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High Prevalence of Non-Hodgkin's Lymphomas in Polish Population – 1106 New Cases Diagnosed according to WHO Classification in Only One District*

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The authors present the true incidence of non-Hodgkin's lymphomas basing on the cases diagnosed in Małopolska district during one-year period. The data point to higher lymphoma morbidity than the incidence of them reported by National Cancer Register. Noteworthy is also the distribution of lymphoma types in Polish population being different from that one reported in majority of other Europe countries. The present report indicate the lymphomas become growing diagnostic and clinical challenge, as they place among the most frequent neoplasms in population.

Introduction

The new era for non-Hodgkin's lymphoma (NHL) starts in 1994, when the members of the International Lymphoma Study Group (ILSG) proposed the Revised European American Lymphoma (REAL) classification [6]. Subsequent validation study, carried out by pathologists external to the ILSG and based on a series of cases collected worldwide showed that the ILSG scheme was superior to both the Kiel classification and Working Formulation in terms of interpersonal and intrapersonal reproducibility [1]. More recently, the World Health Organization (WHO) has adopted the REAL classification as a model for the categorization of all the tumors of the lymphoid and hematopoietic tissues [5, 8]. In Poland the initial skepticism (WORKING but not real, REAL but not working) of the 1990-ties was eventually overcome in the 21st century, and virtually all histopathology departments are using REAL/WHO since year 2000 (Table 1).

NHL are frequent diseases, each year over 175,000 new cases are diagnosed worldwide – they account for 4% of neoplasms in US and 3% in Europe, making them the 5th and the 6th most common cancer. Vast majority of neoplasms derived from hematopoietic system are of lymphatic origin (85% in US) with over 50% of NHL (Fig. 1). There is a slight but clear male predominance (M:F=1.1–1.2:1). Lymphomas are more frequent in the elderly, what can be demonstrated for virtually all histopathological subtypes (Fig. 2). NHL incidence and the relative frequency of their subtypes depends on geographical location: they are most frequent in US and Australia (over 18 cases/100,000/year), less frequent in Europe (9–14 cases/100,000/ year) and least frequent in the Far East and Africa (3–5 cases/100,000/year) (Fig. 3). Therefore, the only way to assess the NHL incidence in Poland is to collect Polish data.

Material and Methods

The incidence of NHL (absolute number of cases per year), crude rate (number of cases per 100,000 persons per year) or ASR (age-standardized rate or age-adjusted rate, necessary when comparing several populations that differ with respect to age) are collected and calculated routinely by cancer registries – in Poland: National Cancer Register (Krajowy Rejestr Nowotworów). The registry data are based on formularies completed in the hospitals, and are as good and as complete, as the system efficiency. In NHL the situation is even more complicated, as hospital administration works on

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TABLE 1
World Health Organization Classification of Lymphoid Neoplasms (according to Jaffe ES, Harris NL et al, IARC 2001)

Precursor B-cell neoplasm	Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)
Mature (peripheral) B-cell neoplasms	B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma B-cell prolymphocytic leukemia Lymphoplasmacytic lymphoma Splenic marginal zone B-cell lymphoma (with or without villous lymphocytes) Hairy cell leukemia Plasma cell myeloma/plasmacytoma Extranodal marginal zone B-cell lymphoma (with or without monocytoid B cells) Nodal marginal zone B-cell lymphoma (with or without monocytoid B cells) Follicular lymphoma Mantle cell lymphoma Diffuse large B-cell lymphoma Burkitt lymphoma/Burkitt cell leukemia
Precursor T-cell neoplasm	Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)
Mature (peripheral) T/NK-cell neoplasms	T-cell prolymphocytic leukemia T-cell granular lymphocytic leukemia Aggressive NK-cell leukemia Adult T-cell lymphoma/leukemia (HTLV1) Extranodal NK/T-cell lymphoma, nasal type Enteropathy-type T-cell lymphoma Hepatosplenic gamma delta T-cell lymphoma Subcutaneous panniculitis-like T-cell lymphoma Mycosis fungoides/Sezary syndrome Anaplastic large cell lymphoma, T/null cell, primary cutaneous type Peripheral T-cell lymphoma, not otherwise characterized Angioimmunoblastic T-cell lymphoma Anaplastic large cell lymphoma, T/null cell, primary systemic type

