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CLINICAL PRACTICE GUIDELINES

Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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Incidence and epidemiology

The crude incidence of Hodgkin lymphoma (HL) in the European Union is 2.3, the mortality 0.4 cases/100 000/year. Young adults aged 20–40 years are most often affected. Slightly more men than women are diagnosed with HL. Histologically, classical HL (cHL) accounting for ∼95% of all HL cases is distinguished from nodular lymphocyte-predominant HL (NLPHL) representing ∼5% of all HL cases.

Diagnosis

Pathological diagnosis should be made according to the World Health Organization (WHO) classification from an excisional lymph node biopsy or a sufficiently large surgical specimen to provide enough material for fresh frozen and formalin-fixed samples. In cHL, the presence of Hodgkin and Reed–Sternberg (HRS) cells is disease-defining, whereas the detection of lymphocyte predominant (LP) cells is required for the diagnosis of NLPHL. The immunophenotype of the malignant cells in cHL and NLPHL differs significantly. In contrast to HRS cells that stain consistently positive for CD30 and CD15, occasionally positive for CD20 and negative for CD45, LP cells are characterised by the expression of CD20 and CD45 but lack CD15 and CD30.

Staging and risk assessment

The diagnostic work-up is shown in Table 1. The medical history including the presence of B symptoms (fever, drenching night sweats, unexplained weight loss > 10% over 6 months) and other disease-related symptoms such as fatigue, pruritus and alcohol-induced pain as well as the results of a physical examination should be recorded [1].

Chest X-ray and a contrast-enhanced computed tomography (CT) scan of the neck, the chest and the abdomen are mandatory. In addition, a baseline whole-body positron emission tomography (PET) should be carried out according to the recommendations for staging and response assessment in lymphoma, if this diagnostic tool is available [1, 2].

Given the high sensitivity of PET–CT for bone marrow involvement, a bone marrow biopsy is no longer indicated in patients undergoing PET–CT evaluation [III, B] [1–3]. However, bone marrow biopsy must be carried out if PET–CT is not available.

Full blood cell count, erythrocyte sedimentation rate (ESR) testing and blood chemistry analysis including C-reactive protein (CRP), alkaline phosphatase (AP), lactate dehydrogenase (LDH), liver enzymes and albumin are obligatory. Screening for hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV) is compulsory [II–III, A].

Staging is carried out according to the Ann Arbor classification in consideration of defined clinical risk factors. After completion of staging, patients are allocated to one of three categories (limited, intermediate and advanced stages) [II–III, A]. Table 2 illustrates the European Organisation for Research and Treatment of Cancer (EORTC)/Lymphoma Study Association (LYSA) and the German Hodgkin Study Group (GHSG) definitions of limited, intermediate and advanced stages.

To identify patients at increased risk for acute and/or long-term complications and to generate baseline values for future

Table 1. Diagnostic work-up in HL

Diagnosis	Lymph node biopsy (or a biopsy from another organ with suspected affection)
Staging and risk stratification	Medical history and physical examination X-ray of the chest Contrast-enhanced CT scan of the neck, chest and abdomen PET Full blood cell count and blood chemistry, ESR HBV, HCV and HIV screening
Pretreatment examinations	ECG Echocardiography Pulmonary function test Reproductive counselling (in patients of reproductive age) Serum pregnancy test (in female patients of reproductive age) Consultation of an ear, nose and throat specialist including a fibreoptic nasolaryngoscopy (if PET–CT scan is not available at initial staging)

CT, computed tomography; ECG, electrocardiography; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; PET, positron emission tomography.

Table 2. Definition of HL risk groups according to the EORTC/LYSA and the GHSG

	EORTC/LYSA	GHSG
Treatment group		
Limited stages	CS I–II without risk factors (supradiaphragmatic)	CS I–II without risk factors
Intermediate stages	CS I–II with ≥ 1 risk factors (supradiaphragmatic)	CS I, CS IIA with ≥ 1 risk factors CS IIB with risk factors C and/or D, but not A/B
Advanced stages	CS III–IV	CS IIB with risk factors A and/or B CS III/IV
Risk factors		
	A: Large mediastinal mass[a] B: Age ≥ 50 years C: Elevated ESR[b] D: ≥ 4 nodal areas[c]	A: Large mediastinal mass[a] B: Extranodal disease C: Elevated ESR[b] D: ≥ 3 nodal areas[c]

[a]Large mediastinal mass: mediastinum-to-thorax ratio ≥ 0.35 (EORTC/LYSA); mediastinal mass larger than one-third of the maximum thoracic width (GHSG).
[b]Elevated ESR: >50 mm/h without B symptoms, >30 mm/h with B symptoms (B symptoms: fever, night sweat, unexplained weight loss >10% over 6 months).
[c]Nodal areas: involvement of ≥ 4 out of 5 supradiaphragmatic nodal areas (EORTC/LYSA); involvement of ≥ 3 out of 11 nodal areas on both sides of the diaphragm (GHSG).
CS, clinical stage; EORTC, European Organisation for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; LYSA, Lymphoma Study Association.

measurements, cardiac and pulmonary function tests should be carried out before the start of treatment.

As chemotherapy (ChT) and abdominal radiotherapy (RT) can cause permanent infertility, reproductive counselling and consideration of sperm banking, oocyte collection or ovarian tissue cryopreservation should be offered to patients of reproductive age before treatment.

Treatment of cHL

Limited-stage disease (Figure 1)

Combined-modality treatment consisting of a brief ChT followed by RT was shown to result in superior tumour control compared with RT alone [I, A] [4, 5].

Two or three cycles of doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) (Table 3) followed by conventionally fractionated RT represent the standard of care for limited-stage HL. A large multicentre trial in which patients were randomly assigned to either two or four cycles of ABVD followed by either 20 or 30 Gy involved-field RT (IFRT) showed similar freedom from treatment failure (FFTF) and overall survival (OS) rates for all treatment groups. Thus, the least toxic approach consisting of two cycles of ABVD followed by 20 Gy IFRT appears to be sufficient for limited-stage HL [I, A] [6]. Comparable disease control was also observed in a randomised trial comparing IFRT at doses of either 20 or 36 Gy in patients achieving a complete remission after six cycles of ChT with the outdated epirubicin/bleomycin/vinblastine/prednisone (EBVP) protocol [7]. However, the current RT guidelines of the International Lymphoma Radiation Oncology Group (ILROG) recommend involved-site RT (ISRT) after ChT in limited stages. Although ISRT has not been randomly compared with IFRT in a prospective study, there is accumulating evidence of excellent disease control with these smaller RT fields [8].

