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MALIGNANT LYMPHOMAS IN SARAJEVO REGION ACCORDING TO W.H.O. CLASSIFICATION OF LYMPHOID NEOPLASMS

**Periods 1989-1991 (before the aggression), 1992-1995 and 1997-1999
(after the aggression)**

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Abstract

Our comparative study concerning malignant lymphoma in Sarajevo Region according to W.H.O. Classification from 1997 in periods 1989-1991 (before the aggression) and 1997-1999 (after the aggression). We expected increased incidence as well as better patient's survival after the war due to better diagnostic and therapeutic procedures.

The study included reclassification of all cases in period 1989-1991 and their immunohistochemical study. We compared results and determined distribution and relative frequency of each subtype. The prognostic indices and parameters are also included in our study.

Keywords: *malignant lymphoma, Hodgkin's disease (HD), Non-Hodgkin lym-phoma (NHL), W.H.O. Classification, Sarajevo Region.*



Introduction

WHO classification of hematological neoplasms is represented by a list of disease entities and its variants, opened for inclusion of new entities, updating of diagnostic criteria and changes of nomenclature. Clinical relevance of the proposed entities has been evaluated by the clinicians, members of Clinical Advisory Committee. The presentation of W.H.O. Classification in our review is limited to lymphoid neoplasms.

In Federation of Bosnia and Herzegovina lymphoid and myeloid neoplasms are fifth leading malignancy. (6.1% of all malignant neoplasms in 2001).

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Hypothesis

We expected increased incidence of malignant lymphoma after the war and longer patient's survival due to diagnostic and therapeutic improvements.

Aims

Reclassification of all malignant lymphoma cases in period 1989-1991 according to W.H.O. Classification of Lymphoid Neoplasms from 1997

Compare results in these two periods (1989-1991 and 1997-1999)

Determine the distribution and relative frequency of each subtype of malignant lymphoma

Make prognostic indices (sex and age distribution, sites of their presentation)

Make prognostic parameters (survival index, Ann Arbor staging, number and sites of extranodal localization and high diameter of tumor)

Materials and methods

Material

The pathology files of Sarajevo Clinical and University Center consist of 178 cases of paraffin tissue and clinical findings for all cases; There were 68 cases for period 1989-1991 and 104 for period 1997-1999. Six (6) cases were not malignant lymphoma. The specimens from all the cases were fixed in 10% unbuffered formalin, processed by routine methods, and embedded in paraffin. Sections of 4- μ m thickness were used for hematoxylin and eosin, histochemical, immunohistochemical stains and in situ hybridization. Reticulin staining was performed in cases with histologic and immunologic features of angioimmunoblastic T-cell lymphoma.

Methods

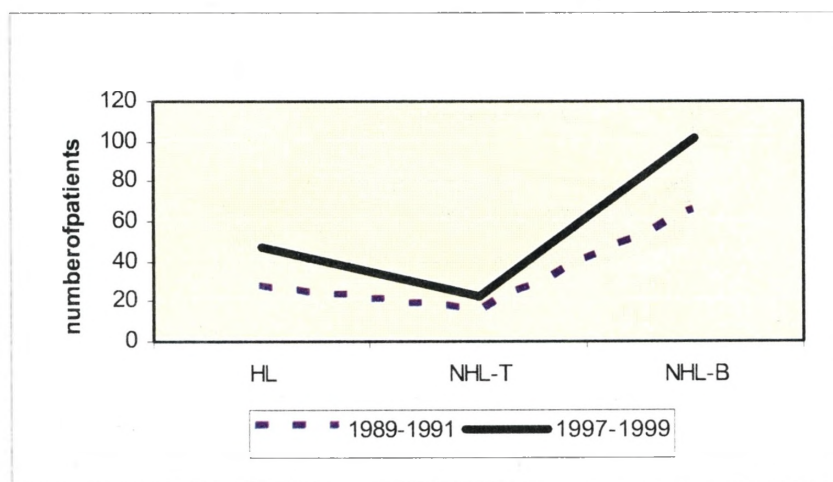
Light microscopy immunohistochemistry.

