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Hodgkin Lymphoma: A Retrospective Clinical and Pathological Analyses with Correlation to Treatment Outcome

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ABSTRACT

Aim of the work: the aim of the study was to analyze the correlation between several clinico-pathological prognostic factors in classical type Hodgkin lymphoma and its effect on response to treatment and survival rates (PFS and OS). The primary endpoint is response rate and secondary endpoints are survival rates.

Patients and methods: this study was performed on 76 patients diagnosed as classical Hodgkin lymphoma that were recruited retrospectively from January 2010 to December 2015 in Nasser Institute Oncology Centre and Ain Shams Clinical Oncology Department. Patients' risk factors in the whole group were analyzed using univariate and multivariate regression analysis. They included age, sex, pathological type, B symptoms, performance status, stage, extranoadal disease, bulky disease, inflammatory markers and their correlation on complete response rate (CR), progression free survival (PFS) and overall survival (OS).

Results: nodular sclerosing type was the most common in 44.7% of patients followed by mixed cellularity in 21.1% of patients followed by lymphocyte predominant in14.4% of patients, while unclassified classical constituted 19.7%. Early disease (Stage I, II) constituted 68.4% of patients and late disease (Stage III, IV) was found in 31.6% of patients. Bulky and extranodal diseases were found in 28.9% and 21.05% of patients respectively. All of patients received first line ABVD with 59.2% of patients received consolidative or palliative radiotherapy. CR rate was 65.8% being 71.2% in the early versus 52% in the advanced stage (p=0.07) with a relapse rate of 7.8%. The CR was negatively correlated with pathological type being worse in nodular sclerosing subtype than mixed cellularity (p=0.02), poor performance status (p=0.016), bulky disease (p=0.004), extranodal disease (p=0.0381), elevated LDH (p=0.045) and leucocytosis and lymphopenia (p=0.005). Median PFS was 17.5 months with a range of 1 to 75 months. 5 year PFS was negatively correlated with advanced stage than early stage (p=0.019), Bulky disease than non bulky (p=0.003), extranodal disease than nodal (p=0.014), leucocytosis and lymphopenia (p= 0.002). Median overall survival is 28 months with a range of 6-81 months with 5 years survival rate of 82.9% and mortality rate of 17.1%. 5 year overall survival was negatively associated with bulky rather than non bulky (p=0.05) and extranodal more than nodal (p=0.007).

Conclusion: this study concluded that both overall and progression free survival and response rates were negatively affected by stage, bulky and extranodal disease mainly. Pathological subtype and elevated ESR and LDH negatively affected CR rate. Leucocytosis and lymphopenia had a significant negative effect on response rate and progression free survival. This allowed the use of risk adapted treatment at several stages tailoring treatment to each patient separately.

Keywords: Hodgkin lymphoma, leucocytosis, consolidative.

INTRODUCTION

Hodgkin lymphoma is an uncommon type of lymphoid malignancy comprising 11% of all lymphomas. In Egypt, age specific incidence rates (ASR) are approximately 1.5/100000 per year with Male to female ratio (1.93/1.11) nearly approaching 250-300 case annually with a mortality of 0.9 per 100000 in 2012 [(1)].

Hodgkin lymphoma is a highly curable disease, with modern treatment strategies more than 95% of patients can be cured in early stages and 80-90% of patients in intermediate and late stages. Therefore, it is important to tailor treatment according to risk factors to minimize the toxicity and avoid unnecessary complications while in the same time optimizing treatment efficacy [(2)]. Certain prognostic factors have been introduced for this purpose to help individualizing treatment. They are used to classify patients to early stage favourable, early stage unfavourable, advanced stage each with different treatment mode [(3)].

Traditionally, the International Prognostic Index Score has been developed to predict the outcome of treatment in advanced stage lymphoma. A study had validated its usefulness. It is a 7 points score with each point known to reduce 5 year freedom from progression survival by 7% to 8% per year. It consisted of: serum albumin < 4 g/dl, hemoglobin < 10.5 g/dl, male sex, stage IV disease, Age ≥ 45, white cell count ≥ 15,000, lymphocyte

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count < 600/mm3 or < 8% of white cell count [4].

