THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Clinical experience with Hodgkin lymphoma, with particular regard for treatment-related late complications, fatigue and mental health

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The Examination takes place at of Lecture Room 2 of the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Debrecen, January 23, 2019. 11:00 AM.

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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, January 23, 2019. 13:00 PM.

1. Introduction

Hodgkin lymphoma (HL) is a malignancy of the lymphatic system of clonal B-lymphocyte origin, with a localised early or advanced form appearance, often accompanied by typical complaints such as weight loss, fever, night sweats (known as B symptoms) and itching. Its clinical profile is the following: it can predominantly be accompanied by an enlargement of supradiaphragmatic nodes and, more rarely, enlargement of infradiaphragmatic nodes, liver and spleen, with extranodal or bone involvement rarely affected. Changes in the blood cell formula (higher white blood cell count, low absolute lymphocyte count, eosinophilia and anaemia) and other laboratory tests (increased erythrocyte sedimentation, elevated LDH and ALP, reduced albumin levels) can be typical. Many of these factors possess prognostic value.

In 2017 65950 new HL patients were diagnosed worldwide and thus HL took the 0.5% of the overall cancer cases. The disease's incidence is 2/100 000 inhabitant in Hungary, which means approximately 200 newly diagnosed cases each year. As a result of the use of modern examination methods as well as risk and response adapted strategies, 80-85% of HL patients today survive or recover. Parallel to this, treatment-related late complications have come to the fore. Of these, patients' long-term life expectancy is mostly affected by the development of second malignancies and appearance of organ damage (heart, lungs, thyroid gland). Several side effects are known to affect patients' quality of life and mental health, and can thus lead to social and psychological disorders in patients. HL primarily affects the young adult active population, with a significant portion of patients at the time of diagnosis being working-age young adults (mean age around 35 years), thus its social and economic importance surpasses its incidence. Long-term survivors' social reintegration and return to work after treatment need to be important targets both for patient and society. At the Clinics of Internal Medicine of the University of Debrecen we examined correlations between fatigue, mental stress, anxiety and depression as well as quality of life in HL patients under treatment. The results of these studies are summed up in my doctoral theses.

2. Literature review

2.1. Pathogenesis

Our knowledge of HL is continuously increasing but the cause of the disease is still not clear. It is known that cHL typical HRS cells and NLPHL lymphocyte predominant cells are of monoclonal, mature B cell origin. HRS cells mostly lose their B cell phenotypes and can display markers characteristics of several, other hemopoetic malignancies, as a result of which cHL and NLPHL, as well as cHL and all other non-Hodgkin lymphomas become distinguishable.

Both endogenous (genetic predisposition, immunological reasons) and exogenous factors may play a role in the pathogenesis of HL. The fact that if, in monozygotic twins, one member has HL, the risk of the disease in the other member of the twins is 100-fold higher compared to dizygotic twins suggests *genetic susceptibility*.

The role of several oncogenes and tumour suppressor genes in HL has been studied, however, no typical, reciprocal translocation was found that could be used in HL diagnostics. It is known that HRS cells in cHL have differences in their chromosomes in practically every case, of which clonal, numeric aberrations affecting 2p, 4p, 9p, 12p and 16p chromosomes are common. Constitutively activated NFκB pathway has a central role in the pathogenesis of HL, and the JAK/STAT pathway is only partially activated – all this has a key role in the development of resistance to apoptosis. Chromosome 9p24.1 is a recurrent genetic abnormality, which leads to overexpression of PD-L1, L2 ligands on HRS cell (especially in the HL-NS subtype, with individually changing expression). The JAK2 gene is located on the same chromosome; its amplification results in PD-L1 and L2 transcription. Increased PD-L1 expression has been detected in Epstein-Barr virus-positive cHL, too. In effect, as a result of the connection between PD-1 cell-surface receptor (on T cells) and PD-L1, apoptosis of cytotoxic T-cells in the lymph nodes and consequential cellular immunodeficiency occurred.

The three main functions of *our immune system* are: to protect its own structures, to seek out and destroy foreign bodies and to inhibit tumour growth. Central to these interactions are different $CD4^+$ T lymphocytes ($T_{regulatory}$, T_{helper}-Th), within which $CD4^+CD25^+FoxP3^+$ immunosuppressive/regulatory T cells play a key role. In HL they are important in creating a TH 2

"background" instead of Th1 predominance (securing a proper antitumor background). The process of conversion is regulated by the tumour micro environment and the cancer cells themselves through secretion of TGF-β, IL-10, galectin-1 and prostaglandin E2. These processes lead to immunosuppression by inhibiting function of CD8$^+$ T-cells, dendritic and NC cells. In addition to this, programmed cell death ligand 1 expression (PD-L1) of cancer and microenvironment cells also greatly contributes to depletion of effector T cells, directly inhibiting cancer cell apoptosis. Involvement of *the immune system* is supported by the fact that the disease is more frequent both in congenital and in acquired immune deficiency conditions (human immunodeficiency virus (HIV), solid organ/bone marrow transplant).

The role of EBV infection as *exogenous factor* in the development of HL is supported by several factors. Epidemiological observations have revealed that the relative risk of the development of HL in patients who have had mononucleosis infectiosa, especially in young adulthood, is three-fold compared to the general population. In a considerable proportion of HL patients elevated EBV antibody titers can be detected years before the development of lymphoma. In 20-60% of cHL cases clonal EBV genome (or its product: latent membrane protein, LMP) can be detected in malignant HRS cells (in particular in MC subtype). EBV genome clonality may suggest the HL developed from a single infected cell.

2.2 Clinical picture, diagnosis

At identification of HL most patients are complaint-free. So-called B symptoms General symptoms such as excruciating itchy skin can be typical and, rarely, pain in the affected lymph node following alcohol consumption. Depending on the locality of the affected lymph node region these can cause compression- type symptoms (oedema of the extremities, vena cava superior syndrome, citrus, paraplegia, etc.).

The typical, often only, symptom of HL is the usually painless enlargement of the lymph nodes. In clinically typical cases it is accompanied by enlarged supradiaphragmatic lymph nodes, (cervical - in 60% of cases, especially on the left side of the neck, and mediastinal, supraclavicular, and axillar - in 20% of cases). Infrequently it is accompanied by infradiaphragmatic lymph node involvement and enlarged liver and spleen. Extranodal and bone marrow involvement is not common, and the central

nervous system and the gastrointestinal tract are also extremely rarely involved. In the case of significant adenomegalia (more than 10 cm in the chest and more than 5 cm on the periphery), we have a case of a „bulky" tumour.

