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ORIGINAL ARTICLE

No difference in treatment outcome between patients with nodal versus extranodal diffuse large B-cell lymphoma

Saqib Raza Khan[1]*, Muhammad Afzal[1], Salman Muhammad Soomar[1], Daania Shoaib[1], Ayesha Arshad Ali[2], Muhammad Tariq[3], Muhammad Nauman Zahir[1], Adnan Abdul Jabbar[1], Yasmin Abdul Rashid[1], Michal Heger[4,5,6], Munira Shabbir Moosajee[1]

[1]Department of Oncology, Aga Khan University Hospital, Karachi, Pakistan, [2]Medical College, Aga Khan University, Karachi, Pakistan, [3]Lady Reading Hospital, Peshawar, Pakistan, [4]Department of Pharmaceutics, Jiaxing Key Laboratory for Photonanomedicine and Experimental Therapeutics, College of Medicine, Jiaxing University, Jiaxing, Zhejiang, P. R. China, [5]Laboratory Experimental Oncology, Department of Pathology, Erasmus MC, Rotterdam, the Netherlands, [6]Membrane Biochemistry and Biophysics, Department of Chemistry, Faculty of Science, Utrecht University, Utrecht, the Netherlands

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**Corresponding author:*
Saqib Raza Khan
Department of Oncology, Aga Khan University Hospital, Karachi, Pakistan.
Email: saqib.raza31@yahoo.com

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ABSTRACT

Background and Aim: Diffuse large B-cell lymphoma (DLBCL) has been classified using various parameters, including the site of origin. Studies have reported conflicting outcomes when DLBLC patients were stratified according to the site of origin. This study aimed to investigate the response rate and survival outcomes in nodal versus extranodal DLBCL and compare the results to a region-matched study covering the 1988 – 2005 period.

Methods: A single-center retrospective cohort study was conducted on all patients diagnosed with DLBCL and treated in a tertiary care hospital in Pakistan during 2014 – 2019. We calculated the mean and median for continuous variables and frequency and percentages for all categorical variables. Progression-free survival (PFS) and overall survival (OS) were calculated using Kaplan–Meier survival curves. A Cox proportional hazards model was used to determine the hazard ratio (HR) for OS.

Results: Of the 118 patients, 49 patients (41.5%) had nodal disease and 69 patients (58.5%) were diagnosed with extranodal DLBCL. The majority of patients in the nodal and extranodal cohorts presented with Stages III and IV disease (73.4% and 62.3%, respectively). A complete response to (immuno) chemotherapy was achieved in 71.4% of nodal DLBCL patients and 65.2% of extranodal DLBCL patients. The 5-year PFS and median PFS in the entire cohort were 0.8% and 17 m, respectively. The PFS and median PFS in the nodal and extranodal DLBCL cohort were 0% and 1.4%, respectively, and 15 m and 19 m, respectively. The 5-year OS and median OS in the entire cohort were 16.1% and 19 m, respectively. The OS and median OS in the nodal and extranodal DLBCL cohort were 8.2% and 21.7%, respectively, and 19 m and 21 m, respectively. Multivariable linear regression revealed that the ABC phenotype (nodal, HR = 1.37, 95% CI = 1.37 – 3.20; extranodal, HR = 1.65, 95% CI = 1.46 – 3.17; GBC as reference) and double and triple hit DLBCL (nodal, HR = 1.29, 95% CI = 1.19 – 2.81; extranodal, HR = 1.87, 95% CI = 1.28 – 2.43; and non-expressors as reference) are independent negative predictors of OS.

Conclusions: DLBCL incidence in the Karachi region has remained comparable but patient composition in the extranodal DLBCL cohort has shifted to predominantly advanced stage. Nodal and extranodal DLBCL were associated with similar PFS and OS profiles and first- and second-line treatment responses. Cell of origin and antigen expression status was independent negative predictors of OS, disfavoring the ABC phenotype and lesions with c-MYC and BCL2 and/or BCL6 overexpression.

Relevance for Patients: DLBCL is an aggressive type of non-Hodgkin's lymphoma, however; patients respond well to standard systemic chemotherapy. Extranodal type of DLBCL patients tend to have more residual disease after first-line systemic chemotherapy, but physicians should keep in mind that the subsequent line treatment mitigates its negative impact on survival.

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1. Introduction

Diffuse large B cell-lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma, accounting for over 30% of all non-Hodgkin's lymphoma cases [1]. Its incidence increases with age [2] and varies with ethnicity (higher rates are found in Caucasians compared to African Americans and Asians [3]) and gender (male predominance [1,4,5]). DLBCL can either arise de novo from a mature B cell or through the transformation of an existing low-grade B cell lymphoma (e.g., Richter's transformation) [6]. The malignantly transformed B cells express pan-B cell antigens CD19, CD20, CD22, CD45, and CD79a as well as surface immunoglobulin [7].

DLBCLs can be classified based on the site of origin (nodal or extranodal), cell of origin (germinal center B cell subtype or non-germinal center B cell subtype, which includes activated B cell-like cells and unclassifiable disease), and molecular signature (dysregulated oncogenes and proto-oncogenes that affect cell survival and proliferation) [8-10].

The 5-year progression-free survival (PFS) rate in patients with the limited disease is 80%, whereas in advanced disease it is approximately 50% [11]. The standard therapeutic regimen for DLBCL entails a combination of rituximab (immunotherapy), cyclophosphamide, doxorubicin, vincristine (chemotherapy), and prednisone (glucocorticoid), collectively referred to as R-CHOP. Patients who relapse may undergo second-line salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell rescue [12]. A better understanding of the tumor cell phenotype and the development of targeted therapies has led to improved treatment outcomes in DLBCL patients [13].

DLBCL is the most common non-Hodgkin's lymphoma subtype in Pakistan [14]. In 2008, our institute published a large cohort study on a predominantly Karachi DLBCL population that spanned the 1988-2005 era [5]. However, the incidence of DLBCL had been rising [4,15], especially during the latter half of the study period [16]. Consequently, the epidemiological status quo of DLBCL in Pakistan is outdated and has likely changed. This study was therefore undertaken to update the information on DLBCL using a high-volume referral center that had previously provided a historical backdrop as template for the region. Moreover, it has been postulated in different reports that the therapeutic efficacy in extranodal DLBCL is inferior to nodal DLBCL [17,18]. The treatment efficacy in nodal vs. extranodal DLBCL patients was therefore also analyzed retrospectively.