On the other hand, there has been no approved risk stratifying system in early disease with each group using its own scoring system. The most common of these are the German Hodgkin Study Group (GHSG) and European Organization for Research and Treatment of Cancer (EORTC) where risk factors in GHSG included: large mediastinal mass, extranodal disease, ESR>50 or >30 with B symptoms, ≥3 nodal sites. The EORTC criteria differs by substituting age ≥50 years in place of the extranodal disease criterion and specifying ≥4 involved regions rather than ≥3 [5].

Our study was a retrospective multivariate study with the aim of studying the correlation between several clinico-pathological prognostic factors in classical type Hodgkin lymphoma and its effect on response to treatment and survival rates (DFS and OS). The primary endpoint is response rate and secondary endpoints are survival rates.

PATIENTS and METHODS

The patients were recruited from Nasser Institute Cancer Center and from Ain Shams University, Clinical Oncology Department from January 2010 to December 2015. A total of 76 patients were recruited, 61 from Nasser Cancer Center and 15 from Ain Shams University, Clinical Oncology Department.

Inclusion criteria includeD: patients with age range between 18 and 65, pathologically proven classical Hodgkin lymphoma by biopsy and immuno-histochemistry, pretreatment evaluation by computed tomography scanning of chest, abdomen, pelvis +/-neck with contrast or PET-CT, bone marrow biopsy in advanced stages and Laboratory markers, response assessment by PET-CT or computed tomography after treatment. While, exclusion criteria included: patients who came for consolidation radiotherapy after first line treatment in other centers, patients who received no treatment or were irregular on first line therapy, patients who did not reassess their response to treatment with CT imaging, patients who were diagnosed before 2010, patients with impaired cardiac function that interfere with giving full dose Adriamycin in first line treatment, Poor PS ≥ 2, abnormal liver and kidney function tests, nodular lymphocyte predominant histology or suspicious of it.

Prognostic factors included age less than 45 or more than or equal 45, sex: male or female, pathology: lymphocyte rich and nodular sclerosing or lymphocyte depleted and mixed cellularity, stage included: stage I and II with less than or equal 3 nodal sites, stage I and II with more than three nodal sites, stage III, Stage IV. Bulky disease and extranodal disease are included, B symptoms : present or absent, laboratory markers: ESR less a 50 or more than 50, LDH less than 300 or more than 300, ECOG performance status: 0 or 1.

The study was approved by the Ethics Board of Ain Shams University.

Statistical analysis

The studied prognostic factors in the whole group were analyzed by univariate regression analysis using log rank Chi-squared test and multivariate using Cox regression model. Kaplan-Meier estimated overall, disease free, progression free survival. Cox regression multivariate analysis was done to show independent effect of variables on survival.

RESULTS

Median age at diagnosis was 36 with range of age 18-65. Approximately 36 patients (47.3%) were in the age range 18-35, 35.5% in the age range 36-49 and only 15.78% equal to or above 50 years of age. Male to female ratio was 1.4:1.

Nodular sclerosing pathological subtype constituted the most common subtype with approximately 44.7% of patients (34 patients) being diagnosed with it, next comes the mixed cellularity subtype with 21.1% of patients followed by lymphocyte predominant with 14.4% of patients while unclassified classical constituted 19.7%. Early disease (Stage I, II) constituted 68.4% of patients and late disease (Stage III, IV) 31.6% of patients. Bulky and extranodal disease was found in 28.9% and 21.05% of patients respectively. Most cases presented by cervical lyphadenopathy (57.8%).

Mediastinal involvement was noted in 23% of patients. B symptoms were found in 50% of patients, absent in 46.1% and unknown in 3.9%. Performance status was 1 in 71.1% of patients and 0 in 28.9% of patients. Inflammatory markers in the form of lactate dehydrogenase and erythrocyte sedimentation rate were elevated in 23 vs 13 patients (30.3% vs 17.1%) the rest of patients were unknown (52.6%) (**Table 1)**.

