The relationships between bone marrow trephine biopsy findings and Fluorine-18 Fluorodeoxyglucose positron emission tomography- computed tomography (F-18 FDG PET-CT) scan bone marrow uptake in Hodgkin's lymphoma at initial staging.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of Master of Medicine in the branch of Nuclear Medicine

Johannesburg 2014

Candidate declaration

I, Ntombifikile Nomasonto Mkhize declare that this research report is my own work. This research report is being submitted for the degree of Masters of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

28 February 2014

Master of Medicine in the branch of Nuclear Medicine

28 February 2014

To whom it may concern,

Re: Dr Ntombifikile Nomasonto Mkhize

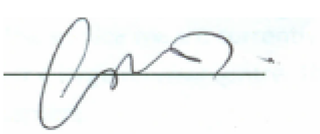
Student number: 9503069A

Staff number: 00400466

MMed Nuclear Medicine

This letter is to certify that Dr N.N. Mkhize has done her research in Nuclear Medicine. Her topic is "The relationships between bone marrow trephine biopsy findings and Fluorine-18 Fluorodeoxyglucose positron emission tomography-computed tomography (F-18 FDG PET-CT) scan bone marrow uptake in Hodgkin's lymphoma at initial staging." She compiled and analyzed the data herself. The patient data from the Red Cross Children's hospital was collected with the help of colleagues in that institution. The candidate did the entire research article with assistance from her supervisor.

Kind regards,



Prof MDTHW Vangu

Head of Radiation services

Head of department Nuclear Medicine Division

Dedication

A very special thanks to my husband, Thembinkosi Macie for his support and understanding, which allows me to pursue my goals.

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I thank the staff of the Nuclear Medicine and Paediatric oncology departments at Charlotte Maxeke Johannesburg Academic hospital, Chris Hani Baragwanath Academic hospital and Red Cross Children's Hospital, also medical oncology at Charlotte Maxeke Johannesburg Academic hospital for graciously allowing me access to archived patient data.

I particularly thank Dr A Brink for assisting with data collection for the Red Cross Children's Hospital group of patients.

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Abstract

Fluorine-18 Fluorodeoxyglucose positron emission tomography-computed tomography (F-18 FDG PET-CT) is now established in the staging, restaging and therapy response monitoring of Hodgkin's lymphoma (HL) and high grade Non-Hodgkin's lymphoma (HG NHL), specifically for nodal disease and extra-nodal disease excluding the bone marrow.

The role of FDG PET-CT for evaluating bone marrow involvement in HL and HG NHL has not been established yet. There are however several publications on this subject but no consensus has been reached.

Bone marrow trephine biopsy (BMB) is the gold standard for bone marrow assessment in lymphoma. Although the occurrence of adverse effects is uncommon, BMB is an invasive procedure that may induce anxiety in patients.

A retrospective review of FDG PET-CT bone marrow findings of HL patients referred for a staging scan from June 2008 to January 2014 was done, these findings were compared to the BMB findings also done as part of initial staging. The findings of 55 patients were reviewed analyzed.

There was concordance between the two modalities in 49 patients (89%), the other 6 patients (11%) showed discordance. Three were positive on BMB alone and the other 3 on FDG PET-CT alone. The agreement between the two procedures was good with a Kappa co-efficient of 0.63.

In addition sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of FDG PET-CT bone marrow evaluation were calculated using BMB as a reference. These were found to be: sensitivity 70%, specificity 93%, accuracy 89%, PPV 70% and NPV 93%.

In conclusion, the specificity and NPV were very good, implying that the absence of bone marrow involvement on FDG PET-CT done at initial staging for HL is a true reflection of absence of disease. A larger study is necessary to certainly consider omission of BMB in patients with no bone marrow involvement on a staging FDG PET-CT in HL.

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Nomenclature

FDG PET-CT tomography	Fluorine-18 Fluorodeoxyglucose positron emission tomography- computed
FDG PET	Fluorine-18 Fluorodeoxyglucose positron emission tomography
BMB	Bone marrow trephine biopsy
BM	Bone marrow
HL	Hodgkin's Lymphoma
NHL	Non-Hodgkin's Lymphoma
PPV	Positive Predictive value
NPV	Negative Predictive value
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CHBAH	Chris Hani Baragwanath Academic Hospital
RCCH	Red Cross Children's Hospital
CS	Clinical stage
Subcut.	Subcutaneous
CT	Computed Tomography
MRI	Magnetic resonance imaging
LN	Lymph node
LNs	Lymph nodes
C-X ray	Chest X-ray
T.B.	Tuberculosis
RVD	Retroviral disease
Rx	Treatment
HAART	Highly active retroviral therapy

Chapter 1

Introduction

Hodgkin's lymphoma (HL) is a malignancy of lymphoid tissue, which may relatively rarely have extra-nodal involvement of the spleen, liver, lungs, bone marrow and other organs.[1,2,3] It is common in the age groups 15 to 35 and 50 to 70.[4,5] This malignancy is very responsive to treatment. The aim of therapy is cure.[6]

Accurate staging at diagnosis is essential so that appropriate treatment is given. The detection of bone marrow involvement is important because it implies stage IV disease and necessitates the stratification to the most intense treatment group. Conversely identification of lack of bone marrow involvement is also essential in order to prevent over treatment that may result in chemotherapy induced organ toxicity.[7,8]

The conventional method of staging HL includes clinical assessment; computed tomography of the neck, chest, abdomen and pelvis; and bone marrow trephine biopsy (BMB).[3,7] Fluorine-18 Fluoro deoxyglucose positron emission tomography- computed tomography (FDG PET-CT) has in the recent years emerged as a key tool in staging, restaging and treatment response of lymphoma, especially HL and high-grade non-Hodgkin's lymphomas (NHL).[9,10,11,12,13,14,15]

There is an abundance of literature on the role of FDG PET and PET-CT in lymphoma management; however its specific role in detection of bone marrow involvement has not been established.[9,10,11,12,13,14,15] Thus, BMB remains the method of choice for bone marrow involvement assessment in HL.

The aim of this study is to evaluate the agreement between BMB findings and FDG PET-CT bone marrow activity in patients newly diagnosed with Hodgkin's lymphoma.

I have systematically reviewed the FDG PET-CT reports of patients with HL referred to the department of Nuclear Medicine at the Charlotte Maxeke Johannesburg Academic hospital and the Red Cross Children's hospital Nuclear Medicine for a staging FDG PET-CT scan from June 2008 to January 2014. The bone marrow findings on FDG PET-CT were correlated with the BMB findings, which were also done as part of initial staging of the patients. There was no treatment administered in the time interval between the two modalities.

Chapter 2

Literature review

Hodgkin's lymphoma (HL) is a group of lymphoid neoplasms named after Thomas Hodgkin who first described abnormalities in the lymphoid glands and spleen in 1832.[1] The disease accounts for less than one percent of all malignancies [16]. There is a bimodal age incidence described, with peaks at ages 15 to 35 and 50 to 70 years; however, in economically disadvantaged countries the first peak is shifted towards childhood [4,5,17]. There is a slightly higher male to female ratio incidence, in South Africa males show a 0.68/ 100 000/ year while females show a 0.49/ 100 000/ year incidence.[16]

The aetiology of HL is unknown but several infections have been associated with it. Epstein-Barr virus (EBV) infection has been shown to have a strong association with HL occurrence.[18,19,20,21] Patients with Human immunodeficiency virus/ acquired immune deficiency syndrome (HIV/AIDS) are at an increased risk for developing HL.[22] The increased risk has been associated with the introduction of highly active antiretroviral therapy (HAART) by some authors.[23,24] Significant differences between HIV related HL and non-HIV related HL have been documented, such as: HIV-HL presents with high risk features like systemic B symptoms and extra-nodal involvement.[22] Mononucleosis infection has also been implicated.[25] Other predisposing factors are familial aggregation and genetic susceptibility.[26] Ferrais et al[26] estimated that four and half percent of HL cases occur as familial HL.

