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Serbian lymphoma study group: demografic characteristics of 257 patients with follicular lymphoma

Srpska limfomska grupa: demografske karakteristike 257 ispitanika sa folikularnim limfomom

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Abstract

Background/Aim. Follicular lymphoma (FL) is a B-cell tumor usually with indolent clinical course, yet in some cases the course of the disease can be very aggressive. The aim of the research was to determine distribution of patients into prognostic groups based on the International Prognostic Index (IPI) and Folicular Lymphoma International Prognostic Index (FLIPI) criteria, as well as to determine the importance of classifying patients into the prognostic groups, since this could potentially have the influence on selection of the treatment modality. **Methods.** The retrospective study was performed on 257 patients with follicular lymphoma diagnosed between January 2000 and April 2011. **Results.** Based on the IPI score, 153 (59.53%) patients had low risk, 57 (22.18%) low intermediate risk, 15 (5.84%) high intermediate risk, 9 (3.50%) high risk, whereas the classification of 23 patients diagnosed with FL remained with unknown risk according to the IPI. Based on the FLIPI prognostic index, 113 (43.97%) patients had low risk, 70 (27.24%) intermediate risk and 51 (19.84%) high risk, whereas the classification of 23 (8.95%) patients remained unknown. On the basis of the FLIPI 2 prognostic index, 48 (18.68%) patients had low risk, 145 (56.42%) intermediate risk and 41 (15.95%) high risk. The classification into prognostic groups for 23 (8.95%) patients remained unknown. According to the IPI, FLIPI and FLIPI 2 there were the patients that required treatment in all the risk groups. **Conclusion.** The FLIPI and FLIPI 2 effectively identify patients at high risk, thus helping in treatment decision for each single patient.

Key words:
lymphoma, follicular; serbia; predictive value of tests; combined modality therapy.

Apstrakt

Uvod/Cilj. Folikularni limfom (FL), B-ćelijski tumor obično je indolentnog kliničkog toka bolesti, ali u nekim slučajevima tok bolesti može biti veoma agresivan. Cilj istraživanja bio je da ce utvrdi raspodela bolesnika u prognostičke grupe u odnosu na internacionalni prognostički indeks (IPI) i folikularni limfom internacionalni prognostični indeks (FLIPI) kriterijume, kao i da se odredi značaj klasifikovanja bolesnika u prognostičke grupe koje bi mogle potencijalno uticati na izbor modaliteta lečenja. **Metode.** Retrospektivno istraživanje izvedeno je na 257 bolesnika sa FL koji su dijagnostikovani od januara 2000. do aprila 2011. **Rezultati.** Na osnovu IPI prognostičkog indeksa, nizak rizik imalo je 153 (59,53%) bolesnika, srednje nizak rizik 57 (22,18%), srednje visok rizik 15 (5,84%), visoki rizik 9 (3,50%) bolesnika, a nepoznato je bilo svrstavanje 23 bolesnika sa dijagnozom folikularnog limfoma prema IPI. Na osnovu FLIPI prognostičkogi indeksa, nizak rizik imalo je 113 (43,97%), srednji 70 (27,24%), visoki rizik 51 (19,84%), a nepoznato je bilo svrstavanje 23 (8,95%) bolesnika. Na osnovu FLIPI 2 prognostičkog indeksa, nizak rizik imalo je 48 (18,68%), srednji 145 (56,42%), a visoki 41 (15,95%) bolesnika sa FL. Nepoznato je bilo svrstavanje 23 (8,95%) bolesnika. Prema IPI, FLIPI i FLIPI 2 bilo je bolesnika koji zahtevaju lečenje u svim prognostičkim grupama. **Zaključak.** FLIPI i FLIPI 2 efikasno grupišu bolesnike u grupu visokog rizika i pomažu pri odluci o lečenju za svakog pojedinačnog bolesnika.

Ključne reči:
limfom, folikularni; srbija; testovi, prognostička vrednost; lečenje, kombinovano.

