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Research Article

The Retrospective Evaluation of Hodgkin lymphoma Cases and The Effects of Prognostic Factors on Survival: A Seven-year-experience

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Abstract

Objectives: In this study, we aimed to present the demographical, histopathological and clinical features of the cases diagnosed as Hodgkin lymphoma; and to determine the effects of negative prognostic grouping in early stage (stage I-II) of Hodgkin lymphoma and International Prognostic Score in late stage (stage III-IV) Hodgkin lymphoma on the survival of the patients.

Methods: The data of the 46 patients diagnosed with Hodgkin lymphoma followed in our center for seven years has been evaluated retrospectively.

Results: Demographical, histopathological and clinical features of the cases are shown in the table 1. The primary treatments were %80.4 ABVD combination chemotheraphy and %19.6 chemotheraphy+radiotheraphy. Treatment methods and disease response rates are shown in the table 2. It was identified that there was an early relapse in the %69 and a late relapse in the %31 of the patients whose diseases relapsed after the primary treatment. The autologous stem cell transplants were done for the %60 of the patients. The median follow-up time was 22 months (change between 4-70). The rate of 5-year-overall survival (OS) was %87 and the rate of the relapse-free survival (RFS) was %71.7. As there was a significant difference between the genders in terms of OS rates, there was not for RFS rates (resp., p=0.01; p=0.07). When the patients were examined due to their responses to the primary treatment, there was a significant difference OS and RFS rates (p=0.002; p<0.001). Furthermore; a significant difference among overall survival rates was identified according to the relapse progression(p=0.019). When a classification of positive and negative prognostic groups was done in terms of German Hodgkin Study Group (GHSG), European Organisation for Research and Treatment of Cancer (EORTC), The National Comprehensive Cancer Network (NCCN) and National Centre for Infections in Cancer (NCIC), no significant difference was found between the rates of OS and RFS (p>0.05). Moreover, in our study, no significant difference among International Prognostic Score, OS and RFS rates was found.

Conclusion: The treatment chart must be designed as taking the stage of the disease and the prognostic factors into consideration. So, the progression risk of the toxidity and treatment complication in long term can be minimized.

Keywords: Clinical features, hodgkin lymphoma, prognostic factors, survival

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Hodgkin lymphoma (HL) was a B lymphocyte origined disease that was firstly described by Thomas Hodgkin in 1832.[1] Generally, HL forms the %1 of all the cancer cases; on the other hand it is the %14 of all the lymphoma cases. In the United States of America (USA), estimated number of the newly diagnosed HL cases was 8490; furthermore the predicted death number was 1320.[2]

Although there is not a right registration system for the cancer in our country, it is estimated that HL forms the %1 of all the cancer cases and the %30 of all the lymphoma cases. [3] Every year, totally 649 newly diagnosed HL cases are expected in Turkey. From the past until now, the biology and pathology of the disease has been more clearly understood with the development of molecular techniques. More than %80 of the patients come out with a complete recovery owing to the improvement in the methods of diagnosis and treatment and to the usage of new chemotheraphy and radiotheraphy drugs.[4] In this study, we aim to reveal the demographical, histopathological and clinical features of Hodgkin lymphoma patients being followed and treated in our clinic, and to determine the effects of negative prognostic grouping in early stage (stage I-II) of Hodgkin lymphoma and International Prognostic Score in late stage (stage III-IV) Hodgkin lymphoma on the survival of the patients.

Methods

The data of the 46 patients diagnosed with Hodgkin lymphoma followed by SamsunOndokuz Mayıs University Faculty of Medicine, Department of Internal Medicine - The Division of Hematology for seven years has been evaluated retrospectively. For evaluating the ages, the genders, the diagnosis materials, the symptoms of consulting, the histopathological and clinical features, the laboratory values, the stages, the treatment methods used, the ultrasonography before and after treatment, the results of CT, MRI and PET, the responding situation of the patients to the treatment, and furthermore to evaluate the rates of overall and relapse-free survival, the data about the first diagnosis dates of the patients, the dates of remission and relapse, the last dates of consulting to the hospital and the death dates of the patients losing their lives were collected through hospital automatisation system and by using the records of the patient files.

