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

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 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?
Hodgkin’s lymphoma is named after Thomas Hodgkin, who first described it in 1832. It is a malignant disease associated with lymphatic system. The malignant neoplasms of the lymphatic system are divided into Hodgkin’s lymphoma associated with histologically detectable Hodgkin and Reed-Sternberg cells, and non-Hodgkin’s lymphomas.

Hodgkin’s disease is a monoclonal B cell lymphoma originating in the lymph nodes. In advanced stages, large prolymphocytes are scattered hematologically from the lymph nodes and resettled 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, with an incidence of approx. 2-4/100,000. The disease has a peak incidence around the 30th and the 60th years of life, with a male-to-female ratio of 3:2. A slight decline in the incidence of monoclonal B cell lymphoma is observed.

Hodgkin’s disease affects even children. The peak age of incidence in children is around 12 years. The gender distribution corresponds to that of adulthood.

Etiology of Hodgkin’s Disease

Causes of Hodgkin’s disease

The etiology of Hodgkin’s disease is not fully understood. It is plausible that oncogenic viruses such as Epstein-Barr virus (EBV) act as triggers since EBV DNA is found in the Hodgkin and Reed-Sternberg cells of about 50% of the patients. In developing countries, EBV DNA is detected in 90% of Hodgkin’s lymphomas.

The risk of developing Hodgkin’s lymphoma is increased 3-fold after infectious mononucleosis (glandular fever). In addition, it is associated with oncogene mutations...
and altered tumor suppressor genes that inhibit apoptosis. **Impaired immune defense** increases the 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 manifests mostly as a **lymph node swelling**. In nearly 60% of the cases, the lymphadenopathy is unilaterally **cervical**. Other areas include the axilla, the inguinal area, the mediastinum, and the abdomen. The lymph node involvement progresses centripetally. The swollen lymph nodes are usually indolent and exhibit solid, rubbery consistency. The mediastinal nodes are involved in 60% of the cases.

**Note:** Every unexplained lymph node swelling, which persists longer than 2–3 weeks, warrants histological evaluation.

![Image: Hodgkin disease. By Yale Rosen, License: CC BY-SA 2.0](image)

**Symptoms of Hodgkin’s disease**

- Very often, the patient exhibits type B symptoms, i.e., fever, night sweats, and weight loss greater than 10% of body weight in 6 months.
- Typically, patients with Hodgkin’s disease manifest the so-called **Pel-Ebstein fever**. It is characterized by an undulant fever pattern lasting a few days to weeks followed by remission.
- **Alcoholic pain** is also rather rare. Patients manifest pain in the affected **lymph nodes** immediately after alcohol consumption, a phenomenon pathognomonic for Hodgkin’s lymphoma.
- **Agonizing itch** may occur as a paraneoplastic symptom. Other paraneoplastic syndromes include ichthyosis and pemphigus.
- The incidence of **Ophelia syndrome** is rare but is characterized by the combination of hippocampal sclerosis and dementia.
- In disseminated systemic disease, **hepatosplenomegaly** often occurs along with the involvement of other non-lymphoid organs, such as **lungs**, **skin** and gastrointestinal tract with symptoms attributed to the organs affected by the disease.
Diagnosis of Hodgkin’s Disease

Histological analysis of Hodgkin’s disease

The diagnosis is confirmed via histological evaluation of the affected lymph node. It is always important to excise an entire lymph node since a lymph node biopsy does not provide adequate material.

The histological evidence of mononuclear Hodgkin and polymorphonuclear Reed-Sternberg cells is diagnostic. Reed-Sternberg cells (also called Hodgkin Reed-Sternberg cells) are giant cells measuring greater than 20 μm in diameter with 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. It was originally identified as a cell surface antigen on Reed-Sternberg cells. CD15 is a marker of late granulocytes, monocytes, and activated T cells, and is not normally expressed by cells of B lineage. The Reed-Sternberg cells 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

A computed tomographic (CT) investigation of the neck, thorax, abdomen, and pelvis is carried out for staging. Currently, PET-CT is also used: the CT provides anatomical details while the superimposed PET scan enhances the disease area.
A bone marrow puncture to rule out bone infiltration is also obligatory.

Note: Pathological staging via laparotomy and splenectomy is obsolete.

The clinical staging is based on Ann Arbor classification, in which the number and the location of affected lymph node stations, the presence of extranodal foci, the diffuse involvement of extra-lymphatic organs, and the presence of B-symptoms are considered.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Infestation of a single lymph node region of single localized extranodal foci</th>
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<tbody>
<tr>
<td>I</td>
<td>Infestation of 2 or more lymph nodes on 1 side of the diaphragm or localized extranodal foci, and infestation of 1 or more lymph nodes on 1 side of the diaphragm</td>
</tr>
<tr>
<td>II</td>
<td>Infestation of 2 or more lymph nodes on both sides of the diaphragm or localized extranodal foci on the diaphragm bilaterally</td>
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Stage IV: Widespread (disseminated) infection of 1 or more extra lymphatic organs or without lymph node involvement.

