BMJ Best Practice

Hodgkin's lymphoma

Straight to the point of care

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Table of Contents

Summary

Hodgkin's lymphoma (HL) most commonly presents with painless cervical and/or supraclavicular lymphadenopathy in a young adult.

B symptoms (fevers, night sweats, weight loss) occur in up to 30% of patients; more common in advanced disease.

Imaging, preferably PET/CT, is essential to determine extent of disease. Biopsy is necessary to confirm diagnosis.

Combined-modality therapy (chemotherapy plus radiotherapy) is highly effective for early (stage I or stage II) classical HL, but it is associated with toxicity and long-term complications. PET-adapted treatment approaches for early-stage disease balance efficacy and safety through avoidance of radiotherapy in chemosensitive patients.

Chemotherapy is the cornerstone of treatment for advanced (stage III or stage IV) classical HL.

Radiotherapy is recommended for patients with early-stage nodular lymphocyte-predominant HL (NLPHL). Patients with advanced-stage NLPHL can be treated with rituximab plus chemotherapy. Observation may be appropriate for asymptomatic patients with early- or advanced-stage NLPHL.

Definition

Hodgkin's lymphoma (HL), also referred to as Hodgkin's disease, is an uncommon haematological malignancy arising from mature B cells. It is characterised by the presence of Hodgkin's cells and Reed-Sternberg cells.

The topic focuses on the diagnosis and management of adults with HL.

Epidemiology

HL is an uncommon malignancy. In the UK, there were 2166 new cases of HL between 2017 and 2019.[6] It is estimated that 8570 new cases of HL and 910 associated deaths will occur in the US in 2024.[7] The age-adjusted incidence rate in the US is approximately 2.5 per 100,000 people per year (based on data from 2017 to 2021).[7]

Incidence is slightly higher among men than women (2.8 vs. 2.2 per 100,000 people).[7] HL is more common among non-Hispanic white people (3.1 new cases per 100,000 men; 2.6 per 100,000 women) than other racial/ethnic groups.[7]

In the US, median age at diagnosis is 39 years.[7] Peak incidence occurs at ages 20-34 years.[7] Data indicate a bimodal distribution of age at diagnosis, with an initial peak at ages 15-35 years followed by a more modest peak among those >55 years.[6] [7][8]

HL incidence rates vary considerably by geographic region, with the highest incidence rates observed in Southern Europe.[8]

Aetiology

The aetiology of HL remains unclear but is likely to be multi-factorial. Furthermore, it may vary with age at presentation, geographic location, and histological sub-type. The presentation of HL (i.e., fevers, night sweats, lymphadenopathy) suggests an infectious aetiology. Indeed, the malignant Reed-Sternberg cells harbour Epstein-Barr virus (EBV) antigens in a significant proportion of cases (20% to 40%).[9] [10] The demonstration that a history of mononucleosis is a risk factor for developing EBV-positive HL further supports this hypothesis.[11] Whether the association between EBV and HL is causal has not been conclusively demonstrated. Furthermore, not all cases of HL are related to EBV or infectious mononucleosis.

There is evidence of a familial predisposition to HL, but this is uncommon (approximately 5% of cases are believed to be familial).[12] [13] [14] If a monozygotic twin is diagnosed with HL, the risk of the second twin developing HL is nearly 100 times greater than that of the general population.[15] The risk among dizygotic twins is lower (approximately 7 times greater than the general population).[16] First-degree relatives of patients with HL are approximately 3 times more likely to develop the disease than the general population.[17] [18]

Pathophysiology

The pathogenesis of HL remains unclear, although several mechanisms have been postulated. Pathogenesis is likely to be different in patients with Epstein-Barr virus (EBV)-positive disease compared with those with EBV-negative disease.

HL is a B-cell malignancy, and immunoglobulin expression is typically absent despite gene re-arrangements and somatic hyper-mutation.[19] Surface immunoglobulin (B-cell receptors) is required for B-cell maturation and survival.[20] [21] In EBV-positive disease, it is thought that viral proteins (LMP1, LMP2A, EBNA1) allow infected, abnormal B cells to evade apoptosis and/or replicate in an uncontrolled manner by mimicking constitutively active cellular receptors that are essential for B-cell growth, survival, and evasion of apoptosis.[22] [23]

Classification

The 5th edition of the World Health Organization Classification of haematolymphoid tumours: lymphoid neoplasms[1]#

Classical HL (95% of cases).[2]

- Within this category:
    - Nodular sclerosis (70%)
    - Mixed cellularity (25%)
    - Lymphocyte-rich (5%)
    - Lymphocyte-depleted (<1%).

Nodular lymphocyte-predominant HL (NLPHL; 5% of cases).

The International Consensus Classification of mature lymphoid neoplasms: a report from the Clinical Advisory Committee[3]

The International Consensus Classification (ICC) of mature lymphoid neoplasms Clinical Advisory Committee has reclassified NLPHL as ‘nodular lymphocyte predominant B-cell lymphoma’. The ICC highlighted biological and clinical differences between NLPHL and classical HL and the close relationship of NLPHL to T-cell/histiocyte-rich large B-cell lymphoma.[3]

The 5th edition of the World Health Organization Classification of haematolymphoid tumours retains the existing terminology and position of NLPHL as a subtype of Hodgkin's lymphoma. However, the WHO recognises ‘nodular lymphocyte predominant B-cell lymphoma’ as an acceptable term, with definitive adoption of these changes under consideration.[1]

Case history

Case history #1

A 25-year-old man presents to his general practitioner with a slowly enlarging, painless right neck mass. He denies recent upper respiratory tract infections, fevers, night sweats, or unintentional weight loss. He is otherwise healthy. Social history and family history are unremarkable. On examination he is afebrile with normal vital signs. Pertinent findings include a 3-cm, firm, round, non-tender, mobile mass in the mid-right neck. There is no other peripheral lymphadenopathy. Liver and spleen are not enlarged.

Other presentations

The most common presentation of HL is painless cervical and/or supraclavicular lymphadenopathy. Axillary and inguinal lymphadenopathy is less common. The mediastinum is frequently involved and occasionally symptoms include shortness of breath and/or cough. Up to 30% of patients present with B symptoms, defined as unexplained, recurrent fevers of 38°C (100.4°F) or higher, drenching night sweats requiring change of bed clothes, and/or >10% weight loss in the last 6 months.[4] [5] B symptoms are more common in patients with advanced disease. Other systemic symptoms not categorised as B symptoms include generalised pruritus and alcohol-induced pain at the site of a tumour mass.

Approach

The most common presentation of HL is persistent cervical and/or supraclavicular lymphadenopathy in a young adult.

HL mainly occurs in early (age 20-34 years) or late adulthood (over 55 years).[6] [7] [8]

Signs and symptoms

Most patients present with a several-month history of persistent lymphadenopathy, which has often been treated empirically with antibiotics. The cervical chain is the most commonly involved site.

Systemic symptoms, referred to as B symptoms, occur in up to 30% of patients and include unexplained recurrent fevers (≥38°C [≥100.4°F]), drenching night sweats necessitating change of bedclothes, and/or unexplained weight loss of >10% of baseline weight in the preceding 6 months.[4] [5] These symptoms are typically associated with advanced disease (stage III to IV), and are more common in older patients (aged >60 years).[33]

Other systemic symptoms include localised or generalised pruritus and alcohol-induced pain at involved sites. Symptoms from enlarged lymph nodes, such as shortness of breath, cough, chest pain, abdominal pain, or superior vena cava syndrome, may occur but are less common.

Clinical assessment

Clinical exam should focus on the lymphatic system, including the cervical, supraclavicular, axillary, and inguinal lymph node chains. Documentation of size, mobility, and tenderness of palpable lymph nodes should be performed.

The abdomen should be examined for hepatomegaly or splenomegaly. The oropharynx should be evaluated for tonsillar enlargement.

A dental evaluation should be carried out because radiotherapy can cause xerostomia and increased caries.

Laboratory evaluation

Full blood count with differential, comprehensive metabolic panel (including alkaline phosphatase, lactate dehydrogenase, liver enzymes, and albumin), and an erythrocyte sedimentation rate are required as part of the diagnostic work-up.

Baseline thyroid function tests are required, particularly in patients receiving radiotherapy to the neck. Radiotherapy to the neck can increase the risk of developing thyroid dysfunction.

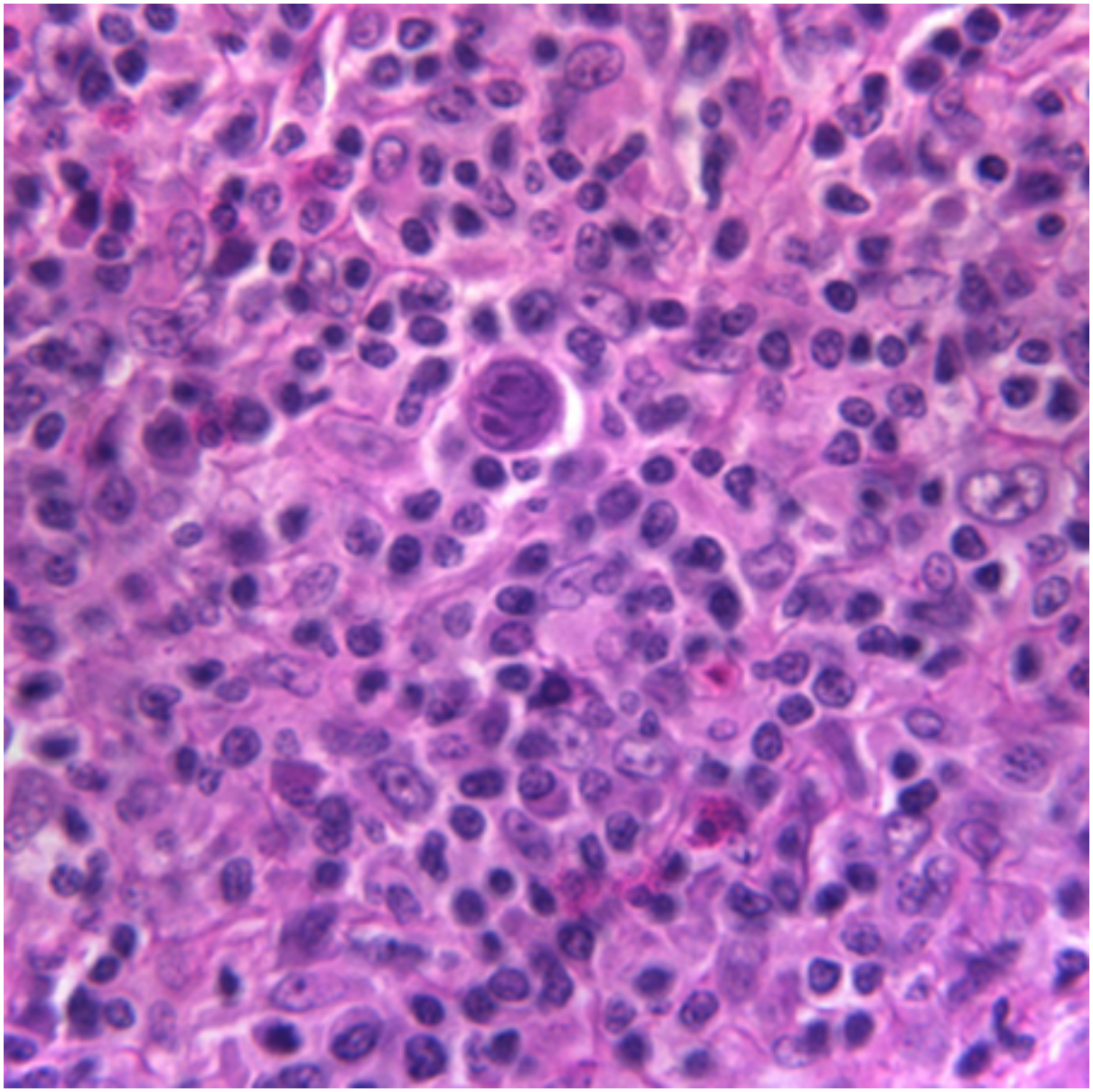
Screening for HIV and hepatitis B and C should be carried out as infection with these viruses may complicate treatment for HL.

Pathology

Pathological confirmation via biopsy is the only acceptable method of diagnosing HL and is essential before treatment can commence. An excisional biopsy of an enlarged lymph node is recommended.[5] [33] Under certain circumstances a core biopsy can be adequate. A fine-needle aspiration biopsy is never suitable for diagnosing HL.

HL is characterised by the identification of Hodgkin's cells with an appropriate background cellular milieu. The Hodgkin's cell can be a characteristic Reed-Sternberg cell or one of its variants, such as the lacunar cell in the nodular sclerosis sub-type. For nodular lymphocyte-predominant HL, the characteristic cell is the lymphocytic and histiocytic (L&H) cell, also referred to as a popcorn cell.

Immunohistochemical studies, which are routinely obtained as part of the pathological assessment, are invaluable in differentiating HL from other lymphomas as well as non-haematological processes.



A diagnostic Reed-Sternberg cell is seen in the centre of the image

From the personal collection of CR Kelsey

Imaging and staging

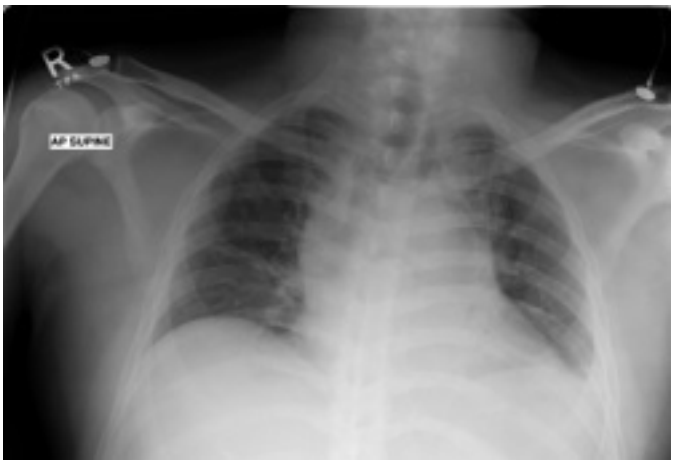
Positron emission tomography/computed tomography (PET/CT) imaging (where available) should be carried out at diagnosis to evaluate the extent of disease (i.e., stage), and throughout treatment to monitor treatment response and guide management.[34] [35]

A pre-treatment PET/CT is recommended to facilitate interpretation of post-treatment PET/CT scans.[36] [37]

Patients adequately staged with PET/CT do not require a bone marrow biopsy to evaluate bone involvement.[38] However, a bone marrow biopsy may be required if PET/CT is unavailable, or if a patient has a negative PET/CT and unexplained thrombocytopenia or neutropenia.[5] [33]

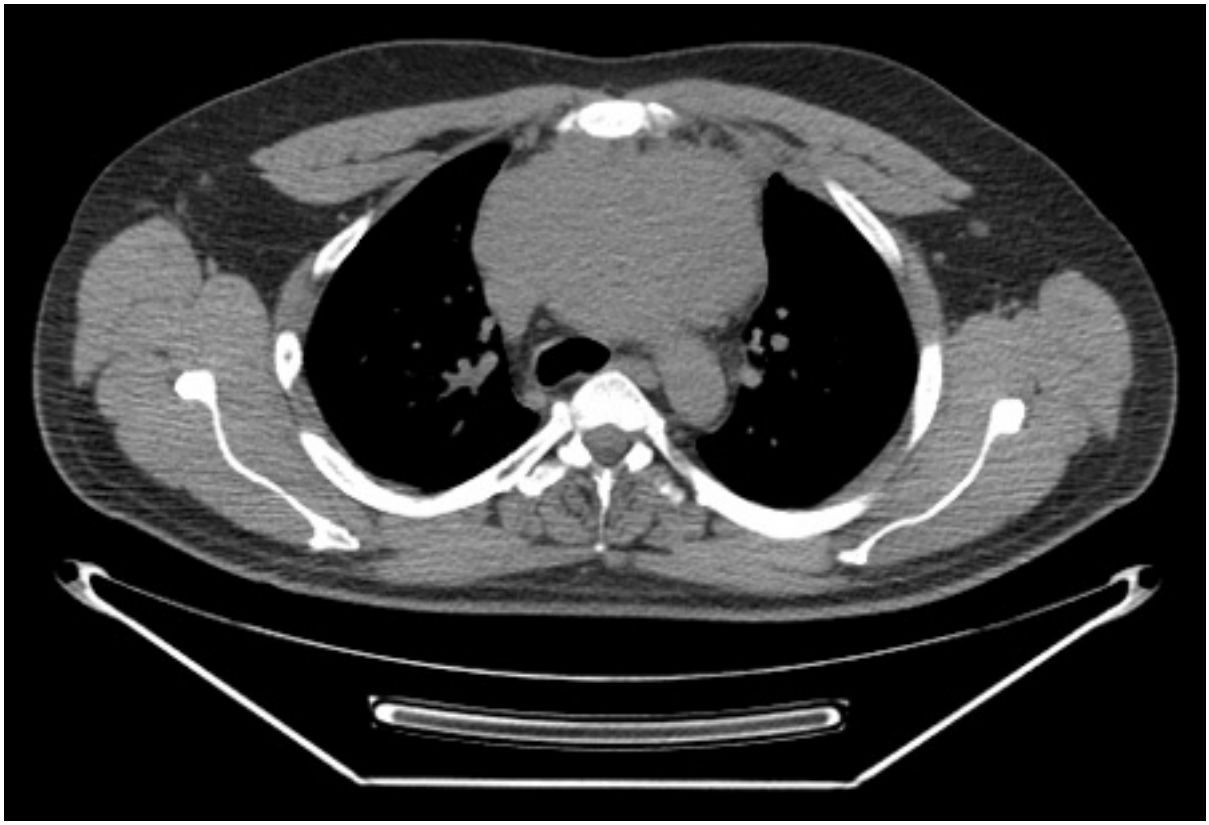
A gallium scan, supplemented with contrast-enhanced CT of the neck, chest, abdomen, and pelvis, can be used if PET/CT is unavailable.

A chest x-ray at diagnosis is helpful to evaluate for bulky mediastinal adenopathy.



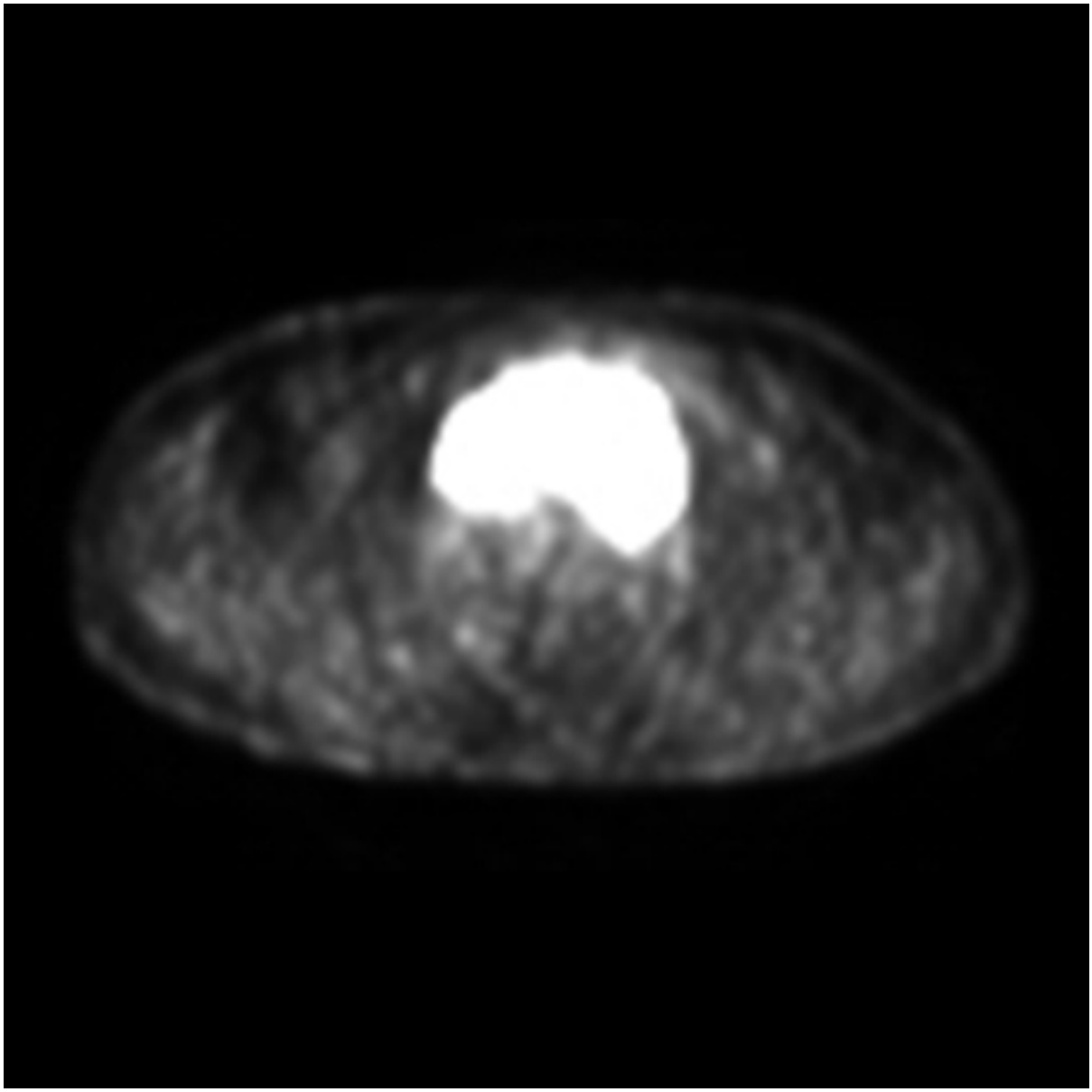
CXR of patient presenting with dyspnoea, showing widened mediastinum and tracheal displacement

From the personal collection of CR Kelsey



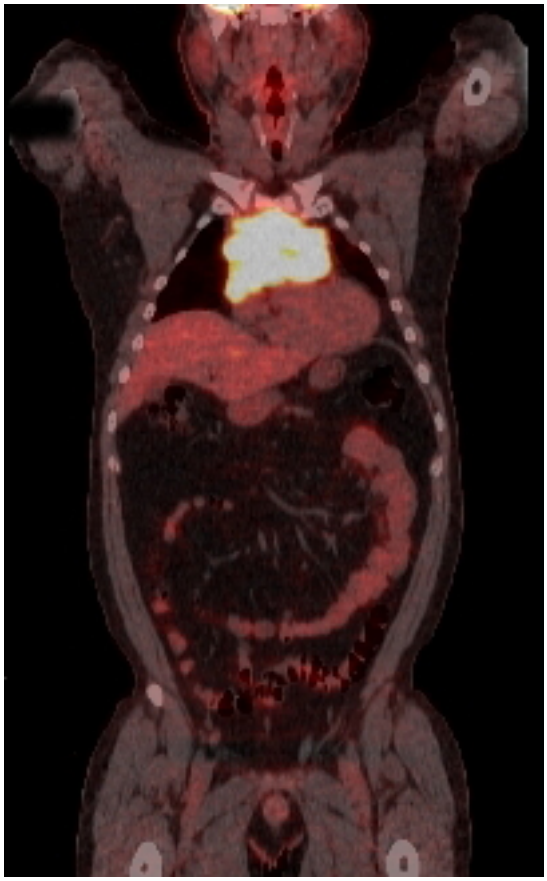
CT scan of patient with nodular sclerosis Hodgkin's lymphoma, showing an 11-cm anterior mediastinal mass

From the personal collection of CR Kelsey



PET scan (axial) showing fluorodeoxyglucose (FDG)-avid mass in the anterior mediastinum

From the personal collection of CR Kelsey



PET scan (coronal) showing fluorodeoxyglucose (FDG)-avid mass in the superior mediastinum

From the personal collection of CR Kelsey

Physiological evaluation

Baseline pulmonary function tests are important in patients receiving mediastinal radiotherapy and/or chemotherapy with potential for pulmonary toxicity (e.g., bleomycin).

A baseline cardiac evaluation (echocardiogram or multi-gated acquisition scan) is required in those patients receiving potentially cardiotoxic chemotherapy agents (e.g., anthracyclines).

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key factors include Epstein-Barr virus infection, positive family history, and young adults from higher socio-economic class.

lymphadenopathy (common)

- Persistent lymphadenopathy, typically painless and most commonly involving the cervical and/or supraclavicular nodal chain, is the most common presenting symptom of HL.
- Mediastinal lymphadenopathy is common and is often asymptomatic. Occasionally, shortness of breath and/or cough may be present.
- Axillary and inguinal lymphadenopathy is less common.