The question of whether RT can be omitted in selected patients with complete metabolic response at interim PET is a matter of debate. Several randomised trials addressing this issue have been conducted within the last years. The available data consistently demonstrate a progression-free survival (PFS) advantage for patients treated with combined-modality approaches despite a negative interim PET (defined as a Deauville score ≤ 2 within the RAPID and H10 studies). Thus, a patient group that can be safely treated with ChT alone could not yet be defined [I, A] [9, 10]. However, as patients treated with ChT alone still have a good overall prognosis, this approach may be offered to individual patients when the late risk of delivering RT is thought to outweigh the

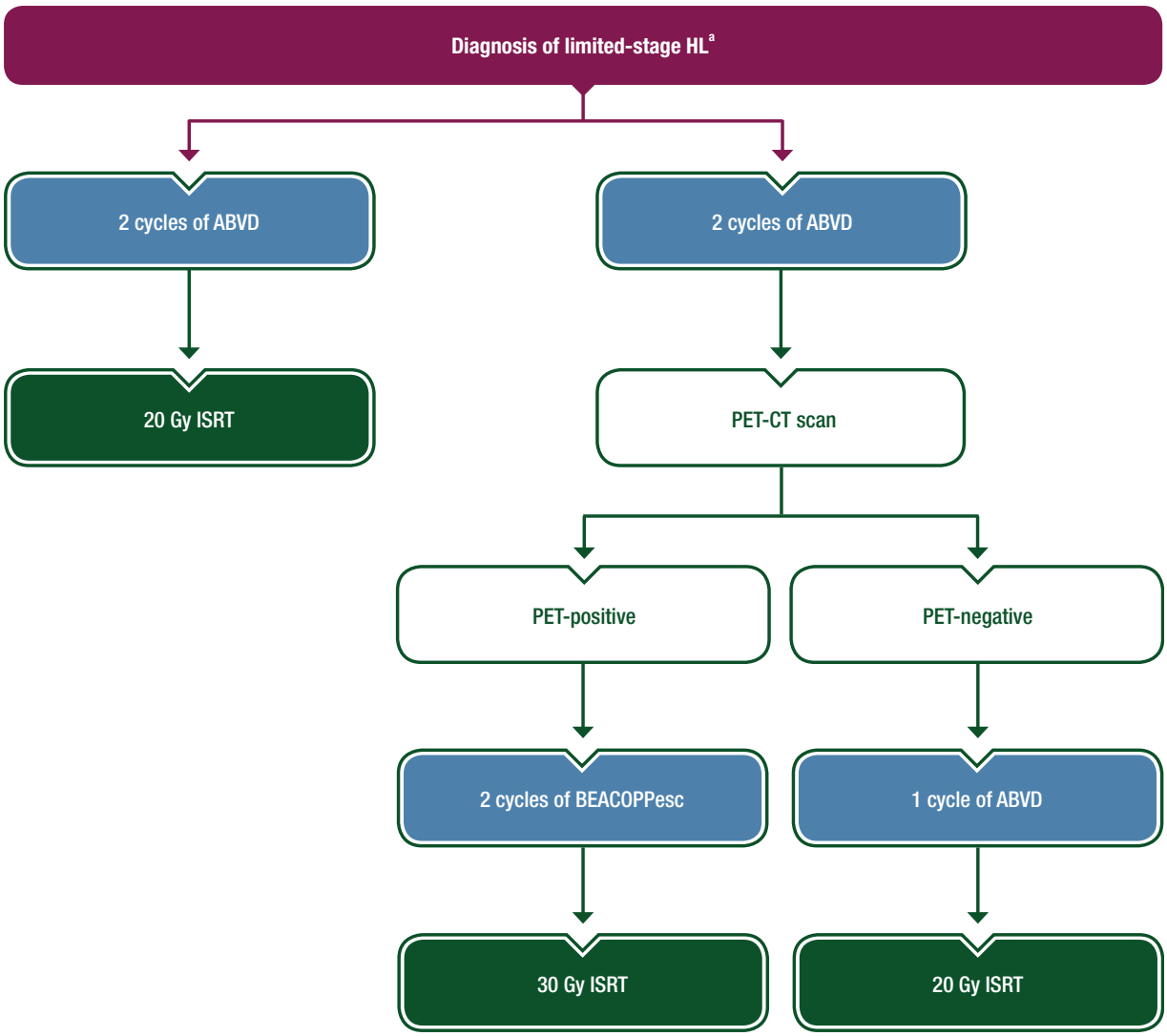

Figure 1. Therapeutic algorithm for newly diagnosed, limited-stage HL in patients ≤ 60 years.
[a]Except for stage IA NLPHL without risk factors (treated with ISRT alone).
The figure includes one approach not guided by interim PET based on the GHSG HD10 study (left) and one PET-guided approach based on the EORTC/LYSA/FIL H10 study (right).
ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; BEACOPPesc, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose; CT, computed tomography; EORTC, European Organisation for Research and Treatment of Cancer; FIL, Fondazione Italiana Linfomi; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; ISRT, involved-site radiotherapy; LYSA, Lymphoma Study Association; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PET, positron emission tomography.