One of the keystones of successful treatment of lymphomas, and thus of HL, is constituted by precise diagnosis of the disease. Even today, an indispensable part of the diagnosis is a classical pathomorphological examination completed with immunohistochemistry. Citological examination is not satisfactory, as it can only raise risk of the disease. Efforts need to be taken to perform a surgical biopsy of the affected lymph node/organ/tissue. If surgical sampling is not possible (old age, frail general condition, inadequate blood coagulation parameters, rapid progression, pregnancy, time factor), lymph node core biopsy can be considered as a quick, acceptable alternative procedure.

2.3 Staging, prognostic factors, determining treatment response

Staging examinations require performance of several propedeutic, laboratory, and imaging examinations. Following precise history-taking performance of detailed physical examination is recommended (affected lymph node(s) region(s), size of liver and spleen). The following laboratory tests are performed: qualitative and quantitative blood tests, We, detailed blood chemistry tests (liver and kidney function tests, LDH, alkaline phosphatase, total protein-albumin, β2-microglobulin, serological samples (HIV, EBV, cytomegalovirus, hepatitis viruses), hemostasis, and, in women of fertile age, pregnancy tests. Furthermore, the patient's cardiopulmonary assessment (ECG, echocardiography, DLCO) can also be recommended if it is possible or is warranted by anamnestic data.

Among imaging techniques used to determine extent of the disease PET/CT scans have a primary, standard role today. Staging PET scans can be important in determining extent of the disease, exploring extranodal localisation(s), and, in some cases, in marking biopsy sites. PET/CT has an indispensable role in measuring early response to therapy, done after the second chemotherapy (CT) cycle. This is the so-called interim PET/CT, the most reliable prognostic factor at present in terms of response to therapy and survival; the prognostic value of interim PET/CT scan performed after second-cycle ABVD (adriablastin, bleomycin, vinblastin, dacarbazin) in advanced

stage HL surpasses that of the International Prognostic Score (IPS), The restaging PET scan used to help in measuring response to therapy after treatment has a function in judging viability of residual tumour mass and identifying patients with an inadequate response to therapy. It can also be used in patient follow-up to confirm suspicion of relapse and, more rarely, to identify biopsy site. Using PET/CT can help us plan response-adapted personalised treatment, which can help us avoid over- or undertreating our patients. Today, evaluation of interim and restaging PET/CT examinations takes place in a standardised way, using the Deauville five-point scoring system incorporating the Deauville criteria.

Earlier clinical staging was done using the 1989 Cotswolds modification of the 1971 Ann Arbor staging system. Today the modified Ann Arbor classification (Lugano classification) is used. PET/CT is a standard examination method indispensable in HL care.

The observation that prognoses of patients with identical clinical stages may be different has resulted in the development of diverse prognostic systems. In HL patients, the European Organization for Research and Treating Cancers (EORTC) prognostic system is used in early stages of the disease, while in more advanced stages Hasenclever and Diehl's IPS is applied in Hungary.

Although long-term survival of HL patients is very good, early screening of patients with unfavourable prognosis and precise risk estimation are not sufficiently effective yet. Several clinical studies have been examining the issue of what prognostic significance can be added to that of the traditional prognostic systems and interim PET/CT by the more recent biological markers (peripheral blood lymphocyte/monocyte ratio, TARC, tumour-associated macrophages, etc.) At present their exact role/function at the time of diagnosis and the follow-up of the disease is not entirely clear.

2.4 Treatment

HL therapy is almost always cure-directed. First choice therapy depends on histology, stage, prognostic and patient-related factors. At present 80-90% of recently identified patients with classical HL recover due to combined polychemo- (CT) and radiotherapy (DT), or chemo-and radiotherapy (CMT). Recognition of treatment-related late complications of earlier treated patients has led to the realisation that early as well late side effects of treatment should

not impair survival and quality of life is at least as important as the best possible treatment results. At present CT has come to the fore and RT has become secondary.

The current treatment of choice for HL first line treatment is ABVD. In early favourable stage (I-IIA) 2-4 cycles ABVD regimen and 20-30 Gy involved field radiotherapy (IFRT) can be recommended. In early-stage unfavourable disease 4-6 cycles ABVD and 30 GY are used. In the GHSG HD11 study each group of patients received 4 cycles of ABVD vs 4 BEACOPP (bleomycin, etoposid, doxorubicin, cyclophosphamid, vincristin, procarbazin, prednison) regime followed by 20 or 30 Gy IFRT. In more advanced stages (III-IV), 8-cycles ABVD regime is standard. If, at the end of treatment, PET/CT scans remain positive (only one region) or a PET positive residual mass is detected after a bulky involvement/tumour mass, IFRT is recommended with a total of 30-36 Gy. It is an open question whether or not it is necessary in the case of negative PET/CT.

In 20-30% of patients relapse/progression occurs after the first treatment. In these cases, if the patient is suitable for autologous peripheral blood stem cell transplantation, intermediate dose CT is used as second-line treatment followed by autologous HSCT in case of chemosensitivity. As a result of the treatment, complete remission (CR) can be achieved in 50-60% of patients. There are several new possibilities to treat relapse/remission after autologous HSCT in HL such as brentuximab-vedotin, PD-1 Inhibitors, (nivolumab, pembrolizumab), haploidentical allogeneic HSCT, and clinical trials. To achieve complete or good partial remission before stem cell transplantation (autologous, rarely allogeneic) rituximab (R)-bendamustin chemotherapy), a less toxic but less effective salvage treatment was earlier used.

2.5 Treatment-related late side effects

Three periods can be distinguished in the history of HL treatment: the first, disease-oriented period, between 1960 and 1985, where the primary concern was to increase HL patients' survival rates. In the treatment-oriented period between 1985 and 1995 the aim was to look for an optimal treatment, and, in the patient-oriented period from 1995 to these days the main aim has become to cure patients with the fewest possible early and late side effects. During patient follow-up it turned out that several early and late side effects may arise which can be linked to the disease and, even more likely, antitumour

treatments (mostly the appearance of organ damage: heart, lungs, thyroid gland and development of second malignancies), which may impair patients' quality of life and life expectancy.