Table 1: patient's characteristics with regard to the variables

		Number	Percentage
Age	<45	54	71.04
	≥ 45	21	31.5
	Unknown	1	1.3
Sex	Female	30	39.5
	Male	46	60.5
Pathological type	Nodular Sclerosing	34	44.7
	Lymphocyte rich	11	14.4
	Mixed Cellularity	16	21.1
	Unclassified Classical	15	19.7
Stage	1	9	11.8
	2	42	55.2
	3	11	18.4
	4	14	14.4
Stage	Early	51	68.4
	Late	25	31.6
Lab markers	Elevated	23	30.3
	Normal	13	17.1
	unknown	40	52.6
Extranodal	Nodal	60	78.9
	Extranodal	16	21.05
B symptoms	A disease	35	46.1
	B disease	38	50
	Unknown	3	3.9
Bone marrow	No Bone marrow	67	88.2
	Bone Marrow	9	11.8
Bulky disease	Non Bulky disease	54	71.1
	Bulky disease	22	28.9
Performance Status	PS0	22	28.9
	PS1	54	71.1

Median overall survival was 28 months with a range of 6-81 months with 5 year survival rate of 82.9% and mortality rate of 17.1% as shown **in figure** 1. Median PFS was 17.5 months with a range of 1 to 75 months as shown in **figure 2**. Mortality was reported in 13 patients, patients who lost follow up were 10 patients (13.1%).

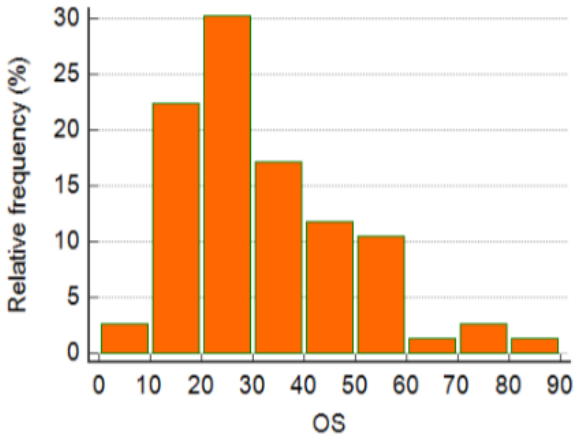

Figure 1: histogram of overall survival.

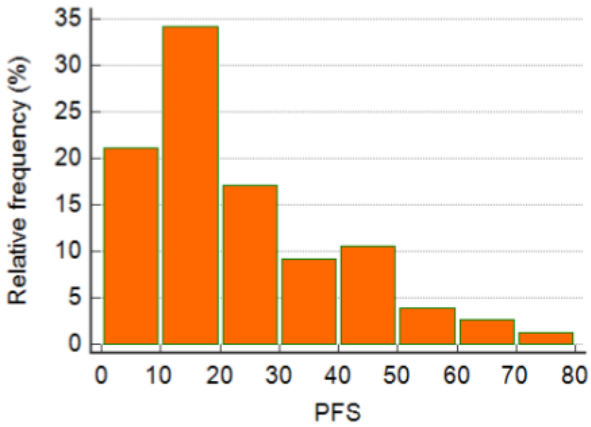

Figure 2: histogram of progression free survival

First line chemotherapy ranged from 2 to 8 cycles of ABVD. Six cycles was the most common number being used in 47 patients, radiotherapy was used in 68.6% of early stage patients and 40% of late stage patients.

Overall response to first line chemotherapy ABVD in all patients was as follows: a total of 50 patients achieved complete remission after the first line chemotherapy (65.8%) with a relapse rate of 7.8% in the follow up period, all of relapses occurred after one year of achieving CR (Mean relapse free survival 23 months with a range of 12-36 months). Rest of patients were as follows: partial remission 14 patients (18.4%), stationary disease 3 patients (3.9%), progressive disease 9 patients (11.8%) 2 of them transformed to non Hodgkin lymphomas (One chronic leukemia and the other diffuse large B cell lymphoma).A total of 20 patients (26.3%) were received second line chemotherapy; 9 of them received 1 salvage regimen (11.8 %), 11 patients more than one salvage regimen (14.4%) with most of patients having progressive disease (50%) and only 5 patients achieving CR (25%) and only 4 patients were undergoing bone marrow transplantation (20%).

Radiotherapy was used as consolidative or palliative treatment in 45 patients (59.2%). PET- CT was used to assess treatment response in 45 patients (59.2%).

