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ORIGINAL ARTICLE

A retrospective comparison of early stage primary extranodal with nodal non-Hodgkin lymphoma patients: A single center experience

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Summary

Purpose: *The primary extranodal non Hodgkin's lymphoma (EN-NHL) is a heterogeneous group of diseases with expression of different oncogenes compared to nodal NHLs. In this study, we aimed to compare the clinical and pathological findings, the prognostic factors, the treatment and the survival data in patients with stage I-II primary EN-NHL with nodal NHL (N-NHL).*

Methods: *Between January 1991 and January 2014, 853 patients with diagnosis of NHL were reviewed. Of 853 patients, 379 (44%) with stage I-II disease were included in the study and were divided into two groups according to involved sites as nodal and extranodal. The N-NHL group consisted of stage I-II patients without extranodal involvement, who were diagnosed by incisional or excisional lymph node biopsy. The EN-NHL group consisted of patients with a single primary extranodal involvement and/or a locoregional lymph node involvement, and who were diagnosed by means of a biopsy from the extranodal region.*

Results: *A total of 112 patients with N-NHL and 267 with EN-NHL were enrolled in the study. About 3/4 of the N-NHL patients had stage II, while 50% of the EN-NHL patients had stage I ($p<0.01$). There was no statistically significant difference between EN-NHL and NHL in terms of 5-year overall survival (OS) ($p=0.25$). The median 5-year OS in the diffuse large B cell lymphoma (DLBCL) subgroup with N-NHL was 52%, while that of the EN-NHL was 68% ($p=0.006$).*

Conclusion: *Patients with stage I-II N-NHL had a poorer prognosis than EN-NHL patients. However, 5-year OS rates were similiar between groups.*

Key words: *extranodal non-Hodgin lymphomas, nodal non-Hodgkin lymphoma, survival*

Introduction

NHLs usually originate from lymphatic tissues such as lymph nodes and the spleen. However, the primary EN-NHL involves extranodal tissues other than lymph node, spleen or bone marrow, and is encountered in 25 to 40% of all patients [1-3]. The definition of EN-NHL remains controversial. In the literature there are different definitions of EN-NHL. Along with the advocates who accept the absolute absence of lymph node involvement, there is also the opinion that accepts the presence of regional lymph node involvement in EN-NHL [4]. However, in cases with a dominant extranodal involvement accompanied by a widespread nodal involvement (stage III-IV), it is unclear whether the nodal involvement is a result of extranodal spread of the disease or a disseminated EN-NHL. The general opinion is to define this group as N-NHL. EN-NHL may derive from almost all tissues. The most common sites of involvement are the gastrointestinal tract

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and Waldeyer's ring (tonsils, nasopharynx, tongue base) [5]. There are also opinions which consider the Waldeyer's ring involvement as N-NHL [6].

DLBCL accounts for 28-30% of newly diagnosed lymphoma cases [7]. The more aggressive disease presents with rapidly enlarging lymphadenopathy, fever, fatigue, and weight loss [8]. Chromosomal translocations, gene amplification, and increased protein expression of tumor suppressor genes may play a role in the outcome of treatment [9,10].

In the last 20 years the International Prognostic Index (IPI) has been used to determine the prognosis of patients with aggressive NHL. After accepting rituximab as a standard treatment of DLBCL, a new IPI scoring system was developed by the National Comprehensive Cancer Network (NCCN). The NCCN-IPI is easy to apply and more powerful than the IPI in predicting the patient survival in the rituximab era [9].

In this study, we aimed to evaluate and compare the clinical and pathological findings, the prognostic factors, the treatment and the survival data in patients with stage I-II EN-NHL with N-NHL, excluding patients with stage III-IV disease.

Methods

Between January 1991 and January 2014, the data of patients diagnosed as NHL were retrospectively reviewed. Of the 853 patients, 379 (44%) with stage I-II disease were included in the study. Patients included in the study were divided into two groups as patients with N-NHL and patients with EN-NHL. The N-NHL group consisted of stage I-II patients without EN-NHL, diagnosed by incisional or excisional lymph node biopsy. The EN-NHL consisted of patients with a single primary extranodal involvement and/or a locoregional lymph node involvement, and who were diagnosed by means of a biopsy from the extranodal region. Stage III-IV patients, patients with multiple extranodal involvement and patients who did not have a positive biopsy from the extranodal region were excluded.