Other diagnostic factors

unexplained fevers (uncommon)

- History of recurrent, unexplained fevers, ≥38°C (≥100.4°F). One of the three B symptoms that occur in up to 30% of patients with HL, usually with advanced disease or other adverse risk factors.[4] [5]

night sweats (uncommon)

- History of drenching night sweats, necessitating change of bedclothes, is one of the three B symptoms that occur in up to 30% of patients with HL, usually with advanced disease or other adverse risk factors.[4] [5]

weight loss (uncommon)

- Unexplained weight loss of >10% of baseline weight in the preceding 6 months is one of the three B symptoms that occur in up to 30% of patients with HL, usually with advanced disease or other adverse risk factors.[4] [5]

dyspnoea (uncommon)

- Mediastinal lymphadenopathy is common but is often asymptomatic. Extensive mediastinal lymphadenopathy can compress the major airways causing dyspnoea.

cough (uncommon)

- Extensive mediastinal lymphadenopathy can cause a dry cough.

chest pain (uncommon)

- Extensive mediastinal lymphadenopathy can cause a vague chest discomfort.

superior vena cava syndrome (SVCS) (uncommon)

- Extensive mediastinal lymphadenopathy can compress the superior vena cava which can result in SVCS.
- Symptoms of SVCS include dyspnoea, cough, orthopnoea, facial and upper extremity oedema, and dilated neck veins.

abdominal pain (uncommon)

- Extensive abdominal lymphadenopathy can result in abdominal pain.

pruritus (uncommon)

- Approximately 10% of patients present with either localised or generalised pruritus.
- Originally, but no longer, considered a B symptom. Several studies have demonstrated that pruritus is of no prognostic significance.[39]

alcohol-induced pain at involved sites (uncommon)

- While rare, pain at sites of lymphadenopathy after drinking alcohol is a distinct and striking symptom characteristic of HL.

hepatomegaly and/or splenomegaly (uncommon)

- May be present in advanced disease.

tonsillar enlargement (uncommon)

- May be indicative of involvement of the tonsillar lymphoid tissue.

Risk factors

Strong

age 20-34 years and >55 years

- Peak incidence occurs at ages 20-34 years.[7]
- Data indicate a bimodal distribution of age at diagnosis, with an initial peak at ages 15-35 years followed by a more modest peak among those >55 years.[6] [7][8]

history of Epstein-Barr virus (EBV) infection

- EBV antigens are found in 20% to 40% of Reed-Sternberg cells.[9] [10] Antibodies against EBV antigens are more likely to be elevated several years prior to the diagnosis of HL than in healthy controls.[24] Infectious mononucleosis, of which EBV is the causative agent, is a risk factor for developing EBV-positive HL.[11] The vast majority of patients who contract EBV do not develop HL.
- EBV-positive HL is more commonly of mixed cellularity histology, and it is predominantly reported in men and children in lower-income settings.[8] [25]
- In populations with European ancestry, 60% to 70% of patients have EBV-negative nodular sclerosis HL.[26]

family history of Hodgkin's lymphoma

- There is evidence of a familial predisposition to HL, but this is uncommon (approximately 5% of cases are believed to be familial).[12] [13] [14]
- If a monozygotic twin is diagnosed with HL, the risk of the second twin developing HL is nearly 100 times greater than that of the general population.[15] The risk among dizygotic twins is lower (approximately 7 times greater than the general population).[16]
- First-degree relatives of patients with HL are approximately 3 times more likely to develop the disease than the general population.[17] [18]

young adults from higher socio-economic class

- Young adults from higher socio-economic classes are at greater risk of developing HL than their peers from lower socio-economic classes, especially with nodular sclerosis sub-type.[26] [27]
- Additionally, among young adults, the risk of developing HL seems to decrease with increasing birth order and increasing sibship size.[28] It is postulated that these associations are secondary to delayed exposure to infectious agents. These trends are not appreciated in children and older adults who develop HL.

Weak

human leukocyte antigen (HLA) types

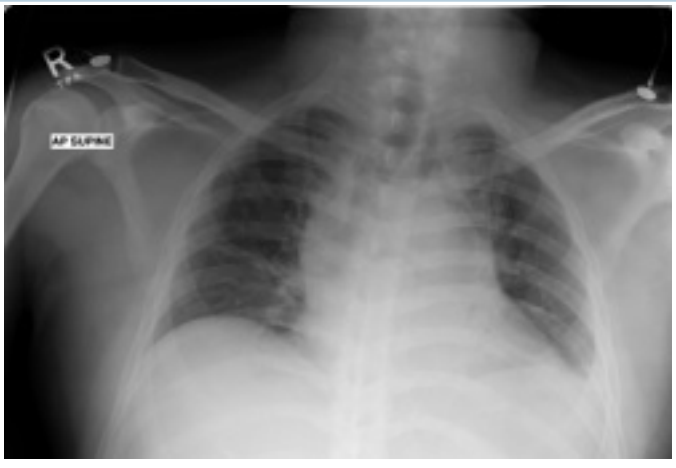
- Numerous HLA types have been associated with an increased risk of HL.[29] [30] These associations have been present in both sporadic and familial cases. The relative magnitude of the effect has been modest.
- Lack of HLA class II expression has been associated with an adverse prognosis, independent of other known prognostic factors.[31]

Jewish ancestry

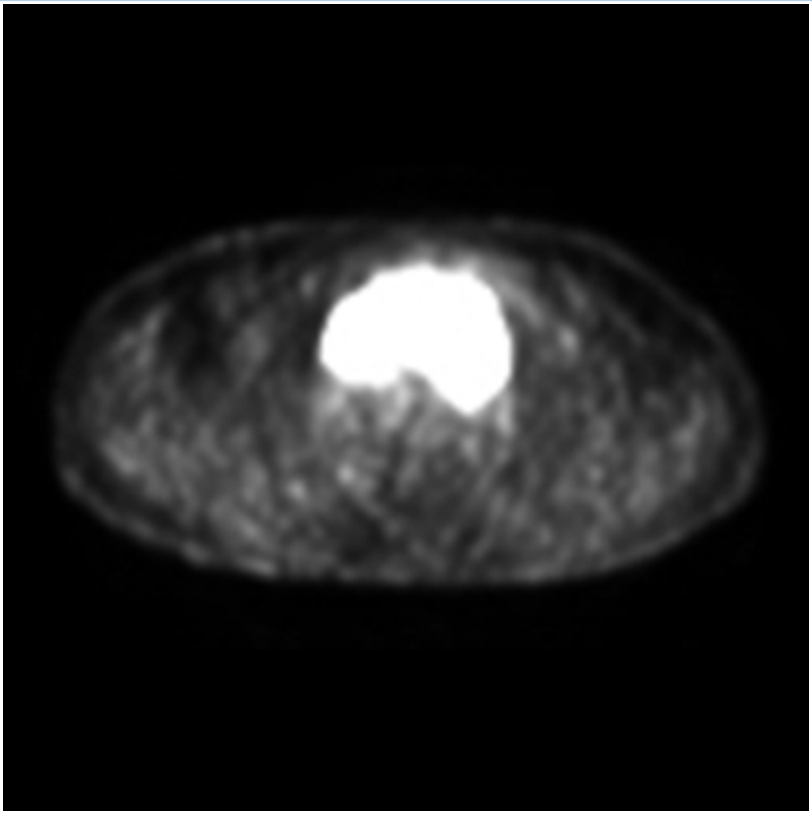
- Jewish ancestry is associated with an increased risk of developing HL, even after adjusting for socio-economic status.[32]

Investigations

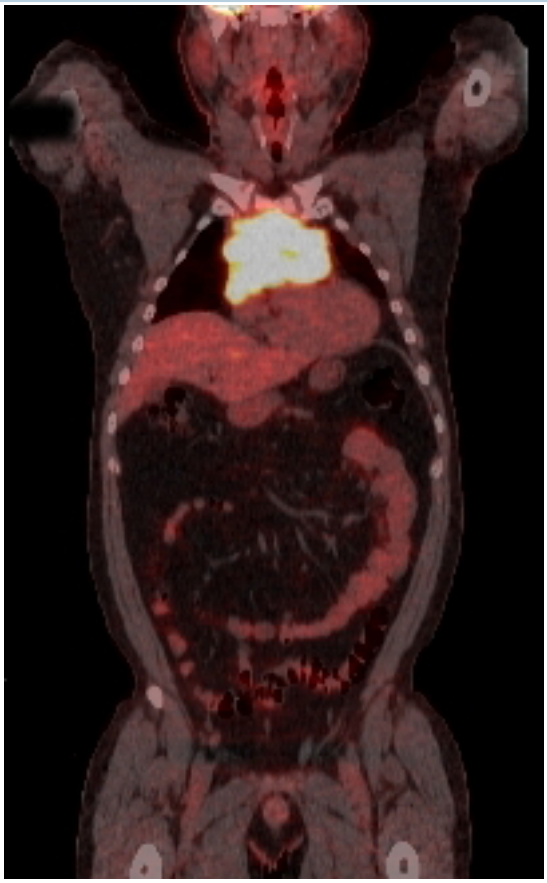
1st test to order

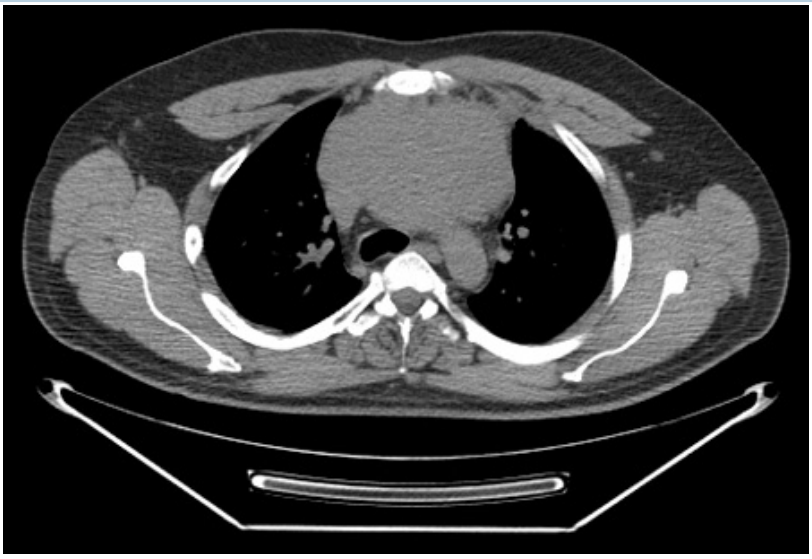
Test	Result
FBC with differential • Required as part of the diagnostic work-up for HL. • Abnormal blood count may suggest bone marrow involvement. • Haemoglobin <10.5 g/dL is an adverse prognostic factor.	**low Hb and platelets; WBC count may be high or low**
comprehensive metabolic panel • Required as part of the diagnostic work-up for HL. • Performed to evaluate baseline liver and renal function prior to commencement of treatment. • Includes alkaline phosphatase, lactate dehydrogenase, liver enzymes, and albumin. • Low albumin (<4 g/dL) is an adverse prognostic factor.	**normal in most patients with HL**
erythrocyte sedimentation rate (ESR) • Required as part of the diagnostic work-up for HL. • ESR >50 mm/hour without B symptoms or >30 mm/hour with B symptoms is an adverse prognostic factor.	**may be elevated**
thyroid function tests • Baseline thyroid function tests are required, particularly in patients receiving radioherapy to the neck. Radiotherapy to the neck can increase the risk of developing thyroid dysfunction.	**may be normal at baseline and abnormal following radiotherapy to the neck**
screening for HIV, hepatitis B, hepatitis C • Infection with HIV, hepatitis B, and/or hepatitis C may complicate treatment.	**may be positive for HIV, hepatitis B, and/or hepatitis C**
CXR • Helpful at diagnosis to evaluate for bulky mediastinal lymphadenopathy. • Bulky mediastinal lymphadenopathy (exceeding one third of the intra-thoracic measurement on an upright posteroanterior film at the T5 to T6 inter-space) is an adverse prognostic factor.  *CXR of patient presenting with dyspnoea, showing widened mediastinum and tracheal displacement* *From the personal collection of CR Kelsey*	**mediastinal mass; bulky mediastinal lymphadenopathy**

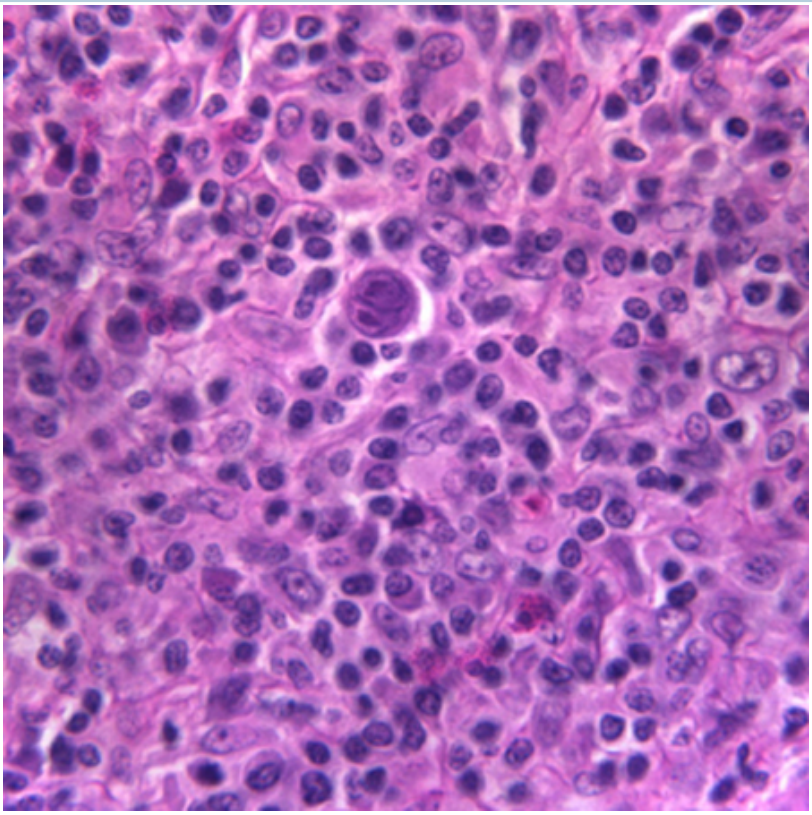
Test	Result
PET/CT scan • PET/CT imaging (where available) should be carried out at diagnosis to evaluate the extent of disease (i.e., stage), and throughout treatment to monitor treatment response and guide management.[34] [35] • A pre-treatment PET/CT is recommended to facilitate interpretation of post-treatment PET/CT scans.[36] [37] • Patients treated with combined-modality therapy should undergo PET/CT imaging after chemotherapy to assess treatment response (e.g., based on the Deauville criteria) and to guide subsequent treatment (e.g., with chemotherapy and/or radiotherapy).[40] • PET appears to be an accurate staging tool. The sensitivity and specificity of PET are reported to be 93% and 87%, respectively.[41] • Patients adequately staged with PET/CT do not require a bone marrow biopsy to evaluate bone involvement.[38]	**involved sites appear FDG-avid (bright) with PET imaging**



PET scan (axial) showing fluorodeoxyglucose (FDG)-avid mass in the anterior mediastinum
From the personal collection of CR Kelsey

Test	Result
 *PET scan (coronal) showing fluorodeoxyglucose (FDG)-avid mass in the superior mediastinum* *From the personal collection of CR Kelsey*	
gallium scan • A gallium scan can be used to assess the extent of disease if PET/CT is unavailable. • Gallium delivers a higher radiation dose to the patient than fluorodeoxyglucose (FDG)-PET. • Gallium scans appear to be less sensitive than FDG-PET scans, and it can take several days to obtain results.[42] • Gallium uptake in the bowel can obscure visualisation of abdominal disease.	**involved sites appear bright on gallium scans**
contrast-enhanced CT (neck, chest, abdomen, pelvis) • Indicated in combination with gallium scan when PET/CT scan is unavailable.	**may show enlarged lymph nodes and other sites of disease**

Test	Result
 *CT scan of patient with nodular sclerosis Hodgkin's lymphoma, showing an 11-cm anterior mediastinal mass* *From the personal collection of CR Kelsey*	
excisional lymph node biopsy or core biopsy • Required to confirm a diagnosis of HL, and essential before treatment can commence. • An excisional biopsy of an enlarged lymph node is recommended.[5] [33] Under certain circumstances a core biopsy can be adequate. • A fine-needle aspiration biopsy is never suitable for diagnosing HL. • The Hodgkin's cell can be a characteristic Reed-Sternberg cell, or one of its variants, such as the lacunar cell in the nodular sclerosis sub-type. In nodular lymphocyte-predominant HL, the characteristic cell is the lymphocytic and histiocytic (L&H) cell, also referred to as a popcorn cell.	**Hodgkin's cells within an appropriate background cellular milieu**

Test	Result
 *A diagnostic Reed-Sternberg cell is seen in the centre of the image* *From the personal collection of CR Kelsey*	
immunohistochemical studies • Immunohistochemical studies are invaluable in differentiating HL from other lymphomas, as well as non-haematological processes.	**classical HL is characteristically CD30-positive and usually, but not always, CD15-positive. Typically, CD45 is negative, while CD20 positivity can be seen in up to 30% to 40% of classical HL. Nodular lymphocyte-predominant HL is usually CD15- and CD30-negative but CD20- and CD45-positive**

Other tests to consider

Test	Result
bone marrow biopsy • Patients adequately staged with PET/CT do not require a bone marrow biopsy to evaluate bone involvement.[38] • Bone marrow biopsy may be required if PET/CT is unavailable or if a patient has a negative PET/CT and unexplained thrombocytopenia or neutropenia.[5] [33]	**presence of Hodgkin's cells**
echocardiogram or multi-gated acquisition (MUGA) scan • Patients receiving potentially cardiotoxic chemotherapy agents (e.g., anthracyclines) should have a baseline cardiac evaluation.	**uneven distribution of technetium in the heart and/or decreased ejection fraction during a MUGA scan is indicative of heart disease; an echocardiogram can evaluate multiple cardiac parameters, including ejection fraction, which may be diminished in patients with heart disease**
pulmonary function tests • Patients receiving mediastinal radiotherapy and/or chemotherapy with potential for pulmonary toxicity (e.g., bleomycin) should have baseline pulmonary function tests. • FEV1 and diffusion capacity of lung for carbon monoxide are the most common parameters.	**may show decreased lung volumes, spirometry, or diffusion capacity in patients with lung disease related to smoking, or who have received pulmonary toxic chemotherapy or mediastinal radiotherapy**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Non-Hodgkin's lymphoma (NHL)	• There are no pathognomonic clinical signs or symptoms that can differentiate HL from NHL. However, generalities can be helpful to differentiate the two entities. In contrast to NHL, HL tends to spread from one lymph node chain to another in contiguous fashion. Involvement of Waldeyer ring and extra-nodal sites is more common with NHL. Although HL and NHL can occur at any age, patients with HL tend to be younger.	• Pathological confirmation, interpreted by a skilled haematopathologist, is the only method to distinguish HL from NHL. The most common NHLs that can be confused with HL are T-cell-rich large B-cell lymphoma and anaplastic CD30+ large-cell lymphoma.
Lymphadenopathy from other malignancies	• A variety of different malignancies present with lymphadenopathy. Cancers of the head and neck often spread to cervical lymph nodes. Breast cancer most commonly spreads to axillary lymph nodes. Malignancies of the anus and vulva characteristically spread to inguinal lymph nodes.	• In addition to the clinical context and supporting imaging studies, performing a biopsy is the best way to differentiate Hodgkin's lymphoma from other malignancies when the aetiology of an enlarged lymph node is in doubt.
Infectious mononucleosis	• As opposed to HL, the enlarged lymph nodes are often tender. Sore throat is common with infectious mononucleosis but unusual with HL. Infectious mononucleosis is a risk factor for HL, with an estimated median incubation time from mononucleosis to Epstein-Barr virus (EBV)-positive HL of 4 years.[11] If HL is suspected, lymph node biopsy is necessary.	• Blood tests can be done to test for EBV, the causative agent of infectious mononucleosis.
Reactive lymph nodes	• Lymph nodes, particularly in the neck, can become enlarged from a variety of infectious/ inflammatory causes. Benign lymphadenopathy typically resolves within a few weeks.	• If enlarged lymph nodes persist or if other symptoms are present (e.g., B symptoms, such as fever, drenching night sweats, and weight loss), a lymph node biopsy should be considered.

Criteria

Lugano staging classification[34]

Staging with definition:

- Stage I: involvement of one lymph node or a group of adjacent nodes; or involvement of single extranodal lesions without nodal involvement
- Stage II: involvement of 2 or more nodal groups on the same side of the diaphragm; or stage I or II nodal extent with limited contiguous extranodal involvement
- Stage II (bulky): as above for stage II, but with bulky disease (i.e., a single nodal mass ≥10 cm in greatest diameter or greater than a third of the transthoracic diameter at any level of thoracic vertebrae)
- Stage III: involvement of lymph node on both sides of the diaphragm (includes involvement of lymph node above the diaphragm and the spleen)
- Stage IV: involvement of additional non-contiguous extranodal site(s) (i.e., beyond extranodal site[s], contiguous or proximal to known nodal site)

Note: Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

Sub-classification suffixes:

- A: no B symptoms
- B: presence of B symptoms (e.g., unexplained fever, drenching night sweats, weight loss >10% of body weight within 6 months of diagnosis)

International Prognostic Score (IPS)[43]

The International Prognostic Score (IPS) is a prognostic tool used to predict 5-year freedom from progression in patients with advanced HL, based on the following adverse prognostic factors:

- Low albumin level (<4 g/dL)
- Low haemoglobin level (<10.5 g/dL)
- Male sex
- Age ≥45 years
- Stage IV disease
- Leukocytosis
- Lymphocytopenia.

A point is given for each factor that is present. The IPS score is the sum of the points (e.g., 0 to 7). Higher score indicates lower risk of freedom from progression. The IPS score can be used for risk stratification and to guide treatment in patients with advanced HL.

Prognostic criteria for favourable early-stage HL

Several groups have published prognostic criteria for favourable early-stage (stage I to II) classical HL to distinguish from unfavourable early-stage disease, in order to optimise treatment and minimise toxicity.[44]

- European Organisation for Research and Treatment of Cancer (EORTC) favourable prognosis criteria:
  - Mediastinal tumour ratio (MTR) <0.35

- Erythrocyte sedimentation rate (ESR) <50 mm/hour if no B symptoms; ESR <30 mm/hour if B symptoms are present
- Involvement of ≤3 nodal sites
- Age <50 years

- German Hodgkin Study Group (GHSG) favourable prognosis criteria:
  - Mediastinal mass ratio (MMR) <0.33
  - ESR <50 mm/hour if no B symptoms; ESR <30 mm/hour if B symptoms are present
  - Involvement of ≤2 nodal sites
  - No extranodal disease
- National Comprehensive Cancer Network (NCCN) favourable prognosis criteria:
  - MMR <0.33
  - ESR <50 mm/hour and no B symptoms
  - Involvement of ≤3 nodal sites
  - Tumour bulk ≤10 cm (on CT scan)

Deauville criteria

The Deauville criteria can be used to assess interim and end-of-treatment response in patients with HL.[40] It is a five-point scale for fluorodeoxyglucose (FDG) uptake at involved sites relative to the mediastinum and liver, as visualised on PET/CT scan:

- No FDG uptake: score = 1
- FDG uptake ≤ mediastinum: score = 2
- FDG uptake > mediastinum but ≤ liver: score = 3
- FDG uptake moderately higher than liver: score = 4
- FDG uptake markedly higher than liver and/or new lesions: score = 5
- New areas of FDG uptake unlikely to be related to lymphoma: score = X

Patients with a negative PET/CT (i.e., Deauville score 1 to 3) are considered to have a complete metabolic response.[40] Patients with a positive PET/CT (i.e., Deauville score 4 or 5) are considered to have a partial metabolic response.

Approach

The management approach outlined in this topic focuses on adults with HL.

Chemotherapy and radiotherapy are the cornerstone of treatment for HL. The goal of treatment for all patients with HL is cure while minimising risk of toxicity and long-term complications.

