

## Evaluation of the Patterns of Bone Marrow Involvement in Non-Hodgkin's Lymphoma by Bone Marrow MRI with Correlation to Bone Marrow Biopsy and Response to Chemotherapy

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### ABSTRACT

**Methods & Materials:** Forty-two consecutive patients with De novo non-Hodgkin's lymphoma were examined by MRI and bone marrow biopsy to detect bone marrow infiltration. MRI of the femoral or humeral marrow was obtained by T1-weighted spin echo method and the short T1 inversion recovery technique.

**Results:** Twenty-three patients (54.8%) had abnormal positive MRIs of the femoral or humeral marrow on both T1-weighted SE and STIR images. In thirteen patients out of them, bone marrow aspiration and biopsy results were co-ordinate with MRI findings and revealed bone marrow infiltration. While, in ten patients, suspected infiltration was detected with MRI, without histologic evidence for bone marrow involvement, follow-up of those ten patients after treatment with chemotherapy, revealed that only one patient (2.4%) still had abnormal signal intensity on MRI. Three abnormal MRI patterns were observed scattered (65.2%), uniform (21.7%) and nodular (13.1%). There was no correlation between the pattern of involvement and histologic subtype. Abnormal MRI studies were not significantly correlated with clinical parameters such as B symptoms, generalized bone pain or biochemical parameters such as elevated serum level of LDH or alkaline phosphatase.

**Conclusion:** In conclusion, the present results showed that MRI may be effective in evaluation of bone marrow infiltration in malignant lymphoma and provide a non-invasive and sensitive approach for imaging of bone marrow, therefore, MR imaging can be included routinely in the staging of malignant lymphoma as an adjunct to blind bone marrow aspiration and biopsy in the evaluation of bone marrow status.

**Key Words:** Non-Hodgkin's lymphoma - Bone marrow infiltration - MRI.

### INTRODUCTION

Detection of bone marrow involvement is

important for staging, treatment decisions and prognosis in patients with malignant lymphoma. Although, routine bone marrow evaluation is based on aspirates and bone marrow biopsies, new diagnostic tools are required to improve diagnostic accuracy. Blind bone marrow biopsies and aspirates may fail to provide an adequate representation of the bone marrow [5,6]. Non-Hodgkin's lymphomas are characterized by a heterogeneous pattern of bone marrow involvement. The incidence of bone marrow involvement in Non-Hodgkin's lymphomas is highest in patients with small lymphocytic lymphoma (> 80%) and mantle cell Non-Hodgkin's lymphoma [5,6,8,9,20]. In diffuse aggressive lymphoma, the incidence of involvement of the marrow ranges from 5% to 34% [11,20]. Visual and quantitative assessment of the bone marrow by magnetic resonance (MR) imaging is useful for detection of occult lymphomatous marrow involvement. In the past, bone marrow imaging was based on conventional radiology, nuclear medicine and computed tomography; they all exhibited some capabilities but also some limitations [16]. Bone image on MR scan is due to bone marrow, with its different components of red and yellow marrow. Since red marrow is mostly liquid and yellow marrow contains large amounts of fat, the signal will vary, on T1-weighted images according to their different proportions [16,17,21]. In T1-weighted spin echo (SE) images, the fatty marrow appears bright, whereas the cellular marrow, with its lower fat content, exhibits a low signal intensity [15]. The

femoral and humeral marrow of adults is largely fatty [3]. They allow for evaluation of malignant involvement and assessment of disease severity over time. MRI of the femoral or humeral marrow, therefore, seems to be the most suitable method for detecting involvement of the marrow in adults with hematologic malignancies [22]. So, our aim was to study patterns of involvement on femoral and/or humeral marrow MRI in De novo non-Hodgkin's lymphoma patients and compare it to the histological finding in bone marrow samples through bilateral bone marrow biopsy and to evaluate the response to chemotherapy in relation to these parameters.

## PATIENTS AND METHODS

### *Patients:*

Forty-two De novo patients with non-Hodgkin's lymphoma who presented to clinical Oncology Unit and Medical Oncology Unit, Zagazig University Hospital and Clinical Oncology Department, Faculty of Medicine and Beni-Sweef Branch of Faculty of Medicine, Cairo University, from September 1997 to May 1999, were examined by bone marrow MRI and bone marrow biopsy to detect bone marrow infiltration. Patients characteristics are listed in Table (1). NHL were subclassified according to the Working Formulation [25]. Extent of disease was determined on the basis of Ann Arbor Staging classification [4].

