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Study Of Treatment Efficacy In Non Hodgkin's Lymphoma With Respect To Radio- Pathological Correlation

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Abstract

Aims and objectives

There is a paucity of Indian studies on clinic-pathological profile and long-term relapse rates of Non-Hodgkin`s lymphoma (NHL). Hence this study was undertaken to assess the clinic-pathological profile & relapse rates in NHL.

Methods

All newly diagnosed patients of NHL from 2017 to 2019 were enrolled in the study. The data was collected prospectively after due IEC clearance. The patients were interviewed using predesignate standardized proforma fully vetted by medical education faculty. Clinical details of pallor, icterus, lymphadenopathy, bulky lymph nodal mass, hepatomegaly, or splenomegaly were examined. These patients underwent a hemogram and findings of peripheral blood smear were noted. Liver function tests, renal function tests, serum electrolytes, serum uric acid, serum LDH, HIV, HBsAg, Anti HCV Ab serology, CT scan, Whole body PET CT, lymph node FNAC/biopsy, and bone marrow studies were performed at a base line and followed up with 06 months, 12 months, 18 months and also at 24 months. All the patients have received a CHOP/R-CHOP/R-CVP regimen for 6 cycles as per B cell or T cell lineage respectively. Collected data was collated and analyzed using appropriate standard statistical tests, where deemed necessary by using spss software.

Results

In this study, a total of 50 cases were enrolled and followed for 2 years. The median age of presentation ranges from 21 years to 82 years of age with a mean of 44.22 years. The commonest clinical presentation noticed was neck, groin, or axillary swelling followed by B symptoms and GI symptoms. Other less common presentations were proptosis, cellulitis, or testicular swelling which account for 6 % of cases, and CNS involvement was seen in 4 % of cases. On examination, the commonest clinical sign was lymph node enlargement (52%) followed by pallor and jaundice. The commonest extranodal presentation was hepatomegaly and splenomegaly. On peripheral blood smear, the commonest finding observed was macrocytic hypochromic anemia (12%) followed by lymphocytosis, normocytic normochromic anemia, bicytopenia and atypical cells. On CT Scan imaging, nodal involvement was seen in 86% of cases out of which generalized lymphadenopathy was seen in 40 % of cases, and extranodal involvement was seen in 50 % of cases. The commonest site of extranodal involvement was the abdomen (34%) followed by head & neck, thorax, skeletal and skin. Whole-body PET imaging shown nodal involvement in 90 % of cases and extranodal involvement in 70 % of cases. We compared CT scan and PET scan results in this study and noticed that PET scan (90%) was a little more sensitive for detecting lymph node involvement over CT scan (86%) imaging. On lymph node biopsy B cell NHL was seen in (84.84%) of cases and the commonest histopathological subtype seen was diffuse large cell B cell lymphoma (DLBCL). Biopsy from extranodal site has shown B cell NHL in (93.33%) of cases. The commonest histopathological subtype was DLBCL (18%), followed by high-grade B cell NHL. It was observed that 82 % of the patients had normal bone marrow and in 18 % of the patients, bone marrow was involved. Combining bone marrow examination and biopsy, 88% of cases were of B cell type and the commonest type found was DLBCL (62%). This study found at presentation 68 % of cases were in stage IV as per the Ann-Arbour system and only 4 % in stage II. The commonest treatment-related toxicity noticed was febrile neutropenia (44 %) followed by pancytopenia (10%). At 6 months, 30 % of the cases were having clinical active disease and PET imaging

revealed radiologic disease activity in 32 % of the cases. At 12 months, 14 % of the cases were having clinical disease, and WB PET imaging revealed disease activity in 14 % of the cases. At 18 months, 5 % of the cases were having clinical disease and WB PET imaging has shown radiologic disease activity in 10 % of the cases. At the end of 24 months, 14 % of the cases were having clinical active disease, and WB PET imaging revealed radiologic disease activity in 14 % of the cases. At the end of the study period, 78 % of cases were in remission, 10 % of cases were relapsed, 6 % cases had progressive disease and 6 % of cases expired.

Conclusion

This study found 02-year survival post standard chemotherapy in NHL cases was 88%. The relapse rate at 24 months was 14 %. The B symptoms were seen less commonly, and bulky disease was noted in one-third of cases. The role of PET in diagnosing and follow up on these cases was good but it was comparable with CT scan.