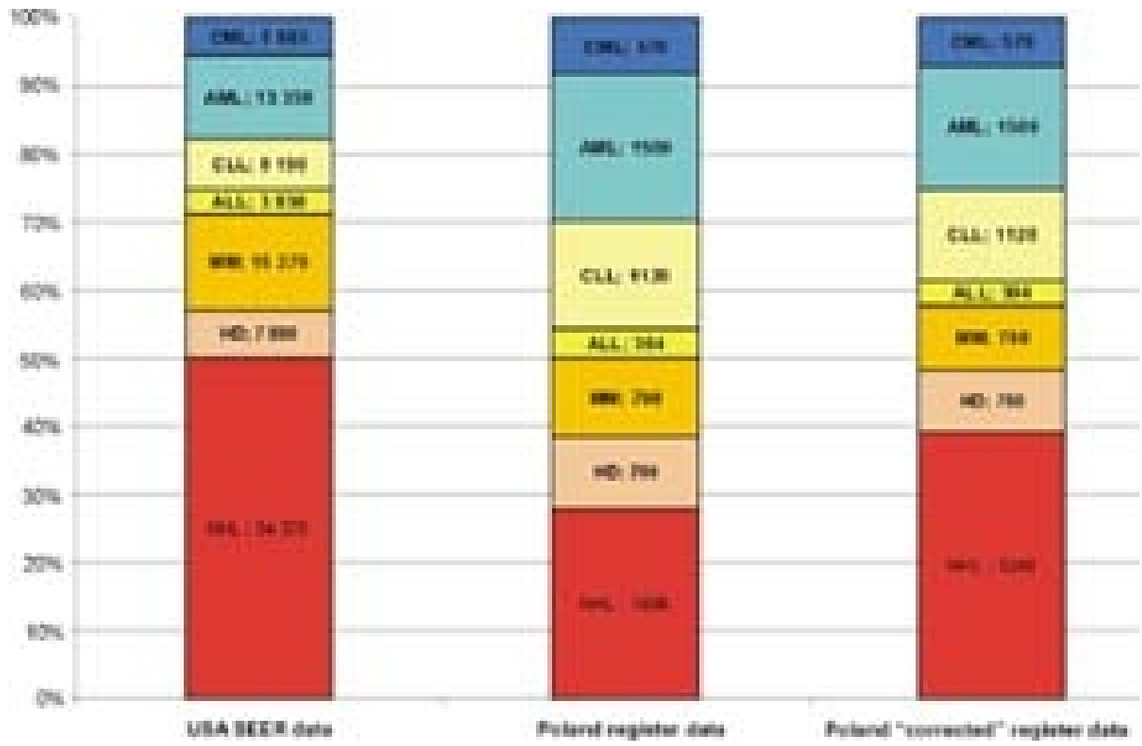

Fig. 1. Comparison of the number of cases and their relative frequency between American SEER data and Polish National Cancer Register before and after correction made by estimations based on Małopolska Lymphoma Register.