Several side-effects are known that impact patient's mental health, potentially leading to physical, social and psychological disorders. Due to the use of modern treatment modalities patients with lymphoma are living longer hence we need to pay attention the development of mental and psychosocial disorders associated with the disease and its treatment.

2.5.1 The concept of quality of life

Quality of life is an extremely complex, subjective, and multidimensional concept, which has become one of the most widely used technical terms of today's medicine, health economics, and health sociology. In medicine the appearance of aspects of quality of life were underpinned by the definition of health issued by WHO in 1948. According to the resolution, health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Health research deals with a part of quality of life more closely related to health: health-related quality of life – HRQoL. In my theses I use the term quality of life as a synonym for health-related quality of life.

As a result of modern medical treatments, a significant proportion of HL patients recover, thus a growing body of literature is available on long-term survival of patients and disease outcome. The clinical end-point of many of these, mostly follow-up, studies is examination of quality of life. Perceived extent of impairment in quality of life is not always in direct proportion to extent of disease/appearance of complications. This was the reason why the concept of Patient Reported Outcome (PRO) was introduced, in which patients report on their own health. The most common method of measuring quality of life is the self-completion questionnaire.

2.5.2 Fatigue

Fatigue is a frequent, cancer-related non-specific symptom. Unlike tiredness experienced in everyday life, fatigue persists, and is not affected by rest. It is one of the most common symptoms experienced by patients with lymphoma accompanied by a pronounced morbidity and reduction of function. Fatigue can appear independently or jointly with numerous psychological and psychiatric diseases. The International Classification of Diseases Rev. 10 defines cancer-related fatigue as „significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level which has been present every day during the same 2-week period in the past month". In order to assess severity of fatigue objective self-completion questionnaires are available. The most widely used of these are Functional Assessment of Cancer Therapy-Fatigue (FACT-F), Functional Assessment of Chronic Illness Therapy (FACIT), EORTC - Quality of Life Core 30, version 3 (EORTC QLQ-C30), and the Multidimensional Fatigue Inventory (MFI-20) questionnaires. The Fatigue-2 study, which analysed 379 cancer patients, showed that fatigue has a much greater impact on quality of life than presence of vomiting, depression, or pain. Fatigue has important emotional, psychological and financial ramifications from the aspect of both the patient and their environment.

2.5.3 Employment status

Based on literature data the employment status of those HL patients who are in durable remission or have been cured varies from 71 to 85%. The unemployment rate in North-East Hungary was 7.2% among the 40-49-year-old inhabitants in both gender in the analyzed timeframe/period (from 2012 to 2015) according to the data of the Central Statistical Office (KSH), and 14.5% percent of the working age population was inactive.

2.5.4 Mental stress, anxiety, and depression

Cancer can present numerous psychological consequences for recovered patients or survivors as well, which are different from the type experienced at onset of disease. Earlier threat of a fatal disease, and the patient's personal fight with death have long-term psychological consequences, and survivors

can dread the return of the disease and treatment-related late complications including secondary malignancies, which can lead to anxiety, depression and damaged body image. In the first year following establishment of diagnosis clinically significant anxiety or depression is likely to develop in 63% of HL patients, which can usually improve within a short time. After treatment, a proportion of patients have to face reduced interest in sex and reduced sexual activity. Their return to work can also be problematic primarily on account of negative discrimination due to psychological disorders and lasting disease, which, in turn, can lead to further adaptation disorders. Advanced disease and greater treatment toxicity may be predisposing factors to post-treatment adaptation problems and development of mental and psychological stress. Recognition of anxiety and depression is of paramount importance as they can be treated with psychotherapy, changes in life style and medications. There is scares literature on examining mental health disorder and pathological stress level among haematological patients, and we have not found any reference in connection with the dysfunctional attitude and perceived stress level in this patient group.

3. Aims

   The overall aim of our study was to examine the long-term improvement of HL patients' quality of life; a realistic goal can be to ensure that their quality of life should not differ from that of the healthy/normal population:

1. To assess incidence of fatigue and changes in quality of life among our regularly followed up HL patients using the EORTC QoL core 30 version 3 questionnaires. To look for correlations between factors related to the patient, the disease, and treatment.

2. To investigate our HL patients' employment status in the context of disease characteristics and treatment.

3. To examine our HL patients' incidence of psychological disorders (anxiety, depression, mental stress, sense of coherence, perceived stress, dysfunctional attitude), using a questionnaire as well as the risk factors contributing to their development.

4. Patients and methods

4.1 Assessing fatigue and quality of life

In the first part of our study we performed assessment of fatigue and quality of life. 168 patients included in the study were treated between Jan 1, 1969 and June 30, 2005. We used the validated, Hungarian-language questionnaire of EORTC QOL core 30 version 3 measuring instrument, the most widely used instrument in the international literature to assess cancer patients' quality of life. It contains 30 items, the first 28 of which can be marked by those who fill in the questionnaire on a 4-point Likert scale while the last two can be scored on a 7-point Likert scale. Application for the scale is dependent on registration approval. After registration EORTC made the Hungarian-language validated version and the attached Scoring Manual available to us. The questionnaire contains 5 functional scales (physical, emotional, cognitive, and role), 3 symptom scales (fatigue, pain, nausea, and vomiting), one scale to assess global health and quality of life as well as 6 simple questions (e.g. loss of appetite). Each question is closed (answers to questions are limited, answers can only take place within the content units provided by the researcher(s). Processing and evaluation of the questionnaire was carried out on the basis of the EORTC Scoring Manual. First Raw Score (RS) was calculated, using the numerical values of the answers given to questions in connection with the given symptom scale (fatigue) and quality of life. (In regard to fatigue, we calculated the answers to 3 questions using scores 1-4, and the 2 answers given to questions on quality of life using scores1-7). Fatigue Score and QL2, signalling quality of life, were also calculated and RS was transformed into a 0-100 scale, using linear transformation. Higher FA scores represented worse „results", i.e., more severe fatigue. Based on results of the GHSG study, fatigue scores lower than 20 do not represent significant pressure ("normal level"), while scores over 40 probably represent great pressure ("pathological level"). Higher QL2 scores represent better quality of life, however, there are no precisely defined values for „normal" or „pathological" fatigue. International literature suggests that a 10% or greater change in QL2 corresponds to a „moderate change" described by patients while a 5-10% change represented „a small change".