HL in older patients (aged >60 years) is associated with poorer outcomes and higher treatment-related toxicity and mortality compared with younger patients.[47] [48] [49] Alternative treatment regimens may be considered for patients >60 years, or with poor performance status or substantial comorbidities. Bleomycin should be used with caution; standard regimens may be adapted to remove bleomycin or restrict its use to only two cycles.[33]

Early-stage (stage I to stage II) classical HL

The absence or presence of specific prognostic criteria determines whether the patient has favourable or unfavourable early-stage disease. German Hodgkin Study Group (GHSG) favourable prognosis criteria (see Diagnostic criteria) are most commonly used in the US:[44] [50]

- Mediastinal mass ratio (MMR) <0.33
- Erythrocyte sedimentation rate (ESR) <50 mm/hour if no B symptoms; ESR <30 mm/hour if B symptoms are present
- Involvement of ≤2 nodal sites
- No extranodal disease.

The most effective treatment for early-stage disease (favourable or unfavourable) is combined-modality therapy, which comprises combination chemotherapy (typically ABVD [doxorubicin, bleomycin, vinblastine, dacarbazine]) followed by radiotherapy.[51] [52] [53] [54] [55] [56] [57] [58] [59] [60] [61]

A chemotherapy-alone approach may be considered if avoiding radiotherapy is preferred (e.g., due to patient age, sex, family history of cancer or cardiac disease, comorbidities, sites of involvement).[33] [62] [63] [64] [65] [66] The decision to omit radiotherapy should involve expert input by a multidisciplinary team, and discussion with the patient regarding risks and benefits. Chemotherapy alone is associated with a slightly lower rate of tumour control and higher rate of relapse compared with combined-modality therapy, but survival rates are similar.[51] [52] [53] [58] [60] [64] [66] [67] [68] [69]

Radiotherapy for early-stage HL

Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70] [71] [72] [73] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

Acute adverse effects of radiotherapy depend on the region treated and the dose employed.

Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radioherapy can cause nausea and/or diarrhoea.

Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

PET-adapted treatment for early-stage HL

A PET-adapted treatment approach is recommended for all patients with early-stage disease (favourable or unfavourable) as it offers the opportunity to balance efficacy and toxicity of treatment.[5] [33] [54] [65] [66] [74] [75] This approach typically involves performing an interim PET/CT scan after two initial cycles of chemotherapy (e.g., ABVD) to assess metabolic response to treatment, and to inform subsequent treatment (e.g., additional chemotherapy and/or radiotherapy).

Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40] Patients with a Deauville score of 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score of 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

Treatment for favourable early-stage HL

Patients with favourable early-stage disease generally receive two initial cycles of ABVD followed by an interim PET/CT scan.[33]

Those intended for combined-modality therapy can receive the following subsequent treatments based on their Deauville score on interim PET/CT:

- Deauville score 1 to 2: 20 Gy radiotherapy, or one additional cycle of ABVD followed by 30 Gy radiotherapy.[60] [61] [65] [67]
- Deauville score 3: 20 Gy radiotherapy, or two additional cycle of ABVD followed by 30 Gy radiotherapy (based on the RAPID study).[61] [65]
- Deauville score 4: two additional cycles of ABVD followed by a restaging PET/CT scan to assess metabolic response and inform subsequent treatment.[60] [65] [67] If restaging PET/CT is negative (Deauville score 1 to 3) then 30 Gy radiotherapy can be given. If restaging PET/CT is positive (Deauville score 4 or 5) then a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]
- Deauville score 5: a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]

Patients with favourable early-stage disease who are intended for a chemotherapy-alone approach can receive the following subsequent treatments based on their Deauville score on interim PET/CT:

- Deauville score 1 or 2: two additional cycles of ABVD.[60] [64] [66] [67]
- Deauville score 3: two additional cycles of ABVD or four additional cycles of AVD.[60] [64] [66] [67] [68]
- Deauville score 4: two additional cycles of ABVD followed by a restaging PET/CT scan to assess metabolic response and inform subsequent treatment.[60] [64] [66] [67] If restaging PET/CT is negative (Deauville score 1 to 3) then 30 Gy radiotherapy should be considered. If restaging PET/CT is positive (Deauville score 4 or 5) then a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]
- Deauville score 5: a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]

Treatment for unfavourable early-stage HL

Patients with unfavourable early-stage disease generally receive two initial cycles of ABVD followed by an interim PET/CT scan to assess metabolic response and inform subsequent treatment.

Those with non-bulky or bulky disease who are intended for combined-modality therapy can receive the following subsequent treatments based on their Deauville score on interim PET/CT:

- Deauville score 1 to 3: two additional cycles of ABVD followed by 30 Gy radiotherapy.[54] [60] [67]
- Deauville score 4 or 5: two additional cycles of ABVD or escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone), followed by a restaging PET/CT scan.[54] [60] [67] If restaging PET/CT is negative (Deauville score 1 to 3) then 30 Gy radiotherapy can be given. If restaging PET/CT is positive (Deauville score 4 or 5) then a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]

Those with non-bulky unfavourable early-stage disease who are intended for chemotherapy alone can receive the following subsequent treatments based on their Deauville score on interim PET/CT:

- Deauville score 1 to 2: two additional cycles of ABVD.[60] [64] [66] [67]
- Deauville score 3: two additional cycles of ABVD or four additional cycles of AVD.[68]
- Deauville score 4: two additional cycles of ABVD followed by a restaging PET/CT scan to assess metabolic response and inform subsequent treatment.[60] [64][66] [67] If restaging PET/CT is negative (Deauville score 1 to 3) then two additional cycles of AVD followed by 30 Gy radiotherapy should be considered. If restaging PET/CT is positive (Deauville score 4 or 5) then a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]
- Deauville score 5: a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]

Those with bulky unfavourable early-stage disease who are intended for chemotherapy alone can receive the following subsequent treatments based on their Deauville score on interim PET/CT:

- Deauville score 1 to 3: four additional cycles of AVD.[68]
- Deauville score 4 or 5: two additional cycles of escalated BEACOPP followed by a restaging PET/CT scan.[54] [60] [68][76] [77] If restaging PET/CT is negative (Deauville score 1 to 3) then two additional cycles of escalated BEACOPP can be given. If restaging PET/CT is positive (Deauville score 4 or 5) then a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]

Advanced (stage III to stage IV) classical HL

Initial treatment options for advanced-stage disease include:[78] [79] [80] [81] [82] [83] [84] [85] [86] [87]

- ABVD
- Brentuximab vedotin (an anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E) plus AVD
- Escalated BEACOPP.

ABVD and brentuximab vedotin plus AVD are the preferred initial treatments for patients with advanced-stage disease.[33] [68]

Brentuximab vedotin plus AVD offers a survival advantage compared with ABVD in patients with advanced-stage disease.[33] [86] [87] [88] However, caution is required when used in older patients (age >60 years) and in those with baseline neuropathy. For older patients, sequential brentuximab vedotin plus AVD may be a preferred option.[84] This involves administering 2 cycles of brentuximab vedotin followed by 6 cycles of AVD followed by 4 cycles of brentuximab vedotin.[84]

Escalated BEACOPP is an intensive chemotherapy regimen that improves disease control compared with ABVD, but is associated with increased risk of toxicity and secondary acute leukaemias.[79] [80] [89] [90]

[91] Furthermore, given the effectiveness of second-line therapy for patients who relapse after ABVD, use of first-line escalated BEACOPP does not offer a survival advantage compared with ABVD.[90] [91] [92] [93] Use of escalated BEACOPP as initial treatment may be considered for younger patients (age <60 years) with a poor prognosis.[33]

PET-adapted treatment for advanced-stage HL

A PET-adapted treatment approach can be used in patients with advanced-stage disease to guide treatment decisions regarding escalation or de-escalation of chemotherapy.[68] [94] [95] [96]

Patients with advanced-stage disease who are intended for standard induction with ABVD chemotherapy typically receive two initial cycles of ABVD, followed by an interim PET/CT scan to assess metabolic response and inform subsequent treatment.[68] Patients can receive the following subsequent treatments based on their Deauville score on interim PET/CT:

- Deauville score 1 to 3: four additional cycles of AVD.[33] [68]
- Deauville score 4 or 5 (patients aged ≤60 years): three additional cycles of escalated BEACOPP, followed by a restaging PET/CT scan.[68] If restaging PET/CT is negative (Deauville score 1 to 3) then one additional cycle of escalated BEACOPP can be given.[68] If restaging PET/CT is positive (Deauville score 4 or 5), then a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]
- Deauville score 4 or 5 (patients aged >60 years): individualised treatment is recommended.[5] [33] Older patients typically have more medical comorbidities and a poorer prognosis than younger patients; therefore, treatment should be individualised to minimise toxicity while maintaining efficacy. Bleomycin should not be used for more than 2 cycles in older patients.[5] [33]

Selected patients (e.g., those with an International Prognostic Score [IPS] ≥4 and age <60 years) may be suitable for upfront intensive induction chemotherapy comprising two initial cycles of escalated BEACOPP, followed by an interim PET/CT scan to assess metabolic response and inform subsequent treatment.[94] [95] [96] Patients can receive the following subsequent treatments based on their Deauville score on interim PET/CT:

- Deauville score 1 to 3: two additional cycles of escalated BEACOPP or four additional cycles of ABVD.[33] [94] [95] [96] Bleomycin may be omitted from ABVD to reduce toxicity.
- Deauville score 4 or 5: a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy or treatment escalation).[33] Patients with a positive biopsy may require salvage therapy. Patients with a negative biopsy can receive two additional cycles of escalated BEACOPP followed by a restaging PET/CT scan.[94] [95] [96] If restaging PET/CT is negative (Deauville score 1 to 3) then two additional cycles of escalated BEACOPP can be given.[33] [94] [95] [96] If restaging PET/CT is positive (Deauville score 4 or 5) then another biopsy is recommended.[33]

Consolidation radiotherapy for advanced-stage HL

Consolidation radiotherapy (i.e., after initial chemotherapy) can be avoided in patients with advanced-stage disease if end-of-treatment PET/CT is negative.[76] [82] [97] [98] [99] [100][101] [102]

Consolidation radiotherapy (30 to 36 Gy) may be considered for patients with residual PET-positive disease following completion of initial treatment with chemotherapy.

Refractory or relapsed classical HL

Refractory or relapsed HL should be confirmed with biopsy.

Treatment for refractory or relapsed HL must be individualised, taking into consideration factors such as previous first-line treatment, patient age, medical comorbidities, duration of first remission, and stage at relapse. The goal of treatment, at least initially, is cure.

Salvage therapy, followed by high-dose chemotherapy (for conditioning) and autologous stem cell transplantation (ASCT), is the standard approach for most patients who relapse following first-line treatment.[33] [103] [104] [105] [106] [107] [108] Radiotherapy may be used alongside high-dose chemotherapy (as part of conditioning) in eligible patients. Allogeneic stem cell transplantation (AlloSCT) may be considered in patients who relapse after ASCT, but this is controversial.[109] [110] In selected patients, radiotherapy alone or chemotherapy alone is appropriate following salvage therapy.[111] [112]

The role of salvage therapy is to reduce tumour burden and mobilise stem cells before conditioning and ASCT.[5] Combination chemotherapy regimens can be used for salvage therapy. The optimal salvage regimen is unclear due to the lack of head-to-head randomised trials; however, the following are commonly used:[106] [107] [113] [114] [115] [116] [117]

- BeGEV (bendamustine, gemcitabine, vinorelbine)
- DHAP (dexamethasone, cytarabine, cisplatin)
- GVD (gemcitabine, vinorelbine, pegylated liposomal doxorubicin)
- ICE (ifosfamide, carboplatin, etoposide)
- IGEV (ifosfamide, gemcitabine, vinorelbine)

Several immunotherapeutic agents are available for patients with relapsed or refractory classical HL. The following immunotherapy-based combination regimens may also be considered for use as salvage therapy before ASCT (in those who have not previously undergone ASCT) in the refractory or relapsed setting:[118] [119] [120] [121] [122]

- Brentuximab vedotin plus bendamustine
- Brentuximab vedotin plus nivolumab
- Brentuximab vedotin plus ICE
- Nivolumab plus ICE
- Pembrolizumab plus GVD

PET-adapted treatment for refractory or relapsed HL

A PET-adapted treatment approach is used for refractory or relapsed HL in order to optimise outcomes following stem cell transplantation. A negative pre-transplantation PET/CT (Deauville score 1 to 3) is associated with optimal outcomes following transplantation and should, therefore, be the goal of salvage therapy prior to ASCT.[123] [124] Patients with a positive PET/CT (Deauville score 4 or 5) following salvage therapy may be considered for a different salvage regimen to achieve a negative PET/CT.[125] [126] [127]

Maintenance therapy following ASCT

Brentuximab vedotin is recommended as consolidation/maintenance treatment following ASCT in patients at high risk for relapse (e.g., those refractory to initial treatment; those who relapse within 12 months following initial treatment with ABVD or escalated BEACOPP; or those with extranodal disease).[128] [129] [130]

Maintenance brentuximab vedotin is recommended for 16 cycles (as per the AETHERA trial) or until unacceptable toxicity or relapse (whichever occurs first).[129] It is not recommended in patients with prior evidence of disease refractory to brentuximab vedotin.[129] However, it may be considered for patients

previously treated with brentuximab vedotin if durable remission (at least 12 months) was achieved before relapse.

Early (stage I to stage II) nodular lymphocyte-predominant HL (NLPHL)

NLPHL is a rare subtype of HL. Most patients with NLPHL present with early-stage disease involving peripheral nodal regions (e.g., groin, axilla, neck). The goal of treatment is cure while minimising risk of late effects. Overall prognosis for patients with early-stage NLPHL is excellent.

Asymptomatic early (stage IA and IIA) non-bulky NLPHL

Radiotherapy alone at a dose 30 to 36 Gy is recommended for most patients with stage IA and IIA non-bulky disease.[33] [70] [131] ISRT is the preferred approach (although most available data are for IFRT).[70]

Retrospective studies have reported excellent remission and survival outcomes with radiotherapy alone for early-stage NLPHL.[132] [133] [134] [135] Randomised trials of treatments for NLPHL are lacking due to the rarity of this disease subtype.

Observation may be appropriate for patients with asymptomatic early-stage non-bulky disease, particularly if there is concern regarding toxicity related to radiotherapy.[136] Observation is also an option for selected patients with stage IA non-bulky disease who have a completely excised solitary lymph node.[33]

Asymptomatic early (stage IA and IIA) bulky NLPHL and symptomatic early (stage IB and IIB) NLPHL

Systemic treatment with rituximab plus combination chemotherapy (e.g., R-ABVD [rituximab, doxorubicin, bleomycin, vinblastine, dacarbazine], R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone], or R-CVbP [rituximab, cyclophosphamide, vinblastine, prednisolone]) followed by radiotherapy (30 to 36 Gy) is recommended for patients with stage IA or IIA bulky disease, and those with stage IB or IIB disease.[33] [131] [137]

The CD20 antigen is present on most NLPHL cells; therefore, anti-CD20 treatment with rituximab is a key component of systemic treatment for NLPHL.

Observation may be appropriate for patients with asymptomatic early-stage bulky disease, particularly if there is concern regarding toxicity related to systemic treatment and radiotherapy.[136]

Advanced (stage III to stage IV) NLPHL

Observation may be appropriate for patients with asymptomatic advanced-stage disease.[33] [131] Systemic treatment with rituximab plus combination chemotherapy (e.g., R-ABVD, R-CHOP, or R-CVbP) with or without radiotherapy is recommended for patients with symptomatic advanced-stage disease or rapid progression.[33] [138] [139]

Refractory or relapsed NLPHL

Refractory or relapsed NLPHL should be confirmed by biopsy to rule out transformation to aggressive non-Hodgkin's lymphoma.

Treatment for refractory or relapsed NLPHL must be individualised, taking into consideration factors such as previous first-line treatment (e.g., R-ABVD with radiotherapy), patient age, medical comorbidities, duration of first remission, and stage at relapse.[131]

Salvage therapy with a rituximab-based chemotherapy regimen or rituximab alone is the preferred approach for most patients with refractory or relapsed NLPHL. Observation may be considered for asymptomatic patients as an initial approach.[33] ASCT may be considered for patients with aggressive disease.

The optimal regimen for salvage chemotherapy is unclear, but the following rituximab-based regimens can be considered if not previously used:[33]

- R-ABVD
- R-CHOP
- R-CVbP
- R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin)
- R-ICE (rituximab, ifosfamide, carboplatin, etoposide)
- R-IGEV (rituximab, ifosfamide, gemcitabine, vinorelbine)
- Rituximab plus bendamustine.

Rituximab alone can be considered for patients who relapse with limited-stage disease and low tumour volume.[33] [140]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)

early (stage I to II) classical HL: favourable disease and intended for combined-modality therapy		
	1st	ABVD (2 cycles) + interim PET/CT
■ interim PET/CT negative (Deauville score 1 to 2)	plus	radiotherapy (20 Gy) or ABVD (1 cycle) plus radiotherapy (30 Gy)
■ interim PET/CT negative (Deauville score 3)	plus	radiotherapy (20 Gy) or ABVD (2 cycles) plus radiotherapy (30 Gy)
■ interim PET/CT positive (Deauville score 4)	plus	ABVD (2 cycles) + restaging PET/CT
	adjunct	radiotherapy (30 Gy) (if restaging PET/CT negative)
	adjunct	biopsy (if restaging PET/CT positive)
■ interim PET/CT positive (Deauville score 5)	plus	biopsy
early (stage I to II) classical HL: favourable disease and intended for chemotherapy alone		
	1st	ABVD (2 cycles) + interim PET/CT
■ interim PET/CT negative (Deauville score 1 or 2)	plus	ABVD (2 cycles)
■ interim PET/CT negative (Deauville score 3)	plus	ABVD (2 cycles) or AVD (4 cycles)
■ interim PET/CT positive (Deauville score 4)	plus	ABVD (2 cycles) + restaging PET/CT
	adjunct	radiotherapy (30 Gy) (if restaging PET/CT negative)
	adjunct	biopsy (if restaging PET/CT positive)
■ interim PET/CT positive (Deauville score 5)	plus	biopsy
early (stage I to II) classical HL: unfavourable disease (non-bulky or bulky) and intended for combined-modality therapy		
	1st	ABVD (2 cycles) + interim PET/CT
■ interim PET/CT negative (Deauville score 1 to 3)	plus	ABVD (2 cycles) + radiotherapy (30 Gy)

MANAGEMENT

Acute (summary)

■ interim PET/CT positive (Deauville score 4 or 5)	plus	ABVD (2 cycles) or escalated BEACOPP (2 cycles) + restaging PET/CT
	adjunct	radiotherapy (30 Gy) (if restaging PET/CT negative)
	adjunct	biopsy (if restaging PET/CT positive)
early (stage I to II) classical HL: unfavourable disease (non-bulky) and intended for chemotherapy alone		
	1st	ABVD (2 cycles) + interim PET/CT
■ interim PET/CT negative (Deauville score 1 to 2)	plus	ABVD (2 cycles)
■ interim PET/CT negative (Deauville score 3)	plus	ABVD (2 cycles) or AVD (4 cycles)
■ interim PET/CT positive (Deauville score 4)	plus	ABVD (2 cycles) + restaging PET/CT
	adjunct	AVD (2 cycles) + radiotherapy (30 Gy) (if restaging PET/CT negative)
	adjunct	biopsy (if restaging PET/CT positive)
■ interim PET/CT positive (Deauville score 5)	plus	biopsy
early (stage I to II) classical HL: unfavourable disease (bulky) and intended for chemotherapy alone		
	1st	ABVD (2 cycles) + interim PET/CT
■ interim PET/CT negative (Deauville score 1 to 3)	plus	AVD (4 cycles)
■ interim PET/CT positive (Deauville score 4 or 5)	plus	escalated BEACOPP (2 cycles) + restaging PET/CT
	adjunct	escalated BEACOPP (2 cycles) (if restaging PET/CT negative)
	adjunct	biopsy (if restaging PET/CT positive)
advanced (stage III to IV) classical HL: intended for standard induction therapy (chemotherapy)		
	1st	ABVD (2 cycles) + interim PET/CT
■ interim PET/CT negative (Deauville score 1 to 3)	plus	AVD (4 cycles)
■ interim PET/CT positive (Deauville score 4 or 5): age ≤60 years	plus	escalated BEACOPP (3 cycles) + restaging PET/CT

Acute (summary)		
	adjunct	escalated BEACOPP (1 cycle) ± radiotherapy (if restaging PET/CT negative)
	adjunct	biopsy (if restaging PET/CT positive)
■ interim PET/CT positive (Deauville score 4 or 5): age >60 years	plus	individualised treatment
advanced (stage III to IV) classical HL: intended for standard induction therapy (chemoimmunotherapy)		
	1st	brentuximab vedotin + AVD
advanced (stage III to IV) classical HL: intended for intensive induction chemotherapy		
	1st	escalated BEACOPP (2 cycles) + interim PET/CT
■ interim PET/CT negative (Deauville score 1 to 3)	plus	escalated BEACOPP (2 cycles) or ABVD (4 cycles)
■ interim PET/CT positive (Deauville score 4 or 5)	plus	biopsy or treatment escalation
asymptomatic early (stage IA to IIA) NLPHL, non-bulky disease		
	1st	radiotherapy (30-36 Gy) or observation
asymptomatic early (stage IA to IIA) NLPHL, bulky disease; and symptomatic early (stage IB to IIB) NLPHL		
	1st	rituximab + chemotherapy + radiotherapy; or observation (if asymptomatic)
advanced (stage III to IV) NLPHL		
	1st	observation or rituximab + chemotherapy (± radiotherapy)

Ongoing		(summary)
refractory or relapsed classical HL		
	1st	salvage therapy (combination chemotherapy) + PET/CT
	adjunct	conditioning + stem cell transplantation (if PET/CT negative)
	adjunct	brentuximab vedotin (maintenance)
	2nd	salvage therapy (immunotherapy regimens)
	adjunct	conditioning + stem cell transplantation (if PET/CT negative)
	adjunct	brentuximab vedotin (maintenance)
refractory or relapsed NLPHL		
	1st	salvage therapy or observation

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

early (stage I to II) classical HL: favourable disease and intended for combined-modality therapy

early (stage I to II) classical HL: favourable disease and intended for combined-modality therapy

1st

ABVD (2 cycles) + interim PET/CT

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

» The goal of treatment for all patients with HL is cure while minimising risk of toxicity and long-term complications.

» The absence or presence of specific prognostic criteria determines whether the patient has favourable or unfavourable early-stage disease. German Hodgkin Study Group (GHSG) favourable prognosis criteria are most commonly used in the US (mediastinal mass ratio [MMR] <0.33; erythrocyte sedimentation rate [ESR] <50 mm/hour if no B symptoms; ESR <30 mm/hour if B symptoms are present; involvement of ≤2 nodal sites; and no extranodal disease; see Diagnostic criteria).[44] [50]

» Patients with favourable early-stage disease generally receive two initial cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) followed by an interim PET/CT scan to assess metabolic response and inform subsequent treatment.[33]

» Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40]

» Patients with a Deauville score of 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score of 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

Acute

» A PET-adapted treatment approach is recommended for all patients with early-stage disease as it offers the opportunity to balance efficacy and toxicity of treatment.[5] [33] [54][65] [66] [74] [75]

» The most effective treatment for early-stage disease is combined-modality therapy, which comprises combination chemotherapy (e.g., ABVD) followed by radiotherapy.[51] [52] [53] [54] [55] [56] [57] [58] [59] [60] [61]

» A chemotherapy-alone approach may be considered if avoiding radiotherapy is preferred (e.g., due to patient age, sex, family history of cancer or cardiac disease, comorbidities, sites of involvement).[33] [62] [63] [64] [65] [66] The decision to omit radiotherapy should involve expert input by a multidisciplinary team, and discussion with the patient regarding risks and benefits. Chemotherapy alone is associated with a slightly lower rate of tumour control and higher rate of relapse compared with combined-modality therapy, but survival rates are similar.[51] [52] [53] [58] [60] [64] [66] [67] [68] [69]

» HL in older patients (aged >60 years) is associated with poorer outcomes and higher treatment-related toxicity and mortality compared with younger patients.[47] [48] [49] Alternative treatment regimens may be considered for patients >60 years, or with poor performance status or substantial comorbidities. Bleomycin should be used with caution; standard regimens may be adapted to remove bleomycin or restrict its use to only two cycles.[33]

» See local specialist protocol for dosing guidelines.

interim PET/CT negative (Deauville score 1 to 2) **plus** **radiotherapy (20 Gy) or ABVD (1 cycle) plus radiotherapy (30 Gy)**

Treatment recommended for ALL patients in selected patient group

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

Acute

» Patients with favourable early-stage disease who are intended for combined-modality therapy and have a Deauville score of 1 to 2 on interim PET/CT (after two initial cycles of ABVD) can receive 20 Gy radiotherapy, or one additional cycle of ABVD followed by 30 Gy radiotherapy.[60] [61] [65] [67]

» Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70] [71] [72] [73] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

» Patients should be assessed for suitability for radiotherapy (e.g., based on age, sex, family history of cancer or cardiac disease, comorbidities, sites of involvement).[33] Those deemed unsuitable for radiotherapy can be considered for treatment with chemotherapy alone.

