Short-term outcome of hodgkin lymphoma patients and its prognostic factors in northeast peninsular Malaysia: A single centre experience

Nurul Fatin Nabilah Ab Wahab, MMed[1,3], Hany Haqimi Wan Hanafi, MMed[1,4], Najib Majdi Yaacob, DrPH[2,4], Abu Dzarr Abdullah, MMed[1,4], Azlan Husin, MMed[1,4]

[1]Clinical Haematology Unit, Department of Internal Medicine, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia, [2]Unit of Biostatistics and Research Methodology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia, [3]Department of Medicine, Hospital Dungun, Jalan Paka, 23000 Dungun, Terengganu, Malaysia, [4]Hospital Pakar Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

ABSTRACT

Introduction: Hodgkin lymphoma (HL) is a hematopoietic malignancy characterized by the presence of Reed Sternberg cells, with generally favourable outcomes compared to other hematological malignancies. This study aims to determine the socio-demographic, clinical and treatment characteristics, as well as the short-term overall survival (OS) and progression-free survival (PFS) rates, of HL patients treated at Hospital Universiti Sains Malaysia (USM), a tertiary centre in northeast peninsular Malaysia.

Materials and Methods: We conducted a retrospective cohort study of HL patients treated from January 1, 2006, to December 31, 2018, with follow-up until December 31, 2021. Data on demographics, clinical features, treatments, and outcomes were analyzed. OS and PFS were estimated using the Kaplan-Meier method.

Results: Among 126 patients, the median follow up was 41 months. Most were male (55.6%) and of Malay ethnicity (97.6%). Nodular sclerosis was the predominant histology (52.4%), with 77.8% presenting with advanced-stage disease. All patients received chemotherapy, while 23.1% underwent combined modality therapy either with radiotherapy or immunotherapy. Post-treatment, only 34.1% achieved complete response. The 3-year OS and PFS rates were 74.9% and 59.5%, respectively—relatively lower than rates reported in developed countries. Independent adverse prognostic factors for OS and PFS included advanced-stage disease, bulky disease, elevated erythrocyte sedimentation rate.

Conclusion: This study highlights the need for tailored treatment approaches to improve HL outcomes in northeast Peninsular Malaysia. The relatively modest OS and PFS rates compared to developed nations suggest potential benefits from enhanced access to advanced therapied and diagnostic tools like positron emission tomography computed tomography (PET-CT) scan.

KEYWORDS:
Hodgkin lymphoma, Malaysia, treatment outcome, prognostic factors, survival

INTRODUCTION

Hodgkin lymphoma (HL) exhibits varied epidemiological patterns across gender, age, and geography. Its incidence follows a bimodal distribution, peaking in adolescence/young adulthood and later in individuals over 55-year-old.[1] In Malaysia, the highest incidence occurs between ages 25-29 and 70-74.[2]

HL classification, primarily divided into classical and nodular lymphocytes-predominant HL, guides treatment decisions. Furthermore, the Ann-Arbor staging system, supplemented by additional risk factors, aids in this process. Early-stage HL is often managed with combined modality therapy, whereas advanced-stage disease may necessitate escalated chemotherapy regimens. However, optimal treatment strategies continue to evolve especially for relapsed or refractory cases, in which highly active immunotherapies, such as brentuximab vedotin (an anti-CD30 monoclonal antibody), checkpoint inhibitors like nivolumab and pembrolizumab, along with high-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT), emerge as a cornerstone.

Understanding the prevalence and treatment outcomes of HL, particularly in Malaysia, is vital for local clinical haematologists. Therefore, this study aims to investigate the short-term outcomes and prognostic factors among HL patients treated at a tertiary centre in northeast Peninsular Malaysia.

MATERIALS AND METHODS

This study was a retrospective cohort study involving a review of medical records of HL patients undergoing treatment and follow-up at Hospital Universiti Sains Malaysia (USM), a tertiary referral centre for haematological cases in northeast Peninsular Malaysia. Data were collected from the medical records of HL patients in the database registry between January 1, 2006, and December 31, 2018, with an additional follow-up period of three years from January 1, 2019, until December 31, 2021. Thus, the total duration of this retrospective observation window was 192 months. During the follow-up period, patients were monitored through

This article was accepted: 24 November 2024
Corresponding Author: Hany Haqimi Wan Hanafi
Email: whhany@usm.my

scheduled clinical assessments, surveillance imaging studies, and laboratory evaluations. These measures were taken to assess treatment response, monitor for disease progression or relapse, and manage any treatment-related complications.