4.2 Assessing employment status and mental health

In the second part of our study we selected 170 out of 201 regularly followed up patients with HL within the framework of cross sectional research. Seven of them refused to participate in the study. Between January 1, 2012 and March 30, we performed the examination of 163 HL patients 2015, whose diagnoses were established between January 1, 1969 and July 1, 2013.

A questioner was applied to evaluate employment state. We considered inactive the disabled and those who stated themselves otherwise inactive, while the others were recorded as active. Among life defining events we asked about the post-treatment loss of employment also.

To assess anxiety and depression the **Hospital Anxiety and Depression Scale (HADS)** questionnaire was used. The measurement instrument was developed by Zigmond and Snaith in 1983 to assess the mood of non-psychiatric patients. According to Hermann et al.'s study, it can be used equally well in both patient and healthy populations. The questionnaire has since been translated into multiple languages. Validation of the Hungarian-language was carried out by Muszbek and colleagues in 2004, on an oncology patient population of more than 700. Completion of the questionnaire takes 5 to 10 minutes; it has a methodologically important feature, namely that it also contains reverse worded items, reducing or preventing response bias or agreement bias. The 14 items (7 for anxiety and 7 for depression) are scored on a 4-point scale (0-3), and is arrived at from a simple addition of the total values, with a maximum of 21 points. Based on the recommendation of Zigmond and Snaith, two cut-off values can be used in interpretation (8 or higher and 11 or higher punts). In this study we regarded the lower cut-off value as pathological.

The General Health Questionnaire (GHQ) is a self-assessment screening tool for the population-level assessment of mental health disorders including mental health issues accompanied by mood and anxiety symptoms and emotional distress. The term „general health questionnaire" may be misleading as it is suited to assess mental health only and not „general health". The questionnaire reflects people's condition in the past two weeks. In the 12-item version each question is to be scored on a 4-point scale. Based on a bimodal scoring method (0-0-1-1 point) the final point is between 1 and 12. In patients with 5 or higher values the risk for anxiety/depression in increased.

Is order to assess sense of coherence, the Hungarian-language, validated version of the **Sense of coherence (SOC)** questionnaire was used, which is suitable for assessing patients' ability to cope with stressful situations. The SOC represents consonance, inner harmony, and structural characteristics. Extent of agreement with the statements of the 13-item questionnaire can be scored on a 7-point Likert scale whose total score is between 13 and 91. Higher values are indicative of a stronger sense of coherence.

To assess chronic stress we used the Hungarian-language, validated version of the **Perceived Stress Scale (PSS)** a stress assessment instrument. The 4-item questionnaire reveals your feelings and thoughts during the last month. For each item, higher scores are correlated with higher numbers of stressful situations and more successful coping. Because of the latter, PSS scores are obtained by reversing responses to the four positively stated items and then summing across all scale items, producing the global indicator of perceived stress.

To assess dysfunctional attitude the **Dysfunctional Attitude Scale form (DAS-A)** was used. Items on the questionnaire disclose cognitive errors and dysfunctional thoughts that become consolidated as a result of earlier experience and influence an individual's thinking about themselves and the world as rigid, incorrect schemes and can predict psychological problems, adaptation difficulties and adaptation deficit. In our study we used the 17-item version also validated on a Hungarian sample, which can be divided into two subscales (perfectionism/performance assessment vs dependence). Each item is to be scored on a 7-item Likert scale with the final score provided by a summation of the scores for the individual answers.

4.3 Statistical methods

Statistical analysis was performed using SPSS 15 and IBM SPSS 20 software. Continuous variables were evaluated using independent samples t-test, Mann-Whitney U test and, to allow comparison of more than two groups, variance analysis and Kruskal-Wallis test were used. To measure the relationship between continuous variables Spearman's correlations were used. Following changes in the characteristics of HL and fatigue, and quality of life were measured using GLM (general linear model) repeated measures. Factors affecting employment characteristics of recovered patients were calculated using binary logistic regression test. Significance level was set at $p < 0.05$.

5. Results

5.1 Patient characteristics in the fatigue and quality of life groups

During our work we assessed frequency and severity of fatigue as well as quality of life in 85 female and 83 male patients with HL using the QLQ-C30 questionnaire. Mean age of the patients at the time of questionnaire completion was 43.11 years (18-77 years) and the survey took place 9.5 years (0.5-36 years) on average since diagnosis.

"Normal fatigue scores" (FA<20) were only found in 23.8% of patients. Patients with lower haemoglobin levels (females <120 g/l, males <135 g/l) at the time of the study showed significantly higher FA scores (FA: 44.42±27.04) than patients with normal haemoglobin levels (FA: 33.71±23.71; p=0.05). In terms of FA values we found no significant correlation between disease (sex, stage, B symptoms, histological subtype) and treatment (CT, RT, CMT) characteristics. In patients with relapsed lymphoma we found higher FA scores compared with patients in remission; however, the difference was not statistically significant.

Assessment of other characteristics of the treatment revealed significant differences between patients who had been disease-free for at least ten years after treatment(s), in other words, they had recovered [mean time after treatment(s) 16.6 years (11-33 years)] as compared to patients who had not been in complete remission for at least 10 years (FA: 41.36±27.60 vs. FA: 32.86±22.68; p<0.05). Patients treated for longer than twenty years had higher FA (FA: 53.37±28.69) as compared to those being treated at the time (FA: 29.35±23.04; p<0.03). Significantly higher FA values were found in patients who developed treatment related late complications than in patients with no such complications (FA: 48.72±28.29 vs. 31.88±22.20; p<0.01). We determined treatment-related late complications (cardiovascular, pulmonary, thyroid glands, secondary malignancies, changes in post-radiation skin and muscles, osteoporosis, ovarian dysfunction, renal damage, gastrointestinal) based on the results of our earlier study.

Quality of life score (QL2) was significantly lower in patients with late complications than in those without (mean QL2: 45.53±25.39 vs. mean QL2: 67.57±21.44; p<0.001). QL2 score was also found to be significantly lower in recovered patients as compared to those who had not recovered (mean QL2: 52.50±25.77 vs. QL2: 67.48±25.79; p<0.001). Mean QL2 score was lower in

patients who had received only RT but the differences were not significant. No correlation was found between the complications determined and fatigue/quality of life.