Table 3. The ABVD regimen

	Dose (mg/m^2)	Administration	Days
Doxorubicin	25	i.v.	1 + 15
Bleomycin	10	i.v.	1 + 15
Vinblastine	6	i.v.	1 + 15
Dacarbazine	375	i.v.	1 + 15

Recycle: day 29.
ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; i.v., intravenous.

short-term benefit of improved disease control. Early treatment intensification appears to improve the prognosis of patients with a positive interim PET (defined as a Deauville score ≥ 3 within the H10 study). A large randomised study including patients with limited- and intermediate-stage HL revealed a significantly reduced relapse rate in those patients with a positive interim PET after two cycles of ABVD who completed ChT with two cycles of bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose (BEACOPPescalated) (Table 4) instead of one (limited stages) or two (intermediate stages) additional cycles of ABVD before involved-node RT (INRT) [10]. However, the study was not powered to analyse patients with limited- and intermediate-stage disease separately. Patients with a

Table 4. The BEACOPPescalated regimen

	Dose (mg/m^2)	Administration	Days
Bleomycin	10	i.v.	8
Etoposide	200	i.v.	1–3
Doxorubicin	35	i.v.	1
Cyclophosphamide	1250	i.v.	1
Vincristine	1.4[a]	i.v.	8
Procarbazine	100	p.o.	1–7
Prednisone	40	p.o.	1–14
G-CSF		s.c.	From day 8

[a]The maximum absolute dose is 2 mg of vincristine.
Recycle: day 22.
BEACOPPescalated, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose; G-CSF, granulocyte colony-stimulating factor; i.v., intravenous; p.o., oral; s.c., subcutaneous.

positive interim PET after two cycles of ABVD should be treated with two cycles of BEACOPPescalated before ISRT [I, A].

Intermediate-stage disease (Figure 2)

Intermediate-stage HL is usually treated with combined-modality approaches.

Four cycles of ABVD followed by conventionally fractionated RT at 30 Gy are widely considered standard of care for intermediate-stage HL [I, A] [5]. In patients $\leq$ 60 years who are eligible for a more intensive treatment, this standard is challenged by a protocol consisting of two cycles of BEACOPPescalated followed by two cycles of ABVD and RT at 30 Gy. After a median follow-up of 43 months, FFTF with this protocol was superior in comparison with four cycles of ABVD followed by RT. An advantage in OS could not be shown [I, B–C] [11].

Although no results of a randomised study comparing both RT fields are available to date, the ILROG guidelines recommend ISRT instead of IFRT after ChT in intermediate stages [8].

The question of whether RT is dispensable in intermediate-stage patients with complete metabolic response at interim PET is unanswered. A large randomised study failed to demonstrate non-inferiority of ChT alone as compared with combined-modality treatment in patients with a negative interim PET (defined as a Deauville score $\leq$ 2 within the H10 study) [I, A] [10]. However, as patients treated with ChT alone still have a good overall prognosis, this approach may be offered to individual patients when the late risk of delivering RT is thought to outweigh the short-term benefit of improved disease control. Early treatment intensification appears to improve the prognosis of patients with a positive interim PET (defined as a Deauville score $\geq$ 3 within the H10 study). A randomised study including patients with limited- and intermediate-stage HL revealed a significantly reduced relapse rate in patients with a positive interim PET after two cycles of ABVD who completed ChT with two cycles of BEACOPPescalated instead of one (limited stages) or two (intermediate stages) additional cycles of ABVD before INRT [10]. Patients with a positive interim PET after two cycles of ABVD should be treated with two cycles of BEACOPPescalated before ISRT [I, A].

Due to the relevant bleomycin-induced toxicity observed in older individuals receiving more than two cycles of ABVD, bleomycin should be discontinued after the second ChT cycle in patients > 60 years [III, B–C] [12].

Advanced-stage disease (Figure 3)

Advanced-stage HL is usually treated with ChT alone. Additional RT is confined to patients with residual disease after ChT.

Patients $\leq$ 60 years are treated with either ABVD (six cycles) or BEACOPPescalated (four to six cycles), optionally followed by localised RT [I, A] [13, 14]. When ABVD is applied, the omission of bleomycin, i.e. the use of doxorubicin/vinblastine/dacarbazine (AVD) in cycles 3–6 in the case of a negative interim PET (defined as a Deauville score $\leq$ 3 within the RATHL study) after two cycles of ChT should be considered, especially in elderly patients and those at an increased risk for lung toxicity, although a randomised multicentre study was not able to exclude a PFS difference of > 5% at 3 years [I, A] [15]. The question of whether consolidating RT can be safely omitted in patients who have a negative PET after two cycles of ABVD or at the end of ChT has also not yet been definitively answered. There is no randomised study evaluating the role of early treatment intensification in advanced-stage patients who have a positive interim PET after two cycles of ABVD. However, several non-randomised studies have suggested that patients with advanced HL who have a positive interim PET (defined as a Deauville score $\geq$ 4 within the RATHL and SWOG S0816 studies and $\geq$ 3 within the HD0801 study) have a better prognosis after switching from ABVD to intensified protocols than after continued treatment with ABVD [II, B] [15–17]. A recent randomised study demonstrated an improved modified 2-year PFS after six cycles of brentuximab vedotin in combination with AVD (A-AVD) as compared with standard ABVD. However, A-AVD was associated with an increased rate of neuropathy and haematological toxicity. Thus, longer follow-up is required to draw final conclusions in terms of the A-AVD regimen [I–II, C] [18].

In patients receiving BEACOPPescalated, treatment can be safely reduced to a total of only four cycles in the case of a negative interim PET (defined as a Deauville score $\leq$ 2 within the HD18 study) compared with a total of six cycles for PET-positive patients [I, A] [19]. In addition, RT can be restricted to the patients with PET-positive (defined as a Deauville score $\geq$ 3 within the HD15 study and most of the HD18 study and a Deauville score $\geq$ 4 within a part of the HD18 study) residual lymphoma $\geq$ 2.5 cm after four and six cycles of BEACOPPescalated, respectively [I, A] [14, 19]. Several trials randomly comparing ABVD and BEACOPPescalated have shown a superior tumour control and a non-significant trend towards a better OS with BEACOPPescalated [20, 21]. A network meta-analysis including 9993 patients also revealed a significantly better OS with BEACOPPescalated when compared with ABVD. The survival benefit was 10% at 5 years [I, A] [22]. However, given the relevant acute toxicity of BEACOPPescalated, appropriate surveillance and supportive care must be available when this protocol is used. In patients > 60 years, the BEACOPP regimen should not be given, as an increased rate of treatment-related mortality has