Keywords: *Non-Hodgkin`s lymphoma, clinic-pathological profile, PET, flow cytometry, biopsy, relapse rate.*

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I. Introduction

Lymphomas are a heterogeneous group of diseases that accounts for up to 3% of all malignancies (1). Lymphomas are divided into two main categories: Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL). About 90% of People with lymphoma have NHL and the rest have Hodgkin lymphoma (2). Generally, NHL is divided into 2 types: indolent Lymphoma and aggressive subtype. (3). DLBCL is the most common type of NHL. It is about 30-40% of the total NHL. DLBCL accounts for 60%–70% of all B cell lymphomas in Asia (4). NHL is more common in men than women (5). There are different methods available to diagnose NHL such as complete blood counts, metabolic profile (renal and liver function tests, electrolytes (potassium, phosphate, and calcium), uric acid, and lactate dehydrogenase (LDH), biopsy, bone marrow study, and for imaging studies (PET/CT) positron-emission tomography/computed tomography of the whole body is performed (6). Treatment of patients depends on whether it is localized (Ann Arbor Stage I-II) or advanced (Ann Arbor Stage III-IV) disease. Generally, combined modality therapy is used, and chemo-immunotherapy is a Standard treatment for most patients with advanced disease (6). Most patients eventually relapse, and this represents a major treatment challenge (7). From the last two decades, the development and use of the monoclonal antibody (mAb) rituximab have intensely improved the prognosis of NHL patients and has been the standard of care in front-line treatment regimens (7). Information about Clinicopathological features and outcomes of Non-Hodgkin's lymphoma (NHL) is very less from developing countries keeping this thought in mind this study has been designed. This study was planned to assess the clinical and pathological profile of NHL patients as well as to assess the relapse rates post-chemotherapy in a tertiary care center in North India.

II. Aims and objectives:

The aim is to study the clinical and pathological profile and analyze the 2-year relapse rates of Non-Hodgkin`s lymphoma in a cohort of Indian patients. The objectives of this study were to assess the clinical and pathological profile of Non-Hodgkin`s lymphoma patients and to assess the relapse rates in Non-Hodgkin lymphoma at the end of two years post treatment.

III. Methodology:

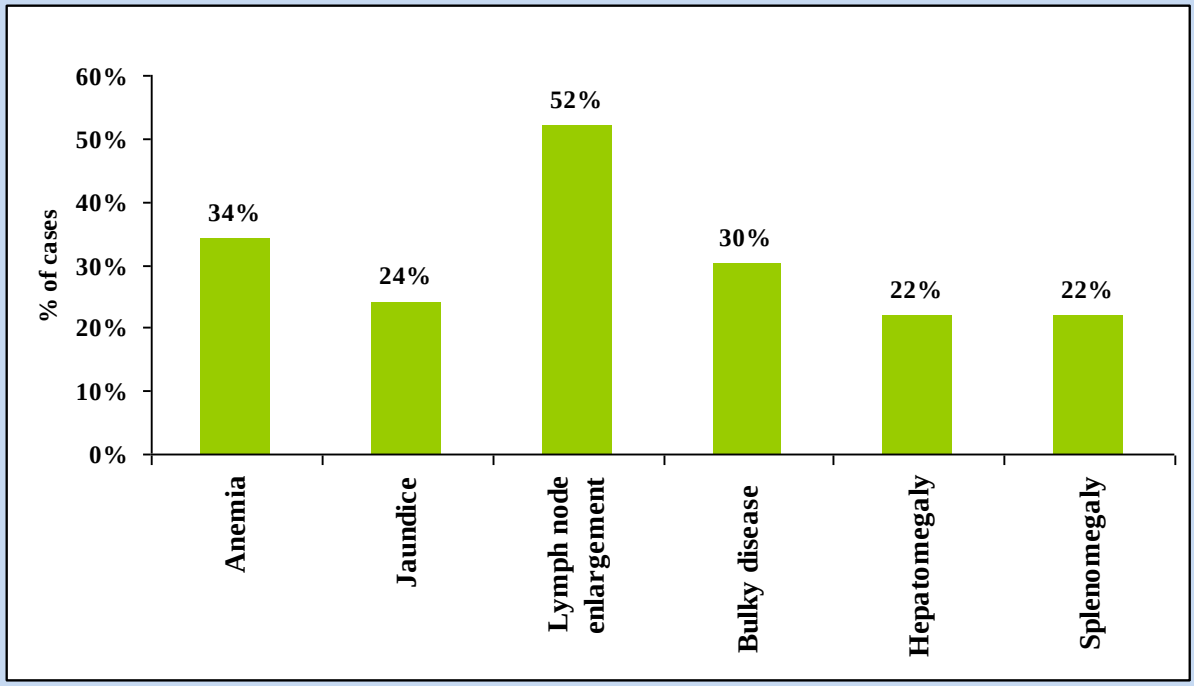
This prospective observational study was conducted in a tertiary care Govt center in Northern India from Jan 2017 to May 2021. The calculated sample size was 50. All Patients diagnosed with Non-Hodgkin's lymphoma from 2017 to 2020 with histopathological confirmation were included in the study. Patients with unconfirmed diagnoses, gray zone lymphomas and were excluded. All the newly diagnosed patients of NHL from 2017 to 2019 were enrolled in the study. The data was collected prospectively after due IEC clearance. The patients were interviewed using predesignate standardized proforma fully vetted by medical education faculty. Clinical details of pallor, icterus, lymphadenopathy, bulky lymph nodal mass, hepatomegaly, or splenomegaly were examined. These patients underwent a hemogram and findings of peripheral blood smear were noted. Liver function tests, renal function tests, serum electrolytes, serum uric acid, serum LDH, HIV, HBsAg, Anti HCV Ab serology, CT scan, Whole body PET CT, lymph node FNAC/biopsy, and bone marrow studies were performed at a base line and followed up with 06 months, 12 months, 18 months and also at 24 months. All the patients have received CHOP/R-CHOP/R-CVP regimen for 6 cycles as per B cell or T cell lineage respectively. Collected data was collated and analyzed using appropriate standard statistical tests, where deemed necessary by using spss software.