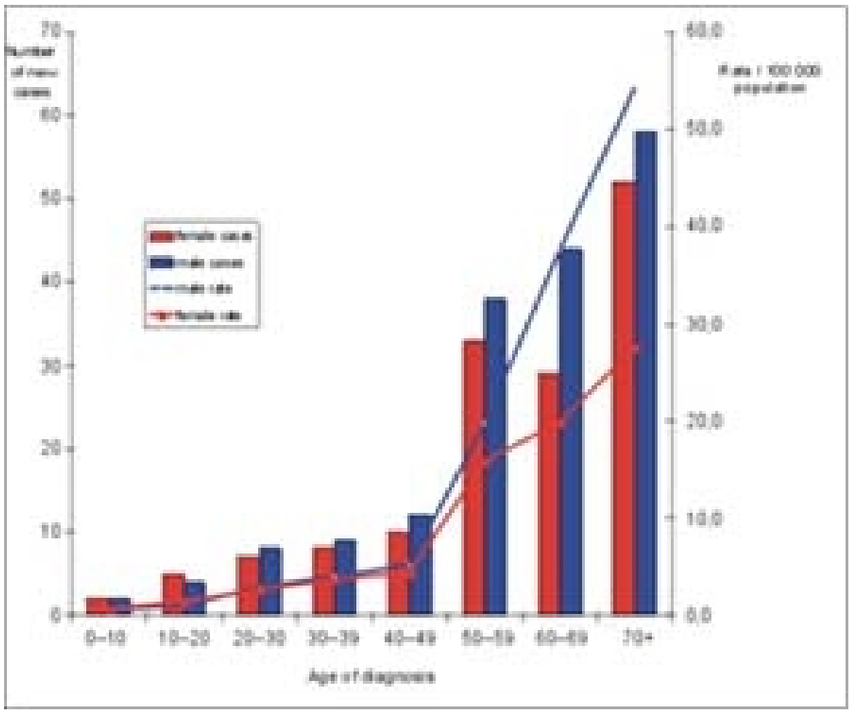

Fig. 2. Number of NHL cases and age specific incidence rates per 100,000 population, by sex, 2005 (data from Małopolska Lymphoma Register).

Fig. 3. Incidence and mortality (crude rates/100,000 population/year) in different countries (according to Cancer Research UK).

ICD-10 (International Classification of Diseases) which is not comparable to REAL/WHO classification. The prevalence of NHL can be defined as the number of persons in a defined population who have been diagnosed and who are still alive at a given point in time, therefore it is necessary to have a complete data on nature of the disease, applied therapies and their efficiency (in terms of overall survival), to calculate it. In this study, for simplicity, we have chosen crude rates per 100,000 population as to express the incidence. Population data were taken from GUS (Główny Urząd Statystyczny) [4].

The latest data released by Polish National Cancer Register are from year 2002 (Table 2). The report is using in ICD-10 classification, required by health officials. This occurred to be a particularly bad solution for NHL: nearly 60% of the cases are put into the category "others-and unclassified". The other problem is the numbers of reported cases: lower than in other Western European countries (Fig. 1). In 2002 there were 1890 new NHL cases in Poland, which – considering the Małopolska population – should mean about 190 new patients in our region, which is less then we treat each year at Department of Hematology (one of the institutions were NHL patients are consulted in our region).

Therefore Polish Lymphoma Research Group, together with Małopolska district consultants in pathology and hematology started the Małopolska Lymphoma Register, using a different approach. Instead of collecting the data through hospitals administration, we addressed the question directly to the pathologists diagnosing lymphomas. All 19 pathology departments in Małopolska and one institution from Cieszyn responded to our questioners – lymphomas occurred to be diagnosed in 9 departments. In the next step, we asked pathol-

TABLE 2
NHL and HD cases diagnosed in Poland in 2002 (National Cancer Register)

ICD–10 code	Description	M	F	M+F	%
C81	Hodgkin's disease	403	356	759	–
C82–88, 96	NHL (altogether)	1034	856	1890	100.0
ghtC82	Lymphoma, non-Hodgkin's – follicular	107	75	182	9.6
C83	Lymphoma, non-Hodgkin's – diffuse	215	165	380	20.1
C84	Lymphoma, peripheral T cell	40	28	68	3.6
C85	Lymphoma, other and undiagnosed	591	503	1094	57.9
C88	Lymphoproliferative diseases	45	64	109	5.8
C96	Other, unspecified	36	21	57	3.0

TABLE 3
Małopolska Lymphoma Register – participating centers, number of cases registered during 12 months

Department of Pathology, CMUJ	167
Center of Oncology	55
Rydygier District Hospital (Kraków)	31
2 District Hospitals in Tarnów	30
Histopathology Lab – Intra (Cieszyn)	21
Other places	15
Institute of Pediatrics	12
Total number of cases	331

ogists to report all cases diagnosed during the last 12 months, between 1st of July 2004 and 30th of June 2005. The data were then centrally reviewed for duplicate cases, and the specimens sent from hospitals outside our region. At the end of that process we were left with 331 cases, later used to calculate the NHL incidence (crude rates) in Małopolska (Table 3). Most of lymphomas were diagnosed either at Department of Pathology, Collegium Medicum, Jagiellonian University or at Histopathology Lab in Center of Oncology. In the next step we collected the available data from those institutions from 3 proceeding years (2001–2004). This gave us additional 775 cases, so eventually there were 1106 lymphomas diagnosed according to REAL/WHO in our database, which was used to calculate the relative frequency of lymphoma subtypes.