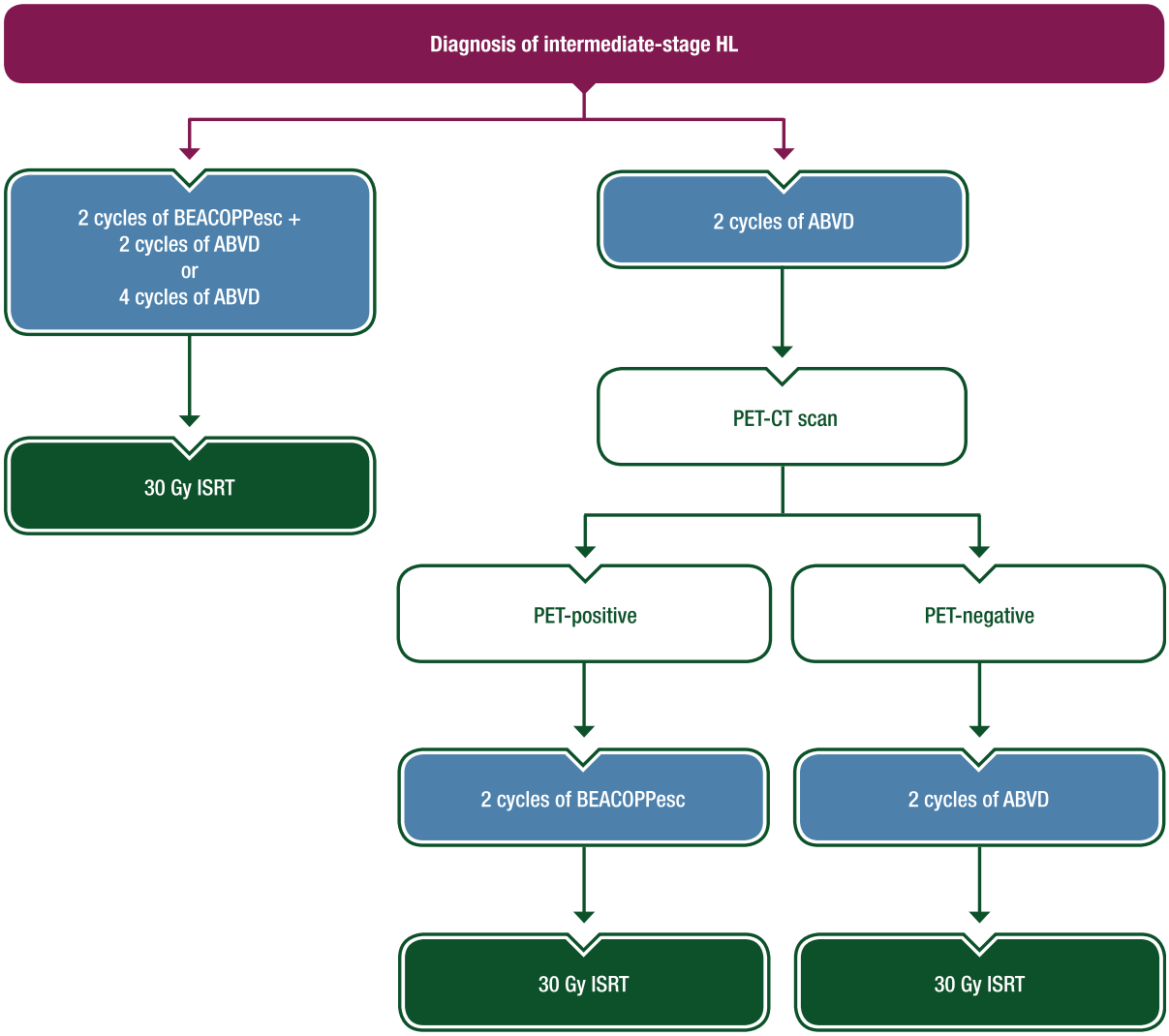

Figure 2. Therapeutic algorithm for newly diagnosed, intermediate-stage HL in patients ≤ 60 years.
The figure includes one approach not guided by interim PET, based on the GHSG HD14 study (left) and one PET-guided approach based on the EORTC/LYSA/FIL H10 study (right).
ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; BEACOPPesc, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose; CT, computed tomography; EORTC, European Organisation for Research and Treatment of Cancer; FIL, Fondazione Italiana Linfomi; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; ISRT, involved-site radiotherapy; LYSA, Lymphoma Study Association; PET, positron emission tomography.

been observed in this age group [II, A] [23]. Thus, ABVD-based ChT represents the standard of care for older HL patients who are fit enough for multi-agent ChT. However, due to the relevant bleomycin-induced toxicity observed in older individuals receiving more than two cycles of ABVD, bleomycin should be discontinued after the second ChT cycle in this patient group [III, B–C] [12].

Relapsed disease

For most patients with refractory or relapsed HL, the treatment of choice consists of high-dose ChT (HDCT) followed by autologous stem cell transplantation (ASCT) [I, A] [24]. High-risk patients may benefit from tandem ASCT [III, B] [25]. Consolidating treatment with the antibody-drug conjugate brentuximab vedotin following HDCT and ASCT was shown to improve the tumour control in patients presenting with at least one of the following risk factors: primary disease progression, early disease recurrence < 12 months after the end of first-line treatment and extranodal disease at the time of relapse [II, B] [26].

Salvage regimens such as dexamethasone/high-dose cytarabine/cisplatin (DHAP), ifosfamide/gemcitabine/vinorelbine (IGEV) or ifosfamide/carboplatin/etoposide (ICE) are given to reduce the tumour burden and mobilise stem cells before HDCT and ASCT [II–III, A] [27–29]. In some patients, single-agent brentuximab vedotin results in a negative PET and may therefore be sufficient as salvage therapy before HDCT and ASCT [III, B] [30]. Achieving a negative PET should be the goal of salvage therapy, irrespective of the applied protocol, because a complete metabolic response before HDCT and ASCT was shown to be associated with an improved clinical outcome [III, B] [31]. The role of RT before HDCT and ASCT is not defined. However, its use may be discussed in patients with single PET-positive lymph nodes after salvage therapy [IV, C] [32].