IV. Results:

In this study, the median age of presentation ranges from 21 years to 82 years of age with a mean of 44.22 years. The commonest comorbidities associated with NHL were hypertension (8 %) followed by chronic kidney disease (2%). The HIV and HBV association was found in 4 %of cases. Commonest clinical presentation noticed was neck, groin, or axillary swelling which were seen in 46 % case (Chart 1). This was followed by B symptoms (32 %) and GI symptoms (10 %). Other less common presentations were proptosis, cellulitis, or testicular swelling which account for 6 % of cases, and CNS involvement was seen in 4 % of cases.

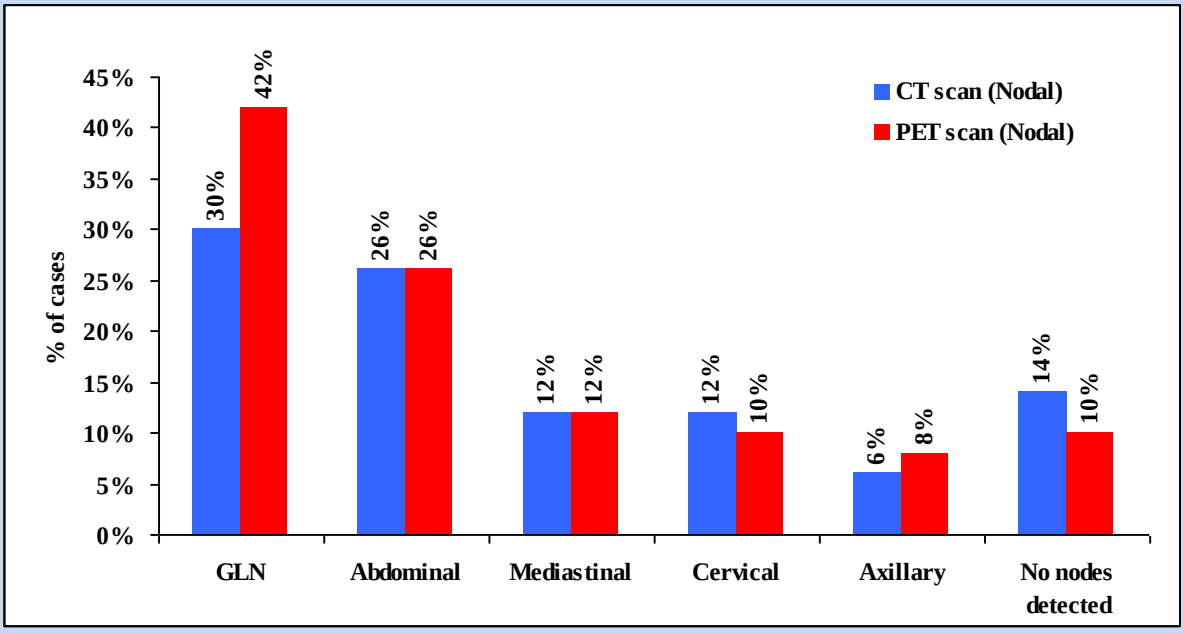
In this study on examination, the commonest clinical sign elicited was lymph node enlargement (52%) followed by pallor (34 %) and thereby jaundice (24 %). The commonest extranodal presentation was hepatomegaly (22 %) and splenomegaly (22%) (Chart 1).