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Introduction

Follicular lymphoma (FL) is an indolent B-cell tumor making 22% of all B-non-Hodgkin's lymphoma and is the second most common type of lymphoma in adults in the countries in the western hemisphere [1]. The annual incidence of FL has increased since 1950 until today from 2 to 3 in 100,000 patients to 5 to 7 in 100,000 patients [2]. The median age of patients at diagnosis is 60 years and the disease is slightly more common in women [3]. It is usually diagnosed in advanced stages, III/IV. Clinical course of FL varies from the cases of spontaneous remission (15–20%), over indolent clinical course with present response to therapy, relapse, and median survival of 9–10 years, to the aggressive clinical cases [4]. Bearing in mind that patients diagnosed with non-Hodgkin's lymphoma can have large variations in clinical presentation, molecular profiles and clinical outcome of the disease, the choice of therapy could be potentially influenced by numerous parameters [5]. The most important prognostic factors that could influence the choice of therapy are: sex, age, factors pointing to the staging of the disease, laboratory (erythrocyte sedimentation rate, the level of serum albumin, hemoglobin, lactate dehydrogenase (LDH), beta 2 microglobulin), pathological (based on correlation of histological grade and clinical outcome of the disease), cytogenetic and other factors [6]. The problem with the current prognostic indices (IPI, FLIPI, FLIPI 2) lies in a limited number of parameters, so that the choice of therapy would require the use of existing indexes together with other parameters [7].

Gene expression pattern in immune response 1 (IR-1) corresponds to the mixed expression of T lymphocytes and macrophages, while the expression patterns in IR-2 corresponds predominantly to macrophage expression with the elements of follicular dendritic cell expression [8]. Examination of the correlation of gene expression and disease outcome pointed to a more favorable course of the disease and significantly longer survival in patients with IR-1. In addition, the predictive value of this model was not in correlation with the IPI.

Application of gene expression profile with 81 genes contributed to the classification of 100% of patients in low-risk and high-risk groups [9].

By the application of the International Prognostic Index – IPI [age, Ann Arbor clinical staging, Eastern Cooperative Oncology Group (ECOG) performance status, serum LDH, extranodal involvement] we classified a very small number of patients into the poor prognostic group, about 10–15% of them, so it could not precisely determine the group of patients in who could be eligible for intensive chemotherapy [4].

The first specific index for follicular lymphoma, ILI, was proposed by the Italian group for investigating lymphoma (Italian Lymphoma Intergroup) in 2000. This index involves demographic, clinical and biochemical factors affecting the prognosis [7].

The follicular lymphoma international prognostic index (FLIPI) (age, Ann Arbor clinical staging, hemoglobin level, serum LDH, the number of involved lymph regions), proposed by the International Cooperative Group in 2004, classified 27% of patients in the high risk group.

A new prognostic index, the Follicular lymphoma international prognostic index 2 (FLIPI 2) was defined at the end of 2009 by the International Cooperative Group headed by Federico et al. [10], after immunochemotherapy had become the standard of care in patients with FL. It includes age, elevated β2 microglobulin (ß2M), diameter of the largest affected lymph node of more than 6 cm, bone marrow infiltration and hemoglobin level as the most important predictive factors for the outcome of the disease. On the basis of this index, 20% of the patients were classified in the high-risk group [9]. In the last few years, the development of immunohistochemistry and molecular techniques contributed to the identification of a large number of new, potentially powerful prognostic markers for all types of non-Hodgkin's lymphomas (NHL) [11].

The aim of this study was to determine the incidence of FL, prognostic groups with respect to the sum of points based on the IPI and FLIPI criteria and to determine the importance of classifying patients into prognostic groups, which could potentially influence selection of treatment modality.

Methods

The research was conducted on the basis of the database of the National Registry for Lymphoma LIRA and included the time period from 31 January 2000 to 25 April 2011.

Patients were classified into different risk groups, on the basis of age, prognostic indices IPI and FLIPI, the presence of unfavourable parameters that are not part of prognostic indices, such as voluminous tumor mass, biological parameters, such as Ki-67 protein, clinical characteristics of the disease and the risk of transformation of indolent into aggressive lymphoma.

The total number of patients diagnosed with FL during the above-mentioned time period was 257.

All the examined parameters were presented as frequencies and percentages.

χ^2 test was used for comparasion of frequencies.

Results

In the study group 151 (58.75%) patients were females and 106 (41.25%) males.

On the basis of the IPI score, most patients, 153 (59.53%) of them, were at low risk, statistically significantly more than the others (χ^2-test, $p < 0.001$), and the number in the other risk groups decreased with increase in the degree of risk.

In our research, the most prominent factor of the IPI was the clinical stage (CS) III or IV, 173 (67.32%) patients, which is statistically more prevalent than other IPI prognostic factors.

Figure 1 shows the number of patients with FL in risk groups on the basis of the FLIPI prognostic index. Most of them, 113 (43.97%) patients, were low-risk patients, statistically significantly more than the others (χ^2-test, $p < 0.001$) and the number of patients decreased in the other risk groups with increase in the degree of risk.