The patients in early stages (I-II) were divided into positive and negative prognostic groups according to German Hodgkin Study Group (GHSG), European Organisation for Research and Treatment of Cancer (EORTC), National Centre for Infections in Cancer (NCIC), The National Comprehensive Cancer Network (NCCN) (NCCN 2012 Guide). Even the existence of only one of the negative prognostic factors was accepted as enough for the case to be included in the negative prognotic group.

To evaluate the data, Statistical Package for the Social Sciences (SPSS) 15.0 software was used. The rates among the categorical variables between two groups were analyzed with Chi-square and Fisher's exact tests. To compare the quantitative variables which were normally distributed, Student's t test was used; however for the comparison of the ordinal variables and the quantitative variables which were not normally distributed, Mann Whitney-U test was used.

The analyze of the survival was made with Kaplan-Meier method. Statistical significance value was p=0.05

Statistical Analysis

The demographical and clinical features of 46 HL diagnosed patients were analyzed (Table 1). The 25 patients (%54.3)

Table 1. The Demographical and Clinical Features of the HL Patients Followed up in Department of Internal Medicine – The Division of Hematology, Ondokuz Mayıs University Faculty of Medicine

	Mean±55	n	%
Gender			
Female/Male		21/25	45.7/54.3
Age	41.5±15.1		
Female/Male	40.3±16.5/42.48±14.2		
Stage			
I		5	10.9
II		15	32.6
III		23	50
IV		3	6.5
Early/Late		20/26	43.5/56.5
Histology			
NLPHL		3	6.5
Classical HL		43	93.5
MCHL		22	47.8
NSHL		19	41.3
LDHL		2	4.3
B Symptom		21	45.7
Spleen Uptake		15	32.6
Liver Uptake		6	13
Bulky Disease		-	-
Nodal Uptake Area			
N<3		10	21.7
N>3		36	78.3
Diagnosis Material			
Cervical LN		22	47.8
Axiller LN		8	17.4
Inguinal LN		5	10.9
Supraclavicular LN		3	6.5
Mediastinal LN		2	4.3
Other		1	2.2

were male and 21 patients (%45.7) were female. The average of their ages was 41.5±15.1. In our study, it was observed that HL occurence frequency increased generally in all the patient groups who were in their 20s; in addition, it showed a bimodal distribution by drawing two peak slopes at the ages 20s and 60s. At the time of diagnosis, %43.5 of the patients were of early stages and %56.5 of them were of late stages. In addition to this, there were B symptoms in the %45.7 of the patients, there was spleen uptake in %32.6 of them, %13 of the patients suffered from liver uptake and the %6.5 of the patients had bone marrow uptake. There was not any bulky disease detected. While the nodular lymphocyte predominant Hodgkin Lymphoma (NLPHL) cases were involved in the %6.5 of all the HL cases, the frequently seen classical HL histological subtype was mixed cellularity Hodgkin lymphoma (MCHL) (%47.8) and the rarely seen histological subtype was lymphocyte deflated Hodgkin lymphoma (LDHL) (%4.3). What was often diagnosed in males was MCHL (%56) whereas it was the nodular-sclerosis Hodgkin lymphoma (NSHL) in females (%47.6) (Fig. 1). As the primary treatment, the patients were given %80.4 ABVD chemotheraphy and %19.6 chemotheraphy+radiotheraphy (Table 2). In the primary treatment, radiotheraphy was radiologically done for residue disease. The %69.6 of the patients responded completely to this first primary treatment while the %15.2 of them gave a partial response. Whereas a stable disease was observed in %10.9 of the group, a progressive disease occurred in %4.3 of those. It was identified that there was an early relapse in the %69 and a late relapse in the %31 of the patients who had a relapse after the primary treatment. The ones who had a relapse were %69.2 females and %30.8 males. Statistically, there was a significant difference between relapse progression and gender (p=0.04) (Fig. 2).

