incidence

- The crude incidence of Hodgkin lymphoma (HL) in the European Union is 2.2 and the mortality is 0.7 cases/100,000/year.

diagnosis

- Pathological diagnosis should be made according to the World Health Organization (WHO) classification from a sufficiently large surgical specimen or excisional lymph node biopsy to provide enough material for fresh frozen and formalin-fixed samples.
- Classical Hodgkin lymphoma (cHL) includes nodular sclerosing (NS), mixed cellularity (MC), lymphocyte-rich (LR) and lymphocyte-depleted (LD) subtypes and represents ~95% of all HL cases. It is distinguished from nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) which accounts for ~5% of all HL cases.

staging and risk assessment

- Chest X-ray and a computed tomography (CT) scan of neck, chest and abdomen are mandatory, as well as bone marrow aspiration and histology.
- Additional positron emission tomography (PET) scan may be considered according to the revised response criteria [1].
- Staging laparotomy is not recommended [II, A].
- Full blood count, erythrocyte sedimentation rate (ESR) and blood chemistry including glucose, alkaline phosphatase (AP), lactate dehydrogenase (LDH), liver enzymes, albumin and thyroid-stimulating hormone (TSH) are obligatory [II–III, A].

examinations before treatment

- To identify patients at increased risk for acute and/or long-term complications, cardiac and pulmonary function tests are mandatory prior to treatment.
- Consultation of an ear, nose and throat specialist should be considered, particularly in patients with involvement of the head and neck region.
- Since chemo- and radiotherapy can potentially cause permanent fertility damage, reproductive counseling should be offered to young patients of both genders prior to treatment.

treatment of cHL

limited stage patients

- Combined modality treatment consisting of a brief chemotherapy followed by radiotherapy was shown to result in superior tumor control compared with radiotherapy alone [I, A] [2, 3].
- Currently, two or three cycles of adriamycin/bleomycin/vinblastine/dacarbazine (ABVD) (Table 2) followed by involved-field radiotherapy (IF-RT) are considered standard of care for limited stage HL. Recently, the final analysis of a large multicenter trial in which patients were randomly assigned to either two or four cycles of ABVD followed by either 20 Gy or 30 Gy IF-RT was performed. As a result, patients of all treatment groups had similar freedom from treatment failure (FFTF) and overall survival (OS) rates so that the least toxic approach consisting of two cycles of ABVD followed by 20 Gy IF-RT appears to be sufficient in limited stage HL [I–II, A] [4].
The question of whether radiotherapy can be omitted in selected patients is a matter of debate and cannot be answered yet. Several trials addressing this issue are ongoing and evaluate whether treatment can be stratified on the basis of \[^{18}F\]fluorodeoxyglucose-positron emission tomography (FDG-PET). However, none of these trials has been finally analyzed to date.

Intermediate stage patients

- Intermediate stage HL is usually treated with combined modality approaches.
- Four cycles of ABVD followed by 30 Gy IF-RT are widely considered standard for intermediate stage HL [1, A] [5]. In patients up to 60 years who are eligible for a more intensive treatment, this standard is currently challenged by a protocol consisting of two cycles of bleomycin/etoposide/adriamycin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose (BEACOPPescalated) (Table 3) followed by two cycles of ABVD and 30 Gy IF-RT. At 4 years, FFTF with this new protocol was superior in comparison with four cycles of ABVD followed by 30 Gy IF-RT. However, long-term results including data on possible late toxicity (e.g. infertility) associated with the regimen are lacking [6].
- Similar to limited stage HL, the question of whether radiotherapy is dispensable in selected patients cannot be answered yet. Ongoing trials are evaluating whether treatment might be stratified on the basis of FDG-PET, but none of the trials has been finally analyzed.

