Hodgkin Lymphoma – Brief Information

Author: Maria Yiallouros, created 2009/02/05, Release: Prof. Dr. med. Christine Mauz-Körholz, English Translation: Dr. med. habil. Gesche Tallen, Last modified: 2024/01/29

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1. General information

Hodgkin lymphoma, also known as Morbus Hodgkin, Hodgkin's lymphoma or Hodgkin's Disease, is a cancer of the *lymphatic system*. Like the large entity of Non-Hodgkin-Lymphomas (NHL), it belongs to the group of malignant *lymphoma*s.

„Malignant lymphoma" literally means „malignant tumour of the lymph node". Medically speaking, the term summarises all cancers that arise from *cell*s of the lymphatic system (*lymphocytes*) and that can cause lymph node swelling.

Malignant lymphomas are classified into two major groups: Hodgkin's lymphoma, which is named after the physician and pathologist Dr. Thomas Hodgkin, and the *Non-Hodgkin lymphoma*s (NHL). Differentiation between these two types of lymphomas is only possible by analysing the affected tissue under the microscope (histological examination).

Hodgkin lymphoma develops from transformed *B lymphocytes*, a type of white blood cells (leukocytes) found in lymphatic tissue. Hodgkin lymphoma can arise from every organ comprised of lymphatic tissue. The most common localisation is the *lymph nodes*, however, liver, *bone marrow*, lungs or spleen can also be affected, especially in advanced stages of the disease. Without adequate treatment, Hodgkin lymphoma is a fatal disease in most patients.

2. Incidence

Hodgkin lymphoma is the most frequent lymphoma disease in childhood. According to the German Childhood Cancer Registry in Mainz, about 160 children and teenagers aged younger than 18 years are newly diagnosed with Hodgkin lymphoma in Germany per year. Thus, Hodgkin lymphoma accounts for approximately 7.5 % of all paediatric malignancies.

Hodgkin lymphoma is a rare diagnosis in children younger than 3 years. With increasing age, incidence gets more and more frequent, and in between ages 15 and 20 years, these tumours are most frequent. The incidence in children and adolescents (between 0 and 17 years) peaks at 15 years of age. Boys are slightly more affected than girls (gender ratio: 1.2:1).

3. Causes

The causes of Hodgkin lymphoma still have to be elucidated. It is known so far that the disease arises from the malignant transformation of cells in the *lymphatic system*, the B lymphocytes, and also, that this transformation is associated with *genetic* alterations of these cells. Why these genetic alterations exist and why they cause the disease in some children but not in others, is not known yet. Most certainly, Hodgkin lymphoma is caused by a specific combination of many factors.

A clustering of Hodgkin lymphoma patients within the white (Caucasian) population may suggest a genetic and also ethnological predisposition to the disease. Furthermore, children with certain congenital diseases of the *immune system* (such as *Wiskott-Aldrich syndrome*, *Louis-Bar syndrome*) or acquired immune deficiencies (for example due to HIV infection) are known to be at a higher risk to develop a Hodgkin lymphoma. Hereditary concomitant diseases associated with a predisposition to develop cancer are also called *cancer predisposition syndrome*s.

In addition, the *Epstein-Barr virus* (EBV), which is well-known as the cause of *glandular fever* (infectious mononucleosis), seems to be associated with the development of Hodgkin lymphoma in some patients. Whether certain environmental factors (such as pesticides) promote Hodgkin lymphoma is currently being examined. However, for the majority of patients, no specific risk factor has been established yet.

4. Symptoms

Hodgkin lymphoma begins subtly. First sign (*symptom*) of the disease is usually a very slowly increasing and painless swelling of one or more *lymph nodes*, for example in the regions of the throat or neck (most frequent sites), the armpits, clavicles (in the clavicular groove above the palpable clavicle), groins, or at multiple sites at the same time.

However, the disease can also arise from lymph nodes that cannot be seen or palpated at all, such as those behind the breastbone, in the chest, abdomen or along the spine. Since the cancer is continuously growing, the affected lymph nodes will soon become space occupying, thereby impairing inner organs and their functions. Therefore, enlarged lymph nodes in certain parts of the chest (*mediastinum*) may cause a dry cough or breathing difficulties, while others, in the abdomen for example, can result in diffuse abdominal pain and indigestion.

Enlargement of the spleen and liver (splenomegaly, hepatomegaly) due to lymphoma cell invasion is less frequent. If the lymphocytes in the *bone marrow* are involved, they occupy space within the hollow interior of bones. As a result, Hodgkin lymphoma can cause reduced production of red and white blood cells and, thus, *anaemia* and a predisposition for *infection*s. However, these cases are rare.

Nonspecific (general) symptoms may include fever, weight loss, drenching night sweats, fatigue, and itchy skin. The first three symptoms are frequent in patients with Hodgkin lymphoma. They are called *B-symptoms*.

The following overview summarizes the most frequent symptoms caused by Hodgkin lymphoma.