Complete remission was strongly related to pathological type with mixed cellularity having the highest CR rates 93.8% (p=0.02), being non bulky compared to bulky (75.9% vs 40.9%, p=0.004), nodal rather than extranodal (71.6% vs 43.7%, p=0.0381) and better performance status (86.4% vs 57.4%, p=0.016), normal LDH and ESR (p=0.049), normal hemoglobin (p=0.041) and total leucocyte count (p=0.005). By analyzing patient's data in univariate analysis using log rank Chi squared test, 5 year overall survival was negatively associated with bulky rather than non bulky (p=0.05) and extranodal more than nodal (p=0.007) **(Figures 3 , 4).**

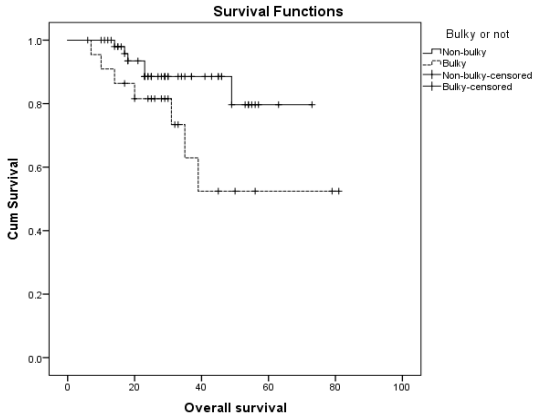

Figure 3: effect of bulky disease on 5 years overall survival.

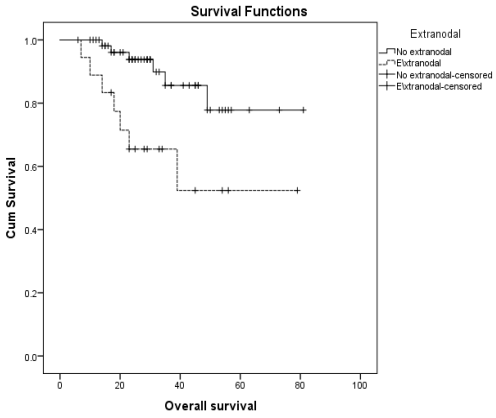

Figure 4: effect of extranodal disease on 5 years overall survival

After using multivariate regression model for overall survival, only extranodal disease had a strong degree of significance with regards to overall survival with a hazard ratio of 6.53 (95 % CI 1 - 42.6).

The wide confidence interval indicates negligible effect in spite of the statistical significance this could be explained by the low mortality of the sample size (13 patients out of 76).

5 year progression free survival was negatively correlated with advanced stage than early stage (p=0.019), Bulky disease than non bulky (p=0.003), extranodal disease than nodal (p=0.014), leucocytosis and lymphopenia (p= 0.002) as shown in figure 5, 6 and 7. Using Cox linear regression, only being bulky disease had a strong significance regarding progression free survival with hazard ratio of 4.38 (95% CI 1.8-13.09).

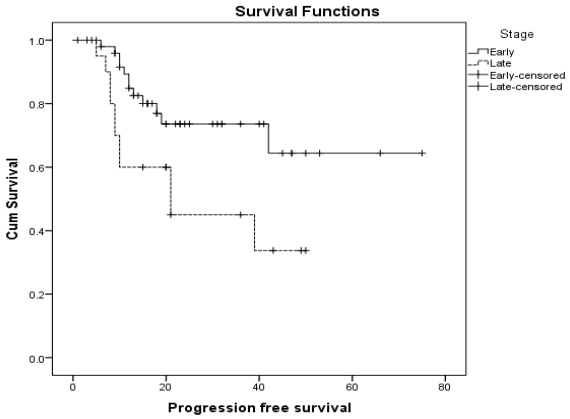

Figure 5: effect of stage on 5 years progression free survival.

