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Extra-nodal Involvement in Adult Lymphomas, Experience, and Outcome

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ABSTRACT

Background: Roughly 20% of lymphoma patients had extra-nodal involvement. With this study.
Objectives: We aimed to present our experience with extra-nodal lymphoma in terms of presentation and outcome.
Material and methods: This is an observational study that explored the PET/CT scan done to lymphoma patients who have either primary extra-nodal lymphoma or extra-nodal involvement in their initial staging workup. The study was conducted between 2019 and 2022. The population were adults who had histological confirmation of lymphoma, no other malignancy, and were presented with extra-nodal involvement were included in this study. All patients had initial and either interim or post-therapy scans.
Results: A total of 27 patients with 54 PET/CT scans were included in this study. The median age was 32 (18-69) years, and 71.7% were males. 26.4% of the scans were done as initial assessment, while 5%, 47%, and 17% were interim assessment, post-therapy evaluation, and follow-up respectively. Hodgkin lymphoma was reported in 45.3% of the scan. The distribution of stage I, II, III and IV was 11.3%, 3.8%, 20.8% and 64.2% respectively. Primar extra-nodal lymphoma were seen in 45.3%. The detection rate of PETCT was higher in the bone marrow (22.6% versus 7.5% for CT, p = 0.008). There was non-significant trend toward higher detection rate for PET in spleen (32.1% versus 26.4%). PETCT changed the primary management of the cases in 42.9% of the cases.
Conclusion: PETCT had upper hand compared to CT in detection rate of lesion especially for the spleen.
Keywords: Lymphoma, Non-Hodgkin's lymphoma, Hodgkin's lymphoma, Extra nodal lymphoma.

INTRODUCTION

Lymphoma represents diverse disease group that originate from lymph nodes. Due to diversity of the disease and the difficulty in diagnosing and stratification, several World Health Organization (WHO) consensus statements have been released over the past two decades. Many demographic studies tried to link the prevalence of lymphoma in specific populations. Genomic alteration, infection, and some chronic inflammatory condition might increase the risk of lymphomas as well as first-degree relatives of patients suffering from non-Hodgkin and Hodgkin lymphomas. The risk was as high as 3.1 folds the normal population risk [(1)].

Painless adenopathy is most common presentation of lymphoma. The enlarged nodes can grow slowly over years in an indolent course or evolve aggressively over weeks in aggressive subtypes. Usually, Hodgkin lymphoma presents as supradiaphragmatic adenopathy, while non-Hodgkin lymphoma can infiltrate any lymphatics elsewhere in the body, with specific predilection to central nervous systems, skin, and gastrointestinal tract in aggressive histologies. Clinically, patients usually complain of unexplained prolonged fever, unplanned weight loss, and night sweats [(2, 3)].

The efficient diagnosis of lymphoma mandates a minimum of core biopsy, or excisional lymph node biopsy. Fine needle aspiration is unacceptable and inefficient in the diagnosis of lymphoma and should not be performed. Although core biopsies are often enough, it should be clear that negative core biopsy should not be used to exclude lymphoma when clinical suspicion is high, due to the possibility of sampling errors. At this instance, repeat core biopsy, or excision of entire lymph node are must [(4)].

Currently, the need to perform bone marrow aspirate and trephine is diminishing in the era of PET/CT. PET/CT could be used to evaluate the bone marrow inside the bones. Diffuse uptake is usually linked to suspicion of infiltrated bone marrow. The use of PET/CT is also mandatory for staging of the disease. It should be done with contrast enhancement computed tomography for the neck, chest, abdomen and pelvis [(4)].

Historically, the staging of lymphoma was based on the Ann-Arbor staging that proposed in 1971 in Ann-Arbor city in USA [(5)]. The philosophy behind this system proposed the idea of lymph nodes regions or groups. Each group consists of lymph nodes with specific anatomical sites. For example, the lymph nodes around the internal jugular vein on one side is considered a group. The nodes around the distal part of axillary vessels is another group, while the proximal nodes draining toward the subclavian vein was another group. Moreover, the entire lymphatic within the mediastinal was considered as a group [(6)].

