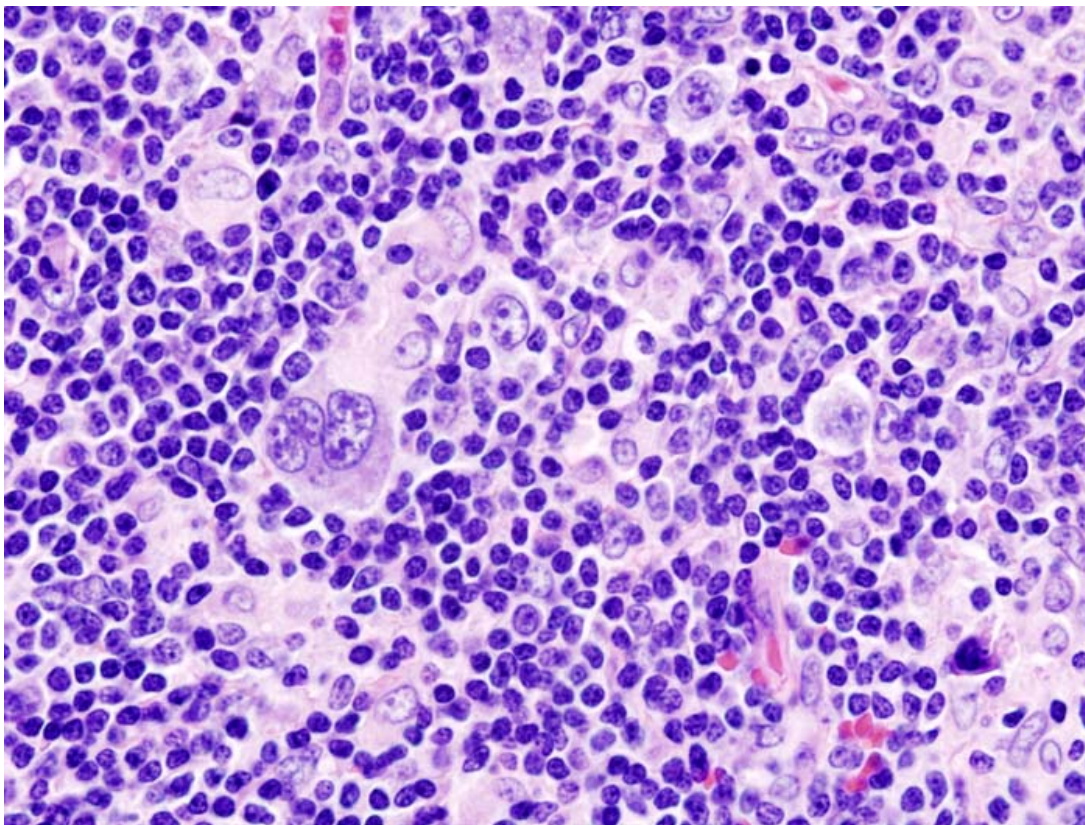


## Hodgkin's Lymphoma (Hodgkin's Disease) — Stages, Classification and Prognosis

[See online here](#)

**Hodgkin's disease is one of the first cancerous diseases for which effective treatment options have been developed. While this disease still ended lethally earlier, the prognosis is very good today. This is particularly due to the radiation sensitivity of lymphoma. 80 % of the patients can be cured permanently. This article provides a comprehensive overview of the hematologic disease, the symptoms, diagnosis and therapeutic principles.**



### Definition of Hodgkin's Disease

What is Hodgkin's disease?



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Hodgkin's lymphoma is named after its describer [Thomas Hodgkin](#) (first description in 1832) and is a malignant disease of the **lymphatic system**. The malignant neoplasms of the lymphatic system are divided into Hodgkin's lymphoma with histologically detectable **Hodgkin and Reed-Sternberg cells** and the **non-Hodgkin's lymphomas**.

It is a **monoclonal B-cell lymphoma** that originates in the lymph nodes. In advanced stages it results in a hematological scattering from the lymph nodes with resettlement in the **bone marrow and extra lymphatic tissues** such as the liver.

## Epidemiology of Hodgkin's Disease

### Spread of the Hodgkin's disease

Hodgkin's lymphomas account for about 30 % of **all lymphomas**. The incidence is about 2 - 4/100,000. The age of manifestation is bimodal, with a **peak incidence** around the **30th** and the **60th year of age**. The ratio of male to female patients is 3:2. In the industrialized nations, a slight decline in incidence rate is observed.

Even children can fall sick with Hodgkin's disease. The peak age is around **12 years of age**. The gender distribution corresponds to adulthood.