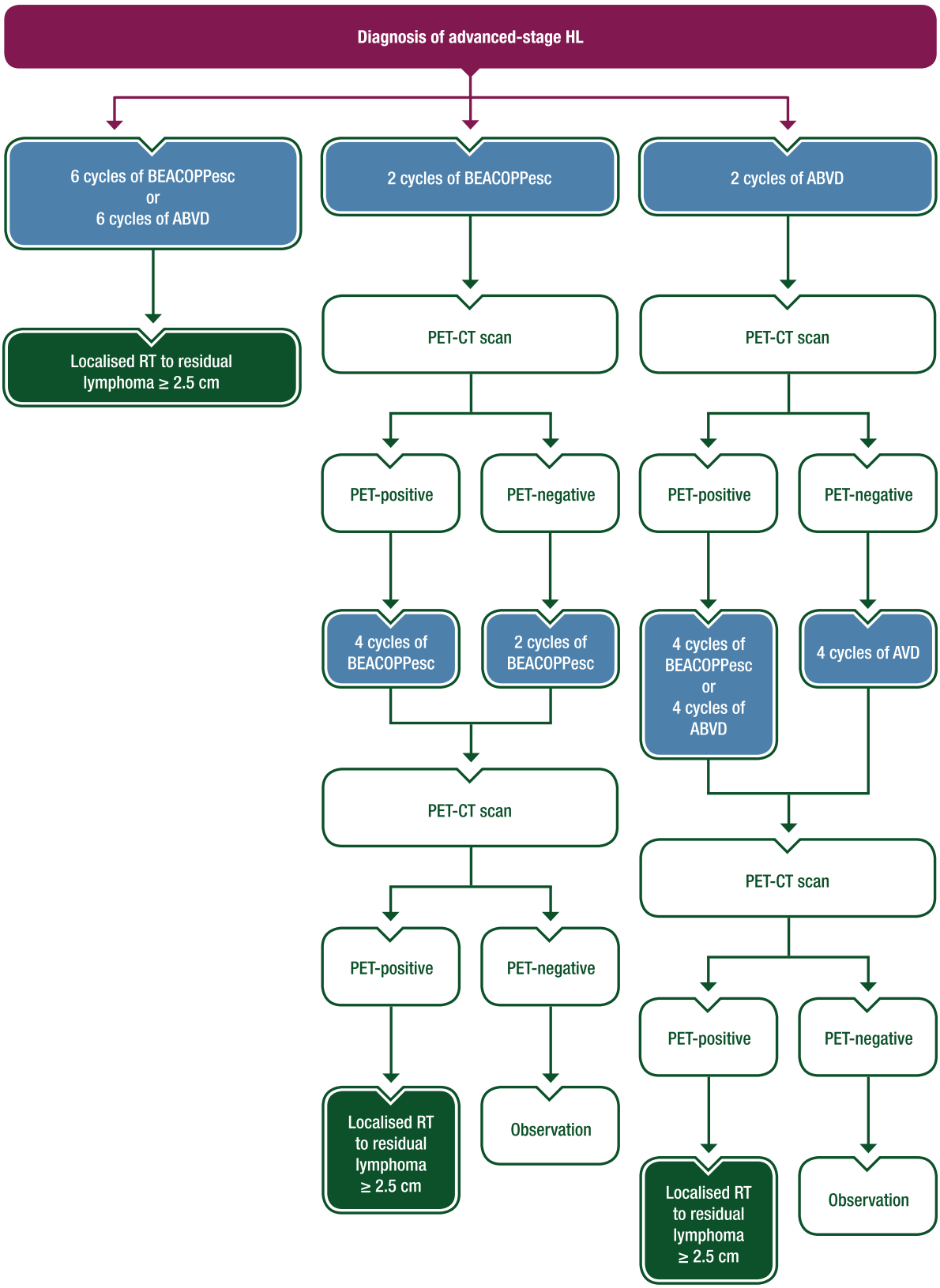

Figure 3. Therapeutic algorithm for newly diagnosed, advanced-stage HL in patients ≤ 60 years.
The figure includes one approach not guided by interim PET (left) and two PET-guided approaches based on the GHSG HD18 study (middle) and the RATHL study (right).
ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; AVD, doxorubicin/vinblastine/dacarbazine; BEACOPPesc, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose; CT, computed tomography; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; PET, positron emission tomography; RT, radiotherapy.

The use of brentuximab vedotin represents an option in patients failing ASCT. After a pivotal phase II study including 102 cHL patients with relapse after HDCT and ASCT had demonstrated an overall response rate (ORR) of 75% with single-agent brentuximab vedotin, the drug was approved for the treatment of such patients [III, B]. A recent follow-up analysis of the study revealed a 5-year OS estimate of 41% for the patients included in the study. However, most patients received additional treatment following brentuximab vedotin. The proportion of patients who achieved long-term remission exceeding 5 years without further treatment was 9% [III, B] [33, 34].

Antibodies targeting the programmed cell death protein 1 (PD-1) represent another novel treatment option for patients with multiple relapses. Early-phase studies evaluating anti-PD-1 antibodies have shown high response rates and durable remissions in a relevant proportion of patients with disease recurrence after HDCT followed by ASCT and brentuximab vedotin therapy [III, B] [35, 36]. On the basis of these results, the anti-PD-1 antibodies nivolumab and pembrolizumab were approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of such patients.

Allogeneic stem cell transplantation represents a potentially curative treatment option for patients failing HDCT and ASCT. This approach should be considered and discussed in young, chemosensitive patients in good general condition after careful evaluation of the risk–benefit ratio [III, C] [37, 38].

In patients with multiple relapses who have no other treatment options, acceptable remission rates, satisfying quality of life and prolonged survival can be achieved with gemcitabine-based palliative ChT and/or regional RT.

In general, patients with multiple relapses should be enrolled in clinical trials evaluating novel agents whenever possible.