The major idea behind WHO classification of lymphoma was to divide the disease based on cell linage, namely myeloid, lymphoid B and T, natural killer or histiocytic/dendritic. The second principle was to subclassify the disease based on the cells' differentiation and maturation, starting from precursors-related leukemia to mature lymphomas. The final principle was the clinical

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course of the disease, ranging from the highly aggressive to the indolent form. The WHO classification does not invent new diseases' spectrum. However, it tries to re-establish the already known knowledge about this diverse disease into a more seemingly way that best suits understanding of the disease [4-11].

Extranodal lymphoma is defined as involvement of any tissues other than lymph nodes. The extra-nodal presentation could be the primary presentation or secondary to systemic involvement of disease. Extranodal involvement can be seen with lymphoma in approximately 25–40% of cases and almost any organ can be involved, primary involvement usually presents at an early stage; up to 74% in stage II [12]. Extranodal involvement is less common with Hodgkin disease (HD) with direct extension into adjacent organs in 15% and hematogenous spread in 5–10%. The presence of extranodal involvement has prognostic indicators. When there is a secondary extranodal extension the disease is considered stage III or IV [13].

However, in patients with primary extranodal involvement, the disease can be considered to be still in stage I or II. Distinct radiologic features are seen when such extranodal involvement is noted. Differentiation between disseminated lymph nodal disease involving an extranodal site and primary extranodal disease is challenging using conventional computerized tomography scanning [14].

Compared to conventional imaging, the PET/CT is advantageous. The PET depends on measuring the annihilation photons, which are generated after positron emission from the radionuclide tracer. The used radionuclide is usually attached to a key substance that is essential to biological processes, such as glucose. Therefore, PET imaging provides a functional image that reflects the biological process inside the biological tissue. It is not necessary to inject the patient with large dose of the radiotracer [15].

MATERIAL AND METHODS

Study design and patients: This is an observations study that was conducted between 2019 and 2022. The study aimed to explore the outcome and evaluation of PET/CT scan done to lymphoma patients who have either primary extra-nodal lymphoma or extranodal involvement of advanced nodal lymphomas. Adult patients who had histological confirmation of lymphoma, no other malignancy, and were presented with extranodal involvement were included in this study. All the patients had initial and either interim or post-therapy scans.

Procedures and measured outcomes: Patients with either primary early stage extranodal lymphoma or with advanced disease harbouring extranodal involvement that be retrieved from the archives and to be analysed (Baseline patients' characteristics were retrieved). These included the age, gender, disease pathological subtypes. Patients' outcome whenever available to be included within the analysis. The DICOM images of the PET/CT scans were analysed using commercially purchased RadiAnt software. The lesion site, characteristic and avidity was analysed for each individual patient and included within the patients' sample.

Patient preparation: The time of PET/CT was scheduled to be either four to six weeks from last session of radiotherapy or recent surgery, two weeks from last cycle of chemotherapy, or last dose of granulocytes colony stimulating factor (G-CSF). The patients' blood glucose level was ensured to be less than 180 mg/dL before the exam. The patient was asked to fast for at least 6 hours before FDG injection.

Technique: Standard PET/CT study (skull base to proximal thighs) was done in most cases using hybrid PET/CT scanner. The used PET/CT scanner was Siemens © biograph horizon PET/CT with low dose non-diagnostic 16 slice CT scan. The CT scan was acquired for attenuation correction and image fusion with PET images and anatomical localization. CT images were acquired at 130 KV, in 5 mm slice thickness for adult, and 1.5 mm slice thickness for paediatrics. The scan window included whole body imaging in craniocaudal direction, followed by PET imaging in 3D mode, which was collected in a caudocranial direction with patient arms up. The whole-body study (skull vertex to toes) was used for patients with cutaneous lymphoma.

Ethical consent: The Academic and Ethical Committee, Sohag University approved the study. Every patient signed an informed written consent for acceptance of the treatment. This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Procedures of descriptive analysis were applied to the retrieved date. The frequency distribution was obtained and recorded. Correlation was done whenever possible. The commercially available statistical software IBM-SPSS (version 27 for Windows; IBM Inc.) was used for data analysis. An alpha level of 5% was used for all tests to consider the statistical significance.