As the first rescue chemotheraphy regimen, frequently DHAP chemotherapy (%57) was given. After this first rescue treatment, the %10.9 of the patients were directed to an advanced healthcare center where high-dose chemotheraphy was given and autologous stem cell transplant was done. The autologous stem cell transplants were done for the %60 of the patients. The average follow-up time was 22 months (change between 4-70). When all the patients were examined, it was determined that the rate of 5-year-overall survival (OS) was %87 and the rate of the relapse-free survival (RFS) was %71.7 (Figs. 3,4).

While it was identified that there was a significant difference between genders in terms of overall survival (OS) rates, no significant difference in terms of relapse-free survival rates was obtained. (resp., p=0.01; p=0.07) (Figs. 5,6).When the data was evaluated according to the responses given to the primary treatment, there was a significant difference between overall (OS) and relapse-free (RFS) survivals. On

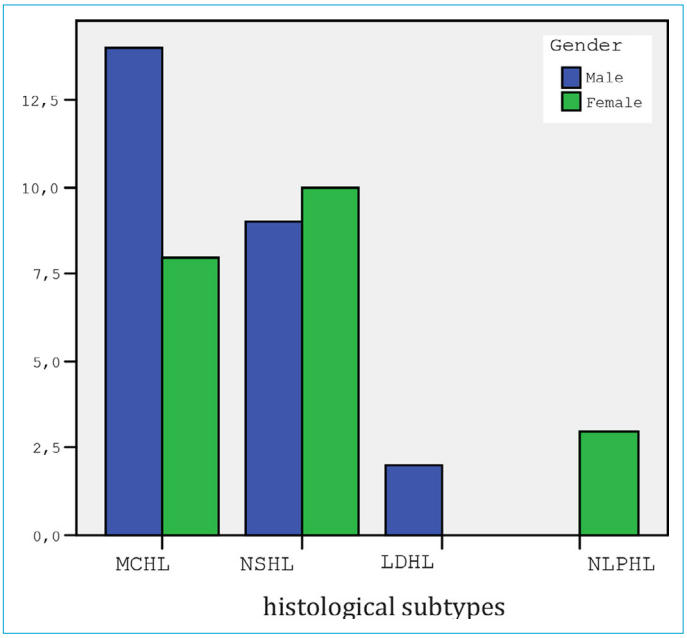

Figure 1. The distribution of histological subtypes acording to the gender.

Table 2. The treatment methods used in the study and the patient responses

	%
The primary treatment	
Chemotheraphy/Chemotheraphy-Radiotheraphy	80.4/19.6
The primary treatment as chemotheraphy	
ABVD chemotheraphy	100
The primary treatment as radiotheraphy	
Cervical	67
Thorax	22
Abdomen	11
Responses to the primary treatment	
Complete response (CR)	69.6
Partial response (PR)	15.2
Stable disease (SD)	10.9
Progressive disease (PD)	4.3
Patients with relapse after the primary treatment	
Early relapse	69
Late relapse	31
Patients given the first rescue treatment	
Chemotheraphy/ Chemotheraphy-Radiotheraphy	86.14
The first rescue treatment as chemotheraphy	
DHAP	57
ICE	22
ABVD	7
ASHAP	7
GVP	7
High-dose chemotheraphy - Autologous stem cell transplant	
Autologous	10.9
Non-autologous	89.1
The number of the patients with relapse	
Relapsed once	85
Relapsed twice	15