Advanced stage patients

- Advanced stage HL is usually treated with chemotherapy alone. Radiotherapy is confined to patients having large residual masses after chemotherapy.
- Patients up to 60 years old are treated with either six (patients with complete remission after four cycles) or eight (patients with partial remission after four cycles) cycles of ABVD or eight cycles of BEACOPPescalated followed by a localized radiation with 30 Gy to residual lymphoma >1.5 cm [I–II, A] [7, 8]. However, recent analyses indicate that radiotherapy might be omitted in patients with residual lymphoma and a negative FDG-PET after completion of chemotherapy [9]. In comparison with ABVD, treatment with BEACOPPescalated leads to superior FFTF and OS rates but is associated with an increased toxicity requiring granulocyte colony-stimulating factor (G-CSF) support.
- Patients older than 60 years should be treated with 6–8 cycles (depending on the remission status after four cycles) of ABVD followed by a localized radiation with 30 Gy to residual lymphoma >1.5 cm. The BEACOPP regimen should not be used in elderly patients since increased toxicity was observed in this age group [I–II, A] [10].
- Ongoing trials are aimed at reducing treatment intensity without compromising efficacy. In most trials, interim FDG-PET is used to distinguish between those patients who can potentially be cured with reduced therapy and those who require standard or even more intensive treatment. This approach seems promising since some trials suggest that interim FDG-PET is a good predictor for treatment failure in patients with advanced HL treated with ABVD [11, 12]. However, treatment stratification on the basis of interim FDG-PET cannot be considered standard yet, and further evidence from randomized trials is necessary.

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### Table 1.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>EORTC/GELA</th>
<th>GHSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited stage patients</td>
<td>CS I–II without risk factors (supradiaphragmatic)</td>
<td>CS I–II without risk factors</td>
</tr>
<tr>
<td>Intermediate stage</td>
<td>CS I–II with ≥1 risk factors (supradiaphragmatic)</td>
<td>CS I, CS IIA with ≥1 risk factors; CS IIB with risk factors C/D, but not A/B</td>
</tr>
<tr>
<td>Advanced stage patients</td>
<td>CS III–IV</td>
<td>CS IIB with risk factors A/B, CS III/IV</td>
</tr>
<tr>
<td>Risk factors</td>
<td>(A) large mediastinal mass(^a)</td>
<td>(A) large mediastinal mass</td>
</tr>
<tr>
<td></td>
<td>(B) age ≥50 years</td>
<td>(B) extranodal disease</td>
</tr>
<tr>
<td></td>
<td>(C) elevated ESR(^b)</td>
<td>(C) elevated ESR</td>
</tr>
<tr>
<td></td>
<td>(D) ≥3 nodal areas</td>
<td>(D) ≥3 nodal areas</td>
</tr>
</tbody>
</table>

\(^a\)Large mediastinal mass: more than one-third of the maximum horizontal chest diameter.
\(^b\)Elevated erythrocyte sedimentation rate (ESR): >50 mm/h without B-symptoms, >30 mm/h with B-symptoms (B-symptoms: fever, night sweat, weight loss).

CS, clinical stage; EORTC, European Organisation for Research and Treatment of Cancer; GELA, Groupe d’Etude des Lymphomes de l’adulte; GHSG, German Hodgkin Study Group.

### Table 2. The ABVD regimen

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Dose [mg/m(^2)]</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin</td>
<td>25</td>
<td>i.v.</td>
<td>1 + 15</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>10</td>
<td>i.v.</td>
<td>1 + 15</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>6</td>
<td>i.v.</td>
<td>1 + 15</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>375</td>
<td>i.v.</td>
<td>1 + 15</td>
</tr>
</tbody>
</table>