Treatment of NLPHL

Stage IA without risk factors

ISRT at 30 Gy alone is the standard treatment for stage IA NLPHL patients presenting without clinical risk factors [III, A] [39]. Although data from prospective studies are only available for IFRT, the current ILROG guidelines recommend the use of ISRT [8]. Of note, the ISRT fields irradiated in this RT alone approach are larger than the ISRT fields in combined-modality approaches to include potential microscopic regional disease.

Other stages

Usually, NLPHL is treated identically to cHL in all patients except for those with stage IA disease presenting without clinical risk factors [III, B] [40]. However, as the malignant LP cells of NLPHL consistently express CD20, the addition of an anti-CD20 antibody may improve treatment efficacy, but prospective data addressing this issue are pending. The largest retrospective study evaluating the combination of an anti-CD20 antibody and conventional ChT revealed promising results with the rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) protocol [V, B] [41].

Relapsed NLPHL

Even more importantly than in cHL, a renewed biopsy should be obtained in patients with suspected NLPHL relapse before salvage therapy is initiated, because transformation into aggressive non-Hodgkin lymphoma (NHL) must be excluded. According to newer analyses, transformation rates appear to be higher than previously reported [IV, A] [42].

Localised NLPHL relapses can be effectively treated with anti-CD20 antibodies such as rituximab or ofatumumab given as single agent [III, B] [43, 44].

Patients with more disseminated disease at relapse and additional poor-risk features may require more aggressive salvage ChT, possibly combined with an anti-CD20 antibody [III, B] [45]. However, salvage therapy should be chosen individually and be based on factors such as time to relapse, extent of disease at relapse and prior treatment [III, B] [46].

Given the lack of CD30 on the malignant LP cells in NLPHL, brentuximab vedotin does not represent a treatment option in this entity.

Response evaluation

If no PET-guided treatment is intended, interim response evaluation by contrast-enhanced CT scan should be carried out before RT in limited and intermediate stages and after four cycles of ChT as well as before RT in advanced stages. If treatment is guided by interim PET, patients who receive ABVD should undergo an interim PET–CT scan after two cycles of ChT, irrespective of the stage at diagnosis. Patients with advanced HL receiving ABVD should also have a PET–CT after the end of ChT. In patients with advanced HL who are treated with BEACOPPescalated, interim PET–CT scans should be carried out after two cycles of ChT and after the end of ChT.

Final staging should be carried out after the completion of treatment. Physical examination, laboratory analyses and contrast-enhanced CT are mandatory. If available, PET–CT should replace CT at final staging according to the guidelines for staging and response assessment in lymphoma [1, 2].

Prognosis

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

Follow-up, long-term implications and survivorship

History, physical examination and laboratory analysis including full blood cell count, ESR testing and blood chemistry should be carried out every 3 months for the first half year, every 6 months until the fourth year and once a year thereafter [V, B].

CT scans and previously pathological radiographic tests must be carried out once to confirm the remission status. Thereafter, the patients should be followed clinically. Surveillance scans are not indicated unless clinical symptoms occur [1, 2].

The thyroid function (thyroid-stimulating hormone) should be evaluated once a year if the neck had been irradiated. Furthermore,

Table 5. Summary of recommendations

Diagnosis

- The presence of HRS cells is disease-defining in cHL; the detection of LP cells is required for the diagnosis of NLPHL

Staging and risk assessment

- Chest X-ray and a contrast-enhanced CT scan of neck, chest and abdomen are mandatory
- A baseline PET should be conducted if this diagnostic tool is available
- A bone marrow biopsy is not indicated in patients undergoing PET–CT evaluation [III, B] but must be carried out if PET–CT is not available
- Full blood cell count, ESR testing and blood chemistry analysis are obligatory. Screening for HBV, HCV and HIV is compulsory [II–III, A]
- Staging is carried out according to the Ann Arbor classification and patients are allocated to one of three categories (limited, intermediate and advanced stages) [II–III, A]
- After staging examinations are completed, HL patients are allocated to distinct risk groups depending on their clinical stage and the presence of clinical risk factors
- Cardiac and pulmonary function tests should be carried out before the start of treatment
- Reproductive counselling and consideration of sperm banking, oocyte collection or ovarian tissue cryopreservation should be offered to patients of reproductive age before treatment

Treatment of HL

- HL patients should be treated within clinical trial protocols whenever possible

Treatment of cHL

- First-line treatment of cHL patients usually consists of combined-modality approaches (limited-stage and intermediate-stage disease) or ChT alone (advanced-stage disease). Intensity of treatment depends on the patient's risk profile at diagnosis and the result of an interim PET-CT evaluation (if PET is available)

Limited-stage disease

- Combined-modality treatment consisting of a brief ChT followed by RT was shown to result in superior tumour control compared with RT alone [I, A]
- Two or three cycles of ABVD followed by conventionally fractionated RT represent the standard of care for limited-stage HL
- ISRT is recommended instead of IFRT after ChT in limited stages

Intermediate-stage disease

- Four cycles of ABVD followed by conventionally fractionated RT at 30 Gy are widely considered standard of care for intermediate-stage HL [I, A]. Two cycles of BEACOPPesc followed by two cycles of ABVD and RT at 30 Gy can be proposed to the patients $\leq$ 60 years who are eligible for a more intensive treatment
- ISRT is recommended instead of IFRT after ChT in intermediate stages

Limited- and intermediate-stage disease

- ChT alone may be offered to the individual patients when the late risk of delivering RT is thought to outweigh the short-term benefit of improved disease control
- Patients with a positive interim PET after two cycles of ABVD should be treated with two cycles of BEACOPPesc before ISRT [I, A]
- Bleomycin should not be given for more than two cycles in patients $>$ 60 years [III, B–C]