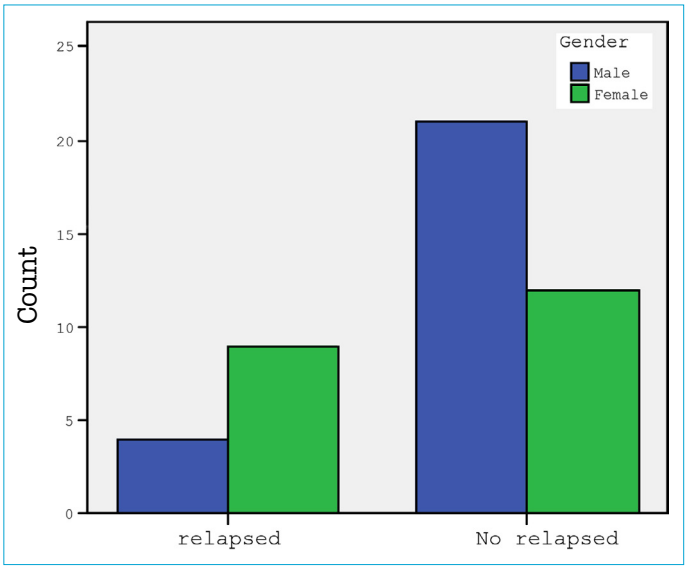

Figure 2. The distribution of the patients relapsed according to the gender.

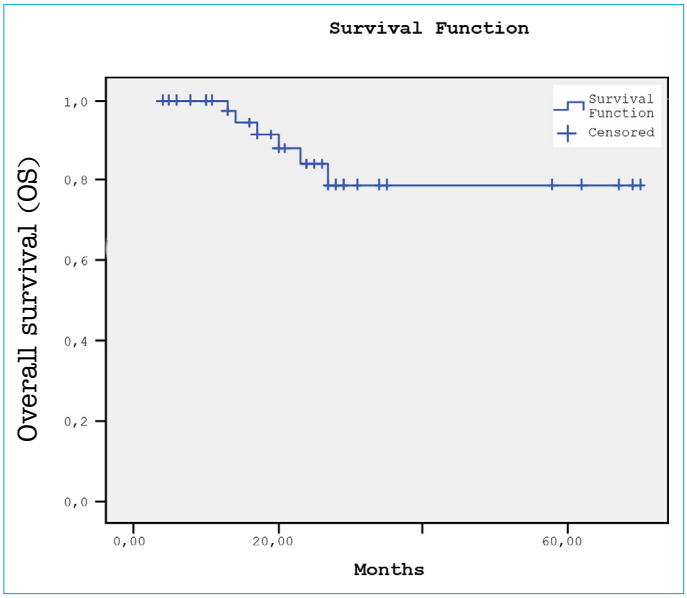

Figure 3. The overall survival slope for all the patients.

the other hand, among overall survival rates, a significant difference was determined due to the relapse progression (p=0.019) (Fig. 7).

As the classification of positive and negative prognostic groups was made in terms of German Hodgkin Study Group (GHSG), European Organisation for Research and Treatment of Cancer (EORTC), The National Comprehensive Cancer Network (NCCN) and National Centre for Infections in Cancer (NCIC), no significant difference was determined between overall (OS) and relapse-free (RFS) survivals (p>0.05); in addition, a significant difference could not be established between overall (OS) and relapse-free (RFS) survivals when an IPS scoring was done in our study.

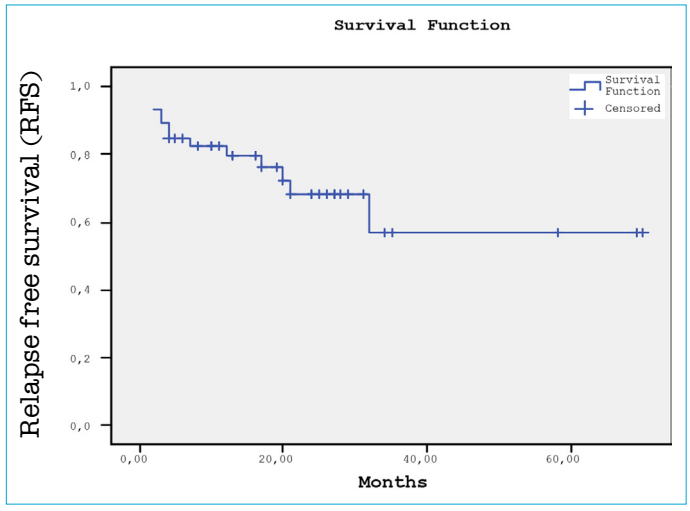

Figure 4. Relapse free survival slope for all the patients.