Clinical stage III or IV was again the most prominent factor of the FLIPI prognostic index in our research, and it was statistically more frequent in comparison to all the other FLIPI prognostic criteria.

Figure 2 shows the number of patients in risk groups on the basis of the FLIPI 2 prognostic index. Most patients, 145 (56.42%) of them, were at intermediate risk, statistically significantly more than in the other risk groups of patients (χ^2-test, $p < 0.001$).

Immunochemotherapy, immunotherapy, radiotherapy and the Watch and Wait strategy were used in treatment of all the stages of the disease.

Figure 3 shows the distribution of therapy on the basis of the IPI score. According to IPI, immunochemotherapy and chemotherapy were used in all the risk groups.

On the basis of the FLIPI score immunochemotherapy, chemotherapy and radiotherapy were used in treatment of all the risk groups.

On the basis of the FLIPI 2 score, immunochemotherapy, chemotherapy and radiotherapy were used in treatment of all the risk groups.

Discussion

Follicular lymphoma is a neoplasm built from follicular (germinal) center cells (centrocytes and centroblasts) which, at least in part, grow in follicular distribution [12].

It is formed by the transformation of germinal center B-

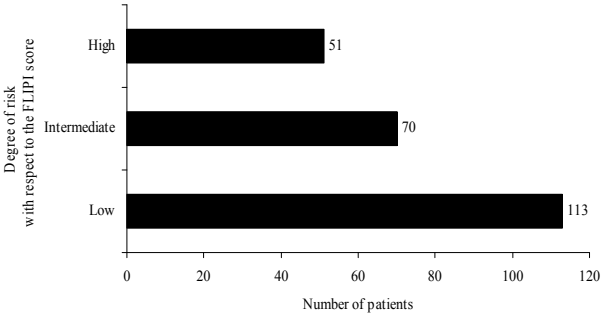

Fig. 1 – Patients with follicular lymphoma on the basis of the Follicular Lymphoma International Prognostic Index (FLIPI) score.

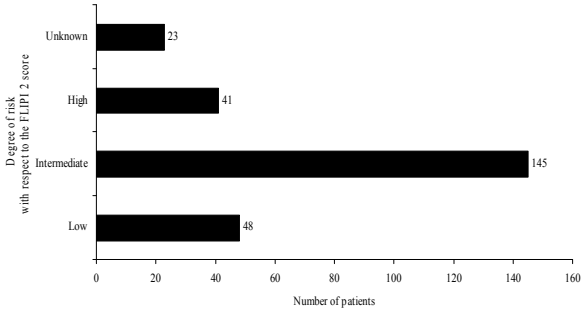

Fig. 2 – Patients with follicular lymphoma on the basis of the Follicular Lymphoma International Prognostic Index (FLIPI 2) score.