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

**Additions:**

A: without B symptoms  
B: with B symptoms  
E: extranodal involvement  
S: splenic infestation

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

Typical laboratory findings include **relative lymphopenia and eosinophilia** in the differential blood count, elevated CRP and LDH, and increased transaminases, which suggests liver involvement. The **erythrocyte sedimentation rate represents a sign of disease activity** and is caused by increased alpha-2 and gamma globulins. Peripheral pancytopenia may be associated with cases involving bone marrow resulting in bone marrow failure.

**Classification of Hodgkin’s Disease**

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

**Classic Hodgkin’s lymphoma**

Classic Hodgkin’s lymphoma accounts for 95% of all cases. It is divided into 4 subtypes:

- **Nodular sclerosing Hodgkin’s lymphoma (60-80%)**: The nodular sclerosing form is characterized by nodular infiltrates and collagen scar. In addition, the typical, binucleate so-called **lacunar cells**, which are a subspecies of the HRS cells are found in young female patients with a mediastinal and supraclavicular infestation.

- **Mixed type (15-30%)**: The mixed form is common in patients in their second peak incidence. Men are affected more often than women by this form, and the infestation is typically cervical or abdominal.

- **Lymphocyte-rich classic Hodgkin’s lymphoma (4%)**: Lymphohistiocytic (B lymphocytes) form involves cervical or axillary lymph nodes, and is predominant in male patients aged around 30 years.

- **Lymphocyte-poor type (1-2%)**: The lymphocyte-poor type involves anaplastic large cells with mitosis and few lymphocytes. This rare form is typically seen in patients at an advanced age and is associated with abdominal manifestations of lymphoma.
Nodular lymphocyte-predominant Hodgkin’s lymphoma

The nodular lymphocyte-predominant type represents 5% of all cases of Hodgkin’s Lymphoma. The nodular lymphocyte-predominant Hodgkin lymphoma (nodular paragranuloma) is characterized by popcorn cells, a special variation of the Reed-Sternberg cells embedded in 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 for Hodgkin’s Disease

Three prognostic and therapeutic groups of Hodgkin’s disease patients

In general, the management of Hodgkin’s lymphoma depends on the subtype. Most clinicians divide classical Hodgkin lymphoma into the following three general groups: 1) Early-stage (favorable); 2) Early-stage (unfavorable); and 3) Advanced-stage disease.

Groups are selected based on the following findings:

- Large mediastinal tumor, the so-called bulk (> 1/3rd of the thorax diameter)
- Extranodal involvement
- Elevated ESR values
- Infestation of 3 or more lymph node stations

However, the definition of a favorable disease varies. The 2 most commonly used definitions are provided by 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
- 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 is based on the following criteria:

- No more than 2 sites of disease
- No extranodal extension
- No bulky mediastinal disease
- ESR < 50 mm/h (or < 30 mm/h if B symptoms present)

Chemotherapy for Hodgkin’s disease

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

In Europe, the following combination therapies are preferred over chemotherapy: combination of bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisolone, and supportive G-CSF (BEACOPP); or the ABVD protocol.
based on adriamycin, bleomycin, vinblastine, and dacarbazine. The duration of treatment is 4–8 months.

Since 2012, an antibody-drug conjugate with 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 2 previous therapies without remission or with relapse.

Note: The lymphocyte-predominant nodular type (nodular paragranuloma) 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 attained in about 90%, and more than 80% of the patients can be cured in the long term. Negative prognostic factors include: age above 60 years, disease relapse within 3 months after completion of the initial treatment, B symptoms, incomplete remission, and progressive disease despite ongoing therapy.

Follow-up and Aftercare

Essential measures to ensure a patient’s reproductive ability must be implemented prior to therapy, e.g., cryopreservation of the sperm, since the cytotoxic drugs, particularly the used procarbazine, are toxic to sperm synthesis.

Restaging in Hodgkin’s disease

In order to assess the efficacy of the therapeutic regimen, diagnostic restaging is adopted at regular intervals. Restaging is conducted using the same investigations that are used for the initial staging. Classically, restaging is implemented after 2, 4 or 6 chemotherapy cycles, and after radiotherapy.

At the end of the treatment, patients are followed up in the 1st year every 3 months, in the 2nd year at 6-month intervals, and yearly after the 5th year. Follow-up entails sonography of the previously infested area along with blood counts. Radiographic evaluation of the thorax and CT is spaced apart to minimize radiation exposure.

Hypothyroidism occurs after thoracic irradiation. Further, there is a risk of heart damage. Therefore, regular monitoring of thyroid values and echocardiography is essential.

Depending on the radiation field, the risk of a second malignancy, e.g., of breast carcinoma, thyroid cancer or AML, also exists. The 20-year incidence rate of secondary neoplasms ranges between 15% and 20%. In order to minimize this risk, it is important to minimize exposure to radiation.

References


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