Recycle: day 29.
For most patients with refractory or relapsed HL, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) can be regarded as the treatment of choice [I, A] [13]. Salvage regimens such as dexamethasone/high-dose ara-C/cisplatin (DHAP), ifosfamide/gemcitabine/vinorelbine/dexamethasone (IGEV) or ifosfamide/carboplatin/etoposide (ICE) are given to reduce the tumor burden and mobilize stem cells prior to high-dose chemotherapy and ASCT [II–III, A] [14–16]. A subset of low-risk patients relapsing after primary treatment with two cycles of chemotherapy followed by radiotherapy can be successfully salvaged with a second, more intensive conventional chemotherapy such as BEACOPPescalated [IV, B] [17]. In some patients with localized late relapse, salvage radiotherapy alone can be considered [IV, B] [18]. There is no standard treatment for patients relapsing after high-dose chemotherapy and ASCT. The decision how to treat these patients has to be made individually. Reduced-intensity conditioning allogeneic stem cell transplantation (RIC-allo) can be considered in young, chemosensitive patients in good general condition [II–III, A] [14–16]. A subset of low-risk patients relapsing after primary treatment with two cycles of chemotherapy followed by radiotherapy can be successfully salvaged with a second, more intensive conventional chemotherapy such as BEACOPPescalated [IV, B] [17]. In some patients with localized late relapse, salvage radiotherapy alone can be considered [IV, B] [18]. There is no standard treatment for patients relapsing after high-dose chemotherapy and ASCT. The decision how to treat these patients has to be made individually. Reduced-intensity conditioning allogeneic stem cell transplantation (RIC-allo) can be considered in young, chemosensitive patients in good general condition [II–III, B] [19, 20]. However, RIC-allo is not a standard approach in HL and should be conducted within clinical trials. In a palliative setting, acceptable remission rates, satisfying quality of life and prolonged survival can be achieved by gemcitabine-based chemotherapy and/or regional radiotherapy. Classical palliative chemotherapy approaches are increasingly challenged by novel agents such as small molecules, antibodies or immunotoxins [21]. These drugs are currently being evaluated in clinical trials either as single agents or in combination with conventional chemotherapy. Patients who might benefit from such novel treatment strategies should be referred to centers participating in studies.

**treatment of NLPHL**

**stage IA without risk factors**
- A dose of 30 Gy IF-RT alone is the standard treatment for stage IA NLPHL patients without risk factors [III, A] [22],

**other stages**
- NLPHL is treated identically to cHL in all stages except for stage IA without risk factors [23].

**relapsed NLPHL patients**
- Even more importantly than in cHL, a renewed biopsy should be obtained in patients with suspected relapse of NLPHL since transformation into aggressive non-Hodgkin lymphoma (NHL) must be excluded. As suggested by recent analyses, the transformation rate appears to be substantially higher than previously reported [III, B] [24].
- In contrast to most cHL cases, the malignant cells of NLPHL are characterized by a strong expression of CD20. Therefore, localized NLPHL relapses can be effectively treated with rituximab alone [III, B] [25].
- NLPHL patients with more advanced relapses require a more aggressive salvage therapy possibly combined with rituximab.

**response evaluation**
- Interim response evaluation in early and intermediate stages should be done after completion of chemotherapy/prior to radiotherapy and after four cycles in advanced stages, respectively. Final staging should be performed after completion of treatment. Physical examination, laboratory analyses and CT scans are mandatory. In studies with advanced stage and relapsed patients, respectively, interim FDG-PET was shown to identify a subset of poor-risk individuals [III, B–D] [26]. However, treatment stratification on the basis of interim PET should be reserved for clinical trials and cannot be considered standard. After completed treatment, positive PET scans may reveal persistent disease activity, but a false-positive PET scan has to be excluded.

**prognosis**
- With modern treatment strategies, 80–90% of patients achieve permanent remission and can be considered cured.

**follow-up**
- History, physical examination and laboratory analysis including full blood cell count, ESR and blood chemistry should be performed every 3 months for the first half year, every 6 months until the fourth year and once a year thereafter [V, D].
- Additional evaluation of the thyroid function (TSH) after irradiation of the neck at 1, 2 and at least 5 years is recommended [III, A]. Furthermore, testosterone and
estrogen levels should be monitored, particularly in younger patients who received intensive chemotherapy.

- CT scans and previously pathologiographic radiographic tests must be performed once to confirm the remission status. Thereafter, they are indicated if suspicious clinical symptoms occur.
- Patients should be asked for symptoms indicating the existence of long-term toxicity, particularly of heart and/or lung.
- Cancer screening (e.g. mammography in irradiated patients) should be conducted regularly due to the increased risk of hematological and solid secondary malignancies after HL treatment.

**note**

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered just standard clinical practice guidelines for the experts (and the ESMO faculty).

**literature**