4.1. General symptoms

- fever of unknown origin (over 38°C for three consecutive days) [B-symptom]
- night sweats [B-symptom]

- unexplained weight loss (more than 10 % in six consecutive months prior to admission) [B-symptom]
- fatigue, loss of appetite, malaise
- itchy skin

4.2. Specific symptoms

- in more than 90 % of patients: painless, palpable, superficial lymph node swellings, for example in the area of the neck (most frequent location), in the armpit, above the clavicle, in the groins or simultaneously at multiple sites
- chronic cough, shortness of breath (if thoracic *lymph nodes*, lungs or pleura are involved)
- abdominal pain, back pain, diarrhea (if abdominal lymph nodes or organs, such as liver or spleen, are involved)
- pallor due to lack of red blood cells (*anaemia*; if the *bone marrow* is involved)
- bone or joint pain (if bones are involved)

Symptoms and complaints usually develop slowly in patients with Hodgkin lymphoma (over weeks or months). They can vary individually as to which symptoms prevail and how pronounced they are.

Good to know: The occurrence of one or more of the above-mentioned symptoms does not necessarily mean that they are caused by a Hodgkin lymphoma. Several of these symptoms, such as lymph node swelling and fever, are exactly those often seen with common childhood diseases like common colds and other viral infections. Nevertheless, it is strongly recommended to have the child or teenager see a paediatrician, in particular, if symptoms persist or progress.

5. Diagnosis

If the paediatrician thinks that the young patient's history (*anamnesis*), *physical examination* and possibly even results from blood tests and/or imaging, such as *ultrasound* or *X-ray examination*, are suspicious of Hodgkin lymphoma, the child should be referred to a hospital with a childhood cancer program (paediatric oncology program), where further diagnostic tests can be initiated and performed by childhood cancer specialists. These tests serve to confirm or rule out the suspected diagnosis and to assess a possible spread of the disease („staging").

5.1. Obtaining a tumour sample (biopsy)

For diagnosis, surgical removal and investigation of a lymph node or another tissue affected by the disease is required. Apart from *histological* investigation based on how the cells look like under the *microscope*, *immunohistochemical* and, if possible, investigations on *molecular genetic*s in these samples allow both the confirmation of the diagnosis and the determination of the subtype of Hodgkin lymphoma. Knowing the subtype of Hodgkin lymphoma helps to plan the treatment.

5.2. Tests to assess spread of the disease

Once the diagnosis of Hodgkin lymphoma has been confirmed, further tests are required to find out if and to which extent the cancer has spread and which organs are involved. These tests include *imaging*, such as ultrasound of the belly (abdomen) and lymph nodes, chest radiographs, *magnetic resonance imaging* (MRI) of the abdomen and pelvis, *computed tomography* (CT), and *positron emission tomography* (PET). Total body-PET is usually combined with a CT scan (PET-CT) and/or an MRI (PET-MRI). Overall, MRI is the preferred imaging procedure, since it is not associated with radiation. However, to check the lungs and/or quickly assess the stage of the disease, CT is required. Sometimes, when bone involvement is suspected, a bone scan (*skeletal scintigraphy*) might be necessary as well.

In order to find out whether the bone marrow is affected by the disease, *bone marrow punch biopsy* and subsequent screening for lymphoma cells in the obtained bone marrow sample has been a diagnostic standard for a while. Since the start of the therapy optimising trial EuroNet-PHL-C2 (now closed), potential bone marrow involvement has been assessed by PET, with biopsy thus no longer being required. This remains to be standard also since the study has been closed.

5.3. Tests before treatment begins

For treatment preparation, tests on the patient's cardiac function (*electrocardiography* and *echocardiography*) are performed. Furthermore, additional blood tests are needed to assess the patient's general health condition and to check whether the function of certain organs (such as liver and kidneys) is affected by the disease and whether there are any metabolic disorders to be considered prior or during therapy. Any changes occurring during the course of treatment can be assessed and managed better based on the results of those initial tests, which thus help to keep the risk of certain treatment-related side effects as low as possible. Also, the patient's *blood group* needs to be determined in case a *blood transfusion* is required during treatment.

Good to know: Not every patient needs the complete check-up. Your caregivers will inform you and your child, which diagnostic procedures are individually required in your case and why.

6. Treatment planning

After having established the diagnosis, the doctors will plan the treatment. In order to provide a therapy that is specifically designed for the patient's individual situation (risk-adapted therapy), the doctors will take into consideration certain factors that have been shown to have an impact on the *prognosis* (so-called risk factors or prognostic factors).

The following characteristics of Hodgkin lymphoma represent important *prognostic factors* and major criteria for treatment planning:

- **histological characteristics** (meaning the microscopically assessed subtype): the subtype of Hodgkin lymphoma decides according to which therapy protocol or therapy optimizing trial the patient will be treated.