Hodgkin's lymphoma usually presents as a localized disease subsequently spreading to contiguous lymphoid structures. Ultimately it disseminates to non-lymphoid tissues. Hodgkin's lymphoma often presents with a newly detected mass or group of lymph nodes that are firm, freely movable and usually non-tender.[27] About fifty percent of patients present with a mass in the neck or supraclavicular area and approximately sixty percent have a mediastinal mass at presentation[27]. Most children (ninety percent) present with painless adenopathy in the neck.[27] The majority of patients with HL have few or no systemic symptoms related to the disease, however twenty five to thirty percent have constitutional symptoms (B symptoms), commonly low grade fever, night sweats and weight loss of greater than ten percent of body weight over a period of 6 months or less.[27] Other symptoms include fatigue, malaise, weakness and pruritus.[27]

The spread of HL is fairly predictable: nodal disease first, then splenic disease, hepatic disease, and finally marrow involvement and extra-lymphatic disease.[28]

The Ann Arbor staging system with Cotswolds' modification is currently used for clinical staging as follows:[29,30]

Stage	Area of Involvement
I	Single lymph node group
II	Multiple lymph node groups on same side of diaphragm
III	Multiple lymph node groups on both sides of diaphragm
IV	Multiple extra nodal sites or lymph nodes and extra nodal disease
X	Bulky disease (maximal dimensions > 10 cm)
E	Extra nodal extension or single, isolated site of extra nodal disease
A/B	B symptoms: weight loss > 10%, fever, drenching night sweats.

The diagnosis of HL requires an excision biopsy of the suspicious lymph node. The identification of Reed-Sternberg cells and their variants in a background of non-neoplastic inflammatory cells is essential for diagnosis.[27,28] Immunohistochemical procedures are used to further classify HL as described by the WHO (world health organization) as two pathological disease entities: nodular lymphocyte predominant HL and classical HL. The latter has 4 subtypes: nodular sclerosing, mixed cellularity, lymphocyte rich and lymphocyte depleted HL.[31]

Appropriate staging of HL is vital to determine the correct treatment and prognosis. The recommended staging procedures include: detailed history; physical examination; laboratory tests; chest X-ray; CT scans of the neck, thorax, abdomen and pelvis; and bone marrow trephine biopsy (BMB).[32]

Bone marrow trephine biopsy in patients with HL is useful in clinical stages more than II A.[33] Stages II A and lower have been shown to have a less than one percent chance of bone marrow infiltration in adults and less than two percent in children.[34,35,36,37]

Currently, a routine BMB is usually obtained from the iliac crest. Bone marrow trephine biopsy is an invasive diagnostic procedure, which allows analysis of a very limited area. Therefore unilateral or multifocal bone marrow infiltration at locations other than the iliac crest can consequently be missed.

Pre-therapy FDG-PET-CT is strongly encouraged for HL because it can facilitate the interpretation of the post-therapy FDG PET-CT scan.[9,10,11,12,13,14,15] The value of FDG-PET for detecting BM involvement however has not been sufficiently defined.

Pakos et al[38] performed a meta-analysis of 13 studies done before 2004, with a total of 587 patients with HL and NHL, to evaluate the value of FDG-PET in bone marrow infiltration. They found that only about fifty percent of patients with bone marrow infiltration on BMB were detected as positive on FDG PET.[38] However over ninety percent of the patients with negative BMB also had negative FDG PET scan for bone marrow infiltartion.[38] On subgroup analysis they found that the sensitivity for bone marrow involvement on FDG PET is seventy six percent for HL and aggressive NHL. They concluded that FDG-PET may not replace but complement BMB and that the encouraging finding in HL should be verified in a larger study.[38]

In a different study, Kabickova et al[39] compared FDG PET with conventional staging methods (CT, sonar, BMB and bone scan) for children with HL and found a sensitivity of hundred percent on FDG-PET versus forty percent for BMB when looking at bone marrow infiltration.[39]

Moulin-Romsee et al[40] retrospectively analyzed 83 patients with HL and their ages were ranging from 7 to 82 years. They all had a BMB and FDG PET-CT at initial diagnosis.[40] FDG PET-CT was negative for bone and BM in sixty of the eighty-three patients and all these patients also had a negative BMB. Eighteen of the eighty-three patients had positive FDG PET-CT bone and bone marrow findings; seven of which correlated with BMB findings. Eleven of the eighteen patients were negative on BMB. It is of note that in all the eleven discordant patients, the iliac crests were not involved on FDG PET-CT. FDG PET-CT bone/ bone marrow findings in five patients were reported as doubtful because they had strictly homogenous F-18 FDG uptake in the axial and proximal appendicular skeleton. None of these patients were treated as stage IV. In this series, FDG PET-CT depicted nine (10.7%) patients with bone/ bone marrow involvement that were missed by conventional staging (BMB and CT).[40]

Six studies published between 2004 and 2010 with a total of 561 patients jointly showed forty-two patients with positive BMB; thirty-six of which were positive on FDG PET. Omitting BMB would have missed just about one percent or six patients out of five hundred sixty one.[15,39,40,41,42,43]

Purz et al[44] in another study compared the results of BMB and FDG-PET for the diagnosis of BM involvement in a large pediatric group of 175 patients with HL.[44] They found that forty-five patients were PET positive for BM involvement. Only seven out of one hundred and seventy five patients had positive BMB results and all seven were concordant with FDG PET bone marrow findings. All the detected lesions were verified either with the use of Magnetic Resonance Imaging (MRI) or CT or follow-up FDG-PET. There were no false negative PET lesions found. Therefore, the sensitivity and negative predictive value (NPV) of PET were hundred percent when using a combination of BMB, CT, or MRI results for reference. They concluded that FDG-PET has a high sensitivity and specificity, thus a routine BMB could be omitted.[44]

Cheng et al[45] did a retrospective review of paediatric patients (age range: 6-24 years) with HL and non-Hodgkin's lymphoma (NHL) who underwent FDG PET-CT for staging at initial diagnosis. They included patients with pathological abnormal bone marrow on BMB, thirty-one HL and twenty-three NHL (total: 54). In HL patients FDG PET-CT showed four out of thirty one patients to have positive bone marrow findings, all these sites resolved on follow-up scans post therapy. Bone marrow trephine biopsy showed 2 positives of these 4 patients. The other two that were positive on FDG PET-CT showed abnormal bone marrow uptake in sites other than the iliac crests. Overall (HL and NHL) the sensitivity of FDG PET-CT was ninety two percent versus BMB at fifty four percent. Specificity was one hundred percent for both.[45]

Muzahir et al[46] retrospectively reviewed one hundred and twenty two patients with HL ages 6 to 78 years. The sensitivity of FDG PET-CT was found to be a hundred percent; specificity seventy seven percent; NPV seventy seven percent; PPV thirty percent. They concluded that FDG PET-CT and BMB are complementary in the evaluation of bone marrow disease.[46]

Cerci et al[43] prospectively analyzed 82 patients with newly diagnosed HL. FDG PET detected all 16 patients who were characterized positive by BMB and identified an additional 4 patients with bone marrow infiltration. They concluded that incorporation of FDG PET in the conventional staging procedures changed management in 15% of their patients.[43]