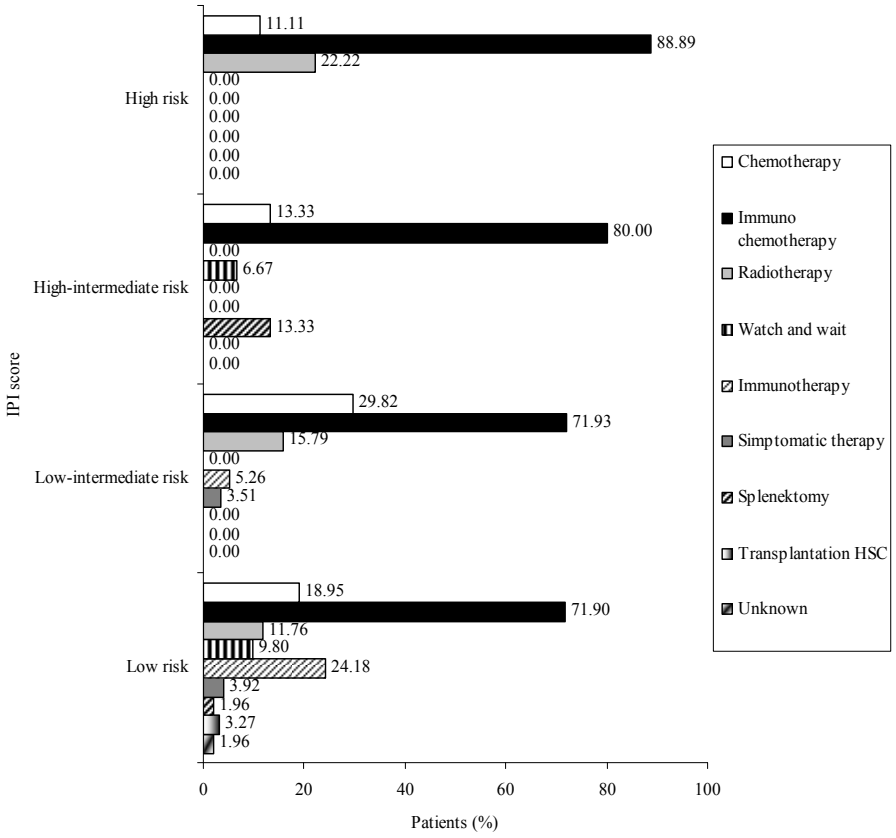

Fig. 3 – The distribution of therapy based on International Prognostic Index (IPI) score.

cells with the translocation t (14; 18) [13]. The hypothesis is that this early formed translocation causes difficulties in eradication of the neoplastic clone by chemotherapy because the IgH gene locus (14q32) gets replaced by proto-oncogene BCL2 (18q21).

The disease usually has indolent course, although relapse occurs in most patients after treatment [4]. The application of different therapeutic protocols starting in the 1980s and early 1990s did not have a significant impact on the survival of patients with FL [14]. The introduction of anti-CD20 monoclonal antibody significantly influenced the treatment of these patients [15]. The treatment could be potentially guided by prognostic indices such as the FLIPI and recently introduced FLIPI 2, what is one of the aims of ongoing clinical trials [16].

A study by Anderson et al. [17] showed a different distribution of certain types of non-Hodgkin lymphoma depending on geographic areas. The icidence of follicular lymphoma was higher in North America, London and Cape Town (31% in all cases) compared to other geographic areas (14%). The lowest icidence was recorded in Hong Kong, only 8% [17].

In our research, all the patients diagnosed with FL were, based on the IPI prognostic factors, divided into the following risk groups: 153 (59.53%) of the patients in the low-risk group, 57 (22.18%) in the low-intermediate risk group, 15 (5.84%) in the high-intermediate risk group, 9 (3.50%) patients were placed in the high-risk group, whereas the classification of 23 patients diagnosed with FL remained unknown. Solall-Céligny et al. [4] point out that, based on the IPI prognostic factors, 10–15% of patients could be classified as high-risk patients, which is a higher percentage than the one presented in our study.

The multicentre colaborative group designed the FLIPI prognostic index of follicular lymphoma registered in the period from 1985 and 1992 based on the database of 4167 registered patients. The FLIPI was able to classify patients older and younger than 60 years [4].

The testing of the FLIPI prognostic index was performed on 919 patients who were classified into low-risk, intermediate-risk and high-risk groups. On the basis of this index, 36% of the patients were placed in the low-risk group, 37% in the intermediate-risk group and 27% in the high-risk group. Thus, it was concluded that the FLIPI prognostic index classifies patients with aggressive FL in a better way compared to the IPI [4].

In our research, the patients with FL were, based on the FLIPI prognostic score, placed in the following risk groups: 113 (43.97%) of the patients were placed in the low-risk group, 70 (27.24%) in the intermediate-risk group, 51 (19.84%) in the high-risk group, whereas the classification of 23 (8.95%) of the patients remained unknown. This result indicates a lower percentage of high-risk patients as compared to the work by Solal-Céligny et al. [4] in which, based on the FLIPI prognostic factors, 27% of the patients belong to the high-risk group. As with the IPI prognostic index, most of the patients were placed in the low-risk group, 113 (43.97%), but unlike the IPI prognostic index, a higher percentage of patients, 51 (19.84%) were classified into the high-risk group, *versus* 9 (3.50%) of the patients according to the IPI [18].

Federico et al. [10] designed FLIPI 2 prognostic index. Different risk groups were made up: low-risk group, intermediate-risk group and high-risk group. Progression-free survival for the period of three years was 91%, 69% and 51%, respectively, depending on the risk group. The 3-year overall survival depending on prognostic was 99%, 96% and 84%, respectively.

In our research, bone marrow involvement was present in 83 (32.30%) of the patients with FL, which is a small percentage compared to the work of Federico et al. [19] who discuss about a larger proportion of bone marrow involvement in 52% of the patients and emphasize its association with poor survival. On the basis of the FLIPI 2, 48 (18.68%) of the patients were placed in the low-risk group, 145 (56.42%) in the intermediate-risk group and 41 (15.95%) of the patients with FL were placed in the high-risk group. Classification into prognostic groups remained unknown for 23 (8.95%) of the patients. Most of them, 145 (56.42%), were in the intermediate-risk group. Our results are in concordance with the work of Federico et al. [10] who proved that the application of the FLIPI 2 prognostic index contributed to the classification of 20% of the patients into the high-risk group.