2. Methods

This retrospective study was conducted at the Department of Oncology in a large tertiary care hospital in Karachi, Pakistan, and spanned a period of 5 year (January 2014 thru December 2018). Data of 143 eligible patients with biopsy-confirmed DLBCL who had received treatment were curated from the patient's medical records. Non-probability purposive sampling was applied for cohort selection. Patients for whom there was a minimum follow-up of 2 year and who had undergone treatment with either immuno-chemotherapy or chemotherapy with or without intrathecal chemotherapy and radiation therapy were included in the analysis. Additional inclusion and exclusion criteria as well as other study details are presented in Figure 1.

2.1. Data collection and processing

All records were screened for medical history and clinical data. Biopsies had been evaluated by histopathologists to confirm the diagnosis and for purposes of further characterization (germinal center B cell-like [GCB] vs. activated B cell-like [ABC] DLBCL) and scoring (International Prognostic Index [IPI], central nervous system [CNS]-IPI, and antigen overexpression). GCB and ABC DLBCL were classified based on CD10, BCL-6, and/or MUM1 positivity [19]. Where available, tissue sections were stained by immunohistochemistry (IHC) for LCA, CD3, CD19, CD20, CD10, CD30, CD22, CD79a, BCL6, BCL2, MUM1, PAX5, c-MYC, and Ki-67 [20,21]. The overexpression cutoff for MYC and BCL2 was ≥40% and ≥50%, respectively, whereas the overexpression cutoff for BCL6 and MUM1 was 30%. Expressors (double hit DLBCL) were defined as histological sections with overexpression of c-MYC and BCL2 and/or BCL6, whereas histological sections with no c-MYC and BCL2 and/or BCL6 overexpression were characterized as non-expressors.

Positron emission tomography (PET) and computed tomography (CT) images were analyzed to stage the patients according to the Lugano modification of the Ann Arbor classification system. Residual disease was determined by PET positivity using the Deauville score. Lesions with a Deauville score of ≥4 were considered positive for residual disease. Tumors predominantly involving lymph nodes were defined as nodal DLBCL and tumors that primarily affected extranodal sites (gastrointestinal tract, testes, mediastinum, CNS, breast, thyroid, nasopharynx, chest wall, bone, and soft tissues) were classified as extranodal DLBCL. The baseline PET-CT scan was performed within 2 weeks before the initiation of treatment, the interim scan was performed after 3 – 4 cycles of systemic (immuno) chemotherapy, and the end-of-treatment scan was performed 8 – 12 weeks after the last dose had been administered. PET-CT following second-line treatment was performed when clinically indicated and/or at the physician's discretion.

PFS was defined as the time until tumor progression or death from any cause. A complete response (CR) was defined as the normalization of ^{18}fluorodeoxyglucose (FDG) uptake with a Deauville score of 1 – 3 in combination with clinical resolution of symptoms in response to treatment. Patients whose disease worsened or returned after achieving partial or CR during the interim scan, respectively, were considered to have a relapse. Patients whose disease did not respond to treatment or progressed after 4 cycles of therapy were considered to have refractory disease.

Frequency and percentages were calculated for categorical variables that included demographics, cell of origin, disease site (nodal vs. extranodal), antigen expression status, DLBCL stage, and IPI scores. IPI score was calculated by assigning one point for each of the following variables: age of >60 year, serum

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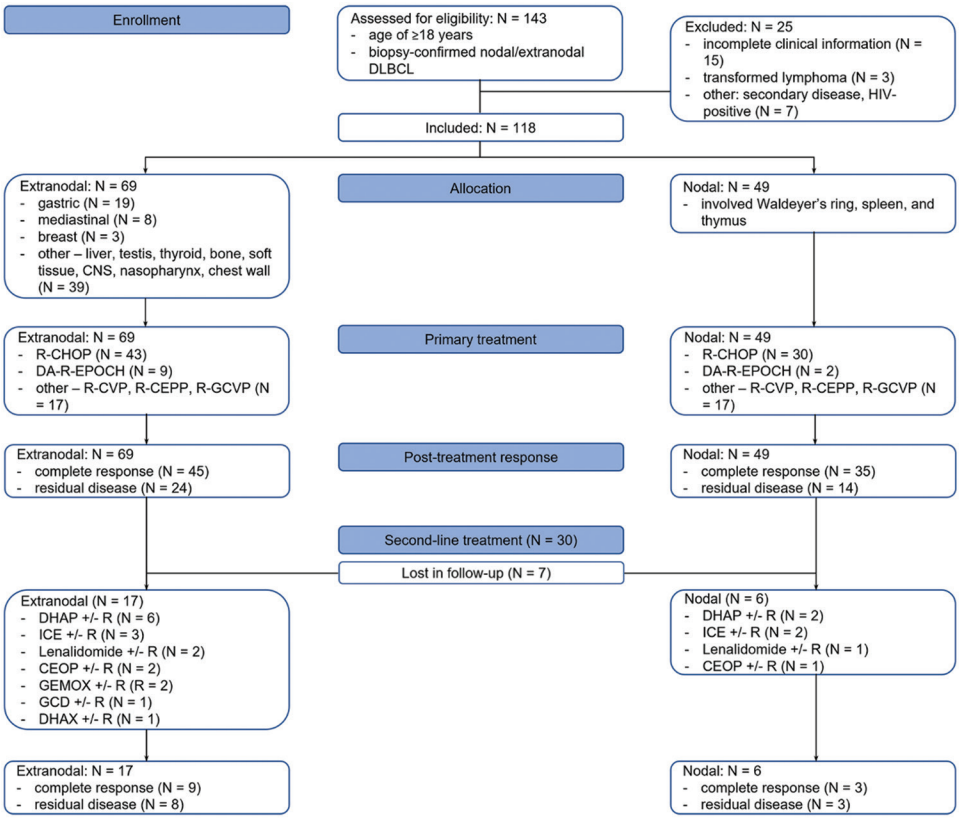

Figure 1. CONSORT flow chart of the DLBCL study.
CEOP: Cyclophosphamide, epirubicin, vincristine, prednisone; CEPP: Cyclophosphamide, etoposide, procarbazine, prednisone; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; CNS: Central nervous system; CVP: Cyclophosphamide, vincristine, prednisone; DA: Dose-adjusted; DHAP: Dexamethasone, cytarabine, cisplatin; DHAX: Dexamethasone, cytarabine, oxaliplatin; DLBCL: Diffuse large B cell lymphoma; EPOCH: Etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; GCD: Gemcitabine, carboplatin, dexamethasone; GCVP: Gemcitabine, cyclophosphamide, vincristine, prednisone; GEMOX: Gemcitabine, oxaliplatin; ICE: Ifosfamide, carboplatin, etoposide; R, rituximab.

