

THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.)

CLINICAL EXPERIENCES IN HODGKIN LYMPHOMA, ESPECIALLY FOCUSED ON
SURVIVALANCE AND LATE TREATMENT COMPLICATIONS

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Introduction

The disorder with enlarged lymph nodes and focal infiltration of the spleen first was described by Sir Thomas Hodgkin in 1832 in connection with 7 cases. Since that time the disease has become one of the success stories of the medicine. The continuously growing clinicopathological and diagnostic knowledge and the modern treatment lead to that large majority of the Hodgkin lymphoma (HL) patients are long-time survivors and recover. The Hungarian and international incidence of HL is 1.5-3/100 000, however view of the fact that it is mainly the disease of young adults, the social significance beyond the frequency.

Based on the results of clinicopathological finding the REAL classification divided the Hodgkin's disease into two groups, namely classical (cHD) and nodular lymphocyte predominant HD (NLPHD) in 1994. It was a milestone that in the same year Küppers verified the clonal B-cell origin of the atypical Hodgkin, Reed-Sternberg cells characteristic to the NLPHD, which was also confirmed from the neoplastic cells of the cHL, so the disease was clearly classified into the lymphomas. However, the immunphenotype studies showed the differences of the two types, which reflects in the WHO classification since 2000. The HL is classified into the lymphomas and two histological types are differentiated, namely the nodular lymphocyte predominant (NLPHL) and the classical Hodgkin lymphoma (cHL). Parallel with this the diagnostic possibilities are also improved, CT scans are applied routinely and practically the whole body 18-fluorodeoxy glucose positron emission tomography and in three centers the combination of them (PET/CT) are also available. These give the possibility of a precise clinical staging and a better prognostic scoring, which is the basis of the modern, risk-adopted treatment. As a result of this the vast majority of HL patients are cured and the 10-year overall survival is more than 80% both in Hungarian and international context.

There are three historical part of the treatment of HL: between 1960-1985 it was disease-oriented, between 1985-1995 it was treatment-oriented and from 1995 until currently

it is patient-oriented. In the changing in perception it played a main role that we had to face with the late treatment complication of the cured HL patients. After 10-15 years of the diagnoses of HL the treatment related death exceeds the disease related mortality. Besides, some treatment related complications decrease the long-term quality of life of patients, their load is reduced. The most serious long-term treatment complications are the second tumors and the cardiovascular alterations, however there are some adverse events mostly impairing the quality of life, such as the mantle field irradiation, which destroys the thyroid glands and impairs the salivation and this may lead to higher caries risk and decreased parodontal status.

The aim of the wider experimental research focusing on the accurate understanding of the HL etiology, the expanding diagnostic possibilities and the modern prognosis assessment, the risk and response adapted treatment is the longer survival with the same life expectancy and quality of life as the “normal” population has got.

Aims

1. The improving clinicopathological knowledge, introduction of REAL/WHO classification, the modern diagnostic tools, which have led to accurate clinical staging, the introduction of new prognostic scores and the recognition of the importance of late treatment complications have led to change the therapeutic approach both in the Hungarian and international practice in the last two decades. Based on these I have decided to survey the clinical features of the HL patients had been diagnosed and treated in the 3rd Department of Internal Medicine, UD between 1995 and 2004, to overview the therapeutic practice of our clinic and to survey the 10-year prognostised overall and event free survival of our patients depending on the applied therapy.
2. The NLPHL is a rarer form of HL with a distinct immunohistochemical and clinical features. Its incidence is 3-5% among HL patients, so there are 6-8 new adult patients annually in Hungary. Because of the altered treatment practice the correct diagnosis has got outstanding importance. By overviewing the database of two Hungarian centers I would like to examine the national incidence of the disease, the clinical characteristics of patients, the applied treatment modalities and the prognostised 10-year overall and event free survival. Through these I have analyzed the pathological features of NLPHL and the aspects of differential diagnose.
3. According to the traditions of our working group I dealt with the late treatment complications of HL patients, especially with the late toxic effect of the irradiation. Besides the second tumors mostly the cardiovascular complications influence the long-time life expectancy of these patients. Both the irradiation and the chemotherapy can destroy the pericardium, the myocardium and also the coronary arteries. Among our patients I surveyed the rate of the chest pain and with traditional (ECG, ergometry, echocardiography) and dual isotope scintigraphic (DISA) methods we examined the occurrence of the coronary artery

disease. I searched for relationship between the recognized structural alterations and the applied treatment modalities.