Chart 1: Distribution of patients according to the clinical signs



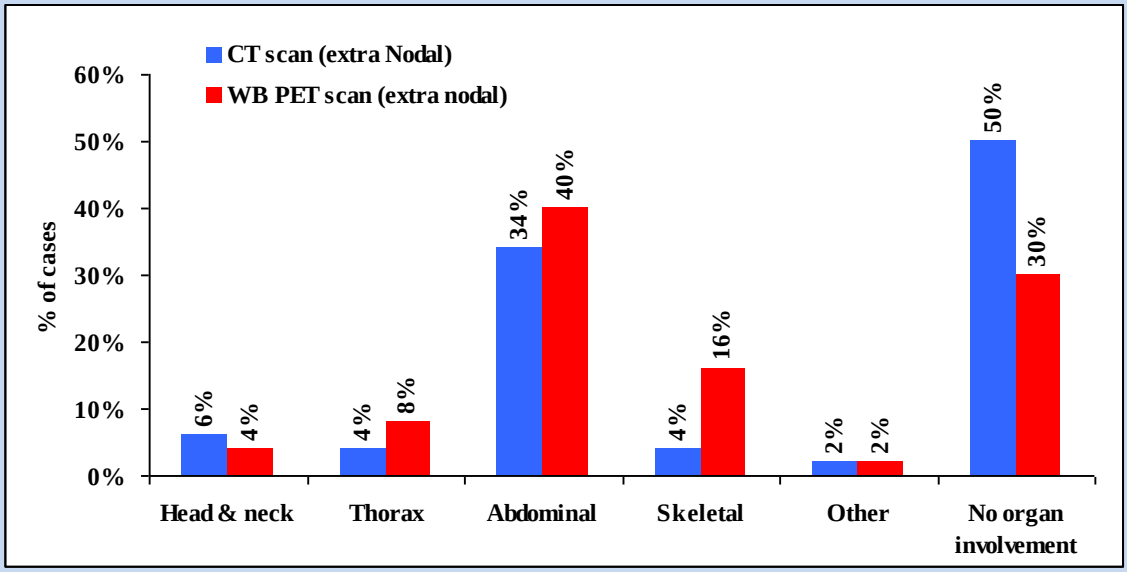
On examination of peripheral blood smear of all the enrolled patients, PBS was normal in 62 % of the patients and the commonest finding observed was macrocytic hypochromic anemia (12%) followed by lymphocytosis (10 %), normocytic normochromic anemia (6%), Bicytopenia (6%) and atypical cells (4%). On CT Scan imaging, nodal involvement was seen in 86% of cases out of which generalized lymphadenopathy was seen in 40 % of cases, and extranodal involvement was seen in 50 % of cases (Chart 2).

Chart 2: Comparison between CT Scan & PET imaging for Non-Hodgkin's lymphoma nodal involvement



The common site of extranodal involvement was the abdomen (34%), followed by head & neck (6%), thorax (4%), skeletal (4 %) and, skin (2%). Whole-body PET imaging shown nodal involvement in 90 % of cases and extranodal involvement in 70 % of cases. (Chart 3).

Chart 3: Comparison between CT Scan & PET imaging for Non-Hodgkin's lymphoma extra nodal involvement.