Wu et al[47] did a meta-analysis of 32 original articles (from 1995 to 2010) to evaluate the detection of bone marrow infiltration during staging and re-staging of lymphoma using FDG PET, FDG PET-CT and MRI. They found that FDG PET-CT had the highest sensitivity and specificity of the three modalities. Sensitivity: FDG PET-CT at 92%, FDG PET at 82%, MRI at 90% and specificity: FDG PET-CT at 90%, FDG PET at 87%, MRI at 76%.[47]

Recently Berthet et al[48] retrospectively reviewed 133 patients with high-grade diffuse large B-cell lymphoma (DLBCL) who had an FDG PET-CT and BMB for initial staging. FDG PET-CT demonstrated bone marrow infiltration in 32 patients and only 8 patients by BMB. The reference was 24 months follow-up and targeted MRI imaging. Therefore the sensitivity, negative predictive value and accuracy for FDG PET-CT versus BMB were 94% vs 24%; 98%

vs 80%; 98% vs 81%, respectively. They concluded assessment of bone marrow infiltration with FDG PET-CT provides better diagnostic performance in newly diagnosed DLBCL than does BMB.[48]

Many authors now agree that FDG PET/ PET-CT improves sensitivity and specificity of bone and bone marrow involvement in patients with HL and high grade NHL.[39,40,41,42,43,44,45,46,47,48] Therefore the role of BMB as a gold standard for bone marrow involvement in these lymphomas should be re-evaluated.

Chapter 3

Materials and methods

3.1 Study Design

This is a retrospective study on patients with HL referred for a staging FDG PET-CT scan at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Nuclear Medicine department. The referrals also included patients from the Chris Hani Baragwanath Academic hospital (CHBAH). To increase the study population, data from Red Cross Children's hospital (RCCH) were also included.

The archived FDG PET-CT and BMB histology reports (and FDG PET-CT images where available) of newly diagnosed HL patients were systematically reviewed and compared. FDG PET-CT images of patients with discordant (FDG PET-CT/ BMB) results were carefully reviewed to attempt to establish the reason for the discordance. The available clinical notes especially of the patients with the discordant findings were also reviewed.

3.2 Inclusion and exclusion criteria

The inclusion criteria are patients with newly diagnosed HL who had a pre-treatment FDG PET-CT scan and BMB as part of the initial staging. FDG PET-CT reports of seventy two patients were reviewed, seventeen of which were excluded for the following reasons: the BMB was not done as part of initial staging or the scan was actually done after commencement of treatment or BMB specimen was suboptimal and one patient had a single equivocal BM finding on PET-CT even on review of the images.

3.3 Study population

A total of 55 patients were included in the study, 41 from the CMJAH-CHBAH complex and 14 from RCCH. This population consists of 43 males and 12 females; ages ranging from 3 to 32 years with a median age of 10 years. All the scans were done for diagnostic purposes in accordance with the international guidelines, European association of nuclear medicine guidelines.[49] Images at the CMJAH and RCCH were acquired on the Siemens Biograph 40 PET-CT scanner (40 slice CT) and a Philips Gemini Big Bore PET-CT scanner (16 slice CT), respectively. Imaging was commenced sixty minutes on average following the intravenous administration of the radiotracer (F-18 FDG). Some scans were contrast enhanced some were not, depending on the patient's renal function or department protocol at the time.

3.4 Data management and analysis

Patients' FDG PET-CT reports were reviewed. The patients' BMB results were sought for analysis. A comparison between the FDG PET-CT BM findings and BMB results was done for each patient. Descriptive analysis of the data was done to show the frequency distribution of variables. Concordance and discordance between the two modalities was documented. Bone marrow findings on FDG PET-CT were evaluated using visual assessment with liver uptake as a reference and the pattern of uptake (heterogenous versus inhomogenous). The maximum standardized uptake value (SUV_{max}) of the FDG accumulation in bone marrow/ bone was used as a semi-quantitative index. The agreement between the two modalities was measured using the Cohen Kappa co-efficient. The sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of FDG PET-CT bone marrow evaluation were calculated using BMB as a standard of reference. Data were analyzed using Statistica 10 package (statsoft Inc, *Tilsa,* Oklahoma, USA).

3.5 Image interpretation

FDG PET-CT bone marrow findings were considered positive when the uptake was above liver uptake and the pattern was heterogenous or focal.[50,51,52,53]

3.6 Ethical issues

Permission was obtained from the CMJAH chief executive officer (CEO), Wits ethics committee, University of Cape Town (UCT) paediatric research committee and faculty ethics committee, as well as the RCCH CEO. Confidentiality was maintained by assigning an alphabetic letter and number to each patient for identification.

Chapter 4

Results

A total of 55 patients with HL, whose initial staging included bone marrow biopsy and FDG PET-CT were included. The characteristics of the population were 43 males and 12 females; ages ranging from 3 to 32 years with a median age of 10 years; Seventy five percent of patients were under the age of 13 years. The patient characteristics and findings are summarized and tabulated in tables 1 and 2, respectively.

4.1 Concordance: negative BMB and negative FDG PET-CT bone marrow findings

Forty-two out of fifty five patients were found to have negative BMB and negative FDG PET-CT bone marrow findings (76.4%).

4.2 Concordance: positive BMB and positive FDG PET-CT bone marrow findings

Seven out of fifty five patients were found to have positive BMB and positive FDG PET-CT bone marrow findings (12.7%). FDG PET-CT scan showed abnormal increased uptake in the pelvis (among other sites) in all seven patients, including iliac blade involvement specifically. Figure 1 shows one of these patients, C28.

Overall concordance was noted in forty-nine out of fifty five patients (89.1%).

4.3 Discordance: negative BMB and positive FDG PET-CT bone marrow findings

Three out of fifty five patients (5.5%) had negative BMB and positive FDG PET-CT bone marrow findings. Two of these patients had bone marrow involvement in sites other than the pelvis: T8, L1 vertebrae and left femur in patient R36 (Figure 2); and L2 vertebra in patient R37 (Figure 3). Patient C30 had pelvic involvement (Figure 4). Table 3 lists the characteristics of these patients.

4.4 Discordance: positive BMB and negative FDG PET-CT bone marrow findings

Three out of fifty five patients (5.5%) had positive BMB and negative FDG PET-CT bone marrow findings. The BMB histology report described minimal infiltration (a single atypical cell) of bone marrow by metastatic HL in the one patient [patient R35 (Figure 5A)]. Another had 50% bone marrow involvement on BMB [patient C7 (Figure 5B)]. The third patient had extensive bone marrow infiltration by HL on BMB histology [patient R44 (Figure 5C)]. These patients' characteristics are listed in table 4.

Overall discordance was six out of fifty five patients (10.9%).

4.5 Agreement

The level of agreement was calculated using the Kappa co-efficient and it was found to be good at K 0.63, 95% CI [0.36 – 0.90].

4.6 Study sensitivity, specificity, PPV, NPV and accuracy

Bone marrow biopsy is the gold standard for marrow evaluation is lymphoma, therefore in this study the sensitivity, specificity, PPV, NPV and accuracy of FDG PET-CT for bone marrow infiltration are calculated with BMB as a reference standard: the **sensitivity** is 70% [0.70 +/- 0.28] (42 to 98%); **specificity** is 93% [0.93+/- 0.07] (86 to 100%); **PPV** is 70% (42 to 98%); **NPV** is 93% (86 to 100%) and **accuracy** is 89% CI 95% (80 to 97%).

Chapter 5

Discussion

Fluorine-18 Fluorodeoxyglucose positron emission tomography-computed tomography (F-18 FDG PET-CT) is a technique which employs the use of a radioactive pharmaceutical F-18 FDG, which is an analogue of glucose. Since the metabolism of glucose is up-regulated in most malignancies, including HL, F-18 FDG is therefore an ideal imaging agent. Many studies have shown the usefulness of FDG PET-CT in staging, restaging and therapy monitoring of patients with lymphoma.[9,10,11,12,13,14,15] In this study we compare FDG PET-CT performance in bone marrow infiltration evaluation in newly diagnosed HL against the current gold standard, BMB.