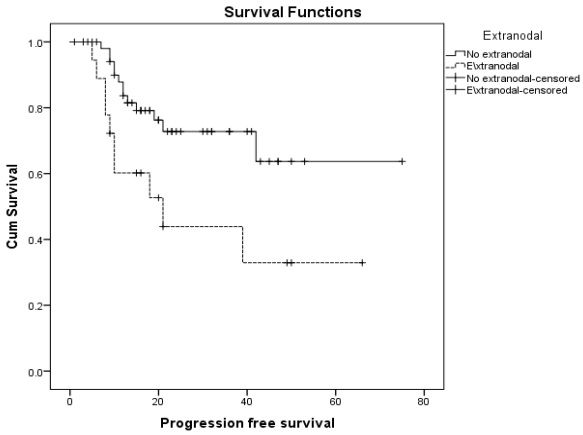

Figure 6: effect of extranodal disease on 5 years progression free survival

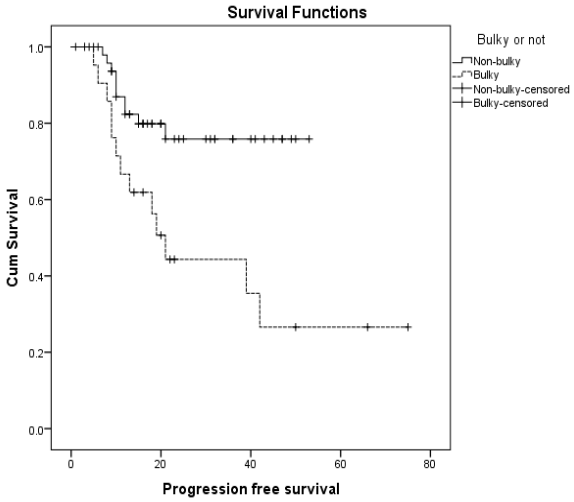

Figure 7: effect of bulky disease on 5 years progression free survival

DISCUSSION

Several studies discussed the issue of prognostic factors in Hodgkin lymphoma. They had more or less similar results. One of them was a study conducted in Turkey [(6)]. Another one was a small retrospective study in Serbia [(7)]**.** The eldest of these was a prospective study done in the National Cancer Institute of Egypt [(8)].

First study retrospectively evaluated the demographic, clinical and pathological features of 391 HL patients followed-up in the Department of Medical Oncology, Cancer Institute, Hacettepe University since 2003 with the objective of studying the effect of variables on overall and progression free survival [(6)]. Second study was a retrospective study that analyzed the medical record of 26 patients who were being treated in the Hematology and Oncology Clinic in Facta University between 2004 and 2008 to assess the prognostic significance of several factors with regard to response to treatment and the predictive power of the simplified IPI score [(7)]. The third study was a prospective study of a group of 100 chemotherapy naive patients that were being treated in the Oncology Department in National Cancer Institute between 1999 to 2001 to compare the standard prognostic factors of Hodgkin's lymphoma (HL) in relation to response to first line chemotherapy (COPP or ABVD or hybrid COPP/ABV), disease free survival (DFS) and overall survival (OS) [(8)].The studied prognostic factors in the first study were clinical variables: stage, extranodal disease, bulky disease, B symptoms, histology, ECOG performance status and laboratory variables: hemoglobin ≤12 or >12, albumin <3.2 or ≥ 3.2, LDH ≤ 460 or >460, white blood cell count ≤ 15000 or >15000/mm3 and lymphocyte count ≤ 600 or >600 [(6)]. Second study used the simplified IPI score as a prognostic relevance to response to treatment which included age>60, clinical stage III and IV, ECOG performance status 2-4, serum lactic dehydrogenase level > 1 upper limit of normal and the number of extranodal sites of the disease> 1 with a point for each. The index divides patients into 4 risk groups: low (0 or 1), low intermediate (2), high intermediate (3) and high (4 or 5) [(7)]**.** The Studied prognostic factors in the third study are: Age (>45 or<45), gender, stage (early vs advanced), B symptoms, ESR>50 or ESR >30 and B symptoms, pathological subtype, extanodal disease, mediastinal involvement, type of first-line chemotherapy (COPP or ABVD or hybrid COPP/ABV). The study also used the IPI score in advanced stage [(8)].

The first study concluded that early-stage patients with good prognostic factors had better overall and relapse-free survival rates. The presence of “B” symptoms, albumin level, Eastern Cooperative Oncology Group (ECOG) performance score, and LDH were prognostic factors that affect the survival in both univariate and multivariate analyses [(6)]. The second study, concluded that significantly associated with the decrease of probability of achieving CR was the increased IPI score itself (p=0.02) (IPI score was: low (score 0-1) in 26.9%, low intermediate (score 2) in 30.8%, high intermediate (score 3) in 34.6% and high (score 4 or 5) in 7.7%) and two of the five factors analyzed: extranodal disease >1 site

(p=0.003) and poor performance status >1 (p=0.04) [7]. The third study, stated that prognostic factors were significant in relation to OS and DFS using univariate and multivariate analysis, also the adequate response and DFS of the early compared to the advanced-stage disease supported the evolving role of risk adapted chemotherapy for HL. ABVD showed borderline significance (p=0.09) compared to other regimens in relation to DFS [8].