The application of prognostic indices could be important for the timely treatment of patients diagnosed with follicular lymphoma and the proper selection of therapy [20]. Friedberg et al. [21] investigated the initial therapy in newly-diagnosed FL during the period from 2004 to 2007. In their work observation was performed in 17.7% of the patients; rituximab monotherapy in 13.9% of the patients; clinical trials in 6.1% patients; radiation therapy in 5.6% of the patients, only chemotherapy in 3.2% of the patients, chemotherapy with rituximab in 51.9% of the patients.

The literature shows that about 20% of patients with FL are characterized by localized disease with no bulky tumors. In case of these patients, application of radiotherapy as the target therapy contributes to a complete remission in 95% of them and to a 10-year survival in about 50% of them [22]. The probability of cure is very small and most patients relapse [22]. In our research, radiation therapy was administered in the treatment of 31 (12.06%) of the patients with FL, which is a smaller percentage compared to the previously mentioned literature data [22]. Radiation therapy was administered in the treatment of the patients with FL in all the prognostic groups based on the IPI, FLIPI and FLIPI 2 and the majority of the patients, 18 (11.76%) of them, which were treated with radiation therapy, were from the low-risk group based on the IPI prognostic index. The Watch and Wait strategy is applied if there is the lack of large tumor masses, the absence of B symptoms, tumor masses smaller than 7 cm in diameter, less than 3 nodules larger than 3 cm, no compressed organs or effusion, normal LDH and B2M. The Watch and Wait strategy was applied in the treatment of patients with follicular lymphoma belonging to the low-risk group and the high-intermediate group (IPI), the low-risk and the high-risk group (FLIPI), the low-risk and the intermediate-risk group (FLIPI 2), whereas the majority of patients, 15 (13.27%), were from the low-risk group based on the FLIPI index.

There is no universal first-line treatment for FL [20]. Until now, the treatment has included: alkylating agents (cyclophosphamide, chlorambucil), purine analogues (fludarabine), combination chemotherapy (CVP –cyclophoshamide, vincristine and prednisone, CHOP – cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine) and prednisolone or FND – fludarabine, mitoxantrone, dexamethasone) and intensive chemotherapy with auto/allo transplantation of bone marrow or peripheral blood [21]. It is likely that early treatment with immunochemotherapy in individual patients encourages the delay of disease progression [15]. In our research, chemotherapy was applied in the treatment of the patients with FL in all the prognostic groups based on the IPI, FLIPI and FLIPI 2 indices, mostly in the patients belonging to the intermediate-risk group, 31 (21.38%), based on the FLIPI 2 prognostic index. Immunochemotherapy was most commonly used, and it was applied in 175 (68.09%) of the patients. Immunochemotherapy was applied in all prognostic groups of the IPI, FLIPI and FLIPI 2 index and the majority of patients, 110 (71.90%) were from the low-risk group based on the IPI index. Immunotherapy was applied in the low-risk and the low-intermediate risk group based on the IPI index, as well as in all the groups of other indices, the FLIPI and the FLIPI 2. Most of the patients, 37 (24.18%), were from the low-risk group based on the IPI index. Splenectomy was performed in 5 (1.95%) of the patients with FL. Hematopoietic stem cell transplantation was applied in 5 (1.95%) of the patients with FL. Coiffier [15] emphasizes that FLIPI prognostic factors do not identify patients with FL in whom the delay of treatment, the Watch and Wait strategy, stands for the best form of treatment. In addition, the aforementioned author points out that FLIPI prognostic index does not identify patients with poor prognosis who require intensive therapy [15]. These patients could have large tumor mass and high LDH values but belong to the low-risk group based on FLIPI. Therefore, some trials use the *Groupe d'Etude des Lymphomes Folliculaires* (GELF) criteria associated with large tumor mass (involvement of 3 or more regional lymph nodes, the presence of nodal or extranodal tumor mass greater than 7 cm, B symptomatology, splenomegaly, pleural effusion or ascites, cytopenia and leukemic phase, ECOG greater than 1, serum LDH or B2M above normal values) [23].

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Conclusion

The application of the IPI, FLIPI 1 and 2 contribute to the classification of a large number of patients in the clinical stage II–IV into risk groups, which potentially could be of help for treatment decision.

