clinical practice guidelines

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

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incidence

The crude incidence of Hodgkin's lymphoma (HL) in the European Union is 2.3 and the mortality is 0.4 cases/100 000/year. Young adults aged 20–40 years are most often affected; however, a second incidence peak is seen in individuals aged 55 and older. 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 a sufficiently large surgical specimen or excisional lymph node biopsy 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 while 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 they 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% of total body weight 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 neck, chest and abdomen are mandatory. In addition, a baseline positron emission tomography (PET) should be carried out according to the recommendations for staging and response assessment in lymphoma whenever 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) and blood chemistry including C-reactive protein, alkaline phosphatase, lactate dehydrogenase, liver enzymes and albumin are obligatory. Screening for hepatitis B, hepatitis C 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 three categories (limited, intermediate and advanced stages). Table 2 illustrates the European Organisation for Research and Treatment of Cancer/Lymphoma Study Association and the German Hodgkin Study Group definitions of limited, intermediate and advanced stages [II–III, A].

To identify patients at increased risk for acute and/or long-term complications, cardiac and pulmonary function tests should be carried out before the start of treatment.

Since chemotherapy and radiotherapy (RT) can potentially cause permanent fertility damage, reproductive counselling must be offered to young patients of both genders before treatment.

treatment of cHL

limited-stage patients

Combined modality treatment consisting of a brief chemotherapy followed by RT was shown to result in superior tumour control compared with RT alone [I, A] [4, 5] (Figure 1).

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Currently, two or three cycles of adriamycin/bleomycin/vinblastine/dacarbazine (ABVD) (Table 3) followed by involved-field RT (IFRT) is considered 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 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]. However, the current RT guidelines of the International Lymphoma Radiation Oncology Group (ILROG) recommend involved-site RT (ISRT) after chemotherapy in limited stages although this recent strategy has not yet been validated in a prospective study [7].

Table 1. Diagnostic work-up in Hodgkin's lymphoma

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 neck, chest and abdomen
PET
Full blood cell count and blood chemistry
HBV, HCV and HIV screening
Pre-treatment examinations
ECG
Echocardiography
Pulmonary function test
Reproductive counselling (in younger patients)
Serum pregnancy test (in younger female patients)

CT, computed tomography; PET, positron emission tomography; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; ECG, electrocardiography.

The question of whether RT can be omitted in patients with complete metabolic response at interim PET is currently a matter of debate and cannot be fully answered to date. Several randomised trials addressing this issue have been initiated in recent years. Emerging data consistently demonstrate a progression-free survival advantage also for patients with a complete metabolic response at interim PET when treatment with combined modality approaches is applied. A population that can be safely treated with chemotherapy alone could not yet be defined [8, 9]. Therefore, interim PET-guided treatment in limited-stage HL is not recommended outside clinical studies.

intermediate-stage patients

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

Four cycles of ABVD followed by 30 Gy IFRT is widely considered standard for intermediate-stage HL [I, A] [5]. In patients ≤60 years who are eligible for a more intensive treatment, this standard is challenged by a protocol consisting of two cycles of bleomycin/etoposide/adriamycin/cyclophosphamide/vincristine/procarbazine/prednisone in escalated dose (BEACOPPescalated) (Table 4) followed by two cycles of ABVD and 30 Gy IFRT. After a median follow-up of 43 months, FFTF with this protocol was superior in comparison with four cycles of ABVD followed by 30 Gy IFRT. An advantage in OS could not be shown [I, B–C] [10]. Although no results of a prospective study addressing this issue are available to date, the ILROG guidelines recommend ISRT instead of IFRT after chemotherapy in intermediate stages [7].