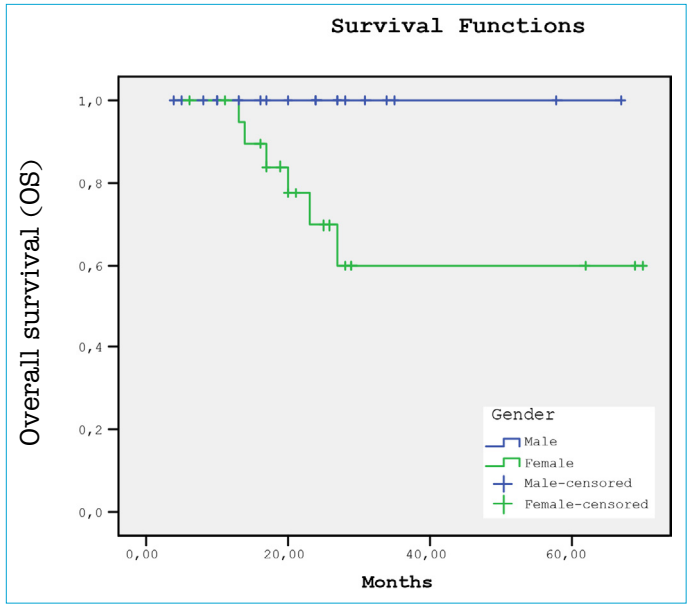

Figure 5. Overall survival slope according to the gender.

Discussion

In the HL cases carried out by GHSG, EORTC, Stanford V and Milano groups in the literature, there are large scaled studies examining the treatment regimens and results. In our country, Kılıçkap et al.,[5] made the largest scaled HL research with 391 patients whereas the second largest scaled HL research belongs to Şener et al.[6] with its 165 patients. Altıntaş et al.,[7] made a 150 patients - including study; while Coşkun et al.[8] made a 30 patients -including study on early stage HL.

The epidemiological studies has put down to the the fact that HL showed a bimodal age distribution; in addition, young adults' socioeconomic status and EBV infection from which they suffered had a great role in etiology.[9-11] In our

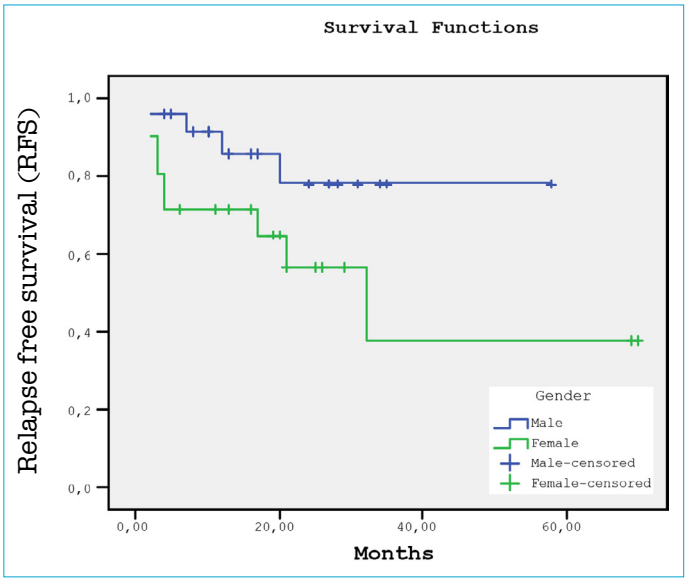

Figure 6. Relapse free survivalslope according to the gender.