Immunochemotherapy was applied in all the clinical stages and all the prognostic groups

R E F E R E N C E S

1. 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(11): 3909−18.
2. *Dreyling M, Ghielmini M, Marcus R, Salles G, Vitolo U*. ESMO Guidelines Working Group. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Ann Oncol 2011; 22(Suppl 6): 59−63.
3. *Agarwal AM, Agarwal N, Glenn MJ, Lim MS*. Blastic Transformation of Low-Grade Follicular Lymphoma. J Clin Oncol 2007; 25(16): 2326−8.
4. *Solal-Céligny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez* R. Follicular Lymphoma International Prognostic Index. Blood 2004; 104(5): 1258−65.
5. *Sehn LH*. Optimal use of prognostic factors in non Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program. 2006: 295−302.
6. *Federico M, Vitolo U, Zinzani PL, Chisesi T, Clò V, Bellesi G*, et al. Prognosis of follicular lymphoma: a predictive model based on a retrospective analysis of 987 cases. Blood 2000; 95(3): 783−9.
7. *Kersten MJ, Jong Dd, Raemaekers JM, Kluin PM, Hagenbeek A*. Beyond the International Prognostic Index: New prognostic factors in follicular lymphoma and diffuse large-cell lymphomaA meeting report of the Second International Lunenburg Lymphoma Workshop. Hematol J 2004; 5(3): 202−8.
8. *Dave SS, Wright G, Tan B, Rosenwald A, Gascoyne RD, Chan WC*, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. N Engl J Med 2004; 351(21): 2159−69.
9. *Glas AM, Kersten MJ, Delahaye LJ, Witteveen AT, Kibbelaar RE, Velds A*. Gene expression profiling in follicular lymphoma to assess clinical aggressiveness and to guide the choice of treatment. Blood 2005; 105(1): 301−7.
10. *Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U, et al.* Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol 2009; 27(27): 4555−62.
11. *Anđelić B, Mihaljević B*. Prognostic factors in follicular lymphoma. Acta Clin 2010; 10(3): 49−62.
12. *Katzenberger T, Ott G, Klein T, Kalla J, Muller-Hermelinek HK, Ott MM*. Cytogenetic alterations affecting bcl6 are predominantly found in follicular lymphomas grade 3B with a diffuse large B cell component. Am J Pathol 2004; 165(2): 481−90.
13. *Stamatopoulos K, Kosmas C, Belessi C, Stavroyianni N, Kyriazopoulos P, Papadaki T*. Molecular insights into the immunopathogenesis of follicular lymphoma. Immunol Today 2000; 21(6): 298−305.
14. *Gilles AS*. Clinical features, prognosis and treatment of follicular lymphoma. ASH Education Book 2007; 216−25.
15. *Coiffier B*. First line treatment of follicilar lymphoma in the era of monoclonal antibodies. Clin Adv Hematol Ocol 2005; 3(6): 484−91.

16. *Salles G, Seymour JF, Offner F, López-Guillermo A, Belada D, Xerri L*, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011; 377(9759): 42−51.
17. *Anderson JR, Armitage JO, Weisenburger DD*. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 1998; 9(7): 717−20.
18. *Perea G, Altés A, Montoto S, López-Guillermo A, Domingo-Doménech E, Fernández-Sevilla A*. Prognostic indexes in follicular lymphoma: a comparison of different prognostic systems. Ann Oncol 2005; 16(9): 1508−13.
19. *Federico M, Vitolo U, Zinzani PL, Chisesi T, Clò V, Bellesi G*, et al. Prognosis of follicular lymphoma: a predictive model based on a retrospective analysis of 987 cases. Intergruppo Italiano Linfomi. Blood 2000; 95(3): 783−9.
20. *Horning SJ*. Natural history of and therapy for the indolent non-Hodgkin's lymphomas. Semin Oncol 1993; 20(5 Suppl 5): 75−88.
21. *Friedberg JW, Taylor MD, Cerhan JR, Flowers CR, Dillon H, Farber CM,* et al. Follicular lymphoma in the United States: first report on the national LymphoCare study. J Clin Oncol 2009; 27(8): 1202−8.
22. *Mac Manus MP, Hoppe RT*. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol 1996; 14(4): 1282−90.
23. *Rosenbaum CA*. Evolving paradigms in follicular lymphoma: Re-evaluating prognostic factors and challenig treatments dogmas. Molec Oncol Rep 2007; 1(2):33-8.

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