This study included patients diagnosed with HL within the specified period, aged over 12 years, who had received at least one cycle of induction chemotherapy after diagnosis. Patients with concurrent malignancy or another type of malignancy prior to the HL diagnosis, those who did not receive or refused any treatment during the study period, and those missing baseline evaluations for more than three variables were excluded. At Hospital USM, 138 HL patients were treated between January 1, 2006, and December 31, 2018, with 126 patients meeting the eligibility criteria. Therefore, no sampling method was applied, and all eligible patients were included in the study.

Data were entered and analysed using IBM Statistical Package for the Social Sciences (SPSS) version 26.0. For categorical variables, the frequency of observations and percentages were calculated. Survival analysis was chosen as the statistical test because the research objectives included time to an event i.e., death or relapse/progression of HL. Overall survival (OS) was defined as the duration from the date of diagnosis to the date of death. The event for survival time was death among HL patients during the study period, regardless of the cause of death. The censored observation for OS were either patients alive at the closure of the study or those lost to follow-up during the study period.

Progression-free survival (PFS) was defined as the duration from the date of diagnosis until the date of disease relapse/progression. The event of the study was the time to disease relapse/progression. The censored observation for PFS were either patients who achieved complete response (CR) at the closure of the study or those lost to follow-up during the study period.

A simple Cox proportional hazards model was conducted on selected independent variables to provide a preliminary idea of potential prognostic importance ($p<0.25$). The significant level was obtained from the Wald statistic. Subsequently, a multiple Cox proportional hazards model was used to identify prognostic factors for death and disease relapse/progression associated with OS and PFS. Two statistical analyses were executed for variables with a p-value less than 0.25 in univariate Cox regression analysis: forward stepwise (Wald) and backward stepwise (Wald). The second analysis included all independent variables in the model based on their statistical significance. The final model with adjusted hazard ratio (HR) and 95% confidence interval, Wald statistic and corresponding p-value were presented. A p-value less than 0.05 was considered statistically significant.

RESULTS

Among the 126 patients with HL, there was a slight male predominance, with 70 males (55.6%) and 56 females (44.4%). The median age was 28 years (range 12-78 years). Most patients were under 45 years old (84.9%) and predominantly Malay (97.6%).

Majority of patients presented with B symptoms (n=68, 54%) and nodal involvement (n=103, 81.7%). Biopsy-proven extra nodal involvement was identified in specific sites, including the bone marrow in 17 patients, the lungs in 5 patients, and the spleen in 1 patient. The most common histologic subtypes were nodular sclerosis (n=66, 52.4%), followed by mixed cellularity (n=35, 27.8%) and unclassified (n=11, 8.7%). Elevated LDH and ESR at diagnosis were recorded in 40.5% and 48.4% of patients, respectively. Among these patients, 98 patients (77.8%) had advanced-stage disease (stage III-IV) at presentation (Table I). Staging was based on the Ann Arbor staging system, which categorizes disease extent into stages I-IV, with further classifications based on symptoms (A or B) and bulk of disease.

The treatment characteristics are presented in Table II. Sixty-two patients (49.2%) received front-line treatment within four weeks of diagnosis. Majority of HL patients received first-line treatment with the ABVD protocol (doxorubicin hydrochloride, bleomycin sulfate, vinblastine sulfate, and dacarbazine) (n=121, 96%). More than half of the patients received one line of treatment (n=67, 53.2%), while 59 patients (46.8%) received two or more lines of treatment. In term of treatment modality, 97 patients (77.0%) received chemotherapy alone, 23 patients (18.3%) received chemo-radiotherapy, and 6 patients (4.8%) received chemo-immunotherapy. About 17.5% of patients (n=22) underwent HDC plus ASCT. Of the 22 transplanted patients, six received brentuximab vedotin during salvage therapy and/or as maintenance therapy.

Among the 126 patients treated, response data was available in 87% of patients either via contrast-enhanced computed tomography (CECT) scan or positron emission tomography computed tomography (PET-CT) scan. In a centre without in-house PET-CT service, 78 patients (61.9%) underwent end-of-treatment (EOT) PET-CT scans, while 32 patients (25.4%) underwent EOT CECT scan. The complete response (CR) rate was 34.1%, partial response (PR) was 26.2%, while stable disease (SD) and progressive disease (PD) were 7% and 22.6%, respectively, after first-line treatment. We assessed treatment response according to the 2007 Cheson criteria for lymphoma, defining CR as the disappearance of all evidence of disease and PR as ≥50% reduction in tumour burden, after completing first-line treatment.