Pakos et al[38] in a meta-analysis of 13 studies done before 2004: 4 studies with HL, 3 studies with NHL patients and 6 mixed population; showed a sensitivity of 76% for the subgroup of HL and HG NHL in detecting bone marrow infiltration using FDG-PET and a specificity of 92%. These findings are similar to our study as we found a sensitivity of 70% and a specificity of 93% (86 to 100%). Sensitivity was reasonable for HL (76%) but very few patients with HL had bone marrow infiltration, therefore they recommended that the sensitivity be verified by larger studies. This is also true for our study, few patients had bone marrow infiltration, seven were positive on both modalities, three on BMB alone and another three on FDG PET-CT alone; therefore overall thirteen positive studies out of fifty five, 23.6%. That is why the sensitivity is not that good at 70% and the range is so wide, 42 to 98% [0.70 +/- 0.28].

Kabickova et al[39] did a prospective study on fifty-five children and adolescents with HL, comparing conventional methods (CT, sonar and BMB) with FDG PET for evaluating extra-nodal involvement at initial staging. They found that in six patients (10.9%) FDG PET revealed focal bone marrow infiltrates, all of which were negative on BMB. In fact a targeted MRI was used and confirmed these findings.[39] In our study three out of fifty five patients (5.5%) had BM infiltration on FDG PET and were negative on BMB. The overall sensitivity of FDG PET for extra-nodal involvement (including lungs, liver, spleen and BM) was 90% whereas the sensitivity for conventional methods was 80%.[39] Their sensitivity is higher than ours (90 vs 70%) because all the other organs were included whereas we only looked at BM.

Pelosi et al[42], in a study of 194 patients in 2008, compared the usefulness of FDG PET versus BMB in patients with HL and aggressive NHL and its impact on therapy, they subsequently followed- up with a similar but multicenter population of 337 patients in 2011 using FDG PET-CT.[50] They initially found a sensitivity of 65.3%, specificity of 98.6% and NPV of 100%.[42] In the multicenter study, the sensitivity was found to be 69%, specificity 99% and NPV of 90%.[54]
The latter findings are similar to ours: sensitivity 70%, specificity 93% and NPV 93%; even though their population was mixed (HL and aggressive NHL).

Purz et al[44] evaluated bone marrow infiltration in a population of 175 children and adolescents with HL above stage II A. Forty five (25.7%) patients had BMI on FDG PET, only seven (4%) of which were also positive on BMB. They found a sensitivity and NPV of PET for BMI to be 100%, when a combination of CT, MRI and BMB were used as standard of reference.[44] There were no false negative findings on FDG PET.[44] This finding of a high NPV is similar to our study (93%) and the other studies of Pelosi et al[42,54] (100 and 90%). The high sensitivity is unlike any of the studies including our own. The possible reason might be because of a selected population of above stage IIA. Another study with a high sensitivity is by Cheng et al[45], with a sensitivity of 92%, their population however was mixed including HL, NHL, Burkitt's lymphoma and T-cell lymphoma. Another study with a high sensitivity was Muzahir et al[46] who retrospectively reviewed 122 patients, eighty-five of which had BM infiltration on FDG PET-CT and all of them were positive BMB, therefore the sensitivity was 100%.[46]

In the previously mentioned multicenter study of Pelosi et al[54], eighty-seven (26%) patients out of 337 had bone marrow infiltration. Twenty-five of these 87 patients (29%) had BM infiltration that was detected by both modalities. Twenty-seven of patients in this group (3%) were detected by BMB alone and 35 patients (40%) by PET-CT alone.[54] In our study, a total of thirteen patients (24%) had positive bone marrow findings. Seven out of these thirteen patients (54%) were positive on both modalities, three (23%) on BMB alone and another three (23%) on PET-CT alone. Their highest pick-up rate was on PET-CT alone (40 %), whereas our highest pick-up rate was noted when both modalities were combined (54%) [Figure1].

Cerci et al[43] studied 82 patients, 5 of which had bone marrow infiltration on PET that were not demonstrated by BMB. They proved 4 of the 5 patients to be true positives by MRI and bone scan and in all 4 patients the bone marrow uptake disappeared after therapy. Only 1 of the 5 was regarded as a false positive because it corresponded to a rib fracture on the CT scan.[43] This however would not be a concern in studies and institutions where integrated PET-CT is used, like ours. Our findings are similar to Cerci et al, all three patients in our study had follow-up scans post therapy to assess response to treatment, which showed disappearance of abnormal bone marrow uptake, therefore they may be regarded as true positives.

Moulin-Romsee et al[40] had 11 out of 83 patients with BM infiltration on FDG PET-CT that were not detected on BMB.[40] In a number of studies including Cerci and Moulin-Romsee et al[43,40] none of the FDG PET positive/ BMB negative patients had pelvic infiltration on the scan.[40,43,45,46] In our study, two of the three patients with BM infiltration on FDG PET-CT but negative BMB (patients: R36 and R37) did not show abnormal FDG activity in the pelvis. This may explain why the BMB findings were negative, since iliac crests are the standard sites of biopsy. In the remaining patient (C30) there was bilateral iliac blade involvement on FDG PET-CT. The discordance may be due to the inhomogenous pattern of infiltration. A sampling error might have occurred (a single core biopsy was obtained, but the side was not specified). Table 3 lists the characteristics of these 3 patients and figures 2, 3 and 4 show the sites and pattern of uptake.

We had 45 patients without BM infiltration on PET-CT and 42 of them were also negative on BMB. Therefore three were discordant with BM infiltration on BMB which was not detected by FDG PET-CT, these are patients C7, R35 and R44 (table 4 and Figure 5). The extent of BM infiltration on BMB ranged from a single lesion to 50% infiltration to extensive infiltration. The extent of infiltration does not seem to be the contributory factor for the lack of detection by the FDG PET-CT. The only notable common characteristic between these patients was the atypical clinical presentation that is none of them had significant cervical, supraclavicular or axillary adenopathy. The diagnosis of HL was made on BMB, thoracotomy and laparotomy. The significance of this fact is however unclear.

5.1 Study Limitations

It is a retrospective study.

This is a small sample size due to the relative newness of the FDG PET-CT imaging modality (about 5 years at CMJAH), thus it is not formally integrated into the staging algorithms of most clinical departments.

Chapter 6

Conclusion and way forward

This study has demonstrated the performance of FDG PET-CT in evaluating bone marrow in patients with HL who are referred for initial staging. We measured the agreement between FDG PET-CT bone marrow uptake and BMB findings in this group of patients. The vast majority of patients without bone marrow infiltration on FDG PET-CT also did not show involvement on BMB, therefore the specificity and NPV were high at 93%. These findings suggest that BMB may not be necessary at initial staging in patients with HL who will have a FDG PET-CT scan as part of staging. A larger study population is required to confirm this finding.