- **stage of the disease:** the extent of the disease in- and outside the lymphatic tissue as well as the presence (or absence) of other stage-defining factors (such as *B-symptoms*, elevated *erythrocyte sedimentation rate*, high tumour load) are crucial for assigning a patient to the appropriate treatment level, Three treatment levels are currently being differentiated, considering patients with early, medium and advanced stages of the disease. Treatment intensities differ accordingly. This risk-adapted approach provides a strategy by which also patients with advanced stages of the disease have a chance of cure.
- **response of the disease to chemotherapy:** a major criteria for decision-making regarding the necessity of *radiation therapy* (radiotherapy).

The following chapters provide information on the histological subtypes of Hodgkin lymphoma and on the different stages of the disease.

6.1. Types of Hodgkin Lymphoma

Based on the different characteristic microscopic features, the World Health Organization (*WHO*) recognises five Hodgkin lymphoma subtypes, four of which are grouped as “classical Hodgkin lymphoma”.

1. Nodular lymphocyte-predominant Hodgkin lymphoma (LPHL)
2. Classical Hodgkin lymphoma:

- Nodular sclerosis subtype (NS)
- Lymphocyte-rich subtype (LR)
- Mixed cellularity subtype (MC)
- Lymphocyte-depleted subtype (LD)

The different subtypes vary regarding incidences, courses of the disease as well as prognosis. In particular, LPHL is now considered a separate disease and treated differently than classical Hodgkin lymphoma. With an incidence of almost 70 %, the NS subtype is the most frequent in Western countries, followed by the mixed cellularity subtype (MS). The other two subtypes are rather rare in children and adolescents.

6.2. Stages of Hodgkin Lymphoma

Staging of Hodgkin lymphoma is crucial for both treatment planning and estimating prognosis. The stage of the disease is primarily assessed based on its spread at the time of initial diagnosis. It describes which lymph node regions of the body are involved and how many. Staging also helps to assess whether the disease has spread to organs outside the lymphatic system (extranodal or extralymphatic disease). If such extralymphatic disease involves a single extralymphatic organ / site that lies adjacent to a known involved lymph node site, it is noted by an “E” (*please see below*).

The stages of Hodgkin lymphoma are classified according to the updated *Ann Arbor staging system* using the terms I through IV as shown in the following table:

Hodgkin lymphoma stage grouping including E-stages:

Stage of Disease	Definition
Stage I	Lymphoma is found in one single lymph node region (stage 1). It may as well extend to one single extralymphatic organ or site, such as chest wall, heart sac or lung (stage IE).
Stage II	Lymphoma is found in two or more lymph node regions on the same side of the *diaphragm* (stage II). It may as well extend to a single adjacent extralymphatic organ or site, such as chest wall, heart sac or lung (stage IIE).
Stage III	Lymphoma is found in lymph node regions on both sides of the diaphragm (stage III). It may as well to an extralymphatic organ/site (stage IIIE) and/or the spleen (stage IIIES or IIIS, respectively).
Stage IV	Non-contiguos involvement of one or more extralymphatic organs or tissues (such as lungs, liver, bone, *bone marrow*) with or without involving (distant) *lymph nodes*

Abbreviations: **E** – extralymphatic, notes that the cancer has spread to organs or tissues outside the lymphatic system (by infiltration from the affected lymph node region); **S** – spleen, notes cancerous involvement of the spleen.

Each of the four stages are subgrouped either into the A- or B-category, depending on

A: the absence of general symptoms
B: the presence of the following symptoms (*B-symptoms*):

- unexplained body weight loss of 10 % or more in the six months prior to admission and/or
- fever higher than 38°C for three consecutive days prior to admission
- drenching night sweats

The presence or absence of B-symptoms is labelled for all stage groups by the suffix B or A, respectively (for example: stage IB or IA).

Further criteria for stage assessment: according to trial EURONet-PHL-C2 (now closed for patient recruitment), two more factors are being considered in addition to E-stages and B-symptoms: elevated *erythrocyte sedimentation rate* (“sed rate”; ESR) and large tumour load ("bulky disease", "bulk"). Both prognostic factors are still included in treatment planning.

Good to know: the presence of E-stages and/or B-symptoms, bulky disease exceeding a defined tumour load or elevated erythrocyte sedimentation rate has shown to negatively impact prognosis. Hence, patients presenting with these findings require a more intensive treatment than patients without these risk factors and are therefore assigned to higher treatment levels.

7. Treatment

Treatment of children and adolescents with *Hodgkin lymphoma* should take place in a children's hospital with a paediatric oncology program. Only such a treatment centre provides highly experienced and qualified staff (doctors, nurses and many more) that is specialised and focussed on the diagnostics and treatment of children and teenagers with cancer according to the most advanced treatment concepts. The doctors in these centres collaborate closely with each other. Together, they treat their patients according to treatment plans (protocols) that are continuously optimised. The goal of the treatment is to achieve high cure rates while avoiding acute or long-term side effects as much as possible.

7.1. Treatment methods

Treatment options for Hodgkin lymphoma include chemo- and radiotherapy as well as high-dose chemotherapy followed by stem cell transplantation.