In the first study, ABVD was the most common regimen,where 71% of patients were treated with it, 20% were treated with COPP or alternate ABVD/COPP and escalated chemotherapy followed by peripheral stem cell transplantation were utilized in 8% of patients, only 8% were treated with radiotherapy alone [6]. In the second study, a uniform scheme of chemotherapy was applied: ABVD or BAECOPP regimens were used as first line treatments. After that appropriate radiotherapy was usually performed [7]. In the third study: the first line chemotherapy was COPP in 40%, ABVD in 35% and COPP/ABV hybrid in 25%, patients with early disease (43% of patients) were referred to radiotherapy after 4 cycles of chemotherapy [8]. In our study all patients received standard ABVD, radiotherapy was used as consolidative or palliative treatment in 45 patients (59.2%).

In the first study cure rate was not reported but 33.2% of the cases (n=130) relapsed (median 25 months; range 6 months-20 years). The most common treatment protocol in relapsing patients was ABVD (36.1%; n=47), especially in patients who previously received COPP. The COPP regimen was used in 15.4% (n=20) of patients who developed relapse. Five- and 10-year overall survival rates were 90% and 84%, respectively. Five- and 10-year survival rates for patients who received ABVD were 88% and 83% respectively. While the 10-year survival rate was 95% among stage I patients, it was 62% for stage IV cases [6].

In the second study, CR was achieved in 18 patients (69%) after the first line therapy. Eight (31%) patients did not achieve CR after the first-line treatment and second line therapy was administered [7]. In the third study, the complete remission (CR) rate for whole group was 69% while it was 87.8% for the early disease versus 54.7% for the advanced disease (p=0.001). At 4 years, the DFS of the whole group was 61.3%, while it was 69.8 and 45.1% for the early and advanced groups; respectively (p=0.16). The overall survival at 4 years was 53.7% for the whole group, while it was 70.7% and 38.9% for the early and advanced groups; respectively (p=0.0001) [8]**.** In the current study, a total of 50 patients achieved complete remission after first line chemotherapy (65.8%) with a relapse rate of 7.8%, CR is 71.2% in the early versus 52% in the advanced stage (p=0.07). The 5 year overall survival is 82.9% with 90.7% in early stage versus 88.1% in advanced stage (p=0.24). 5 year PFS is 69.7% with 84.2% in early stage compared to 52% in advanced stage (p=0.019).

Age was ≥ 60 in 11.5% of patients and < 60 in 88.5% of patients in the second study [7]. It is ≥ 45 in 37% of patients and < 45 in 63% of patients in the third study [8]. In the current study age is ≥ 45 in 31.5% of patients, < 45 in 71.04% and unknown in 1.3% of patients. Mean age at diagnosis in the first study was 35.7+/- 15 years with a male to female ratio 1.6:1(61% male, 39% female) [6]. In the second study, median age at diagnosis was 40 years with a male to female ratio of 1.6:1(61.7% males, 38.3% females) [7]. In the third study, median age at diagnosis was 37 with a male to female ratio (2.1:1) [8]. In the current study, median age 36 with a range of 18-65, male to female ratio is 1.4:1. B symptoms were present in 38.3% of patients in the first study **Kılıçkap *et al.*** [6]**,** in 57.7% of patients in the second study **Ćojbašić and Golubović** [7] and in 31% of cases in the third study **Abd ELHameed *et al.*** [8] while it was present in 50% of patients in the current study. Nodular sclerosing was the most common subtype in the first study being present in 42.7% of patients followed by mixed cellularity (40.4%) of patients [6], the second study (57.7% of patients) [7] and the current study (44.7%), while mixed cellularity was prevalent in the third study being reported in 48% of patients [8].

