Original Article

The Value of Positron Emission Tomography Scan in Staging of Lymphoma in a Sample of Iraqi Patients

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Abstract

Background: A diverse range of illnesses known as lymphomas are caused by immune system constituent cells or their progenitors.[18]F-Fluorodeoxyglucose positron emission tomography (PET)/computerized tomography has been routine practice to improve the characterization and prognosis of both Hodgkin and non-Hodgkin lymphomas (NHLs). **Objectives:** The objective of the study was to assess the role of positron emission tomography (PET) scan in clinical evaluation of lymphoma and its ability to identify the correct stage of lymphoma. **Patients and Methods:** cross-sectional follow-up study was conducted on 50 patients with pathologically proven lymphoma in 2021 who were admitted to the hospital. All patients included in the study performed computed tomography (CT) and PET scan for initial staging. **Results:** In NHL, PET scan staging differed significantly from clinical in two stages; there were 7 patients versus none with Stage II according to clinical and PET scan staging, respectively. Furthermore, only five patients had Stage IV according to clinical staging versus 17 patients in PET scan staging. Accordingly, there was no agreement between the two modalities ($\kappa = 0.085$, 95% = 0.045–0.123, $P = 0.394$). In Hodgkin lymphoma (HL), the two modalities differ significantly in the appraisal of Stage IV, in which there were 2 patients based on clinical staging and 11 patients according to PET scan staging. Thus, there was a poor agreement between the two modalities ($\kappa = 0.314$, 95% confidence interval = 0.283–0.376, $P = 0.002$). PET scan upstaged 50% and 61.54% of the patients with HL and NHL, respectively, with a highly significant difference, whereas there was no change in staging for 50% and 34.62%, respectively, with a highly significant difference. In NHL, PET scan demonstrated higher positive bone marrow (BM) involvement than biopsy (34.62% vs. 19.23%) with a highly significant difference. Similarly, in HL, PET scan revealed far more positive BM involvement than biopsy (45.83% vs. 8.33%) with a highly significant difference. **Conclusions:** There is poor or no agreement between PET scan and clinical staging of lymphoma, with high detection with PET scan for BM involvement compared with CT scan, which leads to the identification of additional involved sites of patients with lymphoma.

Keywords: Bone marrow, lymphoma, positron emission tomography scan, staging

Introduction

A wide variety of hematological cancers with shared lymphoid cell ancestry are known as lymphoid neoplasms. There are currently more than 40 categories of non-Hodgkin lymphoma (NHL) and five categories of Hodgkin lymphoma (HL) in the WHO classification of lymphoid neoplasms.[1] Over the past 50 years, improvements in lymphoma diagnosis and treatment have resulted in significantly better prognoses for the majority of patients.[2] However, effective treatment poses new challenges, such as improving the assessment of treatment response, reducing the risk of relapse, and reducing the patient's risk of toxicity. The use of complex anatomical and functional imaging modalities has expanded and staging recommendations have changed, now focusing on positron emission tomography (PET) imaging.[3]

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Leading representatives of the Lymphoma Clinical and Imaging Subcommittee presented their research at the International Conference on Malignant Lymphoma in 2011 and 2013, and the Lugano classification was most recently published father soon after.[3] With the aim of creating a system of simple, clear, and consistent feedback assessment and reporting steps, this new classification has significant improvements over previous feedback assessment criteria.[4]

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The improved F-fluorodeoxyglucose (FDG) PET/computed tomography (CT) and CT-based response evaluation of lymphoma provided by the new Lugano classification directs therapeutic trials and clinical treatment based on imaging. The majority of common lymphoma forms, including as HL, follicular NHL, diffuse large B-cell NHL, and mantle cell NHL, are frequently FDG avid.[5] For attenuation correction and anatomic localization, PET is often conducted with low-dose unenhanced CT; however, diagnostic CT (which may be included in PET/CT for FDG-avid lymphomas) is advised at baseline staging for anatomic assessment. The staging and response assessment of lymphomas with limited or variable FDG uptake, however, are done using CT.[6]