With a median follow-up of 41 months, the 1-year and 3-year OS were 91.7% and 74.9%. Meanwhile, the 1-year and 3-year PFS were 83.4% and 59.5%, respectively (Figure 1). Various potential prognostic factors were evaluated using simple Cox proportional hazards regression to identify possible significant independent prognostic factors for death in HL patients. There factors included the presence of bulky disease ($p=0.023$), extranodal involvement ($p=0.175$), staging ($p=0.037$), elevated ESR ($p=0.006$), and elevated LDH ($p=0.053$) at diagnosis. These variables (with a p-value < 0.25) were then included in the multiple Cox regression analysis. Only two prognostic factors were found to be significant independent predictors of mortality among HL patients. Patients with bulky disease had a 1.9 times higher hazard of death compared to those without bulky disease ($p= 0.041$). Additionally, patients with elevated ESR had a 2.2-fold higher risk of dying ($p=0.018$) (Table III).

Table I: Baseline characteristics of the patients (n=126)

Baseline characteristics	Frequency (n)	Percentage (%)
B symptoms		
Yes	68	54.0
No	58	46.0
Bulky disease		
Yes	41	32.5
No	85	67.5
Elevated LDH at diagnosis (IU/L)		
Yes (≥500)	51	40.5
No (<500)	75	59.5
Extranodal involvement		
Yes	23	18.3
No	103	81.7
Elevated ESR at diagnosisa (mm/hr)		
Yes (>50)	59	48.4
No (≤50)	63	51.6
Histologic Subtypes		
Classical HL		
Nodular sclerosing	66	52.4
Mixed cellularity	35	27.8
Lymphocytes rich	6	4.8
Lymphocytes depleted	1	0.8
Unclassified	11	8.7
Non-Classical HL		
Nodular lymphocytes predominant	7	5.6
Stage of disease		
I	3	2.4
IIA	25	19.8
IIB	10	7.9
III	37	29.4
IV	51	40.5
Early stage	28	22.2
Advanced stage	98	77.8

[a]Missing data, n =4
n=frequency; %=percentage; SD=standard deviation
ESR, erythrocytes sedimentation rate; LDH, lactate dehydrogenase
Early stage: (I-IIA); Advanced stage: (II with bulky disease, III, IV)
HL, Hodgkin lymphoma

Table II: Treatment characteristics of the HL patients (n=126)

Treatment Characteristics	Frequency (n)	Percentage (%)
Time from diagnosis to treatment (TDT)		
≤ 4 weeks	62	49.2
5-8 weeks	29	23.0
>8 weeks	35	27.8
Line of treatment		
One line of treatment	67	53.2
≥ 2 lines of treatment	59	46.8
Treatment modalities		
Combination chemotherapy alone	97	77.0
Chemo-radiotherapy	23	18.3
Chemo-immunotherapy	6	4.8
Received HDC with ASCT		
Yes	22	17.5
No	104	82.5

Descriptive statistics
n=frequency; %=percentage
HDC, high dose chemotherapy
ASCT, autologous stem cell transplantation
HL, Hodgkin lymphoma

Table III: Prognostic factors of death by using multiple Cox proportional hazards regression model (n=126)

Variables	b	Adjusted HR[a] (95% CI)	Wald statistic	p-value
Bulky disease				
No	0	1	4.169	0.041
Yes	0.662	1.938(1.027,3.657)		
Elevated ESR[b]				
No	0	1	5.580	0.018
Yes	0.795	2.215(1.145,4.285)		

[a]Backward likelihood ratio multivariate cox proportional hazard regression [b]Missing data n=4
b, Regression coefficient; HR, hazard ratio; CI, Confidence Interval
ESR, erythrocyte sedimentation rate

Table IV: Prognostic factors of relapse/disease progression by multiple Cox proportional hazards regression model (n=126)

Variables	b	Adjusted HR[a] (95% CI)	Wald statistic	p-value
Bulky disease				
No	0	1	8.233	0.004
Yes	0.877	2.404(1.320,4.377)		
Elevated ESR[b]				
No	0	1	4.175	0.041
Yes	0.637	1.892(1.026,3.487)		