Immunohistochemical study was performed using the labeled streptavidin-biotin peroxidase method (LSAB kit; Dako Corporation, Carpinteria, CA) and an antigen retrieval technique was applied when needed for each individual antibody. The antibodies we used were bcl-2, CD3, CD5, CD20 (L26), CD68 (PG-M1), wide-spectrum cytokeratin, kappa and lambda light chains, myeloperoxidase, epithelial membrane

antigen (EMA) (Dako Corporation), CD10, CD16, CD56, CD57, cyclin D1 (Novocastra, New Castleupon-Tyne, UK), CD43, CD45, CD45RO (UCHL-1), granzyme B (Monosan, Monosan/Caltag, San Francisco, CA) and T-cell intracellular antigen-1 (TIA-1) (Immunotech, Coulter/Immunotech, Westbrook, ME). All non-B-cell lineage specimens of NHL were stained further with CD30 to exclude anaplastic large cell lymphoma. All T-cell lineage specimens of NHL were stained with CD56 to exclude T-/NK cell lymphoma.

Results

A total of 244 cases were found in computer database at Clinic for Hematology. We analyzed 172 cases. Thirteen cases (5.33%) were not malignant lymphomas than reactive and inflammatory conditions. Twenty three (9.43%) of all were treated out of Sarajevo region. Thirty six (14%) paraffin tissues were destroyed during the war. There were 104 cases for period 1997-1999 and 68 for period 1989-1991. (See graph 2). In period 1989-1991 among 68 cases 21 (30.9%) was HL and 47 (69.1%) were NHL. Among the NHL cases, 64 (62%) were of B-cell lineage and 9 (13%) were of T-cell lineage. In period 1997-1999 among 104 cases HL were 26 (25%) and NHL 78 (75%). (See graph 1). Among the 78 NHL cases, 38 (56%) were of B-cell lineage and 9 (13%) were of T-cell lineage. The ratio between NHL and HL in period 1997-1999 were 4:1 and NHL-B:NHL-T=4:1. These results confirm statistical data in literature. In period 1989-1991 the ratios were NHL:HL=2:1 and NHL-B:NHL-T=4:1.



Graph 1: Ratio between NHL (including NHL-B cell and NHL-T cell) and HL in periods 1989-1991 and 1997-1999

Linear correlation demonstrated no significant difference in distribution of malignant lymphoma in pre- and postwar period related to date in literature.

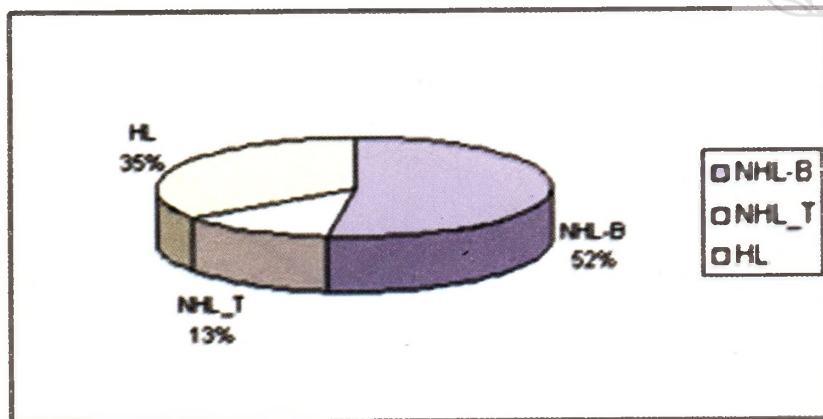
Table 1: *Linear correlation between NHL (including NHL-B cell and NHL-T cell) and HL in periods 1989-1991 and 1997-1999*

Periods	1989-1991	1997-1999	Data in literature
Linear correlation (r)	0.799	0.759	0.767

According to t – test, there is no statistical evidence that histological subtypes differed significantly in two periods (1989-1991, 1997-1999 respectively) except NHL-B lymphoma ($t = 1.966$; $p < 0.05$). The same test was performed for malignant lymphoma classified according to clinical features. It showed only significant difference for indolent lymphoma ($t = 1.946$; $p < 0.10$).