## Etiology of Hodgkin's Disease

### Causes of Hodgkin's disease

To date, the etiology of Hodgkin's disease is not fully understood. It stands to reason that oncogenic viruses such as the **Epstein-Barr virus** could be the triggers, since EBV DNA is found in the Hodgkin and Reed-Sternberg cells of about half of the patients. In developing countries, EBV DNA can even be detected in 90 % of the Hodgkin's lymphomas.

The risk of developing Hodgkin's lymphoma is increased by 3 times after infectious mononucleosis (glandular fever). In addition, oncogene mutations and alterations of

tumour suppressor genes that inhibit apoptosis can be detected. Patients with **impaired immune defenses** have an increased risk, for example, under immunosuppressive therapy after transplantation, but also in HIV infection.

## Signs and Symptoms of Hodgkin's Disease

### Signs of Hodgkin's disease

Clinically the disease presents mostly with **lymph node swelling**. In nearly 60 % of these cases the lymphadenopathy is unilaterally **cervical**. Other areas include the axilla, the inguinal area, the mediastinum and the abdomen, and the lymph node involvement progresses centripetally. The swollen lymph nodes are usually indolent and of solid, rubbery consistency. In 60 % of the cases, the mediastinal nodes are already involved.

**Note:** Every unexplained lymph node swelling, which persists longer than 2 - 3 weeks, must be evaluated via a histological examination.

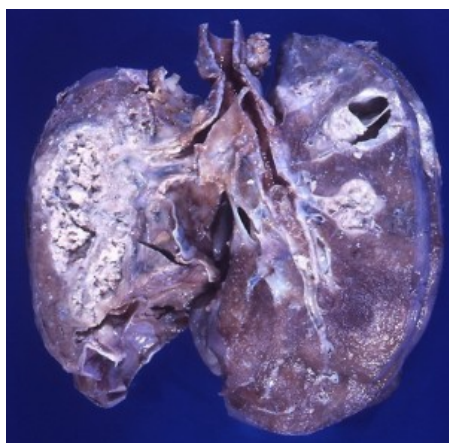


Image: "Hodgkin disease" by Yale Rosen.  
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### Symptoms of Hodgkin's disease

- Very often, the patient also exhibits type B symptoms, i.e. fever, night sweats and weight loss of more than 10 % of body weight in 6 months.
- Typical but not very common is the so-called **Pel-Ebstein fever**. It is characterized by an undulant fever pattern with a period of a few days to weeks and a subsequent fever break.
- The **alcohol pain** is also rather rare. Patients have pain in the affected **lymph nodes** immediately after alcohol consumption, a phenomenon pathognomonic of Hodgkin's lymphoma.
- Agonizing **itching** may occur as a paraneoplastic symptom. Other paraneoplastic syndromes are ichthyosis and pemphigus.
- The **Ophelia syndrome** is indeed rare, but particularly impressive due to the combination of hippocampal sclerosis and dementia.
- In disseminated systemic disease, **hepatosplenomegaly** is often found along with involvement of other non-lymphoid organs, such as the **lungs, skin** and gastrointestinal tract with symptoms attributable to the organs involved.