Staging was performed by computed tomography (CT) of neck, thorax, and abdomen. In addition, all patients underwent a unilateral bone marrow biopsy. Positron emission tomography plus CT (PET-CT) was not performed in all patients since it is a relatively new diagnostic method.

In addition, baseline blood count, liver and renal functions, and lactate dehydrogenase (LDH) levels were measured in all patients. For LDH a value >280 U/L was accepted as high, for albumin a value <35 mg/dl was accepted as low, and for hemoglobin a value below 12 mg/dl was accepted as low.

Demographics, treatment characteristics, and the survival data of the nodal and extranodal groups were compared. The performance status of patients at the time of diagnosis was evaluated according to the Eastern Cooperative Oncology Group (ECOG) scale. In all patients, the IPI was assessed. Since stage III-IV patients and patients with involvement of more than one extranodal site were excluded from the study, the patients were categorized in low, low-intermediate and high-intermediate risk groups. Response evaluation was performed in treated patients and known treatment response.

Patients without response evaluation, who were followed-up without medication, died during treatment and lost to follow-up were not included in the response assessment group.

OS was defined as the time span from diagnosis until death or the last follow-up. For patients who were diagnosed after 2005, and whose Turkish citizenship numbers were available, the official life data were obtained from the Population Administration of the Republic of Turkey.

Statistics

Chi-square test and Fisher's exact test were used to evaluate the association between independent variables. The parameters that may be prognostic indicators of survival were evaluated by univariate analysis. For the parameters with significant results in univariate analysis, Cox regression multivariate analysis was performed. Kaplan-Meier method was used to generate survival curves and log-rank test was used to evaluate the differences in survival between patients with N-NHL and EN-NHL. P values <0.05 were considered as statistically significant. All analyses were performed using SPSS software (SPSS Inc., Chicago, Ill, USA).

Results

Demographic characteristics

A total of 379 patients were enrolled in the study, 112 (29.55%) of which with N-NHL and 267 (70.45%) with EN-NHL. The median age of the entire group was 55 years (range 16-88) and the female-male ratio was approximately 40%/60%. When compared in terms of patient characteristics, the most significant differences between the N-NHL and the EN-NHL groups appeared in the stage of disease. About 3/4 of the N-NHL patients had stage II disease, while 50% of the EN-NHL patients had stage I (p<0.01). The baseline hemoglobin values were lower in the extranodal lymphomas compared to the nodal lymphomas (p=0.03). There were no significant differences between the groups in terms of other patient characteristics such as ECOG, cell type, and IPI scores (p>0.05). Of all the patients, DLBCL sub-

Table 1. Patient demographic features

Features	*Total % (N: 379)*	*Nodal % (N:112)*	*Extranodal % (N:267)*	*p value*
Age (years) median	55	53	55	
Gender				
Male	60.9	58.0	62.2	0.62
Female	39.1	42.0	37.8	
Stage				
I	41.2	24.1	48.3	<0.01
II	58.8	75.9	51.7	
ECOG PS				
0-1	68.9	72.3	67.4	0.35
≥2	31.1	27.7	32.6	
LDH				
Normal	58.4	59.8	57.7	0.72
High	41.6	40.2	42.3	
Albumin				
Normal	73.3	71.6	73.9	0.40
Low	26.7	28.4	26.1	
Hemoglobin				
Normal	63.7	72.3	60.2	0.03
Low	36.3	27.7	39.8	
B symptoms				
Yes	53.6	49.1	45.3	0.50
No	46.4	50.9	54.7	
Cell Type				
B cell	92.3	87.3	93.6	0.05
T cell	7.7	12.7	6.4	
DLBCL				
Yes	55.7	60.7	53.6	0.21
No/unknown	44.3	39.3	46.4	
Bulky disease				
Yes	72.4	38.4	23.0	<0.01
No	27.6	61.6	77.0	
IPI score				
Low, low-intermediate risk	89.4	89.9	89.9	1.00
High-intermediate risk	10.6	10.1	10.1	

DLBCL: diffuse large B cell lymphoma, IPI: international prognostic index, ECOG PS: Eastern Cooperative Oncology Group performance status