Results

Incidence

During a period of 12 months proceeding June 2005, there were at least 331 new NHL cases diagnosed in our region. The Małopolska Lymphoma Register is neither a surrogate to Polish National Cancer Register nor a proper epidemiological survey – the main target was to assess the relative frequency of NHL subtypes in Poland. Therefore, for simplicity reasons, we resigned from checking the home addresses

TABLE 4
Number of new NHL cases and crude rates (per 100,000 population/year) – data from Małopolska Lymphoma Register

	Male cases	Female cases	Male population	Female population	Male crude rate	Female crude rate	M+F crude rate
0–10	2	2	361698	345122	0.6	0.6	0.6
10–20	4	5	382294	363731	1.0	1.4	1.2
20–30	8	7	275063	275063	2.9	2.5	2.7
30–39	9	8	225029	219196	4.0	3.6	3.8
40–49	12	10	230603	229780	5.2	4.4	4.8
50–59	38	33	192334	209212	19.8	15.8	17.7
60–69	46	34	116973	146477	39.3	23.2	30.4
70+	61	52	106500	188644	57.3	27.6	38.3
Total	180	151	1890494	1977225	9.5	7.6	8.6

and registered all the cases treated in our region (determined by address of a hospital which sent original specimens). Such an approach on the other hand provides useful data for NFZ (National Health System) allowing for proper finance planning. Population data were taken from GUS report in 2005. The calculated incidence (crude rate/100,000 inhabitants) is 8.6/100 000 inhabitants (9.5 for males and 7.6 for females). Age and sex specific incidence is summarized in Table 4 and Figure 2.

Relative frequency

All 1106 patients registered (diagnosed during the last 4 years, until June 2005) were used to calculate the relative frequency of NHL subtypes. We did not incorporate in our database any patients with Hodgkin's disease (HD) and multiple myeloma (MM). Acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) were registered if their diagnosis was confirmed by histopathology (lymph node sample or trephine biopsy). In our strong belief there is no reason for distinguishing ALL and LBL (they are regarded the same disease entity in WHO and there are no differences in clinical management). If we agree to that, our data would underestimate the frequency of ALL/LBL, as in most of the cases, their diagnosis is based on bone marrow aspiration biopsy and flow cytometry analysis. The situation is not that clear in CLL/SLL. Although identical histology, with bone marrow involvement in most of SLL cases (like in other indolent lymphomas), some clinicians believe that there is a different clinical management of the cases presenting at diagnosis with lymphadenopathy. Registering all cases with histopathological confirmation of CLL/SLL (including the cases diagnosed in trephine biopsies) we overestimated the relative frequency of SLL. On the other hand, there would be an un-

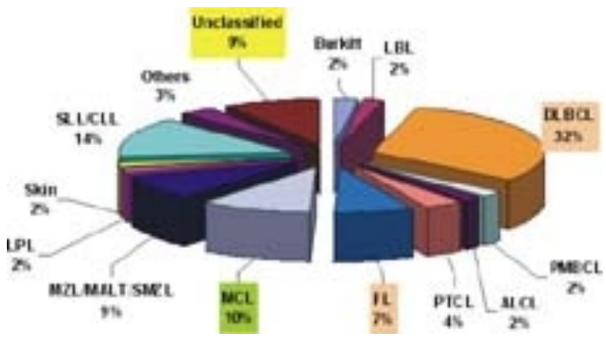

Fig. 4. Relative frequency of NHL (based on 1106 cases diagnosed in Małopolska in 2001–2005).