Table 1: Summary of patient characteristics

Total number of patients	55
Males (M)	43
Females (F)	12
Age range	3 – 32 years
Age median	10 years
Age 1st quartile	6 years
Age 2nd quartile	13 years
Disease stage by PET-CT and BMB	**Number of patients**
I	5
II	25
III	12
IV	13

Key for tables 2, 3 and 4

M	*Male*
F	*Female*
CS	*Clinical stage*
LNs	*Lymph nodes*
BM	*Bone marrow*
BMI	*Bone marrow infiltration*
PMR	*Partial metabolic response*
PLT	*Platelets*
P.T.B.	*Pulmonary Tuberculosis*
T.B.	*Tuberculosis*
RVD	*Retroviral disease*
Rx	*Treatment*
HAART	*Highly active retroviral therapy*
C-X ray	*Chest X-ray*
CT	*Computed Tomography*
MRI	*Magnetic resonance imaging*

Table2: Patient characteristics and findings

Patient	Age (years)	Gender	BMB	FDG PET-CT		Comparison	Time interval (days)	Stage on PET-CT and BMB
					SUV_{max}			
C1	23	M	Negative	Negative	-	Concordant	114	IV (subcut. nodules)
C2	4	F	Negative	Negative	-	Concordant	6	III
C3	12	M	Negative	Negative	-	Concordant	5	IIE (lungs)
C4	10	M	Negative	Negative	-	Concordant	7	II
C5	18	F	Positive	Positive	7.42	Concordant	126	IV (liver and BM)
C6	10	F	Negative	Negative	-	Concordant	265 (defaulted)	IV (lungs)
C7	11	M	Positive	Negative	-	Discordant	13	III
C8	7	M	Negative	Negative	-	Concordant	11	II
C9	6	M	Positive	Positive	5.24	Concordant	18	IVS (BM)
C10	16	M	Negative	Negative	-	Concordant	9	II
C11	8	M	Negative	Negative	-	Concordant	28	IIIS
C12	10	M	Negative	Negative	-	Concordant	1	IIIS
C13	8	M	Negative	Negative	-	Concordant	0	II
C14	14	F	Positive	Positive	?	Concordant	8	IV (BM)
C15	18	F	Negative	Negative	-	Concordant	62	II
C16	11	M	Negative	Negative	-	Concordant	92	III
C17	13	M	Negative	Negative	-	Concordant	9	II
C18	12	M	Negative	Negative	-	Concordant	16	II
C19	9	M	Negative	Negative	-	Concordant	19	IIIS
C20	11	M	Negative	Negative	-	Concordant	3	IIIS
C21	5	F	Negative	Negative	-	Concordant	16	III
C22	7	F	Negative	Negative	-	Concordant	5	II
C23	32	F	Negative	Negative	-	Concordant	26	II
C24	4	M	Negative	Negative	-	Concordant	14	III
C25	10	M	Negative	Negative	-	Concordant	20	IV (liver and lungs)
C26	5	M	Negative	Negative	-	Concordant	10	II
C27	17	F	Negative	Negative	-	Concordant	10	II
C28	4	M	Positive	Positive	6.14	Concordant	1	IV (BM)
C29	29	M	Positive	Positive	5.66	Concordant	29	IV (BM)
C30	27	F	Negative	Positive	5.19	Discordant	1	IV (BM)
C31	11	M	Negative	Negative	-	Concordant	7	II
C32	4	M	Negative	Negative	-	Concordant	10	I
R33	9	M	Negative	Negative	-	Concordant	4	I
R34	5	M	Negative	Negative	-	Concordant	2	I
R35	7	M	Positive	Negative	-	Discordant	3	II
R36	14	M	Negative	Positive	7.99	Discordant	11	IV (BM)
R37	7	M	Negative	Positive	3.96	Discordant	4	IV (BM)
R38	9	M	Negative	Negative	-	Concordant	4	II
R39	6	M	Negative	Negative	-	Concordant	1	II
R40	13	F	Negative	Negative	-	Concordant	2	II
R41	4	M	Negative	Negative	-	Concordant	4	II
R42	3	M	Negative	Negative	-	Concordant	1	II
R43	12	M	Positive	Positive	13.32	Concordant	1	IV (BM)
R44	6	M	Positive	Negative	-	Discordant	15	III
R45	13	M	Negative	Negative	-	Concordant	4	II
R46	5	M	Negative	Negative	-	Concordant	5	I
C47	5	M	Negative	Negative	-	Concordant	0	II
C48	7	M	Negative	Negative	-	Concordant	6	II
C49	8	M	Negative	Negative	-	Concordant	10	II
C50	30	F	Negative	Negative	-	Concordant	24	IIIS
C51	7	M	Negative	Negative	-	Concordant	5	II
C52	22	M	Negative	Negative	-	Concordant	2	IIE (lungs)
C53	5	M	Negative	Negative	-	Concordant	21	IIIS
C54	13	M	Negative	Negative	-	Concordant	1	IE (liver)
C55	12	M	Positive	Positive	4.57	Concordant	10	IV (BM)

Table 3: Characteristics of FDG PET-CT positive and BMB negative patients

No.	Patient ID	Age (yrs)	Gender	Subtype of HL	Clinical stage and presentation	BMB	FDG PET-CT	Follow-up PET-CT Post therapy
1	C30	27	F	Not specified	CS: Stage IIIA. Neck mass. Splenomegaly.	Negative	Positive Stage IV BMI: multiple including iliac crests, inhomogenous, left > right.	PMR: Residual in the LNs. BM clear.
2	R36	14	M	Nodular sclerosing	CS: Stage IIA. Neck and supraclavicular masses. Epistaxis and anaemia.	Negative	Positive Stage IV BMI: T8, L1, Left femur.	PMR: Residual in the mediastinal mass. BM clear.
3	R37	7	M	Not specified	CS: Stage IIB Neck and supraclavicular masses.	Negative	Positive Stage IV BMI:L2.	PMR: Residual in the LNs. BM clear.

Table 4: Characteristics of FDG PET-CT negative and BMB positive patients

Patient ID	**Age (yrs)**	**Gender**	**Subtype of HL**	**Clinically**	**BMB**	**FDG PET-CT**	**Follow-up BMB, mid-chemo.**	**Follow-up PET-CT Post therapy**	**Follow-up BMB, post chemo.**
C7	11	M	Not specified	Epistaxis. PLTs $7x10^9$/l. Hepatomegaly, believed to be drug induced hepatitis. PTB on Rx, 3rd course. RVD on HAART.	Positive. 50% infiltration with HL. (BMB was done for the thrombo-cytopaenia)	Negative for BMI. Stage III. Para-aortic LN. Diagnostic CT also had the same finding.	No infiltration.	-	No infiltration.
R35	7	M	Mixed cellularity	Cough, oedema C-X ray: mediastinal widening. CT Chest: mediastinal adenopathy. Thoracotomy and biopsy of mediastinal LNs.	Positive. Single lesion, minimal infiltration.	Negative for BMI. Stage II. Right supraclavicular and mediastinal adenopathy.	-	Complete resolution of the adenopathy.	No infiltration.
R44	6	M	Nodular Sclerosing	No improvement on T.B. Rx. Hepato-splenomegaly. Sonar: abdominal adenopathy. Laparotomy and biopsy: porta hepatis LN and liver.	Positive. Extensive infiltration.	Negative for BMI. Stage III. Abdominal and pelvic adenopathy.	-	Complete resolution of the adenopathy.	Minimal residual HL.

