# PhD THESES

# LATE COMPLICATIONS OF THE TREATMENT

# OF HODGKIN'S LYMPHOMA

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#### INTRODUCTION

Hodgkin's lymphoma (HL) is a malignant lymphoproliferativ disease that has typical clinical and morphological characters. HL differs from other lymphomas not only clinical characters but also cell content. Hodgkin and Reed-Sternberg cells and variant of these are only 1-2% between reactiv cells. HL is monoclonal B-lymphocyte origin, and divided two groups: nodular lymphocytapredominant HL (NLPHL and classical HL (cHL), which differents in their pathogenesis. Tumour cells don't produce immunoglobulins in cHL, but in NLPHL immunoglobulins are intact and well functioning. HL's international incidence — except Asia, where is rare— 0,9-3,0‰ between women and 1,5-4,5‰ between men, with 1,4-1,5:1 man dominance. There are 160-200 new patients in Hungary in a year. HL has bimodal age distribution, most cases occur in the 20-30 and 50-60 years of age. Characters of HL patients and the disease have important differents. The reason of HL is still unknown. More etiology factors can play a role in the development of HL with interaction of genetics, natural factors and the immunsystem.

In the past few decades, complete remission (CR) in 75–90% of the cases and recovery in most cases were achieved in patients with HL owing to treatment using polychemotherapy and/or radiotherapy (RT), corresponding to the stage and prognostic factors of the disease, as well as high-dose therapy supported by haemopoetic stem cell administration. Three periods in the history of treatment for HL are traditionally distinguished: the disease-oriented period (1960-1985), treatment-oriented period (1985-1995), and patient-oriented period (since 1995). In the first one, the aim was the improvement of overall survival. Having recognised that the late complications of treatment might greately influence survival and the quality of life, minimal curative therapy and quality of life are the main issues today. The general aim is to make the possibly highest number of patients get well again and ensure that their long-term survival was not different from that of the general population. Analysis of the mortality figures of patients treated for HL shows that in 15 years after the treatment, mortality from HL is exceeded by mortality from treatment complications, which keep rising; therefore long-term mortality figures are higher than those of the general population (mainly because of cardiovascular complications and second malignancies).

Treatment and care of patients for HL at the 3<sup>rd</sup> Department of Internal Medicine, Medical and Health Science Center of the University of Debrecen has gone on since 1975. About 600 HL patients are in care nowadays. I cutted in the HL patients' examinations in 1998. We examined late complications of the therapy, especially in radiotherapy regard, and I summarized these i my dissertation.

#### AIMS

My aims in the course of examinations of HL patients (who were treated and cared at the 3<sup>rd</sup> Department of Internal Medicine, Medical and Health Science Center of the University of Debrecen) were:

- To examine the cardiovascular complications —which principally affect the quality of life and survival—, coronary artery disease (to look for connection with therapy) and chronic pericarditis, that caused diagnostic and therapeutic difficulties.
- 2. To present thyroid complications, because these are the most frequent lesions of the late complications of HL therapy [mainly whom got neck radiotherapy (RT)].
- 3. To investigate whether or not the parathyroid glands are damaged similarly to the thyroid during treatment for HL.
- 4. To analyse renal and ureter complications in HL patients after treatment. Although primer manifestation of HL is rare in the genitourinal tract, but chemotherapy (CT) and RT, which were using in the earlier years, often injured these organs.
- 5. To examine carotid artery impairments and to show a young HL patient's case, who had several complications decades after RT (a pharyngocutaneous fistula developed complicated by rupture of the carotid arteries on both sides necessitating their ligation).
- 6. To investigate the late complications in cured Hodgkin's lymphoma patients. To discuss the relationships between the treatment for HL and these complications.