4. The mantle field and the involved field irradiation of the upper neck lymph nodes may can destroy the salivary glands, which can lead to a higher caries risk. This can impair the quality of life and because of the reduced immunity may leads to a higher infection risk. Beside the small international data there is any information about the dental examination of Hungarian HL patients. Based on these I decided to survey the dental and periodontal status of our HL patients and examine their cariogen oral flora. I searched for relationship between the applied treatment and the dental, periodontal status and cariogen oral flora of the patients.

Patients and methods

In my work I searched among the patients had been treated mostly in the 3rd Department of Internal Medicine, UD and partially in the National Oncology Institute. To analyze the data of the patients I used the ambulatory and hospital documentations and the MedSolution medical information system.

The histological diagnoses was determined according to the Rye and later to the REAL/WHO classification, while the clinical stage was determined according to the Cotswolds modification of the Ann-Arbor principals. The prognostic scores was calculated according to the EORTC guidelines in the early and to the International Prognostic Score (IPS) in the advanced stages. In the latter case the prognosis was considered to favorable if the IPS score was between 0 to 3 and to unfavorable if it was at least 4. During the primer staging examinations beside the physical examination chest X-ray, neck, abdominal, pelvic and if it was necessary soft tissue ultrasound, except some cases whole body CT, unilateral crista ilei biopsy, gallium scan and recently PET/CT was done. The primary chemotherapy was COPP protocol until the early 1990s and COPP/ABV until 1998 and ABVD since that. For salvage chemotherapy DHAP (especially before high dose therapy and autologous stem cell transplantation) and basic BEACOPP-14, rarely ICE and previously CEP protocols were used. According to actual the Hungarian guidelines and possibilities the irradiation was extended field until the second part of 1990s, while nowadays mostly involved nodal irradiation is applied. The cumulative irradiation dose is also reduced from 40-44 Gy to 30-36 Gy. Combined modality treatment (CMT) was used according to the actual Hungarian guidelines both in the early and advanced stages. In the non-responder and early or repeatedly relapsed patients HST+aHSCT was applied if it was possible. One month after the end of the treatment restaging examinations were done and to assess the viability of the residual mass FDG-PET also was done if it was possible. The therapeutic response was described according to the

WHO classification in this time, which could be complete remission (CR), partial remission (PR), or non-responder/progression (NR). The unclassified complete remission (CRu) terminology was used according to the Cotswolds recommendations and in these cases FDG-PET or rebiopsy was done.

Our experiences with treating Hodgkin lymphoma patients

We examined the data of 163 HL patient who were diagnosed and primary treated in the 3rd Department of Internal Medicine, UD between 1995 and 2004, the survey was closed in January of 2006, the main follow-up time was 69 (12-132) months. The survivalance was calculated by Kaplan-Meier, the significance was calculated by log-rank test by SPSS statistical program, $p < 0.05$ value was the limit of significance.

Clinicopathological features of nodular lymphocyte predominant HL

After the introduction of REAL/WHO classification we analyzed the data of 536 HL patients who were diagnosed and primary treated in the 3rd Department of Internal Medicine, UD and in the National Oncology Institute, the survey was closed in January of 2007, the main follow-up time was 83 (3-144) months. The survivalance was calculated by Kaplan-Meier, the significance was calculated by log-rank test by SPSS statistical program, $p < 0.05$ value was the limit of significance.

Examination of late myocardial damage

76 HL patients were included in the study, who were treated and followed up at the 3rd Departemnt of Internal Medicine, UD between 1970-2000 or later. The study was conducted in 2006 at our clinic and the Department of Nuclear Medicine. The patients included were in complete remission for at least five years and did or did not have chest pain. However body mass index (BMI) greater than 30 and unstable diabetes mellitus were set as exclusion criteria. Cardiac tests included a 12-lead rest ECG and a Bruce protocol stress ECG as well as echocardiography performed. Beside measuring the size of the heart chambers, we assessed

the segmental wall motion abnormalities, determined the left ventricular ejection fraction and examined the left ventricular diastolic function with pulsatile Doppler technique. Invasive tests (coronary angiography) were performed at the discretion of the treating cardiologist.