» See local specialist protocol for dosing guidelines.

interim PET/CT negative (Deauville score 3) **plus** **radiotherapy (20 Gy) or ABVD (2 cycles) plus radiotherapy (30 Gy)**

Treatment recommended for ALL patients in selected patient group

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

» Patients with favourable early-stage disease who are intended for combined-modality therapy and have a Deauville score of 3 on interim PET/

MANAGEMENT

Acute

CT (after two initial cycles of ABVD) can receive 20 Gy radiotherapy, or two additional cycle of ABVD followed by 30 Gy radiotherapy (based on the RAPID study).[61] [65]

» Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70] [71] [72] [73] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

» Patients should be assessed for suitability for radiotherapy (e.g., based on age, sex, family history of cancer or cardiac disease, comorbidities, sites of involvement).[33] Those deemed unsuitable for radiotherapy can be considered for treatment with chemotherapy alone.

» See local specialist protocol for dosing guidelines.

interim PET/CT positive (Deauville score 4) **plus** **ABVD (2 cycles) + restaging PET/CT**

Treatment recommended for ALL patients in selected patient group

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

» Patients with favourable early-stage disease who are intended for combined-modality therapy and have a Deauville score of 4 on interim PET/CT (after two initial cycles of ABVD) can receive two additional cycles of ABVD followed by a restaging PET/CT scan to assess metabolic

Acute

response and inform subsequent treatment.[60] [65] [67]

» Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40]

» Patients with a Deauville score 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

» See local specialist protocol for dosing guidelines.

adjunct **radiotherapy (30 Gy) (if restaging PET/CT negative)**

Treatment recommended for SOME patients in selected patient group

» If restaging PET/CT is negative (Deauville score 1 to 3) then 30 Gy radiotherapy can be given.[60] [65] [67]

» Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70] [71] [72] [73] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

adjunct **biopsy (if restaging PET/CT positive)**

Treatment recommended for SOME patients in selected patient group

» If restaging PET/CT is positive (Deauville score 4 or 5) then a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]

interim PET/CT positive (Deauville score 5) **plus** **biopsy**

Treatment recommended for ALL patients in selected patient group

MANAGEMENT

Acute

		» A biopsy is recommended to inform subsequent treatment (e.g., salvage therapy) for patients with a Deauville score of 5 on interim PET/CT (after two cycles of ABVD).[33]
early (stage I to II) classical HL: favourable disease and intended for chemotherapy alone		
early (stage I to II) classical HL: favourable disease and intended for chemotherapy alone	**1st**	**ABVD (2 cycles) + interim PET/CT** **Primary options** **ABVD** » doxorubicin **-and-** » bleomycin **-and-** » vinblastine **-and-** » dacarbazine » The goal of treatment for all patients with HL is cure while minimising risk of toxicity and long-term complications. » The absence or presence of specific prognostic criteria determines whether the patient has favourable or unfavourable early-stage disease. German Hodgkin Study Group (GHSG) favourable prognosis criteria are most commonly used in the US (mediastinal mass ratio [MMR] <0.33; erythrocyte sedimentation rate [ESR] <50 mm/hour if no B symptoms; ESR <30 mm/hour if B symptoms are present; involvement of ≤2 nodal sites; and no extranodal disease; see Diagnostic criteria).[44] [50] » Patients with favourable early-stage disease generally receive two initial cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) followed by an interim PET/CT scan to assess metabolic response and inform subsequent treatment.[33] » Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40] » Patients with a Deauville score of 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score of 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria). » A PET-adapted treatment approach is recommended for all patients with early-stage

Acute

disease as it offers the opportunity to balance efficacy and toxicity of treatment.[5] [33] [54] [65] [66] [74] [75]

» The most effective treatment for early-stage disease is combined-modality therapy, which comprises combination chemotherapy (e.g., ABVD) followed by radiotherapy.[51] [52] [53] [54] [55] [56] [57] [58] [59] [60] [61]

» A chemotherapy-alone approach may be considered if avoiding radiotherapy is preferred (e.g., due to patient age, sex, family history of cancer or cardiac disease, comorbidities, sites of involvement).[33] [62] [63] [64] [65] [66] The decision to omit radiotherapy should involve expert input by a multidisciplinary team, and discussion with the patient regarding risks and benefits. Chemotherapy alone is associated with a slightly lower rate of tumour control and higher rate of relapse compared with combined-modality therapy, but survival rates are similar.[51] [52] [53] [58] [60] [64] [66] [67] [68] [69]

» HL in older patients (aged >60 years) is associated with poorer outcomes and higher treatment-related toxicity and mortality compared with younger patients.[47] [48] [49] Alternative treatment regimens may be considered for patients >60 years, or with poor performance status or substantial comorbidities. Bleomycin should be used with caution; standard regimens may be adapted to remove bleomycin or restrict its use to only two cycles.[33]

» See local specialist protocol for dosing guidelines.

interim PET/CT negative (Deauville score 1 or 2) **plus** **ABVD (2 cycles)**

Treatment recommended for ALL patients in selected patient group

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

» Patients with favourable early-stage disease who are intended for chemotherapy alone and have a Deauville score of 1 or 2 on interim PET/

MANAGEMENT

Acute

CT (after two initial cycles of ABVD) can receive two additional cycles of ABVD.[60] [64] [66] [67]

» See local specialist protocol for dosing guidelines.

interim PET/CT negative (Deauville score 3) **plus** **ABVD (2 cycles) or AVD (4 cycles)**

Treatment recommended for ALL patients in selected patient group

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

OR

AVD

» doxorubicin
-and-
» vinblastine
-and-
» dacarbazine

» Patients with favourable early-stage disease who are intended for chemotherapy alone and have a Deauville score of 3 on interim PET/CT (after two initial cycles of ABVD) can receive two additional cycles of ABVD or four additional cycles of AVD (doxorubicin, vinblastine, dacarbazine).[60] [64] [66] [67] [68]

» See local specialist protocol for dosing guidelines.

interim PET/CT positive (Deauville score 4) **plus** **ABVD (2 cycles) + restaging PET/CT**

Treatment recommended for ALL patients in selected patient group

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

» Patients with favourable early-stage disease who are intended for chemotherapy alone and

Acute

have a Deauville score of 4 on interim PET/CT (after two initial cycles of ABVD) can receive two additional cycles of ABVD followed by a restaging PET/CT scan to assess metabolic response and inform subsequent treatment.[60] [64] [66] [67]

» Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40]

» Patients with a Deauville score 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

» See local specialist protocol for dosing guidelines.

adjunct **radiotherapy (30 Gy) (if restaging PET/CT negative)**

Treatment recommended for SOME patients in selected patient group

» If restaging PET/CT is negative (Deauville score 1 to 3) then 30 Gy radiotherapy should be considered.[60] [65] [67]

» Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70] [71] [72] [73] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

adjunct **biopsy (if restaging PET/CT positive)**

Treatment recommended for SOME patients in selected patient group

» If restaging PET/CT is positive (Deauville score 4 or 5) then a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]

Acute

interim PET/CT positive (Deauville score 5)	**plus**	**biopsy** Treatment recommended for ALL patients in selected patient group » A biopsy is recommended to inform subsequent treatment (e.g., salvage therapy) for patients with a Deauville score of 5 on interim PET/CT (after two cycles of ABVD).[33]
early (stage I to II) classical HL: unfavourable disease (non-bulky or bulky) and intended for combined-modality therapy		
early (stage I to II) classical HL: unfavourable disease (non-bulky or bulky) and intended for combined-modality therapy	**1st**	**ABVD (2 cycles) + interim PET/CT** **Primary options** **ABVD** » doxorubicin **-and-** » bleomycin **-and-** » vinblastine **-and-** » dacarbazine » The goal of treatment for all patients with HL is cure while minimising risk of toxicity and long-term complications. » The absence or presence of specific prognostic criteria determines whether the patient has favourable or unfavourable early-stage disease. German Hodgkin Study Group (GHSG) favourable prognosis criteria are most commonly used in the US (mediastinal mass ratio [MMR] <0.33; erythrocyte sedimentation rate [ESR] <50 mm/hour if no B symptoms; ESR <30 mm/hour if B symptoms are present; involvement of ≤2 nodal sites; and no extranodal disease; see Diagnostic criteria).[44] [50] » Patients with unfavourable early-stage disease generally receive two initial cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) followed by an interim PET/CT scan to assess metabolic response and inform subsequent treatment. » Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40] » Patients with a Deauville score of 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with

Acute

a Deauville score of 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

» A PET-adapted treatment approach is recommended for all patients with early-stage disease as it offers the opportunity to balance efficacy and toxicity of treatment.[5] [33] [54] [65] [66] [74] [75]

» The most effective treatment for early-stage disease is combined-modality therapy, which comprises combination chemotherapy (e.g., ABVD) followed by radiotherapy.[51] [52] [53] [54] [55] [56] [57] [58] [59] [60] [61]

» A chemotherapy-alone approach may be considered if avoiding radiotherapy is preferred (e.g., due to patient age, sex, family history of cancer or cardiac disease, comorbidities, sites of involvement).[33] [62] [63] [64] [65] [66] The decision to omit radiotherapy should involve expert input by a multidisciplinary team, and discussion with the patient regarding risks and benefits. Chemotherapy alone is associated with a slightly lower rate of tumour control and higher rate of relapse compared with combined-modality therapy, but survival rates are similar.[51] [52] [53] [58] [60] [64] [66] [67] [68] [69]

» HL in older patients (aged >60 years) is associated with poorer outcomes and higher treatment-related toxicity and mortality compared with younger patients.[47] [48] [49] Alternative treatment regimens may be considered for patients >60 years, or with poor performance status or substantial comorbidities. Bleomycin should be used with caution; standard regimens may be adapted to remove bleomycin or restrict its use to only two cycles.[33]

» See local specialist protocol for dosing guidelines.

interim PET/CT negative (Deauville score 1 to 3) **plus** **ABVD (2 cycles) + radiotherapy (30 Gy)**

Treatment recommended for ALL patients in selected patient group

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-

MANAGEMENT

Acute

» dacarbazine

» Patients with unfavourable early-stage disease (non-bulky or bulky) who are intended for combined-modality therapy and have a Deauville score of 1 to 3 on interim PET/CT (after two initial cycles of ABVD) can receive two additional cycles of ABVD followed by 30 Gy radiotherapy.[54] [60] [67]

» Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70] [71] [72] [73] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

» See local specialist protocol for dosing guidelines.

interim PET/CT positive (Deauville score 4 or 5) **plus** **ABVD (2 cycles) or escalated BEACOPP (2 cycles) + restaging PET/CT**

Treatment recommended for ALL patients in selected patient group

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

OR

BEACOPP

» bleomycin
-and-
» etoposide
-and-
» doxorubicin
-and-

Acute

» cyclophosphamide
-and-
» vincristine
-and-
» procarbazine
-and-
» prednisolone

» Patients with unfavourable early-stage disease (non-bulky or bulky) who are intended for combined-modality therapy and have a Deauville score of 4 or 5 on interim PET/CT (after two initial cycles of ABVD) can receive two additional cycles of ABVD or escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone), followed by a restaging PET/CT scan to assess metabolic response and inform subsequent treatment.[54] [60] [67]

» Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40]

» Patients with a Deauville score 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

» See local specialist protocol for dosing guidelines.

adjunct **radiotherapy (30 Gy) (if restaging PET/CT negative)**

Treatment recommended for SOME patients in selected patient group

» If restaging PET/CT is negative (Deauville score 1 to 3) then 30 Gy radiotherapy can be given.[54] [60] [67]

» Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70] [71] [72] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause

Acute

nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

adjunct **biopsy (if restaging PET/CT positive)**

Treatment recommended for SOME patients in selected patient group

» If restaging PET/CT is positive (Deauville score 4 or 5) then a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]

early (stage I to II) classical HL: unfavourable disease (non-bulky) and intended for chemotherapy alone

early (stage I to II) classical HL: unfavourable disease (non-bulky) and intended for chemotherapy alone

1st **ABVD (2 cycles) + interim PET/CT**

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

» The goal of treatment for all patients with HL is cure while minimising risk of toxicity and long-term complications.

» The absence or presence of specific prognostic criteria determines whether the patient has favourable or unfavourable early-stage disease. German Hodgkin Study Group (GHSG) favourable prognosis criteria are most commonly used in the US (mediastinal mass ratio [MMR] <0.33; erythrocyte sedimentation rate [ESR] <50 mm/hour if no B symptoms; ESR <30 mm/hour if B symptoms are present; involvement of ≤2 nodal sites; and no extranodal disease; see Diagnostic criteria).[44] [50]

» Patients with unfavourable early-stage disease generally receive two initial cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) followed by an interim PET/CT scan to assess metabolic response and inform subsequent treatment.

» Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40]

Acute

» Patients with a Deauville score of 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score of 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

» A PET-adapted treatment approach is recommended for all patients with early-stage disease as it offers the opportunity to balance efficacy and toxicity of treatment.[5] [33] [54] [65] [66] [74] [75]

» The most effective treatment for early-stage disease is combined-modality therapy, which comprises combination chemotherapy (e.g., ABVD) followed by radiotherapy.[51] [52] [53] [54] [55] [56] [57] [58] [59] [60] [61]

» A chemotherapy-alone approach may be considered if avoiding radiotherapy is preferred (e.g., due to patient age, sex, family history of cancer or cardiac disease, comorbidities, sites of involvement).[33] [62] [63] [64] [65] [66] The decision to omit radiotherapy should involve expert input by a multidisciplinary team, and discussion with the patient regarding risks and benefits. Chemotherapy alone is associated with a slightly lower rate of tumour control and higher rate of relapse compared with combined-modality therapy, but survival rates are similar.[51] [52] [53] [58] [60] [64] [66] [67] [68] [69]

» HL in older patients (aged >60 years) is associated with poorer outcomes and higher treatment-related toxicity and mortality compared with younger patients.[47] [48] [49] Alternative treatment regimens may be considered for patients >60 years, or with poor performance status or substantial comorbidities. Bleomycin should be used with caution; standard regimens may be adapted to remove bleomycin or restrict its use to only two cycles.[33]

» See local specialist protocol for dosing guidelines.

interim PET/CT negative (Deauville score 1 to 2) **plus** **ABVD (2 cycles)**

Treatment recommended for ALL patients in selected patient group

Primary options

ABVD

» doxorubicin
-and-
» bleomycin

MANAGEMENT

Acute

-and-
» vinblastine
-and-
» dacarbazine

» Patients with unfavourable early-stage disease (non-bulky) who are intended for chemotherapy alone and have a Deauville score of 1 or 2 on interim PET/CT (after two initial cycles of ABVD) can receive two additional cycles of ABVD.[60] [64] [66] [67]

» See local specialist protocol for dosing guidelines.

interim PET/CT negative (Deauville score 3) **plus** **ABVD (2 cycles) or AVD (4 cycles)**

Treatment recommended for ALL patients in selected patient group

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

OR

AVD

» doxorubicin
-and-
» vinblastine
-and-
» dacarbazine

» Patients with unfavourable early-stage disease (non-bulky) who are intended for chemotherapy alone and have a Deauville score of 3 on interim PET/CT (after two initial cycles of ABVD) can receive two additional cycles of ABVD or four additional cycles of AVD (doxorubicin, vinblastine, dacarbazine).[68]

» See local specialist protocol for dosing guidelines.

interim PET/CT positive (Deauville score 4) **plus** **ABVD (2 cycles) + restaging PET/CT**

Treatment recommended for ALL patients in selected patient group

Primary options

ABVD

» doxorubicin

Acute

-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

» Patients with unfavourable early-stage disease (non-bulky) who are intended for chemotherapy alone and have a Deauville score of 4 on interim PET/CT (after two initial cycles of ABVD) can receive two additional cycles of ABVD followed by a restaging PET/CT scan to assess metabolic response and inform subsequent treatment.[60] [64] [66] [67]

» Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40]

» Patients with a Deauville score 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

» See local specialist protocol for dosing guidelines.

adjunct **AVD (2 cycles) + radiotherapy (30 Gy) (if restaging PET/CT negative)**

Treatment recommended for SOME patients in selected patient group

Primary options

AVD

» doxorubicin
-and-
» vinblastine
-and-
» dacarbazine

» If restaging PET/CT is negative (Deauville score 1 to 3) then two additional cycles of AVD (doxorubicin, vinblastine, dacarbazine) followed by 30 Gy radiotherapy should be considered.[60] [65] [67]

» Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70] [71] [72] [73] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

Acute

» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

» See local specialist protocol for dosing guidelines.

adjunct **biopsy (if restaging PET/CT positive)**

Treatment recommended for SOME patients in selected patient group

» If restaging PET/CT is positive (Deauville score 4 or 5) then a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]

interim PET/CT positive (Deauville score 5) **plus** **biopsy**

Treatment recommended for ALL patients in selected patient group

» A biopsy is recommended to inform subsequent treatment (e.g., salvage therapy) for patients with a Deauville score of 5 on interim PET/CT (after two cycles of ABVD).[33]

early (stage I to II) classical HL: unfavourable disease (bulky) and intended for chemotherapy alone

early (stage I to II) classical HL: unfavourable disease (bulky) and intended for chemotherapy alone **1st** **ABVD (2 cycles) + interim PET/CT**

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

» The goal of treatment for all patients with HL is cure while minimising risk of toxicity and long-term complications.

» The absence or presence of specific prognostic criteria determines whether the patient has favourable or unfavourable early-stage disease. German Hodgkin Study Group

Acute

(GHSG) favourable prognosis criteria are most commonly used in the US (mediastinal mass ratio [MMR] <0.33; erythrocyte sedimentation rate [ESR] <50 mm/hour if no B symptoms; ESR <30 mm/hour if B symptoms are present; involvement of ≤2 nodal sites; and no extranodal disease; see Diagnostic criteria).[44] [50]

» Patients with unfavourable early-stage disease generally receive two initial cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) followed by an interim PET/CT scan to assess metabolic response and inform subsequent treatment.

» Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40]

» Patients with a Deauville score of 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score of 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

» A PET-adapted treatment approach is recommended for all patients with early-stage disease as it offers the opportunity to balance efficacy and toxicity of treatment.[5] [33] [54][65] [66] [74] [75]

» The most effective treatment for early-stage disease is combined-modality therapy, which comprises combination chemotherapy (e.g., ABVD) followed by radiotherapy.[51] [52] [53] [54] [55] [56] [57] [58] [59] [60] [61]

» A chemotherapy-alone approach may be considered if avoiding radiotherapy is preferred (e.g., due to patient age, sex, family history of cancer or cardiac disease, comorbidities, sites of involvement).[33] [62] [63] [64] [65] [66] The decision to omit radiotherapy should involve expert input by a multidisciplinary team, and discussion with the patient regarding risks and benefits. Chemotherapy alone is associated with a slightly lower rate of tumour control and higher rate of relapse compared with combined-modality therapy, but survival rates are similar.[51] [52] [53] [58] [60] [64] [66] [67] [68] [69]

» HL in older patients (aged >60 years) is associated with poorer outcomes and higher treatment-related toxicity and mortality compared with younger patients.[47] [48] [49] Alternative

Acute

treatment regimens may be considered for patients >60 years, or with poor performance status or substantial comorbidities. Bleomycin should be used with caution; standard regimens may be adapted to remove bleomycin or restrict its use to only two cycles.[33]

» See local specialist protocol for dosing guidelines.

interim PET/CT negative (Deauville score 1 to 3) **plus** **AVD (4 cycles)**

Treatment recommended for ALL patients in selected patient group

Primary options

AVD

» doxorubicin
-and-
» vinblastine
-and-
» dacarbazine

» Patients with unfavourable early-stage disease (bulky) who are intended for chemotherapy alone and have a Deauville score of 1 to 3 on interim PET/CT (after two initial cycles of ABVD) can receive four additional cycles of AVD (doxorubicin, vinblastine, dacarbazine).[68]

» See local specialist protocol for dosing guidelines.

interim PET/CT positive (Deauville score 4 or 5) **plus** **escalated BEACOPP (2 cycles) + restaging PET/CT**

Treatment recommended for ALL patients in selected patient group

Primary options

BEACOPP

» bleomycin
-and-
» etoposide
-and-
» doxorubicin
-and-
» cyclophosphamide
-and-
» vincristine
-and-
» procarbazine
-and-
» prednisolone

» Patients with unfavourable early-stage disease (bulky) who are intended for chemotherapy alone and have a Deauville score of 4 or 5 on interim PET/CT (after two initial cycles of ABVD)

Acute

can receive two additional cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone) followed by a restaging PET/CT scan to assess metabolic response and inform subsequent treatment.[54] [60] [68] [76] [77]

» Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40]

» Patients with a Deauville score 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

» See local specialist protocol for dosing guidelines.

adjunct **escalated BEACOPP (2 cycles) (if restaging PET/CT negative)**

Treatment recommended for SOME patients in selected patient group

Primary options

BEACOPP

» bleomycin
-and-
» etoposide
-and-
» doxorubicin
-and-
» cyclophosphamide
-and-
» vincristine
-and-
» procarbazine
-and-
» prednisolone

» If restaging PET/CT is negative (Deauville score 1 to 3) then two additional cycles of escalated BEACOPP can be given.[54] [60] [68] [76] [77]

» See local specialist protocol for dosing guidelines.

adjunct **biopsy (if restaging PET/CT positive)**

Treatment recommended for SOME patients in selected patient group

» If restaging PET/CT is positive (Deauville score 4 or 5) then a biopsy is recommended

MANAGEMENT

Acute

to inform subsequent treatment (e.g., salvage therapy).[33]

advanced (stage III to IV) classical HL: intended for standard induction therapy (chemotherapy)

advanced (stage III to IV) classical HL: intended for standard induction therapy (chemotherapy)

1st

ABVD (2 cycles) + interim PET/CT

Primary options

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

» The goal of treatment for all patients with HL is cure while minimising risk of toxicity and long-term complications.

» ABVD is a preferred initial treatment for patients with advanced-stage disease.[33] [68]

» A PET-adapted treatment approach can be used in patients with advanced-stage disease to guide treatment decisions regarding escalation or de-escalation of chemotherapy.[68] [94] [95] [96]

» Patients with advanced-stage disease who are intended for standard induction therapy with ABVD chemotherapy typically receive two initial cycles of ABVD, followed by an interim PET/CT scan to assess metabolic response and inform subsequent treatment.[68]

» Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40]

» Patients with a Deauville score of 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score of 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

» HL in older patients (aged >60 years) is associated with poorer outcomes and higher treatment-related toxicity and mortality compared with younger patients.[47] [48] [49] Alternative treatment regimens may be considered for patients >60 years, or with poor performance status or substantial comorbidities. Bleomycin

Acute

should be used with caution; standard regimens may be adapted to remove bleomycin or restrict its use to only two cycles.[33]

» See local specialist protocol for dosing guidelines.

interim PET/CT negative (Deauville score 1 to 3) **plus** **AVD (4 cycles)**

Treatment recommended for ALL patients in selected patient group

Primary options

AVD

» doxorubicin
-and-
» vinblastine
-and-
» dacarbazine

» Patients with advanced-stage disease who have a Deauville score of 1 to 3 on interim PET/CT (after two initial cycles of ABVD) can receive four additional cycles of AVD (doxorubicin, vinblastine, dacarbazine).[33] [68]

» See local specialist protocol for dosing guidelines.

interim PET/CT positive (Deauville score 4 or 5): age ≤60 years **plus** **escalated BEACOPP (3 cycles) + restaging PET/CT**

Treatment recommended for ALL patients in selected patient group

Primary options

BEACOPP

» bleomycin
-and-
» etoposide
-and-
» doxorubicin
-and-
» cyclophosphamide
-and-
» vincristine
-and-
» procarbazine
-and-
» prednisolone

» Patients with advanced-stage disease who are aged ≤60 years and have a Deauville score of 4 or 5 on interim PET/CT (after two initial cycles of ABVD) can receive three additional cycles of escalated BEACOPP, followed by a restaging PET/CT scan to assess metabolic response and inform subsequent treatment.[68]

MANAGEMENT

Acute

» Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40]

» Patients with a Deauville score of 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score of 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

» See local specialist protocol for dosing guidelines.

adjunct **escalated BEACOPP (1 cycle) ± radiotherapy (if restaging PET/CT negative)**

Treatment recommended for SOME patients in selected patient group

Primary options

BEACOPP

» bleomycin
-and-
» etoposide
-and-
» doxorubicin
-and-
» cyclophosphamide
-and-
» vincristine
-and-
» procarbazine
-and-
» prednisolone

» If restaging PET/CT is negative (Deauville score 1 to 3) then one additional cycle of escalated BEACOPP can be given.[68]

» Consolidation radiotherapy (i.e., after initial chemotherapy) can be avoided in patients with advanced-stage disease if end-of-treatment PET/CT is negative.[76] [82] [97] [98] [99] [100] [101] [102]

» Consolidation radiotherapy (30 to 36 Gy) may be considered for patients with residual PET-positive disease following completion of initial treatment with chemotherapy.

» Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70] [71] [72] [73] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

Acute

		» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function. » See local specialist protocol for dosing guidelines.
	adjunct	**biopsy (if restaging PET/CT positive)** Treatment recommended for SOME patients in selected patient group » If restaging PET/CT is positive (Deauville score 4 or 5) then a biopsy is recommended to inform subsequent treatment (e.g., salvage therapy).[33]
interim PET/CT positive (Deauville score 4 or 5): age >60 years	plus	**individualised treatment** Treatment recommended for ALL patients in selected patient group » Patients with advanced-stage disease aged >60 years who have a Deauville score of 4 or 5 on interim PET/CT (after two initial cycles of ABVD) are recommended individualised treatment to minimise toxicity while maintaining efficacy.[5] [33] » Bleomycin should be used with caution; standard regimens may be adapted to remove bleomycin or restrict its use to only two cycles.[5] [33]
advanced (stage III to IV) classical HL: intended for standard induction therapy (chemoimmunotherapy)		
	1st	**brentuximab vedotin + AVD** **Primary options** » brentuximab vedotin **-and-** » doxorubicin **-and-** » vinblastine **-and-** » dacarbazine

MANAGEMENT

Acute

» The goal of treatment for all patients with HL is cure while minimising risk of toxicity and long-term complications.

» Brentuximab vedotin plus AVD (doxorubicin, vinblastine, dacarbazine) is a preferred initial treatment for patients with advanced-stage disease.[33] [68]

» Brentuximab vedotin plus AVD offers a survival advantage compared with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) in patients with advanced-stage disease.[33] [86] [87] [88] However, caution is required when used in older patients (age >60 years) and in those with baseline neuropathy.

» HL in older patients (aged >60 years) is associated with poorer outcomes and higher treatment-related toxicity and mortality compared with younger patients.[47] [48] [49] Alternative treatment regimens may be considered for patients >60 years, or with poor performance status or substantial comorbidities. Bleomycin should be used with caution; standard regimens may be adapted to remove bleomycin or restrict its use to only two cycles.[33]

» For older patients, sequential brentuximab vedotin plus AVD may be a preferred option.[84] This involves administeriing 2 cycles of brentuximab vedotin followed by 6 cycles of AVD followed by 4 cycles of brentuximab vedotin.[84]

» See local specialist protocol for dosing guidelines.

advanced (stage III to IV) classical HL: intended for intensive induction chemotherapy

advanced (stage III to IV) classical HL: intended for intensive induction chemotherapy

1st

escalated BEACOPP (2 cycles) + interim PET/CT

Primary options

BEACOPP

» bleomycin
-and-
» etoposide
-and-
» doxorubicin
-and-
» cyclophosphamide
-and-
» vincristine
-and-
» procarbazine
-and-

MANAGEMENT

Acute

» prednisolone

» The goal of treatment for all patients with HL is cure while minimising risk of toxicity and long-term complications.

» A PET-adapted treatment approach can be used in patients with advanced-stage disease to guide treatment decisions regarding escalation or de-escalation of chemotherapy.[68] [94] [95] [96]

» Selected patients with advanced-stage disease (e.g., those with an International Prognostic Score [IPS] ≥4 and age <60 years) may be suitable for upfront intensive induction chemotherapy comprising two initial cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone), followed by an interim PET/CT scan to assess metabolic response and inform subsequent treatment.[94] [95]

» Metabolic response is determined using the Deauville criteria, which assigns a score of 1 to 5 based on fluorodeoxyglucose (FDG) uptake at involved sites.[40]

» Patients with a Deauville score of 1 to 3 (i.e., negative PET/CT) are considered to have a complete metabolic response. Patients with a Deauville score of 4 or 5 (i.e., positive PET/CT) are considered to have a partial metabolic response (see Diagnostic criteria).

» HL in older patients (aged >60 years) is associated with poorer outcomes and higher treatment-related toxicity and mortality compared with younger patients.[47] [48] [49] Alternative treatment regimens may be considered for patients >60 years, or with poor performance status or substantial comorbidities. Bleomycin should be used with caution; standard regimens may be adapted to remove bleomycin or restrict its use to only two cycles.[33]

» See local specialist protocol for dosing guidelines.

interim PET/CT negative (Deauville score 1 to 3) **plus** **escalated BEACOPP (2 cycles) or ABVD (4 cycles)**

Treatment recommended for ALL patients in selected patient group

Primary options

BEACOPP

» bleomycin

MANAGEMENT

Acute

-and-
» etoposide
-and-
» doxorubicin
-and-
» cyclophosphamide
-and-
» vincristine
-and-
» procarbazine
-and-
» prednisolone

OR

ABVD

» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

» Patients with advanced-stage disease who have a Deauville score of 1 to 3 on interim PET/CT (after two initial cycles of escalated BEACOPP) can receive two additional cycles of escalated BEACOPP or four additional cycles of ABVD.[33] [94] [95] [96]

» Bleomycin may be omitted from ABVD to reduce toxicity.

» See local specialist protocol for dosing guidelines.

interim PET/CT positive (Deauville score 4 or 5) **plus** **biopsy or treatment escalation**

Treatment recommended for ALL patients in selected patient group

Primary options

BEACOPP

» bleomycin
-and-
» etoposide
-and-
» doxorubicin
-and-
» cyclophosphamide
-and-
» vincristine
-and-
» procarbazine
-and-
» prednisolone

Acute

» Patients with advanced-stage disease who have a Deauville score of 4 or 5 on interim PET/CT (after two initial cycles of escalated BEACOPP) are recommended a biopsy to inform subsequent treatment (e.g., salvage therapy or treatment escalation).[33]

» Patients with a positive biopsy may require salvage therapy.

» Patients with a negative biopsy can receive two additional cycles of escalated BEACOPP followed by a restaging PET/CT scan.[94] [95] [96] If restaging PET/CT is negative (Deauville score 1 to 3) then two additional cycles of escalated BEACOPP can be given.[33] [94] [95] [96] If restaging PET/CT is positive (Deauville score 4 or 5) then another biopsy is recommended.[33]

» Consolidation radiotherapy (i.e., after initial chemotherapy) can be avoided in patients with advanced-stage disease if end-of-treatment PET/CT is negative.[76] [82] [97] [98] [99] [100] [101] [102]

» Consolidation radiotherapy (30 to 36 Gy) may be considered for patients with residual PET-positive disease following completion of initial treatment with chemotherapy.

» Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70][71] [72] [73] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

» See local specialist protocol for dosing guidelines.

asymptomatic early (stage IA to IIA) NLPHL, non-bulky disease

1st **radiotherapy (30-36 Gy) or observation**

MANAGEMENT

Acute

» Nodular lymphocyte-predominant HL (NLPHL) is a rare subtype of HL.

» Most patients with NLPHL present with early-stage disease involving peripheral nodal regions (e.g., groin, axilla, neck).

» The goal of treatment is cure while minimising risk of late effects. Overall prognosis for patients with early-stage NLPHL is excellent.

» Radiotherapy alone at a dose 30 to 36 Gy is recommended for most patients with asymptomatic early (stage IA and IIA) non-bulky NLPHL.[33] [70] [131]

» Involved-site radiotherapy (ISRT) is the preferred approach (although most available data are for involved-field radiotherapy [IFRT]).[70]

» ISRT focuses radiation only on involved lymph nodes and nearby sites rather than lymph node regions (which is done with IFRT), therefore minimising radiation exposure to uninvolved structures and reduces the risk of adverse effects.

» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Most patients receiving treatment to the mediastinum develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

» Retrospective studies have reported excellent remission and survival outcomes with radio therapy alone for early-stage NLPHL.[132] [133] [134] [135] Randomised trials of treatments for NLPHL are lacking due to the rarity of this disease subtype.

» Observation may be appropriate for patients with asymptomatic early-stage non-bulky disease, particularly if there is concern regarding toxicity related to radiotherapy.[136] Observation is also an option for selected patients with stage IA non-bulky disease who have a completely excised solitary lymph node.[33]

asymptomatic early (stage IA to IIA) NLPHL, bulky disease; and

Acute

symptomatic early (stage IB to IIB)
NLPHL

1st **rituximab + chemotherapy + radiotherapy; or observation (if asymptomatic)**

Primary options

R-ABVD

» rituximab
-and-
» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-
» dacarbazine

OR

R-CHOP

» rituximab
-and-
» cyclophosphamide
-and-
» doxorubicin
-and-
» vincristine
-and-
» prednisolone

OR

R-CVbP

» rituximab
-and-
» cyclophosphamide
-and-
» vinblastine
-and-
» prednisolone

» Nodular lymphocyte-predominant HL (NLPHL) is a rare subtype of HL.

» Most patients with NLPHL present with early-stage disease involving peripheral nodal regions (e.g., groin, axilla, neck).

» The goal of treatment is cure while minimising risk of late effects. Overall prognosis for patients with early-stage NLPHL is excellent.

» Systemic treatment with rituximab plus combination chemotherapy (e.g., R-ABVD [rituximab, doxorubicin, bleomycin, vinblastine, dacarbazine], R-CHOP [rituximab,

Acute

cyclophosphamide, doxorubicin, vincristine, prednisolone], or R-CVbP [rituximab, cyclophosphamide, vinblastine, prednisolone]) followed by radiotherapy (30 to 36 Gy) is recommended for patients with asymptomatic early (stage IA and IIA) bulky NLPHL, and those with symptomatic early NLPHL (stage IB to IIB).[33][131] [137]

» The CD20 antigen is present on most NLPHL cells; therefore, anti-CD20 treatment with rituximab is a key component of systemic treatment for NLPHL.

» Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70] [71] [72] [73] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

» Observation may be appropriate for patients with asymptomatic early-stage bulky disease, particularly if there is concern regarding toxicity related to systemic treatment and radiotherapy.[136]

» See local specialist protocol for dosing guidelines.

advanced (stage III to IV) NLPHL

1st **observation or rituximab + chemotherapy (± radiotherapy)**

Primary options

R-ABVD

» rituximab
-and-
» doxorubicin
-and-
» bleomycin
-and-
» vinblastine
-and-

Acute

» dacarbazine

OR

R-CHOP

» rituximab
-and-
» cyclophosphamide
-and-
» doxorubicin
-and-
» vincristine
-and-
» prednisolone

OR

R-CVbP

» rituximab
-and-
» cyclophosphamide
-and-
» vinblastine
-and-
» prednisolone

» Observation may be appropriate for patients with asymptomatic advanced-stage disease.[33] [131]

» Systemic treatment with rituximab plus combination chemotherapy (e.g., R-ABVD [rituximab, doxorubicin, bleomycin, vinblastine, dacarbazine], R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone], or R-CVbP [rituximab, cyclophosphamide, vinblastine, prednisolone]) with or without radiotherapy is recommended for patients with symptomatic advanced-stage disease or rapid progression.[33] [138] [139]

» The CD20 antigen is present on most NLPHL cells; therefore, anti-CD20 treatment with rituximab is a key component of systemic treatment for NLPHL.

» Involved-site radiotherapy (ISRT) is preferred to traditional involved-field radiotherapy (IFRT) due to its lower risk of adverse effects.[70] [71] [72] [73] ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures.

» Acute adverse effects of radiotherapy depend on the region treated and the dose employed. Patients receiving treatment to the mediastinum can develop oesophagitis, clinically apparent

Acute

as odynophagia that sometimes requires opioid analgesics to maintain oral intake. Infradiaphragmatic radiotherapy can cause nausea and/or diarrhoea. Fatigue is common in all patients receiving radiotherapy. Possible long-term adverse effects of radiotherapy include secondary malignancies, cardiovascular disease, and decreased pulmonary function.

» See local specialist protocol for dosing guidelines.

Ongoing

refractory or relapsed classical HL

1st **salvage therapy (combination chemotherapy) + PET/CT**

Primary options

BeGEV

» bendamustine
-and-
» gemcitabine
-and-
» vinorelbine

OR

DHAP

» dexamethasone
-and-
» cytarabine
-and-
» cisplatin

OR

GVD

» gemcitabine
-and-
» vinorelbine
-and-
» doxorubicin liposomal

OR

ICE

» ifosfamide
-and-
» carboplatin
-and-
» etoposide

OR

IGEV

» ifosfamide
-and-
» gemcitabine
-and-
» vinorelbine

» Refractory or relapsed HL should be confirmed with biopsy.

» Treatment for refractory or relapsed HL must be individualised, taking into consideration factors such as previous first-line treatment,

Ongoing

patient age, medical comorbidities, duration of first remission, and stage at relapse. The goal of treatment, at least initially, is cure.

» Salvage therapy, followed by high-dose chemotherapy (for conditioning) and autologous stem cell transplantation (ASCT), is the standard approach for most patients who relapse following first-line treatment.[33] [103] [104] [105] [106] [107]

» The role of salvage therapy is to reduce tumour burden and mobilise stem cells before conditioning and ASCT.[5]

» Combination chemotherapy regimens can be used for salvage therapy. The optimal salvage regimen is unclear due to the lack of head-to-head randomised trials; however, the following are commonly used: BeGEV (bendamustine, gemcitabine, vinorelbine); DHAP (dexamethasone, cytarabine, cisplatin); GVD (gemcitabine, vinorelbine, pegylated liposomal doxorubicin); ICE (ifosfamide, carboplatin, etoposide); IGEV (ifosfamide, gemcitabine, vinorelbine).[106] [107] [113] [114] [115] [116] [117] [141]

» A PET-adapted treatment approach is used for refractory or relapsed HL in order to optimise outcomes following stem cell transplantation. A negative pre-transplantation PET/CT (Deauville score 1 to 3) is associated with optimal outcomes following transplantation and should, therefore, be the goal of salvage therapy prior to ASCT.[123] [124] Patients with a positive PET/CT (Deauville score 4 or 5) following salvage therapy may be considered for a different salvage regimen to achieve a negative PET/CT.[125] [126] [127]

» See local specialist protocol for dosing guidelines.

adjunct **conditioning + stem cell transplantation (if PET/CT negative)**

Treatment recommended for SOME patients in selected patient group

» Patients with relapsed or refractory disease who are PET/CT negative (Deauville score 1 to 3) following salvage therapy can be considered for high-dose chemotherapy (for conditioning) and autologous stem cell transplantation (ASCT).[103] [104] [105] [106] [107]

Ongoing

» Radiotherapy may be used alongside high-dose chemotherapy (as part of conditioning) in eligible patients.

» Allogeneic stem cell transplantation (AlloSCT) may be considered in patients who relapse after ASCT, but this is controversial.[109] [110] In selected patients, radiotherapy alone or chemotherapy alone is appropriate following salvage therapy.[111] [112]

adjunct **brentuximab vedotin (maintenance)**

Treatment recommended for SOME patients in selected patient group

Primary options

» brentuximab vedotin

» Brentuximab vedotin (an anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E) is approved for use as consolidation/maintenance therapy following ASCT in patients at high risk for relapse (e.g., those refractory to initial treatment; those who relapse within 12 months following initial treatment with ABVD or escalated BEACOPP; or those with extranodal disease).[128] [129] [130]

» Maintenance brentuximab vedotin is recommended for 16 cycles (as per the AETHERA trial) or until unacceptable toxicity or relapse (whichever occurs first).[129]

» It is not recommended in patients with prior evidence of disease refractory to brentuximab vedotin.[129] However, it may be considered for patients previously treated with brentuximab vedotin if durable remission (at least 12 months) was achieved before relapse.

» See local specialist protocol for dosing guidelines.

2nd **salvage therapy (immunotherapy regimens)**

Primary options

» brentuximab vedotin

OR

» brentuximab vedotin
-and-
» bendamustine

OR

Ongoing

» brentuximab vedotin
-and-
» nivolumab

OR

» brentuximab vedotin
-and-
» ifosfamide
-and-
» carboplatin
-and-
» etoposide

OR

» pembrolizumab

OR

» pembrolizumab
-and-
» gemcitabine
-and-
» vinorelbine
-and-
» doxorubicin liposomal

OR

» nivolumab

OR

» nivolumab
-and-
» ifosfamide
-and-
» carboplatin
-and-
» etoposide

» Several immunotherapeutic agents are available for patients with relapsed or refractory classical HL.

» The following immunotherapy-based combination regimens may be considered for use as salvage therapy before ASCT (in those who have not previously undergone ASCT) in the refractory or relapsed setting: brentuximab vedotin plus bendamustine; brentuximab vedotin plus nivolumab; brentuximab vedotin plus ICE (ifosfamide, carboplatin, etoposide); nivolumab plus ICE; or pembrolizumab plus GVD

Ongoing

(gemcitabine, vinorelbine, pegylated liposomal doxorubicin).[118] [119] [120] [121] [122]

» See local specialist protocol for dosing guidelines.

adjunct **conditioning + stem cell transplantation (if PET/CT negative)**

Treatment recommended for SOME patients in selected patient group

» Patients with relapsed or refractory disease who are PET/CT negative (Deauville score 1 to 3) following salvage therapy can be considered for high-dose chemotherapy (for conditioning) and autologous stem cell transplantation (ASCT).[103] [104] [105] [106] [107]

» Radiotherapy may be used alongside high-dose chemotherapy (as part of conditioning) in eligible patients.

» Allogeneic stem cell transplantation (AlloSCT) may be considered in patients who relapse after ASCT, but this is controversial.[109] [110] In selected patients, radiotherapy alone or chemotherapy alone is appropriate following salvage therapy.[111] [112]

adjunct **brentuximab vedotin (maintenance)**

Treatment recommended for SOME patients in selected patient group

Primary options

» brentuximab vedotin

» Brentuximab vedotin (an anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E) is approved for use as consolidation/maintenance therapy following ASCT in patients at high risk for relapse (e.g., those refractory to initial treatment; those who relapse within 12 months following initial treatment with ABVD or escalated BEACOPP; or those with extranodal disease).[128] [129] [130]

» Maintenance brentuximab vedotin is recommended for 16 cycles (as per the AETHERA trial) or until unacceptable toxicity or relapse (whichever occurs first).[129]

» It is not recommended in patients with prior evidence of disease refractory to brentuximab vedotin.[129] However, it may be considered for patients previously treated with brentuximab vedotin if durable remission (at least 12 months) was achieved before relapse.

Ongoing

» See local specialist protocol for dosing guidelines.

refractory or relapsed NLPHL

1st **salvage therapy or observation**

» Refractory or relapsed NLPHL should be confirmed by biopsy to rule out transformation to aggressive non-Hodgkin's lymphoma.

» Treatment for refractory or relapsed NLPHL must be individualised, taking into consideration factors such as previous first-line treatment (e.g., R-ABVD [rituximab, doxorubicin, bleomycin, vinblastine, dacarbazine] with radiotherapy), patient age, medical comorbidities, duration of first remission, and stage at relapse.[131]

» Salvage therapy with a rituximab-based chemotherapy regimen or rituximab alone is the preferred approach for most patients with refractory or relapsed NLPHL. Observation may be considered for asymptomatic patients as an initial approach.[33] Autologous stem cell transplantation (ASCT) may be considered for patients with aggressive disease.

» The optimal regimen for salvage chemotherapy is unclear, but the following rituximab-based regimens can be considered if not previously used: R-ABVD; R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone); R-CVbP (rituximab, cyclophosphamide, vinblastine, prednisolone); rituximab plus bendamustine; R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin); R-ICE (rituximab, ifosfamide, carboplatin, etoposide); or R-IGEV (rituximab, ifosfamide, gemcitabine, vinorelbine).

» Rituximab alone can be considered for patients who relapse with limited stage disease and low tumour volume.[33] [140]

Emerging

Immune checkpoint inhibitors (first-line setting)

Pembrolizumab and nivolumab are monoclonal antibodies that target the programmed death-1 (PD-1) receptor. Phase 2 trials investigating pembrolizumab or nivolumab in the first-line setting in patients with newly diagnosed classical HL have shown promising results.[142] [143] [144] Pembrolizumab and nivolumab are already approved for use in patients with refractory or relapsed classical HL. (See Management approach)

Histone deacetylase (HDAC) inhibitors

HDAC inhibitors are epigenetic modifiers that can induce tumour cell apoptosis by blocking the activity of HDAC enzymes. Several HDAC inhibitors (panobinostat, entinostat, and mocetinostat) have demonstrated activity in patients with relapsed or refractory classical HL.[145] [146] [147] [148]

Chimeric antigen receptor (CAR) T-cell therapy

A phase 1/2 trial investigating CD30-directed CAR T-cell therapy in heavily pre-treated patients with relapsed or refractory CD30-positive HL reported a high rate of durable responses, particularly when lymphodepleting chemotherapy (e.g., cyclophosphamide and fludarabine) was given prior to CAR T-cell therapy.[149]

Camidanlumab tesirine

A phase 1 trial investigating camidanlumab tesirine (an anti-CD25 monoclonal antibody conjugated to pyrrolobenzodiazepine dimer toxin) in heavily pre-treated patients with relapsed or refractory HL reported an overall response rate of 71%.[150]

Patient discussions

After successful treatment of HL, patients must be advised of possible treatment-related toxicities and other sequelae of their diagnosis. Provide patients with a treatment summary, including details of radiotherapy; organs at risk; and the cumulative dosage of anthracycline that they received.[33]

The importance of smoking cessation, breast cancer screening, and aggressive management of cardiac risk factors must be reinforced at follow-up appointments.

Monitoring

Monitoring

Basic blood tests and imaging should be done at baseline and monitored during therapy. Full blood count with differential is monitored to assess treatment-induced bone marrow suppression. Metabolic panel and erythrocyte sedimentation rate are included as clinically indicated.

Thyroid function tests should be done at baseline and annually if patients receive radiotherapy to the neck, given the high incidence of hypothyroidism in this population.[174]

Chest x-ray and computed tomography scan are done at baseline and as clinically indicated during therapy thereafter.

Pulmonary function tests should be repeated during and after treatment as clinically indicated, especially in those patients who may have shown signs of pulmonary toxicity during treatment.

Post-treatment follow-up

It is recommended that patients are followed-up:[33]

- every 3 to 6 months for the first 1 to 2 years after treatment, then
- every 6 to 12 months until year 3, and
- annually thereafter.

Routine blood work and imaging are not necessary unless patients have concerning symptoms or abnormalities on examination.[179] [180] [181] Most recurrences are detected via investigation of symptoms with history, physical examination, and appropriate imaging.

Routine PET/CT surveillance is not recommended.[33]

Breast cancer screening

For women who have received radiotherapy to the chest or axilla, regular breast examination and breast cancer screening should be initiated 8 years after treatment (but not before age 25 years) or at 40 years of age, whichever occurs first.[33]

Mammography and breast magnetic resonance imaging (MRI), alternating every 6 months, are recommended for breast cancer screening in females who have received radiation to the chest between the age of 10 to 30 years.[33] The diagnostic value of breast MRI and mammogram is superior to either test alone to detect breast cancer in survivors of HL.[167]

Cardiac monitoring

Patients at risk for heart disease (due to anthracycline exposure or mediastinal radiotherapy) should be evaluated regularly for cardiac risk factors (smoking, hypercholesterolaemia, glucose intolerance).

Echocardiogram and multi-gated acquisition (MUGA) scan follow-up examinations should be obtained if heart disease is suspected, or monitored if already diagnosed.