### *Methods:*

All patients were clinically examined and subjected to routine laboratory and radiological investigations for proper staging and also specific investigations as regard femoral or humeral MRI and bilateral bone marrow biopsy.

### *Bone marrow MR imaging:*

MRI was performed before biopsy or initiation of therapy, on a 0.5 Tesla superconducting magnet using the body coil. Coronal T1-weighted SE images of the femur or humerus were obtained in a 256 x 256 matrix with (TR/TE = 400/20). Coronal STIR images of the femur and humerus were also obtained by using 2500/20/160 (TR/TE/T1). The section thickness was 5 mm with interslice gap of 1 mm. In patients with bone marrow abnormalities T1-weighted spin-echo MR images were repeated

immediately after I.V administration of 0.1 mmol/kgm of gadoterate megalumine.

### *MR image interpretation:*

The MRI results were evaluated and classified as positive when T1-weighted images and STIR images are abnormal. The positive finding on femoral or humeral marrow MRI were categorized as follows: nodular pattern: characterized by nodular areas of fatty marrow replacement with a signal intensity that was lower than that of the muscle. Scattered pattern: characterized by multiple scattered foci of marrow replacement on a background of uninvolved marrow and uniform pattern: characterized by a uniform replacement of fatty marrow. Enhancement of the lesion signal intensity was assessed after contrast material injection and was categorized as either diffuse homogenous, only peripheral, or absent [16].

### *Histologic assessment:*

The time between MR imaging and bone marrow biopsy ranged from 1 to 7 days (median 3 days). Bone marrow biopsy was obtained by Islam needle from the posterior iliac crest at the time of diagnosis. Bilateral bone marrow biopsy and bone marrow aspiration were performed in all the 42 patients. Three forms of bone marrow infiltration were recognized:

- 1- Interstitial (spaced among the haematopoietic cells).
- 2- In aggregates or nodules (intertrabecular or parasinusoidal, small or large, single or multiple).
- 3- Paratrabecular.

The criteria for neoplastic lymphoid bone marrow infiltration: irregular, cellular atypia, more than 3 mm in diameter, no germinal centers and more than three aggregates per trephine [5,6,13].

### *Treatment and patient follow-up:*

All patients received standard therapy with CHOP protocol. Cycles were repeated every 21 days. A minimum of 6 cycles was given or until 2 cycles after disappearance of the disease. The patients had their re-evaluation by femoral and/or humeral marrow MRI and bilateral bone marrow biopsy after 3 cycles of therapy and at the end of chemotherapy.

*Statistical analysis:*

Data were entered; checked and analyzed using EPI-INFO (version 6.1) software package [7].

**RESULTS***Comparative results of femoral or humeral MRI and bone marrow aspiration and biopsy: (Table 2)**- Before treatment:*

In 42 newly diagnosed patients with NHL, 23 (54.8%) had abnormal positive MRIs of the femoral or humeral marrow on both T1-weighted SE and STIR images. Thirteen patients (30.9%) had positive findings on both the MRI and bone marrow aspiration and biopsy. All patients with positive bone marrow aspiration or biopsy results showed abnormal images on their femoral or humeral marrow MRI. Ten patients (23.8%) showed positive findings on MRI of the femoral or humeral marrow despite normal bone marrow histology.

*- After 3 cycles of chemotherapy:*

After 3 cycles of chemotherapy, six out of ten patients that showed positive findings on MRI despite normal bone marrow histology had complete resolution, 8 patients out of 13 (38.5%) with positive bone marrow aspiration and biopsy and positive MRI showed no abnormal findings on their bone marrow aspiration or biopsy and femoral or humeral marrow MRI.

*- After completion of chemotherapy:*

After chemotherapy, only 2 (15.4%) of patients with positive bone marrow aspiration and biopsy and positive MRI still had abnormalities on bone marrow biopsy and MRI while 1 patient (10%) with positive findings on marrow MRI despite normal bone marrow histology still had abnormality on marrow MRI.

*Patterns of involvement of femoral or humeral marrow on MRI: (Table 3)*

From 23 patients with positive MRI, 3 patients (13.1%) exhibited a nodular pattern (Fig. 1), 5 patients (21.7%) demonstrated a uniform pattern (Fig. 2) and 15 (65.2%) exhibited a scattered pattern of marrow involvement (Fig. 3). In the 13 patients with positive results on bone marrow aspiration and biopsy, 8 showed a scattered pattern on MRI and 5 demonstrated a uniform pattern.