Table 2. Treatment characteristics

Treatment	*Total % (N: 379)*	*Nodal % (N:112)*	*Extranodal % (N:267)*	*p value*
Anthracycline-based				
Yes	88.7	98.0	84.6	<0.01
No	11.3	2.0	15.4	
Rituximab				
Yes	39.7	36.6	39.7	0.40
No	60.3	63.8	60.3	
Radiotherapy				
Yes	51.2	46.6	53.3	0.26
No	48.8	53.4	46.7	

Table 3. Response to treatment and overall survival

Response	*Nodal (N:112) %*	*Extranodal (N:267) %*	*p value*
5-year OS	59	65	0.25
Response			
Complete	67.4	79.0	
Partial	21.1	11.8	0.15
Stable	5.3	4.1	
Progression	6.3	5.1	

OS: overall survival

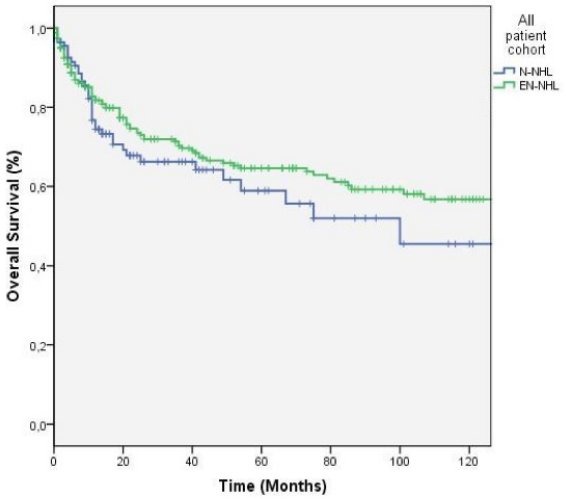

Figure 1. Kaplan-Meier comparison of overall survival of nodal NHL and extranodal NHL patients (p=0.001).

type constituted 55% and there was no significant differences between the groups in terms of DLBCL subtype (p=0.21) (Table 1).

Low grade tumor rate was higher in the EN-NHL group (7.8 vs 16.9%, p=0.02). The most common region of extranodal involvement was the gastrointestinal tract (approximately 50%), and the head and neck region (36%).

Treatment characteristics

Of all the patients, 93.3% received at least one course of systemic therapy, and in about 90% therapy was anthracycline-based. The rate of anthracycline-based therapy was significantly higher in the nodal group compared to the extranodal group (p<0.01). Rituximab treatment and radiotherapy rates were similar in both groups (p>0.05) (Table 2).

Analysis of prognostic factors and survival

The median OS was 171 months in the whole group, 171 months in patients with N-NHL, and 100 months in the EN-NHL group (Figure 1). Although there was a 71-month difference between groups, it did not reach statistically significance (p=0.25). Response evaluation data were available in 290 patients (76.5%). In total, 290 (76.5%) patients responded to therapy. Of all the patients with a response evaluation, 75% achieved complete response and the response rates were similar in both groups (p=0.15) (Table 3).

Regarding the evaluation of parameters that could affect the OS, male gender (p=0.024), stage II disease (p<0.01), elevated LDH levels (p<0.01), low hemoglobin levels (p<0.01), hypoalbuminemia (p<0.01), presence of B symptoms (p<0.01), presence of bulky disease (p<0.01), an upper-middle IPI score (p<0.01), and not receiving radiation therapy (p<0.01) were all found to be associated with poor prognosis (Table 4). In multivariate analysis, male gender, poor performance status, low albumin level at the time of diagnosis and presence of bulky disease were shown to be poor prognostic factors (Table 5).

Table 4. Univariate analysis

Features	*OS (months)*	*p value*
Gender		
Male	107	<0.01
Female	NR	
Stage		
I	132	0.66
II	NR	
ECOG PS		
0-1	171	<0.01
≥2	25	
LDH		
Normal	NR	<0.01
High	44	
Albumin		
Normal	NR	<0.01
Low	26	
Hemoglobin		
Normal	-	<0.01
Low	37	
B symptoms		
No	NR	<0.01
Yes	86	
DLBCL		
Yes	171	
No/unknown	132	0.61
Bulky disease		
No	171	<0.01
Yes	54	
IPI score		
Low, low-intermediate	171	<0.01
High-intermediate risk	12	
Anthracycline-based therapy		
Yes	171	0.94
No	NR	
Rituximab		
Yes	NR	
No	132	0.16
Radiotherapy		
Yes	171	<0.01
No	85	

NR: not reached, DLBCL: diffuse large B cell lymphoma, IPI: international prognostic index, ECOG PS: Eastern Cooperative Oncology Group performance status

To eliminate the differences between the histopathological subtypes, the survival rates of patients with DLBCL were evaluated. The median 5-year OS in the DLBCL subgroup with N-NHL was 52%, while that of the EN-NHL was 68%. The difference was statistically significant (p=0.006) (Figure 2).