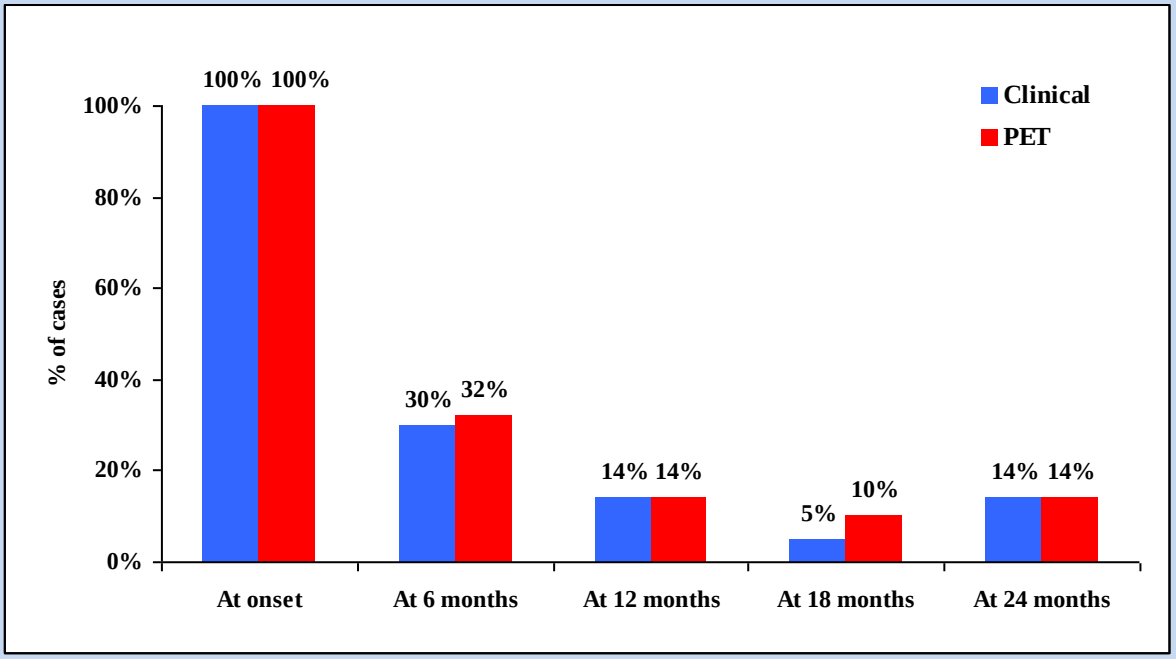


On comparison of CT scan and PET scan results in this study, it was noticed that PET scan (90%) was a little more sensitive for detecting lymph node involvement over CT scan (86%) imaging. On lymph node biopsy B-cell NHL was seen in (84.84%) of cases and, the commonest histopathological subtype seen was Diffuse Large cell B cell lymphoma (DLBCL). Biopsy from the extranodal site was shown B cell NHL in (93.33%) of cases. The commonest histopathological subtype was DLBCL (18%), followed by high-grade B cell NHL. It was observed that 82 % of the patients had normal bone marrow, while 4% of the patients each had ALCL, B cell NHL, DLBCL & T cell lymphoma and 2% had Marginal Zone Lymphoma. Combining bone marrow examination and biopsy, 88% of cases were of B cell type and, the commonest type found was DLBCL (62%). (Table 1).

Table 1: Major Non-Hodgkin's lymphoma types	
Histologic sub type	**Percentage**
B cell NHL	**88%**
Diffuse large cell B cell lymphoma	62%
Follicular lymphoma	8%
Lymphoblastic lymphoma	2%
Mantle cell lymphoma	6%
Nodular marginal zone lymphomas	6%
Burkitt lymphoma	2%
T cell/ histiocytic rich B cell lymphomas	2%
T cell NHL	**12%**
Anaplastic large cell lymphoma T cell type	4%
Angio immunoblastic T cell lymphoma	4%
T cell lymphoblastic lymphomas	4%

This study found at presentation 68 % of cases were in stage IV as per the Ann-Arbour system and only 4 % in stage II. The commonest treatment-related toxicity noticed was febrile neutropenia (44 %) followed by pancytopenia (10%). At 6 months, 30 % of the cases were having clinical active disease and PET imaging revealed radiologic disease activity in 32 % of the cases. At 12 months, 14 % of the cases were having clinical disease, and WB PET imaging revealed disease activity in 14 % of the cases. At 18 months, 5 % of the cases were having clinical disease and WB PET imaging has shown radiologic disease activity in 10 % of the cases. At the end of 24 months, 14 % of the cases were having clinical active disease, and WB PET imaging revealed radiologic disease activity in 14 % of the cases (Chart 4). At the end of the study period, 78% of cases were in remission, 10 % of cases were relapsed, 6 % cases had progressive disease and 6 % of cases expired.