RESULTS

Fifty-four studies, for 27 patients, were included in the analysis. Table (1) showed basic characteristics of the patients. B-symptoms were reported in 15.1% of the cohort.

Table (1): Demographic and clinical data of the patient population

Age (years)	Mean Median Range	**35.6** **32** **(18-69)**	
Scan type (Role of PET/CT)	Initial staging Interim assessment Post therapy evaluation	27 5 22	50% 18.5% 81.4%
Gender	Male Female	20 7	74.7% 25.3%
Pathology	HD NHL	12 15	44.4% 56.6%
Disease stage	Stage I Stage II Stage III Stage IV	3 1 6 17	11.1% 3.7% 22.2% 62.9%
Disease pattern	Primary extranodal Nodal, extranodal	12 15	44.4% 56.6%

The detection rates for patients with initial assessment showed that the median SUV max for the lesion on initial PET/CT was 12.5 range (3.4 – 29). The calculated mean for the SUV max values of the main lesions was 13.9 and 12.25 for HD and NHL respectively. Table (2) showed the difference in detection rate between CT and PET in the overall population.

Table (2): CT and PET/CT detection rates

Anatomical site	Detection Rate		McNemar Test, p value
	PET/CT finding	CT Finding	
Head and Neck	16%	16%	1.0
Lung nodules	30.2%	37.7%	0.344
Spleen	32.1%	26.4%	0.250
BM	22.6%	7.5%	**0.008**
Liver	7.5%	11.3%	0.5
Cervical Nodes	56.6%	60.4%	0.687
Mediastinal Nodes	64.2%	66%	1.0
PA nodes	50.9%	52.8%	1.0

The distribution of uptake within the extra-nodal sites was recorded in table (3).

Table (3): Distribution of uptake within the extra-nodal sites

Parameter		**Adults**
Head and neck	**Positive**	20 (16.4%)
	Negative	102 (83.6%)
Lung nodules	**Positive**	35 (27.3%)
	Negative	93 (72.7%)
Spleen	**Positive**	38 (29.7%)
	Negative	90 (70.3%)
BM	**Positive**	30 (23.4%)
	Negative	98 (76.6%)
Liver	**Positive**	9 (7%)
	Negative	119 (93%)
Musculoskeletal	**Positive**	34 (26.6%)
	Negative	94 (73.4%)
Visceral & others	**Positive**	26 (20.6%)
	Negative	100 (79.4%)

For patients having interim or post-therapy evaluation, 13.2% had Deauville score of 1 and 2, while 2.6% had score of 3. Scores 4 and 5 represented 15.8% and 68.4%, respectively. This was translated into rates of 15.6%, 37.5%, 3.1%, and 43.8% for complete response, partial response, stable disease, and progressive disease. The added Values of PE/TCT changed the management protocol for 42.9% of the patients.

DISCUSSION

Extranodal lymphoma is a cancer that originates in lymphoma cells outside of the lymph nodes. It can affect various organs and tissues throughout the body, such as the stomach, skin, lungs, or bones. Extranodal lymphoma accounts for approximately one-third of all lymphoma cases, and its incidence has been increasing over time [(16)]. Symptoms and treatment of extranodal lymphoma depend on the location and extent of the cancer [(17)]. Diagnostic methods such as biopsy and imaging tests are used to determine the type and stage of extranodal lymphoma, which guide treatment decisions. Overall, early diagnosis and appropriate treatment are essential for improving outcomes in patients with extranodal lymphoma [(3)].

Positron emission tomography/computed tomography (PET/CT) is a nuclear medicine imaging technique that combines two imaging modalities: PET and CT. PET uses radiopharmaceuticals that emit positrons, as well as detectors such as gamma cameras, to produce three-dimensional images of biological processes such as glucose metabolism. CT uses X-rays and detectors to create detailed structural images of the body [(15)].