Patient preparation: Each patient receives 80 mg glucose and 250 mg acipimox (Olbetam, Pharmacia, Hungary) per os 1.5-2 hours before administering iv F-18 fluorodeoxyglucose (FDG) to raise the blood glucose level and decrease the free blood lipid level for the optimal FDG recording of the myocardium. Ten minutes after the iv. injection of 370 MBq F-18 FDG, 850-900 MBq Tc-99m MIBI was injected. Scanning started 60 minutes later. *Acquisition:* Acquisition was performed in single-head mode with an APEX HELIX dual-head gamma camera (Elscent) fitted with an ultra-high energy (511 keV) collimator simultaneously on two energy channels (Tc-99m: $140 \text{ keV} \pm 10\%$, F-18: $511 \text{ keV} \pm 10\%$) in a 64x64 matrix (pixel size: 6.925 mm) at 180° from 45° RAO to 45° LPO (at every 3°). Scanning time was 30 sec per view. *Image processing:* The results were processed with a dedicated 511 keV software package (Elscent). Metz filtering and filtered back projection were applied during reconstruction. Based on the Tc-99m MIBI images, three rows of slices were taken (parallel to the left ventricular short axis, horizontal long axis, and ventricle long axis) identically to the FDG images as well. The polar map was constructed from the short-axis slices based on both radiopharmakon distributions. The polar map shows the average activity (%) of 16 regions relative to the highest activity segment. From among scintigraphic parameters, we assessed the relative radiopharmakon recordings (MIBI and FDG) per segments, the lowest perfusion and metabolic percentage value between segments, and the maximum deviation between relative metabolism and relative perfusion. *Statistical analysis:* The aim of our analysis was to reveal whether myocardial perfusion and metabolic changes show any correlation with the patients' symptoms or the abnormalities found using simple non-invasive cardiac test (chest pain, stress ECG, echocardiography), the type of the therapy. Statistical calculations were

made using the SPSS program suite. The normality of the data groups was checked with Kolmogorov-Smirnov test, while Levene's test was used to assess the equality of variance. The average values of two age groups were compared with t-test; in case of unequal variances, d-test was used. For multiple comparisons, the Bonferroni correction was used for per-segment analysis. The differences were considered significant below the probability level of 0.0032. Variande analysis was used to compare the three treatment groups.

Examination of dental and periodontal status:

We investigated 132 HL patients attended in the 3rd Department of Internal Medicine, UD and 51 control person matched in gender and age, who had no tumor or chemo/radiotherapy in his/her medical history. The HL patients during their treatment received only radiotherapy (RT), or only chemotherapy (CT) or the combination of them (CMT), and we divided them into two groups based on whether the upper cervical region was irradiated or not. The control persons formed the third group. During the selection of the investigated persons we excluded those who had habits or diseases or medication what can influence the saliva production.

We examined the patients in the Department of Periodontology, where first we recorded the history data (former diseases, dental interventions, medication, smoking habit, subjective xerostomia) by a *questionnaire*, then we done sialometry and examined simple general dental and periodontal status, measured the buffer capacity of the saliva and made microbiological sampling to the examination of the cariogenic flora. By *sialometry* we measured the five minutes unstimulated, then after five minutes the stimulated saliva production in a sialometric tube (after a five minutes long examination the saliva production is considered as stimulated). We considered the amount of less than 0.1 ml/min saliva as pathological. We measured the *buffer capacity of the saliva* by CRT semiquantitative strip. To feature the *dental status* we used the DMFT-index what shows the rate of *decayed, missing*

and filled teeth. To survey the *periodontal status* we used the simplified Russel periodontal index. To examine the *cariogenic flora* we got some sample from the lingual surface of the lower incisors with a special sterile stick and we carried it in transport medium to the Institute of Microbiology, where the samples were plated. *Streptococcus mutans*, *Lactobacillus* sps. and *Candida albicans* were bred, and in the case of positive breeding the number of the colony forming units (CFU) also were counted. The *statistical analysis* was made by Statsoft (Version 6.) software with Lilliefors and Kolmogorov-Smirnov test. In the case of parametric distribution we used T-probe, and in non-parametric distribution we applied Mann-Whitney test. If we compared more than two series, the p value was calculated with ANOVA test and we considered it as significant if p value was <0.05 .