Advanced-stage disease

- Advanced-stage HL is usually treated with ChT alone. Additional RT is confined to the patients with residual disease after ChT
- Patients $\leq$ 60 years are treated with either ABVD (six cycles) or BEACOPPesc (four to six cycles), optionally followed by localised RT [I, A]
- After two cycles of ABVD, the omission of bleomycin in cycles 3–6 in the case of a negative interim PET should be considered, especially in elderly patients and those at an increased risk for lung toxicity [I, A]
- Patients with advanced HL who have a positive interim PET after two cycles of ABVD could switch from ABVD to BEACOPPesc [II, B]
- After two cycles of BEACOPPesc, PET-negative patients can safely receive only two more cycles compared with PET-positive patients who need four more cycles [I, A]
- RT can be restricted to the patients with PET-positive residual lymphoma $\geq$ 2.5 cm after four or six cycles of BEACOPPesc [I, A]
- The BEACOPP regimen should not be given to the patients $>$ 60 years [II, A]
- ABVD-based ChT represents the standard of care for older HL patients who are fit enough for multi-agent ChT. Bleomycin should be discontinued after the second ChT cycle in this patient group [III, B–C]

Relapsed disease

- For most patients with refractory or relapsed HL, the treatment of choice consists of HDCT followed by ASCT [I, A]
- High-risk patients may benefit from tandem ASCT [III, B]
- Consolidating treatment with brentuximab vedotin following HDCT and ASCT is recommended in patients presenting with defined poor-risk factors [II, B]
- DHAP, IGEV or ICE can be given before HDCT and ASCT [II–III, A]
- In some patients, single-agent brentuximab vedotin may be sufficient as salvage therapy before HDCT and ASCT [III, B]
- Achieving a negative PET should be the goal of salvage therapy irrespective of the applied protocol [III, B]
- RT before HDCT and ASCT may be discussed in patients with single PET-positive lymph nodes after salvage therapy [IV, C]

Continued

Table 5. Continued

- Single-agent brentuximab vedotin represents an option in patients failing ASCT [III, B]
- Nivolumab and pembrolizumab are approved for the treatment of patients with disease recurrence after HDCT followed by ASCT and brentuximab vedotin therapy [III, B]
- Allogeneic SCT represents a potentially curative treatment option for patients failing HDCT followed by ASCT. This approach should be considered and discussed in young, chemosensitive patients in good general condition after careful evaluation of the risk–benefit ratio [III, C]
- Gemcitabine-based palliative ChT and/or regional RT are recommended in patients with multiple relapses who have no other treatment options

Treatment of NLPHL

- NLPHL is treated identically to cHL in all patients except for those with stage IA disease presenting without clinical risk factors [III, B]
- 30 Gy ISRT alone is the standard treatment of stage IA NLPHL patients presenting without clinical risk factors [III, A]
- A renewed biopsy should be obtained in patients with suspected NLPHL relapse before salvage therapy is initiated
- Localised NLPHL relapses can be effectively treated with anti-CD20 antibodies such as rituximab or ofatumumab given as single agent [III, B]
- Patients with more disseminated disease at relapse and additional poor-risk features may require more aggressive salvage ChT, possibly combined with an anti-CD20 antibody [III, B]
- Salvage therapy should be chosen individually and be based on factors such as time to relapse, extent of disease at relapse and prior treatment [III, B]

Response evaluation

- All patients should undergo interim staging to exclude disease progression during treatment and to stratify treatment if PET–CT is available
- Final staging should be carried out after the completion of treatment. Physical examination, laboratory analyses and contrast-enhanced CT are mandatory
- PET-CT should be conducted if this diagnostic tool is available

Follow-up, long-term implications and survivorship

- Follow-up should be conducted regularly to detect disease recurrence and therapy-related late effects
- History, physical examination and laboratory analysis should be carried out every 3 months for the first half year, every 6 months until the fourth year and once a year thereafter [V, B]
- The thyroid function should be evaluated once a year if the neck had been irradiated
- Testosterone and oestrogen levels should be monitored, particularly in younger patients who had intensive ChT [V, B]
- Cancer screening should be conducted regularly after HL treatment
- Female patients who were $\leq$ 40 years at the time of chest or axillary irradiation should have a mammography once a year starting 8–10 years after RT. Those who were $\leq$ 30 years should have a breast MRI in addition to mammography [V, A]

ABVD, doxorubicin/bleomycin/vinblastine/dacarbazine; ASCT, autologous stem cell transplantation; BEACOPPesc, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose; cHL, classical Hodgkin lymphoma; ChT, chemotherapy; CT, computed tomography; DHAP, dexamethasone/high-dose cytarabine/cisplatin; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HDCT, high-dose chemotherapy; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; HRS, Hodgkin and Reed–Sternberg; ICE, ifosfamide/carboplatin/etoposide; IFRT, involved-field radiotherapy; ISRT, involved-site radiotherapy; IGEV, ifosfamide/gemcitabine/vinorelbine; LP, lymphocyte predominant; MRI, magnetic resonance imaging; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PET, positron emission tomography; RT, radiotherapy; SCT, stem cell transplantation.

testosterone and oestrogen levels should be monitored, particularly in younger patients who had intensive ChT [V, B] [47].

Patients should be asked about symptoms indicating the existence of long-term toxicity, especially affecting the heart and lungs.

Cancer screening should be conducted regularly due to the persistently increased risk for the development of haematological and solid second malignancies after HL treatment [48, 49]. Particular attention should be paid to breast cancer screening in female patients who had received chest or axillary irradiation before the age of 40 years. These patients should have a mammography once a year starting 8–10 years after RT. Individuals who were $\leq$ 30 years at the time of chest irradiation should have a breast magnetic resonance imaging (MRI) in addition to mammography [V, A] [47].

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is provided in Table 5. Levels of evidence and grades of recommendation have been applied using the system shown in Table 6. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

Disclosure

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Table 6. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [50].