Initial staging with F-fluorodeoxyglucose positron emission tomography

Thanks to its low cost and extensive availability, CT is the most widely utilized imaging modality for staging malignant lymphoma.[7] Nevertheless, the lack of functional information in CT makes it difficult to detect lesions that have little contrast with the surrounding tissue and to diagnose disease in organs of normal size.[8] Another disadvantage of CT scans is that they are not reliable in identifying bone marrow (BM) disease, indicating Stage IV disease if present. Patients also receive ionizing radiation during the CT scan. An effective dose of 20–25 mSv is associated with each scan, including the neck, chest, abdomen, and pelvis.[7] In contrast, in an independent whole-body PET study, the effective dose was approximately 3.3–7.6 mSv per scan.[9]

The ^{18}F-FDG's utility in numerous studies has shown the value of PET in the early staging of lymphoma. Its primary benefit over anatomical imaging methods, such CT scans, is its capacity to identify metabolic alterations in malignant lymphoma-affected areas before the manifestation of structural alterations. Compared to CT, it can identify a greater number of lesions, and up to 8%–20% of patients may have their stage changed. Conventional CT may overlook occult lesions, whereas PET may highlight them or pick them up.[10]

There is a great deal of agreement between the BM biopsy and the locations of localized FDG uptake in the BM. Indeed, a significant negative predictive value for ruling out BM involvement has been shown by PET scans. This is especially true for HL in its early stages, and in this case, a BM biopsy may not even be necessary. Being a whole-body imaging technique, FDG-PET/CT also has the primary benefit of guiding the biopsy from a readily accessible and metabolically active region.[11]

Numerous studies have examined PET's capacity to distinguish between indolent and aggressive lymphomas. HL and aggressive NHL, such as diffuse large B-cell lymphoma (DLBCL) and Grade III FLs, are frequently ardent users of FDG. Nonetheless, limited or absent FDG uptake is possible in certain NHL subtypes, primarily indolent lymphomas such MZLs and peripheral T-cell lymphomas.[12] An unfavorable/negative FDG complementary anatomical imaging, such as contrast-enhanced CT or magnetic resonance imaging (MRI), is necessary to increase the detection rate of the lesions because PET scans do not always rule out illness.[11] This is true even though when it comes to staging and restaging patients with indolent lymphoma, PET/CT provides information that is noticeably more accurate than both PET and CT.[13]

In addition and based on the level of FDG avidity, PET/CT can also identify the Richter transformation – a change in a low-grade lymphoma into a more aggressive subtypes.[14]

Interpretation of positron emission tomography/computed tomography staging in lymphoma patients

Visual inspection is considered sufficient to assess whether the PET scan is abnormal in patients classified according to PET/CT. In contrast to normal uptake, highly concentrated uptake in nodal and extranodal regions is often noted in PET/CT reports. When evaluating the pattern, distribution, and characteristics of CT, it is important to distinguish pathological. Uptake from other sources of elevated FDG uptake, such as infection and inflammation.[15]

Lymphatic structures in the head and neck (lymph nodes of Waldeyer's ring) are often the site of physiological or reactive FDG uptake, often observed as FDG accumulation in macrophages and lymphocytes. This type of fixation is easy to explain, especially since it is mild, symmetrical, and does not correspond to any anatomical abnormality. Physiological changes in FDG may be seen in other organs, including salivary glands, muscles, blood vessels, and vocal cords. In these cases, an accompanying CT scan is important for diagnosis and localization.[16]

Study objectives

The objective of the study was to assess the role of PET scan in the clinical evaluation of lymphoma and its ability to identify the correct stage of lymphoma.

Patients and Methods

Design and settings

This prospective cross-sectional study was performed on 50 patients with lymphoma who visited the hematology department in 2022. All cases had their histopathological diagnosis of lymphoma confirmed following surgery or image-guided biopsy. None of the cases had any prior medical treatment.

Inclusions criteria

- All patients with pathologically proven HL and aggressive type NHL from both sexes who did not receive any previous treatment.

Exclusion criteria

- Patients with chronic diseases such as diabetes mellitus and renal failure
- Pregnant and breastfeeding women
- Patients with a history of previous known hypersensitivity reaction to the used contrast material.

Ethical consideration

Verbal informed consent was obtained from each participant before enrollment after explaining the purpose of the study. Data confidentiality throughout the study was assured, and patients were assured that data would be used for research purposes only.

Data collection

Every patient provided the following clinical information: age, gender, clinical stage, extranodal involvement, presence of B symptoms, bulky disease, and WHO-classified histological subtype. Every subject under study had a BM evaluation to determine the degree of BM involvement for staging purposes.