Features of malignant lymphomas in period 1989-1991 ***Prognostic parameters***

Of the 68 cases, 21 (30.8%) were HL, 47 (69.1%) were NHL. NHL-B cell were 38 (56%) and NHL-T cell were 9 (13%) cases. These results are not fully relevant due to missing of paraffin tissue. The ratio between NHL:HL was 2:1 and NHL-B cell : NHL-T cell was 4:1. (See graph 2)



Graph 2. *Distribution of malignant lymphomas for period 1989-1991*

Table 2. Prognostic parameters for period 1989-1991

DIAGNOSIS	No	%	M	F	Age, mean (yrs)	Average of survival
B-cell chronic lymphocytic leukemia	8	11,7	6	2	61	41
MALT- extranodal B cell lymphoma	6	8,8	2	4	54	46
Follicular lymphoma	4	5,8	3	1	54	48
Mantle cell lymphoma	4	5,8	2	2	55	52
Diffuse large B-cell lymphoma	13	19,1	8	5	54	66
Precursor T-lymphoblastic lymphoma/ leukemia	1	1,5	1	0	55	12
Enteropathy-type T-cell lymphoma	1	1,5	0	1	58	56
Peripheral T-cell lymphoma, NOS	4	5,9	3	1	55	39
Anaplastic large cell lymphoma	3	4,4	2	1	24	114
Nodular lymphocyte predominance/Hodgkin lymphoma	2	2,9	1	1	37	137
Nodular sclerosis/Hodgkin lymphoma	10	13,2	6	4	42	112
Mixed cellularity/Hodgkin lymphoma	9	13,2	6	3	40	104
Nodal marginal zone B cell lymphoma	3	4,4	2	1	64	32
Total	68		42	26		

The most common NHL subtypes in period 1989-1991 include Diffuse Large B-cell lymphoma 13 (19.1%), chronic lymphocytic leukemia/small lymphocytic lymphoma 8 (11.8%), MALT-extranodal B cell lymphoma 6 (8.8%) and Peripheral T-cell lymphoma 4 (5.9%). Among HL subtypes the most common are: Nodular sclerosis 10 (13.2%) and mixed cellularity 9 (13.2%). The uncommon types include Precursor T-cell lymphocyte leukemia and Enteropathy-type T lymphoma 1 (1.5%). (See table 2)

The best prognosis with the mean survival 52-114 months include: DLBCL, MALT and ALCL. The worst prognosis was lined with following diagnosis: Precursor T lymphoblastic lymphoma, PTCL and NMZBCL (the mean survival < 40 months).

In period 1989-1991 men form 42 (62%) of all cases while women form 26 (38%) of all cases. Age distributions for HL show

bimodal curve with two peaks, first in period 31 to 40 year, second from 51 to 60 years with levels till 20 years. We noticed increased NHL in older population. (See table 2)

The most common NHL was presented by enlargement of the following lymph node: neck 44 (63%), sternoclavicular 24 (34%), axillary 1 (27%), mediastinal 10 (14%), retroperitoneal 12 (17%) and hilar 7 (10%). Other symptoms include: B symptoms 25 (36%), hepatomegaly 22 (31%) and splenomegaly 17 (24%).

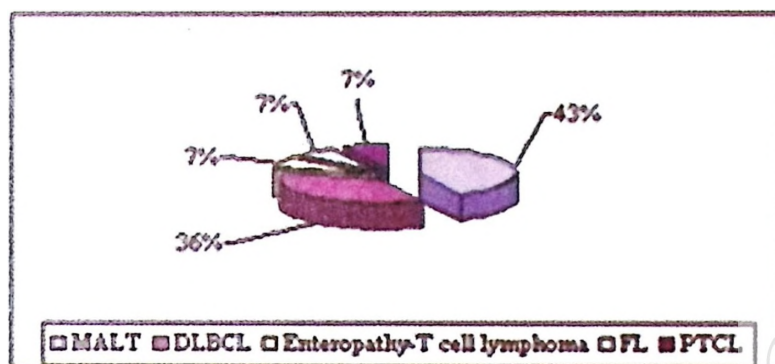
The most common HL presentation was presented by enlargement of the following lymph nodes: neck 18 (86%), supraclavicular 9 (42%), mediastinal and axillary 4 (19%), retroperitoneal 3 (14%) and hilar 2 (9.5%). Other symptoms include: B-symptoms 11 (52%), hepatomegaly 7 (30%) and splenomegaly 5 (23%).