On account of the significant differences (QL2, fatigue) between the group of recovered patients and that of patients with late complications we analysed all functional and symptom sub-scales. In patients with late complications the scores for physical function (PF), role function (RF), and emotional function (EF) were significantly lower while scores for dyspnoe (DY) and pain (PA) were significantly higher as compared to HL patients with no late complications. Physical activity had decreased and the dyspnoe score was higher in the group of recovered patients, in other words, patients who had been in remission for at least 10 years, than in the group of patients who had not recovered and the differences were significant. Of the 52 patients who had been in CR for at least 10 years, 30 had received extended field chest RT (mantle or total nodal RT).

5.2 Patient characteristics in the employment status and mental health group

Relationship between employment status and quality of life was assessed in a total of 163 adult HL patients. Nineteen patients were pensioners (over 65) and employment status of four patients was not known, leading to their exclusion from a further subgroup analysis. We analysed data of 140 patients of working age (71 females, 69 males).

Patients' mean age at the time of diagnosis was 32.13 ± 13.05 years, and 44.82 ± 14.55 years at the time of survey completion. The most common histological subtype was MC (57 patients, 41%). 73 patients (53%) had early-stage disease, 68 patients (49%) had comorbidities, with the most common of them being: cardiovascular: 11%, gastroenterological: 10%, dermatological: 5%, musculoskeletal: 5%, haematological: 2%. 95 patients (67%) received ABVD-t, with 43 patients (31%) receiving other type of chemotherapy. 103 patients (74%) had received irradiation therapy. Incidence of cardiovascular complications was significantly higher in the active than in the inactive group (9 vs. 12 patients, 10% vs. 25%, $p=0.026$), while no significant difference was found between the two groups in terms of other common complications (pulmonology disease: 7 vs 6 patients, thyroid glands: 23 vs. 17 patients, post-radiation skin changes: 4 vs 4 patients).

5.2.1 Assessing employment status

During our work we regarded employment status at the time of questionnaire completion as an important factor of normal life, hence we formed two groups: one active (93 patients) and another, inactive (47 patients).

The age of inactive patients at the time of diagnosis, and survey completion and the incidence of treatment-related late complications was significantly different from that of active patients. Our survivors who were still active were on average 10 years younger, their disease had been identified 7.5 years earlier, the number of patients with higher educational levels was almost twice as high and had about half the number of complications as compared to the inactive group.

5.2.2 Independent predictive factors of employment status

We carried out multiple regression analysis in order to identify determining variables and take out non-significant variables. Our results showed that in inactive HL patients lymphoma was identified at a later advanced stage ($\geq$30 over vs below, p=0.001), their educational levels were lower (elementary school or higher educational level vs. college education p=0.032), and had more late complications (yes vs no, p<0.001) as compared to active patients.

5.2.3 Factors accounting for treatment-related late complications

Significantly more treatment-related late complications were detected in female HL patients under treatment (p=0.011) and in patients who had received non-ABVD type treatment (p<0.001). The 71 female patients in the study had more relapses (p=0.003) and comorbidities (p<0.001) as compared to male patients (data not shown in tables). Both female sex (OR: 2.67 (95% CI 1.327–5.375); p=0.006) and non-ABVD type treatment (OR: 6.17 (95% CI 2.788–13.655); p<0.001) proved to be independent predictive factors in terms of treatment-related late complications.

5.2.4 Job loss as a result of HL treatment

33 patients lost their jobs due to treatment for HL, 13 of them were able to find employment again with 20 becoming permanently inactive. 85% (17/20) of the patients who had become inactive and 38% of active patients (5/13) had treatment-related late complications (p=0.009).

5.2.5 Assessing mental health

The HADS questionnaire identified anxiety in 34 (25%), and depression in 14 patients (10%). Mean scores on the anxiety/depression, perceived stress, and stress/depression/anxiety (DAS total) as well as perfectionism subscales (DAS perfectionism) of the HADS instrument in inactive HL patients were significantly higher as compared to those in active patients. GHQ test results suggested pathological stress in 14 patients (10%), a score 5 times higher in active patients. Assessment of sense of coherence (SOC test) revealed significantly higher mean scores in active HL patients. With the exception of DAS dependence, performance of inactive patients tended to be considerably worse as compared to active HL patients on all questionnaires. Pathological scores on at least three questionnaires were regarded as signs of a severe mental disorder. We identified 15 patients (7 inactive, 5 active, and 3 retired persons) who, on the basis of their results, required immediate medical care. We referred 10 patients to clinical specialist consultation (clinical psychologist/psychiatrist), and a further 5 patients to a psychologist at this time already working in our clinic. Follow-up of patients showed that of the 7 inactive patients 3 had found employment again.

6. Discussion

Treatment of HL has become one of the success stories of oncohematology in recent decades. As a result of modern risk- and response-adapted therapy today 80-85% of patients become long-term survivors and recover. Due to this fact, in patient care, treatment-related late complications have come to the fore. Of these, in our research we examined fatigue, mental health and the determining factors that have an impact on them.

Fatigue is a general, non-specific cancer symptom, which has been reported by literary data to be present in 50% of patients as early as time of diagnosis. Cancer-related fatigue is a persisting, subjective sense of physical, emotional or mental exhaustion, disproportionate to any recent change in activity level. Severe exhaustion considerably affects the everyday lives of both patients under treatment and those in remission. Development of fatigue is multifactorial, influenced by the direct effects of tumour (mass), treatment (CT, RT, CMT) and the side-effects thereof, comorbodities, as well as by the presence and development of numerous mental and psychiatric illnesses. Fatigue remains a real-life problem even after successful treatment of HL as its incidence is 2 or 3 times higher than that of the general population.