Complications

Complications	Timeframe	Likelihood
radiotherapy-related thyroid abnormalities	**long term**	**high**
Thyroid abnormalities have been reported after treatment of HL (e.g., hypothyroidism, Graves' disease, benign nodularity, and thyroid cancer). The most common is hypothyroidism, occurring in approximately 50% of patients depending on the dose of radiotherapy administered.[174] Patients who have received radiotherapy to the neck should be asked about symptoms of hypothyroidism and have thyroid studies checked regularly.		
chemotherapy- and radiotherapy-related secondary malignancies	**long term**	**medium**
The increased risk of secondary malignancies after treatment for HL is likely to be multi-factorial, with underlying genetic susceptibility, altered immune surveillance, and effects of radiotherapy and chemotherapy contributing. Alkylating agents increase the risk of secondary leukaemia. Fortunately this is a relatively rare occurrence with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine).[160] [161] The risk of secondary acute myeloid leukaemia and myelodysplastic syndrome is higher with escalated-dose BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone) compared with ABVD.[89] [90] One Cochrane review reported an increased risk of secondary acute leukaemias with consolidating radiotherapy compared with chemotherapy alone.[89] The risk of secondary solid tumours (breast cancer and lung cancer in particular) is more closely related to radiotherapy and continues to rise with continued follow-up (as opposed to the risk of leukaemia).[162] [163][164] Studies suggest that smaller radiation fields and lower doses may be associated with lower risk, but current evidence is inconclusive.[89] [165] [166] Risk reduction (smoking cessation) and routine breast screening (mammography and breast MRI) are recommended.[33] [167]		
chemotherapy- and radiotherapy-related cardiac disease	**long term**	**medium**
Cardiac disease is an important cause of increased morbidity and mortality after treatment of HL. The risk of pericardial disease is related to the dose and volume of the heart irradiated, and is a rare complication with modern doses and fields.[168] The risk of valvular disease and coronary artery disease is higher in patients treated for HL, and occurs earlier in life, compared with the general population.[169] [170] [171] The effect of chemotherapy, particularly anthracycline-based regimens, on cardiac disease is unclear but it is likely to be a contributing factor.[172] In patients treated with anthracyclines and/or mediastinal radiotherapy, aggressive management of cardiac risk factors is warranted. Using lower doses of radiotherapy and reducing the treatment volume (e.g., using involved-site radiotherapy [ISRT]) in modern combined-modality therapy regimens will probably decrease the risk of these complications.		
chemotherapy- and radiotherapy-related pulmonary toxicity	**variable**	**medium**
Pulmonary toxicity is associated with both mediastinal radiotherapy and chemotherapy, particularly bleomycin. Approximately 20% of patients treated with ABVD develop bleomycin pulmonary toxicity,		

Complications	Timeframe	Likelihood
necessitating careful monitoring of diffusing capacity for carbon monoxide during treatment.[173] Bleomycin is usually discontinued if significant pulmonary toxicity arises during treatment. Mediastinal radiotherapy to post-chemotherapy tumour volumes reduces the volume of lung irradiated and is likely to decrease the risk of pulmonary complications.		
chemotherapy- and radiotherapy-related ovarian dysfunction	**variable**	**medium**
Risk of ovarian dysfunction depends on the intensity of chemotherapy, dose of radiotherapy, and the age of the patient. Younger patients (<30 years) are less likely to develop ovarian dysfunction (with radiotherapy or chemotherapy) than older patients. Reduced recovery of ovarian function has been reported in older women (>35 years) receiving chemotherapy for advanced HL.[175] Patients should be counselled regarding the risk of infertility and options for fertility preservation.[176] A PET/CT-adapted treatment approach (e.g., reducing the intensity of subsequent chemotherapy following a negative interim PET/CT scan) may minimise the risk of ovarian dysfunction in patients with advanced HL.[177] Patients should be counselled regarding the risk of infertility and options for fertility preservation.[176]		
chemotherapy- and radiotherapy-related testicular dysfunction	**variable**	**low**
Risk of sterilisation is lower with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) compared with escalated-dose BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone), although temporary azoospermia is common with ABVD.[178] A PET/CT-adapted treatment approach (e.g., reducing the intensity of subsequent chemotherapy following a negative interim PET/CT scan) may minimise the risk of testicular dysfunction in patients with advanced HL.[177] Radiotherapy can cause sterilisation, even at low doses (1-2 Gy). Much higher doses are required to impact the testosterone-producing Leydig cells, such that with adequate blocking, testosterone levels should not be affected. Patients should be counselled regarding the risk of infertility and options for fertility preservation.[176]		
impaired immunity	**variable**	**low**
Patients with HL are known to have immune deficiencies at diagnosis, particularly with cell-mediated immunity. Following treatment with chemotherapy and/or radiotherapy, patients have a blunted antibody response to antigenic stimulation and are at increased risk of infections that are normally controlled with the cell-mediated immune system (varicella, pneumocystis, fungi). Patients need to be educated about their susceptibility to infection and need for prompt evaluation if concerning symptoms develop.		

Prognosis

Outlook

Using 2014-2020 data, the National Cancer Institute Surveillance, Epidemiology, and End Results Program reports a 5-year relative survival rate of 88.9% among patients with any stage of HL at diagnosis.[151]

Early HL (stage I to stage II)

The prognosis for patients with early-stage HL is excellent with long-term disease control of 80% to 90% following combined-modality therapy (i.e., combination chemotherapy followed by low-dose involved-field radiotherapy [IFRT]).[51] [55] [152]

While recurrent HL is the leading cause of death for the first 15 years after treatment, with continued follow-up patients are more likely to die of secondary malignancies or cardiac disease.[153]

Newer treatment approaches aim to reduce the intensity of treatment yet maintain high cure rates. These include the use of involved-site radiotherapy (ISRT) instead of IFRT. ISRT focuses radiation only on involved lymph nodes and nearby sites, minimising radiation exposure to uninvolved structures and reducing the risk of adverse effects (e.g., secondary malignancies, cardiovascular disease, decreased pulmonary function). Although the evidence for ISRT in HL is evolving, it is the preferred approach and current standard of care.[33][70] [71] [72] [73]

Advanced HL (stage III to stage IV)

Advanced HL is a heterogeneous disease. Overall, the long-term disease control after chemotherapy alone or combined-modality therapy is approximately 60% to 80%.[154] [155] [156]

Nodular lymphocyte-predominant HL (NLPHL)

Most patients with NLPHL present with asymptomatic early (stage I to II) disease. Overall prognosis for patients with NLPHL is good, particularly for early-stage disease. Long-term disease control with current treatment strategies is approximately 80% to 90% for early-stage disease.[133] [157] [158] [159]

Diagnostic guidelines

United Kingdom

Guideline for the first-line management of classical Hodgkin lymphoma (https://b-s-h.org.uk/guidelines/guidelines/guideline-for-the-first-line-management-of-classical-hodgkin-lymphoma)

Published by: British Society for Haematology **Last published:** 2022

Haematological cancers: improving outcomes (https://www.nice.org.uk/guidance/ng47)

Published by: National Institute for Health and Care Excellence **Last published:** 2016

Guidelines for the investigation and management of nodular lymphocyte predominant Hodgkin lymphoma (https://b-s-h.org.uk/guidelines/?category=Haemato-oncology&fromdate=&todate=)

Published by: British Committee for Standards in Haematology **Last published:** 2015

Europe

Hodgkin lymphoma (https://www.esmo.org/Guidelines/Haematological-Malignancies)

Published by: European Society for Medical Oncology **Last published:** 2018

North America

NCCN clinical practice guidelines in oncology: pediatric Hodgkin lymphoma (https://www.nccn.org/professionals/physician_gls/default.aspx)

Published by: National Comprehensive Cancer Network **Last published:** 2024

NCCN clinical practice guidelines in oncology: Hodgkin lymphoma (https://www.nccn.org/professionals/physician_gls/default.aspx)

Published by: National Comprehensive Cancer Network **Last published:** 2024

Treatment guidelines

United Kingdom

Suspected cancer: recognition and referral (https://www.nice.org.uk/guidance/ng12)

Published by: National Institute for Health and Care Excellence **Last published:** 2025

Guideline for the first-line management of classical Hodgkin lymphoma (https://b-s-h.org.uk/guidelines/guidelines/guideline-for-the-first-line-management-of-classical-hodgkin-lymphoma)

Published by: British Society for Haematology **Last published:** 2022

Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (https://www.nice.org.uk/guidance/ta524)

Published by: National Institute for Health and Care Excellence **Last published:** 2018

Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma (https://www.nice.org.uk/guidance/ta462)

Published by: National Institute for Health and Care Excellence **Last published:** 2017

Haematological cancers: improving outcomes (https://www.nice.org.uk/guidance/ng47)

Published by: National Institute for Health and Care Excellence **Last published:** 2016

Guidelines for the investigation and management of nodular lymphocyte predominant Hodgkin lymphoma (https://b-s-h.org.uk/guidelines/?category=Haemato-oncology&fromdate=&todate=)

Published by: British Committee for Standards in Haematology **Last published:** 2015

Long term follow up of survivors of childhood cancer: a national clinical guideline (https://www.sign.ac.uk/our-guidelines)

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2013

Europe

Hodgkin lymphoma (https://www.esmo.org/Guidelines/Haematological-Malignancies)

Published by: European Society for Medical Oncology **Last published:** 2018

International

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of lymphoma (https://www.sitcancer.org/research/cancer-immunotherapy-guidelines/lymphoma)

Published by: Society for Immunotherapy of Cancer **Last published:** 2020

North America

NCCN clinical practice guidelines in oncology: Hodgkin lymphoma (https://www.nccn.org/professionals/physician_gls/default.aspx)

Published by: National Comprehensive Cancer Network **Last published:** 2024

NCCN clinical practice guidelines in oncology: pediatric Hodgkin lymphoma (https://www.nccn.org/professionals/physician_gls/default.aspx)

Published by: National Comprehensive Cancer Network **Last published:** 2024

NCCN clinical practice guidelines in oncology: hematopoietic cell transplantation (HCT) (https://www.nccn.org/guidelines/category_3)

Published by: National Comprehensive Cancer Network **Last published:** 2024

NCCN clinical practice guidelines in oncology: management of immunotherapy-related toxicities (https://www.nccn.org/guidelines/category_3)

Published by: National Comprehensive Cancer Network **Last published:** 2023

REFERENCES

Key articles

- Eichenauer DA, Aleman BM, André M, et al. Hodgkin lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(4 suppl):iv19-29. Full text (https://www.annalsofoncology.org/article/S0923-7534(19)31690-4/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29796651?tool=bestpractice.bmj.com)
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Hodgkin lymphoma [internet publication]. Full text (https://www.nccn.org/professionals/physician_gls/default.aspx)
- Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68. Full text (https://www.doi.org/10.1200/JCO.2013.54.8800) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25113753?tool=bestpractice.bmj.com)
- Follows GA, Barrington SF, Bhuller KS, et al. Guideline for the first-line management of classical Hodgkin lymphoma - a British Society for Haematology guideline. Br J Haematol. 2022 Jun;197(5):558-72. Full text (https://www.doi.org/10.1111/bjh.18083) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35191541?tool=bestpractice.bmj.com)
- McKay P, Fielding P, Gallop-Evans E, et al. Guidelines for the investigation and management of nodular lymphocyte predominant Hodgkin lymphoma. Br J Haematol. 2016 Jan;172(1):32-43. Full text (https://www.doi.org/10.1111/bjh.13842) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26538004?tool=bestpractice.bmj.com)

References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia. 2022 Jul;36(7):1720-48. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9214472) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35732829?tool=bestpractice.bmj.com)
2. Pileri SA, Ascani S, Leoncini L, et al. Hodgkin's lymphoma: the pathologist's viewpoint. J Clin Pathol. 2002 Mar;55(3):162-76. Full text (https://jcp.bmj.com/content/55/3/162.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11896065?tool=bestpractice.bmj.com)
3. Campo E, Jaffe ES, Cook JR, et al. The international consensus classification of mature lymphoid neoplasms: a report from the clinical advisory committee. Blood. 2022 Sep 15;140(11):1229-53. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9479027) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35653592?tool=bestpractice.bmj.com)
4. Kaseb H, Babiker HM. StatPearls: cancer, Hodgkin lymphoma. Treasure Island, FL: StatPearls Publishing; 2019. Full text (https://www.ncbi.nlm.nih.gov/books/NBK499969) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29763144?tool=bestpractice.bmj.com)

5. Eichenauer DA, Aleman BM, André M, et al. Hodgkin lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(4 suppl):iv19-29. Full text (https://www.annalsofoncology.org/article/S0923-7534(19)31690-4/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29796651?tool=bestpractice.bmj.com)

6. Cancer Research UK. Hodgkin lymphoma statistics. 2024 [internet publication]. Full text (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma)

7. National Cancer Institute. Cancer stat facts: Hodgkin lymphoma. 2024 [internet publication]. Full text (https://seer.cancer.gov/statfacts/html/hodg.html)

8. Singh D, Vaccarella S, Gini A, et al. Global patterns of Hodgkin lymphoma incidence and mortality in 2020 and a prediction of the future burden in 2040. Int J Cancer. 2022 Jun 15;150(12):1941-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35080783?tool=bestpractice.bmj.com)

9. Weiss LM, Movahed LA, Warnke RA, et al. Detection of Epstein-Barr viral genomes in Reed-Sternberg cells of Hodgkin's disease. N Engl J Med. 1989 Feb 23;320(8):502-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2536894?tool=bestpractice.bmj.com)

10. Glaser SL, Lin RJ, Stewart SL, et al. Epstein-Barr virus-associated Hodgkin's disease: epidemiologic characteristics in international data. Int J Cancer. 1997 Feb 7;70(4):375-82. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9033642?tool=bestpractice.bmj.com)

11. Hjalgrim H, Askling J, Rostgaard K, et al. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. N Engl J Med. 2003 Oct 2;349(14):1324-32. Full text (https://www.nejm.org/doi/full/10.1056/NEJMoa023141) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14523140?tool=bestpractice.bmj.com)

12. Kerzin-Storrar L, Faed MJ, MacGillivray JB, et al. Incidence of familial Hodgkin's disease. Br J Cancer. 1983 May;47(5):707-12. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6849804?tool=bestpractice.bmj.com)

13. Sud A, Thomsen H, Orlando G, et al. Genome-wide association study implicates immune dysfunction in the development of Hodgkin lymphoma. Blood. 2018 Nov 8;132(19):2040-52. Full text (https://www.doi.org/10.1182/blood-2018-06-855296) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30194254?tool=bestpractice.bmj.com)

14. Sud A, Thomsen H, Law PJ, et al. Genome-wide association study of classical Hodgkin lymphoma identifies key regulators of disease susceptibility. Nat Commun. 2017 Dec 1;8(1):1892. Full text (https://www.doi.org/10.1038/s41467-017-00320-1) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29196614?tool=bestpractice.bmj.com)

15. Mack TM, Cozen W, Shibata DK, et al. Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. N Engl J Med. 1995 Feb 16;332(7):413-8. Full text (https://www.nejm.org/doi/full/10.1056/NEJM199502163320701) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7824015?tool=bestpractice.bmj.com)

16. Grufferman S, Cole P, Smith PG, et al. Hodgkin's disease in siblings. N Engl J Med. 1977 Feb 3;296(5):248-50. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/831107?tool=bestpractice.bmj.com)

17. Paltiel O, Schmit T, Adler B, et al. The incidence of lymphoma in first-degree relatives of patients with Hodgkin disease and non-Hodgkin lymphoma: results and limitations of a registry-linked study. Cancer. 2000 May 15;88(10):2357-66. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10820359?tool=bestpractice.bmj.com)

18. Kharazmi E, Fallah M, Pukkala E, et al. Risk of familial classical Hodgkin lymphoma by relationship, histology, age, and sex: a joint study from five Nordic countries. Blood. 2015 Aug 26;126(17):1990-5. Full text (http://www.bloodjournal.org/content/126/17/1990.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26311361?tool=bestpractice.bmj.com)

19. Marafioti T, Hummel M, Foss HD, et al. Hodgkin and Reed-Sternberg cells represent an expansion of a single clone originating from a germinal center B-cell with functional immunoglobulin gene rearrangements but defective immunoglobulin transcription. Blood. 2000 Feb 15;95(4):1443-50. Full text (http://www.bloodjournal.org/content/95/4/1443.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10666223?tool=bestpractice.bmj.com)

20. Lam KP, Kühn R, Rajewsky K. In vivo ablation of surface immunoglobulin on mature B cells by inducible gene targeting results in rapid cell death. Cell. 1997 Sep 19;90(6):1073-83. Full text (https://www.cell.com/cell/fulltext/S0092-8674(00)80373-6) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9323135?tool=bestpractice.bmj.com)

21. Schweighoffer E, Tybulewicz VL. Signalling for B cell survival. Curr Opin Cell Biol. 2017 Nov 14;51:8-14. Full text (https://www.sciencedirect.com/science/article/pii/S0955067417300534) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29149682?tool=bestpractice.bmj.com)

22. Portis T, Ikeda M, Longnecker R. Epstein-Barr virus LMP2A: regulating cellular ubiquitination processes for maintenance of viral latency? Trends Immunol. 2004 Aug;25(8):422-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15275641?tool=bestpractice.bmj.com)

23. Kilger E, Kieser A, Baumann M, et al. Epstein-Barr virus-mediated B-cell proliferation is dependent upon latent membrane protein 1, which simulates an activated CD40 receptor. EMBO J. 1998 Mar 16;17(6):1700-9. Full text (https://www.embopress.org/cgi/doi/10.1093/emboj/17.6.1700) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9501091?tool=bestpractice.bmj.com)

24. Mueller N, Evans A, Harris NL, et al. Hodgkin's disease and Epstein-Barr virus. Altered antibody pattern before diagnosis. N Engl J Med. 1989 Mar 16;320(11):689-95. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2537928?tool=bestpractice.bmj.com)

25. Lee JH, Kim Y, Choi JW, et al. Prevalence and prognostic significance of Epstein-Barr virus infection in classical Hodgkin's lymphoma: a meta-analysis. Arch Med Res. 2014 Jul;45(5):417-31. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24937173?tool=bestpractice.bmj.com)

26. Glaser SL, Gulley ML, Clarke CA, et al. Racial/ethnic variation in EBV-positive classical Hodgkin lymphoma in California populations. Int J Cancer. 2008 Oct 1;123(7):1499-507. Full text (https://

www.doi.org/10.1002/ijc.23741) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18646185?tool=bestpractice.bmj.com)

27. Clarke CA, Glaser SL, Keegan TH, et al. Neighborhood socioeconomic status and Hodgkin's lymphoma incidence in California. Cancer Epidemiol Biomarkers Prev. 2005 Jun;14(6):1441-7. Full text (https://cebp.aacrjournals.org/content/14/6/1441.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15941953?tool=bestpractice.bmj.com)

28. Westergaard T, Melbye M, Pedersen JB, et al. Birth order, sibship size and risk of Hodgkin's disease in children and young adults: a population-based study of 31 million person-years. Int J Cancer. 1997 Sep 17;72(6):977-81. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9378561?tool=bestpractice.bmj.com)

29. Oza AM, Tonks S, Lim J, et al. A clinical and epidemiological study of human leukocyte antigen-DPB alleles in Hodgkin's disease. Cancer Res. 1994 Oct 1;54(19):5101-5. Full text (https://cancerres.aacrjournals.org/content/canres/54/19/5101.full.pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7923125?tool=bestpractice.bmj.com)

30. Tan GW, Jiang P, Nolte IM, et al. HLA expression in relation to HLA type in classic Hodgkin lymphoma patients. Cancers (Basel). 2021 Nov 20;13(22):5833. Full text (https://www.doi.org/10.3390/cancers13225833) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34830986?tool=bestpractice.bmj.com)

31. Diepstra A, van Imhoff GW, Karim-Kos HE, et al. HLA class II expression by Hodgkin Reed-Sternberg cells is an independent prognostic factor in classical Hodgkin's lymphoma. J Clin Oncol. 2007 Jul 20;25(21):3101-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17536082?tool=bestpractice.bmj.com)

32. Gutensohn NM. Social class and age at diagnosis of Hodgkin's disease: new epidemiologic evidence for the "two-disease hypothesis." Cancer Treat Rep. 1982 Apr;66(4):689-95. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7074638?tool=bestpractice.bmj.com)

33. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Hodgkin lymphoma [internet publication]. Full text (https://www.nccn.org/professionals/physician_gls/default.aspx)

34. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68. Full text (https://www.doi.org/10.1200/JCO.2013.54.8800) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25113753?tool=bestpractice.bmj.com)

35. Barrington SF, Kirkwood AA, Franceschetto A, et al. PET-CT for staging and early response: results from the Response-Adapted Therapy in Advanced Hodgkin Lymphoma study. Blood. 2016 Mar 24;127(12):1531-8. Full text (https://www.doi.org/10.1182/blood-2015-11-679407) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26747247?tool=bestpractice.bmj.com)

36. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007 Feb 10;25(5):571-8. Full text (https://ascopubs.org/

doi/full/10.1200/jco.2006.08.2305) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17242397?tool=bestpractice.bmj.com)

37. Cheson BD, Pfistner B, Juweid ME, et al; International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb 10;25(5):579-86. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17242396?tool=bestpractice.bmj.com)

38. Cheng G, Alavi A. Value of 18F-FDG PET versus iliac biopsy in the initial evaluation of bone marrow infiltration in the case of Hodgkin's disease: a meta-analysis. Nucl Med Commun. 2013 Jan;34(1):25-31. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23111383?tool=bestpractice.bmj.com)

39. Tubiana M, Attié E, Flamant R, et al. Prognostic factors in 454 cases of Hodgkin's disease. Cancer Res. 1971 Nov;31(11):1801-10. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/5121686?tool=bestpractice.bmj.com)

40. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014 Sep 20;32(27):3048-58. Full text (https://ascopubs.org/doi/10.1200/JCO.2013.53.5229) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25113771?tool=bestpractice.bmj.com)

41. Isasi CR, Lu P, Blaufox MD. A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. Cancer. 2005 Sep 1;104(5):1066-74. Full text (https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.21253) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16047335?tool=bestpractice.bmj.com)

42. Wirth A, Seymour JF, Hicks RJ, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography, gallium-67 scintigraphy, and conventional staging for Hodgkin's disease and non-Hodgkin's lymphoma. Am J Med. 2002 Mar;112(4):262-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11893364?tool=bestpractice.bmj.com)

43. Hasenclever D, Diehl V, Armitage JO, et al; International Prognostic Factors Project on Advanced Hodgkin's Disease. A prognostic score for advanced Hodgkin's disease. N Engl J Med. 1998 Nov 19;339(21):1506-14. Full text (http://content.nejm.org/cgi/content/full/339/21/1506) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9819449?tool=bestpractice.bmj.com)

44. Dhakal S, Advani R, Ballas LK, et al. ACR appropriateness criteria® Hodgkin lymphoma-favorable prognosis stage I and II. Am J Clin Oncol. 2016 Dec;39(6):535-44. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27643717?tool=bestpractice.bmj.com)

45. Follows GA, Barrington SF, Bhuller KS, et al. Guideline for the first-line management of classical Hodgkin lymphoma - a British Society for Haematology guideline. Br J Haematol. 2022 Jun;197(5):558-72. Full text (https://www.doi.org/10.1111/bjh.18083) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35191541?tool=bestpractice.bmj.com)

46. McKay P, Fielding P, Gallop-Evans E, et al. Guidelines for the investigation and management of nodular lymphocyte predominant Hodgkin lymphoma. Br J Haematol. 2016 Jan;172(1):32-43. Full text

(https://www.doi.org/10.1111/bjh.13842) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26538004?tool=bestpractice.bmj.com)

47. Jagadeesh D, Diefenbach C, Evens AM. XII. Hodgkin lymphoma in older patients: challenges and opportunities to improve outcomes. Hematol Oncol. 2013 Jun;31 Suppl 1:69-75. Full text (https://onlinelibrary.wiley.com/doi/10.1002/hon.2070) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23775654?tool=bestpractice.bmj.com)

48. Böll B, Görgen H, Fuchs M, et al. ABVD in older patients with early-stage Hodgkin lymphoma treated within the German Hodgkin Study Group HD10 and HD11 trials. J Clin Oncol. 2013 Apr 20;31(12):1522-9. Full text (https://ascopubs.org/doi/10.1200/JCO.2012.45.4181?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23509310?tool=bestpractice.bmj.com)

49. Ballova V, Rüffer JU, Haverkamp H, et al. A prospectively randomized trial carried out by the German Hodgkin Study Group (GHSG) for elderly patients with advanced Hodgkin's disease comparing BEACOPP baseline and COPP-ABVD (study HD9elderly). Ann Oncol. 2005 Jan;16(1):124-31. Full text (https://www.annalsofoncology.org/article/S0923-7534(19)41646-3/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15598949?tool=bestpractice.bmj.com)