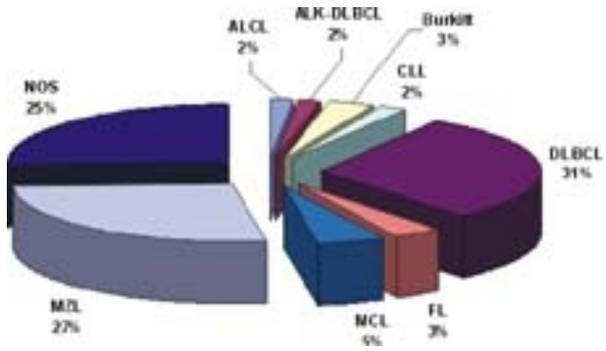

Fig 5. Relative frequency of NHL cases diagnosed in a stomach (based on 61 cases from Dept of Pathomorphology, CMUJ).

TABLE 5
NHL incidence and number of registered cases (data from Polish Cancer Register)

	Males	Females	M+F
Number of new NHL cases/year (Poland)	1034	856	1890
Poland population	18,400,000	19,700,000	38,100,000
Incidence (crude rate/100,000 population/year)	5.6	4.3	4.96
Małopolska population	1,890,494	1,977,225	3,867,719
Estimated number of new NHL cases in Małopolska	106	85	191

TABLE 6
NHL incidence extrapolated for Poland from MLR (Małopolska Lymphoma Register)

	Males	Females	M+F
Number of new NHL cases/year (Małopolska)	180	151	331
Małopolska population	1,890,494	1,977,225	3,867,719
Incidence (crude rate/100,000 population/year)	9.5	7.6	8.6
Poland population	18,400,000	19,700,000	38,100,000
Estimated number of new NHL cases in Poland	1752	1504	3261

TABLE 7
Relative frequency of NHL subtypes (data from Małopolska Lymphoma Register)

	"complete 12 months" data	Dept of Pathomorphology CMUJ (2000–2004)	Center of Oncology (2000–2004)	All cases in database	Relative frequency of NHL subtypes (%)	Incidence (crude rate)/100,000	Estimated number of new cases/year in Poland
LBL	6	11	3	20	1.8	0.15	59
Burkitt	5	19	1	25	2.3	0.19	73
DLBCL	121	189	43	353	31.9	2.73	1037
PMBCL	8	15	0	23	2.1	0.18	68
ALCL	6	14	0	20	1.8	0.15	59
PTCL	8	26	7	41	3.7	0.32	120
SLL/CLL	49	77	24	150	13.6	1.16	441
FL	26	44	17	87	7.9	0.67	256
MCL	32	69	11	112	10.1	0.87	329
MZL/MALT/ SMZL	31	64	4	99	9.0	0.77	291
LPL	8	10	3	21	1.9	0.16	62
skin NHL	7	9	3	19	1.7	0.15	56
Other	7	33	0	40	3.6	0.31	118
Unclassified	17	66	13	96	8.7	0.74	282
Total	331	646	129	1106	100.0	8.55	3249

derestimation of CLL, routinely diagnosed by cytology/flow cytometry of peripheral blood or bone marrow aspirate. The relative frequency data are summarized in Figure 4 and Table 7, including the absolute number of cases, crude rates and estimated number of new cases in Poland. For clarity and simplicity we clustered together some similar or rare entities. For example we analyzed together MZL/SMZL/ MALT (marginal zone lymphoma/splenic marginal zone lymphoma and mucosa-associated lymphoid tissue lymphoma) and ALCL (anaplastic large cell lymphoma) was the only PTCL (peripheral T cell lymphoma) assessed separately. Subtypes like angioimmunoblastic, T-cell enteropathic, T-cell hepatosplenic, NK-nasal or extranasal types were diagnosed, but included as PTCL. The unclassified cases were less then 10%, which is reasonable for the multi-institution approach.

In our series there were 61 cases of gastric lymphoma (samples collected in endoscopic biopsies or gastrectomy – Fig. 5). Surgery is no longer a recommended therapy for gastric lymphomas (side effects after gastrectomy may unnecessarily decrease life quality). MALT lymphoma responsive to anti-Helicobacter therapy is not the only and perhaps even not the main entity. Therefore adequate choice of therapy, depending on a histopathological subtype is the best available treatment.