*Femoral and humeral marrow MRI and histopathological subtype of lymphoma: (Table 4)*

Analysis of patients according to the histopathological type revealed that in low grade NHL, non of the patients showed normal findings on MRI despite positive bone marrow aspiration and biopsy. Positive MRI imaging results despite negative bone marrow aspiration and biopsy results were observed in 1 patient with low grade NHL (10%), 7 patients (28%) with intermediate grade NHL, 1 patient (16.7%) with high grade NHL and 1 patient with unclassified NHL. There was no correlation between the histologic subtype and the pattern of involvement observed on the femoral or humeral marrow MRI (Table 5).

*Immunophenotype and femoral or humeral marrow MRI:*

Both patients with B-cell and T-cell lymphomas demonstrated similar frequency of positive MRI findings despite negative bone marrow aspiration and biopsy (24% and 28.6% respectively), while the frequency of patients with positive findings on both the MRI and bone marrow aspiration and biopsy was higher in patients with T-cell lymphomas (57%) than in those with B-cell lymphomas (20.7%). A uniform pattern of involvement on MRI was observed only in patients with B-cell lymphomas.

*Clinical, biochemical parameters and femoral or humeral marrow MRI: (Table 5)**- Serum LDH level and femoral or humeral MRI:*

In 12 out of 18 patients with elevated level of serum LDH (66.7%), MRI showed positive findings and in 11/24 patients (45.8%) with normal serum level of LDH, MRI were positive. The uniform pattern of involvement is suggested to reflect the highest tumour burden. The serum LDH levels in the patients with a uniform pattern, however, did not differ significantly from those in patients with other MRI patterns.

*- Serum alkaline phosphatase level and femoral or humeral MRI:*

The serum level of alkaline phosphatase was found elevated in 10 patients (62.5%) with positive findings on MRI, while 13 patients (50%) with positive MRI had a normal serum level of alkaline phosphatase.

**- B symptoms and femoral or humeral MRI:**

Abnormal signal intensity on the femoral or humeral MRI was detected in 55% of patients with B symptoms (11/20 patients) while out of 22 patients without B symptoms, 12 patients (54.5%) showed abnormal signal intensity on femoral or humeral MRI.

**- Bone pain and femoral or humeral MRI:**

50% of patients (9/18) complaining of generalized bone pain showed positive findings on femoral or humeral MRI. On the other hand, 58.3% (14/24) of patients without generalized bone pain showed positive MRI findings.

Table (1): Characteristics of 42 patients with malignant lymphoma.

<b>Age:</b>	
Median (range)	53 years (16 to 62)
<b>Sex:</b>	
Male/female	25/17
<b>Histopathology:</b>	
Low grade	10
Intermediate grade	25
High grade	6
Other	1
<b>Immunophenotype:</b>	
B/T	35/7
<b>Ann arbor stage*:</b>	
I	2
II	10
III	18
IV	12
<b>B symptoms:</b>	
Absent	22
Present	20
<b>Bone pain:</b>	
Absent	24
Present	18
<b>Serum LDH level:</b>	
≤ 1 x normal	24
> 1 x normal	18
<b>Serum alkaline phosphatase:</b>	
≤ 1 x normal	26
> 1 x normal	16
<b>Hemoglobin:</b>	
≤ 11 g/dl	10
> 11 g/dl	32

\* Staging was done before MRI examination.

Table (2): Comparative results of femoral or humeral marrow MRI and bone marrow biopsy in 42 patients.

Before treatment:		
Biopsy results	MRI results	
	Normal (%)	Positive (%)
Negative	19 (45.2)	10 (23.8)
Positive	0 (0)	13 (30.9)
After 3 cycles of chemotherapy:		
Biopsy results	MRI results	
	Normal (%)	Positive (%)
Negative	33 (78.6)	4 (40)
Positive	0 (0)	5 (38.5)
After chemotherapy:		
Biopsy results	MRI results	
	Normal (%)	Positive (%)
Negative	39 (92.9)	1 (10)
Positive	0 (0)	2 (15.4)

Table (3): Patterns of involvement on MRI and positive bone marrow biopsy.