LDH above normal range, Eastern Cooperative Oncology Group (ECOG) performance status of ≥2, Ann Arbor stage III or IV, and the number of extranodal disease sites. The CNS-IPI score was calculated using the parameters of the IPI scoring system with additional points for kidney and/or adrenal gland involvement. The sum of the IPI scores and the CNS-IPI scores of these variables was used to classify patients into low-risk (score of 0 – 1), intermediate-risk (score of 2 – 3), and high-risk (score of ≥4 for IPI and score of ≥4 and/or kidney adrenal gland involvement for CNS-IP) categories.

2.2. Statistical analysis

Data were analyzed using STATA software (StataCorp, College Station, TX, USA) and GraphPad Prism software (GraphPad Software, San Diego, CA, USA). Intergroup differences between non-substratified continuous variables (age) were tested using a two-tailed Student's t-test following confirmation that both data sets (nodal and extranodal) were normally distributed (by both the Shapiro–Wilk and Kolmogorov–Smirnov test). The frequency of outcome parameters (cell of origin, site of origin, expression status, stage of the disease, IPI score, and type of primary treatment received) was calculated per nodal and extranodal DLBCL group. Data were also sorted based on the type of response achieved in the nodal and extranodal DLBCL groups at interim analysis and at the end of first-line and second-line treatment. For these categorical variables, the statistical difference between the nodal versus extranodal DLBCL groups was determined using the Chi-square test (> 2 strata per outcome parameter) or Fisher's exact test (2 strata per outcome parameter). Kaplan–Meier plots were constructed in GraphPad Prism and the Mantel-Cox test and Gehan-Breslow-Wilcoxon's test (due to diverging PFS at early time points) were used to determine statistical differences between the curves. A Cox proportional hazards model was employed to determine the hazard ratio (HR). $P \leq 0.05$ was considered statistically significant.

3. Results

A total of 118 patients with DLBCL were included in the study. Of 118 patients, 49 (42%) were diagnosed with nodal DLBCL, while 69 (59%) patients were diagnosed with extranodal DLBCL. None of the baseline characteristics statistically differed between the nodal and extranodal DLBCL cohorts (Table 1). The mean

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Table 1. Baseline characteristics of DLBCL patients, stratified according to site of origin.

Characteristics	Site of origin (N=118)		*P*-value
	Nodal (N=49; 41.5%)	Extranodal (N=69; 58.5%)	
Age (mean±SD)	53.3±14.8	52.3±15.1	0.70[#]
[range]	[23 – 81]	[22 – 80]	
Sex (N, %)	49 (100.0%)	69 (100.0%)	0.70[†]
Male	33 (67.3)	43 (62.3)	
Female	16 (32.7)	26 (37.7)	
Comorbidity (N, %)	49 (100.0%)	69 (100.0%)	0.55*[1]
None	29 (59.2)	36 (52.2)	
Diabetes mellitus	8 (16.3)	8 (11.6)	
Hypertension	3 (6.1)	12 (17.4)	
Ischemic heart disease	4 (8.2)	4 (5.8)	
Other	5 (10.2)	9 (13.0)	
ECOG score (N, %)	49 (100.0%)	69 (100.0%)	0.57*[2]
0	1 (2.0)	3 (4.3)	
1	28 (57.1)	32 (46.4)	
2	14 (28.6)	23 (33.3)	
3	4 (8.2)	11 (15.9)	
4	2 (4.1)	0 (0.0)	
Pathological origin (N, %)	39 (79.6)	45 (65.2)	0.18[†]
GCB	27 (69.2)	24 (53.3)	
ABC	12 (30.8)	21 (46.7)	
Antigen expression pattern (N, %)	26 (53.1)	27 (39.1)	0.78[†]
Expressors	16 (61.5)	15 (55.6)	
Non-expressors	10 (38.5)	12 (44.4)	
Anatomical site (extranodal DLBCL) (N, %)		69 (100.0%)	
Gastric		19 (27.5)	
Mediastinum		8 (11.6)	
Breast		3 (4.3)	
Other (liver, testis, thyroid, bone, soft tissue, CNS, nasopharynx, chest wall)		39 (56.5)	
Surgery (N, %)	49 (100.0%)	69 (100.0%)	0.32[†]
No	39 (79.6)	60 (87.0)	
Yes	10 (20.4)	9 (13.1)	
DLBCL stage (N, %)	49 (100.0%)	69 (100.0%)	0.58*
I	3 (6.1)	7 (10.1)	
II	10 (20.4)	19 (27.5)	
III	13 (26.5)	13 (18.8)	
IV	23 (46.9)	30 (43.5)	
IPI score (N, %)	49 (100.0%)	69 (100.0%)	0.28*
Low	11 (9.3)	19 (16.1)	
Intermediate	25 (29.7)	37 (31.4)	
High	3 (2.5)	13 (11.0)	
CNS IPI score (N, %)	49 (100.0%)	69 (100.0%)	0.77*
Low	23 (46.9)	28 (40.6)	
Intermediate	16 (32.7)	24 (34.8)	
High	10 (20.4)	17 (24.6)	
Primary treatment (N, %)	49 (100.0%)	69 (100.0%)	0.18*
R-CHOP	30 (61.2)	43 (62.3)	
DA-R-EPOCH	2 (4.1)	9 (13.0)	
Other	17 (34.7)	17 (24.6)	

[1]To meet the conditions for a Chi-square test, quantitative data for hypertension and ischemic heart disease were combined under the category cardiovascular disease in the statistical analysis.
[2]To meet the conditions for a Chi-square test, quantitative data for scores 3 and 4 were combined and the data for the score '0' were excluded from the analysis.
[#]Two-tailed student's t-test.
[†]Fisher's exact test.
*Chi-square test.
DLBCL: Diffuse large B cell lymphoma; CR: Complete response; ECOG: Eastern cooperative oncology group; GCB: Germinal center B cell-like; ABC: Activated B cell-like; CNS: Central nervous system; IPI: International prognostic index.

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age of the patients was early fifties. Male patients outnumbered female patients by a ratio of roughly 2:1 and less than half of the patients presented with comorbidities. The median ECOG score was 1 in both groups. The ratio GCB: ABC was about 2:1 in the nodal lesions, whereas equal proportions in the site of origin were found for extranodal lesions. Histological sections, exemplified in Figure 2, were retrieved from 26 nodal DLBCL patients and 27 extranodal DLBCL patients. Of the 26 nodal DLBCL patients, 16 (62%) patient biopsies stained positive, of which 32% stained positive for c-MYC and BCL-2 and/or BCL-6 (i.e., double expressor lymphoma). Of the 27 extranodal DLBCL patients, 15 (56%) patient biopsies stained positive, of which 21% comprised double expressor lymphoma. In some instances, CD10, CD20, and MUM1 positivity was observed and most histological sections exhibited high proliferative propensity (Ki-67).