Performance status was 0 in 45.5% of patients, 1 in 38.6% of patients, 2 in 12.3% of patients, 3 in 3.6% of patients in the first study [6]. In the second study, it was 0-1 in 69.3% of patients and 2 in 30.7% [7]. In the third study it was 1 in 66% of patients, 2 in 30% of patients, 3 and 4 in 3% of patients [8]. In the current study, it is 0 in 28.9% of patients, 1 in 71.1% of patients.

Stage I, II, III, IV was present in 10.5%, 50.4%, 28.1%, 11% of patients respectively in the first study, early stage favorable was noted in 27.6% of patients, early stage unfavorable was reported in 33.5% of patients, advanced stage was

present in 38.6% of patients and unknown in 0.3% of patients [6]. stage I, II, III, IV was reported in 11.5%, 34.6%, 50%, 3.9% in the second study respectively, early stage was found in 47.1% of patients vs advanced stage in 53.9% [7], stage I, II, III, IV was reported in 17%,34%,37%,12% of patients in the third study respectively early stage was observed in 43% vs late stage in 37% of patients [8]. In the current study stage I, II, III, IV was reported in 11.8%, 55.2%, 18.4%, 14.4% of patients respectively, early stage was reported in 68.4% vs late stage in 31.6% of patients.

Extranodal involvement was observed in 7.9% of patients in the first study **Kılıçkap *et al.*** [6], in 30.7% of patients in the second study ***Ćojbašić and Golubović*** [7], in 12% of patients in the third study **Abd ELHameed *et al.*** [8] and in 21.5% of patients in the current study. Bulky disease was noted in 9.2% of patients in first study **Kılıçkap *et al.*** [6] while it was present in 28.9% of patients in this study. Mediastinal involvement was reported in 28% of patients in the third study **Abd ELHameed *et al.*** [8] and in 23% of patients in our study.

ESR was elevated > 50 mm/h in 40.9% of patients and ≤ 50 in 40.9% of patients while LDH was ≤ 460 U/L in 69.3% of patients and > 460 in 30.7% of patients in the first study [6]. LDH was normal in 42.3% of patients and high in 57.7% of patients in the second study [7]. ESR mm/h was ≥ 50 or ≥30 with B symptoms in 79.7% of patients and neither in 20.3%, LDH was >500IU/L in 39.5% of patients in the third study **Abd ELHameed *et al.*** [8]. LDH ≥ 300 IU/L and ESR≥ 50 mm/h were elevated in 23 vs 13 patients (30.3% vs 17.1%) the rest of patients were unknown (52.6%) in this study.

Anemia (Hb ≤ 12 g/dl) was reported in 19.4% of patients, leucocytosis(>15000/mm3) in 8.7% of patients and lymphopenia (≤600/mm3) in 3.8% of patients, hypoalbuminemia (albumin≤ 3.2) in 11.5% of patients in the first study [6]. In the third study anemia was reported (Hb<10.5 g/dl) in 15% of patients, leucocytosis (>15000/mm3) in 15% of patients, hypoalbuminemia (albumin<4 g/dl) in 64.3% of patients [8]. In the current study, anemia (Hb<10.5 g/dl) was noted in 21 patients, normal hemoglobin in 35 patients and unknown in 20 patients. Total leucocytic count was normal in 47 patients, unknown in 21 patients, showing lymphopenia (<600/mm3) in 3 patients and leucocytosis (>15000/mm3) in 5 patients.

Regarding response to fist line treatment, gender significantly affected CR rate only in the third study with better response in females (p = 0.008) [8]. Poor performance status (≥ 1) negatively affected response rates in the current study (p=0.016) and also PS 2-4 in the second study was significant (p=0.04) [7]. Pathological type was only found to be significant in our study with a better response in mixed cellularity (p=0.02). Early stage (I/II) positively affected CR rate (p=0.001) in the third study **Abd ELHameed *et al.*** [8]. Bulky disease was found significant in the current study (p=0.004). Extranodal disease was significant in the current study (p=0.038) and second study (p=0.003) [7], trends for significant correlation in the third study in early stage disease (p=0.09) [8]. Laboratory markers significantly correlated with worse outcome in the current study where leucocytosis (≥ 15000/mm3) and lymphopenia (<600/mm3) have negative effect on CR (p=0.005), elevated LDH (≥ 300 IU/L) and ESR (≥ 50 mm/h) (p=0.049) and anemia (Hb<10.5) (p=0.041) also contributed. Third study showed some trend for significance where hypoalbuminemia (<4 g/dl) is related to worse outcome in advanced stage (p=0.06) [8].