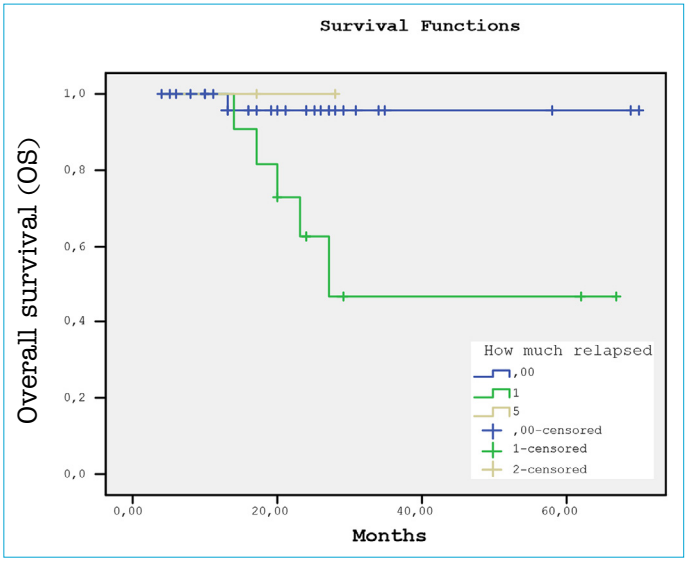

Figure 7. Overall survival slope according to the relapse progression.

study, it was observed that HL occurence frequency generally increased during the ages 20s and that it showed a bimodal distribution by drawing two peak slopes at the ages 20s and 60s. This distribution resembles to the age distribution in the developing countries.

The average of the ages of all the patients is 41.5±15.1. The rate of the male to the female is stated as 1.4.[12] Considering the rate of the the male to female in our study, it has been stated as 1.2 with a male dominance.

MCHL histological subtype is encountered more often in developing or underdeveloped countries. Yet, in developed countries, NSHL histological subtype forms already more than a half of HL cases.[13] In Turkey, mixed cellurarity type is more frequently reported.[14] Additionally, it is known that NSHL occurs more often in females.[15,16] When the results of our study are examined, MCHL cases form an amount of %47.8 of all the HL cases; on the other hand NSHL cases are included in %41.3 of those. Moreover, that the NSHL cases are at the rate of %47.6 in females stands out remarkably. But among the males, MCHL is most often (%56) observed. As all over the world,the results of this study indicate when the LDHL and NLPHL cases are less observed when compared to the other histological types, too. In terms of the age and histological subtype distributions, it is possible to say that our results are usually similar to the ones in the developing countries.

Although it is stated in the literature that most cases are detected in an early stage, in our cases, stage III-IV diseases were found in an amount of %56.5 and the stage I-II disease rate was found as %43.5.[14-17] This can result from the delay ofthe diagnosis due to the lack of a detailed anamnesis and physical examination in the primary and secondary healthcare organizations or from the delay in referral of the patients to the advanced healthcare organizations after the diagnosis. The frequent reason of HL patients' consulting to a doctor is lymphadenopathy, especially the existence of lymph nodes.[18] Compatibly, inour study, the most frequent diagnosis material was cervical lymph node excisional biopsy. The "B" symptom frequency observed between %25 and %40 in the literature for HL cases[15, 17, 19] have been observed much more (%45) in the cases of our study. The cause of this rate surplass may result from the subjectiveness of the mentioned symptoms and from the fact that night sweats and weight loss rates are perceived differently from patient to patient.

In the %10-30 of the cases which treated with a complete remission, a relapse occurs.[20, 21] In this context, the rates of the relapses and progresive diseases in our study are compatible with the literature.

Various studies have been made for determining the prognostic factors in Hodgkin Lymphoma. Among these, the first notable study is the evaluation made by "British National Lymphoma Investigation (BNLI)" in 1985. The index established by BNLI is an index which is valid for localized HL. However at the present time, a different prognostic index developed by GHSG, EORTC, NCIC and NCCN (suitable for NCCN 2012 guide) is used for the early stage HL patients. The prognosis in more progressive cases is examined with the scoring system called "International Prognostic Score (IPS)" or "Hasenclever Index".