Discussion

Incidence

The incidence of lymphomas varies depending on geographical location. In Poland we have one of the highest incidences of Hodgkin's lymphoma with annual incidence 2/100,000 inhabitants (according to National Cancer Register) and 3.3 (according to International Agency for Research on Cancer – IARC) [7]. Non-Hodgkin's lymphoma annual incidence is the highest in Australia and USA (males – over 22, females – over 17 cases/100,000/year), through 16 and 12 cases subsequently (in Western Europe) to less then 4 in Africa and East Asia [3, 10, 11]. In Poland the National Cancer Register data showed a lower incidence than in the neighboring countries (4.96–5.6 in males, 4.3 in females), so it was expected that the true numbers may be higher. The overall annual incidence of NHL in Małopolska per 100,000 population (crude rate) is 8.6 (9.5 for males and 7.6 for females), what is comparable to other central European countries, only slightly less then in Southern Europe (about 10/100,000/year), 20–30% lower then in western and northern Europe.

The discordance between Małopolska Lymphoma Register and Polish National Cancer Register may be either due to low quality of hospital administration data (missing cases) or

to the difference between years 2002 and 2005. Estimations based on the National Register would predict 191 new lymphoma cases in our region instead of 331 really diagnosed (Table 5). On the other hand, if one would use Małopolska Lymphoma Register to estimate the number of new NHL cases in Poland there should be 3261 cases instead of 1890 reported in the National Register (Table 6).

The age specific incidence of NHL is similar to other European countries for the population less then 70 years old (with a slightly 10–15% lower incidence in 40–49 and 60–69 years old category). There is, however, a significantly lower incidence in those above 70: e.g. comparing Poland to UK, the annual incidence per 100,000 inhabitants in males and females is 57 and 27 versus 74 and 54, respectively [3]. This may mean underdiagnosing lymphoma patients among the elderly in Poland, reflecting the worse health care standards within this age group and not the lack of diagnostic skills.

It should be underlined, that lymphomas (even excluding ALL, CLL and MM cases) account for over 50% of all hematological malignancies. The relative proportions after introducing estimated correction, based on Małopolska Lymphoma Register data look similar to other Western countries (Fig. 1).

Relative frequency

There are 59% of unclassified cases (C-85 category "lymphoma, other and unspecified") in National Polish Cancer Register. In our series of 1106 NHL, less then 9% were regarded unclassified, which is an expected result for a multi-centre approach, comparable to other European series. In this respect it could not be compared to REAL/WHO validation study, where all specimens were reviewed centrally by the panel of expert pathologists. It suggests that the vast majority of the unclassified category in the National Polish Cancer Register reflects the problems with ICD-10 coding of WHO/REAL diagnosed cases and not the true diagnostic dilemmas.

The relative frequency of NHL subtypes is summarized in Table 7. Distribution of NHL cases in Małopolska Lymphoma Register is similar to REAL/WHO validation study (Table 8). If we exclude from analysis SLL/CLL cases, for the reasons mentioned previously, there are only three important differences: there are rarer follicular lymphomas and peripheral T cell lymphomas (in our series only 8% and 3.7% of the cases, respectively) and there are more common MCL (10%).

The incidence of follicular lymphoma in different geographical regions is extremely variable [6]. It is most common in Northern America and UK (over 30 new cases annually per 100,000 inhabitants), with a crude rate of 15–20 in Europe, 7–10 in the Middle East to less then 5 in Korea or Thailand. In Europe, the similar low incidence is in Italy. The incidence in Poland (8%) is close to that in Italy (11%). Such a low incidence of FL in Poland may therefore reflect the true geographical variability or the lower rate of adequate diagnosis of this clinically indolent disease. The medium age (64) and sex distribution is comparable to other series (59 years in REAL/WHO validation study) so it appears that we are not missing the cases among the "undiagnosed elderly patients".