The stomach (28%) was the most common site of extranodal DLBCL, followed by the mediastinum (12%), breast (4%), and other sites (57%). A small number of patients (13%) in the extranodal group had undergone surgical resection of the lymphoma following biopsy-confirmed diagnosis, whereas 20% of nodal DLBCL patients had undergone surgery. The majority of diagnoses comprised Stage IV lesions (>43% in both nodal and extranodal groups). The IPI and CNS-IPI scores were evenly divided among groups. R-CHOP was the most frequently administered treatment in both groups, while radiation therapy had been administered in 23% of nodal cases and 40% of extranodal patients complementary to (immuno) chemotherapy.

Of the 118 patients, 80 (68%) patients achieved CR as confirmed by PET-CT performed 8 – 12 week after completion of first-line treatment (Table 2). The CR statistics had improved considerably after the completion of first-line treatment compared to the interim scan results, which had been obtained 3 – 4 cycles after the start of treatment. Thirty-five (71%) patients with CR were in the nodal

Table 2. Treatment responses in nodal and extranodal DLBCL patients.

Characteristics	Site of origin (N=118)		*P*-value
	Nodal (N=49)	Extranodal (N=69)	
Interim scan (N, %)	39 (79.6)	51 (73.9)	0.40†
CR	22 (56.4)	24 (47.1)	
Incomplete response	17 (43.6)	27 (52.9)	
Relapse after interim partial response or CR (N, %)	39 (79.6)	51 (73.9)	0.43†
Yes	1 (2.6)	0 (0.0)	
No	38 (97.4)	51 (100.0)	
End of treatment scan (N, %)	49 (100.0)	69 (100.0)	0.13*
CR	35 (71.4)	45 (65.2)	
Partial response	6 (12.2)	9 (13.0)	
Relapse and refractory response	8 (16.3)	15 (21.7)	
Second-line treatment outcome	6	17	0.90*
CR	3 (50.0)	9 (52.9)	
Refractory	3 (50.0)	8 (47.1)	

†Fisher's exact test.
*Chi-square test.
DLBCL: Diffuse large B cell lymphoma; CR: Complete response

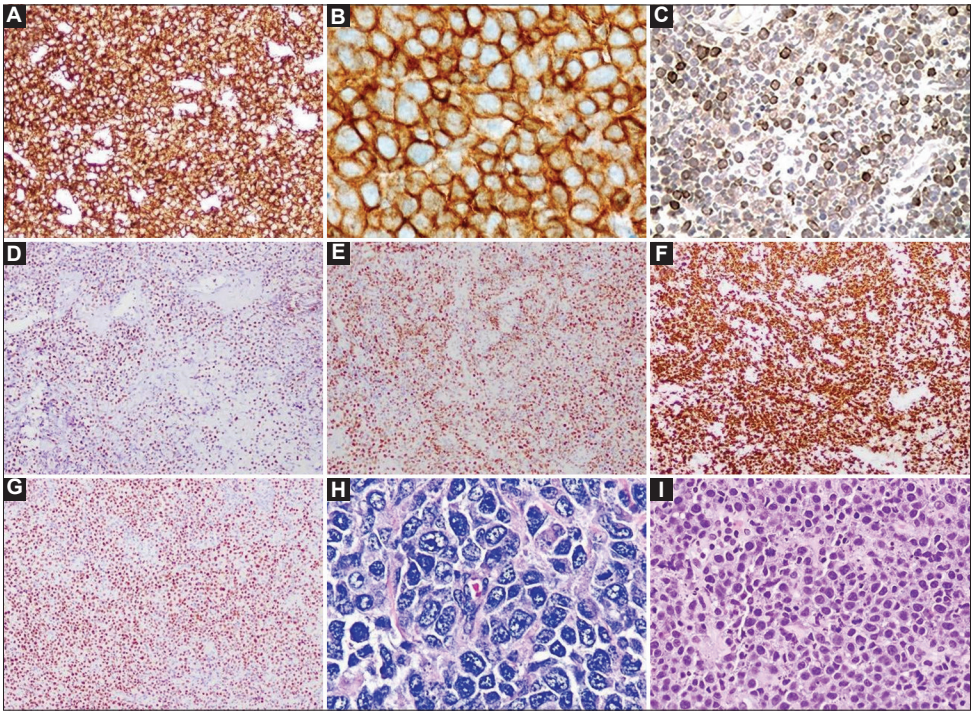

Figure 2. Representative positive immunohistochemical stains of nodal and extranodal diffuse large B cell lymphoma of (A) CD20, (B) CD10, (C) BCL2, (D) BCL6, (E) c-MYC, (F) Ki-67 (70-80% positivity), and (G) MUM1. Furthermore, H&E stains are presented of (H) germinal center B cell-like type and (I) activated B cell-like type. Original magnification is ×20 (A, C, and I), ×40 (B and H), and ×10 (D–G).

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group and 45 (65%) patients with CR had extranodal malignancy. A partial response was noted in 12% of nodal and 13% of extranodal DLBCL patients. Respectively 16% and 22% of nodal and extranodal DLBCL patients exhibited refractory disease or relapse at the end of first-line treatment. None of the differences in treatment outcomes were statistically significant between the nodal and extranodal groups.

Residual disease was found in 30 patients who continued in the study trajectory after the first treatment, based on PET-CT scans performed 8 – 12 weeks after completion of the first-line treatment. Of these, seven patients were lost during follow-up. The proportion of responders and refractory patients after second-line treatment was similar among both groups (Table 2). Representative PET-CT scans of therapy-responsive nodal and extranodal DLBCL patients are presented in Figures 3A-C and 4A-C, respectively. Of the 23 evaluated patients, seven patients had biopsy-proven residual disease. DHAP +/- rituximab was the most used second-line treatment (33%), followed by ICE and lenalidomide +/- rituximab (23% and 12%, respectively). DHAX, GCD, GEMOX, and CEOP comprised some of the other regimens used. Following second-line treatment, 12 (52%) patients achieved complete response, and 11 (48%) had refractory disease. The responses were equally distributed among groups.

For the unstratified patient cohort, the 5-year PFS was 0.8% and the 5-year median PFS was 17 m (Figure 5A). The PFS in nodal and extranodal DLBCL patients was 0% and 1.4%, respectively. The median PFS in nodal and extranodal DLBCL patients was 15 m and 19 m, respectively (P = 0.1406, Mantel-Cox test; Figure 5B). The 5-year OS was 16.1% and the 5-year median OS was 19 m (Figure 5C). The OS in nodal and extranodal DLBCL patients was 8.2% and 21.7%, respectively. The median OS in nodal and extranodal DLBCL patients was 19 m and 21 m, respectively (P = 0.1656, Mantel-Cox test; Figure 5D).