A

B

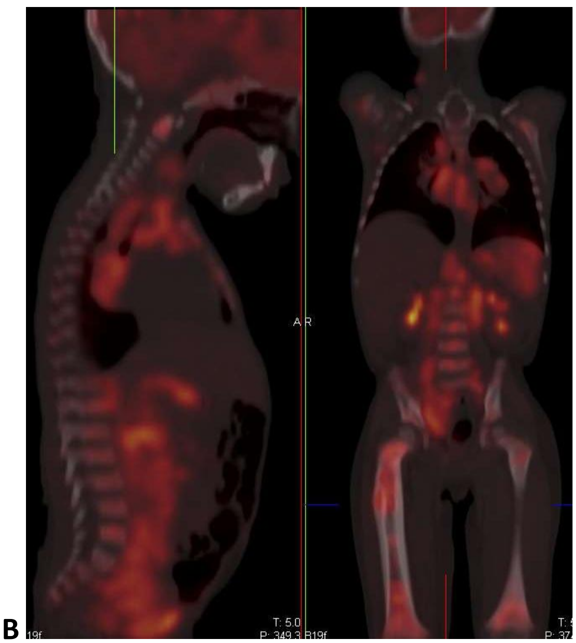

Figure 1: Patient C28, extensive bone marrow infiltration throughout the skeleton with CT bone changes in the right femur. Bone marrow infiltration was also found on BMB. A, coronal FDG PET image and B, sagittal and coronal FDG PET-CT images.

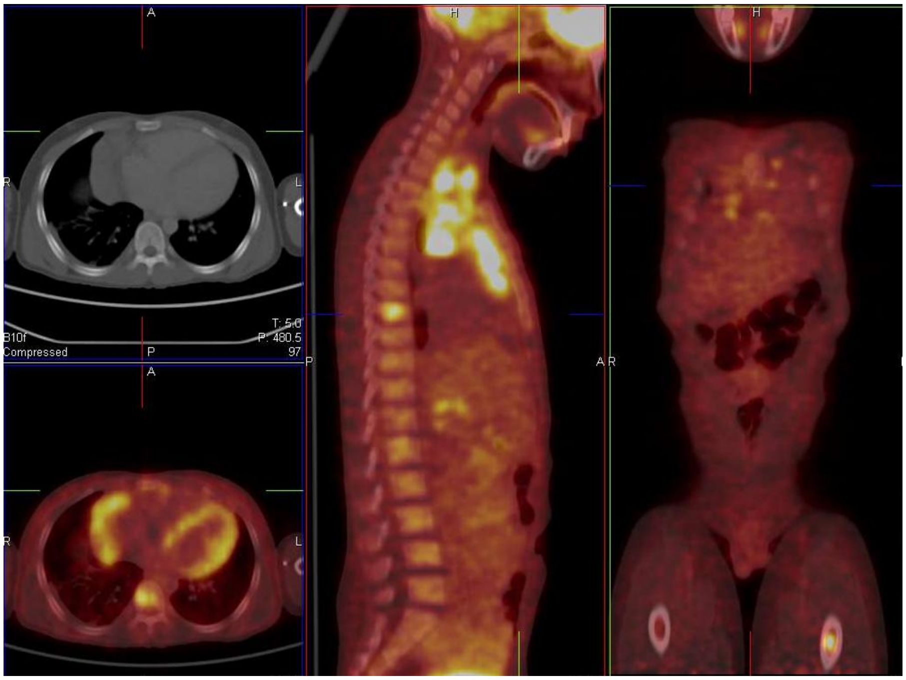

Figure 2: Patient R36. There is bone marrow infiltration in T8 and left femur, the pelvis was not involved. BMB was negative.

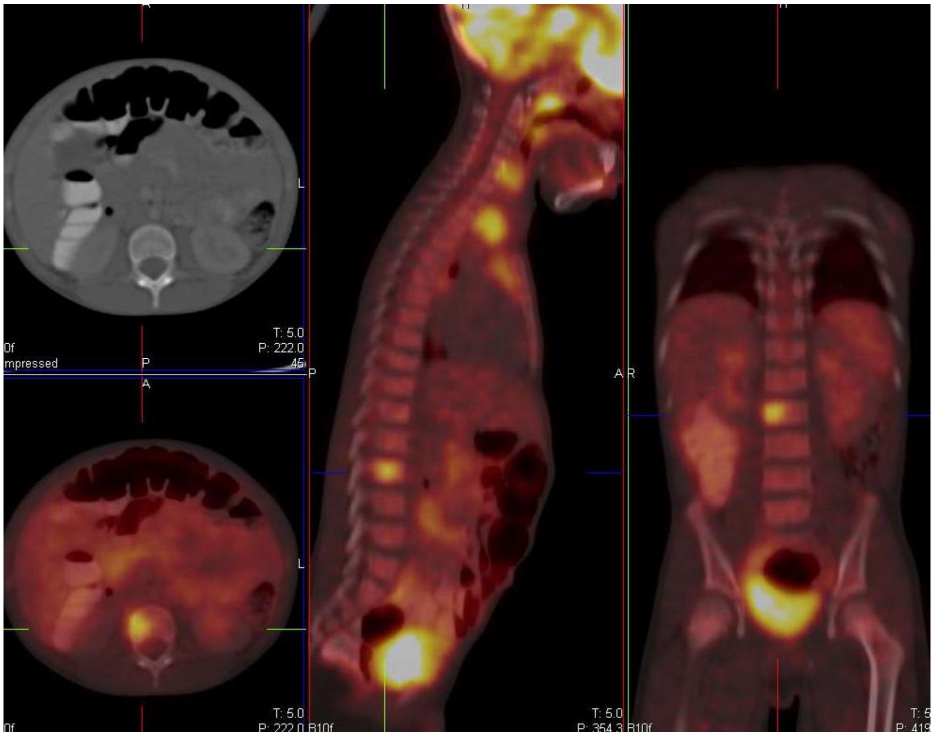

Figure 3: Patient R37, showing bone marrow infiltration in L2 vertebral body. There was no disease in the pelvis on FDG PET-CT. BMB did not demonstrate HL infiltration.

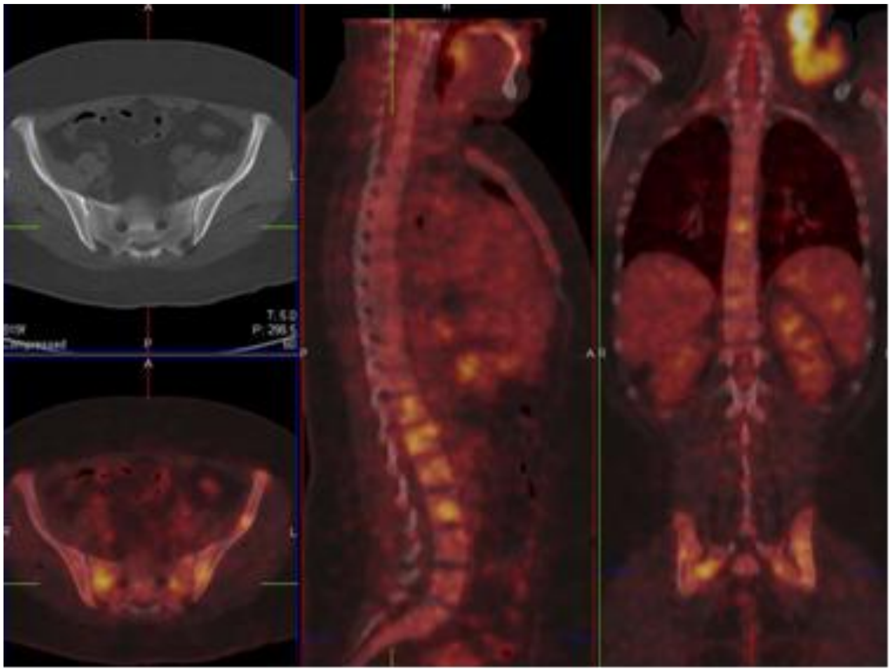

Figure 4: Patient C30 showing BM infiltration on FDG PET-CT in the thoraco-lumbar spine and pelvis which was not demonstrated on BMB, despite the pelvic involvement.