#### PATIENTS AND METHODS

I have surveyed the histories of patients treated and cared for HL at the 3<sup>rd</sup> Department of Internal Medicine, Medical and Health Science Center of the University of Debrecen between 1975 and 2004. I used written and computed documents and the Medsolution medical informatics programme system for collection of data. I only analysed that patients, whose data are fully available. 600 HL patients' data were usable untill 2004 end. At first histological subtyping was done according to Rye's classification, lately REAL/WHO classification has been in use. In the 1970s, occasional staging laparotomy was performed to accurately decide the stage of the disease so 5 patients underwent splenectomy. Basically, the clinical stage of the disease was defined according to Ann Arbor staging, which was later replaced by its modified version, known as Cotswolds staging. The patients were either given RT or CT, and some received combined modality therapy (CMT). RT involved mantle, inversed Y or (sub)total nodal telecobalt irradiation of a total mean dose of 40 Grays (Gy), (30-45 Gy), in 2 Gy daily doses, 5 times a week, the source being a Gravicert telecobalt device manufactured in Hungary. The device was capable of using only static fields of a certain size, it could not be applied for a large-field treatment, and therefore the so-called additive technique of treatment had to be used. The fields were composed of several parts, the focal dose was calculated for the centre of the body and only one direction per day could be used; treatment of the cervical and supraclavicular regions could only be provided from an anterior position. At the beginning, the fields were fitted manually, later, starting from 1980; the process was computer- controlled, based on isodose distribution measurements. At first monochemotherapy was took, after that (till 1990) primary polychemotherapy was CV(O)PP (cyclophosphamide, vinblastine (vincristine), procarbazine, prednisolone), while after 1990, it consisted of treatment using COPP/ABV (cyclophosphamide, vincristine, procarbazine,

prednisolone/adriamycin, bleomycin, vinblastine), and after 1999 ABVD (adriamycin, bleomycin, vinblastine, dacarbazin). We used BEACOPP (bleomycin, etoposid, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisolone), DHAP (dexamethason, cytarabin, cisplatin) and CEP (CCNU, etoposide, chlorambucil, prednisolone) for repeated treatments. Statistical analysis was performed using the chi<sup>2</sup> test, p<0,05 was significant.

#### Cardiovascular complications

I presented coronary artery disease and chronic pericarditis with case reports.

#### Analysing of thyroid functions

160 HL patients with complete remission for at least 1 year were followed up. For the evaluation of thyroid hormone levels and for the determination of supersensitive thyroid stimulating hormone (sTSH) LIA-mat TSH assays was used, which is based on a non-competitive, immunoluminometric sandwich technique (Byk-Sangtec). Free thyroxin (fT4) was measured by competitive luminescent immunoassay (LIA-mat FT4) using free triiodothyronine (fT3) Imx Free T3 assay, which is based on microparticulated enzyme immunoassay (Abbot). Using the above methods, normal ranges should be as follows: sTSH 0,3-3,0 mlU/ml, FT3: 2,6-5,4 pmol/l, fT4: 7,22-23,2 pmol/l. Hypothyroidism is considered to be subclinical, chemical or compensated if sTSH values alone are elevated while fT3, fT4 are in the normal range. In case of an elevated sTSH we find decreased fT3 and/or fT4 sometimes accompanied by clinical symptoms, we speak of manifest clinical hypothyroidism. The majority of patients have been followed up for thyroid function on a yearly basis. Thyroid dysfunction was considered at the first presentation of pathological thyroid hormone results. Ultrasound diagnosis and fine needle thyroid biopsy was performed too, if it was necessary.

But their results' evaluation was not aim in this study.

Examination of parathyroid damages

Calcium, phosphorus and parathormone levels were determined at the Department of Clinical Biochemistry and Molecular Pathology of the University in 143 HL patients, who receiving primary treatment and care for their disease and having been in complete remission for at least two years. In patients with antithyroid antibodies examined earlier, the presence of antiparathyroid antibodies was also checked. The normal values being as follows: calcium – 2.1-2.6 mmol/l; phosphorus – 0.8-1.45 mmol/l; parathormone – 1.2-6.8 pmol/l). ELISA (Elexis 101O) was used to determine intact parathormone. The Immunology Laboratory of our department applied a standardised indirect immunofluorescence technique to detect antiparathyroid antibodies using sections of monkey parathyroid gland (ImmuGlo 2180PARA) provided by ImCO Diagnostics (Buffalo, NY). Sera were diluted 10 times; positive control of a parathyroid gland provided by Euroimmune GmbH (Luebeck, Germany) and normal human serum were used as positive and negative controls, respectively.

#### Investigating of renal and ureter complications

I examined renal, ureter or bladder complications retrospectively between 512 primary treated and followed up patients with HL, who were treated between 1970 and 2000.