Chart 4: Comparison between clinical disease activity and radiology disease activity at various time point



Comparison between clinical disease activity and radiology disease activity at various time points

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of disorders involving malignant monoclonal proliferation of lymphoid cells in lymphoreticular sites, including lymph nodes, bone marrow, the spleen, the liver, and the GI tract. Compared with Hodgkin lymphoma, there is a greater likelihood of disseminated disease at the time of diagnosis. Diagnosis is usually based on lymph node or bone marrow biopsy or both. Since 1970, CHOP regimen is used as standard of care for NHL patients. Recently, Rituximab has been integrated into the treatment therapy which has improved its efficacy but its widespread use in developing countries is limited due to lack of financial coverage. Thus, most of the patients with NHL die either refractory

to the currently available treatment or due to relapse after a period of remission. However, various factors like patient's age, disease extension and growth, clinical-stage and performance status, could help to predict chemotherapy outcomes as well as patient's prognosis. The present study was conducted with aim to study the clinical and pathological profile and analyze 2-year relapse rates of NHL in a cohort of Indian patients under regular follow up at a tertiary care center, Army Hospital (Research & Referral) from Jan 2017 to Dec 2020.

The present study included 50 patients in the age group 20-80 years (84% male and 16% females) based on the defined inclusion-exclusion criteria. The mean of patients was 44.62 ± 15.92 years, and it was observed that maximum patients (48%) were from the age group 20-40 years. After obtaining informed consent, detailed clinical history of patients was collected. Co-morbid factors were recorded, and it was observed that in 86% patients, no comorbidities were present. Hypertension was present in maximum number of patients (12%), followed by diabetes mellitus in 4%, chronic kidney and coronary artery disease in 2% each.

In a similar study, Alyahya N et al, assessed the clinicopathologic patterns of NHL in 100 patients from Saudi Arabia (12). Contrary to our results, they found most affected patients in the age group (> 60 years), followed by 30% patients from age group 40-60 years. The reason for younger patients in our study could be due to the fact that our country's average younger population is more as compared to other countries or due to referral bias toward younger patients for treatment at the higher centre.

B symptoms comprise general symptoms: fever >38°C, night sweats, or weight loss >10% of body weight in the last 6 months, or a combination of these, associated with NHL. They play significant role in prognosis and staging of NHL. It was observed that B-symptoms were present in 38% of patients. Further, patients were distributed based on the clinical presentation and 46 % patients were found to have swelling in neck, groin or axilla, GI symptoms were there in 8% patients, CNS related presentation in 4% patients and 8% patients had other variable clinical presentation. Similar results were reported by Devi AA et al, wherein they found neck swelling as the most common presenting complaint (57.0%), followed by abdominal pain (28.0%) (11). The occurrence of "B" symptoms was noted in 48% of the cases. Contrary to this, Rathore A et al, reported GI tract as the most common extra-nodal lymphoma site (25.9%), while others reported stomach as most common extra-nodal NHL site (9, 12,13).

Patients were distributed based on their clinical signs and symptoms. It was found that lymph node enlargement was present in 52% patients, anaemia in 34% patients, bulky disease in 30% patients, jaundice in 24%, hepatomegaly and splenomegaly in 22% each. Concurrent results were reported by Devi AA et al, with peripheral lymphadenopathy being the most common sign (76%), anaemia in 46% patients, hepatomegaly and splenomegaly in 44% and 30% cases, respectively (11).

There were two patients who were HIV positive and two were HBsAg (hepatitis B surface antigen) positive, indicating Hepatitis B infection.

Changes in the peripheral blood cell counts as well as bone marrow involvement frequently occur in NHL patients. Therefore, their timely evaluation helps to provide information regarding disease staging and its effect the haemopoietic system (14). In the present study 62% patients had normal peripheral blood smear (PBS), however, 12% patient had MCHC (mean corpuscular haemoglobin concentration) anaemia, while 6% had NCNC (normocytic normochromic) anaemia and lymphocytosis was present in 10% patients. Lim E et al, also reported incidences of anaemia, one or more abnormal counts, lymphocytopenia, increased marrow reticulin and marrow eosinophilia at diagnosis (66%, 85.1%, 41.3%, 40.9% and 44.7% respectively) (14). Further, bone marrow involvement was present in 18% patients, among which 4% of the patients each had ALCL, B cell NHL, DLBCL & T cell lymphoma and only 2% had Marginal Zone Lymphoma. Similar results were obtained by Lim E et al, wherein they observed marrow involvement in 46.8% of the patients, with diffuse infiltration noted in 71.4% of these cases (14).