Central backbone of current treatment concepts for Hodgkin lymphoma is *chemotherapy*. It uses drugs (so-called cytostatic agents) that can kill fast-dividing cells, such as cancer cells, or inhibit their growth, respectively. Since one cytostatic agent alone may not be capable of destroying all the lymphoma cells, a combination of *cytostatics* that function in different ways is given (polychemotherapy). The goal is to eliminate as many malignant cells as possible.

For some patients, low-dose *radiation therapy* (radiotherapy) of the affected regions is additionally recommended. However, in order to reduce radiation-induced late effects, radiotherapy has been used continuously less during the last years. Today, only certain patients receive radiotherapy, for example when their disease does not sufficiently respond to chemotherapy (*please see chapter "Course of treatment"*).

In very rare situations, for example in case of non-response to chemo- and radiotherapy or recurrent disease (relapse), respectively, *high-dose chemotherapy* followed by *stem cell transplantation* (SCT) may be considered as an effective treatment option. The high doses of cytostatics given according to this treatment strategy are capable of eliminating the resistant lymphoma cells. Since high-dose chemotherapy also leads to the destruction of the blood-forming cells in the *bone marrow*, the patient will receive blood forming stem cells in a second step. Usually, these stem cells are obtained from the patient's blood or bone marrow prior to high-dose chemotherapy and are given back right after this treatment (so-called *autologous stem cell transplantation*).

Good to know: The duration and intensity of chemotherapy, as well as the necessity of radiation or stem cell transplantation, and last but not least, the patient's individual *prognosis* is dependent on the extent (stage) of the disease at initial diagnosis and how it responds to treatment. The

subtype of Hodgkin lymphoma only marginally determines the treatment strategies for children and adolescents (*see the exception of LPHL below*).

Special considerations for patients with Lymphocyte Predominant Hodgkin Lymphoma (LPHL)

Certain treatment modifications are applied to children and adolescents with LPHL: in contrast to patients with classical Hodgkin lymphoma, patients with early stage LPHL (stage IA) do usually not receive any chemotherapy (and radiation), as long as only one lymph node is affected and can be easily removed completely and without putting the patient in danger or at risk of mutilation (this is very important!). Experience has shown that about two thirds of these patients will defeat their disease without chemo- and radiotherapy. However, regular follow-up examinations are necessary to closely observe the course of the disease (observatory approach). In case of recurrent disease, intensive treatment is recommended.

Patients in stage IA with residual tumour and patients in stage IIA receive – also in contrast to classic Hodgkin lymphoma – a mild chemotherapy at first. The necessity of additional treatment measures depends on how well the disease responds to this chemotherapy. In case of unfavourable treatment response, more rounds of chemotherapy and sometimes also radiotherapy may follow. Treatment as for classical Hodgkin lymphoma is recommended only for those with advanced disease, meaning higher stages (III-IV) of LPHL (standard therapy with COPDAC, *see chapter „Course of treatment below"*). However, more than 80-85 % of patients with LPHL are diagnosed with stage IA or IIA.

7.2. Course of treatment (classical Hodgkin lymphoma)

The following information describes the treatment for patients with classical Hodgkin lymphoma. Therapy is currently given as per protocol of trial EuroNet-PHL-C2, which had been open for Hodgkin lymphoma patients until 31/09/2020 (*see chapter "Therapy optimising trials"*). Chemo- and radiotherapy are important treatment modalities used in these protocols. If *radiation therapy* is indicated, it is usually performed after cessation of *chemotherapy*. The decision whether radiotherapy is necessary or not is primarily based on the response of the disease to chemotherapy (*please see below*).

Note regarding trial EuroNet-PHL-C2:
Within the framework of trial EuroNet-PHL-C2, current standard treatment was being compared with another promising, radiotherapy-sparing, approach for patients with intermediate and advanced stages of Hodgkin lymphoma. The goal was to further reduce radiation-induced late effects. After parents'/guardians' consent, patients with intermediate or advanced stages of disease (treatment levels 2 and 3, respectively) were randomly assigned to two different treatment arms (standard and investigation arm). This strategy is called "randomisation". Chemotherapy as well as radiotherapy differed within the two treatment arms.
The trial has been closed for patient recruitment since October 2020 and the collected data are currently being analysed. First valid results won't be available before August 2023. For newly diagnosed patients, the study centre recommends an individually adjusted treatment according to the standard or randomization arm, respectively.

7.2.1. Chemotherapy

Chemotherapy for patients with classical Hodgkin lymphoma usually consists of multiple treatment cycles or blocks (blocks of *chemotherapy*). The quantity of blocks and, thus, treatment duration and intensity are based on the stage of the disease and the treatment level (TL) they have been assigned to. Usually, patients with

- early stages of the disease (TL 1) receive 2 or 3 cycles of chemotherapy,
- intermediate stages of the disease (TL 2) receive 4 cycles of chemotherapy,
- advanced stages of the disease (TL 3) receive 6 cycles of chemotherapy.