Multivariate Cox regression analysis revealed that ABC phenotype and non-expressor subtypes were independent predictors of worse OS in DLBCL patients when the entire cohort was considered, accounting for an adjusted HR (95% CI) of 1.50 (1.09 – 2.44) and 1.25 (1.16 – 2.29), respectively (Table 3). The cell of origin and expression pattern remained independent predictors of OS when stratified for nodal and extranodal DLBCL, whereby the adjusted HR was greater in extranodal DLBCL patients compared to patients with nodal lesions (Table 4).

4. Discussion

Non-Hodgkin's lymphoma tops the list as the most commonly occurring hematological malignancy in the world [22], with DLBCL comprising 30% of all adult non-Hodgkin's lymphoma in Western countries. In Pakistan, DLBCL accounts for 75% of all non-Hodgkin's lymphomas and for 60% in neighboring countries [23,24]. DLBCL predominates in males and in patients over 60 y [24,25]. Although gender distribution was comparable to previously published studies [1,4,5], our cohort consisted of significantly younger patients with a median age at diagnosis of 52 – 53 year. This is in agreement with other national studies in Asia (India) [26] and regional data from countries in South Asia and the Middle East [27]. It has been hypothesized that

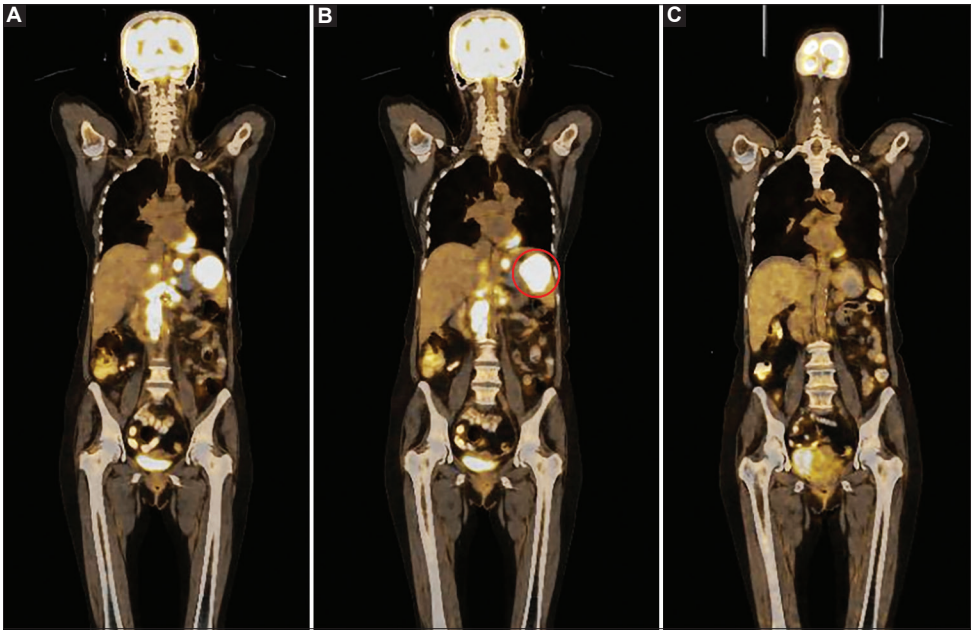

Figure 3. Representative positron emission tomography-computed tomography images of a diffuse large B cell lymphoma patient with nodal disease who was refractory to first-line treatment but responsive to second-line treatment. (A) Before treatment: matted ^{18}fluorodeoxyglucose (FDG)-avid lymphadenopathy in the epigastric region, para-aortic FDG-avid lymph nodes and a large FDG-avid splenic mass are seen. (B) 12 weeks after first-line treatment: improvement noted in metabolic activity in the epigastric matted lymph nodes with sustained splenic activity signifying residual disease (encircled, Deauville 5PS:4). (C) 10 weeks after second-line treatment: complete metabolic response (Deauville 5PS:1).

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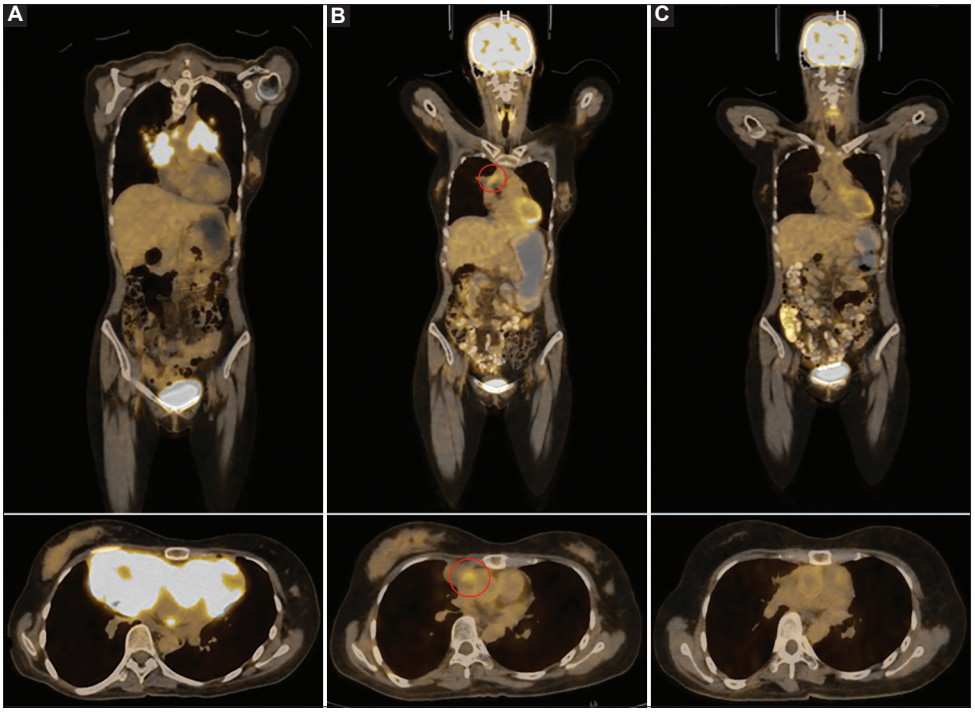

Figure 4. Representative positron emission tomography-computed tomography images of a diffuse large B cell lymphoma patient with extranodal disease who was responsive to first-line treatment and exhibited a complete response to second-line treatment. (A) Before treatment: a large hypermetabolic extranodal anterior mediastinal mass is seen, extending from the thoracic inlet to the base of the heart, measuring 168 × 68 × 132 mm (transverse × anteroposterior × craniocaudal) with volumetric maximum standardized uptake value (SUVmax) of 15.6. FDG-avid bilateral lung nodules are seen, highest SUVmax of 7.1, measuring 14 × 12 mm in the upper lobe of the left lung. (B) 8 – 12 weeks after first-line treatment: interval reduction in size and metabolic activity of anterior mediastinal mass (residual right anterior mediastinum: 31 × 23 mm, SUVmax of 3.9 along pericardium, encircled). Interval normalization of metabolic activity and reduction in the size of bilateral pulmonary nodules (Deauville 5PS:4). (C) 8 weeks after second-line treatment: complete metabolic response (Deauville 5PS:2).

environmental mutagens such as pesticides and herbicides and a higher rate of viral infections (hepatitis B, hepatitis C, and HIV) in these regions contribute to the increasing incidence and younger age at presentation [23,28].