Table 3. Relative frequency, staging, number and size of nodal involvement of NHL and HL according W.H.O. classification for period 1989-1991

Malignant lymphomas for period 1989-1991				
Diagnosis	Count	Stage	No of nodal sites	Size
B-cell chronic lymphocytic leukemia	8	Ila, IIIa (2), IIIb (3), Ivb	5(1), 3(2), 3(2), 4(3)	7.8
MALT- extranodal B cell lymphoma	6	Ia (4), Ie, Iia, IVa,	1(5), 2(1), 3(1)	6.3
Follicular lymphoma	4	Ia, Iia, IIIa, IIIb	1(1), 2(2), 5(1)	5
Mantle cell lymphoma	4	Ila, IIIa, Iva (2)	2(2), 5(2)	3.3
Diffuse large B-cell lymphoma	13	Ia (3), Id, Ie, Iia, IIb (3), IIIa, IIIb (2)	1(7), 2(3), 3(2), 5(1)	5.1
Precursor T-lymphoblastic lymphoma/leukemia	1	IIIa	3(1)	4
Enteropathy-type T-cell lymphoma	1	IIIa	5	6
Peripheral T-cell lymphoma, NOS	4	Ia, Iib, IIIa, IIIb	1(1), 4(2), 5(1)	5.5
Anaplastic large cell lymphoma T/null cell, primary systemic type	3	Ia, Ib, Iib	1(2), 2(1)	3.7
Nodular lymphocyte predominance Hodgkin lymphoma	2	Iib, IIIb	2(1), 3(1)	4
Nodular sclerosis Hodgkin lymphomasis (Grades 1 and 2)	10	Iia (4), Iib (3), IVa, Ivb (2)	2(4), 3(3), 4(2), 5(1)	5.2
Mixed cellularity Hodgkin lymphoma	9	Iia (3), Iib(2), IIIa (3), IIIb	2(3), 3(2), 4(4)	3.7
Nodal marginal zone B cell lymphoma	3	IIb, IIIb, Ie	1(1), 3(2), 4(2)	3
Total	68			

***Distribution between extranodal and nodal lymphomas for period
1989-1991***

There are 14 (20.6%) extranodal lymphoma in this period. The ratio between nodal and extranodal lymphoma was 4:1 (80%:20%). The extranodal lymphoma include the following subtypes of malignant lymphomas: MALT- extranodal B cell lymphoma (\pm monocytoid B cells) 6 (43%), diffuse large B-cell lymphoma 5 (36%), follicular lymphoma 1 (7%), peripheral T-cell lymphoma 1 (7%), enteropathy T-cell lymphoma 1 (7%). (See graphs 3 and table 4.)



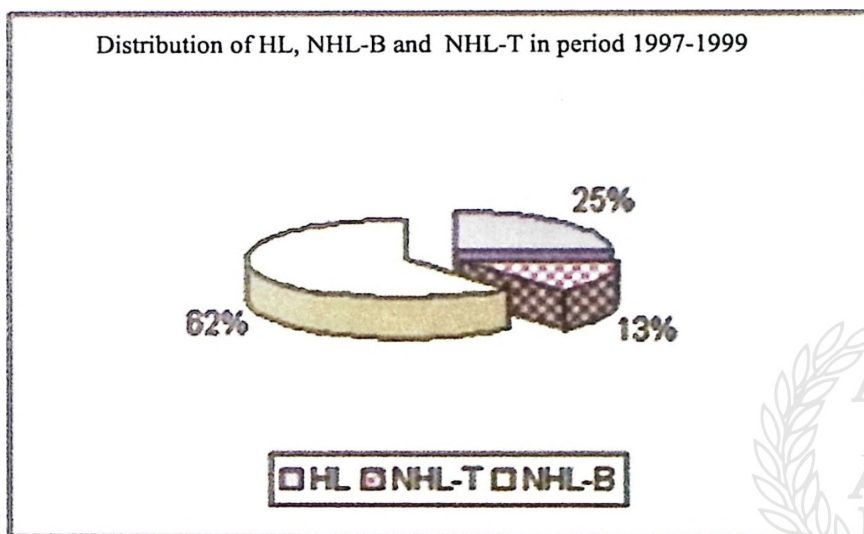
Graph 3: *Frequency of extranodal lymphomas in period 1989-1991*