Every treatment block takes about two weeks and the different cycles partially contain different combinations of cytostatic agents. For example, „OEPA“, a combination of vincristine (oncovin; „O“), etoposide (VP-16; „E“), prednisone („P“) and adriamycin (doxorubicin; „A“) is the current standard for the first two blocks, the so-called „induction phase“. All other blocks („consolidation phase“) include „COPDAC“, the standard combination of cyclophosphamide („C“), vincristine („O“), prednisone („P“) and dacarbacine („DAC“). There are treatment breaks of about two weeks between single blocks. Duration of all chemotherapy is between two to six months if no relapse develops during or after treatment.

Note regarding trial EuroNet-PHL-C2:
In patients with advanced stages of Hodgkin lymphoma (TL 2 and 3), the current standard consolidation therapy (COPDAC combination) was compared to a more intense consolidation treatment: Those patients who were randomly assigned to the standard arm received the standard COPDAC combination (*please see above*) over 28 days („COPDAC-28“), while patients in the investigation arm received COPDAC as well, but in addition the agents etoposide and doxorubicin (“D”). This combination is called “DECOPDAC” and was given over 21 days (“DECOPDAC-21”).
Applying for now: according to the registry, the study centre recommends the standard treatment arm, however, the randomization arm may be chosen in individual cases. The choice is left to the local treatment centres. The attending oncologists are supposed to discuss both options for consolidation treatment with the parents/patients and then make a collaborative decision.

7.2.2. Radiotherapy

According to current treatment recommendations, less than half of all patients receive *radiation therapy* following chemotherapy. The prime decision-making factor regarding radiotherapy is not the stage of the disease (as it was a while ago), but the response of the disease to chemotherapy.

Standard treatment recommendations (according to the trial’s standard arm) are:

- Patients whose disease shows good (adequate) response after two blocks of chemotherapy (assessed by *positron emission tomography*, PET) do not receive radiotherapy, regardless of the patient’s treatment group or stage of the disease.

- Patients whose disease does not sufficiently (not adequately) respond to the first two blocks of chemotherapy receive radiotherapy after chemotherapy.

"Good response" means, that the tumour as found at initial diagnosis now does not contain any live tumour cells any more, thus is PET-negative and also decreased in size for about 50 % of its initial volume.

Radiotherapy usually starts about two weeks after cessation of chemotherapy, which is after a total of two or three (TL1), four (TL2) or six (TL3) blocks, depending on the patient's treatment level. The standard total radiation dose is 20 *gray* (Gy) for all lymph node regions involved at initial diagnosis (more vulnerable organs are treated with lower doses in general, and in individual situations, higher doses are given as well). In order to spare the healthy tissue that is surrounding the cancer, the total radiation dose is not given all at once. Instead, patients receive smaller portions of a maximum of 1.8 Gy per treatment. Duration of radiotherapy comes to two to three weeks total. Radiotherapy is usually not performed over the weekends.

Note regarding trial EuroNet-PHL-C2
The standard radiotherapy as described above was given to all patients (treatment levels 1-3) of the standard chemotherapy arm (COPDAC-28). Patients in the investigation arm (DECOPDAC-21) only received radiotherapy to those parts of the body that still showed live tumour tissue with tumour diameters of more than 1 cm after completion of chemotherapy, thereby remaining PET-positive. Standard total radiation dose for these patients was 30 Gy. The strategy applied to patients in the investigation arm was to find out whether radiotherapy could be reduced after an intensified chemotherapy without jeopardizing treatment efficacy.
Applying for now: according to the registry, the study centre recommends, until trial results are available, that attending physicians and parents collabo-ratively decide upon the type of treatment. Radiotherapy depends on preceding chemotherapy (according to standard versus randomization arm, *see also chapter "Chemotherapy"*).

8. Therapy optimising trials and registries

In Germany, treatment of almost all children and adolescents with Hodgkin lymphoma is performed according to the treatment plans (protocols) of *therapy optimising trial*s or registries. The term "therapy optimising trial" refers to a form of controlled clinical trial that aims at improving current treatment concepts for sick patients based on the current scientific knowledge. With many treatment centres being involved in this kind of standardised treatment, such studies are also called "multicentred" and "cooperative", and most often many countries participate.

Patients who cannot participate in any study, for example because none is available or open for them at that time, or since they do not meet the required inclusion criteria, respectively, are often included in a so-called **registry**. The patients are generally treated according to the recommendations of the trial centre, thus receiving the current best therapy available.

The following registries/recommendations for treatment of children and adolescents with Hodgkin lymphoma are currently active/valid in Germany:

- **Registry GPOH-HD (2020):** registry of the Hodgkin Study Group for children and adolescents with Hodgkin lymphoma, regardless of the type. The registry was opened October 1, 2020, after closure of study EuroNet-PHL-C2 with the aim to ensure optimal treatment for Hodgkin patients also during times without active clinical studies. Eligibility includes patients with first diagnosis or relapse of a classic or lymphocyte-predominant Hodgkin lymphoma (LPHL). Patients from previous studies are eligible to register with the registry as well. The study centre provides therapy recommendations that are based on the trials EuroNet-PHL-C2 and EuroNet-PHL-LP1 (*see below*).