# Diagnosis of Hodgkin's Disease

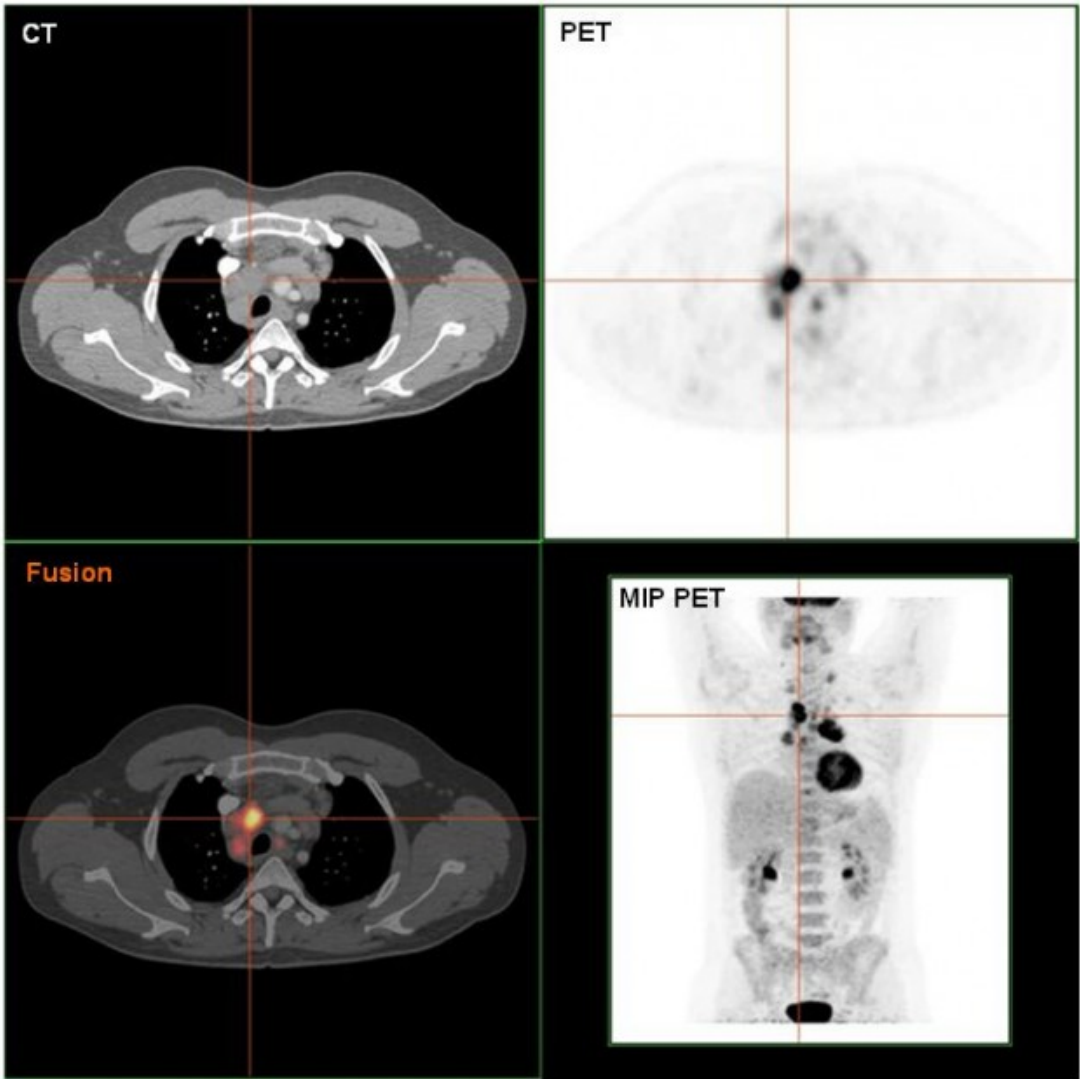
## Histological investigation in Hodgkin's disease

The confirmation of diagnosis is carried out by histological evaluation of a sample of the involved **lymph nodes**. It is always important to **remove an entire lymph node**, since a lymph node biopsy does not provide enough material.

The histologic evidence of **mononuclear Hodgkin and polynuclear Reed-Sternberg cells** is diagnostic. Reed-Sternberg cells (also Hodgkin Reed-Sternberg cells) are giant cells with a diameter greater than 20  $\mu\text{m}$  and prominent eosinophilic nucleoli and vesicular chromatin structure. The Reed-Sternberg cells consistently express the **CD30 (Ki-1) and CD15 (Leu-M1) antigens**. CD30 is a marker of lymphocyte activation that is expressed by reactive and malignant lymphoid cells and was originally identified as a cell surface antigen on Reed-Sternberg cells. CD15 is a marker of late granulocytes, monocytes, and activated T-cells that is not normally expressed by cells of B lineage. They are surrounded by a reactive **inflammatory infiltrate** of lymphocytes, monocytes, eosinophilic granulocytes and fibroblasts. However, they account for only about 1 % of lymphomas.

## Staging in Hodgkin's disease



The computed tomographic investigation of the neck, thorax, abdomen and pelvis is done for **staging**. Nowadays, a **PET-CT** is also used, as the CT provides anatomical details while the superimposed PET scan enhances the diseased area.





PET/CT scan of a Hodgkin lymphoma, confirmed histologically . SUV-max. = 22 g/ml. Patient: 95 kg , injected dose: 275 MBq, recording 75 minutes p.i. Courtesy of the Südwestdeutsches PET Center Stuttgart at Diakonie-Klinikum Stuttgart

A **bone marrow puncture** to rule out bone infiltration is also obligatory.

**Note:** The pathological staging from laparotomy and splenectomy is obsolete nowadays. The clinical staging is based on the **Ann Arbor classification**, in which the number and the location of the affected lymph node stations, the presence of extranodal foci, the diffuse involvement of extra-lymphatic organs and the presence of B-symptoms are taken into consideration.