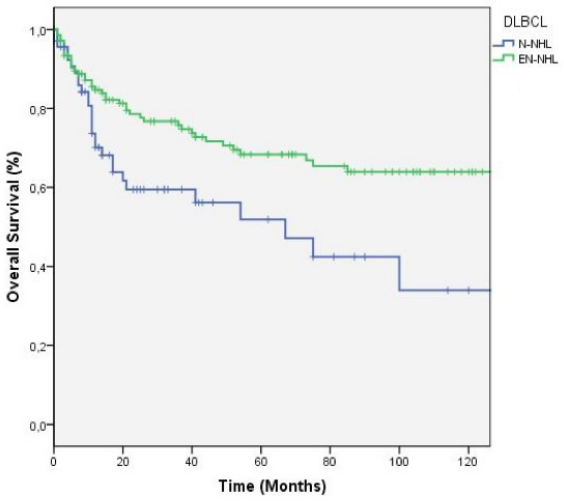

Figure 2. Kaplan-Meier comparison of overall survival of nodal DBCL and extranodal DBCL patients (p-0.006).

Discussion

EN-NHL is a heterogeneous group of diseases which is thought to be under the influence of different oncogenes with various genetic origins [11,12]. There a small number of data indicating that both the clinical courses and the immunophenotypic profiles of N-NHL and EN-NHL are different. For instance, there are studies showing that the Bcl-2/JH rearrangement is more common in N-NHL, as well as studies presenting that Bcl-6 expression is encountered more frequently in EN-NHL [11-14]. The data are usually based on population-based retrospective series. According to our current knowledge, the treatment approach to the patients with EN-NHL is similar to the patients with N-NHL. For this reason, the differences between the two entities are usually not taken into consideration. In this study, our aim was to evaluate and compare the clinical and the pathological findings, the treatment and the prognostic differences in patients with stage I-II NHL and EN-NHL.

EN-NHL comprises approximately one third of all lymphomas. In our study, of all patients with lymphoma, 44% had stage I-II, and 31% had EN-NHL, all in concordance with the literature [1,5]. However, contrary to expectations, 2/3 of stage I-II patients included in the study had EN-NHL. This is probably due to the fact that N-NHL usually remains asymptomatic and the patients

Table 5. Multivariate analysis

Factor	*Hazard ratio*	*95% CI*	*p value*
Gender	0.56	0.34 to 0.61	0.02
ECOG PS	0.37	0.22 to 0.61	<0.01
Albumin	0.46	0.26 to 0.79	0.05
Bulky disease	0.60	0.37 to 0.97	0.03

ECOG PS: Eastern Cooperative Oncology Group performance status, CI: confidence interval

are admitted in advanced stages of disease.

A second matter of debate on the definition of the EN-NHL is whether the lymphomas of Waldeyer's ring are nodal or extranodal. Next to the views defining the Waldeyer's ring lymphomas as nodal lymphomas, there are also authors claiming the Waldeyer's ring is an extranodal region [11,15]. In our study, we accepted the lymphomas of Waldeyer's ring (only if the diagnosis was done with tissue obtained from this area) as primary EN-NHL localized in the head and neck region. As to the regional distribution of our patients with EN-NHL, they were most frequently localized in the gastrointestinal tract, followed by the head and neck lymphomas, as expected.

In our study, nodal lymphomas were associated with more advanced disease and greater tumor burden compared to EN-NHL. However, in a population-based study carried out by Krol et al. the patients with EN-NHL were shown to have worse performance status and higher tumor burden [16]. Unlike our study, however, in that study only stage I patients were included. In another study involving 382 DLBCL patients from a single center, the patients with N-NHL were found to have worse prognosis (higher IPI, higher LDH levels), which was in accordance with our results. However, since about half of the patients in that study had advanced disease associated with identification problems, the interpretation of the data remains limited [11].

