compounds labelled with positron-emitting radionuclides are also possible.

Most PET studies with FDG as tracer use a standard transaxial imaging format, where the anatomic range of the image set was limited by the axial field of view of the tomograph. Several of these studies have shown that FDG-PET is potentially useful in the staging of lymphoma. The number of patients in those studies, however, was relatively small and disease was heterogeneous [24–26]. Okada et al. [26] compared FDG uptake in patients with 23 patients lymphoma (however, only one patient with Hodgkin’s disease) and proliferative activity, estimated by immunohistochemical labeling with the antibody Ki-67. He observed a good correlation between uptake and proliferative activity. In the study performed by Newman et al. [24], 5 patients with Hodgkin’s disease underwent FDG-PET in comparison with computed tomography. All sites of lymphadenopathy seen at computed tomography were detected by PET.

As mentioned above, Bares et al. [9] compared FDG-PET with somatostatin receptor scintigraphy in a small number of patients. PET provided a higher detection rate and better tumor contrast than somatostatin receptor scintigraphy.

Hoekstra et al. [27] performed planar FDG-PET in 13 patients with Hodgkin’s disease for monitoring early treatment response as compared to 67Ga scintigraphy. The FDG imaging was performed with a conventional gamma camera. Hoekstra suggested that 67Ga is preferable to FDG as a tracer because of higher contrast.

A new technique ‘whole-body’ FDG-PET has been developed, which generates tomographic images of the entire patient by incorporating multiple image sets acquired along the full length of the patient’s body in a single one-hour acquisition session.

Some investigators have used this new technique for staging and follow-up of patients with Hodgkin’s and non-Hodgkin’s lymphoma [28, 29]. They showed that whole-body FDG-PET can provide more data than conventional CT scanning. In the study reported by Hoh et al. [29], 70 patients with various cancers (however, only 2 patients with Hodgkin’s disease) underwent whole body FDG-PET. In these 70 patients, whole-body FDG-PET studies were abnormal in 61 patients (sensitivity of 87%). In 4 of 17 patients with nonmalignant biopsies, FDG-PET studies were false positive: FDG uptake in benign inflammatory conditions limited the technique’s specificity (75%) in this study. Bangert et al. [28] performed FDG studies in 20 patients with Hodgkin’s disease as part of the staging procedure. FDG-PET was positive in all lesions detected by conventional methods, such as computed tomography. Additionally, FDG-PET detected extranodal lesions in 15 patients (all proven true positive by additional investigations, such as MRI, biopsy and laparotomy). In another 20 patients FDG-PET was performed for monitoring treatment results. Of these 20 patients,
10 had a positive FDG uptake after therapy, 7 relapsed, and 3 are in clinical complete remission. In the remaining 10 patients, FDG-PET was negative (6 with residual tumor masses on computed tomography), and all of these patients are in complete remission.

Conclusion

The last 10 years have seen great technological advances in diagnostic radiography, yet the ability of clinical and radiographic testing to accurately identify infra-diaphragmatic lymphoma and bone marrow involvement has remained subject to limitations.

Somatostatin receptor scintigraphy has demonstrated its potential in a variety of endocrinologically active neoplasms. However, the number of patients with lymphoma who have been examined with this method is insufficient to draw definitive conclusions. Further studies in a controlled trial should be performed in order to evaluate the efficacy of this method.

MRI, as the established method at present, has shown that it can provide incremental data to that obtained with computed tomography. MRI is very sensitive to detect splenic involvement in patients with Hodgkin’s disease. Another important attribute of MRI is its ability to survey large portions of the bone marrow. A major disadvantage lies in the fact that MRI visualises only a limited portion of the body; hence, it must be performed in areas which are clinically suspect, since ‘whole-body’ MRI is not practicable in a clinical setting.

The role of MRI in the assessment of residual tumor in Hodgkin’s lymphoma after treatment has been demonstrated in several studies, which showed it to be a valuable tool in this setting, more effective than 67Ga scintigraphy, and able to provide useful prognostic information. MRI can not only provide information about tumor involvement not available by conventional techniques and different from computed tomography, but can add important data which are otherwise only obtainable with invasive methods.

Immunoscintigraphy with radiolabeled monoclonal antibodies has been performed in numerous studies, which have confirmed its ability to detect recurrent gastro-intestinal and ovarian cancer much earlier than other methods. Studies in patients with Hodgkin’s lymphoma, however, are very rare. Despite several years’ experience, this method is still in a preclinical or at the most early clinical stage of evaluation. After promising initial clinical studies in a restricted number of patients, most radionuclide-antibody conjugates have been out-run by further developments fuelled by very successful basic research before larger studies could be initiated. Therefore, the results await confirmation in a controlled trial.

After a decade of PET, the technique is still not a routine procedure in clinical oncology, which probably relates to its complexity and limited availability. Planar FDG-PET or axial quantitative PET scanning have no advantage over MRI or computed tomography. The whole-body PET, however, offers the unique capability of visualizing metabolic activity throughout various organs noninvasively and areas of suspected involvement can be assessed by image-guided aspiration or biopsy.

Preliminary data have shown that whole-body FDG-PET seems to be a good method for staging in lymphoma, perhaps as a screening method, performed prior to other investigations. Since biochemical changes in a tumor will occur before morphological changes can be detected, FDG-PET has the potential to monitor the progression or regression of the disease before anatomical changes become apparent at computed tomography.

Presence or absence of distant lesions in lymphoma may be successfully shown at staging and follow-up, whereas diagnosis of locoregional node involvement probably will not be improved very much by this new whole-body imaging method.

It is known that FDG uptake is not specific for malignant tumors, therefore further studies comparing PET to computed tomography or MRI have to be performed in a controlled multicenter study to gain experience in patients with lymphoma and in patients with inflammatory lesions or lesions postoperatively or after radiation, as well as to determine its accuracy and clinical effectiveness.

In the future whole-body FDG-PET will play a prominent role in the staging and treatment of lymphoma. Studies on the pharmacokinetics of cytostatic compounds labeled with positron-emitting radionuclides are possible; immunoscintigraphic studies with radiolabeled monoclonal antibodies, with FDG as tracer and the monoclonal antibodies as carrier for delivering cytotoxic agents (toxins or isotopes) will follow.

Staging laparotomy will remain the ‘gold standard’ in the work-up of suspected abdominal Hodgkin’s disease. Similarly, tissue biopsy will continue to have its role in posttreatment follow-up. The new techniques described above, however, have the potential for providing useful data regarding the size and site of tumor. Perhaps a controlled, multicenter study (FDG-PET versus MRI) may serve to identify a group of patients in whom biopsies and staging laparotomy can be safely avoided.

References


Correspondence to:
M. Bangerter, M.D.
Department of Internal Medicine III
University of Ulm
D-89081 Ulm
Germany