<p><b>Stage I</b></p>	<p>Infestation of a single lymph node region of a single localized extranodal foci</p>	<p style="text-align: center;"></p> <p><small>Image: "Diagram showing stage 1 Hodgkin's lymphoma." by Cancer Research UK. License: <a href="https://creativecommons.org/licenses/by-sa/4.0/">CC BY-SA 4.0</a></small></p>
<p><b>Stage II</b></p>	<p>Infestation of two or more lymph node regions on one side of the diaphragm or localized extranodal foci and infestation of one or more lymph node regions on one side of the diaphragm</p>	<p style="text-align: center;"></p> <p><small>Image: "Diagram showing stage 2 Hodgkin's lymphoma." by Cancer Research UK. License: <a href="https://creativecommons.org/licenses/by-sa/4.0/">CC BY-SA 4.0</a></small></p>

<b>Stage III</b>	Infestation of two or more lymph node regions on both sides of the diaphragm or localized extranodal foci on both sides of the diaphragm	 <p><a href="#">Image</a>: "Diagram showing stage 3 Hodgkin's lymphoma." by Cancer Research UK. License: <a href="#">CC BY-SA 4.0</a></p>
<b>Stage IV</b>	Widespread (disseminated) infection of one or more extralymphatic organs or without lymph node involvement	 <p><a href="#">Image</a>: "Diagram showing stage 4 Hodgkin's lymphoma." by Cancer Research UK. License: <a href="#">CC BY-SA 4.0</a></p>

In children and adolescents, the infection of the bone with cortical destruction or an infestation of the bone marrow is always considered as stage IV, regardless of the affected lymph node stations.

#### Additons:

A: without B symptoms

B: with B symptoms

E: extranodal involvement

S: splenic infestation

X-larger tumour mass (bulk or bulky disease: tumour >10 cm maximum diameter)

Reference: [Hodgkin's Lymphoma](#) via Wikipedia

Typical findings on laboratory tests are a **relative lymphopenia and eosinophilia** in the differential blood count, elevation of CRP and LDH, and an increase in transaminases, which points to a liver involvement. The **erythrocyte sedimentation rate is a sign of activity** of the disease and is caused by the increase of the  $\alpha_2$ -globulins and of the gamma globulins. In case of bone marrow involvement with resulting bone marrow failure, a peripheral pancytopenia can be present.

## Classification of Hodgkin's Disease

Hodgkin's lymphomas can be divided into 2 main groups according to morphological, cytochemical and immunological criteria defined by the **WHO classification**.

### Classic Hodgkin lymphoma

Classic Hodgkin's lymphoma accounts for **95 %**. It is divided into 4 subtypes:

- **Nodular sclerosing form 60 - 80 %**: nodular infiltrates and collagen scar. In addition, the typical binucleate so called **lacunar cells**, which are a subspecies of the HRS cells. This form especially affects young female patients with mediastinal and supraclavicular infestation.
- **Mixed type 15 - 30 %**: This form is common in patients in the second peak incidence. Men are affected more often than women in this form. The infestation is typically cervical or abdominal.
- **Lymphocyte-rich classic Hodgkin's lymphoma 4 %**: Lymphohistiocytic (B lymphocytes) image with involvement of cervical or axillary lymph nodes. Predominant in male patients at the age of 30.
- **Lymphocyte-poor type 1 - 2 %**: Anaplastic large cell with mitosis and few

lymphocytes. This rare form is typical in patients at an advanced age with manifestation of lymphoma in the abdomen.

## Nodular lymphocyte-predominant Hodgkin lymphoma

Represents 5 % of all cases of Hodgkin's Lymphoma. **Nodular lymphocyte-predominant Hodgkin lymphoma** (nodular paragranuloma) is characterized by the **popcorn cells**, a special variation of the Reed-Sternberg cells embedded within a nodular pattern of infiltrating lymphocytes. Unlike Reed-Sternberg cells, popcorn cells are **positive for B-cell antigens, such as CD20, and are negative for CD15 and CD30.**

## Treatments of Hodgkin's Disease

### Three prognostic and therapeutic groups in Hodgkin's disease patients

In general, the management of Hodgkin lymphoma depends on the subtype. Most clinicians divide classical Hodgkin lymphoma into the following three general groups:

- Early-stage favorable
  - Early-stage unfavorable
  - Advanced-stage disease
- Groups are chosen based on the following findings:
- Large mediastinal tumour, so-called bulk ( $> 1/3$  of the thorax diameter)
  - Extranodal involvement
  - Erythrocyte sedimentation rate values highly increased
  - Three or more lymph nodes stations infested

However, favorable disease is defined differently by different groups. The two most commonly used definitions are that of the European Organization for the Research and Treatment of Cancer (EORTC) and the German Hodgkin Study Group (GHSG).