50. German Hodgkin Study Group. Disease stages and risk factors. 2019 [internet publication]. Full text (https://en.ghsg.org/disease-stages)

51. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol. 2005 Jul 20;23(21):4634-42. Full text (https://ascopubs.org/doi/full/10.1200/jco.2005.09.085) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15837968?tool=bestpractice.bmj.com)

52. Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. Blood. 2004 Dec 1;104(12):3483-9. Full text (http://www.bloodjournal.org/content/104/12/3483.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15315964?tool=bestpractice.bmj.com)

53. Blank O, von Tresckow B, Monsef I, et al. Chemotherapy alone versus chemotherapy plus radiotherapy for adults with early stage Hodgkin lymphoma. Cochrane Database Syst Rev. 2017 Apr 27;(4):CD007110. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007110.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28447341?tool=bestpractice.bmj.com)

54. Eich HT, Diehl V, Görgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol. 2010 Sep 20;28(27):4199-206. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20713848?tool=bestpractice.bmj.com)

55. Noordijk EM, Carde P, Dupouy N, et al. Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7

randomized controlled trials. J Clin Oncol. 2006 Jul 1;24(19):3128-35. Full text (https://ascopubs.org/doi/full/10.1200/jco.2005.05.2746) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16754934?tool=bestpractice.bmj.com)

56. Press OW, LeBlanc M, Lichter AS, et al. Phase III randomized intergroup trial of subtotal lymphoid irradiation versus doxorubicin, vinblastine, and subtotal lymphoid irradiation for stage IA to IIA Hodgkin's disease. J Clin Oncol. 2001 Nov 15;19(22):4238-44. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11709567?tool=bestpractice.bmj.com)

57. Specht L, Gray RG, Clarke MJ, et al. Influence of more extensive radiotherapy and adjuvant chemotherapy on long-term outcome of early-stage Hodgkin's disease: a meta-analysis of 23 randomized trials involving 3,888 patients. International Hodgkin's Disease Collaborative Group. J Clin Oncol. 1998 Mar;16(3):830-43. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9508163?tool=bestpractice.bmj.com)

58. Nachman JB, Sposto R, Herzog P, et al; Children's Cancer Group. Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. J Clin Oncol. 2002 Sep 15;20(18):3765-71. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12228196?tool=bestpractice.bmj.com)

59. Fermé C, Thomas J, Brice P, et al. ABVD or BEACOPP(baseline) along with involved-field radiotherapy in early-stage Hodgkin lymphoma with risk factors: results of the European Organisation for Research and Treatment of Cancer (EORTC)-Groupe d'Étude des Lymphomes de l'Adulte (GELA) H9-U intergroup randomised trial. Eur J Cancer. 2017 Aug;81:45-55. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28601705?tool=bestpractice.bmj.com)

60. André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2017 Jun 1;35(16):1786-94. Full text (https://www.doi.org/10.1200/JCO.2016.68.6394) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28291393?tool=bestpractice.bmj.com)

61. Fuchs M, Goergen H, Kobe C, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. J Clin Oncol. 2019 Nov 1;37(31):2835-45. Full text (https://www.doi.org/10.1200/JCO.19.00964) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31498753?tool=bestpractice.bmj.com)

62. Connors JM. The case for chemotherapy alone for limited-stage Hodgkin's lymphoma. Oncologist. 2012;17(8):1011-3. Full text (http://theoncologist.alphamedpress.org/content/17/8/1011.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22807512?tool=bestpractice.bmj.com)

63. Hill-Kayser CE, Plastaras JP, Tochner Z, et al. The case for combined-modality therapy for limited-stage Hodgkin's disease. Oncologist. 2012;17(8):1006-10. Full text (http://theoncologist.alphamedpress.org/content/17/8/1006.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22807513?tool=bestpractice.bmj.com)

64. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med. 2012 Feb 2;366(5):399-408. Full text

(https://www.nejm.org/doi/full/10.1056/NEJMoa1111961) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22149921?tool=bestpractice.bmj.com)

65. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med. 2015 Apr 23;372(17):1598-607. Full text (https://www.nejm.org/doi/full/10.1056/NEJMoa1408648) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25901426?tool=bestpractice.bmj.com)

66. Straus DJ, Jung SH, Pitcher B, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. Blood. 2018 Sep 6;132(10):1013-21. Full text (https://www.doi.org/10.1182/blood-2018-01-827246) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30049811?tool=bestpractice.bmj.com)

67. Raemaekers JM, André MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2014 Apr 20;32(12):1188-94. Full text (https://ascopubs.org/doi/full/10.1200/jco.2013.51.9298) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24637998?tool=bestpractice.bmj.com)

68. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med. 2016 Jun 23;374(25):2419-29. Full text (https://www.nejm.org/doi/full/10.1056/NEJMoa1510093) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27332902?tool=bestpractice.bmj.com)

69. Hay AE, Klimm B, Chen BE, et al. An individual patient-data comparison of combined modality therapy and ABVD alone for patients with limited-stage Hodgkin lymphoma. Ann Oncol. 2013 Dec;24(12):3065-9. Full text (https://www.doi.org/10.1093/annonc/mdt389) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24121121?tool=bestpractice.bmj.com)

70. Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys. 2014 Jul 15;89(4):854-62. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23790512?tool=bestpractice.bmj.com)

71. Roberts KB, Younes A, Hodgson DC, et al. ACR appropriateness criteria® Hodgkin lymphoma-unfavorable clinical stage I and II. Am J Clin Oncol. 2016 Aug;39(4):384-95. Full text (https://www.doi.org/10.1097/COC.0000000000000294) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27299425?tool=bestpractice.bmj.com)

72. Kamran SC, Jacene HA, Chen YH, et al. Clinical outcome of patients with early stage favorable Hodgkin lymphoma treated with ABVD × two cycles followed by FDG-PET/CT restaging and 20 Gy of involved-site radiotherapy. Leuk Lymphoma. 2018 Jun;59(6):1384-90. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28937297?tool=bestpractice.bmj.com)

73. Wirth A, Mikhaeel NG, Aleman BMP, et al. Involved site radiation therapy in adult lymphomas: an overview of International Lymphoma Radiation Oncology Group guidelines. Int J Radiat Oncol Biol

Phys. 2020 Aug 1;107(5):909-33. Full text (https://www.doi.org/10.1016/j.ijrobp.2020.03.019) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32272184?tool=bestpractice.bmj.com)

74. Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med. 2010 Aug 12;363(7):640-52. Full text (https://www.nejm.org/doi/full/10.1056/NEJMoa1000067) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20818855?tool=bestpractice.bmj.com)

75. Aldin A, Umlauff L, Estcourt LJ, et al. Interim PET-results for prognosis in adults with Hodgkin lymphoma: a systematic review and meta-analysis of prognostic factor studies. Cochrane Database Syst Rev. 2020 Jan 13;1(1):CD012643. Full text (https://www.doi.org/10.1002/14651858.CD012643.pub3) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31930780?tool=bestpractice.bmj.com)

76. Gallamini A, Rossi A, Patti C, et al. Consolidation radiotherapy could be safely omitted in advanced Hodgkin lymphoma with large nodal mass in complete metabolic response after ABVD: final analysis of the randomized GITIL/FIL HD0607 Trial. J Clin Oncol. 2020 Nov 20;38(33):3905-13. Full text (https://www.doi.org/10.1200/JCO.20.00935) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32946355?tool=bestpractice.bmj.com)

77. LaCasce AS, Dockter T, Ruppert AS, et al. Positron emission tomography-adapted therapy in bulky stage I/II classic Hodgkin lymphoma: CALGB 50801 (Alliance). J Clin Oncol. 2022 Oct 21:JCO2200947. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36269899?tool=bestpractice.bmj.com)

78. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol. 2009 Nov 10;27(32):5390-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19738111?tool=bestpractice.bmj.com)

79. Federico M, Luminari S, Iannitto E, et al; HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. J Clin Oncol. 2009 Feb 10;27(5):805-11. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19124807?tool=bestpractice.bmj.com)

80. Skoetz N, Will A, Monsef I, et al. Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma. Cochrane Database Syst Rev. 2017 May 25;(5):CD007941. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007941.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28541603?tool=bestpractice.bmj.com)

81. Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol. 2013 Feb 20;31(6):684-91. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23182987?tool=bestpractice.bmj.com)

82. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase

3 non-inferiority trial. Lancet. 2012 May 12;379(9828):1791-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22480758?tool=bestpractice.bmj.com)

83. Forero-Torres A, Holkova B, Goldschmidt J, et al. Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older. Blood. 2015 Sep 16;126(26):2798-804. Full text (http://www.bloodjournal.org/content/126/26/2798.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26377597?tool=bestpractice.bmj.com)

84. Evens AM, Advani RH, Helenowski IB, et al. Multicenter phase II study of sequential brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine chemotherapy for older patients with untreated classical Hodgkin lymphoma. J Clin Oncol. 2018 Sep 4;36(30):3015-22. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30179569?tool=bestpractice.bmj.com)

85. Connors JM, Jurczak W, Straus DJ, et al; ECHELON-1 Study Group. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med. 2017 Dec 10;378(4):331-44. Full text (https://www.nejm.org/doi/10.1056/NEJMoa1708984) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29224502?tool=bestpractice.bmj.com)

86. Straus DJ, Długosz-Danecka M, Alekseev S, et al. Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study. Blood. 2020 Mar 5;135(10):735-42. Full text (https://www.doi.org/10.1182/blood.2019003127) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31945149?tool=bestpractice.bmj.com)

87. Straus DJ, Długosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. Lancet Haematol. 2021 Jun;8(6):e410-21. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34048680?tool=bestpractice.bmj.com)

88. Ansell SM, Radford J, Connors JM, et al. Overall survival with brentuximab vedotin in stage III or IV Hodgkin's lymphoma. N Engl J Med. 2022 Jul 28;387(4):310-20. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35830649?tool=bestpractice.bmj.com)

89. Franklin J, Eichenauer DA, Becker I, et al. Optimisation of chemotherapy and radiotherapy for untreated Hodgkin lymphoma patients with respect to second malignant neoplasms, overall and progression-free survival: individual participant data analysis. Cochrane Database Syst Rev. 2017 Sep 13;(9):CD008814. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008814.pub2/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28901021?tool=bestpractice.bmj.com)

90. Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol. 2009 Sep 20;27(27):4548-54. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19704068?tool=bestpractice.bmj.com)

91. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. N Engl J Med. 2011;365:203-212. Full text (http://www.nejm.org/doi/full/10.1056/NEJMoa1100340#t=article) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21774708?tool=bestpractice.bmj.com)

92. Merli F, Luminari S, Gobbi PG, et al. Long-term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPP-EBV-CAD in untreated patients with advanced Hodgkin lymphoma: a study by Fondazione Italiana Linfomi. J Clin Oncol. 2016 Apr 10;34(11):1175-81. Full text (https://ascopubs.org/doi/full/10.1200/JCO.2015.62.4817) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26712220?tool=bestpractice.bmj.com)

93. Carde P, Karrasch M, Fortpied C, et al. Eight cycles of ABVD versus four cycles of BEACOPP escalated plus four cycles of BEACOPP baseline in stage III to IV, International Prognostic Score ≥ 3, high-risk Hodgkin lymphoma: first results of the phase III EORTC 20012 Intergroup Trial. J Clin Oncol. 2016 Jun 10;34(17):2028-36. Full text (https://ascopubs.org/doi/full/10.1200/JCO.2015.64.5648) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27114593?tool=bestpractice.bmj.com)

94. Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. Lancet. 2017 Dec 23;390(10114):2790-802. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29061295?tool=bestpractice.bmj.com)

95. Casasnovas RO, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. Lancet Oncol. 2019 Feb;20(2):202-15. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30658935?tool=bestpractice.bmj.com)

96. Kreissl S, Goergen H, Buehnen I, et al. PET-guided eBEACOPP treatment of advanced-stage Hodgkin lymphoma (HD18): follow-up analysis of an international, open-label, randomised, phase 3 trial. Lancet Haematol. 2021 Jun;8(6):e398-409. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34048679?tool=bestpractice.bmj.com)

97. Aleman BM, Raemaekers JM, Tirelli U, et al; European Organization for Research and Treatment of Cancer Lymphoma Group. Involved-field radiotherapy for advanced Hodgkin's lymphoma. N Engl J Med. 2003 Jun 12;348(24):2396-406. Full text (https://www.nejm.org/doi/full/10.1056/NEJMoa022628) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12802025?tool=bestpractice.bmj.com)

98. DeVita VT Jr. Hodgkin's disease - clinical trials and travails. N Engl J Med. 2003 Jun 12;348(24):2375-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12802021?tool=bestpractice.bmj.com)

99. Fabian CJ, Mansfield CM, Dahlberg S, et al. Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group randomized study. Ann Intern Med. 1994 Jun 1;120(11):903-12. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8172436?tool=bestpractice.bmj.com)

100. Prosnitz LR. Consolidation radiotherapy in the treatment of advanced Hodgkin's disease: is it dead? Int J Radiat Oncol Biol Phys. 2003;56:605-608. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12788163?tool=bestpractice.bmj.com)

101. Johnson PW, Sydes MR, Hancock BW, et al. Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 randomized controlled trial

(ISRCTN97144519). J Clin Oncol. 2010 Jul 10;28(20):3352-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20498402?tool=bestpractice.bmj.com)

102. Gallamini A, Tarella C, Viviani S, et al. Early chemotherapy intensification with escalated BEACOPP in patients with advanced-stage Hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: long-term results of the GITIL/FIL HD 0607 trial. J Clin Oncol. 2018 Feb 10;36(5):454-62. Full text (https://www.doi.org/10.1200/JCO.2017.75.2543) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29360414?tool=bestpractice.bmj.com)

103. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet. 1993;341:1051-1054. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8096958?tool=bestpractice.bmj.com)

104. Schmitz N, Pfistner B, Sextro M, et al; German Hodgkin's Lymphoma Study Group; Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet. 2002 Jun 15;359(9323):2065-71. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12086759?tool=bestpractice.bmj.com)

105. Baetz T, Belch A, Couban S, et al. Gemcitabine, dexamethasone and cisplatin is an active and non-toxic chemotherapy regimen in relapsed or refractory Hodgkin's disease: a phase II study by the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol. 2003 Dec;14(12):1762-7. Full text (https://www.annalsofoncology.org/article/S0923-7534(19)64251-1/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14630682?tool=bestpractice.bmj.com)

106. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood. 2001 Feb 1;97(3):616-23. Full text (http://www.bloodjournal.org/content/97/3/616.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11157476?tool=bestpractice.bmj.com)

107. Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica. 2007 Jan;92(1):35-41. Full text (http://www.haematologica.org/content/92/1/35.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17229633?tool=bestpractice.bmj.com)

108. Moskowitz AJ, Herrera AF, Beaven AW. Relapsed and refractory classical Hodgkin lymphoma: keeping pace with novel agents and new options for salvage therapy. Am Soc Clin Oncol Educ Book. 2019 Jan;39:477-86. Full text (https://www.doi.org/10.1200/EDBK_238799) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31099645?tool=bestpractice.bmj.com)

109. Anderlini P, Champlin RE. Reduced intensity conditioning for allogeneic stem cell transplantation in relapsed and refractory Hodgkin lymphoma: where do we stand? Biol Blood Marrow Transplant. 2006 Jun;12(6):599-602. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16737932?tool=bestpractice.bmj.com)

110. Moskowitz CH. Should all patients with HL who relapse after ASCT be considered for allogeneic SCT? A consult, yes; a transplant, not necessarily. Blood Adv. 2018 Apr 10;2(7):821-4. Full text (https://www.doi.org/10.1182/bloodadvances.2017011130) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29636328?tool=bestpractice.bmj.com)

111. Josting A, Nogova L, Franklin J, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Lymphoma Study Group. J Clin Oncol. 2005;23:1522-1529. Full text (http://jco.ascopubs.org/cgi/content/full/23/7/1522) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15632410?tool=bestpractice.bmj.com)

112. Constine LS, Yahalom J, Ng AK, et al. The role of radiation therapy in patients with relapsed or refractory Hodgkin lymphoma: guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2018 Jan 9;100(5):1100-18. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29722655?tool=bestpractice.bmj.com)

113. Castagna L, Santoro A, Carlo-Stella C. Salvage therapy for Hodgkin's lymphoma: a review of current regimens and outcomes. J Blood Med. 2020;11:389-403. Full text (https://www.doi.org/10.2147/JBM.S250581) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33149713?tool=bestpractice.bmj.com)

114. Santoro A, Mazza R, Pulsoni A, et al. Bendamustine in combination with gemcitabine and vinorelbine is an effective regimen as induction chemotherapy before autologous stem-cell transplantation for relapsed or refractory Hodgkin lymphoma: final results of a multicenter phase II study. J Clin Oncol. 2016 Sep 20;34(27):3293-9. Full text (https://www.doi.org/10.1200/JCO.2016.66.4466) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27382096?tool=bestpractice.bmj.com)

115. Santoro A, Mazza R, Pulsoni A, et al. Five-year results of the BEGEV salvage regimen in relapsed/refractory classical Hodgkin lymphoma. Blood Adv. 2020 Jan 14;4(1):136-40. Full text (https://www.doi.org/10.1182/bloodadvances.2019000984) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31935284?tool=bestpractice.bmj.com)

116. Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. Ann Oncol. 2002 Oct;13(10):1628-35. Full text (https://www.doi.org/10.1093/annonc/mdf221) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12377653?tool=bestpractice.bmj.com)

117. Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. Ann Oncol. 2007 Jun;18(6):1071-9. Full text (https://www.doi.org/10.1093/annonc/mdm090) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17426059?tool=bestpractice.bmj.com)

118. O'Connor OA, Lue JK, Sawas A, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1-2 trial. Lancet Oncol. 2018 Feb;19(2):257-66. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29276022?tool=bestpractice.bmj.com)

119. Advani RH, Moskowitz AJ, Bartlett NL, et al. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. Blood. 2021 Aug 12;138(6):427-38.

Full text (https://www.doi.org/10.1182/blood.2020009178) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33827139?tool=bestpractice.bmj.com)

120. Lynch RC, Cassaday RD, Smith SD, et al. Dose-dense brentuximab vedotin plus ifosfamide, carboplatin, and etoposide for second-line treatment of relapsed or refractory classical Hodgkin lymphoma: a single centre, phase 1/2 study. Lancet Haematol. 2021 Aug;8(8):e562-71. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34329577?tool=bestpractice.bmj.com)

121. Mei MG, Lee HJ, Palmer JM, et al. Response-adapted anti-PD-1-based salvage therapy for Hodgkin lymphoma with nivolumab alone or in combination with ICE. Blood. 2022 Jun 23;139(25):3605-3616. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35316328?tool=bestpractice.bmj.com)

122. Moskowitz AJ, Shah G, Schöder H, et al. Phase II trial of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin as second-line therapy for relapsed or refractory classical Hodgkin lymphoma. J Clin Oncol. 2021 Oct 1;39(28):3109-17. Full text (https://www.doi.org/10.1200/JCO.21.01056) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34170745?tool=bestpractice.bmj.com)

123. Moskowitz CH, Matasar MJ, Zelenetz AD, et al. Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. Blood. 2012 Feb 16;119(7):1665-70. Full text (http://www.bloodjournal.org/content/119/7/1665.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22184409?tool=bestpractice.bmj.com)

124. Adams HJ, Kwee TC. Prognostic value of pretransplant FDG-PET in refractory/relapsed Hodgkin lymphoma treated with autologous stem cell transplantation: systematic review and meta-analysis. Ann Hematol. 2016 Apr;95(5):695-706. Full text (https://www.doi.org/10.1007/s00277-016-2619-9) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26931115?tool=bestpractice.bmj.com)

125. Fehniger TA, Larson S, Trinkaus K, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood. 2011 Nov 10;118(19):5119-25. Full text (http://www.bloodjournal.org/content/118/19/5119.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21937701?tool=bestpractice.bmj.com)

126. Johnston PB, Pinter-Brown LC, Warsi G, et al. Phase 2 study of everolimus for relapsed or refractory classical Hodgkin lymphoma. Exp Hematol Oncol. 2018;7:12. Full text (https://www.doi.org/10.1186/s40164-018-0103-z) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29774169?tool=bestpractice.bmj.com)

127. Moskowitz AJ, Hamlin PA Jr, Perales MA, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol. 2013 Feb 1;31(4):456-60. Full text (https://www.doi.org/10.1200/JCO.2012.45.3308) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23248254?tool=bestpractice.bmj.com)

128. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;385:1853-1862. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25796459?tool=bestpractice.bmj.com)

129. Kanate AS, Kumar A, Dreger P, et al. Maintenance therapies for Hodgkin and non-Hodgkin lymphomas after autologous transplantation: a consensus project of ASBMT, CIBMTR, and the lymphoma working party of EBMT. JAMA Oncol. 2019 May 1;5(5):715-22. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30816957?tool=bestpractice.bmj.com)

130. Moskowitz CH, Walewski J, Nademanee A, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. Blood. 2018 Dec 20;132(25):2639-42. Full text (https://www.doi.org/10.1182/blood-2018-07-861641) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30266774?tool=bestpractice.bmj.com)

131. Spinner MA, Varma G, Advani RH. Modern principles in the management of nodular lymphocyte-predominant Hodgkin lymphoma. Br J Haematol. 2019 Jan;184(1):17-29. Full text (https://www.doi.org/10.1111/bjh.15616) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30485408?tool=bestpractice.bmj.com)

132. Nogova L, Reineke T, Eich HT, et al. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). Ann Oncol. 2005 Oct;16(10):1683-7. Full text (https://www.annalsofoncology.org/article/S0923-7534(19)45436-7/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16093276?tool=bestpractice.bmj.com)

133. Eichenauer DA, Plütschow A, Fuchs M, et al. Long-term course of patients with stage IA nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin study group. J Clin Oncol. 2015 Sep 10;33(26):2857-62. Full text (https://www.doi.org/10.1200/JCO.2014.60.4363) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26240235?tool=bestpractice.bmj.com)

134. Pinnix CC, Milgrom SA, Cheah CY, et al. Favorable outcomes with de-escalated radiation therapy for limited-stage nodular lymphocyte-predominant Hodgkin lymphoma. Blood Adv. 2019 May 14;3(9):1356-67. Full text (https://www.doi.org/10.1182/bloodadvances.2018029140) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31036721?tool=bestpractice.bmj.com)

135. Binkley MS, Rauf MS, Milgrom SA, et al. Stage I-II nodular lymphocyte-predominant Hodgkin lymphoma: a multi-institutional study of adult patients by ILROG. Blood. 2020 Jun 25;135(26):2365-74. Full text (https://www.doi.org/10.1182/blood.2019003877) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32211877?tool=bestpractice.bmj.com)

136. Borchmann S, Joffe E, Moskowitz CH, et al. Active surveillance for nodular lymphocyte-predominant Hodgkin lymphoma. Blood. 2019 May 16;133(20):2121-29. Full text (https://www.doi.org/10.1182/blood-2018-10-877761) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30770396?tool=bestpractice.bmj.com)

137. Savage KJ, Skinnider B, Al-Mansour M, et al. Treating limited-stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome. Blood. 2011 Oct 27;118(17):4585-90. Full text (https://www.doi.org/10.1182/blood-2011-07-365932) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21873543?tool=bestpractice.bmj.com)

138. Eichenauer DA, Engert A. Nodular lymphocyte-predominant Hodgkin lymphoma: a unique disease deserving unique management. Hematology Am Soc Hematol Educ Program. 2017 Dec

8;2017(1):324-8. Full text (http://asheducationbook.hematologylibrary.org/content/2017/1/324.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29222274?tool=bestpractice.bmj.com)

139. Fanale MA, Cheah CY, Rich A, et al. Encouraging activity for R-CHOP in advanced stage nodular lymphocyte-predominant Hodgkin lymphoma. Blood. 2017 May 18;130(4):472-7. Full text (http://www.bloodjournal.org/content/130/4/472.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28522441?tool=bestpractice.bmj.com)

140. Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). Blood. 2008 Jan 1;111(1):109-11. Full text (https://www.doi.org/10.1182/blood-2007-03-078725) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17938252?tool=bestpractice.bmj.com)

141. Labrador J, Cabrero-Calvo M, Pérez-López E, et al. ESHAP as salvage therapy for relapsed or refractory Hodgkin's lymphoma. Ann Hematol. 2014 Oct;93(10):1745-53. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24863692?tool=bestpractice.bmj.com)