TABLE 8

Distribution of NHL cases in Małopolska Lymphoma Register in regard to REAL/WHO validation study

	Number of cases in MLR	Number of cases in REAL/WHO validation study	% of total cases in MLR	% of total cases in REAL/WHO validation study
	20	23	1.8	1.7
Burkitt, Burkitt-like	25	39	2.3	2.9
DLBCL	353	422	31.9	31.4
PMBCL	23	33	2.1	2.5
ALCL	20	33	1.8	2.5
PTCL	41	96	3.7	7.1
SLL/CLL	150	93	13.6	6.9
FL	87	304	7.9	22.6
MCL	112	83	10.1	6.2
MZL/MALT/SMZL	99	106	9.0	7.9
LPL	21	16	1.9	1.2
skin NHL	19	11	1.7	0.8
Other	40	84	3.6	6.3
Unclassified	96		8.7	0.0
Total	1106	1343	100	100

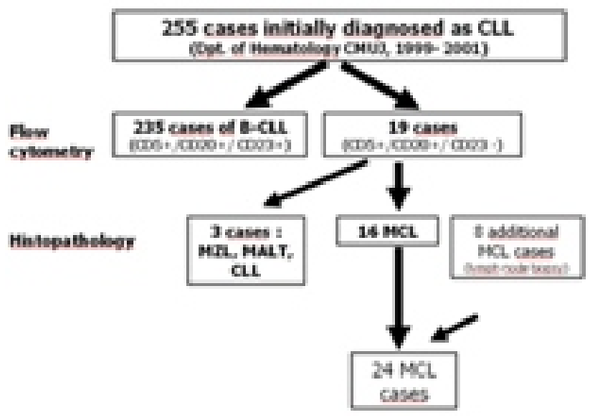

Fig. 6. Different ways leading to MCL diagnosis (cases with primary diagnosis made after flow cytometry and lymph node biopsy).

Geographical variation is also a fact in case of mantle cell lymphoma (crude rate of 3–4 in Northern America, 7–8 in Europe and 10 in Poland) [9]. However the characteristics of our patients are very much different – they were slightly younger than in a validation study (60 versus 63 years) and male predominance is less striking (56% versus 74%). Department of Hematology CMUJ is coordinating national MCL trials run by PLRG, so it could to some extent increase the number of cases of this subtype. The diagnosis of most of MCL cases was confirmed by flow cytometry and immunohistochemistry. In our previous series (unpublished data, Jurczak Wojciech, Dept of Hematology) majority of MCL cases were initially diagnosed as chronic lymphocytic leukemia (CLL), only 1/3 of the cases had initially a lymph node biopsy (Fig. 6).

Some of the organ specific NHL were also analyzed. Most interesting results were found in a series of 61 gastric lymphomas (Fig. 5), where only 27% are MZL (including potentially *H. pylori*-dependent MALT lymphomas). The other subtypes require systemic chemotherapy and not just only *H. pylori* eradication. Nearly 1/4 of the cases were regarded unclassifiable, which strongly supports the necessity of sending all suspected gastric lymphoma cases to a reference center for a thorough analysis, as the choice of adequate chemotherapy depends on the subtype.

Conclusions

Our study demonstrated a relatively good shape of pathomorphology laboratories involved in the study, where good standard was proven in lymphomas, one of the most difficult entities to diagnose, where group collaboration and the access to sophisticated immunohistochemistry and molecular biology techniques is essential. To further improve the situation, the Polish Society of Pathologists together with Roche-Poland is currently working to create a network of laboratories capable to serve as a reference centers for complicated cases. The true annual incidence provides useful practical data for planning NFZ and hospital budgets, therefore we decided to publish them. It is an open question how we could improve the quality of health care in the elderly – underdiagnosing lymphomas in this age group is just one of the problems. In the era of different biological therapies available (like monoclonal antibodies), when in a indolent lymphomas a long lasting remissions may be achieved without a devastating and potentially toxic chemotherapy, age should not be a limiting factor for making diagnosis and planning adequate treatment. Even in a crippling health care we have, one should never forget about those, who paid most, by financing it through decades.

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