Compared to the 2008 report (1988 – 2005 era) [5], the statistics of the present study (2014 – 2019 era) are rather dismal and insinuate a worsening of consequences of DLBCL. The 5-year PFS and median PFS in the entire cohort were 0.8% and 17 m, respectively. The 5-year OS and median OS in the entire cohort were 16% and 19 m, respectively. In contrast, in the region-matched 2008 study, the 5-year OS was 55% and median survival was 67 m [5]. An important factor that contributes to this difference in OS is the fact that the 2008 study had 0 stage III and 0 stage IV extranodal DLBCL patients included in the cohort, whereas Stages III and IV extranodal DLBCL patients accounted for 62% of all extranodal DLBCL patients (of which 70% comprised Stage IV) and that advanced disease (Stage III/IV nodal and extranodal DLBCL) encompassed 67% of the entire patient cohort in the current study. Furthermore, the current study had included a higher proportion of patients with Stage III nodal disease (27% versus 23%) and Stage IV nodal disease (47% vs. 44%) compared to the 2008 study. Given that the 2008 report found that Stage IV extranodal disease was an independent risk factor for mortality (hazard ratio of 2.3 (1.6 – 3.2); $P < 0.001$), it is arguable that the strong overweight in advanced disease in the current cohort brought down the PFS and OS statistics.

One key question that remains to be answered is why so many patients presented with Stages III and IV extranodal disease (or, alternatively, why no patients had presented with advanced extranodal DLBCL during 1988 – 2005 at what was already a high-volume center). In recent years, our institute has received an increasing number of referrals for advanced, symptomatic patients with poorly responding disease, which suggests a referral bias. Until few years ago, Pakistan did not have specialization centers for DLBCL and each hospital therefore treated these patients. Our institute recently became a national referral center, which has contributed to the increase in patients presenting with advanced disease and hence the skewing of originally established proportions during the 1988 – 2005 era. The newly acquired status of our institute, however, did not coincide with an increased annual admission rate in the most recent study period, but rather entailed a reduction compared to the first study period (33 patients/y during 1988 – 2005 [5] vs. 24 patients/year during 2014 – 2019). For context, global figures indicate a 65 – 72% 5-year OS rate [29], with higher figures in cases of limited disease with 5-year PFS ranging from 80 – 85% and roughly 50% for advanced disease [11]. Accordingly, the global statistics pale in comparison to current statistics in Karachi and it is therefore

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Table 3. Multivariate analysis of crude and adjusted hazard ratios (HR) in relation to OS.

Characteristics	Crude HR (95% CI)	*P*-value*	Adjusted HR (95% CI)	*P*-value*
Age	1.05 (0.99 – 1.11)	0.391	-	-
Gender				
Male	1	0.433	-	-
Female	1.17 (0.78 – 1.75)			
Comorbidities				
Others	1	0.941	-	-
Diabetes mellitus	1.24 (0.56 – 2.73)			
Hypertension	1.09 (0.48 – 2.45)			
IHD	1.25 (0.50 – 3.14)			
Cell of origin				
ABC	1	0.018	1	0.009
GCB	1.50 (1.08 – 2.41)		1.50 (1.09 – 2.44)	
Expression pattern				
Expressors	1	0.003	1	0.007
Non-expressors	1.29 (1.02 – 1.79)		1.25 (1.16 – 2.29)	
Surgery				
Yes	1	0.956	-	-
No	1.01 (0.61 – 1.66)			
Disease stage				
I and II	1	0.561	-	-
III	1.31 (0.78 – 2.21)			
IV	1.17 (0.76 – 1.80)			
IPI score				
High	1	0.255	-	-
Low	1.43 (0.75 – 2.73)			
Intermediate	1.60 (0.89 – 2.87)			
CNS IPI score				
High	1	0.312	-	-
Low	1.44 (0.87 – 2.37)			
Intermediate	1.16 (0.69 – 1.97)			

*Cox proportional hazards model.
HR: Hazard ratios; DLBCL: Diffuse large B cell lymphoma; CR: Complete response; ECOG: Eastern cooperative oncology group; GCB: Germinal center B cell-like; ABC: Activated B cell-like; CNS: Central nervous system; IPI: International prognostic index; CI: Confidence interval

Table 4. Adjusted HR when classified by cell of origin and antigen expression pattern in relation to OS of nodal and extranodal DLBCL patients.

Characteristics	Site of origin (adjusted HR [95% CI])		*P*-value*
	Nodal	Extranodal	
Cell of origin			
ABC	1	1	0.001
GCB	1.55 (1.37 – 3.20)	1.65 (1.46 – 3.17)	
Antigen expression pattern			
Expressors	1	1	0.014
Non-expressors	1.29 (1.19 – 2.81)	1.87 (1.28 – 2.43)	

*Cox proportional hazards model.
OS: Overall survival; DLBCL: Diffuse large B cell lymphoma; GCB: Germinal center B cell-like; ABC: Activated B cell-like; HR: Hazard ratios; CI: Confidence interval

quintessential to elucidate the exact cause(s) of these trends. Broader epidemiological studies should be performed to determine whether the incidence of DLBCL subtypes and the lethality of the DLBCL subtypes have been increasing disproportionally in other centers in the region. If indeed the case, the incidence rates should be related to the potential causes mentioned above [23] as well as other known and alleged disease drivers.