Our results led us to conclude that, in terms of fatigue scores, we found no significant correlations between the characteristics of either disease or response to treatment. We found higher FA scores in patients with relapses versus patients in complete remission, and, while quality of life was worse (QL2 score was lower) after single RT as first treatment, the difference was not statistically significant in either case. Today, it is recommended to pay more attention not only to effective salvage treatments but also to patients' quality of life. Based on our experience, rituximab-bendamustin (completed or replaced with rituximab brentuximab-vedotin) therapy can be an effective and safe salvage therapy with a favourable side-effect profile. By using less toxic, alternative treatment modalities we can improve survival and quality of life of our refractory patients with relapses. In our studies we found significantly higher FA scores in patients who had lower haemoglobin levels at survey completion time, were suffering from treatment-related late complications and belonged to the group of recovered patients (disease-free for 10 years). An explanation for the results found in the latter group may be that, due to advanced age, other comorbidities also need to be taken into account during longer survival, and the treatments received in earlier years and decades were

more toxic, hence more likely to be accompanied by treatment-related late complications. Examination of other characteristics of the treatment showed that in the group of recovered patients (disease-free for at least 10 years) FA scores gradually increase while QL2 scores decrease, suggesting that quality of life is worsening. Exceptionally bad scores can be observed in those who have been in remission for at least 20 years (15/52 patients), which may be related to the fact that 57% of these patients had received extended field chest RT therapy and thus had more treatment-related late complications. Our patients with treatment-related late complications had significantly higher FA and lower QL2 scores. In patients with treatment-related late complications physical, role and emotional functions significantly decreased while dyspnoe and pain scores were significantly higher as compared to HL patients with no treatment-related late complications. Results of our study led us to conclude that fatigue is one of the most common conditions accompanied by loss of function to which more attention should be paid during patient care. In newly-treated patients prevention and avoidance of risk factors, if possible, are necessary.

In accordance with our findings, a Norwegian work group's examination of 476 HL patients, found no significant associations between treatment type and persistence of fatigue. Presence of B symptoms at time of diagnosis could be significantly correlated with perceived fatigue; however, we found no such correlation in our work. Examination of 557 HL patients by another Norwegian work found significant associations with clinical stage group but not with other treatment characteristics. Results of 818 HL patients in the HSG study showed that fatigue was more frequent even years after treatment than in the control population. Level of fatigue showed associations with several patient- and disease-related factors (age, sex, B symptoms, occurrence of relapses, haemoglobin level, cancer in the family, smoking). The role of comorbidities in the development of disease has been confirmed by two earlier studies in addition to our own. Comparing their results with those of the „normal" population, Ng et al. concluded that, of comorbidities, it is primarily the occurrence of cardiovascular complications that affect occurrence of fatigue.

It is known that patients with cancer-related fatigue are usually underdiagnosed and not reported to health registers and a considerable proportion of them do not receive treatment. For efficient treatment of cancer-related fatigue precise diagnosis and assessment are necessary, for which today

we have objective measure instruments (questionnaires) at our disposal. Clinical treatment guidelines pay close attention to determining state of the disease - (remission, relapse, progression), treatment type and time and their fatigue-inducing effect (e.g. CT and RT are worse than surgical removal). Resolving potentially reversible factors such as concomitant anaemia, thyroid dysfunction, osteoporosis, cachexia, chronic pain, mental stress, sleep disorder and proper treatment of comorbidities are extremely important and often require multidisciplinary cooperation. An essential element of treatment is education of the patient's family about cancer-related fatigue, its causes, importance and treatment options. According to NCCN guidelines, non-medication treatment options are as follows: increasing physical activity, strengthening exercises, psychological guidance, psychosocial treatment, advice on eating, and sleep therapy. Majority of medication treatments can be suitable for treating concomitant symptoms and diseases (anaemia-eritropoetin, cachexia-megestrol acetate). However, even today, there is not a single registered medicine for cancer-related fatigue. Favourable results have been published in connection with use of two medications. The first is methylphenidate, a psychostimulants, and currently available only in clinical trials. The second one is methylprednisolone, whose short-term use can contribute to improving patients' fatigue, appetite and satisfaction.

Since HL primarily affects the active population, a considerable proportion of patients at time of diagnosis are in young adulthood (mean age around 35 years), thus, its social significance surpasses its incidence. Recovered patients' post-treatment social reintegration and return to work are important objectives for the patient, the therapist and society alike. Work is an organising element in people's everyday lives and a source of livelihood, one of the prerequisites of independent life. We planned assessment of employment status in our patients under treatment (recovered, in remission). At the time of survey completion two-thirds of our patients were in active employment status. Independent predictive symptoms of HL patients were younger age at time of diagnosis, higher qualifications, and absence of treatment-related late complications. No difference was found between the two groups in terms of patients' sex and characteristic determined at the time of HL diagnosis.

Risk factors for late complications were female sex and non-ABVD chemotherapy. Through the reduction of irradiation field and doses and the introduction of ABVD therapy, HL treatment became more targeted, shown by

a decrease in treatment-related late complications among our patients after 2002. Treatment-related late complications, in particular, cardiovascular diseases clearly contribute to inactive employment status.

Literature data suggest that employment status of recovered HL patients/those in permanent remission is 71-85% while in our own patient population this number was 66%. Data of the Central Statistical Office (KSH) (https://www.ksh.hu/), unemployment rate at this time in the north-east of Hungary was 7.2%, (period: 2012-2015, population: 40-49 years population, both sexes), almost twice as high as that of our HL patients (5%). In contrast to this, however, the proportion of inactive HL patients was 1.5 times higher than in the general population (21.0% vs. 14.5%). Both our HL patients' and the Central Statistical Office's data apply to working-age populations; unemployed patients are registered job-seekers unlike inactive patients, who do not seek employment. A quarter of our HL population live on disability support pension (25%). while in Sweden the corresponding number is 9%, and in Denmark 18% of HL patients become permanently disabled after treatment. These data underscore the need for more help for our long-term surviving patients in their return to work and rehabilitation.

Only five studies in the literature have examined employment status of HL patients' in remission, four of which were questionnaire-based. In 1986 Fobair et al. found that male sex, depression, age over 30 and current disease activity showed a close correlation with the number of hours worked. Return to work was not affected by disease stage or treatment type. According to data published in 1998 by Abrahamsen et al., 95% of 557 patients treated between 1971 and 1991 returned to work after 18 months on average following treatment. During the follow-up higher rates of unemployment were found among women (64% of women and 85% of men worked after 18 months following treatment. In 2012 Chen et al. demonstrated a correlation between male sex and scars in the head-and-neck region versus rejection of work(place). A 2015 study by Glimelius et al. showed that the risk of losing their job was greater in advanced-stage patients who had received full-dose chemotherapy, which could not be explained by development of a relapse, secondary malignancy or cardiovascular disease. A German work group examined correlations between social reintegration and treatment results in 5360 HL patients. They found that grave FA scores (50 or greater) negatively influenced employment status both in women and in men (51% and 63%),

whereas in the absence of grave FA scores, the corresponding numbers were 78% and 90%, respectively.