The EORTC definition uses the following patient criteria :

- Limited-stage disease
- Age younger than 50 years
- No bulky mediastinal adenopathy
- Erythrocyte sedimentation rate (ESR) less than 50 mm/h
- No B symptoms (or an ESR  $<30$  mm/h with B symptoms)
- Three or fewer sites of involvement

The GHSG definition uses the following criteria<sup>[39]</sup> :

- No more than two sites of disease
- No extranodal extension
- No bulky mediastinal disease
- ESR  $<50$  mm/h (or  $<30$  mm/h if B symptoms present)

## Chemotherapy in Hodgkin's disease

Patient deemed to be in early-stage disease receive a **combined radiochemotherapy. Advanced stages are treated with intensified chemotherapy without radiotherapy.**

In Europe, the combination of bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisolone and supportive G-CSF (**BEACOPP**) or the **ABVD protocol** from adriamycin, bleomycin, vinblastine and dacarbazine are preferable for chemotherapy. The duration of treatment comprises of 4-8 months.

Since 2012, an **antibody-drug conjugate** with the substance **brentuximab vedotin** is available for the treatment of CD30 + Hodgkin's lymphoma. It is intended for the treatment of patients after autologous stem cell transplantation, or after two previous therapies without remission or with relapse.

**Note:** The lymphocytic predominance, nodular type (*nodular paragranuloma*) constitutes an exception. It is treated solely with radiotherapy and chemotherapy.

## Prognosis of Hodgkin's Disease

### Hodgkin's disease has a good chance of recovery

In all three stages a complete remission can be reached in about 90 % and **over 80 %** of the patients can be **cured in the long term**. Negative prognostic factors are over 60 years of age, relapse disease within three months after completion of the initial treatment, B symptoms, incomplete remission and progress under ongoing therapy.

## Follow-up and Aftercare

Essential **measures to ensure the reproductive ability** of the patient must be taken prior to therapy e.g. cryopreservation of the sperm, since the cytotoxic drugs, particularly the used procarbazine, have a toxic effect on the sperm formation.

## Restaging in Hodgkin's disease

In order to assess the efficacy of the therapeutic regimen, a new diagnosis called **restaging** takes place at regular intervals. During restaging, the same investigation procedures as in the initial staging is used. Classically, restaging takes place after **two, four or six chemotherapy cycles** and after radiotherapy.

After the end of treatment, a follow-up takes place in the first year every 3 months and from the second year on in 6-month intervals and yearly after the fifth year. Follow-up consists essentially of the sonography of the formerly infested area and blood count checks. Radiographs of the thorax and CT examinations are spaced apart to minimize the radiation exposure.

Hypothyroidism can develop after thoracic irradiation. Moreover, there is the risk of heart damage. Therefore, regular checks of **thyroid** values and **echocardiography** should be performed.

Depending on the radiation field, the risk of a **second malignancy** for example of breast carcinoma, thyroid cancer or AML, also exists. The incidence rate of second neoplasms lies at **15 - 20 % in 20 years**. In order to minimize this risk, it is important to reduce exposure to radiation to a minimum.



# Review Questions

The solutions are located below the sources.

## 1. Which cells are not typically be found in Hodgkin's lymphoma?

- A. Reed-Sternberg cells
- B. Eosinophilic granulocytes
- C. Owl's eye cells
- D. Hodgkin cells
- E. Fibroblasts

## 2. Which subtype is the most common of the classical Hodgkin's lymphoma?

- A. Lymphocyte rich form
- B. Nodular sclerosing form
- C. Mixed type
- D. Low lymphocytes type
- E. Nodular Paragranuloma

**3. A 36-year-old obese man presents to your general medicine practice with a painless swelling in the area of his right neck. He cannot say when the swelling began, as it was first noticed by his sister, whom he had seen again a week ago after a long time. He indicates to have sweated heavily in the recent weeks, even at night, and that he has lost weight. You arrange to have a lymph node removed in the operating room and submitted to pathology for histological and immunohistochemical diagnosis. The diagnosis of Hodgkin's lymphoma is made. What further diagnostic measure is NOT a standard part of diagnosis and staging of Hodgkin's disease?**

- A. CT abdomen
- B. Bone marrow puncture
- C. CT thorax
- D. MRI skull
- E. Complete blood count

## References

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**Correct answers:** 1C, 2B, 3D

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