Pattern of MRI involvement	No. on MRI	No. of +ve B.M. biopsy
Scattered	15 (65.2%)	8 (53.3%)
Uniform	5 (21.7%)	5 (100%)
Nodular	3 (13.1%)	0 (0%)

Table (4): Femoral or humeral marrow MRI and histopathology of lymphomas.

Histopathology	MRI/biopsy			
	-ve/-ve ¥	-ve/+ve §	-ve/+ve *	-ve/+ve **
Low grade (n=10)	4	0	1	5
Intermediate grade (n=25)	12	0	7	6
High grade (n=6)	3	0	1	2
Unclassified (n=1)	0	0	1	0

¥ Normal MRI/negative BM biopsy.

§ Normal MRI/positive BM biopsy.

\* Positive MRI/negative BM biopsy.

\*\* Positive MRI/positive BM biopsy.

Table (5): Patterns of involvement of femoral or humeral marrow MRI and histopathologic subtypes of lymphoma.

Histopathologic subtype	Patterns of involvement		
	Scattered	Uniform	Nodular
Low grade (10)	5	4	1
Intermediate grade (25)	7	-	1
High grade (6)	2	1	1
Unclassified (1)	1	-	-

Table (6): Clinical and biochemical parameters and positive femoral or humeral MRI.

<b>Serum LDH:</b>	
≤ 1 X normal	11/24 (45.8%)
> 1 X normal	12/18 (66.7%)
<b>Serum alkaline Phosphatase:</b>	
≤ 1 X normal	13/26 (50%)
> 1 X normal	10/16 (62.5%)
<b>B symptoms:</b>	
Absent	12/22 (54.5%)
Present	11/20 (55%)
<b>Bone pain:</b>	
Absent	14/24 (58.3%)
Present	9/18 (50%)



Fig. (1): 40 years-old man with non-Hodgkin's lymphoma.

(A & B): Coronal T1-weighted SE MR image show multiple nodular area of low signal intensity in the head and shaft of the humerus.

(C): After contrast material injection show diffuse homogenous lesion enhancement.

Fig. (2): 17 years-old man with non-Hodgkin's lymphoma.

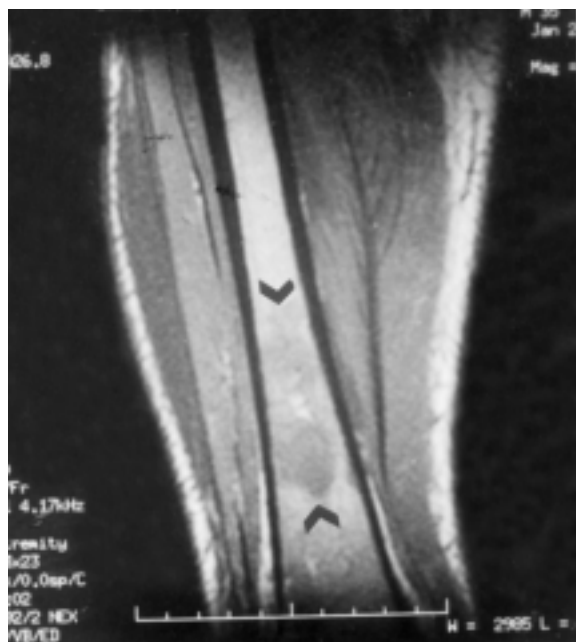


Fig. (2-A): Coronal T1-weighted SE MR image show multiple scattered area of low signal intensity in the shaft of the femur.

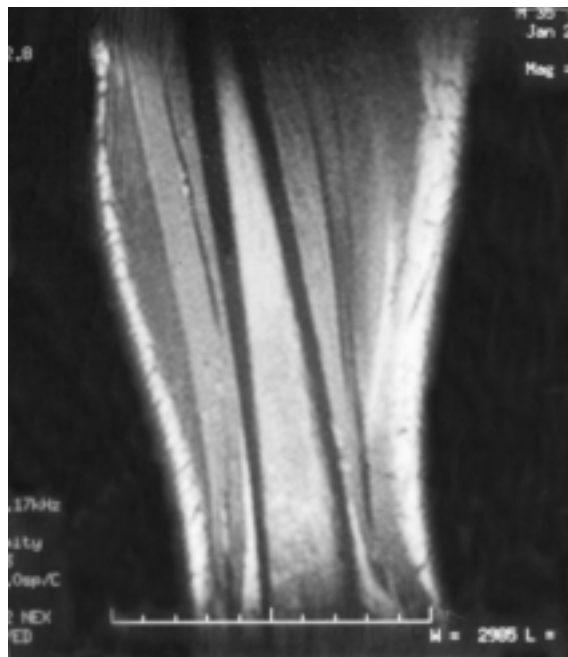


Fig. (2-B): Corresponding MR image after treatment shows the scattered area still present.