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References

1. 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; 32: 3059–3068.
2. 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; 32: 3048–3058.
3. El-Galaly TC, d'Amore F, Mylam KJ et al. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naive patients with Hodgkin lymphoma. J Clin Oncol 2012; 30: 4508–4514.
4. Engert A, Franklin J, Eich HT et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. J Clin Oncol 2007; 25: 3495–3502.
5. Fermé C, Eghbali H, Meerwaldt JH et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 2007; 357: 1916–1927.
6. Engert A, Plütschow A, Eich HT et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 2010; 363: 640–652.
7. Thomas J, Fermé C, Noordijk EM et al. Comparison of 36 Gy, 20 Gy or no radiotherapy after six cycles of EBVP chemotherapy and complete remission in early stage Hodgkin lymphoma without risk factors: results of the EORTC–GELA H9-F Intergroup Randomized Trial. Int J Radiat Oncol Biol Phys 2017; 100:1133–1145.
8. 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; 89: 854–862.
9. 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; 372: 1598–1607.
10. 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; 35: 1786–1794.
11. von Tresckow B, Plütschow A, Fuchs M et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. J Clin Oncol 2012; 30: 907–913.
12. Böll B, Goergen H, Behringer K et al. Bleomycin in older early-stage favorable Hodgkin lymphoma patients: analysis of the German Hodgkin Study Group (GHSG) HD10 and HD13 trials. Blood 2016; 127: 2189–2192.
13. Canellos GP, Niedzwiecki D, Johnson JL. Long-term follow-up of survival in Hodgkin's lymphoma. N Engl J Med 2009; 361: 2390–2391.
14. 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; 379: 1791–1799.
15. 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; 374: 2419–2429.
16. Press OW, Li H, Schöder H et al. US Intergroup trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816. J Clin Oncol 2016; 34: 2020–2027.
17. Zinzani PL, Broccoli A, Gioia DM et al. Interim positron emission tomography response-adapted therapy in advanced-stage Hodgkin lymphoma: final results of the phase II part of the HD0801 study. J Clin Oncol 2016; 34: 1376–1385.
18. Connors JM, Jurczak W, Straus DJ et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med 2018; 378: 331–344.
19. 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; 390: 2790–2802.
20. 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.
21. Mounier N, Brice P, Bologna S et al. ABVD (8 cycles) versus BEACOPP (4 escalated cycles $\geq$ 4 baseline): final results in stage III-IV low-risk Hodgkin lymphoma (IPS 0-2) of the LYSA H34 randomized trial. Ann Oncol 2014; 25: 1622–1628.

22. Skoetz N, Trelle S, Rancea M et al. Effect of initial treatment strategy on survival of patients with advanced-stage Hodgkin's lymphoma: a systematic review and network meta-analysis. Lancet Oncol 2013; 14: 943–952.
23. 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; 16: 124–131.
24. Schmitz N, Pfistner B, Sextro M et al. 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; 359: 2065–2071.
25. Sibon D, Morschhauser F, Resche-Rigon M et al. Single or tandem autologous stem-cell transplantation for first-relapsed or refractory Hodgkin lymphoma: 10-year follow-up of the prospective H96 trial by the LYSA/SFGM-TC study group. Haematologica 2016; 101: 474–481.
26. 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.
27. 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; 13: 1628–1635.
28. 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; 92: 35–41.
29. 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; 97: 616–623.
30. Moskowitz AJ, Schöder H, Yahalom J et al. PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study. Lancet Oncol 2015; 16: 284–292.
31. 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; 119: 1665–1670.
32. Rimner A, Lovie S, Hsu M et al. Accelerated total lymphoid irradiation-containing salvage regimen for patients with refractory and relapsed Hodgkin lymphoma: 20 years of experience. Int J Radiat Oncol Biol Phys 2017; 97: 1066–1076.
33. Younes A, Gopal AK, Smith SE et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 2012; 30: 2183–2189.
34. Chen R, Gopal AK, Smith SE et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood 2016; 128: 1562–1566.
35. Younes A, Santoro A, Shipp M et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol 2016; 17: 1283–1294.
36. Chen R, Zinzani PL, Fanale MA et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol 2017; 35: 2125–2132.
37. Sureda A, Canals C, Arranz R et al. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study—a prospective clinical trial by the Grupo Espanol de Linfomas/Trasplante de Medula Osea (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Haematologica 2012; 97: 310–317.
38. Genadieva-Stavrik S, Boumendil A, Dreger P et al. Myeloablative versus reduced intensity allogeneic stem cell transplantation for relapsed/refractory Hodgkin's lymphoma in recent years: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Ann Oncol 2016; 27: 2251–2257.
39. 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; 33: 2857–2862.
40. Nogová L, Reineke T, Brillant C et al. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. J Clin Oncol 2008; 26: 434–439.
41. Fanale MA, Cheah CY, Rich A et al. Encouraging activity for R-CHOP in advanced stage nodular lymphocyte-predominant Hodgkin lymphoma. Blood 2017; 130: 472–477.
42. Al-Mansour M, Connors JM, Gascoyne RD et al. Transformation to aggressive lymphoma in nodular lymphocyte-predominant Hodgkin's lymphoma. J Clin Oncol 2010; 28: 793–799.
43. 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; 111: 109–111.
44. Eichenauer DA, Goergen H, Plütschow A et al. Ofatumumab in relapsed nodular lymphocyte-predominant Hodgkin lymphoma: results of a phase II study from the German Hodgkin study group. Leukemia 2016; 30: 1425–1427.
45. Akhtar S, Montoto S, Boumendil A et al. High dose chemotherapy and autologous stem cell transplantation in nodular lymphocyte-predominant Hodgkin lymphoma: a retrospective study by the European Society for Blood and Marrow Transplantation-Lymphoma Working Party. Am J Hematol 2018; 93: 40–46.
46. Eichenauer DA, Pluetschow A, Schroeder L et al. Relapsed nodular lymphocyte-predominant Hodgkin lymphoma: an analysis from the German Hodgkin Study Group (GHSG). Blood 2016; 128: 922.
47. Ng AK. Current survivorship recommendations for patients with Hodgkin lymphoma: focus on late effects. Blood 2014; 124: 3373–3379.
48. Eichenauer DA, Thielen I, Haverkamp H et al. Therapy-related acute myeloid leukemia and myelodysplastic syndromes in patients with Hodgkin lymphoma: a report from the German Hodgkin Study Group. Blood 2014; 123: 1658–1664.
49. 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; 373: 2499–2511.
50. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144.