#### Carotid artery injuries

Carotid arteries were examined by B-K Hawk 2102 ultrasound, with 8 MHz, linear transducer. First we took a longitudinal section in B-mode and after that cross section of the place and size of the largest stenosis. Flow speed was measured in this stenosis. Other atherogen factors were examined with anamnesis, physical examination and blood tests (hypertension, diabetes mellitus, hypothyreoidism, hyperlipidaemia).

Late complications of the cured HL patients

We have surveyed the histories of patients diagnosed with and treated for HL between 1975 and 1994. Ninety of the patients had experienced complete remission before December 1994; they had been free of disease for at least 10 years so, according to definitions, they could be regarded 'cured' before December 2004. Based on the results of regular follow-up examinations among these patients we were able to examine late complications resulting from treatment. The investigations included chest X-ray, respiratory function, ECG, ergometry, echocardiography, myocardial perfusion SPECT, laboratory tests (renal function, thyroid function, tumour markers), mammography, breast ultrasound, and, abdominal and cervical ultrasound.

#### RESULTS

#### Cardiovascular complications

Late complications of treatment have become manifest owing to long-term survivals of patients with HL, with cardiovascular complications and secondary malignant tumours having the greatest impact on the patients' survival and quality of life. I presented the case of two young female patients who received mediastinal irradiation after which complete remission was achieved. In 12 and 19 years after the onset of the disease, control examinations revealed ischaemic heart disease, which was confirmed by coronary arteriography and solved by stent implantation in one of the patients and bypass surgery in the other one. The bypass surgery involving three vessels was performed. The immediate postoperative period was eventless, but unsuccessful resuscitation was performed after asystolia on the third postoperative day. On the postmortem examination, her coronary arteries were found sclerotic; in several cases plaques in the intima were found, reducing the lumen of the vessel by 70% at the beginning of the anterior descending branch of the left coronary artery (LAD) and by 90% at the start of the right coronary artery. Histological examination of the arteries found adventitial fibrosis immediately after the LAD anastomosis, which corresponded to irradiation vessel damage, whereas the right coronary artery had atherosclerotic plaque in the tunica intima. In both cases early coronary artery disease led to ischaemic heart disease, in which background were mediastinal RT, hypothyreoidism, early menopause in consequence. Exact incidence of radiation-induced heart disease is still unknown, different studies suggesting it being approximately 6-30%. This represents a wide spectrum of cardiac diseases, including pericarditis, pancarditis, pericardial fluid, valvular diseases, conduction system disease, and coronary artery disease (CAD). The frequency of CAD is difficult to precisely assess; its incidence may be 5,5-12%. After RT, it takes CAD a long time, 13-16 years on average, to develop.

A male patient, who was born in 1966, developed III/A2 clinical stage, mixed cellularity HL in 1992. He got CMT and RT repeated and he came to complete remission. In 1999 he had no symptoms, but the physical examination, routine chest radiography and echocardiography proved pericardial effusion. Apart from the most frequent reasons of pericarditis and pericardial effusion, radiation induced, hypothyreoid and primary manifestation of HL equally arised. After repeated fenestration of the pericardium partial pericardiectomy was necessary. Chronic constrictive pericarditis was proved by the histological evaluation of the pericardial tissue that was probably provoked by the mediastinal RT. Since the pericardiectomy he has being well, he had no relapsed and no signs of pericardial fluid was observed. The references confirm the development of pericarditis in the first place. In the background of the development of pericardial fluid there wasn't infection, autoimmun disease or metabolic disease. We detected subclinical hypothyreoidism, and started levothyroxine. The follow-up simulation showed, that the field of irradiation of the relapse of left mediastinum touched the pericardium. The heavy radiation dose could cause postirradiation chronic pericarditis. We detected cardiovascular disease (early coronary sclerosis, valvulopathy and pericarditis) 37,78% (34 cases) between the cured patients.