Results

Our experiences with treating Hodgkin lymphoma patients

A slight female predominance and bimodal age distribution can be observed among our patients. The mean age was 36 (14-75) years at the time of diagnoses. Among the whole patients the MC, while among the female patients the NS histological subtype was the most frequent, and we observed NLPHL only in 1.8%. Most of the patients (60.7%) were diagnosed in advanced stage, 51.5% had got B symptoms. 38.8% of the early stage cases had got favorable prognoses, while only 15.6% of the advanced stage patients had got unfavorable prognosis ($IPS \geq 4$). 28.2% of the patients had got bulky disease. 155 patients received chemotherapy alone or as a part of CMT. 61 of them got COPP/ABV and 87 got ABVD. Compared the survivalence the ABVD chemotherapy was better. We applied radiotherapy in 99 patients, in 7 cases alone, while in the others as a part of CMT. As the effect of the therapy 90.2% of the patients achieved the complete remission, the overall response rate was 96.3%, and only 3.7% of the patients was non-responder. 18.5% of the patients in complete remission

the disease relapsed. Because the non-respondance and the relapse 26% of the patients got salvage therapy. As second treatment five patients received IFRT. We applied conventional dose salvage chemotherapy in the elderly, the foreigne patients and in thse, whose disease relapsed after more than one year. We initiated HDT+aHSCT in 18 cases, however in three patients only the stem cell collection was done. In 15 cases the HDT+aHSCT was done, and this led to 9 long-term CR and 6 PR. One from the latter allogenic transplantation also was made but without successe. Among the late treatment complication the cardiovascular and pulmonary alterations occurred in a higher proportion and we also observed hypothyreosis often. Second malignancy developed in 10 cases, two of them were NHL, four were pulonary tumor, and other soild tumors in the others. In one patient rare, probably irradiation complication, neurofibrosarcoma was diagnosed after the completion of the study. 18 patients had died during the whole time of the study, nine of them vecause the progression of the lymphoma, two of the in sepsis, which was the consequence of the treatment, six of the in second malignancy and one in other reasone. The 10-year prognostised overall survival was 83%, while the event free was 70%.

Clinicopathological features of nodular lymphocyte predominant HL

536 Hodgkin lymphoma cases were reviewed. 16 cases of them were proved NLPHL, while 520 cHL on the base of histological and immonophenotypical features, among the latter 30 had got lymphocyte rich cHL (LRcHL). NLPHL patients were younger with unimodal age distribution and with male predominance. More than 90% of NLPHL patients were in early stage and nearly two-third of them had favorable prognoses. The peripheral, mostly the cervical regions were involved, only one of them had B singe and none of them had bone-marrow, intracavital or spleen involution neither bulky tumor. In contrast the cHL patients were elder with bimodal age distribution and slight female predominance and among them

significantly more patients had advanced disease. 3NLPHL patients were not treated beside close observation. In I/A stage NLPHL alone radiotherapy was used and in case of unfavorable prognosis we applied CMT, while in advanced stage patients received chemotherapy alone. Near two-thirds of cHL patients received CMT and only 2% of them received radiotherapy alone. All of the NLPHL patients responded to the treatment with complete remission and the overall response rate was good, more than 90% in cHL group too. Relapse rate was similar in the two groups. Among the 536 patients 58 (10.8%) died in the follow-up period, all of them had cHL. 45 died because the progression lymphoma, 6 because second malignancy and 6 because other cases. 10-year prognostised OS was 100%, the EFS was 75% in NLPHL, while in order these were 82 and 70% in cHL cases. Survival data of LRcHL were similar to cHL. Non-Hodgkin lymphoma occurred concurrently or subsequently in 6 of the cHL patients (1.15%) and in 2 of the NLPHL patients (12.5%). One of the NLPHL cases showed concurrent diffuse large B-cell lymphoma (DLBCL) both diseases were confirmed from the diagnostic excised lymph node, while in the other patient micronodular T cell/histiocyte-rich B-cell lymphoma developed 20 months after the diagnoses. The first patient received R-CHOP treatment primary, while the second one after the diagnoses of NHL, both of them are still in complete remission. In 6 patients developed NHL from the 520 cHL cases more than two years after the diagnoses of HL in all of them.