During our work we used numerous validated measurement tools to assess the mental health of our HL patients and were able to show a close correlation between employment status and psychological well-being. Active (employed status) HL patients had significantly less anxiety, depression and pathological performance assessment (perfectionism) and their ability to cope with stressful situations was also better. In a considerable proportion of recovered HL patients and those in permanent remission we do not need to consider development of significant anxiety or depression. Results of clinical examinations (using HADS questionnaires) of patients with lymphoma showed a 15-42%, incidence for anxiety, and 4-35% for depression. In our study population, the HADS questionnaire showed a 25% incidence for anxiety and 10% for depression. There is scarce literature on the use of the GHQ questionnaire in haematological diseases. Dutch authors studied development of mental stress using the GHQ questionnaire for a three-year period after bone-marrow transplantation. 13% of patients showed pathological/excessive stress, which corresponded to data of the general population. A Finnish work group found no correlation in terms of GHQ values between acute lymphoid leukaemia survivors and a control group. Use of the GHQ questionnaire revealed pathological stress in 10% of our HL-s, with the corresponding number in active patients being significantly lower. We detected pathological stress in 5% of active patients and over 20% in inactive patients. A Swedish work group examined HL patients' sense of coherence (SOC questionnaire) and their mean values of their responses (66.8±11.2) were rather similar to our own results (66.90±11.26). No literature is available in connection with the use of DAS and PSS questionnaires in haematological diseases.

Examination of quality of life, employment status and mental health of HL/cancer long-term survivors, as a function of improving treatment results, is becoming an ever more important end-point of clinical research in this field.

In sum, our data have led us to conclude that employment status, educational level, and treatment-related late complications play key roles in HL patients' quality of life. In addition to curing patients using modern treatment modalities, turning them into fully functioning survivors fit for work is also an important objective. An increasing number of clinical studies support the need for work rehabilitation of recovered cancer patients, including HL patients. In Denmark, there is an extensive tax-benefit system to provide work

opportunities for patients with permanently reduced work ability. They receive financial compensation based on the degree of their disability as pensions. In Sweden, multidisciplinary interventions help promote a healthy working environment and healthy way of life with spiritual, psychological and professional support playing a role in them. In Hungary oncology patients have access to a social reintegration programme. At present, the Hungarian for HL patients does not contain guidelines in connection with work rehabilitation. Based on the results of our study, we recommend an extended social reintegration programme also for recovered HL patients in remission. With a view to improving our patients' mental well-being, we have a clinical psychologist working at our clinic and also an Oncohematology Patients' Club. It would be desirable to spend more time during follow-up sessions on the psychological guidance of our recovered patients in remission, potentially helping them in stepping out of their role as a patient.

7. Novel statements

1.   Fatigue was detected in more than three quarters of our HL patients. FA scores of patients with lower haemoglobin levels were significantly higher. We found no correlation between disease and treatment characteristics versus fatigue; however, in patients with relapses FA scores were higher but not significantly.

2.   Fatigue is more frequent among recovered patients and those with treatment-related late complications and their quality of life is worse, too. Physical, role, and emotional functions were significantly decreased in patients with treatment-related late complications, their dyspnoe and pain scores were significantly higher compared with HL patients with no treatment-related late complications.

3.   International data for employment status of HL patients are 71-85% while we found this value to be 66% in our study. Unemployment rate in the examined period was better than that of the general population. In contrast, rate of inactive HL patients (due to the great number of patients on disability pension) was 1.5 times higher than that of the general population.

4.   In our HL patients independent determining factors of employment were younger age at time of diagnosis, higher educational levels and absence of treatment-related late side effects. Risk factors for treatment-related late side effects were female sex and non-ABVD chemotherapy.

5.   Assessment of mental health revealed a close correlation between employment status and mental well-being. We found significantly lower incidence of anxiety, depression and pathological performance assessment (perfectionism) in active HL survivors and their ability to cope with stress was also better.

8. Summary

As a result of the use of modern examination methods as well as risk and response adapted strategies, 80-85% of HL patients today survive or recover, hence treatment of HL has become one of the success stories of oncohaematology over the past decades. Parallel to this, treatment-related (late) complications have come to the fore. Of these patients' long-term life expectancy is mostly affected by the development of second malignancies and appearance of organ damage (heart, lungs, thyroid gland). However, several side effects are known to affect patients' quality of life and mental health, and can thus lead to social and psychological disorders in patients. HL primarily affects the young adult active population, with a significant portion of patients at the time of diagnosis being young adults (mean age around 35).Thus, its social and economic importance surpasses its incidence.

In our study we found fatigue in three-quarters of our HL patients in significant correlation with lower haemoglobin levels. We detected significantly higher fatigue scores and worse quality of life in our recovered patients with treatment-related late complications. One explanation for this is that, due to older age, other comorbidities also need to be reckoned with during longer survival, and treatments in earlier years and decades were more toxic, thus likely to lead to more late complications. Our results have led us to conclude that fatigue is one of the most common conditions accompanied by reduction in function that warrant special attention during patient care.

During our work we used validated measurement tools to assess HL patients' mental health and demonstrated a close correlation between employment status and mental well-being. Our results suggest that independent determining factors of employment were younger age at time of diagnosis, higher educational level, and absence of treatment-related late complications. Risk factors for late complications were female sex and non-ABVD therapy. Based on the results of our study we recommend an extensive social reintegration programme for recovered HL patients in remission. It is also desirable to dedicate more time to the psychological guidance of our recovered patients in remission during their follow-up care.