Table 4. *Extranodal presentation of NHL in period 1989-1991*

Malignant lymphoma	Thyroid Gland	Stomach	Skin	Colon	Small Intestine	Eye	Naso-pharynx	Extranodal
MALT- extranodal B cell lymphoma		6						6
Diffuse large B-cell lymphoma			2	1		1	1	5
Enteropathy-T cell lymphoma					1			1
Follicular lymphoma					1			1
Peripheral T cell lymphoma					1			1
Total		6	2	1	3	1	1	14

Features of malignant lymphomas in period 1997-1999 *Prognostic parameters*

In period 1997-1999 among 104 cases, HL was 26 (25%) and NHL 78 (75%). (See tables 5 and graph 4). Among the 78 NHL cases, 38 (56%) were of B-cell lineage and 9 (13%) were of T-cell lineage (Graph 4). The ratio between NHL and HL in period 1997-1999 was 4:1 and NHL-B:NHL-T=4:1. These results confirm statistical data in literature.



Graph 4: *The ratio between HL, NHL-B and NHL-T cell lymphoma in period 1997-1999*

The most common NHL types in postwar period include diffuse large B-cell lymphoma 24 (23.1%), Extranodal Marginal B-cell Lymphoma 9 (8.6%) and Mantle cell Lymphoma 8 (7.7%). The most common subtypes of Hodgkin lymphoma include Nodular sclerosis 12 (11.5%) and Mixed cellularity 12 (11.5%). The most uncommon NHL types include: Lymphoplasmacytic lymphoma, Hairy cell leukemia, Nodal marginal zone B cell lymphoma, Anaplastic large cell lymphoma, T/null cell, primary cutaneous type; Anaplastic large cell lymphoma, T/null cell, primary systemic type and Nodular lymphocyte predominance Hodgkin lymphoma 1 (0.96%). (See table 5)

Table 5: Prognostic parameters for period 1997-1999

Malignant lymphomas for period 1997-1999						
Diagnosis	No	%	M	F	Age, mean (yrs)	Average of survival*
Precursor B-lymphoblastic leukemia/lymphoma)	2	1,92	2	0	11	27
B-cell chronic lymphocytic leukemia/small lymphocytic leukemia	3	2,9	1	2	57	14
Lymphoplasmacytic lymphoma	1	0,96	0	1	63	18
MALT- extranodal B cell lymphoma	9	8,6	3	6	62	38
Hairy cell leukemia	1	0,9	0	1	43	30
Follicular lymphoma	4	3,8	2	2	55	30
Mantle cell lymphoma	8	7,7	3	5	57	37
Diffuse large B-cell lymphoma	24	23,1	10	14	49	33
Burkitt lymphoma/Burkitt cell leukemia	5	4,8	4	1	40	29
Precursor T-lymphoblastic lymphoma/ leukemia	4	3,8	3	1	49	6
T-cell prolymphocytic leukemia	2	1,9	2	0	75	8
Anaplastic large cell lymphoma, T/null cell, primary cutaneous type	1	0,9	1	0	66	8
Peripheral T-cell lymphoma, NOS	4	3,8	2	2	41	11
Angioimmunoblastic T-cell lymphoma	2	1,9	0	2	48	18
Anaplastic large cell lymphoma, T/null cell, primary systemic type	1	0,9	0	1	27	4
Nodular lymphocyte predominance/Hodgkin lymphoma	2	1,9	1	1	29	2
Nodular sclerosis/Hodgkin lymphoma (Grades 1 and 2)	12	11,5	5	7	34	42
Mixed cellularity/Hodgkin lymphoma	12	11,5	9	3	31	40
TCRBCL - T cell rich B cell lymphoma	6	5,8	3	3	39	18
Nodal marginal zone B cell lymphoma	1	0,9	1	0	45	36
Total	104		52	52		

* For some subtypes it is still too early to bring any conclusions regarding survival in period 1997-1999.

There is approximately same sex distribution of malignant lymphomas for period 1997-1999.

The most common NHL subtypes were presented by enlargement of the following lymph nodes: neck 59 (57%), sternoclavicular 30 (29%), mediastinal and retroperitoneal (16%), hilar 16 (15%), axillary 11 (10%). Other symptoms include: B-symptoms 45 (43%), hepatomegaly 19 (18%) and splenomegaly 26 (25%).