Examination of late myocardial damage

The mean age of the 76 HL patients (33 females, 43 males) was 29.9 (9-63) at the detection of the disease and the beginning of the treatment. For the total duration of the study period, the mean age was 45.8 (25-74). The time elapsed between the treatment and the DISA test was 16.1 (5-33). The patients were divided into two groups based on the DISA results. Myocardial perfusion and/or metabolic disorders were observed in 42 patients, they were

classified as DISA positive. The 34 patients not exhibiting abnormalities composed the DISA negative group. The number of males was higher in the DISA positive group, but the difference was not significant.

Correlation between the results of the non-radioisotopic examinations and the method of treatment:

Although more than half of the patients complained of chest pain, significant ischemic changes were revealed only in a few cases during the non-invasive examination. However, diastolic dysfunction was detected with echocardiography in almost 40% of the cases and its development showed correlation with the method of treatment: it occurred in 44% of patients under irradiation, in 43% of patients under thoracic irradiation as well as chemotherapy, and only in 26% of patients not receiving thoracic irradiation. The difference was considerable but not significant ($p=0.349$).

Correlation between the results of non-radioisotopic tests and the symptoms:

In patients exhibiting chest pain, myocardial perfusion was significantly lower in the inferoapical and anteroapical regions. Glucose metabolism was impaired in segments 9 and 10. The difference in the relative values of perfusion and metabolism was not significant anywhere. The alterations during the stress and the echocardiographic examinations did not go together with significant myocardial perfusion and metabolic changes in any regions. Only the maximum difference between relative perfusion and metabolism reached the significance limit ($p=0.049$) with the abnormal echocardiography records.

Correlations between the results of the radioisotopic tests and the method of treatment:

Relative segmental perfusion, metabolic rates, and the difference of these two showed no significant variation in any segments. However, the minimal value of perfusion was significantly lower ($p=0.0314$) in the group receiving radiotherapy. The positivity of the

DISA test showed unambiguous and significant correlation with the prevalence of chest pain. Based on the results, the cardiologist indicated coronarography for 6 patients; one of them had no significant coronary stenosis, one had triple-vessel disease, so a CABG procedure was performed, and 4 patients had stent implantation.

Examination of dental and periodontal status:

Among the 132 HL patients 68 (32 female and 36 male) received irradiation including the upper cervical region, beside the radiotherapy 54 patients got chemotherapy as well. Their average age was 47.1 (20-79) years, the mean follow-up time was 12.8 (2-37) years after the treatment. 64 HL patients received only chemotherapy, or beside the chemotherapy they got irradiation not including the cervical lymph nodes. In this group the average age of patients was 44.05 (21-75) years, and 11.7 (2-34) years had passed since the treatment. The average age of the 51 control person (25 female, 26 male) was 45.8 (20-68) years. There was no significant alteration between the HL patients' chemotherapy. There was objective xerostomia none of the patients and the control persons. The buffer capacity of the saliva was the lowest in the cervically irradiated group, but the alteration was not significant either. The DMFT index and the periodontal index were the worst in the cervically irradiated HL patients group and the difference between the DMFT of the irradiated HL patients and the control group was significant. Examining the cariogen flora in the sample collected from the dental surface all the three pathogens were detectable in the same ratio in the different group of patients. However the mostly cariogenic *S. mutans* was present in the highest ratio with a significant germ amount (10^5) in the sample of cervically irradiated patients.

Discussion

Our experiences with treating Hodgkin lymphoma patients

Analyzing the epidemiologic data of our patients we determined that in opposition to the international data there was a slight female predominance, of which case is unknown. Another alterations were that the MC subtype was the most frequent and that most of our patients were diagnosed in advanced stage, however it was rarer than previously.