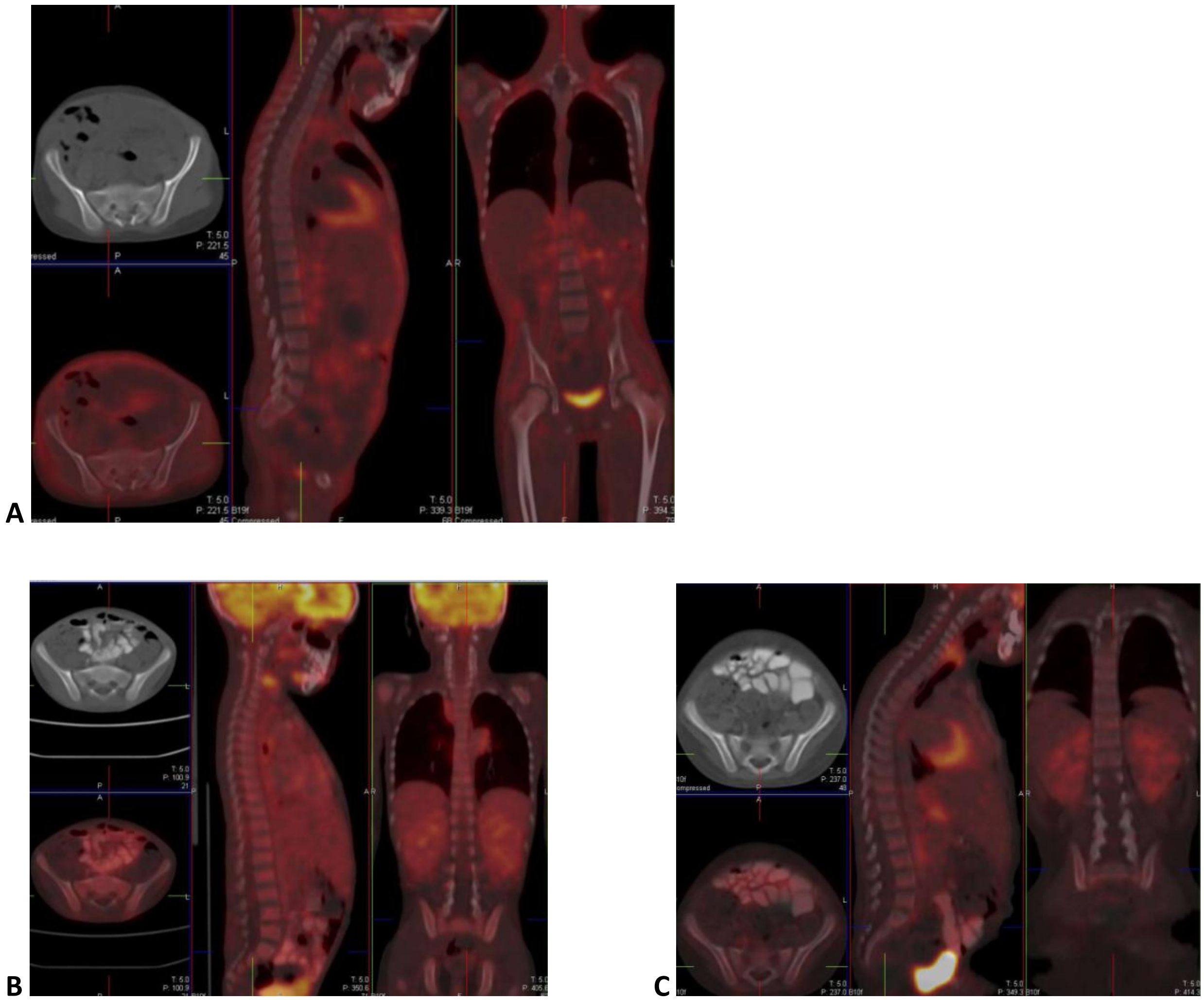

Figure 5: Patients C7, R35 and R44; A, B and C, respectively show no evidence of bone marrow infiltration on FDG PET-CT but BMB was positive of HL. Histology reported: A. C7 a 50% infiltration; B R35 a single lesion; C R44 extensive infiltration.

Chapter 7

References

1. Treseler PA. The pathology of Hodgkin's disease. Grossbard ML, ed. Malignant lymphomas. Vol 1. American cancer society, 2002: 330-352.

2. Guermazi A, Brice P, Kerviler E, et al. Extranodal Hodgkin Disease: Spectrum of Disease. RadioGraphics 2001; 21:161–179.

3. Gobbi P, Ferreri A, Ponzoni M, et al. Hodgkin lymphoma. Crit Rev Oncol/Hematol 2012.

4. MacMahon B: Epidemiology of Hodgkin's disease. Cancer Res 1966, 26: 1189-1200

5. Gutensohn N, Cole P: Epidemiology of Hodgkin's disease. Semin Oncol 1980, 7: 92-102

6. Yung L, Linch D. Hodgkin's lymphoma. Lancet 2003; 361: 943–51.

7. Nadeem M, Naqi N, Hussain I. Frequency of Bone Marrow Involvement in Hodgkin's Lymphoma on First Presentation. J Coll Phys and Surg Pak. 2009, Vol. 19 (12): 768-771.

8. Connors JM. State-of-the-art therapeutics: Hodgkin's lymphoma. J Clin Oncol 2005;23: 6400.

9. Friedberg JW, Fischman A, Neuberg D, et al. FDG PET is superior to gallium scintigraphy in staging and more sensitive in the follow up of patients with de novo Hodgkin Lymphoma: a blinded comparison. Leukemia and Lymphoma 2004; 45: 85–92.

10. Naumann R, Beuthien Baumann B, Reiss A, et al. Substantial impact of FDG PET imaging on the therapy decision in patients with early stage Hodgkin's lymphoma. British Journal of Cancer 2004; 90: 620–5.

11. Hutchings M, Loft A, Hansen M, et al. Position emission tomography with or without computed tomography in the primary staging of Hodgkin's lymphoma. Haematologica 2006; 91: 482–9.

12. Jhanwar Y, Straus D. The role of PET in lymphoma. J Nucl Med 2006; 47:1326–1334.

13. Juweid M, Stroobants S, Hoekstra O, et al. Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007; 25 (5): 571-578.

14. Cheson B, Pfistner B, Juweid M, et al. Revised Response Criteria for Malignant Lymphoma. J Clin Oncol. 2007; 25:579-586.

15. Rigacci L, Vitolo U, Nassi L, Merli F, Gallamini A, Pregno P, et al. Positron emission tomography in the staging of patients with Hodgkin's lymphoma. A prospective multicentric study by the Intergruppo Italiano Linfomi. Ann Hematol 2007;86(12):897–903.

16. South African National cancer registry 2005. Http://www.cansa.org.za/files/2013/09/NCR-Cancer-Tables-2005.pdf

17. Correa P, O'Conor GT. Geographic pathology of lymphoreticular tumors: summary of survey from the geographic pathology committee of the International Union Against Cancer. Journal of the National Cancer Institute 1973;50:1609–17.

18. Hjalgrim H, Engels EA. Infectious aetiology of Hodgkin and non- Hodgkin lymphomas: a review of the epidemiological evidence. Journal of Internal Medicine 2008;264 (6):537–48.

19. Armstrong AA, Alexander FE, Paes RP, et al. Association of Epstein–Barr virus with pediatric Hodgkin Lymphoma. American Journal of Pathology 1993;142: 1683–8.

20. Herbst H, Pallesen G, Weiss LM, et al. Hodgkin lymphoma and Epstein–Barr virus. Annals of Oncology 1992;3(Suppl. 4): 27–30.

21. Mueller N, Evans A, Harris NL, et al. Hodgkin's disease and Ebstein-Barr virus. Altered antibody pattern before diagnosis. New Engl Journal Med 320: 689 – 695.