- **Treatment recommendations based on trial EuroNet-PHL-C2:** for children and adolescents (under 18 years) with a newly diagnosed classical Hodgkin lymphoma the currently active GPOH-HD-Registry is available (*see above*). The treatment within the registry is based on the therapy optimising trial EuroNet-PHL-C2, which had been open for patient recruitment from October 2016 to September 2020. Many childrens' hospitals and paediatric oncology centres all over Germany as well as in other European and non-European countries had participated in this trial. The study results are currently being analysed.

- **Treatment recommendations based on trial EuroNet-PHL-LP1:** for children and adolescents (under 18 years) with an early lymphocyte-predominant Hodgkin lymphoma (LPHL, stages IA or IIA, respectively), the currently active GPOH-HD-Registry is available (*see above*). The treatment according to the registry is based on the therapy optimising trial EuroNet-PHL-LP1, which was closed for patient recruitment in November 2014 in Germany, in other European countries by the end of 2018.

Note: the international and German study centre for the above-mentioned registry and now closed EuroNet-PHL trials is located at the "Zentrum für Kinderheilkunde und Jugendmedizin der Universitätsklinik Gießen" (Department of Paediatrics, University of Gießen, Germany). The Pricipal Investigator is Prof. Dr. med. Dieter Körholz. "EuroNet-PHL" means "European Network Paediatric Hodgkin's Lymphoma".

9. Prognosis

Prognosis for newly diagnosed patients

Nowadays, long-term survival rates of children and teenagers after treatment of Hodgkin lymphoma are high: more than 9 out of 10 (97 %) patients can be cured today, thanks to current modern diagnostics and standardised treatment concepts – and regardless of how advanced the disease had been at diagnosis. This is only possible due to the current treatment strategies that adjust the intensity of therapy (chemo- and radiotherapy) to the patient's individual situation by considering different treatment groups. Patients with more advanced stages of the disease (treatment levels II and III) need a more intensive therapy than patients presenting with earlier stages (treatment level I) in order to provide a comparably favourable *prognosis*.

Prognosis for patients with recurrent disease

According to the Morbus Hodgkin-Study Centre (Gießen, Germany), in about 11 % of patients aged younger than 18 years the disease does either not respond to current treatment strategies (progressive disease) or the patients later develop recurrent disease (*recurrence*, relapse). In general, favourable long-term outcomes can be achieved for patients with relapsed Hodgkin lymphoma, too. Individual prognosis, however, depends primarily upon the timepoint of relapse and how intense primary treatment has been.

Patients with late relapse (more than one year after completion of therapy), who receive a second chemo- and radiotherapy for relapse treatment, have high survival rates (10-year survival of more than 90%). Patients with early stage of the disease at primary diagnosis (treatment group 1) and/ or those who have not received any radiotherapy as part of initial treatment also have a favourable prognosis.

The outcome of patients with early relapse (between three and twelve months after cessation of primary treatment) as well as with non-response or progressive disease have a less favourable outcome, even when given chemo- and radiotherapy for second therapy (10-year survival of about 75 or 50 %, respectively). Comparable outcomes are seen for patients who already received intensified chemo- and radiotherapy for first treatment. Due to their high risk of developing recurrent disease, these patients may only benefit from the very intensive strategy of *high-dose chemotherapy* followed by *autologous stem cell transplantation*.

Note: The survival rates mentioned in the text above are statistical values. Therefore, they only provide information on the total cohort of patients with Hodgkin lymphoma. They do not predict individual outcomes. However, statistics help to estimate probabilities of survival.

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Glossary

anaemia	„lack of blood“; reduction of the red blood pigment (haemoglobin) and/or the proportion of red blood cells (haematocrit) in the blood below the normal value typical for a given age. Signs of anaemia include palor, headache, dizziness, and fatigue.
anamnesis	medical interview, a patient’s history, development of signs of illness; the type, onset and course of the (current) symptoms as well as any risk factors (e.g. hereditary diseases) are evaluated during a medical interview.
Ann Arbor staging system	system for staging malignant lymphomas, especially Hodgkin lymphomas and certain forms of Non-Hodgkin lymphomas
autologous stem cell transplantation	(re)transfer of blood stem cells, e.g. after a chemotherapy or radiotherapy; the patient receives his own cells that were previously taken from their own bone marrow or blood. Autologous stem cell transplantation may be an option, for example, for certain patients with lymphoma, neuroblastoma, soft tissue sarcoma, or a brain tumour.
B lymphocytes	subtype of lymphocytes; they develop in the bone marrow and are responsible for the recognition of pathogens and the formation of antibodies.
B-symptoms	certain non-specific symptoms that often occur simultaneously in cancer patients: recurrent fever (above 38°C) for no apparent reason, night sweats and unintentional weight loss (more than 10% of body weight in six months). The three symptoms are grouped together under the term B symptomatology. In this combination, they occur primarily in patients with Hodgkin lymphoma and Non-Hodgkin lymphoma and are associated with an unfavourable prognosis.
blood group	hereditary, usually stable, structural characteristics (blood group antigens) of blood components (e.g. AB0 blood groups) located on the cell walls of blood and other tissue cells;
blood transfusion	transfer of blood (whole blood) or blood components (e.g. red blood cells or platelets) from a donor to a recipient.
bone marrow	site of blood formation; spongy tissue with a strong blood supply that fills the cavities inside many bones (e.g., vertebrae, pelvic and thigh bones, ribs, sternum, shoulder blade, and collarbone);