Fig. (3): 35 years-old man with non-Hodgkin's lymphoma.

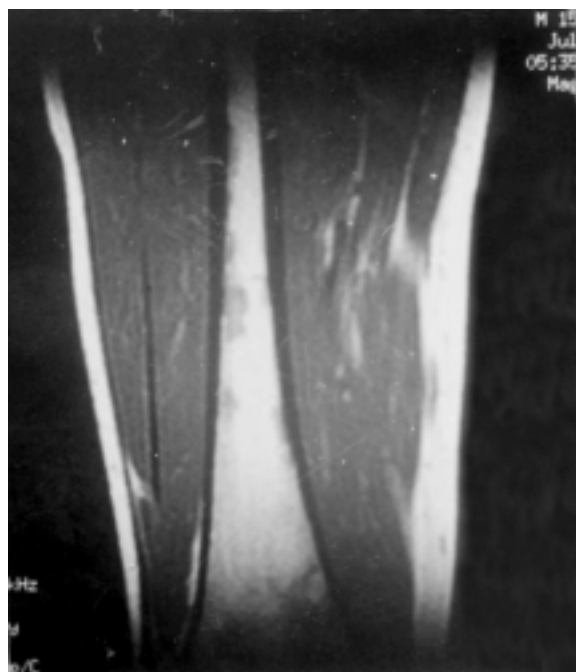


Fig. (3-A): Coronal T1-weighted SE MR image show uniform replacement of the bone marrow with large focal area of low signal intensity in the shaft of the femur.

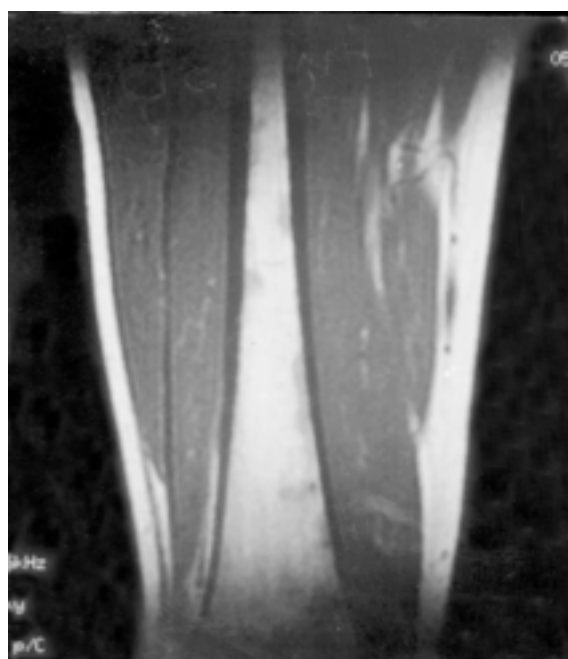


Fig. (3-B): Corresponding MR image after treatment show normal high signal intensity marrow.

## DISCUSSION

MRI is currently the only non-invasive method detecting changes of bone marrow. MRI enables us to visualize the bone marrow with high contrast and spatial resolution by assessing different properties of the biological tissue mainly fat, water and mineral content [18]. The histological examination of bone marrow specimens is one of the standard procedures in staging non-Hodgkin's lymphoma. To investigate the validity of a conventional iliac crest biopsy, we performed a prospective study comparing histological findings in bone marrow samples and MRI of bone marrow. Forty two consecutive patients with non-Hodgkin's lymphoma were studied. In 19 patients (45.2%), MRI and iliac crest biopsies were negative for marrow infiltration. In 30.9% (13 patients) bone marrow involvement was demonstrated by both MRI and bone marrow biopsies. However, in 10 patients (23.8%) MRI showed evidence of lymphomatous involvement despite normal bone marrow histology. Several studies have reported results of comparisons of MRI of bone marrow in patients with malignant lymphomas. In these studies, abnormal findings on marrow MRI were detected in 15 to 46% of patients with malignant lymphomas [12,22,23,24,26]. Some studies reported malignant infiltration of bone marrow in 3.5 to 10% of patients with lymphoma revealed by bone marrow biopsy in absence of bone marrow abnormalities on MRI [2,10,13]. However, in the present study and in the study of Takagi et al., no patient with marrow involvement revealed by bone marrow biopsy showed a normal MRI of the femoral or humeral marrow [21].