PET/CT has been shown to be useful in the diagnosis and staging of extra nodal lymphoma, besides it can guide radiotherapy planning by identifying areas of tumor that should be targeted. Furthermore, PET/CT can also be used for surveillance after treatment to monitor for recurrence [(18, 19)]. PET/CT also plays an important role in the management of extra nodal lymphoma, by identifying changes in metabolic activity as a surrogate marker for tumor location and response. For example, PET/CT was more accurate in diagnosis, staging and response assessment of MALT lymphoma arising from mucosal lining [(20, 11)]. In CNS lymphoma, PET/CT has also been shown to have high sensitivity and specificity in detecting primary brain involvement, providing a non-invasive diagnostic tool that can be obtained quickly even when MRI is contraindicated or difficult to perform [(22, 23)].

In our study, we examined 53 scans obtained from 27 patients with extra-nodal lymphoma. Several Egyptian authors addressed question of prevalence of extra-nodal lymphoma. Two famous studies came from **El-Haddad *et al.*** **[(24)]** and **Alnouby *et al.*** **[(25)]** in 2015 and 2018, respectively [(24, 25)]. Both studies showed comparable distribution between males and females. Similar to theirs, our study showed that Hodgkin lymphoma and diffuse large B-cell lymphoma represented two-thirds of the patients [(24, 25)]. In a study by **Amal Othman *et al.*** 79% of all cases were diagnosed with non-Hodgkin lymphoma (NHL), while Hodgkin disease (HD) made up the remaining 21%. Diffuse large B cell lymphoma (DLBCL) was the most common subtype of NHL, accounting for 63% of all cases. Nodular sclerosis was the most common subtype of HD comprising 5% of all cases [(26)].

Our study pointed to the difference in the distribution of primary and secondary extra-nodal presentations between HD and NHL. The majority of HD presentations came in the form of secondary extra-nodal presentations, roughly 54.7%. In 26.3% of the patients, PET CT was utilized for initial staging. Meanwhile, interim assessment was conducted in one-tenth of the scan, and it was employed in the evaluation of post-therapy progress in nearly half of them. Additionally, during the time of relapse, PET CT was performed in one-tenth of the occasion. The prevalence of disease stages I, II, III, and IV was 11.3%, 3.8%, 20.8%, and 64.2% respectively. Furthermore, when comparing CT to PET/CT, the latter was able to detect more nodal and extra-nodal lesions, especially at the spleen. By using the McNemar test, we found a significant difference in detection rates between PET/CT and CT for spleen (22.6%, 7.5%, $p = 0.008$). Our study is in line with the previously published data that pointed to the value of PET CT in increasing detection rates of positive spleen compared to conventional CT scans [(25)]. The superiority in detection rate of PET CT compared to CT in bone marrow, spleen and liver was proved by several authors previously and is in line with our findings [(27)].

Roughly one-third of patients exhibited splenic infiltration. Moreover, among patients diagnosed with Hodgkin's disease, there was a significantly higher splenic FDG avidity rate compared to those with non-Hodgkin's lymphoma (54.2% versus 48.3%, as validated by chi-square $P = 0.000$). PET/CT scanning was shown to be able to accurately rule out active lymphatic infiltration for a number of detected lesions at different sites, including lung nodules, cervical and mediastinal abdominal lymph nodes. The unique ability of PET CT to characterize lung nodules was also confirmed by previously published data within the literature [(25)].

CONCLUSION

Based on the outcome of our study and the detection rates reflected by different scan types, PET/CT scanning showed that complete treatment response was observed in 15.6% of the population while partial response was seen in 37.5%. In addition, 3.1% demonstrated stable disease while 43.8% displayed disease progression. These findings had ultimately impacted the management of the disease. Overall,

PET/CT scans had a notable influence on inducing changes to the treatment protocol, including the addition of further cycles or changing the line of treatment in 42.9% of the occasions.

- **Limitation:** The sample size of this trial was small to draw definitive conclusions.
- **Role of funding:** The study was fully funded by the Sohag University Hospital and Sohag Faculty of Medicine.
- **Conflict of Interest:** The author(s) had nothing to declare.

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