Kılıçkap et al., in their study, stated that the 5-year-overall survival (OS) was %90; when evaluated in terms of the stages, the overall survival (OS) in early stage positive prognostic group and the relapse free survival (RFS) is %99; the

overall survival (OS) in early stage negative prognostic group is %91 and the relapse free survival (RFS) is %75; the overall survival (OS) in the late stages is %82 and the relapse free survival (RFS) is %78. When all the patients were evaluated in our study, it was observed that the rates of the 5-year-overall survival (OS) and relapse free survival (RFS) were respectively %87 and %71.7. Whereas the overall survival (OS) rate was obtained as %90 in early stages, it was stated as %84.6 in late stages; yet, this decline statistically did not have a significance in our study. As the stage progress, the overall survival rate declines in parallel with this situation. The overall survival results belonging to HL cases involved in our study are compatible with the data in the literature.

In our country, two studies have been published in which the treatment results of the early stage HL patients were examined. Coşkun et al., in their study, found out the 5-year-overall survival (OS) rate as %95 and the disease-free overall survival rate as %55 (97). On the other hand, in their prospective study including early stage HL cases, Yıldız et al.,[22] reported the 5-year-overall survival (OS) rate as %98 and the relapse free survival rate as %95. The overall survival rates obtained from both studies are very similar to the early stage (stage I and II) HL cases stated in our study.

Among the overall survival rates according to the relapse progression, a significant difference was determined in our study. Moreover, there was a significant difference between genders in terms of overall survival (OS) rates, too. That there was a statistical significant difference between genders and relapse progression can be put forward as the reason for this. The effect of the primary treatment on the survival has been revealed.

In their study at Stanford University in 2011, 101 early stage Hodgkin lymphoma patients receiving Stanford V chemotheraphy for 8 weeks were groupped by Ranjana et al.[23] according to the prognostic index developed by EORTC, GHSG and GELA and they compared the overall and the progression free survival (PFS) rates. As a result, a significant difference for progression free survival was obtained only in terms of GHSG prognostic index (p=0.02). In our study, early stage patients were groupped according to (suitable for NCCN 2012 guide) the prognostic index developed by) GHSG, EORTC, NCIC and NCCN; however no significant difference was obtained between the positive and the negative prognostic groups in the sense of overall and relapse free survival rates. This can result from the fact that our early stage patient number was fewer in proportion to the studies we carried out. In addition, contrary to what was expected in our study, any significant difference could not be stated between the overall and relapse free survival rates with IPS scoring. The fact that late stage patient number was not too many, either, may have effected this result. Despite all these things, our study is significant for being one of the notable studies in Turkey which is trying to reveal the relationship of the negative prognostic grouping according to GHSG, EORTC, NCIC, NCCN (NCCN 2012 guide) with the overall and relapse free survival.

As it is emphasized in the study of Kılıçkap et al., the study's being a retrospective research causes that the factors responsible for the etiology especially at the time of diagnosis can not be defined completely. Unfortunately, many factors such as the relationship of the patients with viral infections at the time of diagnosis, the socioeconomical status of the patients, the family structure of the individuals, the educational status of the individual and his family, the individual's life style and environment, tonsillectomy case history and radiation exposition could not be evaluated in this study. Because the information about the mentioned etiological factors is lacking and insufficient, it was impossible to determine the relationship of the HL cases in our study with both the age distribution pattern and the histological subtypes.

In our study, a significant difference was identified between the gender and the relapse progression and survival rates; furthermore between the responses to the primary treatment and survival rates. However; there was not any statistical significant difference stated between positive and negative prognostic groups in terms of overall and relapse free survival according to the prognostic index developed by GHSG, EORTC, NCIC, NCCN.

To conclude, the treatment schema must be specified by bearing the stages and the prognostic factors in mind. So, it can be possible to minimize the progression risk of the toxidity and treatment complication in long term.

The treatment success in HL patients is quite low and the published articles including prognostic factors are very limited in our country. With an increase in the examined patient number, the information about HL patients' demographical features and their treatment results may be much more contributed.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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