[a]Backward likelihood ratio multivariate cox proportional hazard regression [b]Missing data n=4
b, Regression coefficient; HR, hazard ratio; CI, Confidence Interval
ESR, erythrocyte sedimentation rate
p-value < 0.05 is significant

Similarly, the presence of bulky disease (p<0.001), extranodal involvement (p=0.031), elevated ESR (p=0.004), staging (p=0.005), and treatment modality (p=0.039) were potential prognostic factors for disease relapse/progression via simple Cox proportional hazards regression. In multiple Cox regression analysis, two variables were identified as significant prognostic factors for disease relapse/progression: the presence of bulky disease (p=0.004) and elevated ESR (p=0.041) (Table 4). Notably, there was a 2.4 times increased risk of relapse/progressive disease in the presence of bulky disease, and 1.89 times increased risk in HL patients with elevated ESR.

DISCUSSION

Our study reported that the median age at presentation was 28 years, with a slight male preponderance. Majority of patients had classical HL with nodular sclerosis being the most common subtype (52.4%), followed by mixed cellularity subtype (27.8%). The overall age, gender, and HL subtype distribution resembled a previous study in Malaysia.[3] However, our data contradicted results from several studies in developing countries including in Africa and India, where the mixed cellularity HL subtype was reported to be the predominant.[4,5]

More than two-thirds of patients were diagnosed with advanced-stage disease (98 patients, 77.8%), with stage IV (51 patients, 40.4%) being the most frequently encountered. These findings corresponded with previous studies in developing countries.[6,7] In contrast, more than half of HL patients in a retrospective study in Johor, Malaysia and in Iraq presented with stage II disease.[3,8]

Our study revealed 1-year and 3-year OS rates of 91.7% and 74.9%, respectively, and 1-year and 3-year PFS rates of 83.4% and 59.5%, respectively. These figures are comparable to previous studies in India, which reported 5-year OS and PFS rates of 60% and 58%, respectively.[9] However, our figures are significantly lower than those observed in developed countries, especially for advanced-stage disease. Recent studies by Radford et al. and Johnson et al. reported higher 3-year OS rates of 99.0% and 95.8% in early and advanced stages, respectively.[10,11] Another study in Saudi Arabia also reported better survival with 3-year and 5-year OS rates of 93.0% and 91.0%, respectively.[7]

Our study demonstrated that older patients (> 45 years) had lower survival rates compared to the younger age group. This finding corresponds with another study that found younger age groups had greater survival rates across all stages of HL.[12] A study in the United States reported that patients aged 45 or older had a higher hazard ratio of 5.25 for mortality.[13] Several factors could explain why older people had lower survival rates than younger age groups, including the presence of co-morbidities, poor organ function and therefore, increased susceptibility to treatment-related toxicities and poor treatment tolerance.[14] Additionally, older people are associated with a higher frequency of mixed cellularity subtypes compared to younger age groups (nodular sclerosing subtypes) and often present with advanced stages of HL.[15]