142. Ramchandren R, Domingo-Domènech E, Rueda A, et al. Nivolumab for newly diagnosed advanced-stage classic Hodgkin lymphoma: safety and efficacy in the phase II CheckMate 205 study. J Clin Oncol. 2019 Aug 10;37(23):1997-2007. Full text (https://www.doi.org/10.1200/JCO.19.00315) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31112476?tool=bestpractice.bmj.com)

143. Bröckelmann PJ, Goergen H, Keller U, et al. Efficacy of nivolumab and AVD in early-stage unfavorable classic Hodgkin lymphoma: the randomized phase 2 German Hodgkin Study Group NIVAHL trial. JAMA Oncol. 2020 Jun 1;6(6):872-80. Full text (https://www.doi.org/10.1001/jamaoncol.2020.0750) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32352505?tool=bestpractice.bmj.com)

144. Allen PB, Savas H, Evens AM, et al. Pembrolizumab followed by AVD in untreated early unfavorable and advanced-stage classical Hodgkin lymphoma. Blood. 2021 Mar 11;137(10):1318-1326. Full text (https://www.doi.org/10.1182/blood.2020007400) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32992341?tool=bestpractice.bmj.com)

145. Adams H, Obermann EC, Dirnhofer S, et al. Targetable molecular pathways in classical Hodgkin's lymphoma. Expert Opin Investig Drugs. 2011;20:141-151. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21204722?tool=bestpractice.bmj.com)

146. Younes A, Sureda A, Ben-Yehuda D, et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: results of a phase II study. J Clin Oncol. 2012 Jun 20;30(18):2197-203. Full text (https://www.doi.org/10.1200/JCO.2011.38.1350) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22547596?tool=bestpractice.bmj.com)

147. Batlevi CL, Kasamon Y, Bociek RG, et al. ENGAGE- 501: phase II study of entinostat (SNDX-275) in relapsed and refractory Hodgkin lymphoma. Haematologica. 2016 Aug;101(8):968-75. Full text (https://www.doi.org/10.3324/haematol.2016.142406) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27151994?tool=bestpractice.bmj.com)

148. Younes A, Oki Y, Bociek RG, et al. Mocetinostat for relapsed classical Hodgkin's lymphoma: an open-label, single-arm, phase 2 trial. Lancet Oncol. 2011 Dec;12(13):1222-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22033282?tool=bestpractice.bmj.com)

149. Ramos CA, Grover NS, Beaven AW, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma. J Clin Oncol. 2020 Nov 10;38(32):3794-804. Full text (https://www.doi.org/10.1200/JCO.20.01342) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32701411?tool=bestpractice.bmj.com)

150. Hamadani M, Collins GP, Caimi PF, et al. Camidanlumab tesirine in patients with relapsed or refractory lymphoma: a phase 1, open-label, multicentre, dose-escalation, dose-expansion study. Lancet Haematol. 2021 Jun;8(6):e433-45. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34048682?tool=bestpractice.bmj.com)

151. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Hodgkin lymphoma: SEER 5-year relative survival rates, 2012-2018 [internet publication]. Full text (https://seer.cancer.gov/statistics-network/explorer/application.html?site=83&data_type=4&graph_type=5&compareBy=sex&chk_sex_1=1&series=9&race=1&age_range=1&stage=101&

152. Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol. 2003 Oct 1;21(19):3601-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12913100?tool=bestpractice.bmj.com)

153. Ng AK, Bernardo MP, Weller E, et al. Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger. J Clin Oncol. 2002 Apr 15;20(8):2101-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11956271?tool=bestpractice.bmj.com)

154. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med. 2003 Jun 12;348(24):2386-95. [Erratum in: N Engl J Med. 2005 Aug 18;353(7):744.] Full text (https://www.nejm.org/doi/full/10.1056/NEJMoa022473) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12802024?tool=bestpractice.bmj.com)

155. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med. 1992 Nov 19;327(21):1478-84. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1383821?tool=bestpractice.bmj.com)

156. Gobbi PG, Levis A, Chisesi T, et al. ABVD versus modified Stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. J Clin Oncol. 2005 Dec 20;23(36):9198-207. Full text (https://ascopubs.org/doi/full/10.1200/jco.2005.02.907) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16172458?tool=bestpractice.bmj.com)

157. Schlembach PJ, Wilder RB, Jones D, et al. Radiotherapy alone for lymphocyte-predominant Hodgkin's disease. Cancer J. 2002 Sep-Oct;8(5):377-83. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12416895?tool=bestpractice.bmj.com)

158. Wirth A, Yuen K, Barton M, et al. Long-term outcome after radiotherapy alone for lymphocyte-predominant Hodgkin lymphoma: a retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. Cancer. 2005 Sep 15;104(6):1221-9. Full text (https://www.doi.org/10.1002/cncr.21303) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16094666?tool=bestpractice.bmj.com)

159. Chen RC, Chin MS, Ng AK, et al. Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. J Clin Oncol. 2010 Jan 1;28(1):136-41. Full text (https://www.doi.org/10.1200/JCO.2009.24.0945) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19933914?tool=bestpractice.bmj.com)

160. Horning SJ, Hoppe RT, Breslin S, et al. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. J Clin Oncol. 2002 Feb 1;20(3):630-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11821442?tool=bestpractice.bmj.com)

161. Delwail V, Jais JP, Colonna P, et al. Fifteen-year secondary leukaemia risk observed in 761 patients with Hodgkin's disease prospectively treated by MOPP or ABVD chemotherapy plus high-dose irradiation. Br J Haematol. 2002 Jul;118(1):189-94. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12100147?tool=bestpractice.bmj.com)

162. Bhatia S, Yasui Y, Robison LL, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol. 2003 Dec 1;21(23):4386-94. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14645429?tool=bestpractice.bmj.com)

163. Schaapveld M, Aleman BM, van Eggermond AM, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med. 2015 Dec 24;373(26):2499-511. Full text (https://www.doi.org/10.1056/NEJMoa1505949) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26699166?tool=bestpractice.bmj.com)

164. Giulino-Roth L, Pei Q, Buxton A, et al. Subsequent malignant neoplasms among children with Hodgkin lymphoma: a report from the Children's Oncology Group. Blood. 2021 Mar 18;137(11):1449-56. Full text (https://www.doi.org/10.1182/blood.2020007225) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33512412?tool=bestpractice.bmj.com)

165. Koontz BF, Kirkpatrick JP, Clough RW, et al. Combined-modality therapy versus radiotherapy alone for treatment of early-stage Hodgkin's disease: cure balanced against complications. J Clin Oncol. 2006 Feb 1;24(4):605-11. Full text (https://ascopubs.org/doi/full/10.1200/jco.2005.02.9850) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16446333?tool=bestpractice.bmj.com)

166. De Bruin ML, Sparidans J, van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. J Clin Oncol. 2009 Sep 10;27(26):4239-46. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19667275?tool=bestpractice.bmj.com)

167. Mulder RL, Hudson MM, Bhatia S, et al. Updated breast cancer surveillance recommendations for female survivors of childhood, adolescent, and young adult cancer from the International Guideline Harmonization Group. J Clin Oncol. 2020 Dec 10;38(35):4194-207. Full text (https://

www.doi.org/10.1200/JCO.20.00562) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33078972?tool=bestpractice.bmj.com)

168. Stewart JR, Fajardo LF. Dose response in human and experimental radiation-induced heart disease. Application of the nominal standard dose (NSD) concept. Radiology. 1971 May;99(2):403-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/5553580?tool=bestpractice.bmj.com)

169. Heidenreich PA, Hancock SL, Lee BK, et al. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol. 2003 Aug 20;42(4):743-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12932613?tool=bestpractice.bmj.com)

170. Hull MC, Morris CG, Pepine CJ, et al. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. JAMA. 2003 Dec 3;290(21):2831-7. Full text (https://jamanetwork.com/journals/jama/fullarticle/197758) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14657067?tool=bestpractice.bmj.com)

171. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA. 1993 Oct 27;270(16):1949-55. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8411552?tool=bestpractice.bmj.com)

172. Aviles A, Neri N, Nambo JM, et al. Late cardiac toxicity secondary to treatment in Hodgkin's disease. A study comparing doxorubicin, epirubicin and mitoxantrone in combined therapy. Leuk Lymphoma. 2005 Jul;46(7):1023-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16019553?tool=bestpractice.bmj.com)

173. Martin WG, Ristow KM, Habermann TM, et al. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. J Clin Oncol. 2005 Oct 20;23(30):7614-20. Full text (https://ascopubs.org/doi/full/10.1200/jco.2005.02.7243) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16186594?tool=bestpractice.bmj.com)

174. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med. 1991 Aug 29;325(9):599-605. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1861693?tool=bestpractice.bmj.com)

175. Anderson RA, Remedios R, Kirkwood AA, et al. Determinants of ovarian function after response-adapted therapy in patients with advanced Hodgkin's lymphoma (RATHL): a secondary analysis of a randomised phase 3 trial. Lancet Oncol. 2018 Sep 13;19(10):1328-37. Full text (https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30500-X/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30220622?tool=bestpractice.bmj.com)

176. Schmidt KT, Andersen CY; ISFP Practice Committee. Recommendations for fertility preservation in patients with lymphomas. J Assist Reprod Genet. 2012 Jun;29(6):473-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22562284?tool=bestpractice.bmj.com)

177. Demeestere I, Racape J, Dechene J, et al. Gonadal function recovery in patients with advanced Hodgkin lymphoma treated with a PET-adapted regimen: prospective analysis of a randomized phase III trial (AHL2011). J Clin Oncol. 2021 Oct 10;39(29):3251-60. Full text (https://www.doi.org/10.1200/JCO.21.00068) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34156881?tool=bestpractice.bmj.com)

178. Amin MSA, Brunckhorst O, Scott C, et al. ABVD and BEACOPP regimens' effects on fertility in young males with Hodgkin lymphoma. Clin Transl Oncol. 2021 Jun;23(6):1067-77. Full text (https://www.doi.org/10.1007/s12094-020-02483-8) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32944834?tool=bestpractice.bmj.com)

179. Dryver ET, Jernstrom H, Tompkins K, et al. Follow-up of patients with Hodgkin's disease following curative treatment: the routine CT scan is of little value. Br J Cancer. 2003;89:482-486. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12888816?tool=bestpractice.bmj.com)

180. Radford JA, Eardley A, Woodman C, et al. Follow up policy after treatment for Hodgkin's disease: too many clinic visits and routine tests? A review of hospital records. BMJ. 1997;314:343-346. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9040326?tool=bestpractice.bmj.com)

181. Torrey MJ, Poen JC, Hoppe RT. Detection of relapse in early-stage Hodgkin's disease: role of routine follow-up studies. J Clin Oncol. 1997;15:1123-1130. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9060554?tool=bestpractice.bmj.com)

Images

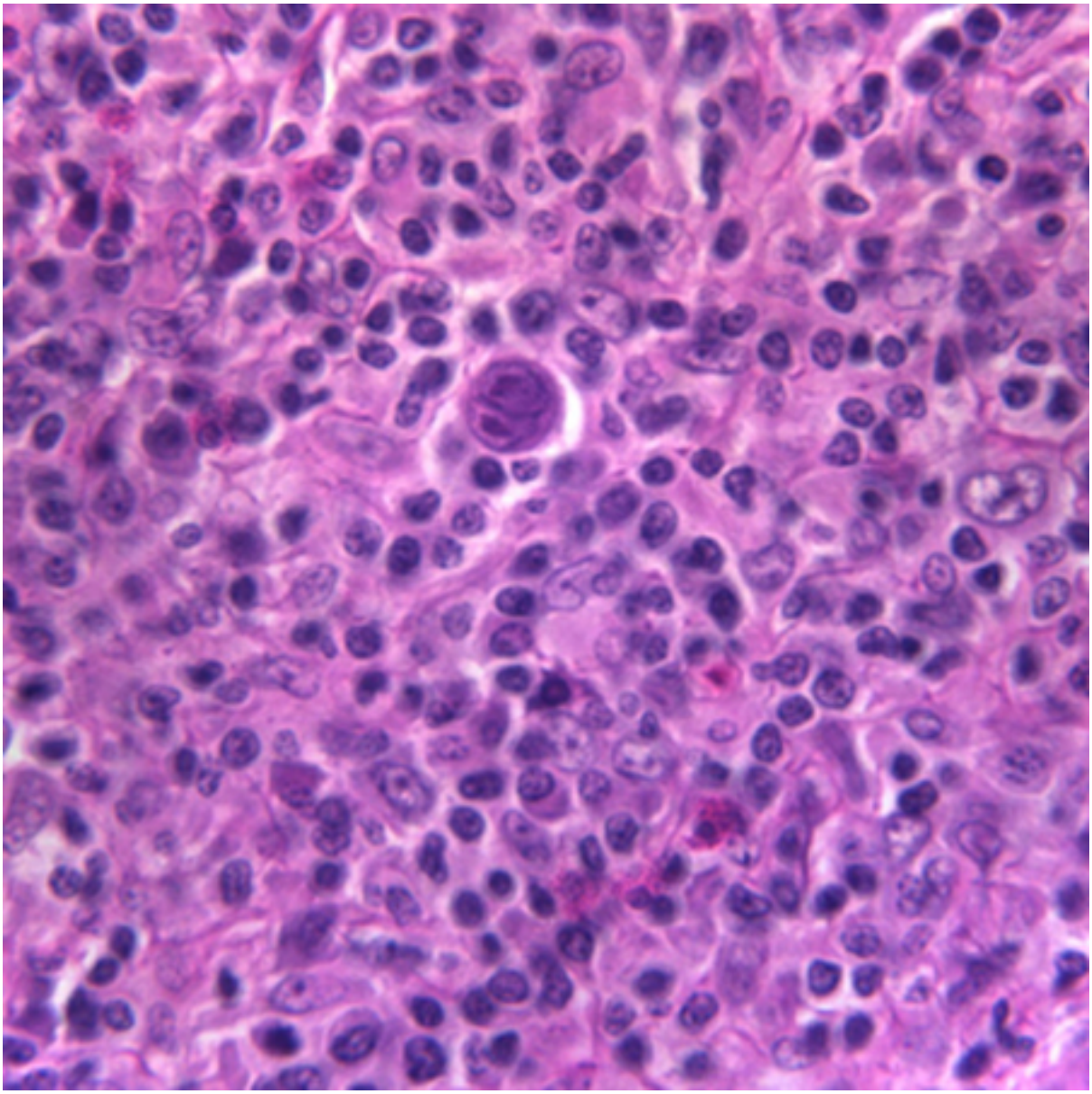


Figure 1: A diagnostic Reed-Sternberg cell is seen in the centre of the image

From the personal collection of CR Kelsey

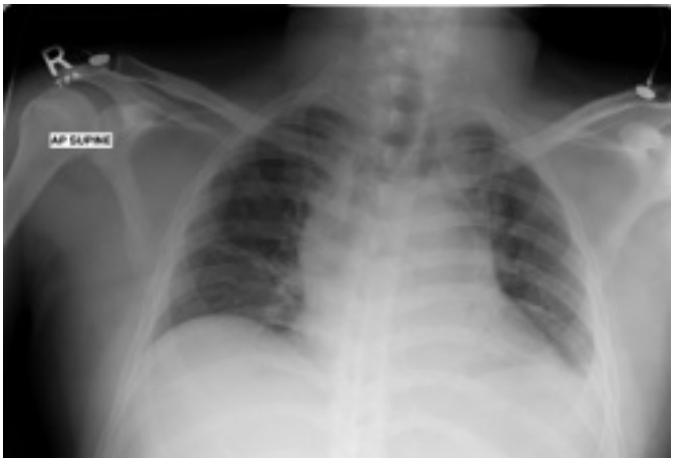


Figure 2: CXR of patient presenting with dyspnoea, showing widened mediastinum and tracheal displacement

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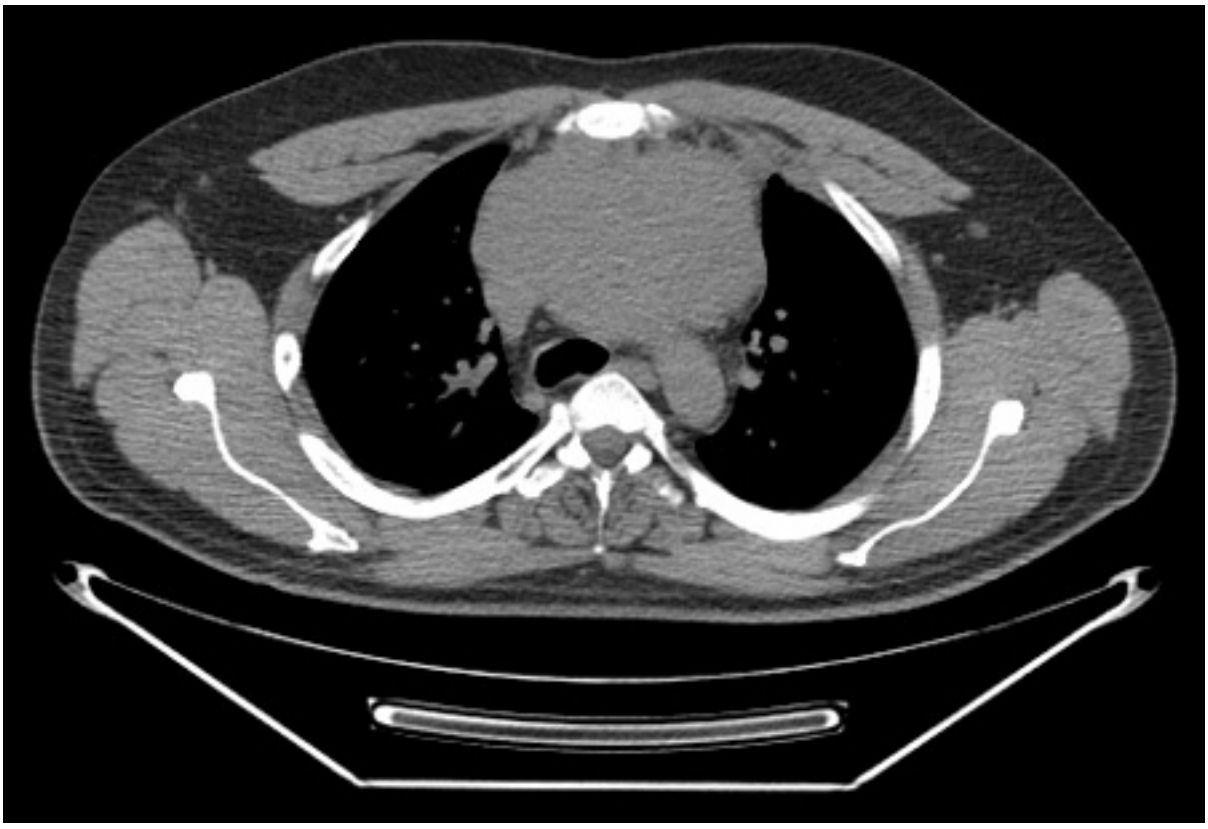

Figure 3: CT scan of patient with nodular sclerosis Hodgkin's lymphoma, showing an 11-cm anterior mediastinal mass

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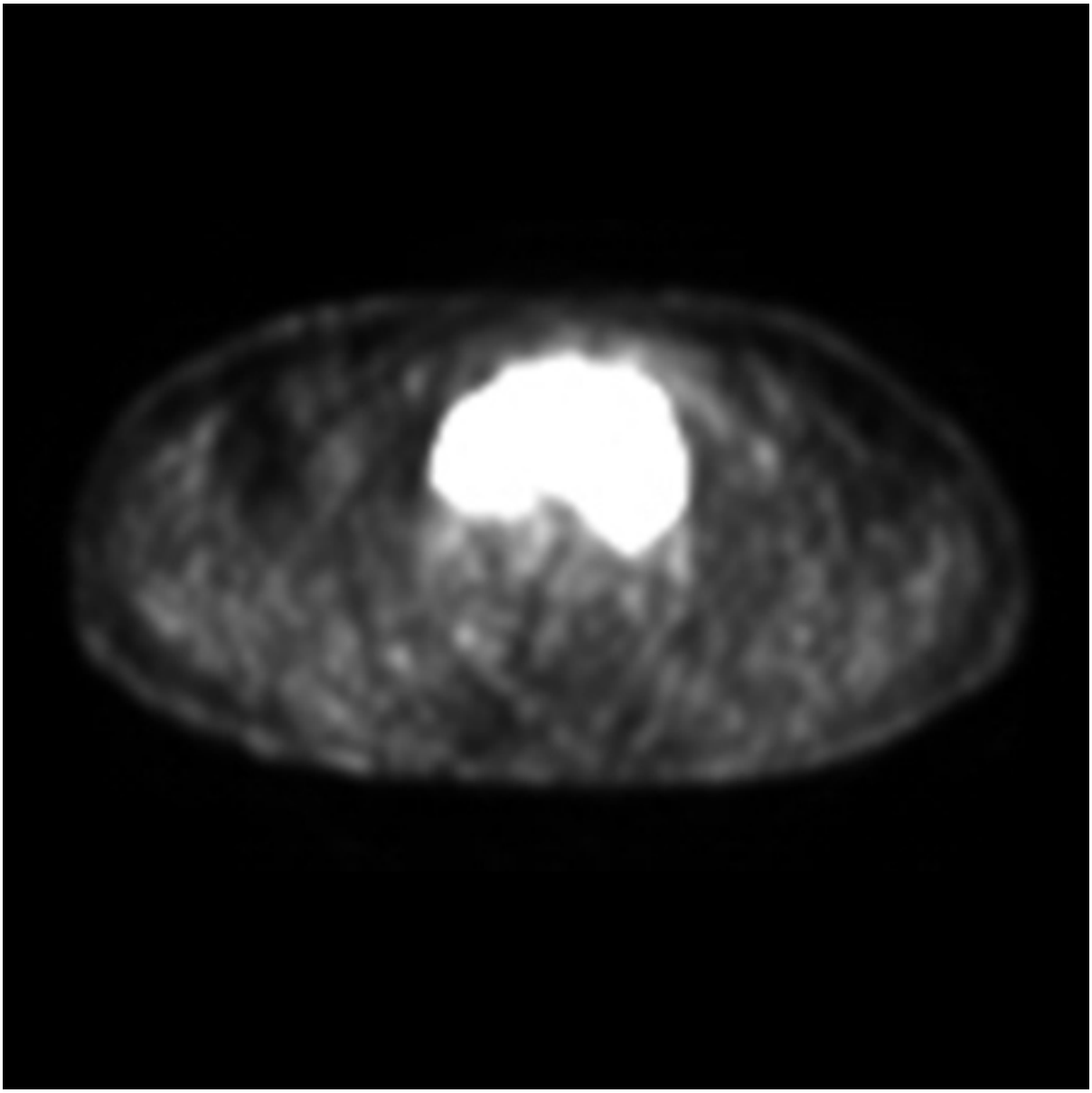

Figure 4: PET scan (axial) showing fluorodeoxyglucose (FDG)-avid mass in the anterior mediastinum

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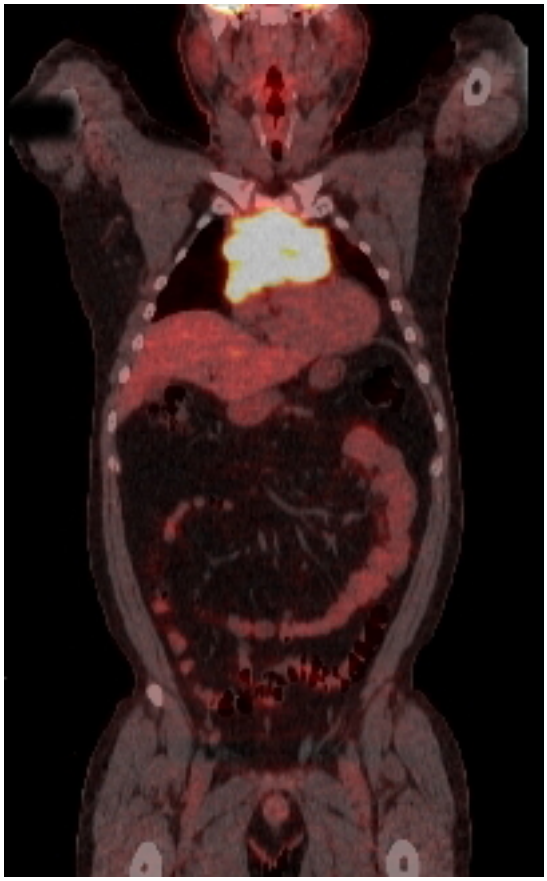

Figure 5: PET scan (coronal) showing fluorodeoxyglucose (FDG)-avid mass in the superior mediastinum

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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