#### Analysing of thyroid functions

The 160 HL patients were examined for thyroid function. In 73,1% the patients were euthyroid, in 17,5% subclinical, in 8,8% clinical hypothyroidism was confirmed and in 1 cases hyperthyroidism was found. The two groups [HL patients with normal and pathological thyroid function (subclinical and manifest hypothyroidism together)] do not show significant differences as regards to mean age, age distribution in decades, histological subtypes, disease

stage, general symptoms, and whether lymphangiography was performed or not. Hypothyroidism was 1,5 times more frequent in women than in men. Significant differences can be seen between the euthyroid and dysfunctional groups in the type of treatment employed: more than 90% of the patients with thyroid dysfunction had received neck or mantle RT either alone or combined with CT. We diagnosed hypothyroidism in one third of patients receiving neck or mantle RT and almost in half of the patients at least six years after the treatment. We diagnosed thyroid dysfunction (mainly hypothyreoidism) in 24,4% of the cured HL patients. We suggest that examination of the thyroid should be performed regular during the follow up of HL patients. For substitution or isohormone therapy, levothyroxine is suggested for use, so that prevention of further complications.

#### Examination of parathyroid damages

The 143 HL patients were examined for calcium, phosphorus and parathormone levels. In 10 patients changes were observed (a slight increase above the normal range) but they were not accompanied by clinical symptoms. Cervical irradiation was given to 104 patients, seven of which had laboratory changes. No antiparathyroid antibodies were found in the sera of the 23 patients who had antithyroid antibodies (18 of them underwent neck irradiation).

#### Investigating of renal and ureter complications

We observed renal, ureter or bladder complications after irradiation in 16 cases (3,125%) between the 512 HL patients and 5,6 % between the cured patients (four patients have injured left kidney and one fibrosis induced pyelon dilatation developed). Acut and chronic irradiation nephropathy are rather anatomic than functional lesions. Ureters are radioresistant, their damage results from the fibrosis of the neighbouring tissues. These rare

complications of HL are usually avoided with the use of modern radiotherapy apparatus and the up to date treatment methods.

#### Carotid artery injuries

We examined carotd arteries of 120 HL patients, who are in complett remission at least 5 years. 70 patients received neck RT. 24 (34,3%) of them had carotid sclerosis or stenosis, and it was significant more than in the controll group [8 out of 60 patients (13,3 %)]. 12 patients of the 50, who didn't get RT, had carotid lesions, and it wasn't significant in propotion to controll group. Ranging from the sclerosis of the interna to 60 % stenosis of the vessel were detected. Significant stenosis of the carotid artery was found in 3 patients, all together received RT. We made for them MRI angiographia, but surgery was not necessary. Bilateral aneurismal rupture of the common carotid arteries developed in one patient, in another case, occlusion of the internal carotid injuries only occur in the RT group, under 40 years of age. RT probably has determinative role in young ages and other atherosclerotic risk factors have less role, but in elders these are important too. Damage to the carotid artery was found in 2.22% of the patients. Fifty per cent or graver stenosis of the carotid artery was found in 2.22% of the patients, but they only complained of aneurismal rupture or occlusion.

#### CONCLUSIONS

I attracted attention that cardiovascular (CV) complications having the greatest impact on the patients' survival and quality of life and these occur the most frequent in cured patients. The CV complications represent a wide spectrum of cardiac diseases, these occur diagnostic and therapeutic difficulties. These focus attention on the necessity of regular CV checkups, mainly who has got high risk.

We represented that hypothyreoidism is frequent between the earlier treated HL patients, and development of this showed significant relationship with neck RT. We diagnosed hypothyroidism in one third of patients receiving neck or mantle RT and almost in half of the patients at least six years after the treatment. We suggest that examination of the thyroid should be performed regular during the follow up of HL patients. For substitution or isohormone therapy, levothyroxine is suggested for use, so that prevention of further complications.

It has been concluded that high-dose external irradiation does not pose a higher risk for the parathyroids in contrast to thyroid.

The chronic kidney, ureter and bladder lesions usually take long and are indolent; they are not a cause of mortality. These rare complications are usually avoided with the use of modern treatment methods.

Carotid stenosis seems doesn't play a role in late mortality in HL, but if patient has increased risk for atherosclerotic changes, that regular examinations are necessary, and other risk factors (smoking, hypertension, diabetes mellitus, hypothyreoidism, early menopause) need to treat. We represented a young HL patient's case who has got multiple complications and therapy requires an interdisciplinary approach.

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A. Articles that directly grounded the PhD theses:

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   IF: 0,203
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  Á: Late complications of cured Hodgkin's lymphoma patients. Magy Belorv Arch accepted for publication (In Hungarian).
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### B. Other articles

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## **SCIENTOMETRY**

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#### Late complications of the treatment of Hodgkin's lymphoma

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