For the precise staging chest X-ray, abdominal and soft tissue ultrasound were always made, and usually whole body CT also. Gallium scan had only additional role and 18-FDG-PET was not made for primer staging in this period. It had significance in the observation of the viability of the residual tumor and in the recognition of the relapse. In one of our IV/AX stage (mediastinal bulky) patient after the successful treatment of the HL Graves' disease and myasthenia gravis were diagnosed, and based on this the paraneoplastic syndrom associated to the relapse of the HL emerged, but the repeated PET scans did not verify metabolic hyperactivation in the residual mass. We probabled a genetic predisposing factor in the background of the three B-cell mediated disease. After the follow-up time the patient died in postirradiation neurofibrosarcoma, the persistence of the HL was closed in the section also. During the follow-up period the PET scens giuided us in making therapeutic decisions.

In the study period the patients received radiotherapy alone only in rare cases, RT was applied mostly as a part of CMT. The irradiated field reduced, the invonved field irradiation came into view. In this period the chemotherapy also was changed: while until 1998 the COPP/ABV was applied more after it the ABVD protocol became the treatment of choice, which led to a better overall and event free survival in our study also. Applying the ABVD and IFRT the risk of late treatment comlication may impair. Second malignancies were recognized in ten patients, two of the were NHL, the others were solid tumors.

In the case of inadequate treatment response (PR, NR) or relapse salvage treatment is needed, in 26% of the patients got second therapy. In case of residual tumor or localized relapse the IFRT may lead to CR. While in case of disseminated disease or repeated relapse salvage chemotherapy is needed, which can be conventional or middle dose chemotherapy and/or HDT+aHSCT. The advantage of HDT+aHSCT to conventional dose chemotherapy was verified by more studies. However, the allogeneic transplantation is more likely to a theoretic possibility in HL, because the posttransplantation mortality is very high, so this is not recommended routinely, although by using RIC the TRM is improved significantly. Among our patients we indicated HDT+aHSCT in 18 cases, which was made in 15 patients. Nine of them are still in complete remission, while three of them during the study period another three of them after the completion of the study had died. Our results are good in comparison to the international data. According to the literature in HL the 10-year overall survival is 80-85%, while the event free is 60-70%, the data of our patients are similar to this. The improvement of the survival can be expected from two intentions. The first is the less late treatment related toxicity in the early stages with favourable prognosis, the second is the more effective antilymphoma treatment of the advanced stages with unfavourable prognosis. From the improvement of the diagnostic and treatment tools the adequate survey of the treatment response can be expected, which may lead to a response adapted treatment and through of this to a better survival and less treatment complication.

Clinicopathological features of nodular lymphocyte predominant HL

According to the literature in the western countries the occurrence of NLPHL is 5-7% among the patients diagnosed according to the REAL/WHO classification. The 3% found in our survey is slightly lagged behind from this. Beside the pathological alterations NLPHL also has proper clinical appearance. It does not show expression of CD15 and CD30, the

typical markers for cHL. NLPHL is not related to EBV infection, LMP1 and EBNA negative, while 20-80% of cHLs in the Western world are EBV positive. The cellular background of cHL is more heterogenic, besides the CD3 positive T cells contain a lot of plasma cells, eosinophils and histiocytes. Both the HRS and the L&H cells origin from the germinal centre but the HRS cells express slight or even no the B-cell receptor (BCR) and the immunoglobulin specific transcription factors, as for example the PU1, BOB-1 and OCT-2. Beside the pathological alterations NLPHL also has proper clinical appearance. Characteristically this is the disease of young and middle-aged men. Based on data of large studies (ETFL, GSHG) the average age of patients is between 30 to 40 years, age-distribution is unimodal, usually nearly two-thirds of them are male similar to our findings. In usual the disease is diagnosed in early stage and mostly the peripheral lymph nodes are involved. In our survey only one patient had advanced stage lymphoma. Although LRcHL shows large morphological similarity to NLPHL its clinical course is closer to the classical form. More than one-third of our LRcHL patients had advanced disease although their prognosis was favorable in every case. Similar to this 40% of cHL patients had advanced stage disease, however nearly one-third of this group had unfavorable prognosis and this also suits to the international data. The 10-year prognostised overall survival (OS) is more than 90% in case of NLPHL, our data agree with this, the prognostised 10-year OS was 100%. Because of the favourable course of the disease the treatment toxicity have to be taken into the consideration of the therapeutic decision. Beside close follow-up the “watch and wait” is also approved. In early, limited, favorable NLPHL cases (I, perhaps II stage) use of radiotherapy alone as primary treatment is evidence and it is also clear that apply of involved field is as good as the extended field was. In advanced stages the chemotherapy is suggested. To moderate the late treatment toxicities apply of rituximab in NLPHL can be a logical therapeutic decision known the CD20 positivity of L&H cells. Use of the non-mutagenic rituximab would be glad as it may helps to reduce the