Imaging

At the time of diagnosis, all study participants had CT and ^{18}F-FDG PET/CT.

The Ann Arbor staging method[3] served as the basis for the staging definition. Rituximab 375 mg/m^2 and bendamustine 70–90 mg/m^2 were used as treatments for NHL. 750 mg/m^2 of cyclophosphamide, 50 mg/m^2 of doxorubicin, 1.4 mg/m^2 of vincristine, 40 mg/m^2 of prednisone, and 375 mg/m^2 of rituximab were the prescribed doses for DLBCL. The Nordic Lymphoma Group's treatment recommendations were followed for HL in its early stages. The first line of treatment was dacarbazine, vinblastine, bleomycin, and adriamycin at standard doses every 2 weeks (one cycle =4 weeks), with or without local irradiation.

Image analysis

By consensus, two experienced observers in nuclear medicine and radiology blindly assessed all of the ^{18}F-FDG PET/CT scans. To evaluate 18-FDG uptake, maximum standardized uptake value (SUVmax) values for each group of enlarged nodes or mass lesions were utilized in all cases. In the follow-up investigations, values were compared while maintaining the region of interest (ROI) position as close to the target as was practical.

Remaining masses with a gestational trophoblastic disease of 1.1–1.9 cm are only considered PET positive if their activity is greater than the background activity in the area. In contrast, residual masses with a greatest transverse diameter of 2 cm or more and ^{18}F-FDG activity that is visually greater than that of mediastinal blood pool structures are classified as PET positive, according to the International Harmonization Project definitions.[12] By consensus, two experienced observers in nuclear medicine and radiology blindly assessed all of the ^{18}F-FDG PET/CT scans. To assess 18-FDG uptake, SUVmax values for each set of enlarged nodes or mass lesion were utilized in all cases. In the follow-up investigations, values were compared while maintaining the ROI position as usual. A partial reaction was defined as more than 50% in SPD. A 50% decrease in SPD or less was regarded as stationary standard deviation (SD). A new lesion or an increase in SPD of more than 50% from the lowest point of any lymph node was interpreted as an indication of a recurrence or progressing illness.

Statistical analysis

Continuous variables were described in terms of mean (± SD), whereas categorical variables were expressed by frequencies and percentages. For comparing categorical data, Chi-square test was performed. $P < 0.05$ was considered statistically significant. All statistical calculations were done using SPSS Inc., (Chicago, IL, USA).

Results

Baseline characteristics of the patients

This study included 50 patients with lymphoma. Table 1 shows the demographic characteristics of the patients. Mean age was 43.04 ± 17.36 years (range: 14–75 years). The male: female ratio was 1:1. NHL was reported in 26 patients (52%), whereas HL was encountered in 24 patients (48%). The most common subtype of NHL was DLBCL affecting about three-fourth (73.08%) of the patients with this lymphoma. The details of other subtypes are mentioned in Table 1.

The most common stage in patients with NHL was Stage III encountered in 45.83% of the patients, followed by Stage II (33.33%), Stage I (12.5%), and finally Stage IV (8.33%) [Table 2]. Similarly, 46.15% of HL patients had Stage III lymphoma, followed by Stage II accounting for 26.92%, Stage IV (19.23%), and finally Stage I (7.69%).

Positron emission tomography scan staging of lymphoma

None of the patients with NHL had Stage I or Stage II disease, 65.38% had Stage IV, and 34.62% of the patients had Stage

Table 1: Demographic data and clinical characteristics of the included lymphoma patients

Variables	Value, *n* (%)
Age (years)	
Mean±SD	43.04±17.36
Range	14–75
Gender	
Male	25 (50)
Female	25 (50)
Histological type	
NHL	26 (52)
Classical HL	24 (48)
Histological subtype of NHL	
DLBC	19/26 (73.08)
T cell lymphoma	4/26 (15.38)
Burkitt lymphoma	1/26 (3.85)
Anaplastic lymphoma	1/26 (3.85)
Follicular lymphoma	1/26 (3.85)
BMB	
Positive	6 (12)
Negative	9 (18)
Not performed	35 (70)

HL: Hodgkin lymphoma, NHL: Non-HL, BMB: Bone marrow biopsy, SD: Standard deviation, DLBC: diffuse large B-cell

III, regarding HL patients, Stage IV was reported in 45.58% of patients, followed by Stage III (41.67%) and Stage II (12.5%), whereas none of the patients had Stage I [Table 3].