Key words: Hodgkin lymphoma, mental health, fatigue, quality of life, treatment-related late complications

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1. **Magyari, F.**, Kósa, K., Berecz, R., Illés, A., Miltényi, Z., Simon, Z., Illés, Á.: Employment status and health related quality of life among Hodgkin-lymphoma survivors'- results based on data from a major treatment center in Hungary.
   Health Qual. Life Outcomes. 15 (1), 1-9, 2017.
   DOI: http://dx.doi.org/10.1186/s12955-017-0758-x
   IF: 2.143 (2016)

2. **Magyari, F.**, Barna, S., Husi, K., Simon, Z., Miltényi, Z., Váróczy, L., Udvardy, M., Illés, Á.: Alternative salvage regimens for relapsed/refractory classical Hodgkin-lymphoma.
   Hematology. 21 (7), 404-410, 2016.
   IF: 1.244

3. **Magyari, F.**, Simon, Z., Barna, S., Udvardy, M., Váróczy, L., Illés, Á.: Successful administration of rituximab-bendamustine regimen in the relapse of Hodgkin lymphoma after autologous hemopoietic stem cell transplantation.
   Hematol. Oncol. 30 (2), 98-100, 2012.
   DOI: http://dx.doi.org/10.1002/hon.1004
   IF: 2.036

4. Miltényi, Z., **Magyari, F.**, Simon, Z., Illés, Á.: Quality of life and fatigue in Hodgkin's lymphoma patients.
   Tumori. 96 (4), 594-600, 2010.
   IF: 1.014

További közlemények

5. **Magyari, F.**, Bedekovics, J., Décsy, J., Ilonczai, P., Illés, Á., Simon, Z.: A korai/praefibroticus primer myelofibrosis kivizsgálása és kezelése egy eset kapcsán.
   Orvosi Hetilap. 159 (15), 603-609, 2018.
   DOI: http://dx.doi.org/10.1556/650.2018.30995
   IF: 0.349 (2016)

6. Illés, Á., Simon, Z., Udvardy, M., **Magyari, F.**, Jóna, Á., Miltényi, Z.: Így kezeljük az autológ őssejt-transzplantáció után kiújult Hodgkin-lymphomát.
   Orvosi Hetilap. 158 (34), 1338-1345, 2017.
   DOI: http://dx.doi.org/10.1556/650.2017.30823
   IF: 0.349 (2016)

7. Simon, Z., Barna, S., Miltényi, Z., Husi, K., **Magyari, F.**, Jóna, Á., Garai, I., Nagy, Z., Ujj, G., Szerafin, L., Illés, Á.: Combined prognostic value of absolute lymphocyte/monocyte ratio in peripheral blood and interim PET/CT results in Hodgkin lymphoma.
   Int. J. Hematol. 103 (1), 63-69, 2016.
   DOI: http://dx.doi.org/DOI 10.1007/s12185-015-1884-z
   IF: 1.61

8. Pinczés, L. I., Miltényi, Z., Jóna, Á., **Magyari, F.**, Husi, K., Illés, Á.: How the Epidemiology of Hodgkin Lymphoma changed in Debrecen, Hungary.
   Med. Res. Arch. 4 (6), 1-13, 2016.

9. **Magyari, F.**, Barna, S., Miltényi, Z., Rajnai, H., Csomor, J., Udvardy, M., Illés, Á., Váróczy, L.: Histopathological Difficulties in an Adolescent Lymphoma Patient.
   Pathol. Oncol. Res. 21 (1), 213-217, 2015.
   DOI: http://dx.doi.org/10.1007/s12253-014-9810-x
   IF: 1.94

10. Miltényi, Z., Barna, S., Garai, I., Simon, Z., Jóna, Á., **Magyari, F.**, Gergely, M., Nagy, Z., Keresztes, K., Pettendi, P., Illés, Á.: Prognostic value of interim and restaging PET/CT in Hodgkin lymphoma: results of the CHEAP (Chemotherapy Effectiveness Assessment by PET/CT) study - long term observation.
   Neoplasma. 62 (4), 627-34, 2015.
   DOI: http://dx.doi.org/10.4149/neo_2015_075
   IF: 1.961

11. **Magyari, F.**, Rajnai, H., Barna, S., Miltényi, Z., Váróczy, L., Csomor, J., Udvardy, M., Illés, Á.: Diagnosztikus nehézségek adolescens lymphomás betegünknél.
    LAM. 24 (4), 191-195, 2014.

12. Illés, Á., **Magyari, F.**, Barna, S.: Nyirokcsomók daganatai, a lymphomák a háziorvosi gyakorlatban.
Granum. 16 (3), 14-19, 2013.

13. Páyer, E., Miltényi, Z., Simon, Z., **Magyari, F.**, Barna, S., Méhes, G., Illés, Á.: Diagnostic and Therapeutic Difficulties in Diffuse Large B-cell Lymphoma Arising From HHV8 Positive Castleman Disease.
J. Hematol. 1 (2-3), 65-69, 2012.

14. Simon, Z., Illés, Á., Miltényi, Z., **Magyari, F.**, Váróczy, L., Péter, N., Gergely, L.: Immunológiai változások diffúz nagy B-sejtes lymphomában Rituximab-CHOP kezelést követően: saját adatok elemzése és irodalmi áttekintés.
Orv. Hetil. 153 (42), 1658-1666, 2012.
DOI: http://dx.doi.org/10.1556/OH.2012.29471

15. Váróczy, L., Páyer, E., Kádár, Z., Gergely, L., Miltényi, Z., **Magyari, F.**, Szodoray, P., Illés, Á.: Malignant lymphomas and autoimmunity - a single center experience from Hungary.
Clin. Rheumatol. 31 (2), 219-224, 2012.
DOI: http://dx.doi.org/10.1007/s10067-011-1807-1
IF: 2.037

16. **Magyari, F.**, Páyer, E., Barna, S., Simon, Z., Miltényi, Z., Udvardy, M., Váróczy, L., Illés, Á.: Az első tapasztalatok rituximab-bendamustin kezeléssel Hodgkin-lymphoma autológ perifériás őssejt-transzplantációt követő progressziójában.
Magyar Belorv. Arch. 2011 (64), 167-169, 2011.

17. Miltényi, Z., Barna, S., **Magyari, F.**, Tóth, Z., Garai, I., Illés, Á.: Segít-e a 18FDG-PET/CT vizsgálat a T/NK sejtes lymphomák ellátásában?
Magyar Belorv. Arch. 64 (3), 160-166, 2011.

18. Váróczy, L., Gergely, L., Simon, Z., Miltényi, Z., **Magyari, F.**, Illés, Á.: Myeloma multiplex és autoimmunitás.
Hematológia-Transzfuziológia. 43 (4), 311-315, 2010.

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