The question of whether RT is dispensable in intermediate-stage patients with complete metabolic response at interim PET is unanswered. Trials addressing this issue are ongoing.

advanced-stage patients

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

Table 2. Definition of Hodgkin's lymphoma risk groups according to the European Organisation for Research and Treatment of Cancer /Lymphoma Study Association and the German Hodgkin Study Group

Treatment group	EORTC/LYSA	GHSG
Limited stages	CS I–II without risk factors (supra-diaphragmatic)	CS I–II without risk factors
Intermediate stages	CS I–II with ≥1 risk factors (supra-diaphragmatic)	CS I, CS IIA with ≥1 risk factors; CS IIB with risk factors C/D, but not A/B
Advanced stages	CS III–IV	CS IIB with risk factors A/B, CS III/IV
Risk factors	(A) Large mediastinal mass	(A) Large mediastinal mass
	(B) Age ≥50 years	(B) Extranodal disease
	(C) Elevated ESR	(C) Elevated ESR
	(D) ≥4 nodal areas	(D) ≥3 nodal areas

Elevated ESR: >50 mm/h without B symptoms, >30 mm/h with B symptoms.
Large mediastinal mass: more than one-third of the maximum horizontal chest diameter.
B symptoms: fever, night sweat, unexplained weight loss >10% over 6 months.
EORTC: European Organisation for Research and Treatment of Cancer; LYSA: Lymphoma Study Association; GHSG: German Hodgkin Study Group; CS: clinical stage; ESR: erythrocyte sedimentation rate.

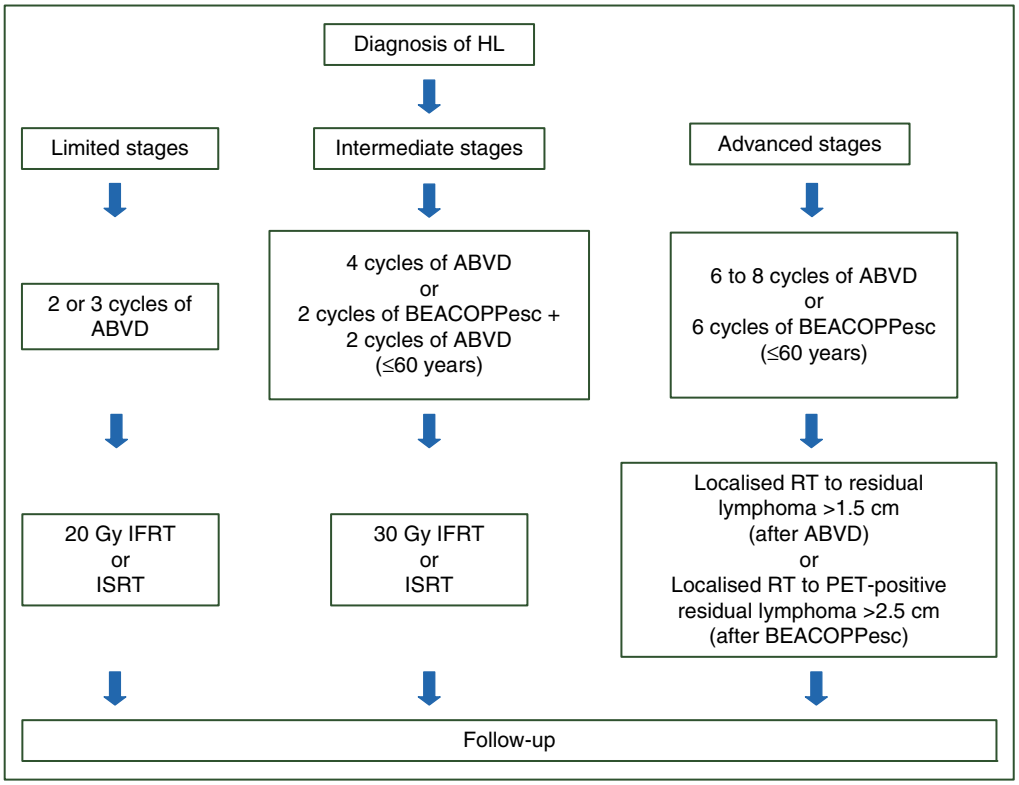

Figure 1. Therapeutic algorithm for newly diagnosed Hodgkin's lymphoma. HL, Hodgkin's lymphoma; RT, radiotherapy; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPPesc, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone escalated dose regimen; ISRT, involved-site radiotherapy; PET, positron emission tomography; NLPHL, nodular lymphocyte-predominant Hodgkin's lymphoma; IFRT, involved-field RT.