	in the bone marrow, all forms of blood cells develop from blood progenitor cells (blood stem cells).
bone marrow punch biopsy	removal of bone marrow tissue for the purpose of examining the cells; with the help of a special hollow needle, a tissue cylinder about 2 cm long is punched out of the bone. The examination is always carried out under anesthesia. A bone marrow punch biopsy may be necessary in addition to or instead of a bone marrow puncture if the latter does not provide sufficient tissue for a reliable examination. Like the bone marrow puncture, it is usually performed from the posterior iliac crest bone. There, the bone marrow is only separated from the skin by a relatively thin layer of bone, so that the removal can take place without significant risk.
cancer predisposition syndrome	genetic disorders that can include malformations and intellectual disability in addition to an increased risk of tumors; according to current knowledge, about 10% of childhood and adolescent cancers develop due to a known hereditary change or cancer predisposition syndrome. Cancer predisposition syndromes include Louis Bar syndrome (= ataxia telangiectatica), Beckwith-Wiedemann syndrome, Down syndrome, Hippel-Lindau syndrome, Li-Fraumeni syndrome, MEN syndrome, neurofibromatosis and WAGR syndrome. The familial form of retinoblastoma is also part of it.
cell	the smallest functional unit in organisms with the ability to perform metabolism, involuntary muscle movement and reproduction and to respond to stimuli; each cell contains a nucleus and a cell body (cytoplasm) and is externally bounded by the cell membrane.
chemotherapy	here: use of drugs (chemotherapeutic agents, cytostatics) for the specific inhibition of tumor cells in the organism
computed tomography	imaging, X-ray diagnostic procedure; it produces an image by computer-controlled evaluation of a large number of X-rays from different directions. This makes it possible to produce sliced images of body parts (tomograms, transverse or longitudinal sections of the human body)
cytostatics	drugs that inhibit cell growth; cytostatics can affect the metabolism of different types of cells, thereby destroying them and/or preventing them from multiplying. Cells that divide frequently are particularly affected.
echocardiography	ultrasound examination of the heart to check its performance (cardiac function); the position or structure of the heart valves and walls, the wall thickness of the heart muscle, the size of the heart

	and the ejected blood volume (pumping function of the heart) are examined and assessed, among other things.
electrocardiography	method of measuring the electrical activity of the heart
Epstein-Barr virus	causative agent of glandular fever;
erythrocyte sedimentation rate	determines how quickly the red blood cells (erythrocytes) sink within one hour (sometimes additionally within two hours) in a special measuring tube; for example, the test can indicate inflammation in the body. In certain diseases, erythrocytes settle in the blood either more slowly or faster than usual.
genetic	concerning the (level of) inheritance or genes; inherited
glandular fever	common, often harmless viral disease that occurs mainly in children and young adults; is caused by the Epstein-Barr virus (EBV) and affects the lymphatic tissue (e.g. lymph nodes, spleen). Pfeiffers glandular fever is associated with characteristic changes in blood counts (conspicuous increase in white blood cells; leukocytosis).
gray	unit of measurement for the dose of energy caused by ionising radiation (e.g. in the context of radiotherapy) and absorbed by a given mass (kilogram of body weight)
high-dose chemotherapy	the use of a particularly high dose of cell growth-inhibiting drugs (cytostatics); in the case of cancer, it aims to destroy all malignant cells. Since the haematopoietic system in the bone marrow is also destroyed, the patients own or foreign blood stem cells must then be transferred (autologous or allogeneic stem cell transplantation).
histological	concerning the tissues of the body; in a histological (fine tissue) examination, tissue samples are examined under the microscope after special preparation (preparation of tissue sections and use of certain staining techniques).
Hodgkin lymphoma	malignant disease of the lymphatic system; belongs to the malignant lymphomas and accounts for about 5% of malignant diseases in childhood and adolescence.
imaging	diagnostic procedures generating images of the inside of the body, such as ultrasound and X-ray examination, computed tomography, magnetic resonance imaging, and scintigraphy
immune system	the bodys own system for maintaining a healthy organism by defending against foreign substances and destroying abnormal body cells (e.g. cancer cells); the immune system has the ability to