The most common HL presentation were presented by enlargement of the following lymph nodes: neck 18 (69%), supraclavicular 13 (50%), hilar 9 (34.6%), axillary, mediastinal and retroperitoneal 5 (19.2%). Other symptoms include: B-symptoms 13 (50%), hepatomegaly 7 (27%) and splenomegaly 11 (42.3%).

Table 6: *Relative frequency, staging, number and size of nodal involvement of NHL and HL according W.H.O. classification for period 1997-1999*

Malignant lymphomas for period 1997-1999				
Diagnosis	No	Stage	No of nodal sites	Size
Precursor B-lymphoblastic leukemia/lymphoma	2	IVb	5(2)	3
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma	3	IIIa, IVa, IVb	3(1), 1(1), 7-1	3
Lymphoplasmacytic lymphoma	1	IVb	1	
MALT- extranodal B cell lymphoma	9	Ia(4), Id, IIa(2), IVa	1(6), 2(2)	4.75
Hairy cell leukemia	1	IVb	1(1)	4
Follicular lymphoma	4	IIa(2), IIIa, IIIb	1(3), 2(1)	3
Mantle cell lymphoma	8	Ia(3), Ib; IIb, IIIa, IIIb, IIa	1(7), 2(1)	3.8
Diffuse large B-cell lymphoma	24	I(3), Ia(2), IIa(6), IVa(2), IVb, IVd, IIIb(5); IIb(2), Ib	2(5), 3(9), 1(10)	4.7
Burkitt lymphoma/Burkitt cell leukemia	5	IIa(2), IIIa(2), IVb	1(4), 7(1)	4.3
Precursor T-lymphoblastic lymphoma/leukemia	4	IIb(2), IIb, IVb,	1(1), 2(2), 6(1)	4.7
T-cell prolymphocytic leukemia	2	IIIb, IVa	1(1), 5(1)	15
Anaplastic large cell lymphoma, T/null cell, primary cutaneous type	1	Ivb	7(1)	3
Peripheral T-cell lymphoma, NOS	4	Ia(2), IIa, IIIb, IVb,	1(1), 2(3), 6(1)	7
Angioimmunoblastic T-cell lymphoma	2	IIIb(2)	1(1), 2(1)	2
Anaplastic large cell lymphoma, T/null cell, primary systemic type	1	Ivb	7(1)	7
Nodular lymphocyte predominance/Hodgkin lymphoma	2	Ivb	1(1)	2
Nodular sclerosis/Hodgkin lymphoma (Grades 1 and 2)	12	Ia(2), IIa(3), IIb(3), IIIa, IIIb, Ivb(2),	2(8), 3(2), 4-1, 5(1)	3.5
Mixed cellularity/Hodgkin lymphoma	12	Ia(2), IIa(2), IIb(2), IIIa, IIIb, IVa, IVb(4)	1(4), 2(4), 6-2	2.4
TCRBCL - T cell rich B cell lymphoma	6	Ib, IIb(2), IIIb(2), IVb	1(6)	4
Nodal marginal zone B cell lymphoma	1	Ivb	6	3
Total	104			

***Distribution between extranodal and nodal lymphomas for period
1997-1999***

The ratio between nodal and extranodal lymphomas for period 1997-1999: 19 (18.3%) patients with extranodal and 85 (81.7%) with nodal lymphomas. The extranodal presentation includes following subtypes of malignant lymphomas: MALT-extranodal B cell lymphoma (\pm monocytoid B cells) 9 (47%), diffuse large B-cell lymphoma 5 (26%), Burkitt lymphoma/Burkitt-cell leukemia 2 (11%), precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia) 1 (5%), T-cell prolymphocytic leukemia 2 (11%).

Graph 5: *Frequency of extranodal lymphomas in period 1997-1999*

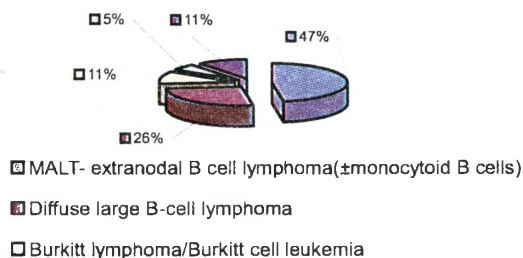


Table 7: *Extranodal presentation of NHL in period 1997-1999*

Malignant lymphoma	Thyroid gland	Stomach	Skin	Parathyroid gland	Colon	Small Intestine	Extranodal
MALT-extranodal B cell lymphoma	1	5		1	1	1	9
Diffuse large B-cell lymphoma	2	1	1			1	5
Burkitt lymphoma			1		1		2
Precursor B-lymphoblastic leukemia			1				1
T-cell prolymphocytic leukemia		1			1		2
Total	3	7	3	1	3	2	19