Regarding disease free and progression free survival using univariate analysis, advanced age (>45) negatively affected DFS in the early stage group (p=0.05) and gender significantly affected DFS in the advanced stage group with better survival in females in the third study (p=0.03) [8]. B symptoms correlated with worse DFS in the first study (p=0.001) [6] and third study in early stage group (p=0.03) [8]. Poor ECOG performance status (0 vs >1) negatively correlated with survival in the first study only (p=0.001) [6].

Also, advanced stage (III/IV) was found significant in the first study (p=0.0001) [6] and the current study (p=0.019). Elevated ESR (≥ 50 vs <50) was significant in the first study (p=0.0001) [6] and the third study in early stage group (p=0.04) [8]. Also, elevated LDH (≤ 460 vs >460) was significant in the first study (p=0.0001) [6]. Extranodal disease was markedly significant in the current study (p=0.014) and the first study (p=0.0001) [6]. Bulky disease was also significant in the current study (p=0.003) and the first study (p=0.028) [6]. Anemia was significant in the first study (p=0.0001) [6] while leucocytosis and lymphopenia was significant in the current study (p=0.002). Hypoalbuminemia negativley affected survival in the first study (p=0.0001) [6].

Using multivariate analysis, the independent prognostic factors that correlated with worse outcomes were B symptom in the first study (p=0.003, 95% CI=1.4-5.4) [(6)], and third study OR= 3.3 (95% CI =1.3-8.7) [(8)]. ECOG performance score was significant in the first study (p=0.001, 95% CI = 5.7-54.1). Also, hypoalbuminemia (p=0.02) and elevated LDH (p=0.021) were significant in the first study [(6)]. The only factor that was significant is bulky disease in the current study HR= 4.38(95% CI =1.69-13). Regarding overall survival using univariate analysis in third study, age > 45 correlated with worse OS in the whole group and in advanced stage (p=0.04). Male sex was associated with worse OS of the whole group and advanced stage (p=0.005). B symptoms negatively affected survival (p=0.006). Stage III/IV was significant (p=0.0001) [(8)]. Using multivariate analysis, advanced age (>45) was found significant in the second study with OR= 2.1 (95% CI 1-4.2) [(8)]. Also, male sex was significant in the third study with OR= 3 (95% CI 1.2-7.4) [(8)]. Stage (III/IV) was significant in the third study with OR = 3.7 (1.6-8.7) [(8)]. In the current study, extranodal disease was the only independent factor with a hazard ratio 6.5 (95% CI from 1-42).

To conclude, some of the results of our study were comparable with the previous studies. Some of the parameters in our study were not statistically significant such as age, sex, B symptoms despite being significant in previous studies. Advanced Stage, bulky and extranodal diseases were found to affect both the OS and PFS so that risk-adapted treatment can be adopted at different stages. To give an example, treating an elderly male with bulky stage III disease accompanied with B symptoms and high ESR would be different than treating a young female with localized non bulky cervical stage IA disease in terms of number of chemotherapy cycles, dosage of radiotherapy if used or the use of frontline aggressive regimens. Inflammatory markers were found to be related to response to treatment and survival in the current and previous studies respectively. New observation is the relationship between pathological subtype and response to treatment. Also, leucocytosis and lymphopenia had a significant negative effect on response rates and survival.

Recognized flaws of the study were that it did not compare prognostic variables in 2 different groups early versus advanced. Also the limited availability of erythrocyte sedimentation rate and lactate dehydrogenase, albumin, total leucocyte count, hemoglobin which precluded the classification of early stage to favourable and unfavourable category and using the IPS score. In addition, the low mortality and relapse rate negatively impacted the study. As these prognostic factors are not specific markers, future recommendations are the use of serum markers "cytokines" such as Interleukin 10, 6 and soluble CD 30, tumour necrosis factor alpha, thymus and activation regulated chemokine (TARC) and Pathologic markers by immunophenotyping such as characteristic of HRS cells, Bcl2 expression, tumour infiltration by macrophages to correlate with outcome and guide intensity of treatment together with interim assessment by PET-CT as published in another paper [(9)].

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