DLBCL is commonly classified by the anatomical origin of the malignant transformation, namely lymph nodes (primary nodal) and non-lymph node tissues (primary extranodal). Primary extranodal DLBCL has a diverse pathological manifestation with various primary sites. Over the past decades, the incidence of extranodal DLBCL has increased more rapidly than the nodal type, likely due to improved diagnostic modalities [5]. The global incidence of primary extranodal disease ranges from 10% to 40%, with a gradual increase in incidence reported in more recent studies [5,30]. At the same time, there is a paucity of literature on the site-stratified DLBCL entities and their clinical characteristics in particularly the Middle East. Our analysis demonstrated a higher percentage of extranodal DLBCL compared to nodal DLBCL, that is, 58% versus 42%, respectively, which is considerably higher than what has been reported in literature [31-34] but equivalent to what was reported in the 2008 study [5]. The 5-year PFS and

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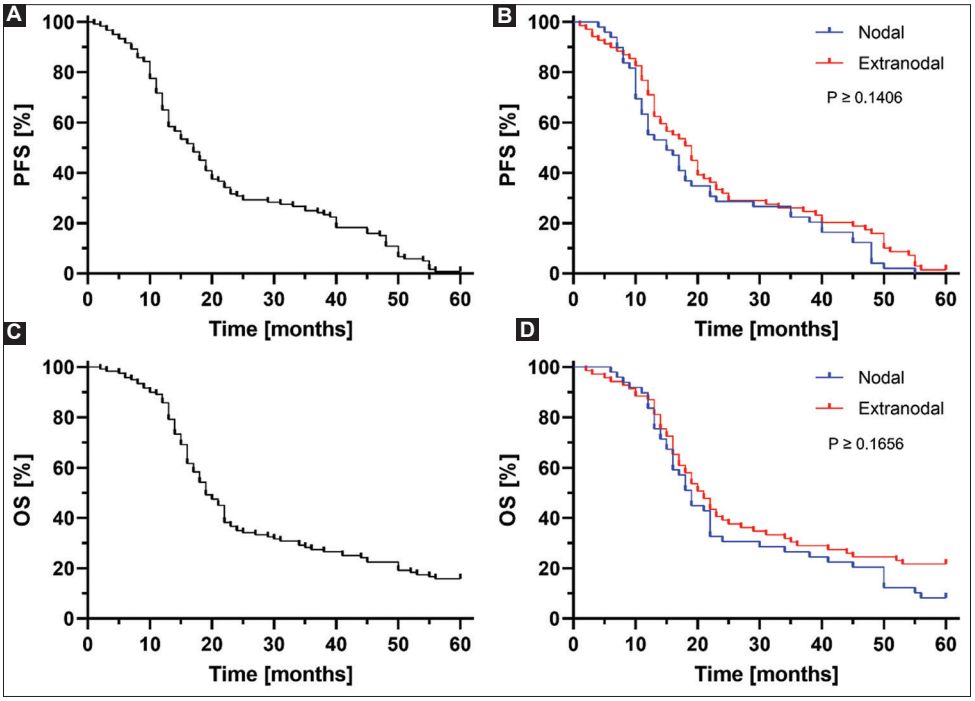

Figure 5. Kaplan-Meier plots of (A) progression-free survival (PFS) and (C) overall survival (OS) in the non-stratified diffuse large B cell lymphoma (DLBCL) patient cohort and (B) PFS and (D) OS in the DLBCL patient cohort stratified by tumor location (nodal versus extranodal). The 5-year PFS and median PFS in the entire cohort were 0.8% and 17 m, respectively. The PFS and median PFS in the nodal and extranodal DLBCL cohort were 0% and 1.4%, respectively, and 15 m and 19 m, respectively. The 5-year OS and median OS in the entire cohort were 16.1% and 19 m, respectively. The OS and median OS in the nodal and extranodal DLBCL cohort were 8.2% and 21.7%, respectively, and 19 m and 21 m, respectively. Statistical differences between the nodal and extranodal curves were determined using the Mantel-Cox test and Gehan-Breslow-Wilcoxons test. The lowest *P*-value of both tests is reported.

median PFS in the nodal and extranodal DLBCL cohort were 0% and 1.4%, respectively, and 15 m and 19 m, respectively. The 5-year OS and median OS in the nodal and extranodal DLBCL cohort were 8.2% and 21.7%, respectively, and 19 m and 21 m, respectively. In terms of survival, the 2008 study had reported a 62% 5-year OS for extranodal DLBCL compared to 43% for the nodal DLBCL ($P < 0.001$), although statistically significant differences were lost when corrected for IPI score (low risk vs. high risk) in multivariable analysis [5]. The stark inter study difference in survival may be attributed to the overwhelming rate of advanced disease in the present study. Corroboratively, a recent retrospective cohort study by Shen *et al.* [35], which entailed 141 Chinese patients with extranodal DLBCL of which 38% were Stage III/IV (compared to 62% extranodal Stage III/IV lesions in our study), reported survival data that approximated those found in our study. The median OS of patients was 36.5 m for primary GI tract-, 29 m for CNS-, 14 m for adrenal gland-, 25 m for breast-, 20 m for female genital system-, 22 m for thyroid-, and 18.5 m for bone lesions. The PFS was 25.5 m for primary GI tract-, 24 m for CNS-, 10 m for adrenal gland-, 20 m for breast-, 11 m for female genital system-, 22 m for thyroid-, and 12.5 m for bone lesions. Based on multivariable analysis, both studies from our institute as well as studies by others [34,36,37] found that site of origin was not an independent predictor of survival, altogether indicating that there were no site of origin-specific differences in therapeutic efficacy. In contrast, López-Guillermo *et al.* [34] reported that the complete response rate and 5-year OS were considerably lower in nodal DLBCL and the 5-year risk of relapse was higher in the nodal group. On the other hand, other studies revealed that the therapeutic efficacy in extranodal DLBCL is inferior to nodal DLBCL [17,18].

Primary sites of extranodal disease include the gastrointestinal tract, mediastinum, CNS, breast, bone, and the liver. The gastrointestinal tract is commonly implicated [24,35], with gastric lymphomas as the most common site of involvement [24,38]. In an analysis of 118 patients with extranodal DLBCL, López-Guillermo *et al.* [34] demonstrated that the GI tract was the most frequent primary site, followed by soft tissue and the liver. Our results partly echo these data, with the stomach being the most common extranodal site. Thirty patients were found to have significant residual disease activity on PET-CT, of which the majority belonged to the extranodal group. Given the unique characteristics of the extranodal DLBCL owing to its location, residual disease may be more commonly seen on scans than nodal DLBCL [18,39]. Accurate characterization requires a biopsy to differentiate between post-treatment inflammatory and necrotic changes versus true PET-positive disease before deciding on salvage/second-line treatment [40,41]. In our study cohort, a minimal number of patients underwent a biopsy. In low- and middle-income populations, there is often significant hesitancy

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among patients to undergo repeated testing. This is most likely due to additional cost accrual of already financially strained patients as a result of first-line treatment expenses. Nevertheless, second-line treatment was provided to patients with positive scans who were clinically symptomatic and resistant to consenting to a biopsy even after extensive discussions. All patients who underwent a repeat biopsy were in fact positive for residual disease. Regardless, a biopsy for an accurate assessment should be standard of care even in low- and middle-income populations.