More recently, PET/computed tomography (CT) has been shown to stage lymphoma with a higher accuracy than PET alone (8, 15-16). In present study, whole body PET and CT-Scan was done to evaluate the nodal and extra-nodal site of lymphoma. Comparing the two techniques, both PET and CT-imaging showed that generalized lymphadenopathy was most common (42% and 32%, respectively), followed by abdominal region (26% each), mediastinal region (12% each), Cervical region (10% and 12%, respectively), axillary (8% and 6%, respectively) and no nodes were found in 10% patients on PET scan and 14% on CT-Scan.

Further, the two imaging techniques were compared for extra-nodal sites and it was found that abdominal site was the most common identified by both PET and CT-Scan (34% and 40%, respectively). While PET showed involvement of skeletal (16%) and thorax (8%) as other prominent sites, CT-Scan showed involvement of head and thorax in 6% patients.

To understand the histopathological sub-types of NHL, lymph node biopsy was done and it was found that 81.82% of the patients had B-cell NHL and 18.18% had T-cell NHL. Among B-cell NHL, DLBCL was the most common (70.4%), followed by Follicular lymphoma (14.8%), while in T-cell NHL, Anaplastic large cell lymphoma (ALCL) and Angio immunoblastic t cell lymphoma (AITL) was most common (33.33% each).

Biopsy was done to evaluate the histopathology of lymphomas at extra-nodal sites. We observed that among the extra-nodal sites' lymphomas, again B-cell NHL was more prominent than T-cell NHL (93.33% vs

6.66%). Among the B-cell NHL subtypes, DLBCL was most common (85.7%), followed by Nodular marginal zone lymphomas in 14.3% patients, while among T-cell NHL subtype all patients had ALCL.

Overall, in our study population B-cell NHL was more common as compared to T-cell NHL (88% vs 12%). Among the B-cell NHL, DLBCL sub-type was most common (62%) and among T-cell NHL, ALCL, AITL and T cell lymphoblastic lymphomas (T-LBL) subtypes were equally present (4% each). Our results were concurrent with study by Rathore A et al, Devi AA et al, Temmim L et al, Khera R et al, wherein they observed DLBCL as most common histology among B-cell lymphomas (79.16%, 45%, 58.6%, 59.3% respectively) (13,11,9-10)

DLBCL has been reported as most common NHL subtype, with an incidence rate of 20% in USA to 50.5% in Thailand (17), 59% in Saudi Arabia (12) and as high as 76.4% in Pakistan (18).

Further, patients were distributed according to the stage of cancer. Maximum patients (68%) were in stage IV, 16% in stage III, 12% in stage II and only 4% in stage I. Alyahya et al, also found stage IV to be most common among their subjects, however, in majority of patients (59%), stage of NHL was unknown (12).

All patients were subjected to chemotherapy and post-therapy toxicity levels were evaluated. Although, 28% of the patients showed no signs of toxicity, febrile neutropenia was present in 44% of the patients, followed by pancytopenia in 10%.

Disease activity was evaluated both clinically as well as through PET scan over a period of 2 years. A decrease in positivity rate was observed from 100% at the time of onset to a positivity of only 14% at 24 months. Further, while evaluating overall outcome, it was observed that 78% of cases were in remission, in 10% of cancer relapsed, 6% had progressive disease and 6% died.

V. Conclusion

This study found 02 years' survival post standard chemotherapy in NHL cases was 88%. The relapse rate at 24 months was 14 %. The B symptoms were seen less commonly, and bulky disease was noted in one-third of cases. The role of PET in diagnosing and follow up on these cases was good but it was comparable with CT scan.

Recommendation of this study

With the increasing incidence of NHL worldwide, a wide variation in its clinical presentation and pathological profile has been observed. Therefore, a thorough insight into the clinical spectrum of NHL is necessary for optimum management and improved treatment outcome.

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Introduction:

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