22. Patel M, Philip V, Fazel F. Human immunodeficiency virus infection and Hodgkin's lymphoma in South Africa: An emerging problem. Advances in Heam. 2011. Article ID 578163.

23. Biggar R, Jaffe E, Goedert J, et al. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. BLOOD. 2006;108(12):3786-3791.

24. Chimienti E, Spina M, Gastaldi R, et al. "Clinical characteristics and outcome of 290 patients with Hodgkin's disease and HIV infection (HD-HIV) in pre and HAART (highly active anti-retroviral therapy) era," Annals of Oncology, vol. 19, 2008, abstract no. 168.

25. Hjalgrim H, Askling J, Rostgaard K, et al. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. New England Journal of Medicine 2003;349(14):1324–32.

26. Ferrais AM, Racchi O, et al. Familial Hodgkin's disease: a disease of young adulthood? Ann Hematol 1997; 74: 131-134.

27. Longo DL, Fauci AS, Kasper DL, et al. Malignancies of lymphoid cells. Chpt 113.707-711. Harrison's principles of internal medicine. 14th edition. McGraw-Hill.

28. Jon C, Aster MD. Disease of white blood cells, lymph nodes, spleen and thymus. Robbins and Cotran Pathologic basis of disease. 7th edition. Chpt 14. 686-690. Elsiever Saunders.

29. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin Lymphoma Staging Classification. Cancer Research 1971;31:1860–1.

30. Lister TA, Crowther D, Sutcliffe SB. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Onc 1989; 7 (11) 1630-1636.

31. Hansmann ML, Willenbrock K. WHO classification of Hodgkin's lymphoma and its molecular pathological relevance. Pathologe 2002;23 (3):207-18. Abstract.

32. De Vita VT, Mauch PM and Harris NL. Hodgkins disease. In: Cancer principles and practice of oncology (ed. by VT De Vita, S Hellman and SA Rosenberg) pp 2242-2283. Lippincott. Philadephia. 1997.

33. Howell SJ, Grey M, Chang J, Morgenstern GR, Cowan RA, Deakin DP, Radford JA. The value of bone marrow examination in the staging of Hodgkin's lymphoma: a review of 955 cases seen in a regional cancer centre. 2002 Nov;119(2):408-11.

34. Doll DC, et al. Bone marrow biopsy in the initial staging of Hodgkin's disease. Med and Paed Oncol. 17; 1-5.

35. Munker R, Hasenclever D, Brosteanu O, Hiller E, Diehl V. Bone marrow involvement in Hodgkin's disease: an analysis of 135 consecutive cases. German Hodgkin's Lymphoma Study Group. J Clin Oncol.1995;13(2):403-9.24.

36. Simpson CD, Gao J, Fernandez CV, Yhap M, Price VE, Berman JN. Routine bone marrow examination in the initial evaluation of paediatric Hodgkin lymphoma: the Canadian perspective. Br J Haematol. 2008;141(6):820-6.

37. Mahoney DH, Jr., Schreuders LC, Gresik MV, McClain KL. Role of staging bone marrow examination in children with Hodgkin disease. Med Pediatr Oncol. 1998;30(3):175-7.

38. Pakos EE, Fotopoulos AD, Ioannidis JPA. 18F-FDG PET for Evaluation of Bone Marrow Infiltration in Staging of Lymphoma: A Meta-Analysis. J Nucl Med. 2005; 46:958–963.

39. Kabickova E, Sumerauer D and Cumlivska E. Comparison of 18F-FDG-PET and standard procedures for the pretreatment staging of children and adolescents with Hodgkin's disease. Eur J Nucl Med Mol Imaging. 2006; 33:1025–1031.

40. Moulin-Romsee G, Hindié E, Cuenca X, et al. (18)F-FDG PET/CT bone/bone marrow findings in Hodgkin's lymphoma may circumvent the use of bone marrow trephine biopsy at diagnosis staging. Eur J Nucl Med Mol Imaging. 2010. 37(6):1095-105.

41. Munker R, Glass J, Griffeth LK, Sattar T, Zamani R, Heldmann M, et al. Contribution of PET imaging to the initial staging and prognosis of patients with Hodgkin's disease. Ann Oncol 2004;15(11):1699–704.

42. Pelosi E, Penna D, Deandreis D, Chiappella A, Skanjeti A, Vitolo U, et al. FDG-PET in the detection of bone marrow disease in Hodgkin's disease and aggressive non-Hodgkin's lymphoma and its impact on clinical management. Q J Nucl Med Mol Imaging 2008;52(1):9–16. (Abstract)

43. Cerci JJ, Pracchia LF, Soares Junior J, Linardi Cda C,Meneghetti JC, Buccheri V. Positron emission tomography with 2-[18F]-fluoro-2-deoxy-D-glucose for initial staging of Hodgkin's lymphoma: a single center experience in Brazil. Clinics (Sao Paulo) 2009;64:491–8.

44. Purz S, Mauz-Ko¨rholz C, Ko¨rholz D, et al. [18F]Fluorodeoxyglucose Positron Emission Tomography for Detection of Bone Marrow Involvement in Children and Adolescents with Hodgkin's Lymphoma. J Clin Oncol. 2011. 29 (26): 3523-3528.

45. Cheng G, Chen W, Chamroonrat W, et al. Biopsy versus FDG PET/CT in the initial evaluation of bone marrow involvement in pediatric lymphoma patients. Eur J Nucl Med Mol Imaging 2011. 38:1469–1476.

46. Muzahir S, Mian M, FRCR, FCPS, Munir R, et al. Clinical utility of 18F FDG-PET/CT in the detection of bone marrow disease in Hodgkin's lymphoma. Brit J Radiol. 2012. 85: e490-e496.

47. Wu L, Chen F, Jiang X, Gua H, Yina Y, Xua J. 18F-FDG PET, combined FDG-PET/CT and MRI for evaluation of bone marrow infiltration in staging of lymphoma: A systematic review and meta-analysis. European Journal of Radiology 2012. 81 303–311.

48. Berthet L, Cochet A, Kanoun S, Berriolo-Riedinger A, Humbert O, Toubeau M, Dygai-Cochet I, Legouge C, Casasnovas O, and Brunotte F. In newly diagnosed diffuse large B-cell lymphoma determination of bone marrow involvement with 18F-FDGPET/CT provides better diagnostic performance and prognostic stratification than does biopsy. J Nucl Med 2013; 54:1244–1250.

49. Http://www.eanm.org/publications/guidelines

50. Salaun P, Gastinne T, Bodet-Milin C, et al. Analysis of 18F-FDG PET diffuse bone marrow uptake and splenic uptake in staging of Hodgkin's lymphoma: a reflection of disease infiltration or just inflammation? Eur J Nucl Med Mol Imaging. 2009; 36(11):1813-21.

51. Abouzied MM, Crawford ES, Nabi HA. 18F-FDG Imaging: Pitfalls and Artifacts. J Nucl Med Technol 2005; 33:145–155.

52. Lin EC, Alavi A. PET and PET/CT a clinical guide. Thieme medical publisher, Inc. 2005. 42-77.

53. Sarji SA. Physiological uptake in FDG PET simulating disease. Biomed Imaging Interv J 2006; 2(4):e59.

54. Pelosi E, Penna D, Douroukas A, Bellò M, Amati A, Arena V, Passera R, Bisi G. Bone marrow disease detection with FDG-PET/CT and bone marrow biopsy during the staging of malignant lymphoma: results from a large multicentre study. Quart J of Nucl Med and Mol imaging. 2011; 55(4):469-75. (Abstract).

Appendix

Ethics clearance certificates