early and late treatment toxicity. Beside of these Younes et al (MD. Anderson Cancer Center) found that rituximab also influence the microenvironment of the malignant cells (polyclonal B-cell depletion) so this can be favorable in CD20 negative cHL cases too. According present studies –among others in the John Hopkins University- the HRS cells may have malignant precursor cells what are CD20 positives, so these can be a newer target of monoclonal antiCD20 antibodies. It is well known that NHLs occur more commonly in NLPHL (3-7%) than in cHL. Mostly DLBCL or a variant histological type of it the T/HrBCL develops. There were two hypotheses to the simultaneous occurrence of HL and NHL; the first said that the two lymphoma origin from a common cell, the other suggested that there is a NHL-HL or HL-NHL transformation. Single-cell analyses confirmed the first one. Mouse-model studies showed that the loss of different transcription factors (Pax5, E2A, EBF) leads to variable B-cell differentiation what demonstrates the B-cell plasticity what can explain the occurrence of variant B-lymphomas in a single patient. In two of our 16 NLPHL patients developed NHL in one case it was composite DLBCL, while in the other sequential T/HrBCL developed 20 months after CMT. Both of them were well-curable and they are in complete remission. Based on the international and our own experiences the NLPHL is a rare disease with excellent clinical course and especially of this its precise diagnosis has overriding importance. To differential diagnosis the use of immunohistochemistry is indispensable and special hematopathological knowledge is also necessary.

Examination of late myocardial damage

Among the late treatment complications of HL beside the second malignancies the cardiovascular complications are the most frequent and the most serious. Our own study revealed that although cardiac damages of some extent were detected in more than half of our patients, these changes were significant only in few of the cases.

The cardiac damages of HL patients are various types – irradiation and chemotherapy playing a decisive role in this. It is well known from the cases of mammary carcinoma and HL patients that irradiation does cause myocardial impairment. The estimated rate of the incidence of cardiac damages caused by irradiation is 6-30%, while the prevalence of the coronary disease is 5.5-12% among HL patients in various studies. The atherogenic effect of radiotherapy is supported by the fact that value of minimal perfusion was significantly lower in the group of radiated patients than in ones not receiving radiotherapy. The incidence and severity of coronary disease are further increased by the traditional CV risk factors. Among our patients, perfusion disorder at rest occurred mainly on the inferior wall and in the basal segments that could be affected both the mantle and the inverted Y fields. Glanzman et al. also concluded that if no traditional CV risks are presented, irradiation does not imply increased CV risks. All these lead to the conclusion that the efficient treatment of the traditional risk factors must be key importance in this patient group. The data of long-term follow-up show that increased CV risk can be detected even after 25 years and the risks are higher in patients who were younger than 25 at the time of the treatment. Beside traditional risk factors, cardiac damage caused by irradiation may be intensified by anthracyclin-based polychemotherapy as well. In adult patients, toxic effect is expected above the cumulative dose of 480 mg/m², and it certainly occurs above 800 mg/m², toxic effect is caused by the direct damage of the myoepithelium. Regarding our cases, no cardiomyopathy or heart failure deriving definitely from anthracyclin toxicity occurred, which can mainly be explained by the fact that our patients rarely received doxorubicin treatment with a cumulative dose above 400 mg/m², and such treatment were applied mainly in the second half of the 1990s, so its complications will probably arise later. The incidence of diastolic dysfunction detected by echocardiography was significant more than one third of the patients were affected. At the same time, this abnormality was observed in more than 40% of the patients receiving thoracic

irradiation but only in 26% in cases lacking thoracic irradiation. This difference is unequivocally connected to the presence or absence of mediastinal radiotherapy and it is considerable but not significant. It is known that HL treatment may lead to various CV complications. International studies and our own observations both reveal that these complications are of different severity but never to be ignored, as they can progress very fast in a short time. DISA test used in this study provided the possibility of distinguishing between chest pains induced by metabolic and perfusion disorders. Through DISA is a suitable method for screening the majority of macroangiopathy patients who can undergo intervention, this kind of sensitivity of the method could be increased by physical/chemical stress. In recently diagnosed lymphoma patients, risk-adapted treatments should be favored and therapeutic toxicity should be reduced. All these are supported by the interim FDG PET/CT scans as well as echocardiography that may be used before or, if necessary, during treatment. Depending on the results, the less cardiotoxic EBVD (epirubicin) protocol can be applied. In addition, patient education and efficient control of blood pressure, blood glucose, and cholesterol are crucial.