	distinguish between self and foreign or dangerous and harmless; mainly the organs of the lymphatic system as well as cells distributed throughout the body (e.g. leukocytes) and molecules (e.g. immunoglobulins) are involved.
infection	penetration of the smallest organisms (e.g. bacteria, viruses, fungi) into the body and subsequent multiplication within it. Depending on the characteristics of the microorganisms and the immune system of the infected person, various infectious diseases can occur after infections.
Louis-Bar syndrome	hereditary disease; it is mainly characterized by degeneration of the central nervous system (CNS), an impairment of the immune system (immunodeficiency), dilated blood vessels of the eyes and skin (so-called telangiectasias) and an increased risk of cancer (so-called cancer predisposition syndrome). Degeneration of the CNS is associated with various neurological disorders, such as movement disorders (ataxia) and abnormal eye movements. The immunodeficiency often causes recurrent infections.
lymph nodes	small lenticular to bean-shaped organs that are part of the bodys immune system and are located in many parts of the body; they serve as filter stations for the tissue water (lymph) of a region of the body and contain cells of the immune system.
lymphatic system	collective term for lymphatic vessels, lymphatic vessel trunks, lymph nodes, lymphatic tissues (lymphocytes in connective tissue, mucous membranes, glands) and lymphatic organs (spleen, pharyngeal tonsils, bone marrow, thymus gland).
lymphocytes	subgroup of white blood cells that are responsible for the bodys own defenses, especially the defense against viruses; there are B and T lymphocytes. They are formed in the bone marrow, but partly only mature to full functionality in the lymphatic tissue (e.g. lymph nodes, spleen, thymus gland). They eventually enter the blood via the lymphatic vessels, where they take over their respective tasks.
magnetic resonance imaging	diagnostic imaging method; very precise, radiation-free examination method for the visualization of structures inside the body; with the help of magnetic fields, cross-sectional images of the body are generated, which usually allow a very good assessment of the organs and many organ changes.
mediastinum	middle section of the thoracic cavity located between the two lungs

molecular genetic	referring to structure, formation, development, function and interactions of cells and cell building blocks (e.g. nucleic acids, proteins) at the molecular level; the focus is on the analysis of the genetic information stored in the nucleic acids (DNA and RNA) and its processing in the context of protein synthesis as well as gene regulation.
Non-Hodgkin lymphoma	a large group of malignant diseases of the lymphatic system, which can provoke lymph node swelling as a main feature; like Hodgkin lymphoma, NHL is a malignant lymphoma. It accounts for about 7 % of malignant diseases in childhood and adolescence.
physical examination	an important part of diagnostic examinations; includes palpation and listening to certain body organs as well as testing reflexes to obtain indications of the nature or course of a disease.
positron emission tomography	an imaging, nuclear medicine procedure based on the principle of scintigraphy, which can be used in cancer medicine to visualize tumours or metastases. To detect tumour tissue, a radioactively labeled sugar compound is administered. Since tumours have a higher metabolism than healthy tissue, the radioactive substance is increasingly taken up and stored by the tumour cells. The tumour cells enriched with this substance emit signals that are captured by a special camera (PET scanner) and converted into an image (tomogram).
prognosis	prediction of the course and outcome of a disease / prospect of recovery
prognostic factors	factors that allow an approximate assessment of the further course of the disease (i.e. the prognosis);
radiation therapy	controlled use of ionizing (high-energy) radiation for the treatment of malignant diseases
recurrence	relapse, recurrence of a disease after recovery
skeletal scintigraphy	an imaging, nuclear medicine procedure that is mainly used in cancer medicine to detect or exclude bone metastases; radioactive technetium (99Tc), which is bound to a phosphate compound, is used for the investigation. Since phosphate is a natural component of the basic substance of bones, the radioactive compound is taken up by the bone cells, especially in those with increased metabolism. A special camera locates the suspicious areas.
stem cell transplantation	transfer of haematopoietic stem cells after conditioning chemotherapy, radiation or immunosuppression of the recipient;

	the stem cells can be obtained either from the bone marrow or from the bloodstream. In the first case, the procedure of their transfer is called bone marrow transplantation, in the second case peripheral stem cell transplantation. Depending on the type of donor, a distinction is made between two forms of SCT: allogeneic SCT (stem cells from a foreign donor) and autologous SCT (own stem cells).
symptom	sign of illness
therapy optimising trial	a controlled clinical trial (study) that aims to provide the best possible treatment for patients and at the same time to improve and develop treatment options; therapy optimisation is aimed not only at improving the chances of recovery, but also at limiting treatment-related side effects and long-term effects.
ultrasound	an imaging technique used to examine organs, in which ultrasound waves are sent through the skin into the body; at tissue and organ boundaries, the sound waves are reflected back, picked up by a receiver (transducer) and converted into corresponding images with the help of a computer.
WHO	abbreviation for World Health Organization; international federation for cooperation in the field of public health
X-ray examination	imaging procedure that uses X-rays to visualize organs or parts of organs