Conclusions

- All malignant lymphomas from period 1989-1991 were reclassified according to W.H.O. Classification of Lymphoid Neoplasms from 1997.
- There is no significant difference in frequency of HL, NHL-B and NHL-T lymphoma in both periods.
- There is no significant difference in diagnosis frequency in both periods compared with data in literature.
- Immunohistochemical study was performed for all cases from period 1989-1991.
- The ratio between NHL and HL was 2:1 and 4:1 (1989-1991 and 1997-1999 periods, respectively). The ratio between NHL-B and NHL-T was 4:1 in both periods.
- According to t-test, there is no statistical evidence that histological subtypes differed significantly in two periods (1989-1991 and 1997-1999) except NHL-B lymphoma ($t=1.966$; $p < 0.05$). The same test was performed for malignant lymphoma classified according to their clinical features. It showed only significant difference for indolent lymphoma ($t=1.946$; $p < 0.10$).
- The most common NHL lymphomas in period 1989-1991 include: Diffuse Large B-cell Lymphoma 13 (19%), chronic lymphocytic leukemia/small lymphocytic lymphoma 8 (11.8%) and MALT-extranodal B-cell Lymphoma 8 (8.8%). The most common NHL lymphomas in period 1997-1999 include Diffuse Large B-cell Lymphoma 24 (23%), MALT-extranodal B-cell Lymphoma 9 (8.6%) and Mantle cell Lymphoma 8 (7.7%). Diffuse Large B-cell Lymphoma is the most common type in both periods with higher ratio in period 1997-1999 (23%).
- Nodular sclerosis and mixed cellularity were the most common subtypes of HL in both periods (13% and 11.5%, respectively).
- Decreased number of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma was found in period 1997-1999 (11.7% and 2.8%, respectively).
- Increased number of Burkitt lymphoma/Burkitt cell leukemia was found in postwar period (5 cases, 4.8% of all malignant lymphomas).
- A higher frequency of nodal lymphoma in both periods (80-82%). The ratios between nodal and extranodal lymphoma were 1:4.8 and 1:4 for periods 1989-1991 and 1997-1999, respectively. According to data in literature the frequency of extranodal lymphoma should be at least 40%. (Significance $t = 4.588$ for period 1997 – 1999 and $t' = 3.841$ for period 1989-1991).

- The most common sites of primary extranodal NHL include gastrointestinal tract (stomach particularly) and skin in both periods. The high seropositive rate for *Helicobacter pylori* may account for the high incidence rate of MALT-extranodal B-cell lymphoma (8.8% and 8.6% respectively).
- A higher ratio of malignant lymphoma was found in women in period 1997-1999 (50%) related to 38% in period 1989-1991. (Chi-square test did not show any significance between genders in both periods).

Apstrakt

Naša studija zasniva se na komparativnoj analizi malignih limfoma u sarajevskoj regiji u vremenskom intervalu od šest godina (tri godine prije agresije [1989-1991] i tri godine poslije agresije [1997-1999]). Polazna teza je uključivala povećanu incidencu malignih limfoma u poslijeratnom periodu ali i bolje preživljavanje pacijenata prevashodno zbog poboljšanih dijagnostičkih i terapijskih procedura.

Svi su limfomi klasificirani prema Klasifikaciji hematoloških neoplazija datoj od strane Svjetske zdravstvene organizacije iz 1997. godine, odnosno izvršena je reklasifikacija malignih limfoma iz prijeratnoga perioda kao i njihova imunohistohemijska analiza. Također je određena distribucija i učestalost svakoga podtipa limfoma, te su izrađeni prognostički indeksi i parametri za svaki podtip.

Ključne riječi: maligni limfomi, Hodgkinova bolest, ne-Hodgkinovi limfomi, Klasifikacija hematoloških neoplazija Svjetske zdravstvene organizacije, Sarajevo.

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