Table 3. The adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) regimen

Adriamycin	25 mg/m^2	i.v.	Days 1 + 15
Bleomycin	10 mg/m^2	i.v.	Days 1 + 15
Vinblastine	6 mg/m^2	i.v.	Days 1 + 15
Dacarbazine	375 mg/m^2	i.v.	Days 1 + 15

Recycle: day 29.

Table 4. The bleomycin/etoposide/adriamycin/cyclophosphamide/ vincristine/ procarbazine/ prednisone in escalated dose (BEACOPPescalated) regimen

Bleomycin	10 mg/m^2	i.v.	Day 8
Etoposide	200 mg/m^2	i.v.	Days 1–3
Adriamycin	35 mg/m^2	i.v.	Day 1
Cyclophosphamide	1250 mg/m^2	i.v.	Day 1
Vincristine	1.4 mg/m^2 (maximum: 2 mg)	i.v.	Day 8
Procarbazine	100 mg/m^2	p.o.	Days 1–7
Prednisone	40 mg/m^2	p.o.	Days 1–14
G-CSF		s.c.	From day 8

Recycle: day 22.
G-CSF, granulocyte colony-stimulating factor.

Patients ≤60 years are treated with either six to eight cycles of ABVD followed by localised RT of residual lymphoma larger than 1.5 cm or six cycles of BEACOPPescalated followed by localised RT of PET-positive residual lymphoma larger than 2.5 cm [I, A] [11, 12]. Several trials randomly comparing ABVD and BEACOPPescalated have shown a superior tumour control with BEACOPPescalated [13–15]. A recent network meta-analysis including 9993 patients also indicated a significantly better OS with BEACOPPescalated when compared with ABVD. The survival advantage was 10% at 5 years [16]. 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 been observed in this age group [II, A] [17]. Thus, ABVD represents the standard regimen for older HL patients who are fit enough for treatment with multi-agent chemotherapy.

Retrospective analyses have indicated that early interim PET might be a good predictor for treatment failure in patients with advanced HL receiving ABVD chemotherapy [18, 19]. Therefore, ongoing trials aim at guiding treatment on the basis of early interim PET which is used to distinguish between patients who can potentially be cured with reduced therapy and patients who require standard or even more intensive treatment. However, given a lack of mature prospective data, treatment stratification on the basis of early interim PET cannot be considered standard as yet and further evidence from randomised trials is necessary.

relapsed disease

For most patients with refractory or relapsed HL, the treatment of choice consists of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) [II, A] [20, 21]. High-risk patients may benefit from tandem ASCT [III, B] [22].

Salvage regimens such as dexamethasone/high-dose Ara-C/cisplatin (DHAP), ifosfamide/gemcitabine/vinorelbine (IGEV) or ifosfamide/carboplatin/etoposide (ICE) are given to reduce the tumour burden and mobilise stem cells before high-dose chemotherapy and ASCT [II–III, A] [23–25].

A subset of low-risk patients relapsing after primary treatment with two cycles of chemotherapy followed by RT can be successfully salvaged with a second, more intensive conventional chemotherapy such as BEACOPPescalated [IV, B–C] [26].

In some patients with localised late relapse, salvage RT alone appears to be sufficient [IV, B–C] [27].

The use of the antibody-drug conjugate brentuximab vedotin represents an option in patients failing ASCT. After a pivotal phase II study including 102 HL patients with relapse after ASCT had revealed an overall response rate (ORR) of 75% with single-agent brentuximab vedotin, the drug was recently approved for the treatment of such patients [III, B] [28]. Alternatively, patients can be enrolled in clinical trials evaluating novel agents.

Reduced-intensity conditioning allogeneic stem cell transplantation (RIC-aSCT) can be considered in young, chemosensitive patients in good general condition who relapse after high-dose chemotherapy and ASCT [III, C] [29]. However, RIC-aSCT is not a standard approach in HL and should be conducted within clinical trials whenever possible.