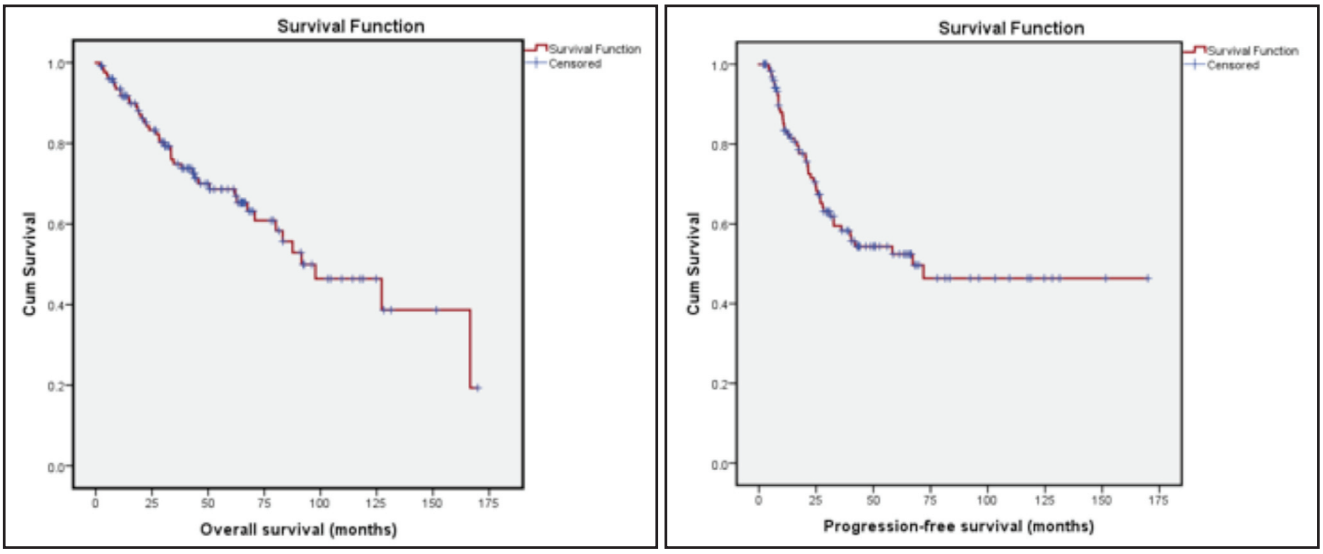

Fig. 1: Kaplan-Meier survival curve for 1-year and 3-year overall survival & 1-year & 3-year progression-free survival in HL patients in Hospital USM

In general, early initiation of combination chemotherapy alone or combined modality therapy provides better survival compared to patients without any treatment. However, in this study, there was no significant correlation between the time from diagnosis to treatment initiation (TDT), and OS and PFS. In a study by Brooks et al., investigating 810 patients with classical HL treated with ABVD, the 5-year OS was 92% for TDT <4 weeks, 92% for TDT 5–8 weeks, and 83% for TDT > 8 weeks (p=0.007).[16] This is an area of interest that we would like to explore, as patient refusal for treatment following a cancer diagnosis remains a significant issue.

Our study demonstrates that bulky disease and high ESR are two significant prognostic factors for death and disease relapse/progression among our HL patients. This finding aligns with previous studies that highlighted the influence of bulky disease and high ESR on patient survival, in addition to factors like high LDH, low albumin level, poor performance status and B symptoms.[17,18]

Several factors might have contributed to the low survival of our HL patients. Late presentation leading to advanced stage at diagnosis, difficult access to novel medications for salvage treatment such as highly active immunotherapy and checkpoint inhibitors, and most importantly, difficult access to PET-CT scans for staging and interim assessments make it challenging to adapt treatment escalation or de-escalation and decide on incorporating combined-modality treatment (chemo-radiotherapy). The use of early (interim) PET-CT scan for early treatment adaptation has significantly improved survival in HL patients.[19]

In relapse refractory setting, only small proportions of our patient received effective salvage therapy using novel agent modalities such as immunotherapy or check point inhibitor, mainly due to cost issue. This reflect the small proportion of our patients who were chemo sensitive able to undergo HDC plus ASCT.

For patients with relapsed or refractory HL who do not respond adequately to standard therapies, allogeneic stem cell transplantation (allo-SCT) may be considered. However, none of our patients were able to undergo this procedure due to its complexity. Although allo-SCT offers the potential for long-term remission, it is associated with significant risks, including graft-versus-host-disease, and increased transplant-related mortality, making careful patient selection essential.

CONCLUSION

This study provides a comprehensive analysis of the short-term outcomes and prognostic factors of HL in northeast Peninsular Malaysia, highlighting significant findings such as the predominance of nodular sclerosis subtype and the high prevalence of advances-stage disease at presentation. We observed relatively modest OS and PFS rates compared with those reported in more developed nations, with advanced-stage disease, bulky disease, and elevated ESR identified as significant adverse prognostic factors. These findings highlight the need for tailored treatment strategies that consider these risk factors and emphasize the importance of timely access to advanced diagnostic tools, such as PET-CT, to improve patient outcomes. Moving forward, longer-term studies are essential to refine treatment protocols, address the challenges of relapse and refractory cases, and enhance survival rates for patients in this setting.

ACKNOWLEDGEMENT

We extend our sincere gratitude to the staff of the daycare and clinical haematology wards at Hospital Pakar USM for their invaluable technical contributions.

ETHICAL CONSIDERATIONS

This study adhered to the ethical guidelines established by the 18th World Medical Assembly (Helsinki, 1964), including all subsequent revisions. Patient identities and clinical data were treated with strict confidentiality, reported only in aggregate form without personal identifiers. Approval for the study was granted by the USM Ethics Committee under JEPeM Code: USM/JEPeM/22010077 on March 13, 2022.