Studies have shown that primary extranodal DLBCLs tend to relapse more frequently, especially in high-risk populations such as testicular or CNS lymphoma or those with more than one site involved [42,43]. Testicular lymphomas tend to have a very high rate of CNS relapse [44], with a pattern of involvement displaying a propensity for parenchymal involvement and late relapses [45] and dismal prognosis [46]. Primary breast lymphomas run a significant risk of contralateral breast involvement along with other extranodal sites and CNS involvement [47]. In our analysis, 23 patients were identified with either relapsed or refractory disease at the end of initial treatment, with no significant difference between the nodal and extranodal cohorts with respect to therapeutic efficacy.

DLBCL is further classified by the cell of origin (i.e., cells with CD10, BCL-6, and/or MUM1 overexpression), which is accordingly sorted into a GCB and ABC subtype [19]. In general, the GCB phenotype is more prevalent and ABC DLBCLs are associated with worse clinical outcomes [48]. In our study, nearly 70% of nodal DLBCL patients were of the GCB subtype, and 53.3% of the extranodal DLBCL patients comprised the GCB subtype. Furthermore, ABC DLBCL was associated with significantly worse outcomes, which aligns with findings by other groups where DLBCL was treated with standard chemoimmunotherapy [10,48-51]. The GCB subtype is not the predominant phenotype in all studies and the ABC subtype is not consistently predictive of worse outcomes; both seem to rely on the geographic origin of the study population. For instance, in a Korean cohort of DLBCL patients (N = 124), Kim *et al.* [37] found no difference between the GCB and ABC subtype incidence rate when comparing nodal and extranodal DLBCL. Multivariable analysis further revealed that GCB subtype was not an independent predictor of OS. The aforementioned Spanish study (N = 382) [34] found that GCB marker expression varied among nodal and extranodal lesions. CD10 positivity was equal between nodal and extranodal disease, BCL-6 positivity was more pronounced in extranodal DLBCL, while MUM1 positivity was more prevalent in nodal DLBCL. Similarly, a study on Chinese DLBCL patients (N = 207) [36] reported that the GCB phenotype was dependent on disease site (GBC positivity in 56.0% of Waldeyer's ring lymphomas, 46.5% of gastrointestinal lymphomas, 27.8% of other extranodal sites, and 18.2% of glands compared to 34.5% of primary nodal lymphomas; P = 0.035). However, GBC marker expression (CD10, BCL-6, and/or MUM1) did not differ between nodal and the various extranodal lesions ($P \geq 0.268$). The ABC DLBCL hazard ratio (95% CI) in terms of OS was 2.678 (1.194-6.008), which is in lockstep with the majority of other reports, including this study.

The so-called double-hit and triple-hit lymphomas represent 6 – 14% of patients with DLBCL [52] and are typically associated with resistance to chemotherapy and poor outcome [53,54]. In our study, data for double expressor status were available only for a relatively small fraction of the patients, with no difference in proportionality between the two groups. In multivariate analysis, dual expressor status was identified as poor prognostic factor in the entire cohort and the subgroup analysis on the nodal versus extranodal group. This is in accordance with the available literature [5,55].

The IPI is an important clinical tool in predicting the outcomes of patients with DLBCL [37,49,56,57]. Studies looking at differences between extranodal DLBCL and nodal DLBCL have shown no difference in IPI between the two disease categories [34]. Our study reverberated the IPI outcomes in nodal and extranodal DLBCL reported by others. Initially, it was suggested that primary sites might serve as important prognosticators that account for differences in survival [30]. However, it has become more evident that the stage of disease at presentation, biological aspects of the disease, as well as other compounding factors are more critical in determining the outcome [5].

As per international standards, our patients received R-CHOP as primary treatment. Garcia *et al.* reported a statistically significant benefit of rituximab in nodal but not in extranodal DLBCL that were treated with CHOP [18]. Contrastingly, Hui *et al.* [58] did not report any difference in outcomes between nodal and extranodal DLBCL when treated with R-CHOP. Our study demonstrated that 56% of patients in the overall population achieved CR, of which 51% had received R-CHOP, which is better than some other reports [57] and equivalent to other clinical studies, where durable remissions have been achieved in up to 60% of patients [59]. There was no difference in therapeutic efficacy between nodal and extranodal DLBCL, which is in line with the findings by Hui *et al.* [58].

Autologous stem cell transplantation is currently the standard of care for patients with DLBCL who relapsed or progressed after the first-line chemotherapy or immunochemotherapy. Poorer outcomes were reported by Korean colleagues with autologous stem cell transplantation when concurrent nodal and extranodal involvement was indicated [60]. But little to no available data directly compares the efficacy of autologous stem cell transplantation in primary nodal vs. primary extranodal disease. In most studies looking at the efficacy of autologous stem cell transplantation, nodal and extranodal DLBCL cases are clustered. Naturally, it is impossible to draw conclusions on therapeutic efficacy in the location-stratified cohorts based on clustered data. Furthermore, not all relapse patients proceed to autologous stem cell transplantation, and the number of patients is likely too few to have any conclusive results. In our study population, long-term follow-up showed that only two of the patients received autologous stem cell transplantation as second-line treatment. An issue at our institute is mainly the high treatment costs and the relatively difficult logistics of the procedure, which constitute serious limiting factors in low- and middle-income countries in general.

Our study had several limitations owing to its retrospective nature, including some datasets being incomplete and the possibility

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that medical records may contain inaccurate information. Moreover, our small sample size might not be representative of the entire Pakistani population and suffer from selection bias. These limitations notwithstanding, our data provides valuable information on clinical behavior and outcomes of nodal and extranodal DLBCL treated in the rituximab era in Pakistan, which is classified as a lower middle-income country by the World Bank. In addition, the study also sheds light on the areas of improvement, such as biopsy confirmation of PET-positive disease, access to treatment options such as autologous stem cell transplantation, and more vigilant follow-up of the relapsed patients to improve outcomes.

5. Conclusions

DLBCL incidence at our high-volume, referral center has remained comparable during the 2014-2019 era compared to the 1988-2005 era (first cohort study). However, the composition of the extranodal DLBCL patient cohort has shifted to predominantly patients with advanced (Stages III and IV) disease, while the make-up of the nodal DLBCL patient cohort had remained the same. Consequently, the survival statistics of the present cohort were reduced by more than half nominally (median survival in months) and percentually (fraction of patients who survived for at least 5 years after diagnosis) compared to the first study. Stratification of the cohort into nodal and extranodal DLBCL did not yield statistical difference in treatment responses following the first treatment session as well as after relapse. No difference was found in PFS and OS between nodal and extranodal DLBCL patients. Cell of origin (ABC vs. the reference GBC) and expressor status (double or triple hit DLBCL vs. the reference non-expressors) were independent negative predictors for OS. Extranodal lesions fared worse for both negative predictors.

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Conflicts of Interest

The authors declare that they have no competing interests.

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