In patients with multiple relapses who have no other treatment options, acceptable remission rates, satisfying quality of life and prolonged survival can be achieved by palliative single-agent chemotherapy with gemcitabine or bendamustine and/or regional RT [30, 31]. As brentuximab vedotin has also been approved for the treatment of HL patients with disease recurrence after at least two lines of treatment who are not candidates for high-dose chemotherapy followed by ASCT, its use can also be considered in this patient group.

treatment of NLPHL

stage IA without risk factors

30 Gy IFRT alone is the standard treatment for stage IA NLPHL patients without risk factors [III, A] [32].

other stages

Usually, NLPHL is treated identically to cHL in all stages except for stage IA without risk factors [33]. As the malignant LP cells of NLPHL consistently express CD20, addition of an anti-CD20 antibody may improve treatment efficacy [V, C]. However, prospective data on this issue are not yet available.

relapsed NLPHL patients

Even more importantly than in cHL, a renewed biopsy should be obtained in patients with suspected NLPHL relapse before salvage therapy is initiated, since transformation into aggressive non-Hodgkin's lymphoma must be excluded. According to newer analyses, transformation rates appear to be substantially higher than previously reported [IV, A] [34, 35].

Localised NLPHL relapses can be effectively treated with rituximab alone [III, B] [36].

Patients with more advanced disease at relapse often require a more aggressive salvage therapy possibly combined with an anti-CD20 antibody. However, prospective data on the use of high-dose chemotherapy followed by ASCT are not available yet.

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

Interim response evaluation by contrast-enhanced CT should be carried out after completion of chemotherapy/before RT in limited and intermediate stages and after four cycles of chemotherapy as well as before RT in advanced stages. Retrospective studies including advanced-stage and relapsed patients, respectively, have shown that interim PET appears to be a useful tool to identify poor-risk individuals [18, 19, 37]. However, interim PET-guided treatment cannot be considered standard and should be restricted to clinical trials except for the decision of whether patients with advanced HL receiving BEACOPPescalated require RT [12].

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

prognosis

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

personalised medicine

In HL, personalised treatment based on certain genetic features as known for some malignancies is not established.

Treatment intensity is chosen according to the clinical stage and the presence or absence of clinical risk factors (as described in the staging and risk assessment section). The use of risk-adapted therapy has led to excellent cure rates in HL patients irrespective of the stage at diagnosis.

Prospective studies evaluating interim PET-guided strategies have been initiated, with the aim to discriminate between low-risk patients who may be sufficiently treated with reduced-intensity approaches and high-risk patients who require standard or even intensified treatment. In patients with limited and intermediate stages, the goal is to define a group of patients with complete metabolic response after chemotherapy not requiring consolidating RT. In advanced HL, it has been shown that RT is dispensable in patients without PET-positive residual lymphoma larger than 2.5 cm after BEACOPPescalated chemotherapy. Ongoing trials in advanced HL evaluate whether it is possible to modify the intensity of chemotherapy based on the result of

Table 5. Summary of recommendations

- After staging is completed, Hodgkin's lymphoma (HL) patients are allocated to distinct risk groups depending on their clinical stage and the presence of clinical risk factors.
- First-line treatment of HL patients usually consists of combined modality approaches or chemotherapy alone. Intensity of treatment depends on the patient's risk profile.
- The standard of care for most patients with disease recurrence after first-line treatment consists of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT).
- Brentuximab vedotin is approved for the treatment of patients failing ASCT and those with multiple relapses.
- HL patients should be treated within clinical trial protocols whenever possible.
- Follow-up should be conducted regularly to detect disease recurrence and therapy-related late effects.

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 with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts 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 [38].

early interim PET. However, no mature data addressing this issue are available to date.

follow-up

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

Additional evaluation of thyroid function (thyroid-stimulating hormone) after irradiation of the neck at one, two and at least five years is recommended. Furthermore, testosterone and oestrogen levels should be monitored, particularly in younger patients who had intensive chemotherapy.

CT scans and previously pathologic radiographic tests must be carried out once to confirm the remission status. Thereafter, surveillance scans are not indicated unless clinical symptoms occur [IV, B] [1, 2].

Patients should be asked for symptoms indicating the existence of long-term toxicity, particularly of heart and lung.

Cancer screening should be conducted regularly due to the increased risk of haematological and solid secondary malignancies after HL treatment.

note

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.

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conflict of interest

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