After completion of chemotherapy, 15.4% (2 patients) had bone marrow involvement revealed by both MRI and bone marrow biopsy and only 10% (1 patient) in the group which had abnormal signal intensity on MRI and normal bone marrow histology, still have abnormal signal intensity on MRI. The observation of resolution or progression of abnormal signal intensity on follow-up MRI may provide indirect evidence of lymphomatous marrow involvement in these patients. Further bone marrow biopsies may increase the yield of positive bone marrow biopsies. MR images of additional areas may increase the probability of a correct diagnosis, although the present study is limited to femoral or humeral marrow. Van de Berg et al., have re-

ported that the causes of abnormal signal intensity on marrow MRI were confirmed in 60% of patients with positive MRI findings despite a normal bone marrow histology, after such follow-up [26]. In the present study, follow-up examinations confirmed that abnormal MRI of the femoral or humeral marrow may represent occult marrow involvement in 90% of these patients. The patients with untreated lymphomas in the present study showed nodular, scattered, or uniform MRI patterns. If a nodular pattern implies a limited involvement of the bone marrow by lymphoma cells and conversely, if a uniform pattern indicates a diffuse involvement of the marrow, the frequency of lymphomatous involvement of the marrow detected by bone marrow biopsy from posterior iliac crest should be correlated with these MRI patterns. In the present study, the frequency of marrow involvement detected by bone marrow biopsy in patients with nodular, scattered and uniform patterns was 0%, 53.3% and 100% respectively. Linden et al., in their series reported similar results, 0% for nodular pattern, 52% for scattered pattern and 100% for uniform pattern of involvement on MRI and positive bone marrow biopsy [13]. If these MRI patterns of femoral or humeral marrow represent lymphomatous involvement of the marrow, there may be some correlation between the distribution or extent of marrow involvement and histopathological type and immunophenotype of the lymphoma cells. In the present study, neither the pathology of lymphomas nor the immunophenotype influenced the MRI pattern. Interestingly, all patients who showed a uniform pattern on the MRI in the present study had B-cell lymphomas. Further study is needed to determine whether B-cell lymphomas involves the bone marrow more uniformly than do T-cell lymphomas.

Marrow involvement in lymphoma patients indicate advanced disease. Clinical and biochemical parameters such as the presence of B symptoms, generalized bone pain, serum level of LDH, serum level of alkaline phosphatase may reflect the extent of disease [19]. However, in the present study, these clinical and biochemical parameters failed to show significant correlation with abnormal signal intensity on MRI or with the MRI patterns. Also, Takagi et al., in their series did not show a significant correlation between an elevated LDH level with abnormal signal intensity on MRI or with MRI pat-

terns [21]. Although, Tardivon et al., reported that abnormal MRI studies were significantly associated with constitutional symptoms, bone pain and an elevated alkaline phosphatase level [24].

An abnormal signal intensity on the femoral or the humeral marrow MRI may be influenced by physiological factors as age-related changes in marrow distribution and by pathological conditions such as anemia or the presence of other space-occupying bone marrow diseases [1,12,14,16,23,26]. In our study, the median age of 42 patients was 53 years and only 2 patients were under the age of 20, therefore, the age-related changes of the marrow from red to yellow did not influence our MRI results. The hemoglobin level of our patients at the time of MRI evaluation was unrelated to the MRI patterns. In addition, none of our patients had other bone marrow diseases that could influence the MRI.

In conclusion, the present results showed that MRI is effective in evaluation of bone marrow infiltration in malignant lymphoma and provide a non-invasive and sensitive approach for imaging of bone marrow. MRI is recommended for optimal staging of lymphoma, as blind bone marrow biopsies appear to have low sensitivity for bone marrow infiltration because of frequent involvement in noncrest marrow. In addition MRI can also be used to follow-up the disease as well as therapy by showing regression of these bone marrow lesions therefore, MR imaging should be included routinely in the staging of malignant lymphoma as an adjunct to blind bone marrow aspiration and biopsy in the evaluation of bone marrow status but large number of patients are needed to confirm the findings of this study.

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