Clinical versus positron emission tomography scan staging of lymphoma

The two modalities differed significantly in the two stages of NHL patients; there were 7 patients versus none with Stage II according to clinical and PET scan staging, respectively [Table 4]. Furthermore, only five patients had Stage IV according to clinical staging versus 17 patients in PET scan staging. Accordingly, there was no agreement between the two modalities ($\kappa = 0.085$, 95% = 0.045–0.123, $P = 0.394$).

For HL patients, the two modalities differ significantly only in appraisal of Stage IV, in which there were 2 patients based on clinical staging and 11 patients according to PET scan staging [Table 5]. Thus, there was a poor agreement between the two modalities ($\kappa = 0.314$, 95% confidence interval [CI] = 0.283–0.376, $P = 0.002$).

Thus, PET scan upstaged 50% and 61.54% of the patients with HL and NHL with a highly significant difference, respectively, whereas there was no change in staging for 50% and 34.62%, respectively, with a highly significant difference [Table 6].

Bone marrow assessment

In NHL, PET scan demonstrated higher positive results than biopsy (34.62% vs. 41.67%) with a highly significant difference. Similarly, in HL, PET scan revealed far more positive results than biopsy (45.83% vs. 50%) with a highly significant difference as shown in Table 7.

Discussion

The present study aimed to evaluate the role of PET scan in staging of lymphoma. The most accessible and widely utilized method for lymphoma staging is CT. The size-based recognition of lymph node involvement and the potential difficulties in detecting BM and extranodal tissue involvement are the fundamental limitations of CT.[16] PET/CT not only more accurately depicts lymphoma nodal sites than CT but it also has the ability to detect lesion activity and has a higher sensitivity for sites of extranodal involvement. As a result, it has been discovered to enhance baseline staging when contrasted with conventional staging that relies solely on CT.[17]

In this study, the average age of patients was 43.04 ± 17.36 years and men accounted for 50% of the patients. In fact, the incidence of lymphoma worldwide varies significantly depending on race and social characteristics. This observation holds true for different types of lymphoma. In an observational study of patients with follicular lymphoma, Nebhan *et al*. reported that Black patients typically presented under the age of 45 years; however, the median age of disease onset in whites at the time of data collection was 64 years.[18] In addition to follicular lymphoma and marginal zone lymphoma, the frequency of lymphoma is higher in men. This may be due to occupational exposures and environmental factors commonly associated with lymphoproliferative processes that tend to occur in industries previously dominated by men.[1]

The study's findings show that although there was no change in staging for 50% and 34.62% of the patients with extremely significant differences, the PET scan upstaged 50% and 61.54%

Table 2: Staging of lymphoma according to clinical and computed tomography staging

Lymphoma	Frequency (%)
NHL	
Stage I	2 (7.69)
Stage II	7 (26.92)
Stage III	12 (46.15)
Stage IV	5 (19.23)
HL	
Stage I	3 (12.5)
Stage II	8 (33.33)
Stage III	11 (45.83)
Stage IV	2 (8.33)

HL: Hodgkin lymphoma, NHL: Non-HL

Table 3: Staging of lymphoma according to positron emission tomography scan

Lymphoma	Frequency (%)
NHL	
Stage I	0
Stage II	0
Stage III	9 (34.62)
Stage IV	17 (65.38)
HL	
Stage I	0
Stage II	3 (12.5)
Stage III	10 (41.67)
Stage IV	11 (45.58)

HL: Hodgkin lymphoma, NHL: Non-HL

Table 4: Clinical versus positron emission tomography scan staging of non-Hodgkin lymphoma

Stage	Clinical	PET scan	*P*
Stage I	2	0	0.490
Stage 2	7	0	0.01
Stage III	12	9	0.397
Stage IV	5	17	0.001

PET: Positron emission tomography

Table 5: Clinical versus positron emission tomography scan staging of Hodgkin lymphoma

Stage	Clinical	PET scan	*P*
Stage I	3	0	0.234
Stage 2	8	3	0.168
Stage III	11	10	0.771
Stage IV	2	11	0.002

PET: Positron emission tomography

Table 6: Staging appraisal according to positron emission tomography scan

PET appraisal	HL	*P*	NHL	*P*
Upstaging	12 (50)	0.002	16 (61.54)	0.001
Down staging	0		1 (3.85)	
No change	12 (50)		9 (34.62)	