IPI is a clinical tool developed by oncologists to aid in predicting the prognosis of patients with aggressive NHLs. The parameters that determine the IPI score are stage, age, serum LDH levels, performance status, and the number of extranodal sites of disease [17]. Stage III-IV patients and patients with multiple sites of extranodal involvement remain undefined with regard to EN-NHL. Therefore, the assessment of the IPI score is performed with three parameters instead of five. In our study, the assessment performed with these three parameters did not reveal any significant difference between N-NHL and EN-NHL.

DLBCL is the most common type of NHL, comprising about 30% of all lymphomas [7,18]. About one-third of DLBCL is primarily of extranodal origin. In a study with patients with stage II disease the nodal/extranodal ratio was 31%/40%, while Krol et al. found a ratio of 34%/50%, respectively [14,16]. In our series, the DLBCL rate was high in both groups (60%/53%). Furthermore, 23% of the patients had B cells without a defined subtype. The higher rate of DLBCL in our group is probably due to the inclusion of stage II patients in the study, as well as to geographical, social and genetic factors.

The anthracycline-based regimens constitute the standard initial therapy in NHL (except for low grade tumors). The addition of rituximab to anthracycline-based therapy results in an approximately 15% increase in 5- and 10-year OS in DLBCL [19,20]. Regarding the treatment characteristics in our study, while the rate of rituximab and radiation therapy was similar, the number of anthracycline courses was higher in nodal lymphomas, since the low grade tumor rate was higher in EN-NHL (98 vs 84%). The number of patients treated with rituximab was lower than expected in DLBCL, since the patients treated in the 1990s were included in the study.

The aim of this study was to compare N-NHL and EN-NHL in terms of survival, clinical presentation, prognostic parameters, and treatment. In our study, although the 5-year OS rate was much lower in N-NHL compared to EN-NHL, the difference was not significant (p=0.20). This was probably due to the higher number of stage II patients, an increased tumor burden and lower number of low grade patients in this group. The multivariate analysis of the factors that may influence survival showed that male gender, ECOG PS II or more, low albumin levels and the presence of bulky disease were associated with shorter survival.

Contrary to our data, in another study comparing the nodal and the extranodal patients, the

patients with EN-NHL were shown to have a lower OS rate compared to the patients with N-NHL. However, in that study only the patients with stage I disease were included, and the EN-NHL patients had a higher tumor burden and higher histological grade [16]. In the same study, similar to our series, poor performance status, elevated LDH levels, and the presence of bulky tumor were found to be correlated with a short lifespan . In another population-based study with a group of patients similar to our series, patients with EN-NHL were found to have better rates of 10-year OS (19 vs 34%) and median OS ($p<0.001$) [14].

In the present study, no statistically significant difference was noticed between the nodal and extranodal lymphomas in terms of survival. However, lymphomas of various histopathological subtypes were included in our study. In order to eliminate this heterogeneity, survival analysis was performed in the DLBCL subgroup. According to this analysis, EN-NHL was found to have a significantly longer survival compared to N-NHL ($p=0.006$).

In a series of 382 patients with DLBCL Waldeyer's and gastrointestinal lymphomas in particular were shown to have a higher 5-year OS compared to N-NHL (Waldeyer's lymphoma 77%, gastrointestinal lymphoma 68%, nodal lymphoma 45%) [11]. In a similar study from Spain, in both rituximab-treated and control arms, 5-year OS of Waldeyer's and gastrointestinal lymphomas was higher compared to nodal lymphomas. The difference in OS was even more pronounced in patients who were not treated with rituximab (in the control arm: Waldeyer's lymphoma 100%, gastrointestinal lymphoma 92%, nodal lymphoma 36%; in the rituximab arm: Waldeyer's lymphoma 80%, gastrointestinal lymphoma 90%, nodal lymphoma 66%) [21].

Our study has limitations despite the high number of patients. The limitations can be summarized as the retrospective character of the study, inadequate histopathologic evaluation and lack of PET-CT staging, especially in earlier patients.