CONFLICT OF INTEREST

None

REFERENCES

1. Bröckelmann PJ, Eichenauer DA, Jakob T, Follmann M, Engert A, Skoetz N. Hodgkin lymphoma in adults. Dtsch Arztebl Int 2018; 115(31-32): 535-40.
2. Malaysia National Cancer Registry Report 2012-2016 [cited Oct 2022]. Available from: https://www.moh.gov.my/moh/resources/Penerbitan/Laporan/Umum/2012-2016%20(MNCRR)/MNCR_2012-2016_FINAL_(PUBLISHED_2019).pdf.
3. Boo YL, Ting HS, Yap DF, Toh SG, Lim SM. Clinical features and treatment outcomes of Hodgkin lymphoma: a retrospective review in a Malaysian tertiary hospital. Blood Res 2019; 54(3): 210-17.
4. Adam M, Bekueretsion Y, Abubeker A, Tadesse F, Kwiecinska A, Howe R, et al. Clinical characteristics and histopathological patterns of Hodgkin lymphoma and treatment outcomes at a tertiary cancer center in Ethiopia. JCO Glob Oncol 2021; 7(1): 277-88.
5. Jain H, Sengar M, Nair R, Menon H, Laskar S, Shet T, et al. Treatment results in advanced stage Hodgkin's lymphoma: a retrospective study. J Postgrad Med 2015; 61(2): 88-91.
6. Avagyan A, Danielyan S, Voskanyan A, Sargsyan L, Hakobyan L, Zohrabyan D, et al. Treating adults with Hodgkin lymphoma in the developing world: a hospital-based cohort study from Armenia. Asian Pac J Cancer Prev 2016; 17(1): 101-4.
7. Shafi RG, Al-Mansour MM, Kanfar SS, Al Hashmi H, Alsaeed A, Al-Foheidi M, et al. Hodgkin lymphoma outcome: a retrospective study from 3 tertiary centers in Saudi Arabia. Oncol Res Treat 2017; 40(5): 288-92.
8. Shamoon RP, Ali MD, Shabila NP. Overview and outcome of Hodgkin's lymphoma: experience of a single developing country's oncology centre. PLoS One 2018; 13(4): e0195629.
9. Jain H, Sengar M, Nair R, Menon H, Laskar S, Shet T, et al. Treatment results in advanced stage Hodgkin's lymphoma: A retrospective study. J Postgrad Med 2015; 61(2): 88-91.
10. Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, Johnson P, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 2015; 372(17): 1598-607.
11. Johnson P, Federico M, Kirkwood A, Fossså A, Berkahn L, Carella A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med 2016; 374(25): 2419-29.
12. Mukhtar F, Boffetta P, Dabo B, Park JY, Tran CT, Tran TV, et al. Disparities by race, age, and sex in the improvement of survival for lymphoma: findings from a population-based study. PLoS One 2018; 13(7): e0199745.
13. Shenoy P, Maggioncalda A, Malik N, Flowers CR. Incidence patterns and outcomes for Hodgkin lymphoma patients in the United States. Adv Hematol 2011; 2011(1): 725219.
14. Mukhtar F, Boffetta P, Risch HA, Park JY, Bubu OM, Womack L, et al. Survival predictors of Burkitt's lymphoma in children, adults and elderly in the United States during 2000–2013. Int J Cancer 2017; 140(7): 1494-502.
15. Evens AM, Carter J, Loh KP, David KA. Management of older Hodgkin lymphoma patients. Hematology Am Soc Hematol Educ Program 2019; 2019(1): 233-42.
16. Brooks EG, Connors JM, Sehn LH, Gascoyne RD, Savage KJ, Shenkier TN, et al. Impact of time from diagnosis to initiation of curative-intent chemotherapy on clinical outcomes in patients with classical Hodgkin lymphoma. Leuk Lymphoma 2016; 57(4): 872-9.
17. Glimelius I, Molin D, Amini RM, Gustavsson A, Glimelius B, Enblad G. Bulky disease is the most important prognostic factor in Hodgkin lymphoma stage IIB. Eur J Haematol 2003; 71(5): 327-33.
18. Kilickap S, Barişta İ, Ülger Ş, Çelik İ, Selek U, Yildiz F, et al. Clinical features and prognostic factors of Hodgkin's lymphoma: a single center experience. Balkan Med J 2013; 2013(2): 178-85.
19. André MP, Girinsky T, Federico M, Reman O, Fortpied C, Gotti M, et al. Early positron emission tomography response–adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol 2017; 35(16): 1786-94.