PET: Positron emission tomography, HL: Hodgkin lymphoma, NHL: Non-HL

Table 7: Bone marrow assessment according to biopsy and positron emission tomography scan

Lymphoma	BMB, *n* (%)	BM/PET, *n* (%)	*P*
NHL			
Positive	5 (41.67)	9 (34.62)	0.622
Negative	7 (58.33)	17 (65.38)	
HL			
Positive	2 (50)	11 (45.83)	0.817
Negative	2 (50)	13 (54.17)	

HL: Hodgkin lymphoma, NHL: Non-HL, BM: Bone marrow, BMB: BM biopsy, PET: Positron emission tomography

of the patients with HL and NHL, respectively. These results are consistent with research conducted globally. In a related investigation, Elsammak A.[12] compared PET-CT with CT in staging lymphoma patients in Egypt. A statistically significant difference in pretreatment period was found in the study ($P = 0.0001$). Different from 7 cases (23.3%) based on PET-CT, 6 cases (20%) based on CT were Stage II, and 9 cases (30%) based on PET-CT were Stage III. According to Elshafey *et al*., individuals with Stage I or II disease may benefit greatly from PET-CT early on before starting treatment.[19]

The current study's findings indicate that in NHL and HL, PET scan demonstrated BM involvement more strongly than biopsy (34.62% vs. 41.67% and 45.83% vs. 50%, respectively), with no discernible differences. According to Angelopoulou *et al*.,[20] staging by PET resulted in a 17% increase in BM participation, compared with 8% for BMB. In addition, no patient with BM uptake had positive BMB. Current research has demonstrated that PET scans are 100% specific for BM, which is exactly what it shows. El-Galaly *et al*.[21] showed a negative predictive value of 99% for BM involvement based on PET and an increase in BM involvement from 6% to 18% by PET/CT, similar to the present study. These results show PET can detect focal or multifocal bone and marrow involvement in lymphoma patients with a negative BM biopsy, which is then confirmed by histopathology or MRI.[22]

In a different investigation, 162 consecutive HL patients were retrospectively examined by Angelopoulou *et al*.[22] Of the patients, 26 (16%) had an upstaged disease, whereas 9 (6%) had a downstaged disease. A recent study by Xiao-Xue *et al*. that evaluated the BM infiltration in patients with newly diagnosed lymphoma supports these findings. The PET-CT results of BM infiltration showed high accuracy of 88.1% and 83.3%, respectively. The PET scan showed no metabolic activity and the CT revealed enlarged lymph nodes.[23]

In the present study, there was a poor agreement between the two modalities CT and PET scan ($\kappa = 0.314$, 95% CI = 0.283–0.376, $P = 0.002$) in staging of HL.

However, there was no agreement in NHL staging between the two modalities, Pelosi *et al*.[24] included 65 consecutive patients (30 HL and 35 NHL) in a related trial. The patients received FDG-PET/CT and conventional disease staging. 93.8% of recruited patients (61 / 65) were accurately staged by PET, compared to 89.2% by traditional methods. In 54 out of 65 patients (83.1%), there was total concordance; in the 11 cases that remained, PET downstaged three patients (all false negative) and upstaged eight patients (seven true positive and one false positive). In a research by Kandeel *et al*., they used PET scan and CT scan for staging and PET/CT seemed to be an excellent diagnostic test in the initial assessment and staging of patients with Hodgkin lymphoma, with high concordance between the two modalities that is much greater than ours.[25]

Using the previous arguments, it can be recommended to include PET scan in all newly diagnosed NHL and HL in addition to routine follow-up study by PET Scan to assess the response.

Limitations

The present study has many limitations:

1. It is a single-center study with a relatively low sample size which does not allow the generalization of the results
2. The efficiency of PET scan staging in the evaluation of treatment response and its role in directing treatment were not performed due to the limited time period.

Conclusions

Staging by PET scan leads to the identification of additional affected sites in patients with lymphoma and usually associated with upstaging of clinical staging especially for the early stage of HL and NHL; nevertheless, there was poor or no agreement between PET scan and clinical staging of lymphoma in spite of the high detection of BM involvement compared with CT scan.

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Conflicts of interest

There are no conflicts of interest.

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