Conclusion

In conclusion, our results have shown that patients with N-NHL seem to have a poor prognosis compared to patients with EN-NHL. In addition, although patients with EN-NHL had a longer survival compared to N-NHL, the difference was not statistically significant. The patients were enrolled in the study starting from the 1990s, which led to insufficient histopathological subtyping. For this reason, in order to eliminate the bias regarding the evaluation of the pathological data, a subgroup analysis was performed in patients with DLBCL who were found to have a significantly longer survival rate compared to patients with EN-NHL and N-NHL. Parameters such as ECOG PS and bulky disease, which are generally accepted as prognostic factors in NHL, were shown to have prognostic significance in stage I-II NHL patients in this study. Furthermore, male gender and low albumin levels had also prognostic significance. When the extranodal lymphomas are defined as "extranodal region +/- regional lymph node involvement", the use of the IPI score in this patient group is restricted.

There is a limited number of studies which highlights the differences between EN-NHL and N-NHL in molecular level and in terms of survival. Currently, prospectively designed studies are needed for a detailed histopathological and molecular evaluation of EN-NHL. These studies can lead to new insights for prognostic assessments and different treatment approaches.

References

1. d'Amore F, Christensen BE, Brincker H et al. Clinicopathological features and prognostic factors in extranodal non-Hodgkin lymphomas. Danish LYFO Study Group. Eur J Cancer 1991;27:1201-1208.
2. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer 1972;29:252-260.
3. Newton R, Ferlay J, Beral V, Devesa SS. The epidemiology of non-Hodgkin's lymphoma: comparison of nodal and extra-nodal sites. Int J Cancer 1997;72:923-930.
4. Zucca E, Roggero E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 1: Gastrointestinal, cutaneous and genitourinary lymphomas. Ann Oncol 1997;8:727-737.
5. Otter R, Gerrits WB, vd Sandt MM, Hermans J, Willemze R. Primary extranodal and nodal non-Hodgkin's lymphoma. A survey of a population-based registry. Eur J Cancer Clin Oncol 1989;25:1203-1210.
6. Hoppe RT, Burke JS, Glatstein E, Kaplan HS. Non-Hodgkin's lymphomas: involvement of Waldeyer's ring. Cancer 1978;42:1096-1104.
7. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006;107:265-276.
8. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998;16:2780-2795.
9. Zhou Z, Sehn LH, Rademaker AW et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014;123:837-842.
10. Iqbal J, Liu Z, Deffenbacher K, Chan WC. Gene expression profiling in lymphoma diagnosis and management. Best Pract Res Clin Haematol 2009;22:191-210.
11. Lopez-Guillermo A, Colomo L, Jimenez M et al. Diffuse large B-cell lymphoma: clinical and biological characterization and outcome according to the nodal or extranodal primary origin. J Clin Oncol 2005;23:2797-2804.
12. Raghoebier S, Kramer MH, van Krieken JH et al. Essential differences in oncogene involvement between primary nodal and extranodal large cell lymphoma. Blood 1991;78:2680-2685.
13. Kramer MH, Hermans J, Wijburg E et al. Clinical relevance of BCL2, BCL6, and MYC rearrangements in diffuse large B-cell lymphoma. Blood 1998;92:3152-3162.
14. Krol AD, le Cessie S, Snijder S, Kluin-Nelemans JC, Kluin PM, Noordijk EM. Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. Ann Oncol 2003;14:131-139.
15. Krol AD, Le Cessie S, Snijder S, Kluin-Nelemans JC, Kluin PM, Noorduk EM. Waldeyer's ring lymphomas: a clinical study from the Comprehensive Cancer Center West population based NHL registry. Leuk Lymphoma 2001;42:1005-1013.
16. Krol AD, Hermans J, Dawson L et al. Treatment, patterns of failure, and survival of patients with Stage I nodal and extranodal non-Hodgkin's lymphomas, according to data in the population-based registry of the Comprehensive Cancer Centre West. Cancer 1998;83:1612-1619.
17. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993;329:987-994.
18. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-3918.
19. Feugier P, Van Hoof A, Sebban C et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117-4126.
20. Coiffier B, Thieblemont C, Van Den Neste E et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-2045.
21. Gutierrez-Garcia G, Colomo L, Villamor N et al. Clinico-biological characterization and outcome of primary nodal and extranodal diffuse large B-cell lymphoma in the rituximab era. Leuk Lymphoma 2010;51:1225-1232.