Examination of dental and periodontal status:

In this survey we discussed the late irradiation damage of the salivary glands, which was less examined in this patient group. The previously most commonly used total nodal and the mantle field irradiation both involved the cervical lymph nodes and the submandibular and sublingual salivary glands and a part of the parotis with them and the nowadays used upper cervical involved field irradiation may also can damage them. The caries formation is a multicausal course whose development the dietetic habits, the micro-organisms of the plaque, the dental surface and the unfavorable qualitative and quantitative change of salivation, which may lead to caries formation after some time.

Beside the hypothyreosis the xerostomia is one of the most common complication of the upper cervical irradiation. In head and neck tumor patients it was found that decrease of the saliva flow correlates with the cumulative radiation dose. Under the limit of maximum 50-52 Gy cumulative dose the decrease of salivation can be reversible, but using more than 58-64 Gy cumulative dose the damage is surely irreversible. In the course of Hodgkin lymphoma's treatment the cumulative irradiation dose comes at the critical 50 Gy level only in a few cases so the chronic damage of the saliva glands is very rare as we also saw in our work. . The oral flora will be cariogenic because of the proliferation of the *S. mutans*, *Lactobacillus* sps. and the *C. albicans*. As soon as at the beginning of the treatment Keene et al. observed the unfavorable proliferation of the micro-organisms parallelly with which the dental status were decreasing in patients with Hodgkin lymphoma or head and neck tumor. In our work we observed that although neither the cariogenic oral flora nor the periodontal index show significant differences between the altering groups the general dental status was significantly worse in the cervically irradiated patients than in the control group. This allowed us to conclude that even though the decrease of the salivary flow and the proliferation of the oral flora are reversible processes the damages developing during the treatment significantly worsen the HL patients dental status in a long term, and the irradiation plays an important role in this. The irradiation beside of the higher caries risk may lead to the destruction of the dental alveoli, osteoradionecrosis, which mostly develops in the mandibula with a worse blood flow. This complication can be prevented with the extraction of the incurable tooth before the treatment, which emphasizes the importance of the pre-treatment screening by the dentist. The irradiation has an unequivocally unfavorable effect on the salivary flow and the oral flora, which means a higher cariogenic risk. That's why it is relevant to emphasize the importance of the increased oral hygiene and the regular visits at the dentist, which may also can help in the early detection in the secuder (oral cavity, head and neck) tumors.

Summary, new findings

1. With analyzing the clinical characteristics of the HL patients who had diagnosed and treated in the 3rd Department of Internal Medicine of UD I have concluded that unlike to the international experience in our region there is a slight female predominance and most of the patients have been recognized in advanced stages. Among the whole patients the mixed cellularity histological subtype was the most common. I observed that by using ABVD protocol both the overall and the event free survival were better, and these were similar to the international data.
2. By examination the rare co-existence of Myasthenia gravis, Graves' disease and Hodgkin lymphoma I recognized, that genetic predisposition can be proposed.
3. I have done a comprehensive survey about the clinical characteristics of cHL and NLPHL first time in Hungary. I observed that the frequency of NLPHL is lower than the international data, otherwise the overall and the event free survival are similar to that. Because of the rarity and the favorable clinical outcome of NLPHL the exact histological diagnoses is very important.
4. I have examined the myocardial injury of HL patients with DISA technique first time and I found that the chest irradiation had lowered the minimal perfusion value significantly and that the inferoapical and anteroapical myocardial perfusion were significantly worse in the patients with chest pain what can confirmed the late side effects of the treatment.
5. I have examined the periodontal status of HL patients in long term remission first time and I have found that the general periodontal status was significantly worse in those who had got neck irradiation during the treatment compared to the age and gender matched control group, which can be explained by the worsen salivation.

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